Journal of Infection (2017) 74, 60—71

BIAM British Infection Association

www.elsevierhealth.com/journals/jinf

Estimating the burden of invasive and serious fungal disease in the United Kingdom

Matthew Pegorie [a], David W. Denning [b,c,d,*], William Welfare [a,d]

[a] Public Health England North West Health Protection Team (Greater Manchester), UK
[b] National Aspergillosis Centre, University Hospital of South Manchester, Manchester, UK
[c] The University of Manchester, Manchester, UK
[d] Manchester Academic Health Sciences Centre, University of Manchester, UK

Accepted 18 October 2016
Available online 24 October 2016

KEYWORDS
Candida;
Aspergillus;
Cryptococcus;
Morbidity

Summary *Background:* The burden of fungal disease in the UK is unknown. Only limited data are systematically collected. We have estimated the annual burden of invasive and serious fungal disease.
Methods: We used several estimation approaches. We searched and assessed published estimates of incidence, prevalence or burden of specific conditions in various high risk groups. Studies with adequate internal and external validity allowed extrapolation to estimate current UK burden. For conditions without adequate published estimates, we sought expert advice.
Results: The UK population in 2011 was 63,182,000 with 18% aged under 15 and 16% over 65. The following annual burden estimates were calculated: invasive candidiasis 5142; *Candida* peritonitis complicating chronic ambulatory peritoneal dialysis 88; *Pneumocystis* pneumonia 207—587 cases, invasive aspergillosis (IA), excluding critical care patients 2901—2912, and IA in critical care patients 387—1345 patients, <100 cryptococcal meningitis cases. We estimated 178,000 (50,000—250,000) allergic bronchopulmonary aspergillosis cases in people with asthma, and 873 adults and 278 children with cystic fibrosis. Chronic pulmonary aspergillosis is estimated to affect 3600 patients, based on burden estimates post tuberculosis and in sarcoidosis.
Conclusions: Uncertainty is intrinsic to most burden estimates due to diagnostic limitations, lack of national surveillance systems, few published studies and methodological limitations. The largest uncertainty surrounds IA in critical care patients. Further research is needed to produce a more robust estimate of total burden.

* Corresponding author. 2nd Floor Education and Research Centre, Wythenshawe Hospital, Southmoor Road, Manchester, M23 9LT, UK.
E-mail address: ddenning@manchester.ac.uk (D.W. Denning).

http://dx.doi.org/10.1016/j.jinf.2016.10.005

Background

Invasive fungal disease is thought to be increasing in the United Kingdom (UK) due to a variety of factors including increased survival time from previously fatal illnesses and an increase in immunosuppression from disease treatment. Understanding of the overall burden of invasive fungal disease in the UK is limited as there is no formal systematic or mandatory surveillance programme specific to fungal infections, although active surveillance networks exist for candidaemias (voluntary laboratory reporting[1]) and specifically for candidaemias in neonates (voluntary reporting[2]).

An analysis of laboratory reports of fungal infections was published in 2001,[3] which highlighted the likely underestimate of the total burden due to the challenges involved in laboratory diagnosis and the voluntary nature of the laboratory reporting system. In 2008, the UK Health Protection Agency issued "Fungal Diseases in the UK: The current provision of support for diagnosis and treatment: assessment and proposed network solution".[4] The UK community of medical mycologists has been active in developing best practice standards for the UK and beyond for the diagnosis and clinical management of fungal disease.[5–9] A necessary next step for healthcare and research prioritisation is to quantify these burdens of invasive fungal disease with improved tools and an expanded range of serious fungal infections.

Methods

We used the UK Office for National Statistics 2011 Census data[10] to estimate UK population size. We used this as the 2011 census is the most recent census in the UK.

We estimated the annual incidence of the following invasive fungal infections: cryptococcal disease and meningitis; *Pneumocystis* pneumonia; invasive aspergillosis; candidaemia; *Candida* peritonitis; and oesophageal candidiasis. In addition, we estimated the prevalence of chronic pulmonary aspergillosis, allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS). Information on incidence, prevalence and total burden of these conditions in the UK is limited. Where such information was available for the UK or countries within the UK (where UK estimates were not available), we included it in the study, for example the data from the voluntary surveillance of candidaemia in England, Wales and Northern Ireland.[1]

Where the information was not available we took a pragmatic approach. For each fungal condition, we considered which populations were most at risk of the condition, sought published estimates for incidence or prevalence measures for the fungal condition in these specific risk populations, and applied these rates to available published estimates of size of these high risk populations in the UK (or certain countries within the UK where UK estimates were not available).

Where multiple estimates of incidence or prevalence were published, we considered both internal and external validity of the studies in deciding on which estimate to use. The methods used for estimating burden of the specific fungal conditions are outlined below.

Selection criteria for published estimates of incidence: for many of the severe fungal infection, there is a paucity of published estimates of incidence, therefore we had to be pragmatic in our approach. Where more than one published estimate was available, we prioritised studies with the best applicability to the UK population (i.e. where UK studies were available we used these, if not we used studies from countries with as comparable a population as possible, where non-UK studies were selected, this is made clear in italics in the fungal infection section of the Methods) and those with the largest sample sizes (where multiple studies were considered, this is made clear in the fungal infection section of the Methods).

Pneumocystis pneumonia

First method

Prior to March 2013, no published estimates of incidence, prevalence or total burden were available for England except for people living with AIDS (PHE HIV in the UK report[16]).

The high risk populations identified and the data source used to estimate their current size included people living with AIDS[16] and people who had received various solid organ transplants (Tx): Heart Kidney Liver and Lung or Heart and Lung.[11]

Using the estimate of total burden amongst people living with AIDS for 2011—2013,[16] we divided this estimate by three to obtain an average yearly estimate.

The incidence rates specific to solid organ transplant patients were found from a variety of studies.[12,13]

Second method

A UK study estimating the incidence of *Pneumocystis* pneumonia over an 11 year period was published in March 2013.[14] This showed that the incidence had increased significantly over the study period. We aimed to estimate the total burden for the most recent year of the study (2010) based on figures reported in the paper for each of the four data sources: Hospital Episode Statistics (HES) data — the paper reported the number of cases in 2010; Routine Laboratory Reporting — the paper reported a range for number of cases in 2008—2010, we used the central point of this range; Death Certificate Data — the paper reported the number of cases in 2010; HIV Surveillance Data — the paper did not report a number or range for total number of cases in the later years of the study, we obtained an estimate by extrapolating from figure 3 of the paper.

Cryptococcal meningitis

No published estimates of incidence, prevalence or total burden were found for the UK. We obtained an estimate based on a simple direct question to the largest mycology referral laboratories in the UK (Bristol, Leeds and Manchester) of the frequency of positive cryptococcal antigen test results. One publication was found which reported on trends in incidence and numbers of fungal meningitis,[15] but this covered all fungal infections and was not specific to cryptococcal infection.

