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Hospital-treated serious and invasive aspergillosis and candidiasis infections during the COVID-19 pandemic: retrospective analysis of hospital episode statistics data from England

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Hospital-treated serious and invasive aspergillosis and candidiasis infections during the COVID-19 pandemic: retrospective analysis of hospital episode statistics data from England

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ABSTRACT

Objectives To investigate the impact of COVID-19 on the incidence and burden of hospital-treated *Aspergillus* and *Candida* infections in England.

Design Retrospective study using Hospital Episodes Statistics (HES) data to estimate the burden of serious and invasive fungal infections (SIFIs) in all patients admitted in England during March 2018–February 2020 (pre-COVID-19) and during March 2020–October 2021 (the COVID-19 period).

Setting Hospitals in England.

Population All patients with codes corresponding to serious and invasive aspergillosis and candidiasis in any diagnosis position during their admission pre-COVID-19 and during the COVID-19 period.

Outcome measures Age, spells, patient counts, mean length of stay, admission to critical care unit (CCU), length of stay in CCU, 30-day readmissions, failed discharges (readmission within 7 days), and comorbidities.

Results During the COVID-19 period, hospitalisation spells with an invasive candidiasis code fell by 3.2% and spells with an aspergillosis code by 24.8%. Mean length of stay increased during the pandemic for patients with aspergillosis, candidiasis and aspergillosis plus COVID-19 but decreased for patients with candidiasis plus COVID-19. Of patients with a previous diagnosis of COVID-19, 52.5% with aspergillosis and 60.0% with candidiasis were treated in CCU compared with 13.2% and 37.1%, respectively, without a previous COVID-19 diagnosis. The percentage of 30-day readmissions and failed discharges for patients with SIFI was higher for those with COVID-19 than for those without.

Conclusions The incidence and burden of aspergillosis and candidiasis have been affected by COVID-19. Aspergillosis incidence fell among hospitalised patients during the pandemic, while candidiasis continued to fluctuate in patterns similar to pre-COVID-19. A higher burden for patients with SIFI was observed, whether or not they also had a diagnosis of COVID-19. Our findings highlight extra considerations and burden on management of serious SIFI as a result of the COVID-19 pandemic.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This analysis used recent real-world data from the HES dataset, which includes all patients using secondary care services in England.

- The data are coded based on information documented within medical records and are therefore dependent on the quality of the coding. Accuracy of diagnosis of fungal infections is recognised as a clinical and coding issue.

- The codes used were carefully considered to minimise inclusion of any non-severe fungal infections, such as topical *Candida* infections; the results are therefore likely to underreport candidal infections.

- Data on final destination and all mortality are not available from HES, which can impact on understanding of patient outcomes.

Key words: aspergillosis, candidiasis, COVID-19, serious invasive fungal infection

INTRODUCTION

In recent years, global health awareness around infectious diseases has increased. However, the profile of fungal infections has lagged behind that of bacterial and viral diseases, despite serious and invasive fungal infections (SIFIs) often resulting in poorer patient outcomes, more complexity, and increased burden on healthcare systems.

Invasive fungal infections

Invasive aspergillosis

Aspergillus spp. is a ubiquitous environmental mould that grows on organic matter.[1-3] It produces aerosolised conidia, which can be inhaled by humans, potentially leading to colonisation and infection, primarily in immunocompromised individuals.[1] *Aspergillus* causes a spectrum of pulmonary disorders and clinical manifestations, depending on the competence of the host's immune response, including local colonisation of the respiratory tract, hypersensitivity reactions, chronic infections, and acutely invasive disease.[1-4] Aspergillosis is a significant cause of morbidity and mortality in the immunocompromised population.[4] Invasive aspergillosis (IA) is characterised by invasion of pulmonary vasculature by the *Aspergillus* hyphae, which can progress to angioinvasive pulmonary aspergillosis.[1 2] Both are serious conditions that can complicate the management of critically ill patients, with up to 95% mortality if not treated.[1 4]

Invasive candidiasis

Candida spp. is a widespread genus of commensal yeasts that can be detected on the mucosal surfaces (skin and gut) of healthy humans and in the hospital environment.[1 5] They are typically non-pathogenic in immunocompetent people, but at least 15 *Candida* species can cause human disease.[1 5-7]

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As with *Aspergillus*, *Candida* spp. are implicated in a broad spectrum of infections, with candidiasis an umbrella term covering cutaneous, mucosal and deep-seated organ infections.[7] Invasive disease results from a combination of increased or abnormal colonisation, disruptions in the cutaneous and gastrointestinal barriers, and local or general defects in host defences, including weakened immunity.[7] More than 95% of invasive disease is caused by six species, most commonly *C. albicans* and increasingly *C. auris and C. glabrata*.[5-7] Invasive candidiasis can range from minimally symptomatic candidaemia to deep-seated infection with or without candidaemia, including fulminant sepsis, which has >70% mortality.[7] Surveillance data from the UK in 2020 show the highest rate of candidaemia observed in the past 10 years at 3.5 per 100,000 population.[8]

Impact of COVID-19

The coronavirus disease 2019 (COVID-19) pandemic has presented many challenges to healthcare systems, including the emergence of associated and secondary infections, especially in severe cases treated in the intensive care unit.[1] COVID-19 infection leads to conditions favourable for opportunistic fungal pathogens, such as hypoxia, immunosuppression, host iron depletion, hyperglycaemia secondary to diabetes, and prolonged hospitalisation, even in previously immunocompetent people.[9] The prevalence of COVID-19-associated pulmonary aspergillosis (CAPA) varies. A national French study reported rates of 15% in mechanically ventilated patients and higher mortality in patients with CAPA than in those without (61.8% versus 32.1%).[10]

The risk of candidiasis may also significantly increase in patients with severe COVID-19 due to treatment with broad-spectrum antibacterials, parenteral nutrition, invasive examinations, prolonged neutropenia and other immune impairment.[11] COVID-19-associated candidiasis (CAC) has been reported in 0.7–23.5% of patients with severe infection and with mortality of 83.3%.[9 10]

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Any variation in incidence of fungal infections could lead to a significant change in the burden on healthcare systems.[12] Even before the COVID-19 pandemic, invasive fungal disease was thought to be increasing in the United Kingdom (UK) due to a variety of factors, including increased survival time from previously fatal illnesses and an increase in immunosuppression from the treatment of other diseases.[12] Comorbid COVID-19 and fungal infections will have further added to the burden on healthcare systems and critical care services during the pandemic.

Understanding of the overall burden of invasive fungal disease in the UK is limited, as active surveillance is in place only for candidaemia, and even then the burden is likely to be underestimated as reporting of candidaemia by laboratories has been voluntary.[12] We therefore investigated the impact of COVID-19 on the reported incidence and disease burden of serious and invasive *Aspergillus* and *Candida* infections in England.

PATIENTS AND METHODS

We used Hospital Episodes Statistics (HES) data to estimate the burden of serious and invasive aspergillosis and candidiasis infections in all patients admitted in England pre-COVID-19 (March 2018–February 2020) and during March 2020–October 2021 (the COVID-19 period). We initially identified patients with all diagnosis codes corresponding to aspergillosis and candidiasis in any diagnosis position during their admission (i.e. as primary diagnosis or secondary diagnosis) pre-COVID-19 and during the COVID-19 period. The codes for candidiasis initially included B37.8 (candidiasis of other sites – candida; cheilitis and enteritis) and B37.9 (candidiasis, unspecified – thrush not otherwise specified); however, these were later removed from the analysis so as to minimise inclusion of any non-severe fungal infections, such as topical *Candida* infections. Details on coding used are given in Appendix A and Supplementary Tables A and B in the Supplementary materials. Throughout

the rest of this paper, 'candidiasis' refers to serious and invasive candidiasis and 'aspergillosis' refers to invasive aspergillosis. The analysis is based on the date of discharge – i.e. the month in which the patient was discharged from hospital is the month in which the admission is counted. Only patients registered at a GP practice in England at the time of admission have been included in the study.

