mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Supplement article

Estimated burden of fungal infections in Germany

Markus Ruhnke,[1] Andreas H. Groll,[2] Peter Mayser,[3] Andrew J. Ullmann,[4] Werner Mendling,[5] Herbert Hof,[6] David W. Denning[7] and The University of Manchester in association with the LIFE program

[1]MVZ Hematology & Oncology, Paracelsus-Kliniken, Osnabrueck, Germany, [2]Department of Pediatric Hematology and Oncology, Center for Bone Marrow Transplantation, University Children's Hospital, Muenster, Germany, [3]Center for Dermatology, Venerology and Allergology, Justus Liebig University, Giessen, Germany, [4]Division of Infectious Diseases, Department of Internal Medicine II, University Hospital Wuerzburg, Wuerzburg, Germany, [5]German Center for Infections in Obstetrics and Gynecology, Wuppertal, Germany, [6]MVZ Labor Limbach u. Kollegen, Heidelberg, Germany and [7]Manchester Academic Health Science Centre, The National Aspergillosis Centre University Hospital of South Manchester, The University of Manchester, Manchester, UK

Summary

In the late 1980's, the incidence of invasive fungal diseases (IFDs) in Germany was estimated with 36.000 IFDs per year. The current number of fungal infections (FI) occurring each year in Germany is still not known. In the actual analysis, data on incidence of fungal infections in various patients groups at risk for FI were calculated and mostly estimated from various (mostly national) resources. According to the very heterogenous data resources robust data or statistics could not be obtained but preliminary estimations could be made and compared with data from other areas in the world using a deterministic model that has consistently been applied in many countries by the LIFE program (www.LIFE-worldwide.org). In 2012, of the 80.52 million population (adults 64.47 million; 41.14 million female, 39.38 million male), 20% are children (0–14 years) and 16% of population are ≥65 years old. Using local data and literature estimates of the incidence or prevalence of fungal infections, about 9.6 million (12%) people in Germany suffer from a fungal infection each year. These figures are dominated (95%) by fungal skin disease and recurrent vulvo-vaginal candidosis. In general, considerable uncertainty surrounds the total numbers because IFDs do not belong to the list of reportable infectious diseases in Germany and most patients were not hospitalised because of the IFD but a distinct underlying disease.

Key words: Fungal diseases, superficial, invasive, epidemiology, incidence, Germany.

Introduction

In the late 1980's to the early 1990's, the incidence of invasive fungal diseases (IFDs) in Germany was estimated with 36.000 IFDs per year.[1,2] The current number of fungal infections occurring each year in Germany is not known. The aim of this work was to estimate the burden of serious fungal infections in Germany, a country, with an population of 80.52 millions in 2012[3] and a gross domestic product per person of $46 269 in 2013. As IFD are not reportable, exact data are not available. For this reason, we have taken different approaches to explore the current number of IFDs. First, we have estimated fungal infections based on populations at risk, with data from published German or international cohort studies and clinical trials[4,5] and secondly, we analysed discharge diagnoses from hospital treatment as provided by the National Institute for Statistics ('Statistische Bundesamt') [3,6].

*Correspondence: Markus Ruhnke, Paracelsus-Klinik Osnabrück, Am Natruper Holz 6949076 Osnabrück, Germany.
Tel.: +49 541 966-3040. Fax: +49 541 966-3046.
E-mail: markruhnke@online.de

The University of Manchester in association with the LIFE program – www.LIFE-worldwide.org

Submitted for publication 13 May 2015
Revised 31 July 2015
Accepted for publication 4 August 2015

Methods

Published epidemiology papers reporting fungal infection rates from Germany were identified. First, a literature search was conducted to identify relevant publications. PubMed was searched using the following terms: 'fungal infections', 'fungal disease', 'invasive mycosis', 'superficial mycosis', 'dermatomycosis'. These terms were used in combination with 'epidemiology', 'Germany' and 'statistics'. Further relevant references not identified by this strategy were retrieved from the primary, mostly national publications and conference reports. The search included articles published between January 1975 and December 2013. Second, where no data existed, we used specific populations at risk and fungal infection frequencies in those populations to estimate national incidence or prevalence, depending on the condition. 2011/12 population statistics (ICD10 coding) were derived from the National Institute for Statistics ('Statistische Bundesamt'; www.gbe-bund.de, https://www.destatis.de/EN/Homepage.html).[3,6,7] Unfortunately, information from National Health Institution is restricted to the DRG (diagnosis related groups) system and only in part to the ICD10 coding system. This categorisation is exclusively for patients hospitalised in German hospitals.