The high risk populations identified included newly diagnosed HIV infection. We used the PHE HIV in the UK report[16] to estimate the current size of this population. The incidence rate for this high risk population was obtained from Patel et al.[17]

Invasive aspergillosis

We took a pragmatic approach to estimating the burden of invasive aspergillosis. The high risk populations identified and the data source used to estimate their current size included: Allogeneic hematopoietic stem cell transplantation (HSCT) and autologous HSCT patients[18]; solid organ transplants[11]; people living with AIDS[16]; Acute myeloid leukaemia (AML), Acute lymphoblastic leukaemia (ALL), Chronic myeloid leukaemia (CML), Chronic lymphocytic leukaemia (CLL), Non Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and Myeloma patients[19]; Chronic granulomatous disease (CGD) patients[20]; Chronic obstructive pulmonary disease (COPD): emergency hospital admissions[d,21]; critical care patients[22]; patients with lung cancer.[19]

The incidence rates specific to the above high risk populations were found from a variety of studies: Lortholary et al.[23] (for Allogeneic and Autologous HSCT patients, and for solid organ transplant patients) —*these estimates were not for the UK population but the French population*; Keshishian[24] (for people living with AIDS); Pagano et al.[25,e] (For AML, ALL, CML, CLL, NHL, HL and myeloma patients) — *these estimates were not for the UK population but the Italian population*; Beauté et al.[26,f] (for CGD patients) — *this estimate was not for the UK population but the French population*; Guinea et al.[27] (for COPD: emergency hospital admissions) — *this estimate was not for the UK population but the Spanish population*, another study reporting an incidence estimate was considered (Xu et al.[28]) but the sample size for the study was significantly smaller than that of Guinea et al. so we did not include it; A wide range of estimates from different studies[29] for critical care patients, see sensitivity analysis discussion below — *these estimates were not for the UK population but the Belgian and Spanish populations*; Yan X et al.[30] was used for patients with lung cancer — *this estimate was not for the UK population but the Chinese population*.

Critical care patients: sensitivity analysis

The largest risk group population by far for invasive fungal infection was patients in critical care at risk of invasive aspergillosis, regardless of which type of critical care unit is considered. Any variation in incidence rate could lead to a significant change in estimated burden. We carried out a sensitivity analysis to reflect this.

Activity data is available for a broad range of critical care units in England.[22] The most common type of admission to ICU amongst cases of invasive aspergillosis is medical admission, and the most common reasons for admission respiratory and cardiovascular disease,[31] therefore we considered two broad groups of critical care units in the sensitivity analysis. The first was medical intensive care units (ICUs) and other ICUs where length of patient stay is likely to be similar to that of medical ICUs,[g] the second was all ICUs, excluding spinal units.

There is a wide range of published estimates for incidence of invasive aspergillosis in patients in critical care: from 0.3% to 19%.[29] Key factors include: the type of critical care unit considered, and whether or not studies were autopsy controlled. No non-invasive diagnostic test (for example isolation of *Aspergillus* from respiratory cultures) is sensitive or specific enough to establish a definite diagnosis.[32] It is difficult to distinguish colonisation with *Aspergillus* from infection with *Aspergillus*.[32]

We focused on those studies that specifically examined the incidence of invasive aspergillosis in critical care units. Four such studies were found, one had a small sample size (n = 24) and did not report an incidence estimate so was not considered further.[33] The other three, from which incidence rates estimates were used, are listed in Table 4 with their characteristics and the populations they apply to.

We adjusted estimates of burden to account for double counting of patients already counted in other groups. We assumed that the majority of those who developed invasive aspergillosis would require ICU admission.

Chronic pulmonary aspergillosis

Chronic pulmonary aspergillosis complicates a wide spectrum of underlying lung diseases of which the commonest are pulmonary tuberculosis (PTB), non-tuberculous mycobacterial lung infection, COPD, sarcoidosis, and allergic aspergillosis complicating asthma.[39]

An estimate of the annual number of patients with chronic pulmonary aspergillosis after pulmonary tuberculosis (PTB) has recently been published.[34] For most countries, this was based on a 22% rate of chronic pulmonary aspergillosis after PTB in those with cavities of 2.5 cm or greater and 2% in those without a residual cavity. In the absence of UK data, we assumed a rate of residual cavitation after PTB of 12% (range in other countries 21—35%[35—37]). To generate a five year period prevalence,

[d] We used the HES-based 4 year study to estimate yearly average number of COPD emergency admissions. We excluded the day cases as these were unlikely to develop invasive aspergillosis. We used the estimated incidence in the last year of the study (2007).

[e] The paper reports total yearly number of cases of invasive mould infections according to malignancy type. It also reports that 90% of mould infections were caused by *Aspergillus* spp. We calculated malignancy-specific incidence rates for invasive aspergillosis by applying the 90% rate to the total number of cases of mould infection per malignancy type and dividing this by the total number of patients with the malignancy.

[f] The paper reported an overall incidence of invasive fungal disease (IFD) per patient year, and reported that 40% of IFDs were cause by invasive aspergillosis. The overall incidence rate was applied to the estimated population size, and 40% of the resulting estimate of overall IFD burden was used for the burden of invasive aspergillosis.

[g] Critical care episodes were counted from table 14 of the Critical Care report 2013—2014,[20] critical care unit functions included in this group were: Non-specific general adult critical care, Medical adult patients, Liver patients predominate, Renal patients predominate.

a 15% attrition rate was assumed, accounting for surgical resection and death.

A recent estimate of the rate of chronic pulmonary aspergillosis complicating sarcoidosis in the UK was also available.[38] Numerous other antecedent underlying pulmonary conditions are found in patients with chronic pulmonary aspergillosis,[39] and the relative proportions of these were used to estimate the total UK burden.

A separate approach was taken using referrals to the National Aspergillosis Centre from the North West England, based on population and regional variation in directly age-standardised mortality rates (DSR). Just over 100 new patients are referred annually to the National Aspergillosis Centre.[40] It was assumed that referral was near complete in NW England to the National Aspergillosis Centre because of excellent clinical links and proximity. Using published directly age-standardised respiratory disease mortality rate for under year 75 olds (DSR)[41] and regional populations,[42] we derived an annual potential diagnosable burden, based on current respiratory medicine practice, which approximates to an annual incidence (Table 1 in Supplementary Materials).

Allergic bronchopulmonary aspergillosis (ABPA)

ABPA complicates asthma and cystic fibrosis (CF). The global burden of asthma has been re-estimated recently, a total of 334 million in all ages (4.85% of the global population)[43] and 193 million adults with active asthma.[44] The UK has one of the highest rates of asthma in the world, an estimated 16–18.2% of adults with clinical asthma,[45] or nearly 8.2–9 million (age 15 and older).[46] Other more recent data of asthma prescription data from the UK put the total rate at approximately 5.4 million, including children. As the prevalence in children is 88% of the adult rate, we derived an adult number of asthmatics of 4.4 million (our lowest and base case estimate).

There are no population data for ABPA or any surrogate marker such as IgE from the UK. An abstract from one hospital tracking IgE and Aspergillus IgE levels in 330 consecutive referrals to an asthma clinic found a 1.5% rate of probable ABPA with most diagnostic features and 13% with both an elevated total IgE and Aspergillus IgE.[47] A base case estimation of ABPA rates in adults was made, using a median prevalence of 2.5% from referrals to secondary care. This 2.5% rate is derived from rates of 0.78% and 4.1%[44,48] from 6 national studies in consecutive referrals over a defined period to a specialist chest physician for problematic asthma. Deterministic sensitivity analyses relating to different asthma populations rates and ABPA rates were also derived.