Specific characteristics of interest included age, spells, patient counts, mean length of stay (MLOS), admission to critical care unit (CCU), length of stay in CCU, 30-day readmissions, failed discharges (readmission within 7 days), and comorbidities. Mean length of stay was defined as total bed-days in a spell divided by the number of spells with a SIFI diagnosis. Thirty-day readmissions were defined as a non-elective admission with a diagnosis of SIFI that was within 30 days of a discharge for a spell where the patient also had SIFI. Failed discharges were defined as non-elective admissions with a diagnosis of SIFI within 7 days of a discharge for a spell where the patient also had SIFI. We identified the top 15 most common comorbidities in SIFI spells during the pre-COVID-19 period and the top 15 most common comorbidities in SIFI spells during the COVID-19 period.

As required by NHS Digital when using HES data, values for patients, spells, patients in critical care, spells in critical care, critical care days, 30-day readmissions and count of failed discharges above 7 were rounded to the nearest 5; totals therefore may not sum across columns/rows. Values for patients, spells, patients in critical care, spells in critical care, critical care days, 30-day readmissions and count of failed discharges between 1 and 7 (inclusive) were suppressed for data presented at an aggregated level. MLOS were suppressed where spells were suppressed.

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RESULTS

Population

During the period before COVID-19 (March 2018–February 2020), 6,255 patients had aspergillosis and 3,445 had candidiasis. Of the patients with SIFI during the COVID-19 period (March 2020 to October 2021), 4,350 with aspergillosis and 2,385 with candidiasis had no previous diagnosis of COVID-19, while 600 with either infection had had a diagnosis of COVID-19.

Hospitalisation spells with a candidiasis code fell by 3.2% over the entire COVID-19 period compared with before COVID-19 and spells with an aspergillosis code fell by 24.8%. Patient counts are shown in Figure 1.

Distribution of aspergillosis across patients younger than 65 and older than 65 years remained similar prior to and during the pandemic, with comparable decreases at the beginning of the pandemic for the two age groups and a slow recovery to pre-COVID-19 baseline levels (Supplementary Figure A in Supplementary materials). The incidence of candidiasis in both age groups was broadly similar throughout the study period. However, although a trend for higher incidence of candidiasis was observed among patients older than 65 years compared with those younger than 65 years before the pandemic, the incidence in the younger age group was higher than in the older age group at points during the pandemic (see Supplementary Figure A in Supplementary materials).

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Mean length of stay

Before the COVID-19 pandemic, annual average MLOS was 9.6 days and 34.8 days, respectively, for patients who received an aspergillosis or candidiasis code (Figure 2; Supplementary Table B in Supplementary materials). During the COVID-19 pandemic, this increased to 13.4 days and 42.4 days, respectively. For patients with SIFI plus COVID-19 infection, MLOS increased to 25.9 days for aspergillosis but decreased to 34.2 days for candidiasis. Mean length of stay for a patient with COVID-19 alone was 11.9 days.

Admission to critical care and length of stay

Of the patients with a previous diagnosis of COVID-19, 52.5% with aspergillosis and 60.0% with candidiasis were treated in CCU. In comparison, of the patients with no previous diagnosis of COVID-19, 13.2% with aspergillosis and 37.1% with candidiasis were treated in CCU.

Mean length of stay in CCU for patients without COVID-19 was 18.1 days for patients with aspergillosis and 22 days for those with candidiasis; this increased to 26 days and 22.4 days, respectively, for patients who also had COVID-19 (Figure 3).

The percentage of 30-day readmissions for patients with SIFI was higher for those with COVID-19 than for those without COVID-19: 12.6% *versus* 8.6% for patients with aspergillosis and 3.7% *versus* 2.5% for those with candidiasis (Figure 4). A similar trend was seen for rates of failed discharge for those with COVID-19 and those without COVID-19: 7% *versus* 4%, respectively, for patients with aspergillosis and 3% *versus* 2%, respectively, for patients with candidiasis (Figure 4).

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Comorbidities

For patients with aspergillosis, four codes not in the top 15 comorbidities prior to COVID-19 were ranked in the top 15 during the COVID-19 period: special screening examination for other viral diseases, other physical therapy, personal history of long-term (current) use of anticoagulants, and acute renal failure, unspecified (Table 1).

For patients with candidiasis, five codes not in the top 15 comorbidities prior to COVID-19 were ranked in the top 15 during the COVID-19 period: COVID-19, virus identified; other viral pneumonia; coronavirus as the cause of diseases classified to other chapters; respiratory failure, unspecified – Type I (hypoxic); and special screening examination for other viral diseases (Table 1).

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Table 1 Top 15 most common comorbidities (ordered by rank during the COVID-19 period) in hospital spells of patients with aspergillosis or candidiasis before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021).

Rank during COVID-19 period	Aspergillosis				Candidiasis			
	Rank before COVID-19	ICD-10 code Diagnosis description	Occurrence (%)		Rank before COVID-19	ICD-10 code Diagnosis description	Occurrence (%)	
			Before COVID-19	During COVID-19			Before COVID-19	During COVID-19
1	1	J99.8 Respiratory disorders in other diseases classified elsewhere	52.6	51.1	2	N17.9 Acute renal failure, unspecified	24.1	34.0
2	2	J47.X Bronchiectasis	32.0	30.8	1	I10.X Essential (primary) hypertension	33.7	32.0
3	3	I10.X Essential (primary) hypertension	21.8	25.1	4	J17.2 Pneumonia in mycoses	18.1	20.6
4	5	Z86.4 Personal history of psychoactive substance abuse	19.7	19.8	–	U07.1 COVID-19, virus identified	Not ranked in top 15	20.0
5	4	J45.9 Asthma, unspecified	20.2	19.7	5	J90.X Pleural effusion, not elsewhere classified	14.5	18.7

6	–	Z11.5 Special screening examination for other viral diseases	Not ranked in top 15	16.1		–	J12.8 Other viral pneumonia	Not ranked in top 15	18.1
7	–	Z50.1 Other physical therapy	Not ranked in top 15	12.3		–	B97.2 Coronavirus as the cause of diseases classified to other chapters	Not ranked in top 15	17.8
8	9	Z86.7 Personal history of diseases of the circulatory system	10.3	12.2		13	Z50.1 Other physical therapy	11.6	17.7
9	8	Z86.1 Personal history of infectious and parasitic diseases	11.0	12.1		3	J99.8 Respiratory disorders in other diseases classified elsewhere	19.0	17.4
10	6	J44.0 COPD with acute lower respiratory infection	11.9	11.9		6*	E11.9 T2DM – Without complications	13.9	17.0
11	7	J44.9 COPD, unspecified	11.7	11.8		15	Y95.X Nosocomial condition	10.7	14.5
12	11	J43.9 Emphysema, unspecified	9.9	11.2		10	I48.9 Atrial fibrillation and atrial flutter, unspecified	12.6	13.4

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13	10	E11.9 T2DM – without complications	10.0	11.0		–	J969.0 Respiratory failure, unspecified – Type I (hypoxic)	Not ranked in top 15	13.0
14	–	Z92.1 Personal history of long-term (current) use of anticoagulants	Not ranked in top 15	10.2		–	Z11.5 Special screening examination for other viral diseases	Not ranked in top 15	13.0
15	–	N17.9 Acute renal failure, unspecified	Not ranked in top 15	9.7		11	J18.1 Lobar pneumonia, unspecified	12.6	12.9

COPD, chronic obstructive pulmonary disease; ICD-10, International Classification of Diseases and Related Health Problems 10th revision; T2DM, type 2 diabetes mellitus.

*Formerly coded as 'emergency use of U07.1', updated to 'COVID-19, virus identified'.

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DISCUSSION

Overall hospital admissions decreased at the start of the COVID-19 pandemic. This effect was mirrored in the number of patients admitted with an aspergillosis diagnosis, with pre-COVID-19 pandemic levels of aspergillosis coding only returning after 12 months. However, this did not apply to candidiasis, where a slight decrease was observed but not to the extent observed with aspergillosis.

