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Laboratory surveillance of candidaemia in England, Wales and Northern Ireland: 2017

Health Protection Report
Volume 12 Number 34
21 September 2018

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These analyses are based on data relating to diagnoses of bloodstream infections caused by *Candida* spp. between 2009 and 2017 in England, Wales and Northern Ireland. Data for England were extracted on 15 August 2018 from Public Health England's (PHE) voluntary surveillance database, Second Generation Surveillance System (SGSS). Data for Wales and Northern Ireland were extracted separately (DataStore on 10 April 2018 and CoSurv on 03 July 2018 respectively).

The data presented here may differ from data in previous publications due to inclusion of late reports.

Rates of laboratory reported candidaemia were calculated using mid-year resident population estimates for the respective year and geography [1]. Geographical analyses were based on residential postcode of the patient if known (otherwise GP postcode if known, or failing that the postcode of the reporting laboratory) with cases in England being assigned to one of nine local PHE Centres (PHCs) formed from administrative local authority boundaries.

The report includes analyses on the trends, age and sex distribution and geographical distribution of cases of candidaemia in England, Wales and Northern Ireland. In addition, antimicrobial susceptibility three-year trends for England have been included in the report.

A web appendix is available featuring the findings of this report including only data submitted via SGSS from laboratories in England.

Key points

- the overall rate of candidaemia in England, Wales and Northern Ireland was 3.6 per 100,000 population in 2017, the same as that seen in 2016
- the reported incidence rate in 2017 was 3.5 per 100,000 population for England, 5.2 per 100,000 population for Wales and 5.1 per 100,000 population for Northern Ireland
- within England the rate of candidaemia ranged from 2.0 per 100,000 population in Yorkshire and the Humber to 4.3 per 100,000 population in the East of England
- the highest rates of candidaemia were seen in the elderly (≥75 years; males: 19 per 100,000 population and females: 7 per 100,000 population)
- the majority of candidaemia reports were identified to species level (87%)
- in 2017 the three most frequently identified *Candida* species from blood were *Candida albicans* (42%), *C. glabrata* (24%) and *C. parapsilosis* (10%)
- in England, there were 5 reports of candidaemia caused by *C. auris* in 2017, a reduction from 16 candidaemia reports in 2016
- *C. albicans* blood isolates reported as resistant to commonly tested antifungals ranged from <1% to amphotericin B and fluconcazole to 8% to flucytosine in England in 2017
- resistance to commonly tested antifungals in *C. glabrata* blood isolates reduced or stayed the same in England between 2016 and 2017.

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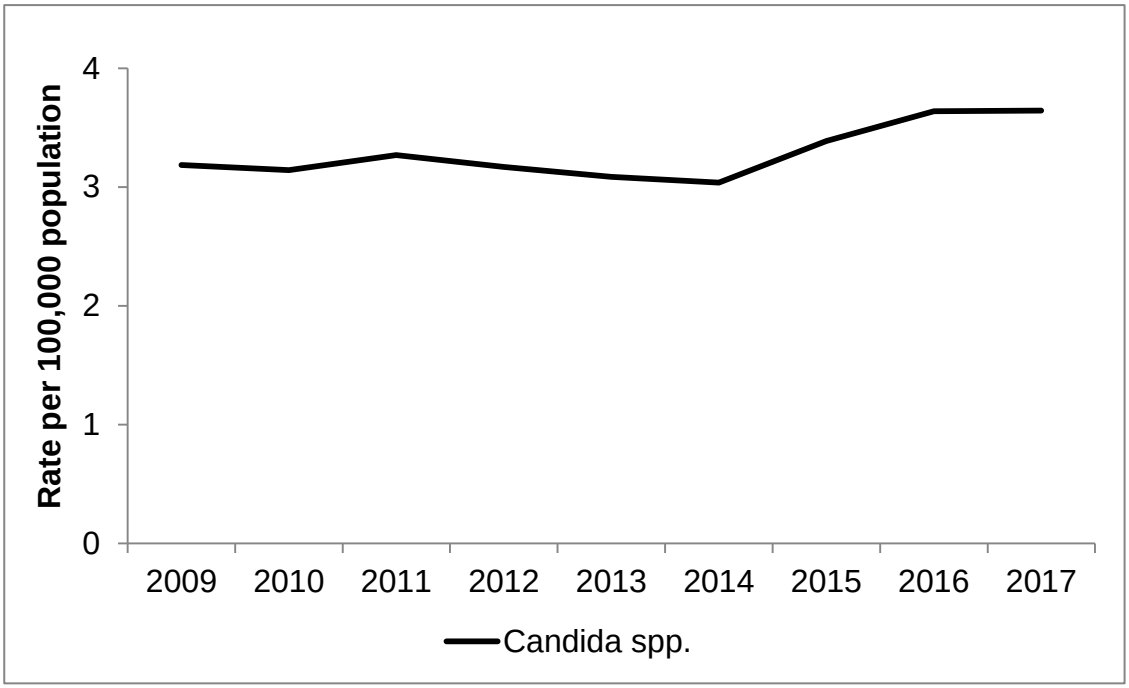
Trends