ABPA has been reported in children, but is probably rare,[49] and there are no epidemiology studies published to estimate a rate.

We ascertained the number of individuals in the UK over the age of 18 with CF from 2011 annual report.[50] Using the distribution frequency described by Baxter et al.,[51] we derived the likely numbers of adults with aspergillosis in CF in the UK. ABPA in CF is well recognised in older children and teenagers, and we have used the annual CF report for this purpose.[52]

Severe asthma with fungal sensitisation (SAFS)

As SAFS is another distinctive pattern of asthma usually associated with sensitisation to multiple fungi and responsive to antifungal medication[53–56] we estimated the UK burden of this entity. While recently described in children,[57] it is rare, and so this was not estimated. Severe asthma was defined by a poor level of current clinical control including a risk of frequent severe exacerbations (or death) and/or chronic morbidity. Severe asthma includes untreated severe asthma, difficult-to-treat severe asthma, and treatment-resistant severe asthma. In a multi-country comparison of the role of fungal sensitisation in severe asthma, 21% were defined as severe.[58] In other studies[59] lower frequencies of severity are recorded,[60] including a recent estimate of 3.6%. We used 5% as our base case to embrace both severe refractory and compliant difficult to control asthmatics. We have also computed a sensitivity analysis.

Fungal sensitisation becomes more common the worse the asthma, with rates ranging from approximately 25% of patients referred to a specialist to 75% for those with repeated hospital admissions. We used a rate of 60%.[61–64]

Candidaemia

There is a voluntary surveillance system in England that collects laboratory reports of all microorganisms isolated (including fungi) at approximately 400 NHS and other laboratories throughout England, Wales and Northern Ireland.[65]

Blood culture has a poor sensitivity for detecting Candida species: a 2011 systematic review of the diagnostic accuracy of PCR techniques for invasive candidiasis[66] identified 10 studies reporting the sensitivity of blood cultures. The pooled culture positivity rate in patients with proven or probable invasive candidiasis was 0.38 (95% CI: 0.29–0.46).[66] A more recent US study using PCR and beta 1.3-D-glucan detection derived a similar figure.[67] Therefore we made the assumption that the total number of positive blood culture samples represented 38% cases of proven or probable invasive candidiasis tested by blood culture techniques.

Candida peritonitis

We took a pragmatic approach to estimating the burden of Candida peritonitis.

The two main risk groups for this condition in the UK are: surgical ICU patients and people on chronic ambulatory peritoneal dialysis (CAPD).

Surgical ICU patients

We assumed that the majority of cases in surgical ICU patients would be counted in the estimate of total number of cases of invasive candidiasis discussed above.

CAPD patients

For the number of patients on CAPD in England every year, we used estimates from NICE.[68]

To estimate the incidence of peritoneal candidiasis in patients on CAPD, we used an estimate reported on the Leading International Fungal Education (LIFE) website.[69] This incidence estimate was reported as episode per patient year. In our calculation of attributable burden, we assumed that all CAPD patients in England stay on CAPD for at least a year.

Oesophageal candidiasis

The main risk group for this condition in the UK is probably people with AIDS. Oesophageal candidiasis is an AIDS defining illness. The number of cases reported in the UK between 2011 and 2013 was reported in the PHE HIV in the UK report.[16] We divided this figure by three to obtain a yearly estimate of burden.

Another approach to estimating the burden was also taken using published estimates of yearly incidence amongst HIV patients on anti-retroviral therapy[70] — *this estimate was not for the UK population but the USA population* — and estimates of numbers of HIV patients on anti-retroviral therapy in the UK.[16]

Mucormycosis

Occasional cases of mucormycosis occur in the UK, usually highly immunocompromised patients, occasionally in intravenous drug addicts, burn or trauma patients or people with diabetes, and rarely related to hospital transmission. Most diagnoses are made histologically or on direct microscopy specimens, culture sensitivity is low. No data are collected systematically.

To estimate the number of mucormycosis cases in the UK, we applied *the French population incidence* found from published studies[71,72] to the UK population (no UK estimate of incidence available).

Other rarer infections

Other rarer infections are not well tracked in the UK, including imported endemic mycoses (histoplasmosis and coccicioidomycosis for example) and are rare based on the experience of the National Aspergillosis Centre. Likewise serious infections related to unusual filamentous fungi such as *Fusarium* or *Scedosporium* spp. do occur, the former in leukaemic patients, the latter in some cystic fibrosis patients and rarely as an invasive pathogen.

Results

The UK population in 2011 was 63,182,000 with 18% aged under 15 and 16% over 65.[10]

Pneumocystis pneumonia

An average yearly total burden of 157 *Pneumocystis* pneumonia (PCP) diagnoses was found for those people living with AIDS in the UK[16] using our first estimation approach.

The estimates of population size, population-specific incidence rate and yearly burden of disease obtained for patients who had received various transplants in the UK are outlined in Table 1.

The total estimate of burden of PCP for both people living with AIDS and solid organ transplant populations in the UK was 207. This estimate ignores other immunocompromised patients, such as haematological malignancy and severe autoimmune disease.

Second method

Our second estimation approach yielded a total UK burden of 587 cases of PCP for 2010.

Cryptococcal disease and meningitis

An estimate of up to 100 cases per year for the UK was obtained from the reference laboratories.

It is unclear whether this is an underestimate or an overestimate as it is estimated that in 2011 there were a total of 51 fungal meningitis cases (all fungi, based on culture). However this 2011 estimate is based on voluntary laboratory reporting and furthermore, there is some evidence that cryptococcal infections are under-reported.[15] Many diagnoses of cryptococcal disease are based on cryptococcal antigen alone, and while meningitis is the commonest manifestation of disease, other organs are affected. It is likely that the vast majority of these cases were in people living with HIV and in 2013 approximately 6000 new HIV infections were diagnosed.[16]

Invasive aspergillosis

The estimates of population size and, population-specific incidence rate and burden of disease obtained for high risk populations in the UK excluding critical care units patients are outlined in Table 2.

Therefore a total of 568—579 patients develop IA in well recognised at risk groups. Some cases in haematological patients will have been prevented with antifungal prophylaxis. Only lung Tx recipients with true IA are included, omitting those with airways infection and colonisation, all of whom are treated.

The estimates for patients with pulmonary disease are outlined in Table 3.

Therefore the estimate for the total yearly burden of IA in the UK for the all of the above groups is 2901—2912.

Sensitivity analysis

The results of the sensitivity analysis of IA in critical care are displayed in Table 5. The variation between highest and lowest burden estimates for medical type ICUs and all type ICUs (spinal units excluded) was over 10-fold. This highlights the level of uncertainty over this estimate of burden. Our view is that the rate of IA in the UK is probably at the low end of the estimates above, with ~50% of the cases occurring in COPD patients,[73] even though IA is the most common missed infectious diagnosis at autopsy.[75] So a total ICU caseload of between 821 and 2737 is likely, of which 50% is attributable to COPD. Adjusting downwards by 50% for probable double counting of cases of COPD emergency hospital admissions (we assumed most of these would

Table 1 Estimates of population size, specific incidence rates and yearly burden of *Pneumocystis* pneumonia for solid organ transplant populations.

