# Morbidity and mortality of candidaemia in Europe: an epidemiologic meta-analysis

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**Abstract**

*Background:* Candidemia is a serious hazard to hospitalized patients, but European epidemiological data is restricted to national studies focusing on Northern Europe, population-based surveillance programs or studies conducted in distinct local areas.

*Objectives:* To provide current data on the overall burden and epidemiological development of candidemia in Europe.

*Data sources:* Web of Knowledge™ search from January 2000 and February 2019.

*Study eligibility criteria:* Appropriate data on total cases, study duration, incidence, species distribution and/or mortality rates.

*Interventions:* Meta-analysis to pool individual studies. Heterogeneity was examined by $I^2$ statistic. Calculation of pooled incidence and mortality rates, subgroup analysis by geographical origin, study period and scenarios. Extrapolation of daily candidaemia incidence and mortality rates in Europe.

*Methods:* Systematic review and meta-analysis to determine incidence and mortality of candidemia in the UN European region. Complete datasets were categorized into population-based and hospital-based epidemiological studies and were analyzed separately. Subgroup analyses were performed for geographic distributions and time-dependent developments.

*Results:* In population-based studies, 43,799 cases of candidemia were diagnosed in 1,885,271,885 person-years, revealing an overall pooled incidence rate of 3.88/100,000. The highest pooled incidence rate was observed in intensive care units (5.5/1,000 admissions, Day 30 mortality rate 37%), followed by tertiary care centers (0.96/1,000 admissions, pooled day 30 mortality rate 38%) and the mixed group of teaching and general hospitals (0.52/1,000 admissions, pooled Day 30 mortality rate 37%). European incidence of candidemia was

extrapolated to approximately 79 cases per day, of which an estimated 29 patients might have fatal outcome at day 30.

*Conclusion:* Pooled incidence rates, species distribution and outcome of candidemia differ considerably between clinical groups, European regions and over time. We observed an increasing overall pooled incidence rate of candidemia and a higher proportion of *Candida* spp. other than *C. albicans* in the current decade in population-based data.

## Introduction

Over the last decades, the management of candidaemia has continuously evolved with respect to advanced treatment algorithms and availability of new antifungal drugs.[1,2] However, candidaemia remains a serious hazard to hospitalized patients and increases health care costs.[3-5] Most guidelines define candidaemia as isolation of *Candida* spp. from at least one peripheral or central line blood culture, a diagnostic method with a 50–75% overall sensitivity.[2,6-8] *Candida* spp. are the fourth most common cause of nosocomial bloodstream infections (BSI) in the United States of America (9%) with a mean of 22 days from admission to infection.[9] BSI surveillance showed 6% of BSI being caused by *Candida* spp. in Estonia,[10] in contrast to only 1% in Spain.[11] The majority of European data on candidaemia originates from single institutions,[12-15] hospital networks,[16-19] and national surveillance programs.[20-23] *Candida albicans* remains the most prevalent species.[9,20,24-26] A shift towards *Candida* spp. other than *C. albicans* (non-*albicans Candida*, NAC), in particular *C. glabrata* complex, has been observed globally,[25-27] and *Candida auris* sets a worrisome trend with globally reported outbreaks.[28,29]

Nationwide population-based surveillance programs on morbidity and mortality of candidaemia were executed in Northern Europe (Denmark, Iceland, Sweden),[20,21,25] and in the United States.[30-33] In Western Europe, most studies are limited to smaller geographical regions.[34-37] In addition to population-based surveillance programs, hospital and laboratory-based studies allow characterization of epidemiology in teaching hospitals (TH), general hospitals (GH), and intensive care units (ICU). Published epidemiological data is highly divergent and heterogeneous. Standardized work-up and reporting strategies currently do not exist. Epidemiological efforts are needed to improve the understanding of the impact of candidaemia on patient outcomes in Europe and are important for tracking trends across geography, time and hospital settings. The contemporary epidemiology of candidaemia in the

era of modern antifungal therapy warrants more study. Therefore, we conducted a systematic literature review and meta-analysis focusing on incidence and mortality in different periods, regions and clinical groups to synthesize the results available from European assessments.

## Methods

### Search strategy and selection criteria

We conducted a Web of Knowledge™ search for English language articles on candidemia and *Candida* epidemiology with predefined search algorithms (Table S4 and S5). The latest search was performed in 28th of February 2019. Time span was defined as publication date between January 1, 2000 and February 28, 2019. Given progressive changes in clinical and microbiological diagnostic methods, older studies were not included for lack of relevance and comparability. Concerning mortality analysis, we differentiated between crude mortality and Day 30 mortality rates. Additional information on the methodology of data selection, extraction and calculation is part of the Supplement (Data extraction and selection, and formulary).

### Meta-analysis

A meta-analysis was conducted to pool individual studies by using a random effect model of DerSimonian and Laird.[38] Heterogeneity was examined by using the $I^2$ statistic.[39] We calculated the pooled incidence and mortality rates and performed subgroup analysis by geographical origin, study period and scenarios (laboratory vs. hospital-based data, prospective vs. retrospective) to compare heterogeneity. We further conducted a random meta-regression model to determine the influence of the different study factors on pooled

estimate effects.[40] Significance was set at the α level of 0·05. Statistical analysis used Stata version 14.0.

**Stratification**

We grouped studies according to their median time point during study period and differentiated according to three decades, 1990-2000, 2001-2010 and 2011-Now. Studies were allocated to European sub-regions according to United Nations geoscheme for Europe defined by the United Nations Statistics Division.[41] It divides the European continent into Northern, Eastern, Southern and Western Europe. *C. albicans* and NAC candidaemia distribution was plotted in bar charts according to the observed species percentages in the studies. *Candida parapsilosis* sensu stricto, *Candida orthopsilosis* and *Candida metapsilosis* were grouped as *Candida parapsilosis* complex.[42] In addition, *Candida glabrata* sensu stricto, *Candida nivariensis* and *Candida bracarensis* were summarized as C. *glabrata* complex.[43,44]

**Extrapolation**

We extrapolated daily candidaemia incidence and mortality rates in Europe using the number of UN European region inhabitants (740,813,959)[45] and the population-based pooled incidence rate and mixed group based pooled D30 mortality rate.

## Results

The search algorithms identified 3,209 articles. Of these, we rated 979 as potentially relevant. We retrieved corresponding articles if needed for detailed review and evaluation. 872 studies did not match our inclusion criteria after detailed review (Figure 1). In total, we included 107 studies in our analysis.[13-16,18-22,25,26,34,36,37,46-137] Fifty[13-16,22,37,52,55-86,114-116,120,121,126,128,129,133,136] of 107 studies[13-16,18-22,25,26,34,36,37,46-108] were teaching hospital-based, 18 were population-based,[20-22,25,26,34,36,87-100,123] 22 were ICU-based[18,19,46-51,53,54,110-113,117,119,122,125,131,132,135,137] and 17 reported data on the mixed group.[34,36,93,101-109,118,124,127,130,134] Seven studies comprised data on multiple subcategories (e.g. population-based plus mixed group).[22,34,36,52,93,94,106] Eighty-one studies were hospital-based[13-16,18-22,25,26,34,36,37,46-108,110-120,122,125-127,129-132,134-137] and 26 were laboratory-based (Figures S3, S12 and S17).[20,21,25,26,36,56,57,87-92,94-97,100,102,105,109,121,123,124,128,133] Sixty-seven studies were retrospective[13-15,18,20,22,26,49,51-55,57-60,62-66,68,72,75,77-86,88,89,91-95,100,101,103-105,111-116,118-121,123,126-128,132,133,135-138] and 40 prospective.[16,19,21,25,34,36,37,46-48,50,56,61,67,69-71,73,74,76,87,90,96-99,102,106-110,117,122,124,125,129-131,134] Twenty-eight studies had their study midpoint within the 1990-2000 decade,[22,48,49,53,69,72,77,79,80,82-86,97-100,105-108,112,113,122,124,126,133] 54 between 2001 and 2010[13-16,18-21,25,26,34,36,37,46,47,50,51,54,55,60,61,63-68,70,71,73-76,78,81,90,92,93,95,96,102-104,110,111,116,117,121,125,128,130,131,134,136,137] and 25 between 2011 and now.[52,56-59,62,87-89,91,94,101,109,114,115,118-120,123,127,129,132,134,135,138] Fifty-five studies were conducted in Southern,[13,14,16,19,34,36,47,48,51-54,56-58,60-66,68,69,71,73-77,79,80,83,84,86,98,101,102,111,114-122,128-131,135,136,138] 27 studies in Northern,[20-22,25,26,70,72,78,81,82,87-91,93-97,99,100,104,107,123,126,137] 20 in Western[15,18,37,46,49,50,55,67,85,92,105,108,110,112,113,125,127,132-134] and four in Eastern Europe (Tables S1-S3). [59,103,109,124] One study comprised a pan-European survey.[27]

The articles reported 43,799candidaemia episodes in a population of 1,885,271,885person-years in population-based surveys. In hospital-based studies, teaching hospitals observed

9,092 candidaemias per 12,191,293 admissions, and the mixed group of teaching and general hospitals yielded 5,387 candidaemias per 13,782,442 admissions. In ICU-based surveys, 1,756candidaemia episodes per 450,607admissions were reported.