The rate of candidaemia in England, Wales and Northern Ireland (EW&NI) remained relatively stable between 2009 and 2014 with only slight fluctuations (between 3.0 to 3.3 per 100,000 population). By 2016 the rate had increased to 3.6 per 100,000 population, at which it remains in 2017 (Figure 1).

The observed increase in candidaemia rates between 2014 and 2017 may be in part due to more extensive laboratory reporting following the launch of the Second Generation Surveillance System (SGSS) in 2014; this has been credited with the improvement of lab-based voluntary surveillance. Other relevant laboratory changes included the widespread adoption of MALDI-TOF, changes to molecular identification methods in a number of laboratories making it easier for laboratories to identify and report Candida species, as well as increased awareness following publications such as British Society of Medical Mycology (BSMM) updated diagnostic recommendations [2].

Figure 1. Rates of fungaemia per 100,000 population (England, Wales and Northern Ireland) caused by *Candida* spp.: 2009 to 2017



The leading *Candida* species, *Candida albicans,* was the 18th most commonly identified organism in reported mono-microbial (bacterial and fungal) bloodstream infections (BSI) in 2017, comprising 0.6% of BSI in EW&NI [3]. Overall, *Candida* spp. were identified in 1.2% of mono-microbial BSI and 1.1% of poly-microbial BSI in 2017 [4].

Geographic distribution

The combined candidaemia rate for England, Wales and Northern Ireland was 3.6 per 100,000 population in 2017; an increase of 17% since 2013. However, an increase has not been noted in all countries across the 5-year period; for the rate increased by 24% in England,, whereas a 2% and a 21% decrease has been reported in Northern Ireland (5.2/100,000 population to 5.1/100,000) and Wales (6.6/100,000 to 5.2/100,000) respectively (Table 1).