The pattern of incidence for patients with aspergillosis who were younger or older than 65 years was broadly similar; however, prolonged divergence was seen for patients with candidiasis during the first wave of the pandemic. Of note, the incidence of candidiasis was higher in those younger than 65 years compared with those older than 65 years at some points during the pandemic, generally corresponding with national lockdowns, which is a reversal of the typical trend prior to the pandemic. The reason for this is uncertain, but it may relate to the fact that older patients were at much higher risk of mortality from COVID-19,[13] which may have impacted the prevalence of secondary infections such as candidiasis. Surprisingly, despite this divergence between the age groups, with fewer over 65s developing serious and invasive candidiasis than under 65s, the overall number of patients developing candidiasis during the pandemic actually increased compared to pre-pandemic (+3.8%).

Attempting to establish the burden of SIFI during the pandemic is complex, but there is clear evidence of an increase in the number of days patient spent in hospital, the care required, and the complexities experienced. This includes increased renal disorders such as acute kidney injury (AKI), which is one of the most frequent organ complications in patients with severe COVID-19,[14] with studies indicating >30% of patients hospitalised with COVID-19 develop kidney injury and >50% of patients in CCU with kidney injury may require dialysis.[15] Accordingly, our analysis saw acute renal failure appear in the top 15 comorbidities for patients with aspergillosis and increase from rank 2 to rank 1 for those with candidiasis.

Coagulopathies have been associated with COVID-19 in patients with aspergillosis,[16] and personal history of long-term (current) anticoagulants emerged in the top 15 comorbidities in patients with aspergillosis during the COVID-19 period in our analysis. Further investigation to identify any correlation between preidentified comorbidities and subsequent development of serious and invasive aspergillosis and candidiasis during the COVID-19 pandemic may provide further insight.

During the pandemic, patients with aspergillosis or candidiasis who also had a COVID-19 diagnosis code, with some exceptions, showed increased disease burden and worse outcomes compared with patients with aspergillosis or candidiasis without a COVID-19 diagnosis code. This included increases in admission rates to CCU, CCU MLOS, 30-day readmissions, and failed discharges. Patients with codes for aspergillosis plus COVID-19 also showed increases in overall MLOS and MLOS in CCU compared with patients with COVID-19 alone. Notably, patients with COVID-19 and candidiasis co-infection had shorter lengths of stay than those with candidiasis alone (see Figure 2).

During the pandemic, increased use of codes for viral screening; coronavirus; COVID-19, virus identified; and respiratory comorbidities would be expected (see Table 1). The appearance of other physical therapy, renal failure (a known complication of COVID-19), and increased use of oral anticoagulants for patients with aspergillosis is unsurprising, as renal tropism and coagulopathies are known to develop in patients with COVID-19, as well as a requirement for rehabilitation;[14] [15] [17-25] however, it is notable that these appeared in the top 15 codes for aspergillosis but not for candidiasis.

Strengths and limitations

This analysis used recent real-world data from the HES dataset, which includes all patients using secondary care services in England.

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The data were coded based on information documented within the medical records and are therefore dependent on the quality of the coding, including the accuracy of diagnosis of fungal infections. Excluding codes B37.8 (candidiasis of other sites – candida cheilitis and enteritis) and B37.9 (candidiasis, unspecified – thrush not otherwise specified) to minimise inclusion of any non-severe fungal infections, such as topical *Candida* infections, means that the results presented are likely to underreport infections, with some cases of invasive candidiasis and candidaemia missed. Data on final destination and all mortality are not available from HES, which can have an impact on understanding of patient outcomes. Patients not registered at a GP practice in England at the time of admission could not be included and so the incidence may be underestimated.

Conclusions

The incidence and burden of aspergillosis and candidiasis have both been affected by COVID-19. While aspergillosis incidence fell among hospitalised patients during the pandemic, candidiasis continued to fluctuate in patterns similar to pre-COVID. However, a higher burden for patients with SIFI was observed, irrespective of whether or not they also had a diagnosis of COVID-19. Compared with patients with SIFI or COVID-19 alone, patients with both codes had an increased incidence of CCU admissions and longer CCU MLOS, as well as higher 30-day readmission and failed discharge rates. The amplified care needs of patients with both codes suggests complexity in care that increased the disease burden of SIFIs on the English healthcare system. Our findings highlight the extra considerations and burden on management of serious SIFI as a result of the COVID-19 pandemic, not only in England but countries globally. Further work is required to fully understand the impact of the COVID-19 on hospital-treated SIFIs.

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Contributors

All authors (bar JSL) contributed to the idea of the study and protocol development. ST performed the data analysis. JKS and JSL drafted the manuscript. and reviewed all drafts. All authors reviewed the manuscript and approved the final version for submission. GK is guarantor for the study.

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Competing interests

The study was funded by Pfizer Inc. and conducted by Wilmington Healthcare. AHS is an employee of Pfizer Inc and holds stock or stock options in Pfizer Inc. MS and GK are employees of Pfizer Ltd and hold stock or stock options in Pfizer Ltd. JS and ST are employees of Wilmington Healthcare. Jemma S Lough received funding provided by Pfizer Inc through Wilmington Healthcare for medical writing.

Data availability statement

Data are available on reasonable request to the corresponding author.

Patient and public involvement

Patients and/or the public were not involved in this study.

Patient consent for publication

Not applicable.

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FIGURE LEGENDS

Figure 1 Monthly trends in aspergillosis (a) and candidiasis (b) patient count before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021).

Figure 2 Mean length of stay (MLOS) for spells with SIFI and/or COVID-19 spells before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021).

Figure 3 Patients admitted to critical care (a) and mean length of stay in critical care (b) for spells with aspergillosis and candidiasis during the COVID-19 period (March 2020 to October 2021).

Figure 4 Readmissions within 30 days and failed discharges for patients with aspergillosis and candidiasis during the COVID-19 period (March 2020 to October 2021).

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Caption : Figure 1a Monthly trends in aspergillosis (a) and candidiasis (b) patient count before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021).
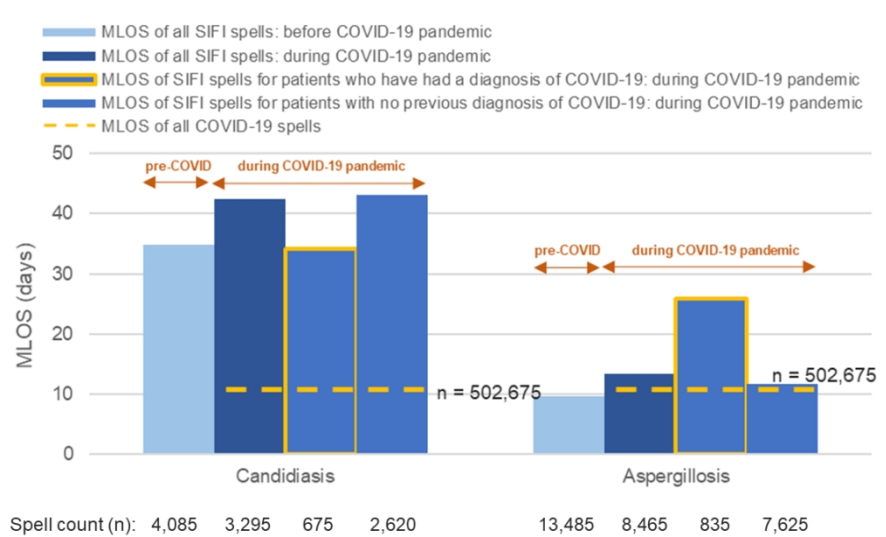
855x481mm (38 x 38 DPI)