**Population-based epidemiology of candidaemia in Europe**

Population-based surveys yielded an overall pooled incidence rate (IR) of candidaemia of 3.88 per 100,000 inhabitants per year (95% CI 3.42–4.35) (Figure 2 and Table 1).[20-22,25,26,34,36,87-98,100,123] Reported incidence rates per 100,000 people varied from 1.0 in England and Wales (1990-1999)[100] to 10.4 in Denmark (01/2004-12/2006).[95] Pooled analysis indicated that studies with a study median between 2001-2010 had a higher incidence rate of candidaemia (4.67; 95% CI 4.12–5.21)[20,21,25,26,34,36,90,92-96] compared to studies with a study median between 1990 and 2000 (2.18; 95% CI 1.25–3.12)[22,97,98,100] and studies with a study median between 2011 and now (3.22; 95% CI 2.88–3.56) (Figure 2) (p-value for interaction <0.001).[87-89,91,94,123] Studies from southern European countries had a higher incidence rate of candidaemia (5.29; 95% CI 2.79–7.78)[34,36,98] compared to studies from northern (3.77; 95% CI 3.19–4.34)[20-22,25,26,94-97,100,123] and western European countries (2.5; 95% CI 2.46–2.54) (Figure S1) (p-value for interaction <0.001).[92] Retrospective studies on the incidence of candidaemia in population-based studies showed a pooled IR of 3.39 (95% CI 2.832–3.95)[20,26,88,89,91-95,100,123] compared to prospective studies with 4.64 (95% CI 3.61–5.67) (Figure S2) (p-value for interaction <0.001).[21,22,25,34,36,87,90,96-98] The degree of heterogeneity between population-based studies was high with $I^2$= 99.8% (p <0·0001).. In population-based studies, *C. albicans* was the most prevalent cause of candidaemia, followed by *C. glabrata* complex and *C. parapsilosis* complex (Figure 7).[20-22,25,26,34,36,87-98,100,123] Recent studies reported a trend to a higher share of Non-*albicans Candida* species compared to older studies over time (Figure 7).

## Hospital-based incidence of candidaemia in Europe

For the total hospital-based study setting without studies solely reporting ICU data, the estimated overall pooled incidence rate of candidaemia was 0.83 per 1,000 admissions per year (95% CI 0.72–0.94) (Figure S8 and Table 1). Reported incidence rates per 1,000 admissions varied from 0.17 in Finland (01/1995-12/1999)[22] to 2.19 in Portugal (01/2004-12/2006).[73]

In studies only reporting teaching hospital data, the pooled IR of candidaemia was 0.96 per 1,000 admissions per year (95% CI 0.79–1.12) (Figure 3) [13-16,22,52,55-63,66,71,73-75,77,79,81,83-85,114,115,120,136]. Pooled analysis indicated that studies with a study median between 2001 and 2010 had a higher IR with 1.11 (95% CI 0.83–1.39)[13-16,55,60,61,63,66,71,73-75,81,136] compared to studies with a study median between 1990 and 2000 with 0.62 (95% CI 0.41–0.83),[22,77,79,82-85] and studies with a study median between 2011 and now with 0.97 (95% CI 0.56–1.39) (Figure 3) (p-value for interaction <0.001).[52,56-59,62,114,115,120] Studies from southern European countries had a higher pooled IR (1.13, 95% CI 0.9–1.35)[13,14,16,52,56-58,60-63,66,71,73-75,77,79,83,84,114,115,120,136] compared to studies from northern (0.31; 95% CI 0.16–0.45),[22,81,82] and western European countries (0.47; 95% CI 0.35–0.59).[15,55,85] A single study from an eastern European country showed an IR of 0.25 (95% CI 0.05–0.91) (Figure S4) (p-value for interaction <0.001).[59] Retrospective studies on the incidence of candidaemia in teaching hospitals showed a pooled IR of candidaemia of 0.9 (95% CI 0.71–1.09)[13-15,22,52,55,57-60,62,63,66,75,77,79,81-85,114,115,120,136] compared to prospective studies with 1.23 (95% CI 0.54–1.92) (Figure S5) (p-value for interaction <0.001).[16,56,61,71,73,74] The degree of heterogeneity between teaching hospital-based studies was high with $I^2$= 99.4%, p <0·0001. In teaching hospital-based studies, *C. albicans* was the most prevalent cause of candidaemia followed by *C. parapsilosis* complex and *C. glabrata* complex (Figure S18)[13-16,20-22,25,26,34,36,37,52,55-64,66-98,100,105,114,115,120,136,138]

For the mixed group (studies reporting on teaching plus general hospitals) without studies solely reporting ICU data, the overall pooled IR of candidaemia was 0.52 per 1,000 admissions per year (95% CI 0.38–0.65) (Figure 4 and Table 1).[34,36,93,102,105-109,127,130,134] Studies with a study median between 2001 and 2010 had a higher pooled IR with 0.75 (95% CI 0.42–1.07)[34,36,93,102,130] compared to studies with a study median between 1990 and 2000 with 0.30 (95% CI 0.28–0.32)[105-108] or 2011 and now with 0.52 (95% CI 0.21–0.83)[109,127,134] (p-value for interaction <0.001) (Figure 4).[105-108] Southern European countries had a higher pooled IR with 0.78 (95% CI 0.56–1.01)[34,36,102,106,130] compared to studies from northern (0.29; 95% CI 0.23–0.35)[93,106,107] and western European countries (0.3; 95% CI 0.23–0.37).(Figure S6) (p-value for interaction <0.001).[105,106,108,127,134] Retrospective studies on the incidence of candidaemia in the mixed group showed a pooled IR of candidaemia of 0.24 (95% CI 0.19–0.28)[93,105,127] compared to prospective studies with 0.61 (95% CI 0.44–0.78) (Figure S7).[34,36,102,106-109,130,134] The degree of heterogeneity between mixed group-based studies was high with $I^2$= 98.8%, p value for heterogeneity<0·0001. In the mixed group hospital-based studies, *C. albicans* was the most prevalent cause of candidaemia, followed by *C. parapsilosis* complex and *C. glabrata* complex.[17,34,36,93,101-109,127,130,134] (Figure S19)

In the ICU-only setting, the pooled IR of candidaemia was 5.5 per 1,000 admissions per year (95% CI 4.31–6.69) ($I^2$= 97.0%, p <0·0001) (Figure 5).[19,46,48,49,51-53,110,112,113,122,135]. *C. albicans* was the most prevalent cause of candidaemia, followed by *C. glabrata* complex *and C. tropicalis*[19,46-51,53,110,112,113,122,135] Recent studies reported higher shares of Non-*albicans Candida* species (Figure S20).