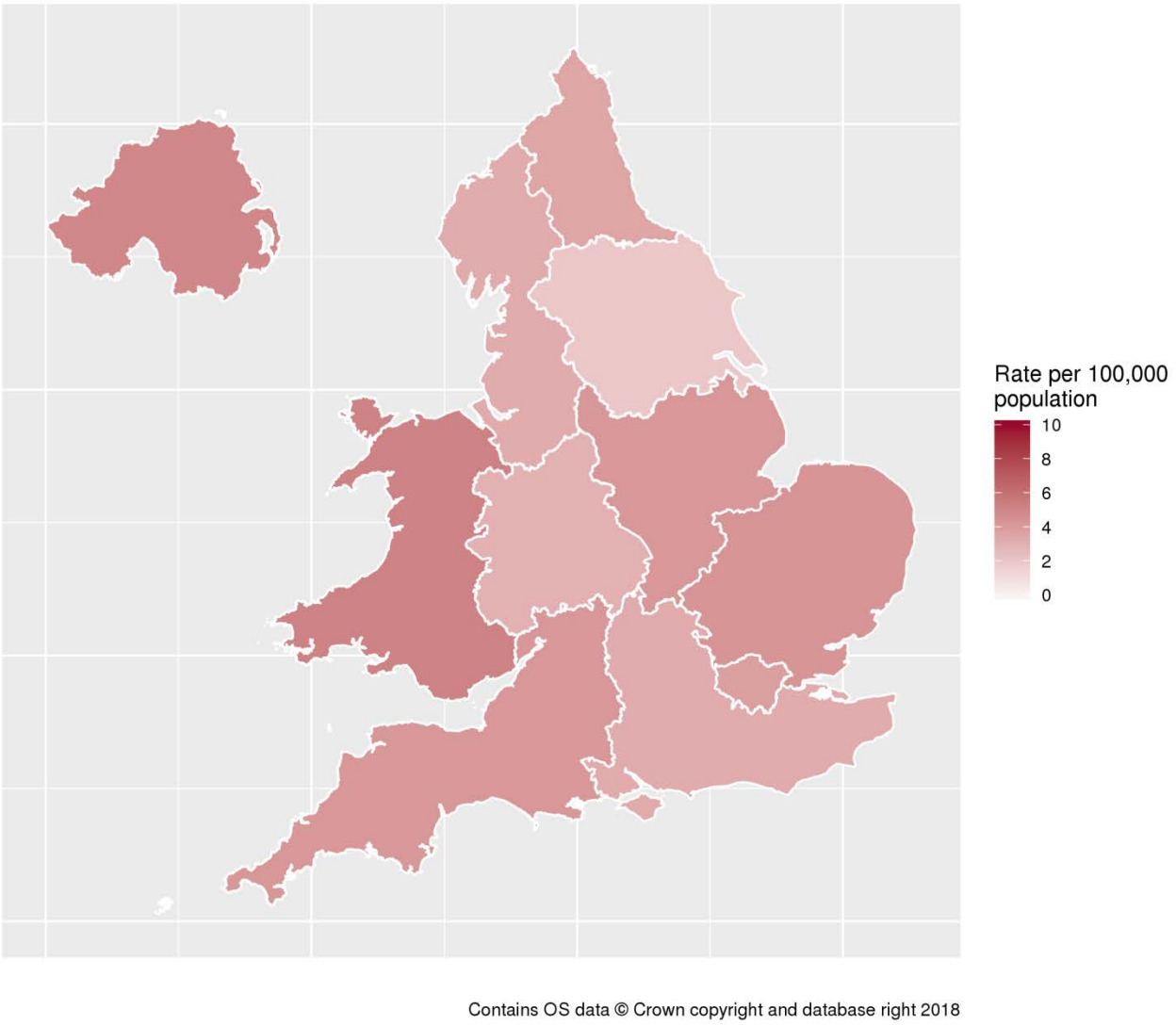
Table 1. Candidaemia per 100,000 population by region (England, Wales and Northern Ireland): 2013 to 2017

		Rate per 100,000 population				
Region	**PHE Centre**	**2013**	**2014**	**2015**	**2016**	**2017**
North of England	North East	2.3	2.1	2.2	2.7	3.6
	Yorkshire and Humber	1.9	2.1	2.0	1.9	2.0
	North West	3.7	3.2	3.3	3.9	3.3
Midlands and East of England	West Midlands	2.7	2.9	3.4	3.6	3.0
	East Midlands	2.3	2.0	3.3	3.8	4.2
	East of England	2.9	3.0	3.9	3.5	4.3
London	London	3.6	3.8	4.0	4.0	3.9
South of England	South West	2.3	2.7	3.4	3.7	4.2
	South East	2.8	2.7	2.8	3.4	3.3
England		2.8	2.8	3.2	3.5	3.5
Northern Ireland		5.2	5.0	7.2	5.0	5.1
Wales		6.6	5.3	5.1	4.2	5.2
England, Wales and Northern Ireland		**3.1**	**3.0**	**3.5**	**3.6**	**3.6**

Within England, areas of public health are consolidated into 9 PHCs. All PHCs had higher rates of candidaemia in 2017 compared to 2013, except for the North West which reported an overall11% decrease over the 5-year time period .

In 2017, the East of England PHC recorded the highest rate of candidaemia in England with 4.3/100,000 population, followed by the East Midlands and South West PHCs, both at 4.2 per 100,000 population. The lowest recorded rate in England in 2017 was in the Yorkshire and Humber PHC, at 2.0/100,000 (Figure 2).