Prevalence of skin fungal diseases was obtained from data in the pan-European survey (Achilles project) on fungal skin disease.[8] We estimated recurrent vulvo-vaginal candidosis (VVC) by taking the population of women between 15 and 50 years of age and using a 'discounted' rate of 6%, based on the frequency obtained from a six country internet questionnaire of normal women, reduced from 9% as the self-diagnosis of VVC is often over-estimated.[9]

The number of HIV/AIDS patients was obtained from epidemiological surveillance of AIDS in Germany by the Robert-Koch-Institute, Berlin [10]. Similar, annual new AIDS cases (at risk of opportunistic infections), proportion of AIDS patients presenting with *Pneumocystis* pneumonia (PCP), Candida oesophagitis and with cryptococcal meningitis in 2010 were obtained from publications by the Robert-Koch-Institute, Berlin [10,11]. The hospital infection surveillance system (Krankenhaus-Infektions-Surveillance-System, KISS) is a nationwide surveillance project for the voluntary registration of nosocomial infections in Germany which collects data on the frequency of nosocomial infections and pathogens and on the appearance of pathogens of special epidemiological importance.[12,13] In 2011, more than 800 hospitals and 586 intensive care units (ICUs) in Germany participated in this surveillance system (KISS).[14] Incidence and prevalence of fungal infections in haematological diseases were taken from 'KISS' and estimations according results from clinical multicenter trials, and data from public health institutions in Germany.[5,6,15,16] The number of tuberculosis (TB) cases (from 2011) were taken from epidemiological surveillance registry in Germany by the Robert-Koch-Institute, Berlin (www.rki.de) [17].

Using the approach taken in Denning *et al.* the 5-year point prevalence of chronic pulmonary aspergillosis (CPA) following TB, assuming a 12% cavitation rate following therapy. It was assumed that TB was the underlying diagnosis of CPA in 20% of cases.[18,19]

Asthma rates in adults were obtained from multiple sources and 7% of the adult population was used for estimates.[6,20] The risk of allergic bronchopulmonary aspergillosis (ABPA) was estimated at 2.5% based on previous studies.[18] The rate of severe asthma with fungal sensitisation (SAFS) was estimated as the worst 10% of the total asthma population of whom at least 33% have fungal sensitisation.[18,19,21]

Serious fungal infections are defined as life-threatening diseases occurring either immediately or over months or years, sight-threatening together with a high morbidity level.

Results

In 2012, the year of the last national consensus ('Volkszählung'), of the 80.52 million population (adults 64.47 million; 41.14 million female, 39.38 million male), 20% are children (0–14 years) and 16% of population are ≥65 years old.[3] Hospitalisation was recorded for 18.8 million patients in 2013. From 893 825 individuals who died in German hospitals 18 480 individuals (=2.1%) died by or linked to an infectious disease (ICD10 coding A00 to B99 as primary diagnosis) including fungal diseases in 2013.[3] However, details about the ratio of fungal diseases relative to other infectious diseases (e.g. bacterial, viral, protozoal) are not provided. Total number of estimated cases of fungal infections is shown in Table 1.

Dermatomycosis

In a pan-European survey (Achilles project) on fungal skin disease 33% of patients visiting a general practitioner had evidence of a superficial fungal infection (SFI).[8] Most common SFI were Tinea pedis, Tinea corporis and onychomycosis, respectively. Tinea capitis

Table 1 Burden of fungal diseases in Germany according the selected underlying diseases.