## Mortality of candidaemia in Europe

Concerning mortality analysis, we differentiated between D30 and crude mortality rates (Tables 2 and 3). For the total study the pooled D30 mortality rate (MR) was 0.37 (95% CI 0.35–0.39) (Figure S9 and Table 2).[15,16,19,20,22,26,34,36,37,56,58-62,67-72,76,78,80,81,85-87,93,99,101-104,106,107,109,127,129,138,139] Reported D30 mortality rates varied from 0.25 to 0.51.[56,59] Overall pooled crude MR was 0.46 (95% CI 0.42–0.49) (Figure S13 and Table 3).[13,18,37,46-51,54,55,64,73,74,82-84,92,98,110,112,113,116-119,122,131,135-137] Reported crude mortality rates varied from 0.24 to 0.83.[18,135]

Population-based studies reported a pooled D30 MR of 0.34 (95% CI 0.29–0.39)[20,26,34,36,87,99], teaching hospital-based studies showed a pooled D30 MR of 0.38 (95% CI 0.35–0.40)[15,16,22,37,56,58-62,67-72,76,78,80,81,85,86,129,138,139], the mixed group yielded a pooled D30 MR of 0.37 (95% CI 0.34–0.40),[36,93,101-104,106,107,109,127] and one ICU study reported 0.46 (95% CI 0.40–0.52) (Figure S9) (p-value for interaction <0.001).[19] For subgroup analysis, we excluded studies solely reporting on ICU patients. Studies with a study median between 1990 and 2000, accounted for a pooled D30 MR of 0.36 (95% CI 0.32–0.39).[22,69,72,80,85,86,99,106,107] Pooled analysis showed that studies with a study median between 2011 and now had a higher D30 MR with 0.4 (95% CI 0.36–0.44) (Figure 6)[56,58,59,62,87,101,109,127,129,138] compared to studies with a study median between 2001 and 2010 (0.36; 95% CI 0.32–0.39) (p-value for interaction <0.001).[15,16,20,26,34,36,37,60-62,67,68,70,71,76,78,81,93,102-104,139] Studies from eastern European countries had a higher pooled D30 MR with 0.42 (95% CI 0.33–0.52)[59,103,109] compared to studies from southern (0.37; 95% CI 0.34–0.40)[16,34,36,56,58,60-62,68,69,71,76,80,86,101,102,129,138,139], western (0.37; 95% CI 0.32–0.43)[15,37,67,85,127] and northern European countries (0.35; 95% CI 0.32–0.39) (Figure S10) (p-value for interaction <0.001).[20,22,26,70,72,78,81,87,93,99,104,107] Retrospective studies showed a pooled D30 MR of 0.39 (95% CI 0.36–0.41)[15,20,22,26,58-60,62,68,72,78,80,81,85,86,93,101-106,109,127,138,139] compared to prospective

studies with 0.35 (95% CI 0.32–0.38) (Figure S11) (p-value for interaction <0.001).[16,34,36,37,53,56,61,67,69-71,76,87,99,102,129,140] For studies regarding D30 MR the degree of heterogeneity was high with $I^2$= 85.39%, p value for heterogeneity<0·001.

Population-based studies reported a pooled crude MR of 0.40 (95% CI 039–0.41),[92,98] teaching hospital-based studies showed a pooled crude MR of 0.43 (95% CI 0.39–0.47),[13,55,64,73,74,82-84,122] and the ICU-only studies reported 0.49 (95% CI 0.43–0.55) (Figure S13 and Table 3) (p-value for interaction <0.001).[18,37,46-51,54,110,112,113,117,119,122,131,135,137] For subgroup analysis, we excluded studies solely reporting on ICU patients. The pooled crude MR among studies indicated that studies with a study median between 2001 and 2010 had a higher crude MR with 0.43 (95% CI 0.39–0.47)[13,55,64,73,74,92,116,136] compared to studies with a study median between 1990 and 2000 with 0.41 (95% CI 0.37–0.45) (Figure S14) (p-value for interaction <0.001).[82-84,98] The pooled crude MR among studies indicated that studies from southern European countries had a higher crude MR with 0.44 (95% CI 0.41–0.47)[13,64,73,74,83,84,98,116,136] compared to studies from western (0.40; 95% CI 0.39–0.41)[55,92] and northern European countries (0.35; 95% CI 0.27–0.44) (Figure S15) (p-value for interaction <0.001).[82]

Retrospective studies showed a pooled crude MR of 0.41 (95% CI 0.38–0.44)[13,55,64,82-84,92,116,118,136] compared to prospective studies with 0.46 (95% CI 0.37–0.55) .[73,74,98] For crude relative risk of death the degree of heterogeneity was high with $I^2$= 67.88%, p value for heterogeneity<0.001.[73,74,98] [73,74,98] [72,73,97] [70,71,95] [70,71,95] [70,71,95] [70,71,95]

**Comparative statistical analysis and meta-regression**

Patients in teaching hospitals were at a higher risk of contracting candidaemia compared to patients from the mixed group (pooled IR 0.96; 95% CI 0.79–1.12 (Figure 3) vs. 0.52; 95% CI 0.38–0.65 (Figure 4 and Table 1). Candidaemia yields a slightly higher pooled D30 MR in teaching hospitals alone in comparison to the mixed group of teaching and general hospitals (pooled MR 0.38; 95% CI 0.35–0.40 vs. 0.37; 95% CI 0.34–0.40) (Figure S9 and Table 2). Patients on ICUs showed higher pooled D30 MR with 0.46 compared to the mixed group of general and teaching hospitals (pooled MR 0.37; 95% CI 0.34–0.40) and teaching hospitals (pooled MR 0.38; 95% CI 0.35–0. 40) (Figure S9 and Table 2). To assess geographical differences by comparative statistical analysis, we regrouped studies according to geographical region. Studies solely reporting on ICU-based studies were excluded. The pooled incidence rate of candidaemia in Southern Europe was significantly higher than in Western and Northern Europe (Figures S1, S4, S6 and Table 1). Over time, there was significant increase of candidaemia incidence with a slight decrease during the current decade (Figures 2, 3, 4 and Table 1). Pooled D30 and crude mortality rates were highest in eastern and southern regions (Figures S10, S15 and Tables 2 and 3). Over time, there was an increase of pooled D30 and crude MR (Figures 6, S14, Tables 2 and 3). Further information regarding incidence rates and mortality rates with respect to scenario (retrospective vs. prospective) and type of study (hospital-based vs. laboratory based – Figures S12 and S17) are shown in the Supplement.

Applied to an overall UN-European region population of 740,813,959[45], a daily incidence rate of 79 *Candida* BSI (95% CI 69-88) can be extrapolated as a rough estimate for the UN-European region (28,744 per year (95% CI 25,336 - 32,225)). Given the pooled D30 MR observed in the mixed group of this meta-analysis, we estimate 29 patients (95% CI 27–31) die in Europe from candidaemia every day. The uni-and multivariable meta-regression

analysis did not reveal any significant interaction between the IR of candidaemia and geographical origin, study period, scenario, and type of hospital. Similar findings were elucidated for crude and D30 MR of candidemia (Table S6). The variation explained by the covariates geographical origin, study period, scenario, and type of hospital ranged from 38.59%, for IR in population based studies, up to 85.50% for crude MR. A meta-regression model for the crude MR and hospital-based IR was not applicable due to the low number of studies and lack of information.

Publication bias by Egger`s test was examined and detected potential bias in ICU-based (Egger`s test $p<0.002$) and population-based studies (Egger`s test $<0.001$). We did not detect any evidence for publication bias among studies reporting crude or D30 MR (Egger's test: $p=0.228$ and $p=0.966$).

## Discussion

Candidaemia epidemiology in Europe currently relies on individual efforts of engaged researchers in the field of clinical mycology and microbiology. Our meta-analysis summarizes the available evidence on the incidence rate and mortality rate of candidaemia. We identified considerable differences between the observed clinical groups, European regions, as well as over time.

Incidence and mortality rates of candidaemia were higher in teaching hospitals than in the mixed group. Some reasons for this observation may be more severe underlying diseases, more complex surgical procedures and higher numbers of intensive care beds in teaching hospitals.[141,142] As expected, the highest incidence and mortality rates were found in the ICU setting.[140] Intensive care patients harbour many of the well-established risk factors for candidaemia[34,141-144] and are at higher risk for adverse outcomes.

In our analysis, we observed an increasing incidence of candidaemia over time, which is supported by other surveillance studies.[25,97] A common explanation for this finding is the rising number of patients at risk for invasive candidiasis,[142,145] as the number of elderly patients[20,26,95,97] with complex and severe underlying conditions increases in European health care systems.[68] Other causes that have been proposed are increased survival rates of pre-term neonates and of critical care patients, expanding indications for antineoplastic and immunosuppressive therapies, increased numbers of surgical procedures, solid organ and hematopoietic stem cell transplantations and implantation of indwelling devices, as well as use of parenteral nutrition and broad-spectrum antibiotics.[140,142,146,147]

Our meta-analysis shows that mortality increases over time. It is possible that the increasing case severity and the associated worse outcomes counterbalanced advances in antifungal therapy.