Figure 2 Mean length of stay (MLOS) for spells with SIFI and/or COVID-19 spells before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021).
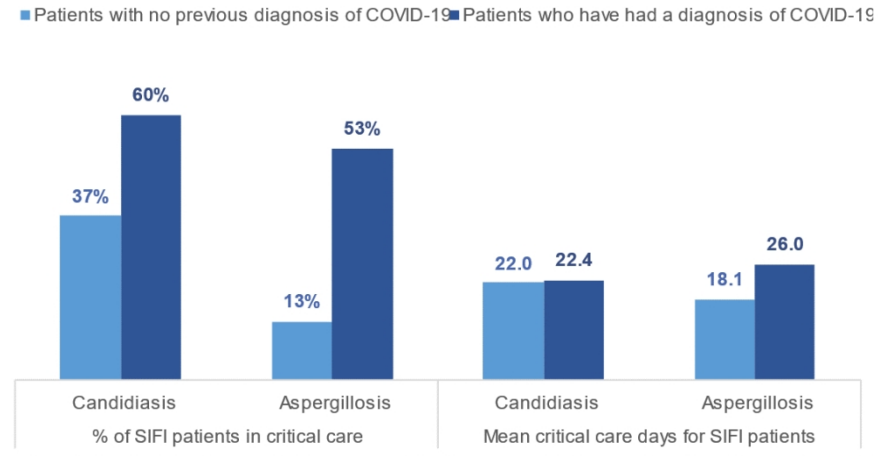
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Figure 3 Patients admitted to critical care (a) and mean length of stay in critical care (b) for spells with aspergillosis and candidiasis during the COVID-19 period (March 2020 to October 2021).
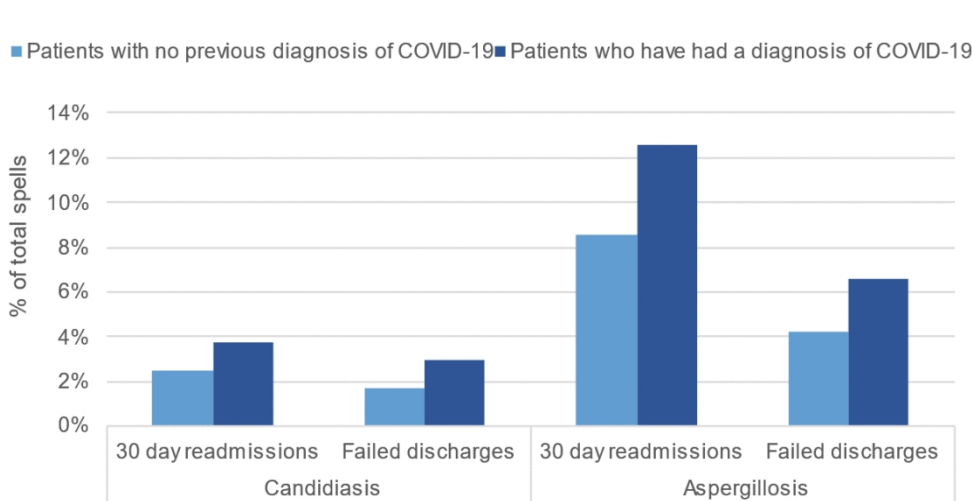
855x481mm (38 x 38 DPI)

Figure 4 Readmissions within 30 days and failed discharges for patients with aspergillosis and candidiasis during the COVID-19 period (March 2020 to October 2021).

855x481mm (38 x 38 DPI)

SUPPLEMENTARY MATERIALS

Appendix A: Study methods

Patient-level secondary care records were extracted from the Hospital Episode Statistics (HES) database for all patients diagnosed with either aspergillosis or candidiasis over the period March 2018 to October 2021; the diagnosis could be either a primary diagnosis or secondary diagnosis.

In addition, during the COVID-19 period (March 2020–October 2021) patients with a previous diagnosis of COVID-19 were identified by analysing all previous secondary care records for patients admitted to hospital with a diagnosis of aspergillosis or candidiasis (a patient is deemed to have had a diagnosis of COVID-19 if it occurs within the same spell as their aspergillosis or candidiasis diagnosis or in a previous spell).

These records were subsequently aggregated in order to produce an analysis around the impact of COVID-19 on serious and invasive fungal infections in England. Patient data from the pre-COVID-19 period has been compared to patient data in the COVID-19 period; and within the COVID-19 period itself, the data of patients with a previous diagnosis of COVID-19 has been compared to those with no previous diagnosis of COVID-19.

For the purposes of the study, the pre-COVID-19 period has been defined as March 2018–February 2020 and the COVID-19 period as March 2020–October 2021.

In order to identify patients with a relevant diagnosis of aspergillosis or candidiasis, the following ICD-10 codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision were used:

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Diagnosis group	ICD-10 code	Diagnosis description
Aspergillosis	B44.0	Invasive pulmonary aspergillosis
	B44.1	Other pulmonary aspergillosis
	B44.7	Disseminated aspergillosis
	B44.8	Other forms of aspergillosis
	B44.9	Aspergillosis, unspecified
Candidiasis	B37.1	Pulmonary candidiasis
	B37.5	Candidal meningitis
	B37.6	Candidal endocarditis
	B37.7	Candidal sepsis

In order to identify patients with a relevant diagnosis of COVID-19, the following ICD-10 codes

from the International Statistical Classification of Diseases and Related Health Problems, 10th

Revision were used:

ICD-10 code	Diagnosis description
U07.1	COVID-19, virus identified
U07.2	COVID-19, virus not identified

Data access

Secondary care data is taken from the English Hospital Episode Statistics (HES) database

produced by NHS Digital, the new trading name for the Health and Social Care Information

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Appendix B: HES disclaimer

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2. HES Data must be used within the licencing restrictions set by NHS Digital, which are summarised below. Wilmington Healthcare accept no responsibility for the inappropriate use of HES data by your organisation.

   2.1. One of the basic principles for the release and use of HES data is to protect the privacy and confidentiality of individuals. All users of HES data must consider the risk of identifying individuals in their analyses prior to publication/release.

      2.1.1. Data should always be released at a high enough level of aggregation to prevent others being able to 'recognise' a particular individual. To protect the privacy and confidentiality of individuals, Wilmington Healthcare have applied suppression to the HES data - '*' or '-1' represents a figure between 1 and 7. All other potentially identifiable figures (e.g. patient numbers, spell counts) have been rounded to the nearest 5.

      2.1.2. On no account should an attempt be made to decipher the process of creating anonymised data items.

   2.2. You should be on the alert for any rare and unintentional breach of confidence, such as responding to a query relating to a news item that may add more information to that already in the public domain. If you recognise an individual while carrying out any analysis you must exercise professionalism and respect their confidentiality.

   2.3. If you believe this identification could easily be made by others you should alert a member of the Wilmington Healthcare team using the contact details below. While

appropriate handling of an accidental recognition is acceptable, the consequences of deliberately breaching confidentiality could be severe.

2.4. HES data must only be used exclusively for the provision of outputs to assist health and social care organisations.

2.5. HES data must not be used principally for commercial activities. The same aggregated HES data outputs must be made available, if requested, to all health and social care organisations, irrespective of their value to the company.

2.6. HES data must not be used for, including (but not limited to), the following activities:

    2.6.1. Relating HES data outputs to the use of commercially available products. An example being the prescribing of pharmaceutical products

    2.6.2. Any analysis of the impact of commercially available products. An example being pharmaceutical products

    2.6.3. Targeting and marketing activity

2.7. HES data must be accessed, processed and used within England or Wales only. HES data outputs must not be shared outside of England or Wales without the prior written consent of Wilmington Healthcare.

2.8. If HES data are subject to a request under the Freedom of Information Act, then Wilmington Healthcare and NHS Digital must be consulted and must approve any response before a response is provided.

3. 2021/22 HES data are provisional and may be incomplete or contain errors for which no adjustments have yet been made. Counts produced from provisional data are likely to be lower than those generated for the same period in the final dataset. This shortfall will be most pronounced in the final month of the latest period, e.g. September from the April to September extract. It is also probable that clinical data are not complete, which may in particular affect the last two months of any given period. There may also be errors due to coding inconsistencies that have not yet been investigated and corrected.