	Number of infections per underlying disorder per year						
	Unknown	HIV/AIDS	Respiratory	Cancer/Tx	ICU	Total burden	Rate/100K[2]
Fungal skin diseases	6 721 000	n.a.[1]	n.a.	n.a.	n.a	6 721 000	8347
Oral candidosis	n.a.	15 600	n.a.	97 965	n.a.	113 565	141
Oesophageal candidosis[3]	3685	100[4]	n.a.	n.a.	n.a.	3785	4.7
Candidaemia	n.a.	n.a.	n.a.	n.a.	3712	3712	4.6
Candida peritonitis	n.a.	n.a.	n.a.	n.a.	3700	3700	4.6
Recurrent vaginal candidosis (4× year^{-1} or more)	2 470 200	n.a.	n.a.	n.a.	n.a.	2 470 200	3068[5]
Allergic bronchopulmonary aspergillosis	n.a.	n.a.	123 960	n.a.	n.a.	123 960	154
Severe asthma with fungal sensitisation	n.a.	n.a.	163 131	n.a.	n.a.	163 131	203
Chronic pulmonary aspergillosis	n.a.	n.a.	2320	n.a.	n.a.	2320	2.9
Invasive aspergillosis	n.a.	n.a.	n.a.	2569	1711	4280	5.1
Mucormycosis	19	n.a.	n.a.	n.a.	n.a.	19	0.02
Cryptococcal meningitis	42	15	n.a.	n.a.	n.a.	57	0.07
Pneumocystis pneumonia	n.a.	860	n.a.	153	n.a.	1013	1.3
Histoplasmosis	5	10	n.a.	n.a.	n.a.	15	0.02
Fungal keratitis	32	n.a.	n.a.	n.a.	n.a.	32	0.04
Total burden estimated						9 610 789	

[1]n.a. = not applicable or unknown.

[2]Rate/100K = rate per 100 000 individuals from total population in Germany.

[3]According ICD10 code 37.8 (mostly EC).

[4]New AIDS-defining disease per year with about 280 AIDS per year in Germany (~20% have oesophageal candidosis) Source: www.gbe-bund.de.

[5]According to survey by Foxman *et al.* 2012, 9% of woman in Germany have VVC, we have used a 6% rate to account for some misdiagnosis. Rate per 100 000 is for all females.

was rare. From these data, it can be calculated, that 6 721 000 individuals are affected by SFIs in Germany according to a 1-year survey from 1997 to 1998. Age-specific effects were observed, with the most pronounced effect in children (<18 years) for Tinea pedis and onychomycosis. More recent data are not available.

Vulvo-vaginal candidosis (VVC)

The number of women between 14 and 55 years was obtained from the National Institute for Statistics ('Statistische Bundesamt') [3]. According to an epidemiological survey from Foxman *et al.* including a sample of 6010 women aged 16–65 years from six countries (1000 women from Germany) who participated in an online omnibus opinion poll the prevalence rate was 9%. Because an over-self-diagnose VVC cannot be excluded, a conservative approach was used according the published literature. A 6% rate was assumed in women to have recurrent vaginal candidosis (four or more episodes per year), which correlates with 2 470 200 German women with recurrent vaginal thrush in any 1 year.[9]

Oral candidosis/oesophageal candidosis

HIV-infected patients with CD4 counts <200 cells per mm^3 may be at greatest risk for oral candidosis (OC). These are patients with advanced HIV disease and mostly AIDS. Currently, the number of individuals living with HIV/AIDS is estimated to 78 000 (66 000–99 000) with a rate of unreported cases of 10 000 resulting in a total of 88 000 individuals in Germany.[10] The overall proportion of individuals receiving highly active antiretroviral therapy (HAART) is calculated at 65% (n = 50 000).[10] Earlier data from an US cohort study showed that OC may occur in 16% of HIV/AIDS individuals on HAART in contrast with 20% without HAART.[22] These findings result in 15 600 OC cases per year. Another major patient group at risk for OC is patients with cancer. According to a recent review of oral fungal infections in patients receiving cancer therapy, for all cancer treatments, the weighted prevalence of clinical oral fungal infection was found to be 7.5% pretreatment, 39.1% during treatment, and 32.6% after the end of cancer therapy.[23] These rates may differ each year but may be used as an estimate for current calculations. The absolute number of patients living with cancer in

Germany is unknown. Each year 230 500 new cancer diseases (incl. 12 630 hematological cancers) are recorded. Assuming that the majority of cancer patients (>90%) receive anticancer treatment, 17 290 (pretreatment) – 80 675 (35% during/after cancer treatment) episodes of OC can be calculated resulting in a total of 97 965 episodes each year.[7]

Candida oesophagitis was documented according to the ICD coding (B37.81) in 3758 hospitalised patients in 2011.[6] In the HIV population, 500 patients each year present with an AIDS-defining illness, and ~20% have oesophageal candidosis.[10,24] Since this is only captured as a primary diagnosis this number could be underestimated.