We found a higher incidence for candidaemia in Southern Europe in comparison to Northern or Western Europe throughout the groups. Numerous reasons may be considered for this observation: differences in climate, antibiotic prescription policy, candidaemia management, demographic development and setting of local health care systems may have significant impact on candidaemia incidence. To uncover the reasons for this difference, a comparative prospective study on individual risk factors is needed.

The increasing rate of infections by NAC species represents a potentially hazardous development. Similar developments have been reported for the Americas and in various parts of the world by international authors.[148-150] Increasing use of azoles, the standard antifungal drug of choice for *Candida* infections in many countries, lead to marked pressure on local epidemiology with elevated yields of NAC species. Intensity of the shifts varied throughout the observed groups and stresses the need for species identification and susceptibility testing after microbiological diagnosis and the obligation to consider local epidemiology. Especially

313 the increasing share of *C. parapsilosis* complex is of concern, as it may provide a challenge
314 for current antifungal treatment strategies.[1,8,51,151] Virulence and pathogenicity of some NAC
315 species result in significant morbidity and mortality leading to increasing health care
316 associated costs by prolonged hospital stays in nosocomial NAC candidaemia; this is
317 especially of relevance in the growing group of immunocompromised patients. Recent studies
318 report worrisome trends concerning *Candida auris* outbreaks.[28,29] In the studies included in
319 our analysis no identification of *Candida auris* was reported, such that cases could be
320 misclassified in the group of unidentified, declared as other or *Candida* spp., or non-specified
321 *Candida* due to potential misidentification by conventional biochemical testing.[152]

322 Our meta-analysis has some inherent limitations. The included studies showed marked
323 heterogeneity. We identified potential publication bias in population- and hospital based
324 studies reporting incidence of candidaemia, which needs to be considered when interpreting
325 the pooled results. In addition, bias could develop due to unrecognized confounders as all of
326 the included studies were observational studies.[153,154] Observed differences in local and
327 national epidemiology may be confounded by the type of underlying study. These issues raise
328 the question how to read a pooled IR of our meta-analyses. Still, meta-analysis is the only
329 option to determine the overall population burden of candidaemia based on the available data
330 and to investigate key determinants of individual risk by site and geographic region. Meta-
331 regression analysis was used to control for some potential confounders.

332 Another limitation was the need to exclude a majority of articles due to insufficient reporting
333 (Figure 1). We could not identify sources of heterogeneity in the meta-regression model,
334 illustrating the pressing need to identify risk factors associated with IR and MR of
335 candidaemia in future studies. Due to the varying length of study periods, we had to allocate
336 studies by study median, with the possibility of allocating studies to distinctive decades with
337 overlapping time periods, so that our classification is just the best possible approximation. It

must be considered that studies are published after conclusion of the observation period and sometimes after considerable delay, inevitably leading to a dwindling number of reports in the final study period. We still believed it is better to incorporate all available evidence instead of censoring the past years for the sake of homogeneity. Measurement biases may affect our presented results. Minor deviations in practice regarding pre-analytical (e.g. choice of culture system, blood draw volume, number and frequency of blood cultures, blood draw technique, and transport) and analytical (e.g. laboratory processing, culture duration, detection method, or identification method) procedures all have impact on the rate of detection, thus the measured incidence rate. As it is impossible to control for all such confounders and to balance each potential confounder against the others, the risk of bias should be considered high for all included studies. In addition, specific medical treatment standards and facilities are likely to influence epidemiology of candidaemia, but was not sufficiently reported. The reviewed publications did not always differentiate between unique patients or candidaemia episodes. Regarding species identification, we could not distinguish between studies with molecular from those with conventional identification, which has to be taken into consideration analysing rare and emerging *Candida* species.

In summary, many excellent studies on candidaemia have been published across Europe, allowing some conclusions on the varying epidemiology in different hospital settings and geographic regions. However, a pan-European effort is clearly missing. It is needed to close gaps in our understanding of the epidemiology of candidaemia and to monitor trends in antifungal resistance and species shifts.

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## Contributors

PK – conceived the study idea, designed the study, performed literature research, analysed and interpreted data, created the manuscript, created tables and figures, revised and approved the final manuscript

MS analysed and interpreted data, performed the meta-analysis, created the manuscript, created tables and figures, revised and approved the final manuscript

OAC – conceived the study idea, designed the study, interpreted data, revised and approved the final manuscript

DK – interpreted data, revised and approved the final manuscript

MJGTV – interpreted data, revised and approved the final manuscript

JB – interpreted data, revised and approved the final manuscript

HW – analysed and interpreted data, revised and approved the final manuscript

JJV – conceived the study idea, designed the study, analysed and interpreted data, created figures, revised and approved the final manuscript