4. ICD-10 codes, terms and text © World Health Organization, 1992-2022

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Supplementary Table A. *Candida*-related codes excluded from the analysis

ICD-10 code	Diagnosis description
B37.0	Candial stomatitis • Oral thrush
B37.2	Candidiasis of skin and nail • Candidal onychia • Candidal paronychia
B37.3	Candidasis of vulva and vagina • Candidal vulvovaginitis • Monilial vulvovaginitis • Vaginal thrush
B37.4	Candidiasis of other urogenital sites • Candidal balanitis • Candidal urethritis
B37.8	Candidiasis of other sites • Candidal cheilitis • Candidal enteritis
B37.9	Candidiasis, unspecified • Thrush not otherwise specified

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Supplementary Table B. Outcomes in patients with aspergillosis and candidiasis before COVID-19 (2 years between March 2018–February 2020) and during the COVID-19 period (18 months between March 2020 to October 2021).

Outcome	Aspergillosis	Candidiasis
Patients with SIFI before COVID-19	6,255	3,445
Patients with SIFI during COVID-19 period	4,880	2,990
All admitted patients with no previous COVID-19 diagnosis, n	4,350	2,385
Of all admitted patients with no previous COVID-19 diagnosis, those admitted to CCU, n (%)	575 (13.2)	885 (37.1)
All admitted patients who had had a diagnosis of COVID-19, n	600	600
Of all admitted patients who had a diagnosis of COVID-19, those admitted to CCU, n (%)*	315 (52.5)	360 (60.0)
Mean length of stay for SIFI before COVID-19, days	9.6	34.8
Mean length of stay for SIFI during COVID-19 period, days	13.4	42.4
All spells for SIFI for patients who had had a diagnosis of COVID-19, days	25.9	34.2
All spells for SIFI for patients with no previous COVID-19 diagnosis, days	11.6	43.2
All COVID-19 spells, days	11.9	11.9
Mean length of stay in CCU during COVID-19 period		
Patients with SIFI in CCU who had had a diagnosis of COVID-19, days	26.0	22.4
Patients with SIFI in CCU with no previous COVID-19 diagnosis, days	18.1	22.0
All COVID-19 spells in CCU, days	10.8	10.8
30-day readmission during COVID-19 period		
Patients who had had a diagnosis of COVID-19, %	12.6	3.7
Patients with no previous diagnosis of COVID-19, %	8.6	2.5
Failed discharge during COVID-19 period		

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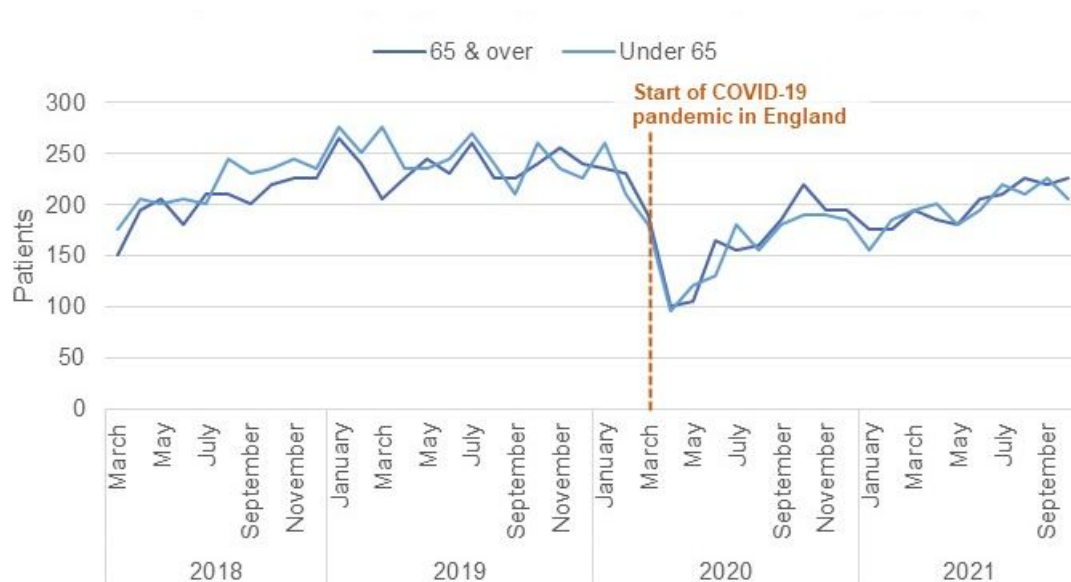|		
Patients who had had a diagnosis of COVID-19, %	6.6	3.0
Patients with no previous diagnosis of COVID-19, %	4.2	1.7

CCU, critical care unit.

*If a patient had COVID and SIFI within the same spell, they are part of the 'had had a diagnosis of
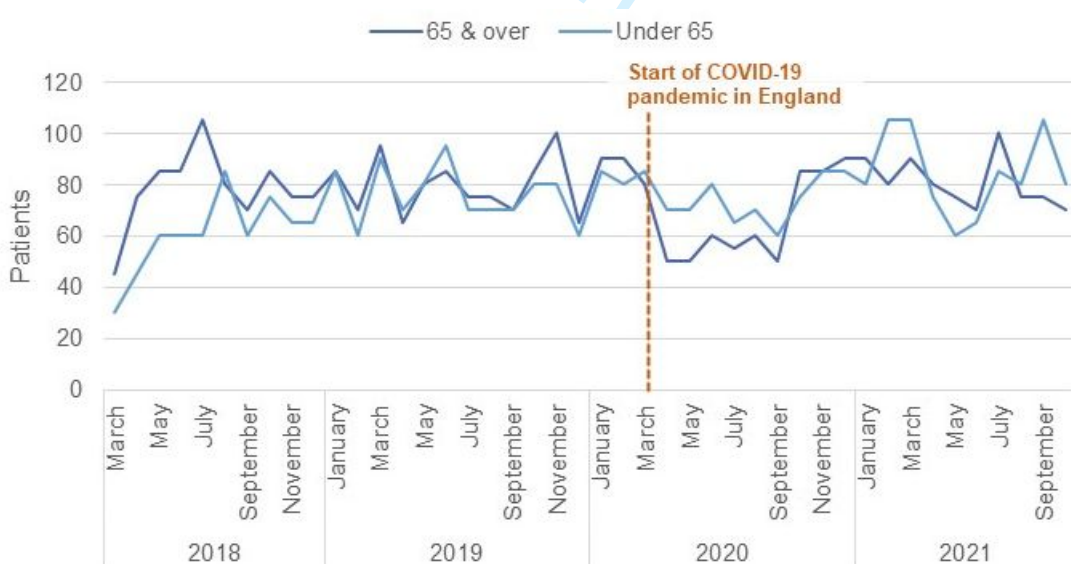
COVID' group.

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Supplementary Figure A. Monthly trend in serious invasive fungal infection (SIFI) patient count by broad age group, March 2018 to October 2021: aspergillosis (a) and candidiasis (b).

(a)

(b)

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2–3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4–6
Objectives	3	State specific objectives, including any prespecified hypotheses	2, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6–8, Supplementary materials 2–3,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6–7, Supplementary materials 2–3,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6–7, Supplementary materials 2–3,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7, Supplementary materials 2–3,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6–8, Supplementary materials 2–3,7
Bias	9	Describe any efforts to address potential sources of bias	3,6–8, Supplementary materials 2–3
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6–8, Supplementary materials 2–3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6–8, Supplementary materials 2–3
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Supplementary materials 10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8–13, Supplementary materials 8–10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8–13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8–13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14–15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	3,15–16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14–16
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Hospital-treated serious and invasive aspergillosis and candidiasis infections during the COVID-19 pandemic: retrospective analysis of hospital episode statistics data from England

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Tables/figures 5/5 figures

1

ABSTRACT

Objectives To investigate the impact of COVID-19 on the burden of hospital-treated *Aspergillus* and *Candida* infections in England.

Design Retrospective study using Hospital Episodes Statistics (HES) data to estimate the burden of serious and invasive fungal infections (SIFIs) in all patients admitted in England during March 2018–February 2020 (pre-COVID-19) and during March 2020–October 2021 (the COVID-19 period).

Setting Hospitals in England.