Candidaemia/*Candida* peritonitis

Nationwide data for candidaemia from the German Institute for the Hospital Remuneration (Institut für das Entgeltsystem im Krankenhaus, InEK) system (all hospitals in the country, both primary and secondary bloodstream infections) revealed that the number of patients with candidaemia in 2008 in Germany accounted to 3712 cases as identified by presence of the International Statistical Classification of Diseases and Related Health Problems ICD-10 diagnosis code for candidaemia.[25] Other public health resources counted only 460 cases in the same year which reflects major differences due to different data sampling approaches.[6]

Rate of candidaemia (ICD10 B37.7) in Germany was calculated as 4.7 per 100 000 inhabitants, with a similar rate for invasive Candida infections (IC) at other body sites including but not limited to *Candida* peritonitis (ICD10 B37.8).[3] In 682 ICU's, the ratio of albicans to non-albicans candidaemia is 63% vs. 37%.[4] For children, the prevalence rate is lower according to a 10 year period survey (1998–2008) from a representative tertiary children hospital.[26] The pooled average annual incidence was 0.47 cases per 1000 hospital discharges.

Tuberculosis

Of the 4317 cases of TB in 2011, mostly in HIV negative people, 3346 (79.6%) had pulmonary TB.[17] It is estimated that 147 new cases of CPA occurred post-TB following a scenario-based model by Denning *et al.* [18,19].

The total caseload of CPA after TB is estimated to be 464 individuals (5-year period prevalence), and assuming TB is the underlying disease in 20% of cases, the total number of CPA cases is estimated at 2320.

Asthma and cystic fibrosis

Estimates of asthma prevalence in adults are around 7% (in total 4.9 million). Assuming 2.5% of asthmatics have ABPA, 123 960 patients with ABPA are likely and an additional 163 131 patients with SAFS.[6,20] It is likely that some overlap exists between these groups, depending on the severity of asthma in the ABPA patients and the number of SAFS patient sensitised to fungi other than *Aspergillus*. A separate estimate of ABPA and *Aspergillus* bronchitis in cystic fibrosis in adults has been made based in 2011 data; 492 with ABPA and 835 with *Aspergillus* bronchitis.[27] Among children, 117 (4.8%) of Germany's children with cystic fibrosis (CF) were documented to have ABPA.

Invasive pulmonary aspergillosis

Invasive aspergillosis (IA; ICD10 B44) was coded in 1595 hospitalised patients.[6] In 2011, from overall 16 714 adult patients with acute myelogenous leukaemia IFD (moulds and yeast) may be assumed in 5 (−10) % (n = 836) of all patients.[5] However, practices in antifungal therapy and prophylaxis change over time and incidence may vary. Recently published data from a multicenter study on antifungal prophylaxis with posaconazole vs. fluconazole or itraconazole in patients with acute leukaemia resulted in 2% IA in patients on posaconazole prophylaxis vs. 8% on fluconazole or itraconazole prophylaxis.[28] Data on IA from other patient groups (e.g. ICU patients) are not available but earlier data suggest that patients with haematological malignancies account for 60–70% of all IA cases and 30–40% of cases for other patients groups at risk.[29] We have used a figure of 5% for acute myeloid leukemia (AML) patients and assumed that all the other haematological malignancies contribute and equal number, we estimated at a total of 2047 cases annually.

The Hospital Infection Surveillance System for Patients with Hematologic/Oncologic Malignancies (ONKO-KISS) study was initiated to provide ongoing surveillance of granulocytopenic patients for nosocomial bloodstream infections and pneumonia, which are the most frequent and most important nosocomial infections in adult patients who have recently undergone bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT).[15] In 18 haematological centres in Germany, Switzerland and

Austria during a 38-month period (until 2003) in 119 (71%) of 168 cases of pneumonia, no pathogen could be isolated. Only 63 (pathogenic) microorganisms were isolated in 49 cases. Of these 63 isolates, 14 (22%) were *Candida* species, and 10 (19%) were *Aspergillus* species.