## Conflict of Interest

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## Figures

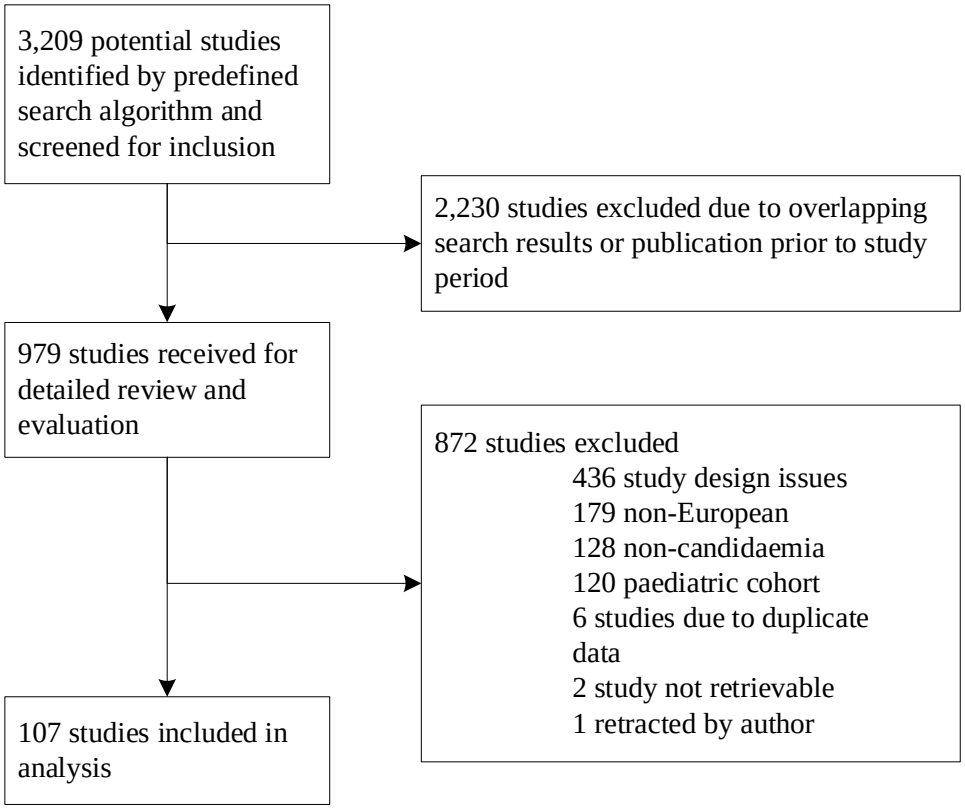


**Figure 1: Study selection.**

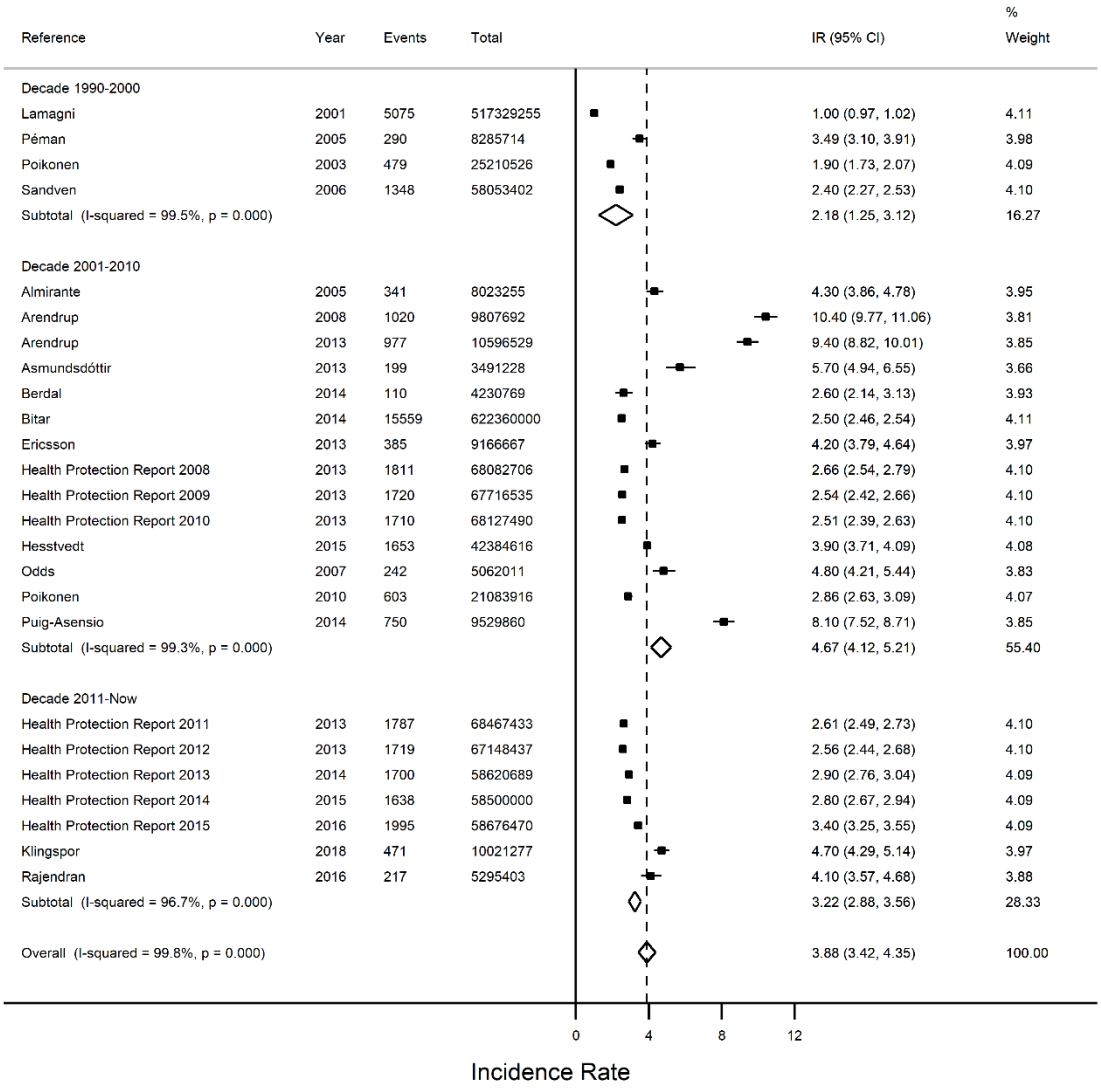


**Figure 2: Forest plot of the incidence of candidaemia for population-based studies by decade.**

Studies are identified by the name of the first author and year of publication. Sorted alphabetically. Total=admissions. Events=candidaemia cases. IR=incidence rate. CI=confidence interval. Weights are from random-effect analysis. Size of squares are analogous to the study's weight. Diamonds represent the pooled incidence rates.

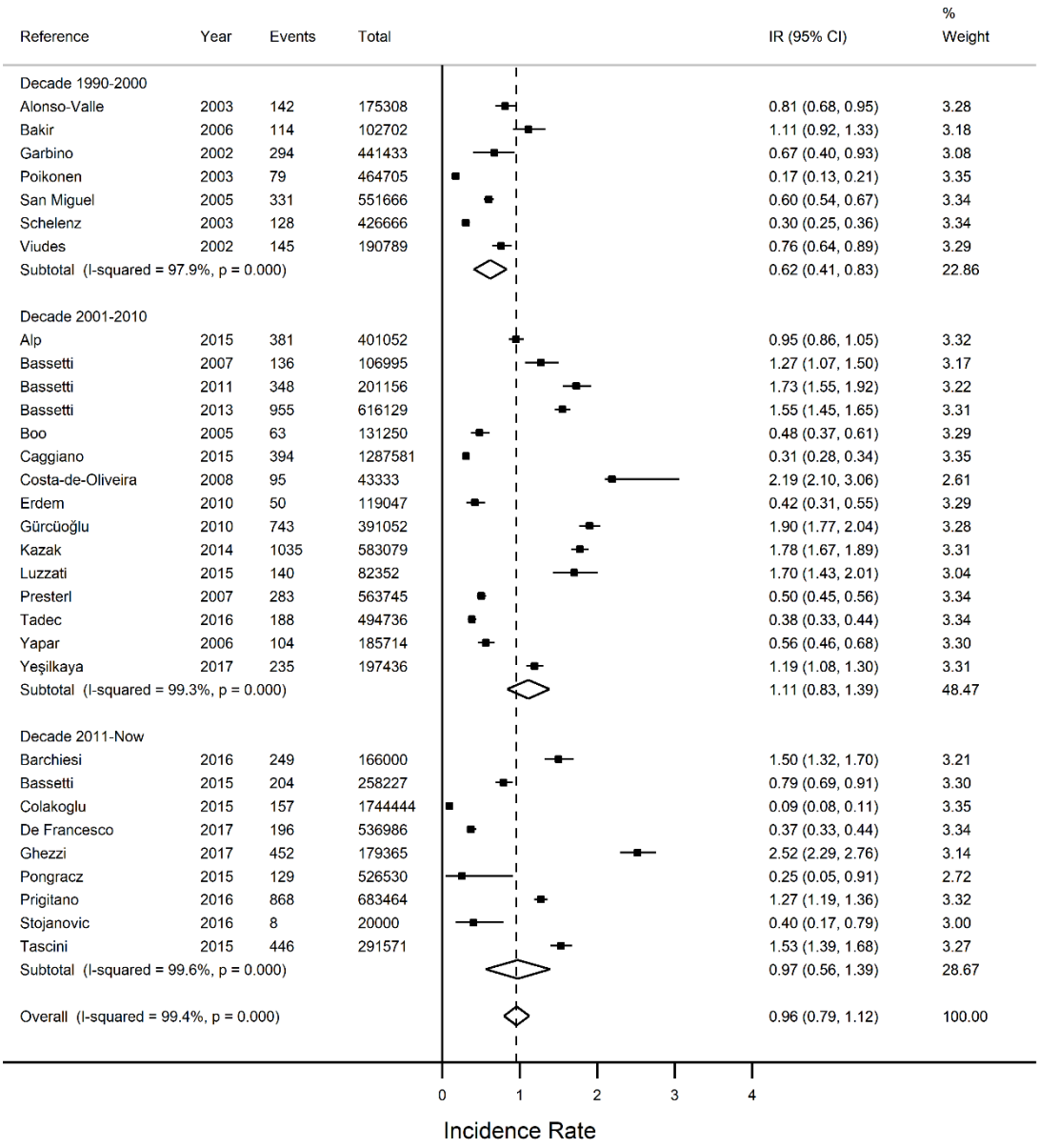


**Figure 3: Forest plot of the incidence of candidaemia for studies on teaching hospitals by decade.**

Studies are identified by the name of the first author and year of publication. Sorted alphabetically. Studies reporting solely on ICU are excluded. Total=admissions. Events=candidaemia cases. IR=incidence rate. CI=confidence interval. Weights are from random-effect analysis. Size of squares are analogous to the study's weight. Diamonds represent the pooled incidence rates.