Figure 2. Geographical distribution of candidaemia rates per 100,000 population (England, Wales and Northern Ireland): 2017

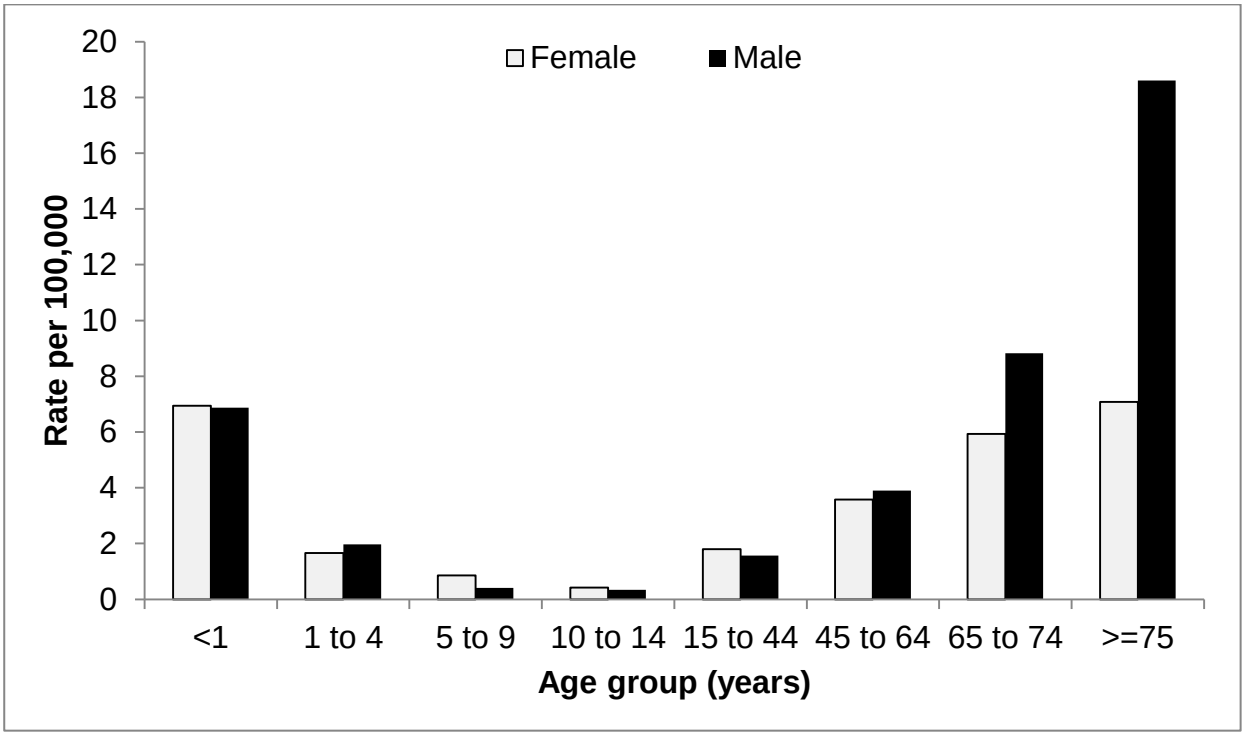


Age and sex distribution

In England, Wales and Northern Ireland in 2017, candidaemia continues to be observed in the youngest and oldest age groups. This age distribution is consistent with what has been seen in previous years [4]. Rates of candidaemia were highest in persons aged 75 years and over (males: 18.6 and females: 7.1 per 100,000 population), followed by those aged between 65 and 74 years (males: 8.8 and females: 6.0/100,000) and those under one year (males: 6.9 and females: 6.9/100,000) (Figure 3).

Variations in candidaemia rates by gender have been observed. For the majority of age groups, higher rates were reported in males than females. Rates in those aged 75 years and over presented the most noticeable difference.

Figure 3. Candidaemia rate by age and sex (England, Wales and Northern Ireland): 2017



Species distribution

In 2017, 87% of candidaemia reports were identified to species level in England, Wales and Northern Ireland, similar to the 88% reported in 2016 (Table 2). *Candida albicans* was the most frequently identified species within England (748; 41%), Wales (68; 42%) and Northern Ireland (53; 55%) in 2017, and has consistently been the most frequently identified species across the 5-year time period. The proportion of all candidaemia identified as *C. albicans* in England, Wales and Northern Ireland has decreased over the last 5 years, from 47% in 2013 to 42% in 2017.