Post-transplant cases of IA also occur and contribute 522 cases to the annual total. These are estimated using approximate rates of 10% in haematopoetic stem cell recipients (HSCT; total $n = 314$ IA cases from $n = 3141$ recipients of allogeneic HSCT in 2013) according to the PIMDA study in Europe and the 'Deutsches Register für *Stammzelltransplantationen'*.[30,31] For recipients of solid organ transplantation, incidence rates from the US Transplant-Associated Infection Surveillance Network (TRANSNET) were used and estimated for Germany (http://www.dso.de/) according to data on solid organ transplantation from 2012.[32,33] Incidence of IA in Germany was calculated with 1%, 20%, 6% and 4% in renal ($n = 21$ from 2128 Tx), lung ($n = 70$ from 352 Tx), heart ($n = 18$ from 302 Tx) and liver ($n = 37$ from 937 Tx) transplant recipients (total $n = 146$ IA cases). We also attempted to estimate the number of chronic obstructive pulmonary disease (COPD) patients with IA based on the rate documented in Madrid of 1.3% of COPD admissions (lower than the rate in China of 3.9%).[34,35] The number of COPD admissions differs by 10-fold from 14 812 using ICD10 J40 and J42 codes, to the OECD (Organisation for Economic Co-operation and Development) report of 201 per 100 000 adults or 131 605 patients.[36] The lower figure of admissions suggests 193 and the higher figure 1711 IA in this population. We have used the higher figure. Overall, the burden of IA in Germany is approximately 4280 cases annually (4.6 per 100 000).

Cryptococcosis

Of the 78 000 estimated HIV positive patients in 2012, 15 (5%) of 280 new AIDS cases each year develop cryptococcal meningitis.[10] During 2004–2010, 385 cases of cryptococcosis were recorded according to the Reference Laboratory for cryptococcosis by the RKI/Berlin.[11] In this time period, 47–60 (median 57 cases) were documented each year in German hospitals. In a population of 80.52 million, the prevalence is 0.07 hospitalisations per 100 000 inhabitants. The most frequently isolated pathogens were *Cryptococcus neoformans* variety *grubii* (66%), *C. neoformans* var. *neoformans* (19%) and *C. gattii* (3%), respectively.

Other invasive pulmonary mould infections

Mucormycosis (IC10 B46) has been coded for 19 cases in 2011. Endemic IFD (e.g. histoplasmosis, blastomycosis, coccidiodomycosis) are rare and can be estimated as 10–15 new (imported) cases per year. According to a review from the German Reference Laboratory for *Pseudallescheria/Scedosporium* spp. about 2–5 infections with *Scedosporium prolificans* are recorded each year during 1993–2007.[37] Using data from Denmark, we estimate 32 patients annually with fungal keratitis, usually caused by *Aspergillus* spp. or *Fusarium* spp.[38]

Pneumocystis jirovecii pneumonia (PCP)

The annual incidence of *PCP* in hospitalised patients is relatively constant with 1.8 cases per 100 000 resulting in 1013 cases in 2012.[6] In 2012, 153 new AIDS cases caused by PCP were recorded (0.19 new AIDS cases per 100 000 people).[6] About 40–50% of all annual AIDS cases are related to PCP in Germany.[10,24]

Discussion

There are currently no epidemiology papers that have reported on the fungal infection rates in Germany, so every estimate is based on modelling. This is in line with the deterministic model that has consistently been applied in many countries by the LIFE program (www.LIFE-worldwide.org). This approach was already used in the very first reports from other countries (e.g. Spain, Nigera, Dominican Republic).[39–41] The first attempt to obtain epidemiological data on the prevalence of serious fungal diseases in Germany was undertaken in the late 1980's to early 1990's.[1,2] According to regional surveillance in Southern Germany, the calculation lead to an estimated incidence of 600 IFD per million populations per year.[1] A ratio of 15 : 1 for invasive candidosis vs. IA was reported. For invasive candidosis (IC) no underlying disease was identified in up 60%, but major abdominal surgery, stay in the ICU, diabetes mellitus, dialysis, organ transplantation and central venous catheters were the most frequent risk factors. From 274 ICUs in Germany, data of 590 695 patients were collected from 1997 until 2002.[13] In 18 073 device associated infections, 11.2% ($n = 2024$) were caused by *Candida* spp. which are currently the fourth most frequently isolated pathogen.