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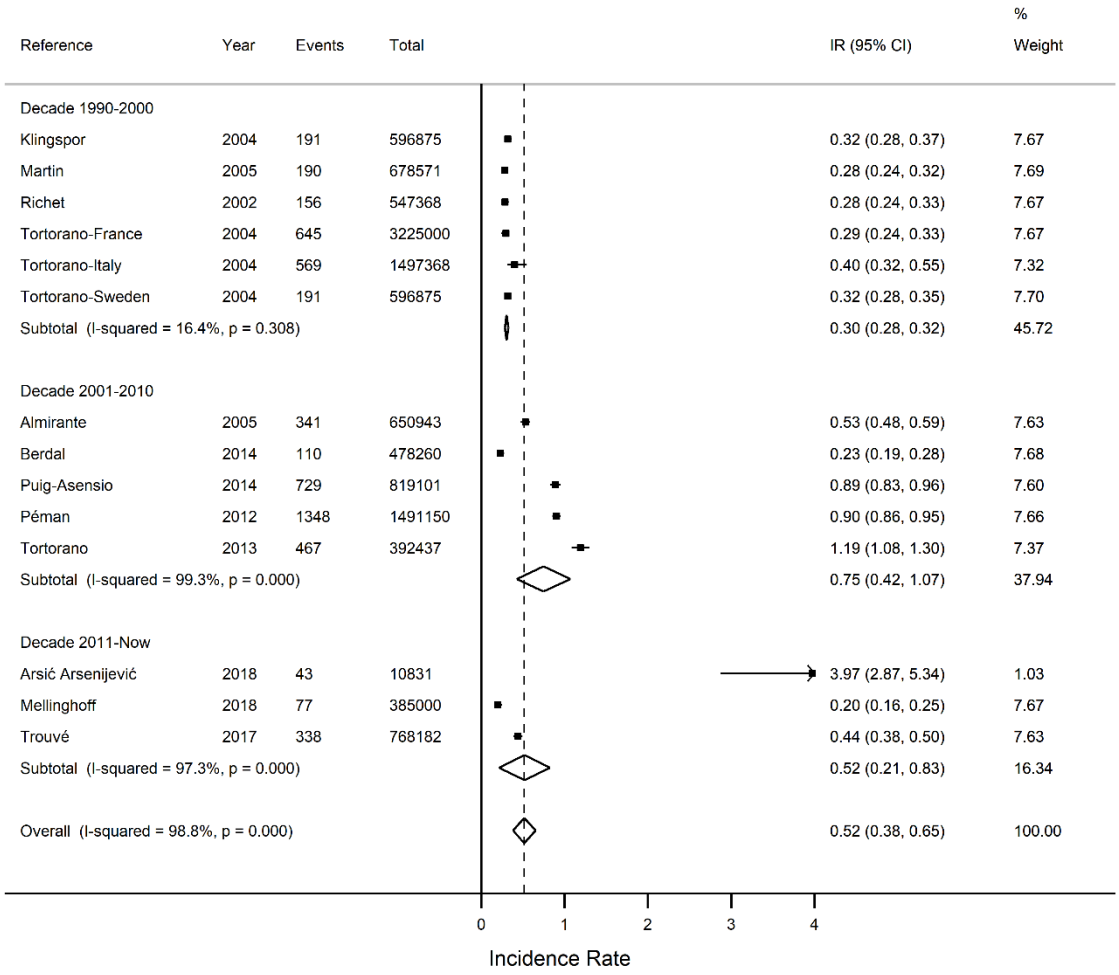



879

880 **Figure 4: Forest plot of the incidence of candidaemia for studies in the mixed group**
881 **(general and teaching hospitals) by decade.**

882 Studies are identified by the name of the first author and year of publication. Sorted
883 alphabetically. Studies reporting solely on ICU are excluded. Total=admissions.
884 Events=candidaemia cases. IR=incidence rate. CI=confidence interval. Weights are from
885 random-effect analysis. Size of squares are analogous to the study's weight. Diamonds
886 represent the pooled incidence rates.

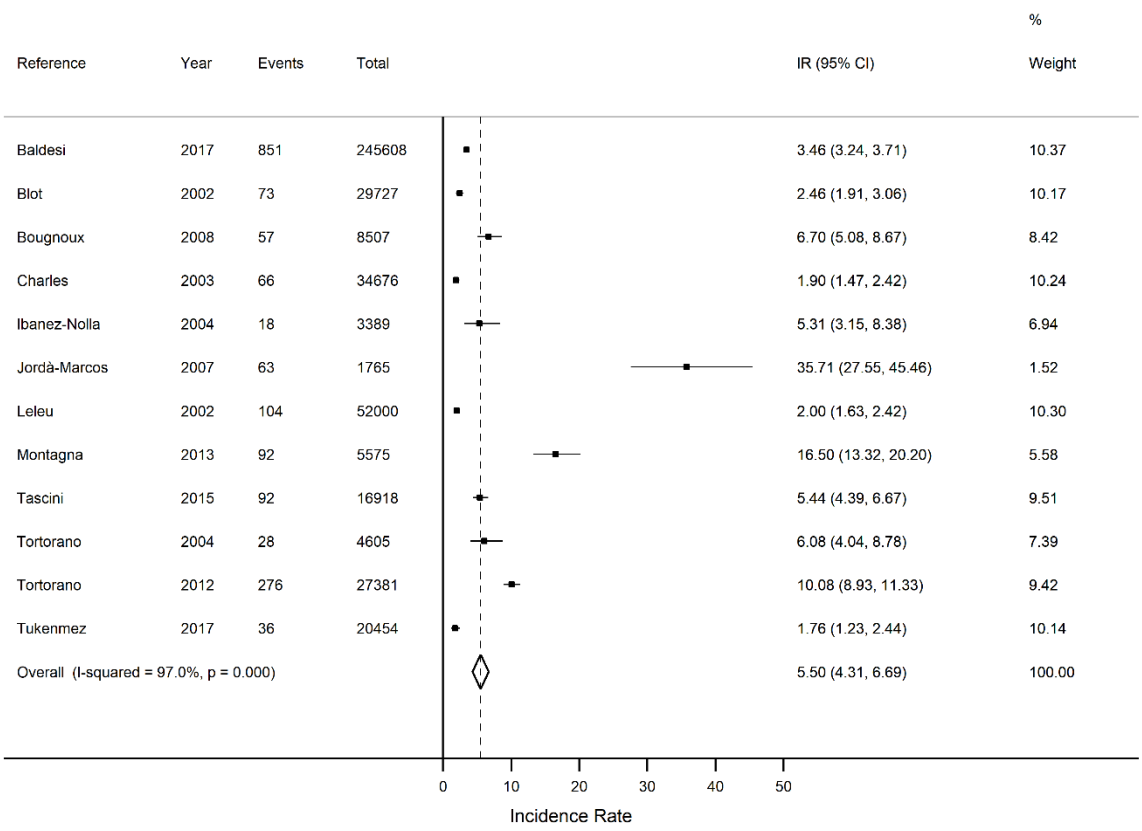



**Figure 5: Forest plot of the incidence of candidaemia for ICU-based studies.**

Studies are identified by the name of the first author and year of publication. Sorted alphabetically. Total=admissions. Events=candidaemia cases. IR=incidence rate. CI=confidence interval. Weights are from random-effect analysis. Size of squares are analogous to the study's weight. Diamonds represent the pooled incidence rates.