Population	Population size	Incidence rate	Yearly burden of disease
Heart Tx	195	5.5%	11
Kidney Tx	2244	0.3%	7
Liver Tx	830	1.15%	9
Lung Tx or heart and lung Tx patients	397	5.78%	23
Total			50

Table 2 Estimates of population size, specific incidence rates and yearly burden of invasive aspergillosis for well recognised at risk groups.

Population	Population size	Incidence rate	Yearly burden of disease
Allogeneic HSCT	1615	8.1%	131
Autologous HSCT	2225	0.9%	20
Heart Tx	195	4.8%	9
Lung Tx	397	4.1%	7
Liver Tx	830	0.8%	7
Kidney Tx	2801	0.3%	8
AIDS	320	0.6%—4%	2—13
AML	2921	7.1%	207
ALL	654	3.8%	25
CML	675	2.3%	15
CLL	3233	0.5%	16
NHL	12,783	0.8%	103
HL	1845	0.4%	7
Myeloma	4792	0.2%	9
CGD	119	$i_{all\ IFD} = 0.040$/patient-years**	$n_{all\ IFD} = 4.76$, $n_{CGD} = 2$
Total			**568—579**

**Overall incidence of invasive fungal disease (IFD).

Table 3 Estimates of population size, specific incidence rates and yearly burden of invasive aspergillosis for pulmonary disease.

Population	Population size	Incidence rate	Yearly burden of disease
COPD emergency hospital admissions	89,466	1.3%	1163
Patients with lung cancer	44,488	2.63%	1170

be admitted to ICU), and solid organ transplant recipients (n = 24) resulted in adjusted estimates of 387—1345 cases.

The total estimate of burden of IA amongst the high risk populations is 2901—2912 (excluding ICU populations) and 3288—4257 (including ICU populations). This estimate ignores those with solid tumours other than lung tumours, autoimmune disease, liver failure and other conditions treated with corticosteroids.

Chronic pulmonary aspergillosis

Chronic pulmonary aspergillosis complicates many conditions[39] some estimates of the annual incidence and 5 year period prevalence have been published for pulmonary tuberculosis and pulmonary sarcoidosis complicating an estimated 16,270 cases of pulmonary sarcoidosis in the UK.[38] The anticipated annual incidence of each was 118 and 240 respectively. Together these two conditions account for about 30% of patients with CPA[38] and so an annual diagnosable incidence is around 358 cases for these conditions and a total of 1193 cases. We compared this total, with current referral to the National Aspergillosis Centre (Table 1 of Supplementary Materials), which is actually 110 per year and should be about 204, if all cases are diagnosed and referred in NW England. Either estimate suggests major under-diagnosis.

Computing prevalence and assuming a 15% annual mortality, including 370 cases following PTB[34] and 830 (range 415—1660). Together these 2 conditions account for about 30% of patients with CPA,[38] consistent with a total UK burden of CPA of approximately 3600 cases. As many are asymptomatic in the early stages, this number is an overestimate of those at the more severe end of the spectrum requiring therapy.

Allergic bronchopulmonary aspergillosis (ABPA)

Using our base case of a rate of 2.5% for ABPA among patients with asthma, 110,667—235,070 adults would be

Table 4 Sources of estimates of the incidence of invasive aspergillosis in critical care patients.

Study	Study characteristics	Population studied
Meersseman et al.[73]	Sample size 127 Autopsy controlled Study aim: to determine the incidence of IA in medical ICUs Retrospective, single centre	Patients in medical critical care units
Garnacho-Montero et al.[74]	Sample size 1756 Not autopsy controlled Study aim: to describe the characteristics of patients with positive samples for *Aspergillus* species Prospective, multi-centre (73 mixed ICUs)	Patients in any type of critical care unit
Vandewoude et al.[32]	Sample size 172 Not autopsy controlled Study aim: to describe characteristics of patients with positive samples for *Aspergillus* species Retrospective, single centre, mixed ICU	Patients in any type of critical care unit

expected in the UK. However, the sensitivity analyses vary by over 10-fold from 34,528—385,515 affected patients. The only partial population based studies from Republic of Ireland and the USA[76,77] suggests rates at the lower estimate of published estimates. Referral and discharge patterns across the UK are not uniform, so ABPA is likely to be diagnosed in some areas more often than others. However ABPA is only one fungal complication of asthma, as discussed below under SAFS.

Of the 4933 adults with CF in the UK, we estimate that 873 adults have ABPA (95% CIs: 597—1243) and 631 people over 15 years old (12.5% of 5062 patients) were documented, indicative of a diagnostic gap of 242. The annual report[52] also described 278 children and adolescents with ABPA (7.4% of 3732 children). In addition, an estimated 1480 (95% CI: 1125—1894) have *Aspergillus* bronchitis. If all patients with ABPA and *Aspergillus* bronchitis benefit from therapy (which needs to be established), this totals 2353 patients.

Severe asthma with fungal sensitisation (SAFS)

Asthma severity and fungal sensitisation rise in parallel.[64] There are approximately 65,000 admissions to hospital with asthma annually, approximately 40,250 in adults.[78] Fungal sensitisation rates are not well studied in the UK, especially as patients may be sensitised to one or more fungi.[63] In a series of 121 patients with severe asthma in the UK, sensitisation rates by either skin prick testing or IgE were *Aspergillus fumigatus* 45%, *Candida albicans* 36%, *Penicillium* spp. 29%, *Cladosporium herbarum* 24%, *Alternaria alternata* 22%, and *Botrytis* spp. 18%; 41 (34%) were not sensitised to any fungus tested.[63] The minimum proportion of poorly controlled asthmatics who would be sensitised to a fungus is about 35%, rising to >75% in the worse patients.[61] Using a uniform estimate of 60% fungal sensitisation of the most severe asthmatics (3.6—10%) between 95,617 and 564,169 UK adults have SAFS or severe asthma with ABPA (Table 6).

There is some duplication between ABPA and SAFS, as sensitisation to *A. fumigatus* is common to both and some ABPA patients have severe asthma. These patients are grouped by some authors as having 'fungal asthma' or 'fungal-associated airways disease'. Part of the definition of severe asthma is continuous use of corticosteroids, which is advocated for ABPA, irrespective of the control of asthma. Therefore the overlap is uncertain, and requires detailed study. However given that 75% of SAFS patients

Table 5 Sensitivity analysis for estimation of burden of invasive aspergillosis amongst patients in critical care in the UK.

Study	Risk group in UK to which study applies	Number in Risk Group in the UK	Incidence Rate	Number of expected cases in the UK
Meersseman et al.[73]	Patients admitted to medical ICUs	166,645	5.8%[73]	9665
Garnacho-Montero et al.[74]	Patients admitted to any ICU (Spinal Units excluded)	248,811	1.1%[74]	2737
Vandewoude et al.[32]	Patients admitted to any ICU (Spinal Units excluded)	248,811	0.33%[32]	821

Table 6 Sensitivity analyses of ABPA prevalence in adults with asthma in the UK.