Population All patients with codes corresponding to serious and invasive aspergillosis and candidiasis in any diagnosis position during their admission pre-COVID-19 and during the COVID-19 period.

Outcome measures Age, spells, patient counts, mean length of stay, admission to critical care unit (CCU), length of stay in CCU, 30-day readmissions, failed discharges (readmission within 7 days), and comorbidities.

Results During the COVID-19 period, hospitalisation spells with an invasive candidiasis code fell by 3.2% and spells with an aspergillosis code by 24.8%. Mean length of stay was higher for patients with aspergillosis with or without COVID-19 and candidiasis with or without COVID-19 during the pandemic than before the pandemic. During the pandemic, mean length of stay was higher for patients with aspergillosis with COVID-19 than those with aspergillosis alone but slightly lower for patients with candidiasis with COVID-19 than for those with candidiasis alone. Of patients with a diagnosis of COVID-19, 52.5% with aspergillosis and 60.0% with candidiasis were treated in CCU compared with 13.2% and 37.1%, respectively, without a COVID-19 diagnosis. The percentage of 30-day readmissions and failed discharges for patients with SIFI was higher for those with COVID-19 than for those without.

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Conclusions The burden of aspergillosis and candidiasis has been affected by COVID-19. Aspergillosis diagnoses fell among hospitalised patients during the pandemic, while candidiasis continued to fluctuate in patterns similar to pre-COVID-19. A higher burden for patients with SIFI was observed, whether or not they also had a diagnosis of COVID-19. Our findings highlight extra considerations and burden on management of serious SIFI as a result of the COVID-19 pandemic.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This analysis used recent real-world data from the HES dataset, which includes all patients using secondary care services in England.

- The data are coded based on information documented within medical records and are therefore dependent on the quality of the coding.

- Accuracy of diagnosis of fungal infections is recognised as a clinical and coding issue.

- The codes used were carefully considered to minimise inclusion of any non-severe fungal infections, such as topical *Candida* infections; the results are therefore likely to underreport candidal infections.

- Data on final destination and all mortality are not available from HES, which can impact on understanding of patient outcomes.

Key words: aspergillosis, candidiasis, COVID-19, serious invasive fungal infection

INTRODUCTION

In recent years, global health awareness around infectious diseases has increased. However, the profile of fungal infections has lagged behind that of bacterial and viral diseases, despite serious and invasive fungal infections (SIFIs) often resulting in poorer patient outcomes, more complexity, and increased burden on healthcare systems.

Invasive fungal infections

Invasive aspergillosis

Aspergillus spp. is a ubiquitous environmental mould that grows on organic matter.[1-3] It produces aerosolised conidia, which can be inhaled by humans, potentially leading to colonisation and infection, primarily in immunocompromised individuals.[1] *Aspergillus* causes a spectrum of pulmonary disorders and clinical manifestations, depending on the competence of the host's immune response, including local colonisation of the respiratory tract, hypersensitivity reactions, chronic infections, and acutely invasive disease.[1-4] Aspergillosis is a significant cause of morbidity and mortality in the immunocompromised population.[4] Invasive aspergillosis (IA) is characterised by invasion of pulmonary vasculature by the *Aspergillus* hyphae, which can progress to angioinvasive pulmonary aspergillosis.[1 2] Invasive aspergillosis and angioinvasive pulmonary aspergillosis are serious conditions that can complicate the management of critically ill patients, with up to 95% mortality if not treated.[1 4]

Invasive candidiasis

Candida spp. is a widespread genus of commensal yeasts that can be detected on the mucosal surfaces (skin and gut) of healthy humans and in the hospital environment.[1 5] They are typically non-pathogenic in immunocompetent people, but at least 15 *Candida* species can cause human disease.[1 5-7]

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As with *Aspergillus*, *Candida* spp. are implicated in a broad spectrum of infections, with candidiasis an umbrella term covering cutaneous, mucosal and deep-seated organ infections.[7] Invasive disease results from a combination of increased or abnormal colonisation, disruptions in the cutaneous and gastrointestinal barriers, and local or general defects in host defences, including weakened immunity.[7] More than 95% of invasive disease is caused by six species, most commonly *C. albicans* and increasingly *C. auris and C. glabrata*.[5-7] Invasive candidiasis can range from minimally symptomatic candidaemia to deep-seated infection with or without candidaemia, including fulminant sepsis, which has >70% mortality.[7] Surveillance data from the UK in 2020 show the highest rate of candidaemia observed in the past 10 years at 3.5 per 100,000 population.[8]

Impact of COVID-19

The coronavirus disease 2019 (COVID-19) pandemic has presented many challenges to healthcare systems, including the emergence of associated and secondary infections, especially in severe cases treated in the intensive care unit.[1] COVID-19 infection leads to conditions favourable for opportunistic fungal pathogens, such as hypoxia, immunosuppression, host iron depletion, hyperglycaemia secondary to diabetes, and prolonged hospitalisation, even in previously immunocompetent people.[9] The prevalence of COVID-19-associated pulmonary aspergillosis (CAPA) varies. A national French study reported rates of 15% in mechanically ventilated patients and higher mortality in patients with CAPA than in those without (61.8% versus 32.1%).[10] A small number of studies from outside of the United Kingdom (UK) have identified extrapulmonary mould infections in patients with COVID-19, including disseminated aspergillosis (pulmonary and cerebral) and rhinosinusitis.[11] [12]

The risk of candidiasis may also significantly increase in patients with severe COVID-19 due to treatment with broad-spectrum antibacterials, parenteral nutrition, invasive examinations,

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prolonged neutropenia and other immune impairment.[13] COVID-19-associated candidiasis (CAC) has been reported in 0.7–23.5% of patients with severe infection and with mortality of 83.3%.[9] [10] Candidal infections of the bloodstream and abdomen, most frequently *Candida albicans* but also other species including *Candida auris*, in patients with COVID-19 have also been reported worldwide, including the UK.[14]

Any variation in incidence of fungal infections could lead to a significant change in the burden on healthcare systems.[15] Even before the COVID-19 pandemic, invasive fungal disease was thought to be increasing in the UK due to a variety of factors, including increased survival time from previously fatal illnesses and an increase in immunosuppression from the treatment of other diseases.[15] Comorbid COVID-19 and fungal infections will have further added to the burden on healthcare systems and critical care services during the pandemic.

Understanding of the overall burden of invasive fungal disease in the UK is limited, as active surveillance is in place only for candidaemia, and even then the burden is likely to be underestimated as reporting of candidaemia by laboratories has been voluntary.[15] We therefore investigated the impact of COVID-19 on the reported disease burden of serious and invasive *Aspergillus* and *Candida* infections in hospitals in England.

PATIENTS AND METHODS

We used Hospital Episodes Statistics (HES) data to estimate the burden of serious and invasive aspergillosis and candidiasis infections in all patients admitted in England pre-COVID-19 (March 2018–February 2020) and during March 2020–October 2021 (the COVID-19 period). During the COVID-19 period, we estimated the burden of serious and invasive aspergillosis and candidiasis infections in patients with and without a diagnosis code for COVID-19. We initially identified patients with all diagnosis codes corresponding to aspergillosis and candidiasis in any diagnosis position during their admission (i.e. as primary

diagnosis or secondary diagnosis) pre-COVID-19 and during the COVID-19 period. The codes for candidiasis initially included B37.8 (candidiasis of other sites – candida; cheilitis and enteritis) and B37.9 (candidiasis, unspecified – thrush not otherwise specified); however, these were later removed from the analysis so as to minimise inclusion of any non-severe fungal infections, such as topical *Candida* infections. Details on coding used are given in Appendix A and Supplementary Tables A and B in the Supplementary materials. Throughout the rest of this paper, 'candidiasis' refers to serious and invasive candidiasis and 'aspergillosis' refers to invasive aspergillosis. The analysis is based on the date of discharge – i.e. the month in which the patient was discharged from hospital is the month in which the admission is counted. Only patients registered at a GP practice in England at the time of admission have been included in the study.