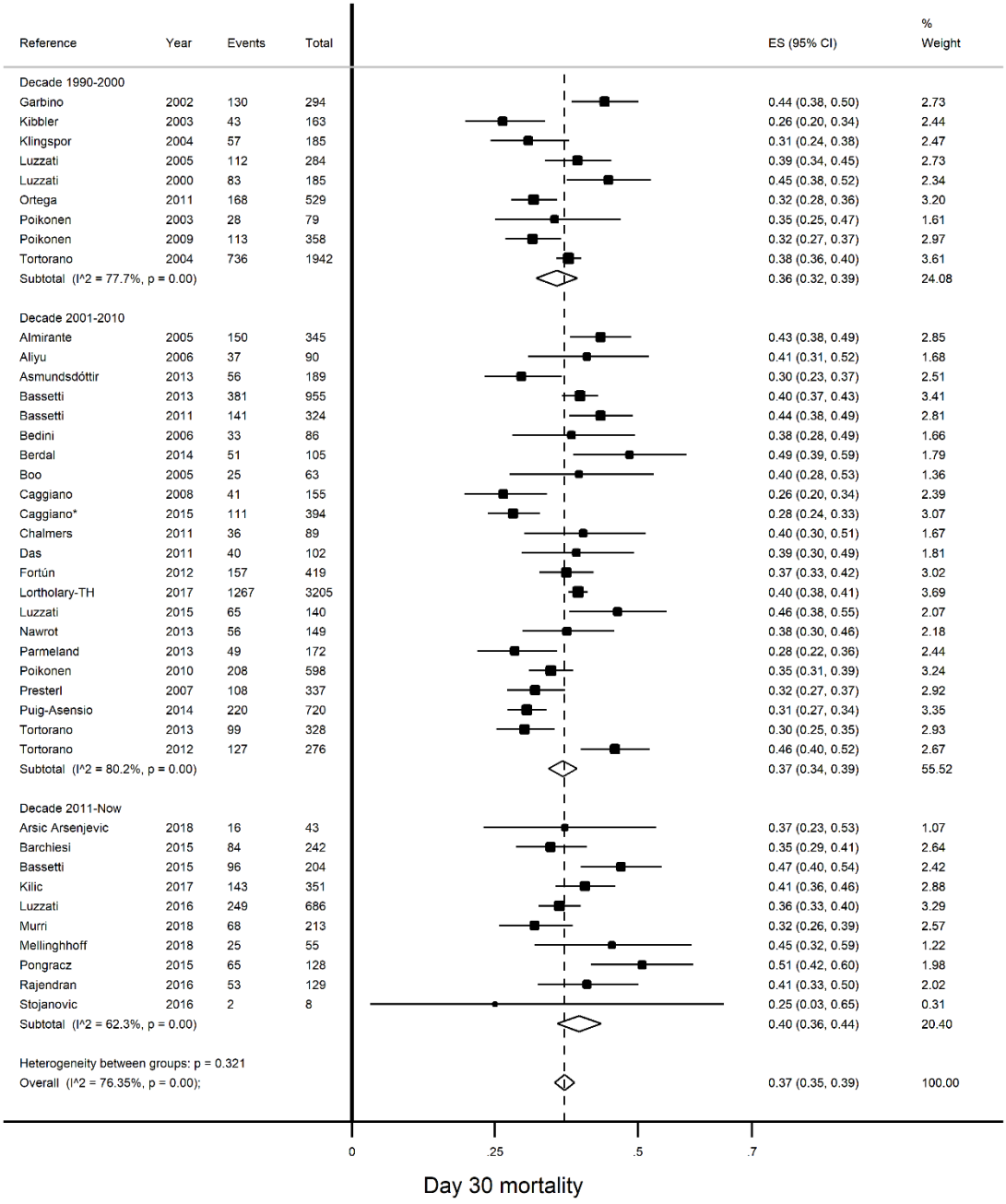
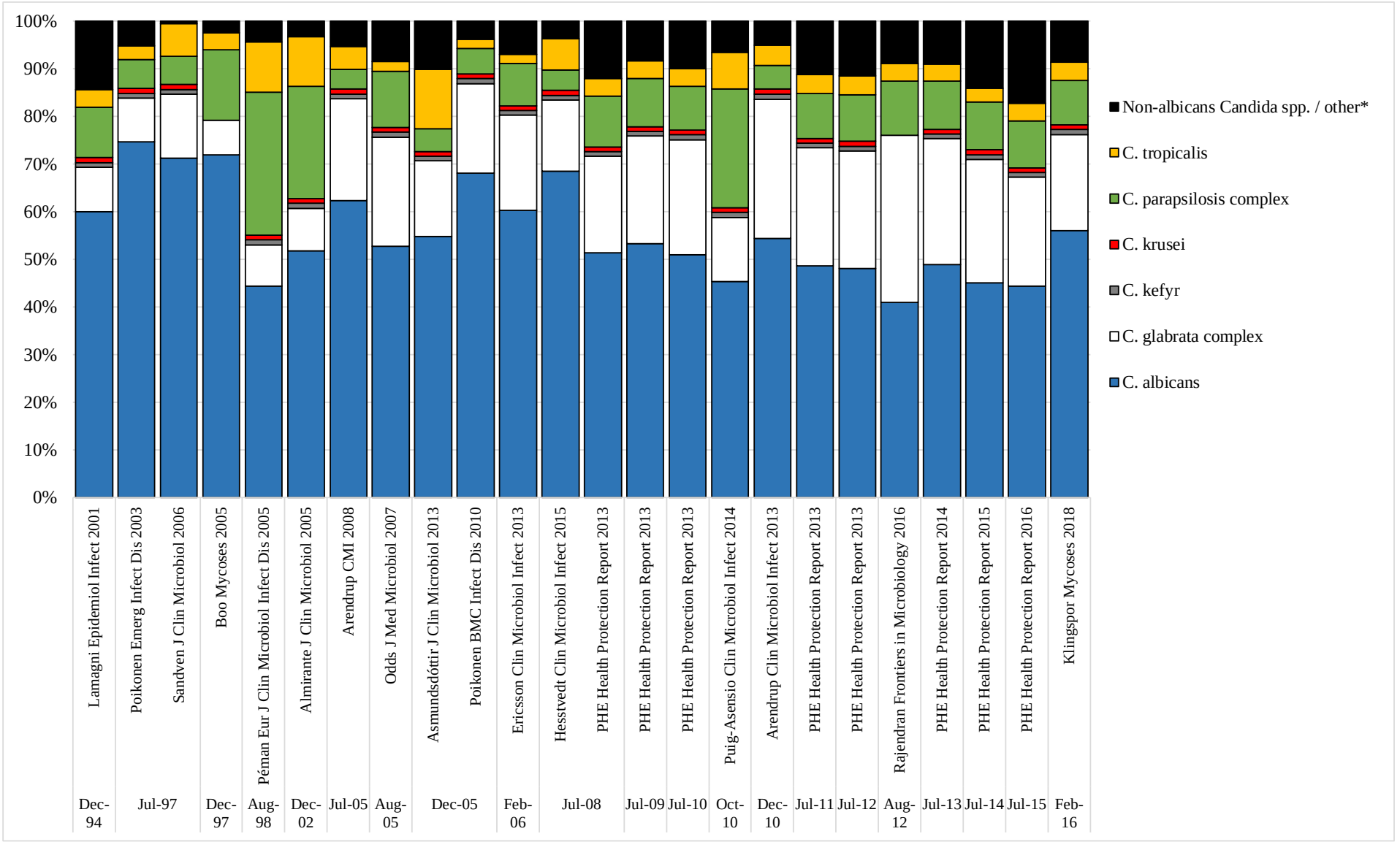



**Figure 6: Forest plot of the day 30 mortality of candidaemia by decade.**

Studies are identified by the name of the first author and year of publication. Sorted alphabetically. Studies reporting solely on ICU are excluded. Total=cases. Events=deaths. ES=effect estimates. CI=confidence interval. Weights are from random-effect analysis. Size of squares are analogous to the study's weight. TH=teaching hospital subgroup of total study population. Diamonds represent the pooled D30 mortality rates. *=reported Day 20 mortality.


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Non-albicans Candida spp. / other*
C. tropicalis
C. parapsilosis complex
C. krusei
C. kefyr
C. glabrata complex
C. albicans
Lamagni Epidemiol Infect 2001
Poikonen Emerg Infect Dis 2003
Sandven J Clin Microbiol 2006
Boo Mycoses 2005
Péman Eur J Clin Microbiol Infect Dis 2005
Almirante J Clin Microbiol 2005
Arendrup CMI 2008
Odds J Med Microbiol 2007
Asmundsdóttir J Clin Microbiol 2013
Poikonen BMC Infect Dis 2010
Ericsson Clin Microbiol Infect 2013
Hesstvedt Clin Microbiol Infect 2015
PHE Health Protection Report 2013
PHE Health Protection Report 2013
PHE Health Protection Report 2013
Puig-Asensio Clin Microbiol Infect 2014
Arendrup Clin Microbiol Infect 2013
PHE Health Protection Report 2013
PHE Health Protection Report 2013
Rajendran Frontiers in Microbiology 2016
PHE Health Protection Report 2014
PHE Health Protection Report 2015
PHE Health Protection Report 2016
Klingspor Mycoses 2018
Dec-94
Jul-97
Dec-97
Aug-98
Dec-02
Jul-05
Aug-05
Dec-05
Feb-06
Jul-08
Jul-09
Jul-10
Oct-10
Dec-10
Jul-11
Jul-12
Aug-12
Jul-13
Jul-14
Jul-15
Feb-16

907 **Figure 7: *Candida* species differentiation by population-based studies.**
908 Studies are identified by the name of the first author, the journal and year of publication. Sorted by chronologically by median of study period from left to right.
909 *=*C. ciferrii*, *C. dubliniensis*, *C. famata*, *C. guilliermondii*, *C. humicola*, *C. inconspicua*, *C. kefyr*, *C. lipolytica*, *C. lusitaniae*, *C. norvegensis*, *C. pelliculosa*, *C.*
910 *rugusa*, *C. sake*, *C. utilis*, unidentified, declared as other or *Candida* spp., or non-specified *Candida*.