Asthma cases	Asthma in UK adults using different estimates		
	Low	Medium	High
	4,426,699	8,288,978	9,402,809
ABPA prevalence			
0.78%	34,528	64,654	73,342
1.5%	66,400	124,335	141,042
2.5%	110,667	207,224	235,070
3.5%	154,934	290,114	329,098
4.1%	181,495	339,848	385,515
Severe asthma prevalence			
3.6%	95,617	179,042	203,101
5%	132,801	248,669	282,084
10%	265,602	497,339	564,169
Fungal asthma prevalence			
50% overlap	121,734	227,947	258,577
33% overlap	163,124	305,449	346,494
20% overlap	194,775	364,715	413,724

are sensitised to *A. fumigatus* and that only a minority of ABPA patients remain on long term steroids, we show a sensitivity analysis with 20%, 33% and 50% overlap in Table 4, using the mid-point estimates for ABPA (2.5%) and severe asthma (5%).

The overall estimate of adults with 'fungal asthma' varies by 3.4 fold, from 121,734 to 413,724, primarily dependent on the number of adults with asthma.

Invasive candidiasis

Candidaemia

There were 1700 laboratory reports of candidaemia in 2013. Assuming that these represent 38% cases of proven or probable invasive candidiasis tested by blood culture techniques, the resulting estimate for the total number of cases in England, Wales and Northern Ireland in 2013 was: 4473.

Scotland had a rate of candidaemia of 4.8 cases per 100,000 population per year shortly after the millennium,[79] 254 bloodstream and 669 invasive *Candida* cases annually.

The total estimate of invasive candidiasis burden for the UK was therefore: 5142.

This estimate of burden of candidaemia is likely to be an underestimate as reporting from laboratories is voluntary, therefore likely to be a degree of under-reporting. Population based estimates have been reported in Northern Ireland and Scotland with rates of 6.1 and 4.8 per 100,000 population[79,80] which if extrapolated to the whole population would suggest 2995–3806 cases annually, as compared to the 1700 reported for England and Wales (~90% of the population). Further a six sentinel hospital study in England and Wales found an incidence of 18.7 episodes of candidaemia per 100,000 finished consultant episodes (or 3.0/100,000 bed days) in 1997–1999[81] which translates for 2014–2015 for England only to 3497 as there were 18.7 million Finished Consultant Episodes,[82] assuming no substantial change in *Candida* bloodstream rate over time.

Considering that the estimate is likely to be an underestimate, within the range of UK candidaemia burden estimates between 2995 and 5142, we selected the higher end of the range (5142) as our estimate.

These data indicate a population rate in the UK of candidaemia and invasive candidiasis of 3.1/100,000 and 10.1/100,000 respectively.

Candida peritonitis in CAPD patients

The estimated number of patients on CAPD in England was 1768. The estimated number of episodes per patient year attributable to *Candida* in this patient group was 0.05. The resulting estimate for total yearly burden in England was 88 cases.

Oesophageal candidiasis

An average yearly total burden of 43 diagnoses was found as AIDS indicator infections.

Many additional cases occur, and one estimate was 0.5% of those on anti-retroviral treatment annually.[70] If applied to the UK population of 73,300 on anti-retroviral treatment in 2013,[16] this would equate to 367 episodes annually, although these data derive in part from patients without full HIV suppression, so could be an overestimate. Other patient groups also get oesophageal candidiasis, but modelling is not realistic currently.

Mucormycosis

The UK population in 2011 was 63,182,000,[10] and the estimated population incidence of Mucormycosis in France was 0.09 per 100,000 population per year (averaged over 10 years). This resulted in a UK estimate of 57 cases per year.

Other rare infections

Based on expert opinion, there are probably fewer than 25 such patients annually in the UK.

Totals

Table 7 summarises the estimates for total expected number of cases for each invasive fungal infection and rates per 100,000 population.

The estimated total burden of invasive fungal illness in the UK is between 241,525 and 662,987 cases per year.

Discussion

Estimating the burden of invasive fungal infection accurately is challenging due to the lack of a dedicated mandatory systematic surveillance system, and the wide range of incidence estimates for the largest high risk populations. This is likely to be compounded by the combination of lack of clinical suspicion and limited sensitivity of traditional diagnostic tests used for invasive fungal illness, making it difficult to obtain laboratory confirmation

Table 7 Total estimates of burden.

Invasive fungal infection	Risk group	Number of cases expected	Rates per 100,000 population
Pneumocystis pneumonia	All risk groups	207—587	0.33—0.93
Cryptococcal meningitis	Primarily AIDS patients	100	0.16
Invasive aspergillosis	All risk groups except critical care patients	2901—2912	4.59—4.61
	Critical care patients	387—1345	0.61—2.13
Chronic pulmonary aspergillosis — all	All risk groups	204—3600	0.32—5.70
Allergic bronchopulmonary aspergillosis (ABPA)	All risk groups	110,667—235,070	175—372
Severe asthma with fungal sensitisation (SAFS)	All risk groups	121,734—413,724	192—654
Invasive candidiasis	All risk groups	5142	8.14
Candida peritonitis	CAPD patients	88	0.14
Oesophageal candidiasis	AIDS patients	43—367	0.07—0.58
Mucormycosis	All risk groups	57	0.09
Other rare infections	All risk groups	25	0.04
Total		**241,525—662,987**	**382—1049**

for a significant number of cases. This issue is exemplified for IA as this was the commonest error in infection diagnoses missed in critical care patients examined at autopsy.[75]

There is a significant level of inaccuracy as our estimation methods have relied on limited published information, and there is a wide range of estimates for some of the published incidence rates. This high level of uncertainty is reflected in the results of our sensitivity analysis for the estimation of the burden of invasive aspergillosis in ICU patients, and in the difference between the estimates of PCP burden resulting from the two different calculation methods used.

The estimate of burden for PCP obtained by the first method is likely to be an underestimate as other high risk populations, notably patients with haematological malignancy and those on high dose corticosteroid regimens were not included as no overall incidence rate of PCP could be found in the literature for these groups.

The estimate of burden for PCP obtained by the second method should be considered in the light of methodological limitations outlined by the authors[14]: laboratories may be under-reporting as samples are not processed for *Pneumocystis* diagnosis unless clinically requested, and cytological techniques can also be used (cases diagnosed in this manner would not be counted in this study) and there is potential for double counting of cases captured both in the hospital admission data and the laboratory reporting data. In addition many cases are clinically diagnosed and treated, many correctly, without a respiratory sample being obtained to enable laboratory diagnosis.

The estimates of chronic respiratory disorders associated with *Aspergillus* and other airborne moulds are much larger than any prior estimate, even if the more conservative assumptions are made. There is certainly some double counting which we have tried to adjust for but the population prevalence range of fungal asthma of 121,734—413,724 is still wide. Epidemiological studies in primary care are required to establish a more precise estimate. Our data excludes children, in whom fungal asthma occasionally occurs.[83,57]

The lower end of our estimate of total invasive fungal diseases burden range is likely to be an underestimate, as some condition-specific estimates are for England only. There was potential for double counting of cases, although we have attempted to account for this.

