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

Matthew Pegorie, David W. Denning, William Welfare

Public Health England North West Health Protection Team (Greater Manchester), UK
National Aspergillosis Centre, University Hospital of South Manchester, Manchester, UK
The University of Manchester, Manchester, UK
Manchester Academic Health Sciences Centre, University of Manchester, UK

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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.

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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) and specifically for candidaemias in neonates (voluntary reporting). An analysis of laboratory reports of fungal infections was published in 2001, 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". 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.

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 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.

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).

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

Using the estimate of total burden amongst people living with AIDS for 2011–2013, 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.

Second method

A UK study estimating the incidence of Pneumocystis pneumonia over an 11 year period was published in March 2013. 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, 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\textsuperscript{16} to estimate the current size of this population. The incidence rate for this high risk population was obtained from Patel et al.\textsuperscript{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;\textsuperscript{18} solid organ transplant patients;\textsuperscript{19} people living with AIDS;\textsuperscript{20} 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;\textsuperscript{21} Chronic granulomatous disease (CGD) patients;\textsuperscript{22} Chronic obstruction pulmonary disease (COPD): emergency hospital admissions;\textsuperscript{23} critical care patients;\textsuperscript{24} patients with lung cancer.\textsuperscript{25}

The incidence rates specific to the above high risk populations were found from a variety of studies: Lortholary et al.\textsuperscript{26} (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\textsuperscript{27} (for people living with AIDS); Pagano et al.\textsuperscript{28} (For AML, ALL, CML, CLL, NHL, HL and myeloma patients) -- these estimates were not for the UK population but the Italian population; Beaute et al.\textsuperscript{29} (for CGD patients) -- this estimate was not for the UK population but the French population; Guinea et al.\textsuperscript{30} (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.\textsuperscript{31}) 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\textsuperscript{32} 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.\textsuperscript{33} 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.\textsuperscript{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,\textsuperscript{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,\textsuperscript{8} 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%. 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.\textsuperscript{32} It is difficult to distinguish colonisation with *Aspergillus* from infection with *Aspergillus*.\textsuperscript{22}

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.\textsuperscript{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.\textsuperscript{34}

An estimate of the annual number of patients with chronic pulmonary aspergillosis after pulmonary tuberculosis (PTB) has recently been published.\textsuperscript{35} 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%).\textsuperscript{36} To generate a five year period prevalence,

\textsuperscript{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).

\textsuperscript{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.

\textsuperscript{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.

\textsuperscript{g} Critical care episodes were counted from Table 14 of the Critical Care report 2013–2014.\textsuperscript{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.\(^{48}\) Numerous other antecedent underlying pulmonary conditions are found in patients with chronic pulmonary aspergillosis,\(^ {49}\) 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.\(^{50}\) 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)\(^ {51}\) 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 (4.8% 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 asthematics 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\(^ {46}\) 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-glucan detection derived a similar figure.\(^ {67}\) Therefore we made the assumption that the total number of positive blood culture samples represented 38% of 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. 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. 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 — 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.

**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 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 coccidioidomycosis 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.

**Pneumocystis pneumonia**

An average yearly total burden of 157 *Pneumocystis* pneumonia (PCP) diagnoses was found for those people living with AIDS in the UK 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.

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.

**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 all 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, even though IA is the most common missed infectious diagnosis at autopsy. 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
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 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. The anticipated annual incidence of each was 118 and 240 respectively. Together these two conditions account for about 30% of patients with CPA 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 and 830 (range 415–1660). Together these 2 conditions account for about 30% of patients with CPA 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>
<thead>
<tr>
<th>Table 1</th>
<th>Estimates of population size, specific incidence rates and yearly burden of <em>Pneumocystis</em> pneumonia for solid organ transplant populations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Population size</td>
</tr>
<tr>
<td>Heart Tx</td>
<td>195</td>
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<tr>
<td>Kidney Tx</td>
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<tr>
<td>Liver Tx</td>
<td>830</td>
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<tr>
<td>Lung Tx or heart and lung Tx patients</td>
<td>397</td>
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<tr>
<td>Total</td>
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<tr>
<th>Table 2</th>
<th>Estimates of population size, specific incidence rates and yearly burden of invasive aspergillosis for well recognised at risk groups.</th>
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<tbody>
<tr>
<td>Population</td>
<td>Population size</td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>1615</td>
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<td>Autologous HSCT</td>
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<td>Kidney Tx</td>
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<td>AML</td>
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<td>ALL</td>
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<td>CML</td>
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<td>CLL</td>
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<tr>
<td>NHL</td>
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<tr>
<td>HL</td>
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<tr>
<td>Myeloma</td>
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<tr>
<td>CGD</td>
<td>119</td>
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<tr>
<td>Total</td>
<td></td>
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* *Overall incidence of invasive fungal disease (IFD).

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<th>Table 3</th>
<th>Estimates of population size, specific incidence rates and yearly burden of invasive aspergillosis for pulmonary disease.</th>
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<tbody>
<tr>
<td>Population</td>
<td>Population size</td>
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<tr>
<td>COPD emergency hospital admissions</td>
<td>89,466</td>
</tr>
<tr>
<td>Patients with lung cancer</td>
<td>44,488</td>
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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 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 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. There are approximately 65,000 admissions to hospital with asthma annually, approximately 40,250 in adults. Fungal sensitisation rates are not well studied in the UK, especially as patients may be sensitised to one or more fungi. 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. The minimum proportion of poorly controlled asthmatics who would be sensitised to a fungus is about 35%, rising to >75% in the worse patients. 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

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<th>Table 4</th>
<th>Sources of estimates of the incidence of invasive aspergillosis in critical care patients.</th>
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<tr>
<td>Study</td>
<td>Study characteristics</td>
</tr>
<tr>
<td>Meersseman et al.</td>
<td>Sample size 127&lt;br&gt;Autopsy controlled&lt;br&gt;Study aim: to determine the incidence of IA in medical ICUs&lt;br&gt;Retrospective, single centre</td>
</tr>
<tr>
<td>Garnacho-Montero et al.</td>
<td>Sample size 1756&lt;br&gt;Not autopsy controlled&lt;br&gt;Study aim: to describe the characteristics of patients with positive samples for Aspergillus species&lt;br&gt;Prospective, multi-centre (73 mixed ICUs)</td>
</tr>
<tr>
<td>Vandewoude et al.</td>
<td>Sample size 172&lt;br&gt;Not autopsy controlled&lt;br&gt;Study aim: to describe characteristics of patients with positive samples for Aspergillus species&lt;br&gt;Retrospective, single centre, mixed ICU</td>
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<th>Table 5</th>
<th>Sensitivity analysis for estimation of burden of invasive aspergillosis amongst patients in critical care in the UK.</th>
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<tr>
<td>Study</td>
<td>Risk group in UK to which study applies</td>
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<tr>
<td>Meersseman et al.</td>
<td>Patients admitted to medical ICUs</td>
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<tr>
<td>Garnacho-Montero et al.</td>
<td>Patients admitted to any ICU (Spinal Units excluded)</td>
</tr>
<tr>
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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, 81 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.
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:44; 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.64,76

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 published99 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

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

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**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**

Burden of invasive and serious fungal disease in the UK

84. http://www.gaffi.org/media/academic-papers/