For IA, the most frequent underlying disease was haematological cancer and organ transplantation according to an international survey including the USA, Canada and Europe in 1994–1995.[29] In recent

years, IA became more prevalent and the current ratio is probably 4 or 5 : 1 for IC vs. IA. Such observations suggest a major increase of invasive and other forms of aspergillosis in Germany in recent years probably reflecting corticosteroid use particularly among those with pre-existing chronic lung disease.[42] In an autopsy study from Germany in the early 1990's in patients with haematological malignancies, IA was the most prevalent IFD in this patient cohort.[43] IFD were detected in up to 30% of autopsied patients. In recent years, the prevalence of IFD's decreased to 21.4% according to current data.[44]

According to preliminary data from the PIMDA (prospective invasive mould disease audit) survey in 1205 patients, which recently assessed frequencies of invasive mould infections in patients with AML/myelodysplastic syndrome (MDS) and neutropenia as well as patients post alloHSCT across 17 european countries the rate of proven/probable IA was about 10% in Germany.[30]

However, the overall rates of autopsies decreased markedly over the years in Germany with currently less than 10% of deceased patients undergoing a formal autopsy. Better and earlier diagnosis of IFD as well as the use of more active antifungal agents (e.g. for therapy and prophylaxis) may have lead to this epidemiological trend. For these reasons, autopsy statistics may not be adequate to calculate the current incidence and prevalence of IFD. Robust epidemiological 'live' data are very difficult to obtain for several reasons. The diagnosis of IA is the most often missed diagnosis in critically ill patients. No fungal specific registries in Germany exist and opportunistic infections such as mycoses are not mandatory to be reported to public health authorities. Even more difficult, data on non-hospitalised patients (outpatients treated in private practice by general practitioners, dermatologists, gynecologists etc.) can only be estimated from cohort studies and other published literature.

The burden of outpatient fungal diseases far exceeds those of patients in hospital. In pulmonary medicine, for example over 250 000 patients have chronic or allergic fungal disease. Recurrent VVC is clearly a very substantial problem for women with over a 1 million affected annually. The estimate of cutaneous fungal infections numbering over 6 million is based on older data and may have decreased, but even if the current numbers are 50% of those we have estimated, it is still a large number of people affected. Globally SFIs of the hair, nails and skin is the 4th most common problem, after dental caries and headaches.[45]

In summary, using local data and available national and international literature estimates of the incidence or prevalence of fungal infections, almost 9.6 M or 12% of the population in Germany are affected each year by a fungal infection. Given these estimates, increased public health efforts are required to document and control this substantial burden of disease.

Conflict of Interest

MR reports grants from commercial sponsor (Pfizer, Roche Molecular Diagnostics), personal fees from commercial sponsor (Astellas, Gilead, Pfizer, Janssen), outside the submitted work. AHG declares no conflict of interest. PM declares no conflict of interest. AJU has received support for travel to meetings from Basilea, MSD and Pfizer. He is a consultant and on the speakers' bureaus of Astellas, Gilead, MSD, and Pfizer. He has also received support for travel and accommodation from Astellas, Boehringer Ingelheim, Gilead, MSD, and Pfizer for activities unrelated to the current study. His institution has received grants from Astellas, Gilead, MSD, and Pfizer. WM eports personal fees from Abbott GmbH & Co. KG Hannover, personal fees from Aristo Pharma GmbH Berlin, personal fees from Bayer Healthcare Leverkusen, personal fees from Dr. August Wolff GmbH & Co. KG Bielefeld, personal fees from johnson & Johnson GmbH Neuss, personal fees from Medinova Zurich, outside the submitted work. HH declares no conflict of interest. DWD holds Founder shares in F2G Ltd a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Myconostica real-time molecular assays and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, NorthWest Lung Centre Charity, Medical Research Council, Astellas and the Fungal Infection Trust. He acts as a consultant to T2 Biosystems, GSK, Sigma Tau, Oxon Epidemiology and Pulmicort. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is also a member of the Infectious Disease Society of America Aspergillosis Guidelines and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups. He is also President of the Global Action Fund for Fungal Infections.