Estimates of the burden of serious fungal disease for individual countries have been published[69] for Austria, Belgium, Brazil, Czech Republic, Denmark, Dominican Republic, Germany, Greece, Hungary, Ireland, Israel, Jamaica, Kenya, Mexico, Nepal, Nigeria, Qatar, Russia, Senegal, Sri Lanka, Tanzania, Trinidad and Tobago, Uganda, Ukraine, Vietnam, along with estimates of chronic and allergic aspergillosis in India.[84] Burden estimates for many other countries and other prospective epidemiology studies are in press and can be used to compare the relative rates of infections to address strategies for prevention and clinical management.

We have not attempted to estimate mortality related to fungal disease in the UK, although others have done so for other countries. The overall and attributable mortality is not always clearly discernable, the estimates we have provided have much uncertainty attached to them, and adding mortality in addition is likely to add another layer of uncertainty. However, undiagnosed invasive fungal infections such as PCP and IA are always fatal without specific therapy and Candida bloodstream infections and invasive candidiasis have mortalities in excess of 90% untreated. With treatment, mortality falls especially with PCP in AIDS (~10% mortality) and ~30% with IA in non-ICU patients. An estimate of mortality would require specific therapy rates, which is unknown for most of these disorders.

Strengths and limitations of the study: We acknowledge that the estimates produced in this paper and the methods reached to achieve them are crude and vulnerable to significant error due to lack of robust surveillance information and paucity of published burden studies in the field. We have made the best attempt possible by: drawing on

surveillance data where available; rigorously identifying the relevant high risk groups, the best available estimates of population size for these, and the best available population-specific incidence rates for these; being explicit about the methods used for each individual estimate; and attempted to account for under and over-estimations as well as potential double counting. We are not aware of any other comprehensive burden study for serious and invasive fungal disease in the UK and therefore would argue that although imperfect, this study is a useful contribution to the limited body of knowledge in this field.

Conclusion

There is a high degree of uncertainty around the total estimate of burden due to: diagnostic limitations, the lack of a systematic national surveillance system, the limited number of studies published on the topic and the methodological limitations of calculating the burden.

To our knowledge, this is the first attempt at a comprehensive estimation of burden of invasive fungal infection in the UK. Further studies will likely need to combine methods (pragmatic and surveillance-based), take into account any new published information on specific incidence rates, and consider using alternative data sources such as the Hospital Episodes System (HES). An accurate estimate of total burden will ultimately rely on improved diagnostic testing and laboratory reporting.

Conflict 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 Health Research, Medical Research Council, Global Action Fund for Fungal Infections and the Fungal Infection Trust. He acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Scynexis, Cidara, Biosergen and Pulmocide. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer.

Acknowledgement

No funding has been received for this research.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2016.10.005.

References

1. Public Health England (PHE). Voluntary surveillance of candidaemia in England, Wales and Northern Ireland: 2012. *HPA* 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/356740/hpr3614_cnddm13.pdf.
2. http://www.neonin.org.uk/index.
3. Lamagni TL, Evans BG, Shigematsu M, Johnson EM. Emerging trends in the epidemiology of invasive mycoses in England and Wales (1990–9). *Epidemiol Infect* 2001 Jun;**126**(3):397–414.
4. http://www.hpa.org.uk/webc/hpawebfile/hpaweb_c/1196942156347 [Now archived: http://webarchive.nationalarchives.gov.uk/20080728173910/http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947363235].
5. Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA, Lortholary O, European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. *Clin Microbiol Infect* 2014 Apr;**20**(Suppl. 3):76–98. http://dx.doi.org/10.1111/1469-0691.12360. PubMed PMID: 24102785.
6. Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Akdagli S, Bille J, Donnelly JP, et al., ESCMID Fungal Infection Study Group. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures. *Clin Microbiol Infect* 2012 Dec;**18**(Suppl. 7):9–18. http://dx.doi.org/10.1111/1469-0691.12038. PubMed PMID: 23137134.
7. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al., ESCMID Fungal Infection Study Group. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect* 2012 Dec;**18**(Suppl. 7):19–37. http://dx.doi.org/10.1111/1469-0691.12039. PubMed PMID: 23137135.
8. Ameen M, Lear JT, Madan V, Mohd Mustapa MF, Richardson M. British Association of Dermatologists' guidelines for the management of onychomycosis 2014. *Br J Dermatol* 2014 Nov;**171**(5):937–58. http://dx.doi.org/10.1111/bjd.13358. PubMed PMID: 25409999.
9. Schelenz S, Barnes RA, Barton RC, Cleverley JR, Lucas SB, Kibbler CC, et al., British Society for Medical Mycology. British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal diseases. *Lancet Infect Dis* 2015 Apr;**15**(4):461–74. http://dx.doi.org/10.1016/S1473-3099(15)70006-X. Epub 2015 Mar 12. Review. PubMed PMID: 25771341.
10. Office for National Statistics. *2011 Census: population estimates for the United Kingdom, March 2011*. ONS; Dec 2012. http://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/2011censuspopulationestimatesfortheunitedkingdom/2012-12-17#the-structure-of-the-population-of-the-united-kingdom.
11. *Organ donation and transplantation activity report 2013/14*. NHSBT; 2014.
12. Cardenal R, Medrano F, Varela J, Ordoñez A, Regordan C, Rincon M, et al. *Pneumocystis carinii* pneumonia in heart transplant recipients. *Eur J Cardiothorac Surg* 2001;**20**(4):799–802.
13. Wang EH, Partovi N, Levy RD, Shapiro RJ, Yoshida EM, Greanya ED. Pneumocystis pneumonia in solid organ transplant recipients: not yet an infection of the past. *Transpl Infect Dis* 2012;**14**(5):519–25.
14. Maini R, Henderson KL, Sheridan EA, Lamagni T, Nichols G, Delpech V, et al. Increasing *Pneumocystis* pneumonia, England, UK, 2000–2010. *Emerg Infect Dis [Internet]* 2013. http://dx.doi.org/10.3201/eid1903.121151.
15. Okike IO, Ribeiro S, Ramsay ME, Heath PT, Sharland M, Ladhani SN. Trends in bacterial, mycobacterial, and fungal meningitis in England and Wales 2004–11: an observational study. *Lancet Infect Dis* 2014 Apr;**14**(4):301–7.
16. Public Health England (PHE). *HIV in the United Kingdom: 2014 report*. PHE; 2014.