The second most frequently reported species in England, Wales and Northern Ireland in 2017 was *Candida glabrata* (525; 24%), and the third most frequently identified species was *Candida parapsilosis* (229; 10%). Other notable species in 2017 were: *Candida tropicalis* (3% of candidaemias), *C. krusei* (2%), *C. dubliniensis* (2%) and *C. auris* (<1%).

Table 2. Reports of candidaemia by species (England, Wales and Northern Ireland): 2013-2017

	2013		2014		2015		2016		2017	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Candida spp.	**1829**	**100**	**1796**	**100**	**2065**	**100**	**2150**	**100**	**2211**	**100**
C. albicans	853	47	793	44	919	45	905	42	919	42
C. auris	0	0	0	0	3	<1	16	<1	5	<1
C. dubliniensis	13	<1	23	1	36	2	32	1	48	2
C. famata	7	<1	2	<1	2	<1	4	<1	3	<1
C. glabrata	465	25	460	26	473	23	539	25	525	24
C. guilliermondii	16	<1	7	<1	8	<1	17	<1	12	<1
C. kefyr	2	<1	8	<1	9	<1	5	<1	2	<1
C. krusei	21	1	38	2	26	1	21	<1	37	2
C. lusitaniae	21	1	28	2	32	2	31	1	28	1
C. parapsilosis	192	10	193	11	205	10	200	9	229	10
C. tropicalis	67	4	48	3	77	4	67	3	71	3
Candida spp., other named	40	2	40	2	33	2	45	2	40	2
Candida spp., sp. not recorded	132	7	156	9	242	12	268	12	292	13

† data presented are for routine laboratory reports only and may not match those presented in other sources

* including *C. blankii, C. catenulate, C. ciferrii, C. fabianii, C. fermentati, C. haemulonii, C. inconspicua, C. lipolytica, C. magnolia, C. metapsilosis, C. navariensis, C. orthopsilosis, C. pararugosa, C. pelliculosa, C. peltata, C. utilis, C. zeylandoides*

Antimicrobial resistance: England

Antimicrobial resistance data were only available for England. Susceptibility results for the antifungal agents amphotericin B, caspofungin, fluconazole, flucytosine and voriconazole were provided by SGSS AMR for reported candidaemia. Between 30% (flucytosine) and 61% (fluconazole) of candidaemia isolates were tested for susceptibility to the listed antifungal agents in 2017.

The proportion of candidaemia (caused by any species) found to be resistant has increased between 2015 and 2017 for each of the antifungal agents except fluconazole which has decreased slightly (8% to 7%; table 3a). Overall 67% of *C. albicans* candidaemia isolates were tested for fluconazole susceptibility, 59% for voriconazole susceptibility and 58% for amphotericin susceptibility in 2017; of those tested, <1% were resistant to fluconazole or amphotericin, and 2% were resistant to voriconazole (table 3b).

Table 3a. Antimicrobial susceptibility* for candidaemia isolates (England): 2015 to 2017

Antifungal agent	2015			2016			2017		
	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
Amphotericin B	97	<1	2	98	<1	1	99	<1	1
Caspofungin	98	<1	<1	95	1	4	94	2	4
Fluconazole	86	6	8	81	9	9	84	9	7
Flucytosine	94	1	5	93	1	6	90	<1	9
Voriconazole	94	2	4	91	2	6	89	6	6

* S = susceptible; I = intermediate (reduced susceptibility); R = resistant

Table 3b. Antimicrobial susceptibility* for *C. albicans* candidaemia (England): 2015 to 2017

Antifungal agent	2015			2016			2017		
	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
Amphotericin B	98	<1	1	99	<1	<1	99	<1	<1
Caspofungin	100	<1	0	97	0	3	96	0	4
Fluconazole	99	<1	<1	98	1	<1	98	1	<1
Flucytosine	95	0	5	94	0	6	92	0	8
Voriconazole	99	0	1	98	0	2	97	1	2

* S = susceptible; I = intermediate (reduced susceptibility); R = resistant

C. glabrata susceptibility test results to amphotericin B were reported for 73% of isolates in 2017, with resistance being reported in 2% (table 3c). In reported *C. glabrata* isolates over the last three years, resistance to voriconazole and to fluconazole have fluctuated, between 13% - 17% for voriconazole, and 12% - 20% for fluconazole (table 3c). Interpreting trends in *C. glabrata* resistance is more difficult due to revisions in standard breakpoints used by laboratories for antifungal susceptibility testing. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology does not currently have a voriconazole breakpoint because of insufficient evidence that the antifungal should be used for treatment of *C. glabrata* [5].