References

1 Muller J, Kappe R, Kubitza D, Fessler R, Scheidecker I. The incidence of deep-seated mycoses in Freiburg i. Br. (Federal Republic of Germany). *Mycoses* 1988; (Suppl 1): 9–28.
2 Polak A, Muller J. Epidemiology of aspergillosis and cryptococcosis in Germany. *Mycoses* 1998; **41**(Suppl 1): 86–9.

3 Statistisches Bundesamt. Statistisches Bundesamt Wiesbaden 2015. URL https://www.destatis.de/EN/Homepage.html. [accessed on 25 March 2015].
4 Meyer E, Geffers C, Gastmeier P, Schwab F. No increase in primary nosocomial candidemia in 682 German intensive care units during 2006 to 2011. *Euro Surveill* 2013; **18**: 24–31.
5 Maschmeyer G, Heinz WJ, Hertenstein B *et al.* Immediate versus deferred empirical antifungal (IDEA) therapy in high-risk patients with febrile neutropenia: a randomized, double-blind, placebo-controlled, multicenter study. *Eur J Clin Microbiol Infect Dis* 2013; **32**: 679–89.
6 Statistische Bundesamt, Zweigstelle Bonn and Robert-Koch-Institut. Das Informationssystem der Gesundheitsberichterstattung des Bundes. URL http://www.gbe-bund.de [accessed on 16 March 2015].
7 Robert-Koch-Institut. Krebs in Deutschland 2003-2004. Haeufigkeiten und Trends. 6. ueberarbeitete Auflage. Robert Koch-Institut (Hrsg) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V.(Hrsg). Berlin, 2008.
8 Caputo R, De BK, Del RJ, Nowicki R. Prevalence of superficial fungal infections among sports-active individuals: results from the Achilles survey, a review of the literature. *J Eur Acad Dermatol Venereol* 2001; **15**: 312–16.
9 Foxman B, Muraglia R, Dietz JP, Sobel JD, Wagner J. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey. *J Low Genit Tract Dis* 2013; **17**: 340–5.
10 Robert-Koch-Institut. Schätzung der Prävalenz und Inzidenz von HIV-Infektionen in Deutschland, Stand Ende 2012. *Epidemiologisches Bull* 2012; **47**, 465–78.
11 Robert-Koch-Institut. Epidemiologie der Kryptokokkose in Deutschland von 2004 bis 2010. *Epidemiologisches Bull* 2012; **29**: 275–82.
12 Gastmeier P, Sohr D, Schwab F *et al.* Ten years of KISS: the most important requirements for success. *J Hosp Infect* 2008; **70**(Suppl 1): 11–16.
13 Geffers C, Zuschneid I, Sohr D, Ruden H, Gastmeier P. Microbiological isolates associated with nosocomial infections in intensive care units: data of 274 intensive care units participating in the German Nosocomial Infections Surveillance System (KISS). *Anasthesiol Intensivmed Notfallmed Schmerzther* 2004; **39**: 15–19.
14 Geffers C, Gastmeier P. Nosocomial infections and multidrug-resistant organisms in Germany: epidemiological data from KISS (the Hospital Infection Surveillance System). *Dtsch Arztebl Int* 2011; **108**: 87–93.
15 Dettenkofer M, Wenzler-Rottele S, Babikir R *et al.* Surveillance of nosocomial sepsis and pneumonia in patients with a bone marrow or peripheral blood stem cell transplant: a multicenter project. *Clin Infect Dis* 2005; **40**: 926–31.
16 Laws HJ, Kobbe G, Dilloo D *et al.* Surveillance of nosocomial infections in paediatric recipients of bone marrow or peripheral blood stem cell transplantation during neutropenia, compared with adult recipients. *J Hosp Infect* 2006; **62**: 80–8.
17 Robert-Koch-Institut. Welttuberkulosetag 2013 - Fuer ein Leben ohne Tuberkulose. *Epidemiologisches Bull* 2013; **11**: 92–5.
18 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; **51**: 361–70.
19 Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. *Bull World Health Organ* 2011; **89**: 864–72.
20 To T, Stanojevic S, Moores G *et al.* Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012; **12**: 204.
21 Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis complicating sarcoidosis. *Eur Respir J* 2013; **41**: 621–6.