17. Patel S, Shin GY, Wijewardana I, Vitharana SR, Cormack I, Pakianathan M, et al. The prevalence of cryptococcal antigenemia in newly diagnosed HIV patients in a southwest London cohort. *J Infect* 2013;**66**:75—9.
18. The British Society of Blood and Marrow Transplantation (BSBMT). *BSBMT registry: 2013 activity*. BSBMT; 2013. http://bsbmt.org/2013-activity/.
19. UK Cancer Registry, accessed via Cancer Research UK CancerStats web page: http://www.cancerresearchuk.org/cancer-info/cancerstats/.
20. Jones LB, McGrogan P, Flood TJ, Gennery AR, Morton L, Thrasher A, et al. Chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry. *Clin Exp Immunol* 2008;**152**:211—8.
21. DiSantostefano R, Baxter R, Dale P, McQuire S, Smith H. Emergency Inpatient admissions for COPD in England based on hospital episode Statistics (HES) 2005—2008. *Am Thorac Soc Int Conf Abstr* 2011. Chapter DOI: 10.1164/ajrccm-conference.2011.183.1_MeetingAbstracts.A1731. ISSN: 1073-449X.
22. HES online and the NHS Information Centre (NHSIC). *Hospital Episode Statistics, adult critical care in England: April 2013 to March 2014*. NHSIC; 2015.
23. Lortholary O, Gangneux JP, Sitbon K, Lebeau B, de Monbrison F, Le Strat Y, et al., French Mycosis Study Group. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005—2007). *Clin Microbiol Infect* 2011;**17**(12):1882—9.
24. Keshishian C. *Health Protection (HPA) mycology network — rapid evaluation of incidence estimates (unpublished)*. HPA Mycology Network; 2004.
25. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica* 2006;**91**:1068—75.
26. Beaute J, Obenga G, Le Mignot L, Mahlaoui N, Bougnoux ME, Mouy R, et al., the French PID Study Group CEREDIH. Epidemiology and outcome of invasive fungal diseases in patients with chronic granulomatous disease a multicenter study in France. *Pediatr Infect Dis J* 2011;**30**:57—62. http://dx.doi.org/10.1097/INF.0b013e3181f13b23.
27. Guinea J, Torres-Narbona M, Gijón P, Muñoz P, Pozo F, Peláez T, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. *Clin Microbiol Infect* 2010;**16**(7):870—7.
28. Xu H, Li L, Huang WJ, Wang LX, Li WF, Yuan WF. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: a case control study from China. *Clin Microbiol Infect* 2012;**18**:403—8. http://dx.doi.org/10.1111/j.1469-0691.2011.03503.x.
29. Meersseman W, Lagrou K, Maertens J, Wijngaerden E. Invasive aspergillosis in the intensive care unit. *Clin Infect Dis* 2007;**45**(2):205—16.
30. Yan X, Li M, Jiang M, Zou LQ, Luo F, Jiang Y. Clinical characteristics of 45 patients with invasive pulmonary aspergillosis: retrospective analysis of 1711 lung cancer cases. *Cancer* 2009 Nov 1;**115**(21):5018—25. http://dx.doi.org/10.1002/cncr.24559. PubMed PMID: 19637340.
31. Taccone FS, Van den Abeele AM, Bulpa P, Misset B, Meersseman W, Cardoso T, et al., on behalf of the AspICU Study Investigators. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. *Crit Care* 2015;**19**:7. http://dx.doi.org/10.1186/s13054-014-0722-7.
32. Vandewoude KV, Blot SI, Depuydt P, Benoit D, Temmerman W, Colardyn F, et al. Clinical relevance of *Aspergillus* isolation from respiratory tract samples in critically ill patients. *Crit Care* 2006;**10**:R31.
33. Bulpa PA, Dive AM, Garrino MG, Delos MA, Gonzalez MR, Evrard PA, et al. Chronic obstructive pulmonary disease patients with invasive pulmonary aspergillosis: benefits of intensive care? *Intensive Care Med* 2001;**27**:59—67.
34. Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to tuberculosis. *Bull WHO* 2011;**89**:864—72.
35. Hamilton CD, Stout JE, Goodman PC, Mosher A, Menzies R, Schluger NW, et al., Tuberculosis Trials Consortium. The value of end-of-treatment chest radiograph in predicting pulmonary tuberculosis relapse. *Int J Tuberc Lung Dis* 2008;**12**:1059—64. PMID: 18713505.
36. Lee JJ, Chong PY, Lin CB, Hsu AH, Lee CC. High resolution chest CT in patients with pulmonary tuberculosis: characteristic findings before and after antituberculous therapy. *Eur J Radiol* 2008;**67**:100—4. http://dx.doi.org/10.1016/j.ejrad.2007.07.009. PMID: 17870275.
37. Bombarda S, Figueiredo CM, Seiscento M, Terra Filho M. Pulmonary tuberculosis: tomographic evaluation in the active and post-treatment phases. *Sao Paulo Med J* 2003;**121**:198—202. http://dx.doi.org/10.1590/S1516-31802003000500004. PMID: 14666291.
38. Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis complicating sarcoidosis. *Eur Resp J* 2013;**41**:621—6.
39. Smith N, Denning DW. Underlying pulmonary disease frequency in patients with chronic pulmonary aspergillosis. *Eur Resp J* 2011;**37**:865—72.
40. NHS England National Commissioning Group Chronic Pulmonary Aspergillosis national service. The National Aspergillosis Centre Annual Report 2013—2014. http://www.nationalaspergillosiscentre.org.uk/.
41. Public Health England. Public Health Outcomes Framework. http://www.phoutcomes.info/public-health-outcomes-framework#page/3/gid/1000044/pat/6/par/E12000002/ati/102/are/E06000008/iid/40701/age/163/sex/4.
42. Office for National Statistics. *Annual mid-year population estimates: 2014*. ONS; 2015.
43. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990—2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2163—96.
44. 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. http://dx.doi.org/10.3109/13693786.2012.738312. Epub 2012 Dec 4. PubMed PMID: 23210682.
45. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012;**12**:204.
46. Anandan C, Gupta R, Simpson CR, Fischbacher C, Sheikh A. Epidemiology and disease burden from allergic disease in Scotland: analyses of national databases. *J R Soc Med* 2009;**102**:431—42.
47. Lee JCW, Seher Z, Ukeleghe E, Howell R, Niven R, Denning D, et al. *Prevalence of possible Severe Asthma with Fungal Sensitisation (SAFS) and Allergic Bronchopulmonary Aspergillosis (ABPA) in a UK secondary care hospital*. European Respiratory Society Annual Congress 2013. 2013. http://erj.ersjournals.com/content/42/Suppl_57/P977.full.pdf.
48. Varshokar K. Diagnosis of allergic bronchopulmonary aspergillosis in asthmatic patients. *J Semnan Univ Med Sci* 2001-2002;**3**(1, 2):39—45.
49. Singh M, Das S, Chauhan A, Paul N, Sodhi KS, Mathew J, et al. The diagnostic criteria for allergic bronchopulmonary aspergillosis in children with poorly controlled asthma need to be re-evaluated. *Acta Paediatr* 2015 May;**104**(5):e206—9. http:

//dx.doi.org/10.1111/apa.12930. Epub 2015 Mar 13. PubMed PMID: 25620428.
50. Cystic Fibrosis Trust. *UK cystic fibrosis registry annual data report 2011*. London. 2013.
51. Baxter CG, Dunn G, Jones AM, Webb K, Gore R, Richardson MD, et al. Classification of aspergillosis in adult cystic fibrosis. *J Allergy Clin Immunol* 2013;**132**:560–6.
52. Cystic Fibrosis Trust. *UK cystic fibrosis registry annual data report 2012*. London. 2013.
53. Denning DW, O'Driscoll BR, Powell G, Chew F, Atherton GT, Vyas A, et al. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: the Fungal Asthma Sensitization Trial (FAST) study. *Am J Respir Crit Care Med* 2009;**179**(1):11–8.
54. Pasqualotto AC, Powell G, Niven R, Denning DW. The effects of antifungal therapy on severe asthma with fungal sensitization and allergic bronchopulmonary aspergillosis. *Respirology* 2009;**14**(8):1121–7.
55. Bush A, Pedersen S, Hedlin G, Baraldi E, Barbato A, de Benedictis F, et al., PSACI (Problematic Severe Asthma in Childhood Initiative) group. Pharmacological treatment of severe, therapy-resistant asthma in children: what can we learn from where? *Eur Respir J* 2011;**38**(4):947–58.
56. Chishimba L, Niven RM, Cooley J, Denning DW. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. *J Asthma* 2012 May;**49**(4):423–33.
57. Castanhinha S, Sherburn R, Walker S, Gupta A, Bossley CJ, Buckley J, et al. Pediatric severe asthma with fungal sensitization is mediated by steroid-resistant IL-33. *J Allergy Clin Immunol* 2015 Aug;**136**(2). 312–322.e7.
58. Zureik M, Neukirch C, Leynaert B, et al. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *Br Med J* 2002;**325**:411–5.
59. Lommatzsch M, Virchow CJ. Severe asthma: definition, diagnosis and treatment. *Dtsch Arztebl Int* 2014 Dec 12;**111**(50): 847–55. http://dx.doi.org/10.3238/arztebl.2014.0847. PubMed PMID: 25585581; PubMed Central PMCID: PMC4357024.
60. Hekking PPW, et al. The prevalence of severe refractory asthma. *Am Acad Allergy Asthma Immunol* 2014. http://dx.doi.org/10.1016/j.jaci.2014.08.042.
61. O'Driscoll BR, Hopkinson LC, Denning DW. Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions. *BMC Pulm Med* 2005;**18**(5):4.
62. Agarwal R, Aggarwal AN, Gupta D, Jindal SK. *Aspergillus* hypersensitivity and allergic bronchopulmonary aspergillosis in patients with bronchial asthma: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2009;**13**(8):936–44.
63. O'Driscoll BR, Powell G, Chew F, Niven RM, Miles JF, Vyas A, et al. Comparison of skin prick tests with specific serum immunoglobulin E in the diagnosis of fungal sensitization in patients with severe asthma. *Clin Exp Allergy* 2009;**39**(11): 1677–83.
64. Denning DW, Pashley C, Hartl D, Wardlaw A, Godet C, Del Giacco S, et al. Fungal allergy in asthma-state of the art and research needs. *Clin Transl Allergy* 2014 Apr 15;**4**:14. http://dx.doi.org/10.1186/2045-7022-4-14.
65. Public Health England. Voluntary surveillance of candidaemia in England, Wales and Northern Ireland: 2013. *Health Prot Rep Wkly Rep* Sept 2014;**8**(36).
66. Avni T, Leibovici L, Paul M. PCR diagnosis of invasive candidiasis: systematic review and meta-analysis. *J Clin Microbiol* Feb 2011:665–70.
67. Nguyen MH, Wissel MC, Shields RK, Salomoni MA, Hao B, Press EG, et al. Performance of Candida real-time polymerase chain reaction, β-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. *Clin Infect Dis* 2012 May; **54**(9):1240–8. http://dx.doi.org/10.1093/cid/cis200. Epub 2012 Mar 19. PubMed PMID: 22431804.
68. National Institute for Health and Clinical Excellence (NICE). *NICE clinical guideline 125: kidney disease: peritoneal dialysis: costing report, implementing NICE guidance*. NICE; 2011.
69. Leading International Fungal Education (LIFE) website: http://www.life-worldwide.org/fungal-diseases/candida-peritonitis/ last accessed on 01.07.13.
70. Buchacz K, Baker RK, Palella Jr FJ, Chmiel JS, Lichtenstein KA, Novak RM, et al., HOPS Investigators. AIDS-defining opportunistic illnesses in US patients, 1994–2007: a cohort study. *AIDS* 2010 Jun 19;**24**(10):1549–59.
71. Bitar D, Morizot G, Van Cauteren D, Dannaoui E, Lanternier F, Lortholary O, et al. Estimating the burden of mucormycosis infections in France (2005–2007) through a capture-recapture method on laboratory and administrative data. *Rev Epidemiol Sante Publique* 2012 Oct;**60**(5):383–7. http://dx.doi.org/10.1016/j.respe.2012.03.007. Epub 2012 Sep 26. PubMed PMID: 23020929.
72. Bitar D, Lortholary O, Le Strat Y, Nicolau J, Coignard B, Tattevin P, et al. Population-based analysis of invasive fungal infections, France, 2001–2010. *Emerg Infect Dis* 2014 Jul; **20**(7):1149–55. http://dx.doi.org/10.3201/eid2007.140087. PubMed PMID: 24960557; PubMed Central PMCID: PMC4073874.
73. Meersseman W, Vandecasteele SJ, Wilmer A, Verbeken E, Peetermans WE, Wijngaerden EV. Invasive aspergillosis in critically ill patients without malignancy. *Am J Respir Crit Care Med* 2004;**170**:621–5.
74. Garnacho-Montero J, Amaya-Villar R, Ortiz-Leyba C, et al. Isolation of *Aspergillus* spp. from the respiratory tract in critically ill patients: risk factors, clinical presentation outcome. *Crit Care* 2005;**9**:R191–9.
75. Winters B, Custer J, Galvagno Jr SM, Colantuoni E, Kapoor SG, Lee H, et al. Diagnostic errors in the intensive care unit: a systematic review of autopsy studies. *BMJ Qual Saf* 2012 Nov; **21**(11):894–902. http://dx.doi.org/10.1136/bmjqs-2012-000803. Epub 2012 Jul 21. PubMed PMID: 22822241.
76. Donnelly SC, McLaughlin H, Bredin CP. Period prevalence of allergic bronchopulmonary mycosis in a regional hospital outpatient population in Ireland 1985–88. *Ir J Med Sci* 1991; **160**:288–90.
77. Gergen PJ, Arbes Jr SJ, Calatroni A, Mitchell HE, Zeldin DC. Total IgE levels and asthma prevalence in the US population: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol* 2009;**124**:447–53.
78. Royal College of Physicians. *Why asthma still kills, The National Review of Asthma Deaths (NRAD). Confidential enquiry report*. May 2014.
79. Odds FC, Hanson MF, Davidson AD, Jacobsen MD, Wright P, Whyte JA, et al. One year prospective survey of Candida bloodstream infections in Scotland. *J Med Microbiol* 2007 Aug;**56**(Pt 8):1066–75. PubMed PMID: 17644714; PubMed Central PMCID: PMC2884937.
80. Dorgan E, Denning DW, McMullan R. Burden of fungal disease in Ireland. *J Med Microbiol* 2015 Apr;**64**(Pt 4):423–6. http://dx.doi.org/10.1099/jmm.0.000020. Epub 2015 Jan 16.
81. Kibbler CC, Seaton S, Barnes RA, Gransden WR, Holliman RE, Johnson EM, et al. Management and outcome of bloodstream infections due to Candida species in England and Wales. *J Hosp Infect* 2003;**54**:18–24.
82. Hospital Episode Statistics Analysis. *Health and Social Care information Centre. Hospital Episode Statistics. Admitted patient care, England 2104–15*. Health and Social Care Information Centre; November 2015.
83. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, et al., U-BIOPRED Study Group. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts. *Eur Respir J* 2015 Nov;**46**(5):1322–33.
84. http://www.gaffi.org/media/academic-papers/.