Specific characteristics of interest included age, spells, patient counts, mean length of stay (MLOS), admission to critical care unit (CCU), length of stay in CCU, 30-day readmissions, failed discharges (readmission within 7 days), and comorbidities. Patient counts refers to the number of unique patients who have been admitted to hospital with a diagnosis of interest in the specified time period (using Person Identifier in HES). Spell counts refers to the total number of admissions to hospital where a patient has been coded with a diagnosis of interest over the specified time period (using Spell Identifier in HES). A unique patient may have more than one hospital spells over a given time period but will only be counted once in patient counts. Mean length of stay was defined as total bed-days in a spell divided by the number of spells with a SIFI diagnosis. Thirty-day readmissions were defined as a non-elective admission with a diagnosis of SIFI that was within 30 days of a discharge for a spell where the patient also had SIFI. Failed discharges were defined as non-elective admissions with a diagnosis of SIFI within 7 days of a discharge for a spell where the patient also had SIFI. We identified the top 15 most common comorbidities in SIFI spells during the pre-COVID-19 period and the top 15 most common comorbidities in SIFI spells during the COVID-19 period.

As required by NHS Digital when using HES data, values for patients, spells, patients in critical care, spells in critical care, critical care days, 30-day readmissions and count of failed discharges above 7 were rounded to the nearest 5; totals therefore may not sum across columns/rows. Values for patients, spells, patients in critical care, spells in critical care, critical care days, 30-day readmissions and count of failed discharges between 1 and 7 (inclusive) were suppressed for data presented at an aggregated level. MLOS were suppressed where spells were suppressed.

Secondary care data is taken from the English Hospital Episode Statistics (HES) database produced by NHS Digital, the new trading name for the Health and Social Care Information Centre (HSCIC) Copyright © 2023 the Health and Social Care Information Centre. Re-used with the permission of NHS Digital. All rights reserved. Access to licenced HES data provided through Wilmington Healthcare. See Appendix B in Supplementary materials for full HES disclaimer.

Patient and public involvement

Patients and/or the public were not involved in this study.

RESULTS

Population

During the period before COVID-19 (March 2018–February 2020), 6,255 patients had aspergillosis and 3,445 had candidiasis. Of the patients with SIFI during the COVID-19 period (March 2020 to October 2021), 4,350 with aspergillosis and 2,385 with candidiasis had no previous diagnosis of COVID-19, while 600 with either infection had a diagnosis of COVID-19. Monthly patient counts are shown in Figure 1.

Hospitalisation spells with a candidiasis code fell by 3.2% over the entire COVID-19 period compared with before COVID-19 and spells with an aspergillosis code fell by 24.8%.

Distribution of aspergillosis across patients younger than 65 and older than 65 years remained similar prior to and during the pandemic, with comparable decreases at the beginning of the pandemic for the two age groups and a slow recovery to pre-COVID-19 baseline levels (Supplementary Figure A in Supplementary materials). Monthly counts of candidiasis in both age groups were broadly similar throughout the study period. However, although a trend for higher counts of candidiasis was observed among patients older than 65 years compared with those younger than 65 years before the pandemic, counts in the younger age group were higher than in the older age group at points during the pandemic (see Supplementary Figure A in Supplementary materials).

Mean length of stay and readmissions

Mean length of stay was higher during the pandemic than before the pandemic for patients with aspergillosis with and without COVID-19 (10.2 days during pandemic vs 7.7 days before pandemic) and for patients with candidiasis with and without COVID-19 (28.6 days during pandemic vs 23.3 days before pandemic) (see Figure 2; Supplementary Table B in Supplementary materials). During the pandemic, MLOS was higher for patients with aspergillosis and COVID-19 than those with aspergillosis alone (20.2 days vs 9.0 days, respectively) but slightly lower for patients with candidiasis and COVID-19 than for those with candidiasis alone (27.2 days vs 28.8 days, respectively).

The percentage of 30-day readmissions for patients with SIFI was higher for those with COVID-19 than for those without COVID-19: 12.6% *versus* 8.6% for patients with aspergillosis and 3.7% *versus* 2.5% for those with candidiasis (Figure 3). A similar trend was seen for rates of failed discharge for those with COVID-19 and those without COVID-19: 7% *versus* 4%,

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respectively, for patients with aspergillosis and 3% *versus* 2%, respectively, for patients with candidiasis (Figure 3).

Admission to critical care and length of stay

Of the patients with a previous diagnosis of COVID-19, 52.5% with aspergillosis and 60.0% with candidiasis were treated in CCU. In comparison, of the patients with no previous diagnosis of COVID-19, 13.2% with aspergillosis and 37.1% with candidiasis were treated in CCU (Supplementary Table B in Supplementary materials).

Mean length of stay in CCU for patients without COVID-19 was 18.1 days for patients with aspergillosis and 22 days for those with candidiasis; this increased to 26 days and 22.4 days, respectively, for patients who also had COVID-19 (Figure 4).

Comorbidities

For patients with aspergillosis, four codes not in the top 15 comorbidities prior to COVID-19 were ranked in the top 15 during the COVID-19 period: special screening examination for other viral diseases, other physical therapy, personal history of long-term (current) use of anticoagulants, and acute renal failure, unspecified (Table 1).

For patients with candidiasis, five codes not in the top 15 comorbidities prior to COVID-19 were ranked in the top 15 during the COVID-19 period: COVID-19, virus identified; other viral pneumonia; coronavirus as the cause of diseases classified to other chapters; respiratory failure, unspecified – Type I (hypoxic); and special screening examination for other viral diseases (Table 1).

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Table 1 Top 15 most common comorbidities (ordered by rank during the COVID-19 period) in hospital spells of patients with aspergillosis or candidiasis before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021).

| Rank during COVID-19 period | Aspergillosis | | | | Candidiasis | | | |
| | Rank before COVID-19 | ICD-10 code Diagnosis description | Occurrence (%) | | Rank before COVID-19 | ICD-10 code Diagnosis description | Occurrence (%) | |
			Before COVID-19	During COVID-19			Before COVID-19	During COVID-19
1	1	J99.8 Respiratory disorders in other diseases classified elsewhere	52.6	51.1	2	N17.9 Acute renal failure, unspecified	24.1	34.0
2	2	J47.X Bronchiectasis	32.0	30.8	1	I10.X Essential (primary) hypertension	33.7	32.0
3	3	I10.X Essential (primary) hypertension	21.8	25.1	4	J17.2 Pneumonia in mycoses	18.1	20.6
4	5	Z86.4 Personal history of psychoactive substance abuse	19.7	19.8	–	U07.1 COVID-19, virus identified	Not ranked in top 15	20.0
5	4	J45.9 Asthma, unspecified	20.2	19.7	5	J90.X Pleural effusion, not elsewhere classified	14.5	18.7

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6	–	Z11.5 Special screening examination for other viral diseases	Not ranked in top 15	16.1		–	J12.8 Other viral pneumonia	Not ranked in top 15	18.1
7	–	Z50.1 Other physical therapy	Not ranked in top 15	12.3		–	B97.2 Coronavirus as the cause of diseases classified to other chapters	Not ranked in top 15	17.8
8	9	Z86.7 Personal history of diseases of the circulatory system	10.3	12.2		13	Z50.1 Other physical therapy	11.6	17.7
9	8	Z86.1 Personal history of infectious and parasitic diseases	11.0	12.1		3	J99.8 Respiratory disorders in other diseases classified elsewhere	19.0	17.4
10	6	J44.0 COPD with acute lower respiratory infection	11.9	11.9		6*	E11.9 T2DM – Without complications	13.9	17.0
11	7	J44.9 COPD, unspecified	11.7	11.8		15	Y95.X Nosocomial condition	10.7	14.5
12	11	J43.9 Emphysema, unspecified	9.9	11.2		10	I48.9 Atrial fibrillation and atrial flutter, unspecified	12.6	13.4

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13	10	E11.9 T2DM – without complications	10.0	11.0		–	J969.0 Respiratory failure, unspecified – Type I (hypoxic)	Not ranked in top 15	13.0
14	–	Z92.1 Personal history of long-term (current) use of anticoagulants	Not ranked in top 15	10.2		–	Z11.5 Special screening examination for other viral diseases	Not ranked in top 15	13.0
15	–	N17.9 Acute renal failure, unspecified	Not ranked in top 15	9.7		11	J18.1 Lobar pneumonia, unspecified	12.6	12.9

COPD, chronic obstructive pulmonary disease; ICD-10, International Classification of Diseases and Related Health Problems 10th revision; T2DM, type 2 diabetes mellitus.