22 Patton LL, McKaig R, Strauss R, Rogers D, Eron JJ, Jr. Changing prevalence of oral manifestations of human immuno-deficiency virus in the era of protease inhibitor therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **89**: 299–304.
23 Lalla RV, Latortue MC, Hong CH *et al.* A systematic review of oral fungal infections in patients receiving cancer therapy. *Support Care Cancer* 2010; **18**: 985–92.
24 Robert-Koch-Institut. HIV/AIDS Folien. Robert-Koch-Institut. Berlin, URL http//:www.rki.de [1 September 2012].
25 Institut für das Entgeltsystem im Krankenhaus [GermanInstitute for the Hospital Remuneration System] (InEK). Auswertungen im Rahmen der Begleitforschung für das Datenjahr 2008. [Analysis for the data year 2008 in the frame of accompanying research]. 2008. Siegburg, InEK. 31-1-2009.
26 Tragiannidis A, Fegeler W, Rellensmann G *et al.* Candidaemia in a European Paediatric University Hospital: a 10-year observational study. *Clin Microbiol Infect* 2012; **18**: E27–30.
27 Armstead J, Morris J, Denning DW. Multi-country estimate of different manifestations of aspergillosis in cystic fibrosis. *PLoS ONE* 2014; **9**: e98502.
28 Cornely OA, Maertens J, Winston DJ *et al.* Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–59.
29 Patterson TF, Kirkpatrick WR, White M *et al.* Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. *Medicine (Baltimore)* 2000; **79**: 250–60.
30 Donnelly JP, Cordonnier C, Cuenca-Estrella JM *et al.* European period-prevalence study to estimate the rate of invasive pulmonary mould disease (PIMDA study). ESCMID library online Abstract P0028a 24th ECCMID, Barcelona, Spain, 10-13 May 2014. 2015.
31 DRST-Datenzentrale, c/o ZKRD Zentrales Knochenmarkspender, and Register für die Bundesrepublik Deutschland gGmbH. Deutsches Register für *Stammzelltransplantationen*, 2015. URL http://www.drst.de/download/jb2013.pdf [accessed on 20 July 2015]
32 Pappas PG, Alexander BD, Andes DR *et al.* Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis* 2010; **50**: 1101–11.
33 Deutsche Stiftung Organtransplantation. Koordinierung der Organspende in Deutschland, 2015. URL http://www.dso.de/ [accessed on 20 July 2015].
34 Guinea J, Torres-Narbona M, Gijon P *et al.* Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. *Clin Microbiol Infect* 2010; **16**: 870–7.
35 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.
36 OECD. *Health at a Glance 2013: OECD Indicators*. Paris: OECD Publishing, 2013: 1–213.
37 Tintelnot K, Just-Nubling G, Horre R *et al.* A review of German *Scedosporium prolificans* cases from 1993 to 2007. *Med Mycol* 2009; **47**: 351–8.
38 Nielsen SE, Nielsen E, Julian HO *et al.* Incidence and clinical characteristics of fungal keratitis in a Danish population from 2000 to 2013. *Acta Ophthalmol* 2015; **93**: 54–8.
39 Rodriguez-Tudela JL, Alastruey-Izquierdo A, Gago S *et al.* Burden of serious fungal infections in Spain. *Clin Microbiol Infect* 2015; **21**: 183–9.
40 Oladele RO, Denning DW. Burden of serious fungal infection in Nigeria. *West Afr J Med* 2014; **33**: 107–14.
41 Gugnani HC, Denning DW. Burden of serious fungal infections in the Dominican Republic. *J Infect Public Health* 2015 May 28; pii: S1876–0341 (15)00094-5. doi: 10.1016/j.jiph.2015.04.026. [Epub ahead of print].
42 Groll AH, Shah PM, Mentzel C, Schneider M, Just-Nuebling G, Huebner K. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect* 1996; **33**: 23–32.
43 Donhuijsen K, Pfaffenbach B, Samandari S, Leder LD. Autopsy results of deep mycoses in hematologic neoplasms (1053 patients. *Mycoses* 1991; **34**(Suppl 1): 25–7.
44 Donhuijsen K, Petersen P, Schmid WK. Trend reversal in the frequency of mycoses in hematological neoplasias: autopsy results from 1976 to 2005. *Dtsch Arztebl Int* 2008; **105**: 501–6.
45 Hay RJ, Johns NE, Williams HC *et al.* The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol* 2014; **134**: 1527–34.