The EUCAST and revised CLSI MIC breakpoints for testing of fluconazole susceptibility for *C. glabrata* differ in interpretation. EUCAST breakpoints allow for a high level of reports to be classified as reduced susceptibility ('intermediates'), whereas CLSI have high levels of 'susceptible-dose-dependent'. The latter is a combination of what was previously recorded as 'intermediate' with susceptible results, classifying the isolate as susceptible alongside advice to treat with high-dose fluconazole [6,7].

Table 3c. Antimicrobial susceptibility* for *C. glabrata* candidaemia (England): 2015 to 2017

Antifungal agent	2015			2016			2017		
	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
Amphotericin B	96	1	3	99	<1	<1	98	0	2
Caspofungin	98	<1	1	94	3	3	94	3	3
Fluconazole	61	21	18	51	28	20	61	28	12
Flucytosine	99	<1	0	95	0	5	95	<1	5
Voriconazole	83	4	13	76	7	17	72	15	13

* S = susceptible; I = intermediate (reduced susceptibility); R = resistant

Of *C. parapsilosis* isolate reports, the most frequently tested antifungal susceptibility was to fluconazole (76%), and the lowest susceptibility testing was for flucytosine (37%). Resistance levels have remained relatively stable, with the exception of resistance to flucytosine which has seen an increase from 2% to 8% over the last two years (2015 to 2017) (table 3d) although neither EUCAST nor CLSI currently provide breakpoint

interpretations for this drug. Previous flucytosine breakpoints were established with little clinical data and are now considered to be incorrect [8].

Table 3d. Antimicrobial susceptibility* for *C. parapsilosis* candidaemia (England): 2015 to 2017

Antifungal agent	2015			2016			2017		
	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
Amphotericin B	99	0	<1	99	<1	<1	99	0	1
Caspofungin	97	2	1	96	<1	3	92	3	5
Fluconazole	98	0	2	99	<1	<1	96	2	2
Flucytosine	98	0	2	97	0	3	92	0	8
Voriconazole	98	2	0	99	0	<1	99	0	<1

* S = susceptible; I = intermediate (reduced susceptibility); R = resistant

In interpreting these results it should be remembered that the presented antifungal resistance prevalence levels may be biased by low levels of susceptibility testing and selective testing of patients failing to respond to therapy, therefore over-estimating the true prevalence of resistance. The British and European guidelines on fungal diagnostics and management [9,10] may have assisted in raising awareness and improving antifungal susceptibility test reporting in fungal isolates from blood specimens. However, further improvements in levels of antifungal testing and reporting are needed to better understand and interpret trends in antifungal resistance with a view to informing antifungal stewardship activities and improving outcomes for patients with invasive *Candida* infections.

Microbiology Services

In 2017, 13% of reported candidaemia isolates were not fully identified; this is a slight increase on the 12% reported in 2016. Identification of isolates to species level would improve the monitoring of trends for emerging species, as well as assisting with appropriate treatment.

For advice on treatment of fungal infections or for reference mycology services including species identification and confirmation of susceptibility testing results, laboratories can contact or submit isolates to the PHE Mycology Reference Laboratory in Bristol [10].

Acknowledgements

These reports would not be possible without the weekly contributions from microbiology colleagues in laboratories across England, Wales, and Northern Ireland, without whom there would be no surveillance data. The support from colleagues within Public Health England, the PHE Mycology Reference Laboratory [11], Public Health Wales and HSC Public Health Agency (Norther Ireland) in particular, is valued in the preparation of the report. Feedback and specific queries about this report are welcome and can be sent to hcai.amrdepartment@phe.gov.uk.

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Published: September 2018
PHE publications
gateway number: 2018463

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