911 **Table 1. Incidence rate stratified by different explanatory variables**

| | | Studies (N) | ES Incidence Rate (95% CI) | p-value for subgroup interaction |
|---|---|---|---|---|
| Population-based | | | | |
| Overall | | 25 | 3.88 (3.42, 4.35) | |
| Decade | | | | p<0.001 |
| | 1990-2000 | 4 | 2.18 (1.25, 3.12) | |
| | 2001-2010 | 14 | 4.67 (4.12, 5.21) | |
| | 2011-Now | 7 | 3.22 (2.88, 3.56) | |
| Region | | | | p<0.001 |
| | Northern | 21 | 3.77 (3.19, 4.34) | |
| | Southern | 3 | 5.29 (2.79, 7.78) | |
| | Eastern | - | - | |
| | Western | 1 | 2.50 (2.46, 2.54) | |
| Scenario | | | | p<0.001 |
| | Retrospective | 15 | 3.39 (2.83, 3.95) | |
| | Prospective | 10 | 4.64 (3.61, 5.67) | |
| Type | | | | p<0.001 |
| | Hospital-based | 4 | 4.62 (2.57, 6.66) | |
| | Laboratory-based | 21 | 3.74 (3.25, 4.24) | |
| Hospital-based | | | | |
| Overall | | 45 | 0.83 (0.72, 0.94) | |
| Scenario | | | | p <0.001 |
| | Retrospective | 28 | 0.83 (0.68, 0.98) | |
| | Prospective | 17 | 0.82 (0.66, 0.98) | |
| Teaching Hospital | | | | |
| Overall | | 31 | 0.96 (0.79, 1.12) | |
| Decade | | | | p<0.001 |
| | 1990-2000 | 7 | 0.62 (0.41, 0.83) | |
| | 2001-2010 | 15 | 1.11 (0.83, 1.39) | |
| | 2011-Now | 9 | 0.97 (0.56, 1.39) | |
| Region | | | | p<0.001 |
| | Northern | 3 | 0.31 (0.16, 0.45) | |
| | Southern | 24 | 1.13 (0.90, 1.35) | |
| | Eastern | 1 | 0.25 (0.05, 0.918) | |
| | Western | 3 | 0.47 (0.35, 0.59) | |
| Scenario | | | | p<0.001 |
| | Retrospective | 25 | 0.90 (0.71, 1.09) | |
| | Prospective | 6 | 1.23 (0.54, 1.92) | |
| Mixed Group | | | | |
| Overall | | 14 | 0.52 (0.38, 0.65) | |
| Decade | | | | p<0.001 |
| | 1990-2000 | 6 | 0.30 (0.28, 0.32) | |
| | 2001-2010 | 5 | 0.75 (0.42, 1.07) | |
| | 2011-Now | 3 | 0.52 (0.21, 0.83) | |
| Region | | | | p<0.001 |
| | Northern | 3 | 0.29 (0.23, 0.35) | |
| | Southern | 5 | 0.78 (0.56 1.01) | |
| | Eastern | 1 | 3.97 (2.87, 5.34) | |
| | Western | 5 | 0.30 (0.23, 0.37) | |
| Scenario | | | | p<0.001 |
| | Retrospective | 3 | 0.24(0.19, 0.28) | |
| | Prospective | 11 | 0.61 (0.44, 0.78) | |
| ICU | | | | |
| Overall | | 12 | 5.50 (4.31, 6.69) | |

912

913 N=number. ES=estimate. CI=confidence interval. Weights are from random-effect analysis.

914

**Table 2. Day 30 mortality of candidaemia stratified by different explanatory variables**

| | Studies (N) | ES D30 Mortality (95% CI) | p-value for subgroup interaction |
|---|---|---|---|
| Setting | | | p < 0.001 |
| Overall | 41 | 0.38 (0.36, 0.40) | |
| Population-based | 6 | 0.34 (0.29, 0.39) | |
| Teaching-Hospital | 25 | 0.38 (0.35, 0.40) | |
| Mixed Group | 9 | 0.37 (0.34, 0.40) | |
| ICU | 1 | 0.37 (0.35, 0.39) | |
| Decade* | | | p < 0.001 |
| Overall | 40 | 0.37 (0.35, 0.39) | |
| 1990-2000 | 9 | 0.36 (0.32, 0.39) | |
| 2001-2010 | 21 | 0.36 (0.34, 0.39) | |
| 2011-Now | 10 | 0.40 (0.36, 0.44) | |
| Region* | | | p < 0.001 |
| Overall | 40 | 0.37 (0.35, 0.39) | |
| Northern | 12 | 0.35 (0.32, 0.39) | |
| Southern | 19 | 0.37 (0.34, 0.40) | |
| Eastern | 3 | 0.42 (0.33, 0.52) | |
| Western | 5 | 0.37 (0.32, 0.43) | |
| Europe | 1 | 0.38 (0.36, 0.40) | |
| Scenario* | | | p < 0.001 |
| Overall | 40 | 0.37 (0.35, 0.39) | |
| Retrospective | 23 | 0.39 (0.36, 0.41) | |
| Prospective | 17 | 0.35 (0.32, 0.38) | |
| Type* | | | p < 0.001 |
| Overall | 40 | 0.37 (0.35, 0.39) | |
| Hospital-based | 33 | 0.38 (0.36, 0.40) | |
| Laboratory-based | 7 | 0.33 (0.30, 0.35) | |

N=number.ES=Estimate. D30=Day 30. CI=confidence interval. Weights are from random-effect analysis. *=Studies reporting solely on ICU are excluded.

**Table 3. Crude mortality of candidaemia stratified by different explanatory variables**

| | Studies (N) | ES Crude Mortality (95% CI) | p-value for subgroup interaction |
|---|---|---|---|
| Setting | | | p < 0.001 |
| Overall | 31 | 0.46 (0.42, 0.49) | |
| Population-based | 2 | 0.40 (0.39, 0.41) | |
| Hospital-based | 11 | 0.43 (0.39, 0.47) | |
| ICU | 18 | 0.49 (0.43, 0.55) | |
| Decade* | | | p < 0.001 |
| Overall | 13 | 0.42 (0.39, 0.45) | |
| 1990-2000 | 4 | 0.41 (0.37, 0.45) | |
| 2001-2010 | 8 | 0.43 (0.39, 0.47) | |
| 2011-Now | 1 | 0.40 (35-0.46) | |
| Region* | | | p < 0.001 |
| Overall | 13 | 0.42 (0.39, 0.45) | |
| Northern | 1 | 0.35 (0.27, 0.44) | |
| Southern | 10 | 0.44 (0.41, 0.47) | |
| Eastern | - | - | |
| Western | 2 | 0.40 (0.39, 0.41) | |
| Scenario* | | | p < 0.001 |
| Overall | 13 | 0.42 (0.39, 0.45) | |
| Retrospective | 10 | 0.41 (0.38, 0.44) | |
| Prospective | 3 | 0.46 (0.37, 0.55) | |
| Type* | | | p < 0.001 |
| Overall | 13 | 0.42 (0.39, 0.45) | |
| Hospital-based | 12 | 0.42 (0.39, 0.46) | |
| Laboratory-based | 1 | 0.40 (0.39, 0.41) | |

N=number.ES=Estimate. D30=Day 30. CI=confidence interval. Weights are from random-effect analysis. *=Studies reporting solely on ICU are excluded.