*Formerly coded as 'emergency use of U07.1', updated to 'COVID-19, virus identified'.

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DISCUSSION

Overall hospital admissions decreased at the start of the COVID-19 pandemic. This effect was mirrored in the number of aspergillosis diagnoses, with pre-COVID-19 pandemic levels of aspergillosis coding only returning after 12 months. However, this did not apply to candidiasis, where a slight decrease was observed but not to the extent observed with aspergillosis.

Our data suggest that invasive aspergillosis is more frequent than invasive candidiasis, whereas candidiasis is more common in clinical practice.[15][16] We only included codes specific to invasive infection in our study – for example, we excluded code B37.9 'Candidiasis, unspecified', which is applicable to 'Thrush not otherwise specified', a non-invasive form of candidiasis. Consequently, cases of invasive *Candida* infection that were miscoded as non-invasive forms would have been excluded from our analysis, resulting in an apparently lower rate for invasive candidiasis. Mean length of stay for candidiasis in our analysis was longer than for aspergillosis. Other studies have shown variation in this, with some demonstrating longer lengths of stay for aspergillosis whilst others aligned with our findings.[17-19]

The pattern of monthly counts for patients admitted with aspergillosis who were younger or older than 65 years was broadly similar; however, prolonged divergence was seen for patients with candidiasis during the first wave of the pandemic. Fewer bronchoscopies and necropsies were performed during the pandemic, especially in the first months, due to the risks of aerosol generation,[20-22] which may have resulted in an apparent reduction in the occurrence of invasive aspergillosis during the pandemic due to reduced diagnoses, although the actual number of infections may not have reduced. Conversely, some cases of *Aspergillus* spp. colonisation may have been incorrectly interpreted as invasive aspergillosis as the classification and severity of aspergillosis – for example devised by Koehler *et al* for CAPA[23] – is not available from the HES data.

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Of note, the number of cases of candidiasis was higher in those younger than 65 years compared with those older than 65 years at some points during the pandemic, generally corresponding with national lockdowns, which is a reversal of the typical trend prior to the pandemic. The reason for this is uncertain, but it may relate to the fact that older patients were at much higher risk of mortality from COVID-19,[24] which may have impacted the prevalence of secondary infections such as candidiasis. Surprisingly, despite this divergence between the age groups, with fewer patients older than 65 years diagnosed with serious and invasive candidiasis than those younger than 65 years, the overall number of patients diagnosed with candidiasis during the pandemic actually increased compared to pre-pandemic (+3.8%).

Attempting to establish the burden of SIFI during the pandemic is complex, but there is clear evidence of an increase in the number of days patient spent in hospital, the care required, and the complexities experienced. This includes increased renal disorders such as acute kidney injury (AKI), which is one of the most frequent organ complications in patients with severe COVID-19,[25] with studies indicating >30% of patients hospitalised with COVID-19 develop kidney injury and >50% of patients in CCU with kidney injury may require dialysis.[26] Accordingly, our analysis saw acute renal failure appear in the top 15 comorbidities for patients with aspergillosis and increase from rank 2 to rank 1 for those with candidiasis. Coagulopathies have been associated with COVID-19 in patients with aspergillosis,[27] and personal history of long-term (current) anticoagulants emerged in the top 15 comorbidities in patients with aspergillosis during the COVID-19 period in our analysis. Further investigation to identify any correlation between preidentified comorbidities and subsequent development of serious and invasive aspergillosis and candidiasis during the COVID-19 pandemic may provide further insight.

During the pandemic, patients with aspergillosis or candidiasis who also had a COVID-19 diagnosis code, with some exceptions, showed increased disease burden and worse outcomes compared to patients with aspergillosis or candidiasis without a COVID-19

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diagnosis code. This included increases in admission rates to CCU, CCU MLOS, 30-day readmissions, and failed discharges. Patients with codes for aspergillosis or candidiasis with a COVID-19 diagnosis in the readmission spell or in any previous spell had higher readmission rates than those with no record of a COVID-19 diagnosis in the readmission or any previous spell. This increase in readmission rates could be because of their combined history of COVID-19 along with SIFI suggesting a worse prognosis and more complicated disease course than those SIFI patients who have never had COVID-19. Patients with codes for aspergillosis plus COVID-19 also showed increases in overall MLOS and MLOS in CCU compared with patients with COVID-19 alone. Notably, during the pandemic, patients with codes for candidiasis and COVID-19 had shorter lengths of stay than those with candidiasis alone (see Figure 2).

During the pandemic, increased use of codes for viral screening; coronavirus; COVID-19, virus identified; and respiratory comorbidities would be expected (see Table 1). The appearance of other physical therapy, renal failure (a known complication of COVID-19), and increased use of oral anticoagulants for patients with aspergillosis is unsurprising, as renal tropism and coagulopathies are known to develop in patients with COVID-19, as well as a requirement for rehabilitation;[25] [26] [28-36] however, it is notable that these appeared in the top 15 codes for aspergillosis but not for candidiasis.

Strengths and limitations

This analysis used recent real-world data from the HES dataset, which includes all patients using secondary care services in England.

The data were coded based on information documented within the medical records and are therefore dependent on the quality of the coding, including the accuracy of diagnosis of fungal infections. Excluding codes B37.8 (candidiasis of other sites – candida cheilitis and enteritis) and B37.9 (candidiasis, unspecified – thrush not otherwise specified) to minimise inclusion of

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any non-severe fungal infections, such as topical *Candida* infections, means that the results presented are likely to underreport infections, with some cases of invasive candidiasis and candidaemia missed. Data on final destination and all mortality are not available from HES, which can have an impact on understanding of patient outcomes. Patients not registered at a GP practice in England at the time of admission were not included and so diagnoses may be underestimated.

Conclusions

The burden of aspergillosis and of candidiasis has been affected by COVID-19. While diagnoses of aspergillosis fell among hospitalised patients during the pandemic, candidiasis continued to fluctuate in patterns similar to before COVID. However, a higher burden for patients with SIFI was observed, irrespective of whether or not they also had a diagnosis of COVID-19. Compared with patients with SIFI or COVID-19 alone, patients with both codes had increased CCU admissions and longer CCU MLOS, as well as higher 30-day readmission and failed discharge rates. The amplified care needs of patients with both codes suggests complexity in care that increased the disease burden of SIFIs on the English healthcare system. Our findings highlight the extra considerations and burden on management of serious SIFI as a result of the COVID-19 pandemic, not only in England but countries globally. Further work is required to fully understand the impact of the COVID-19 on hospital-treated SIFIs.

Contributors

MS, AS, JKS and ST contributed to the idea of the study and protocol development. ST performed the data analysis. JKS and JSL drafted the manuscript. All authors reviewed all drafts of the manuscript and approved the final version for submission. GK is guarantor for the study.

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Data availability statement

Data are available on reasonable request to the corresponding author.

Ethics statement

No ethics approval was required for this study.

Patient consent for publication

Not applicable.

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FIGURE LEGENDS

Figure 1 Monthly trends in aspergillosis (a) and candidiasis (b) patient count before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021).

Figure 2 Mean length of stay (MLOS) for spells with SIFI and/or COVID-19 spells before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021).

Figure 3 Readmissions within 30 days and failed discharges for patients with aspergillosis and candidiasis during the COVID-19 period (March 2020 to October 2021).

Figure 4 Patients admitted to critical care (a) and mean length of stay in critical care (b) for spells with aspergillosis and candidiasis during the COVID-19 period (March 2020 to October 2021).

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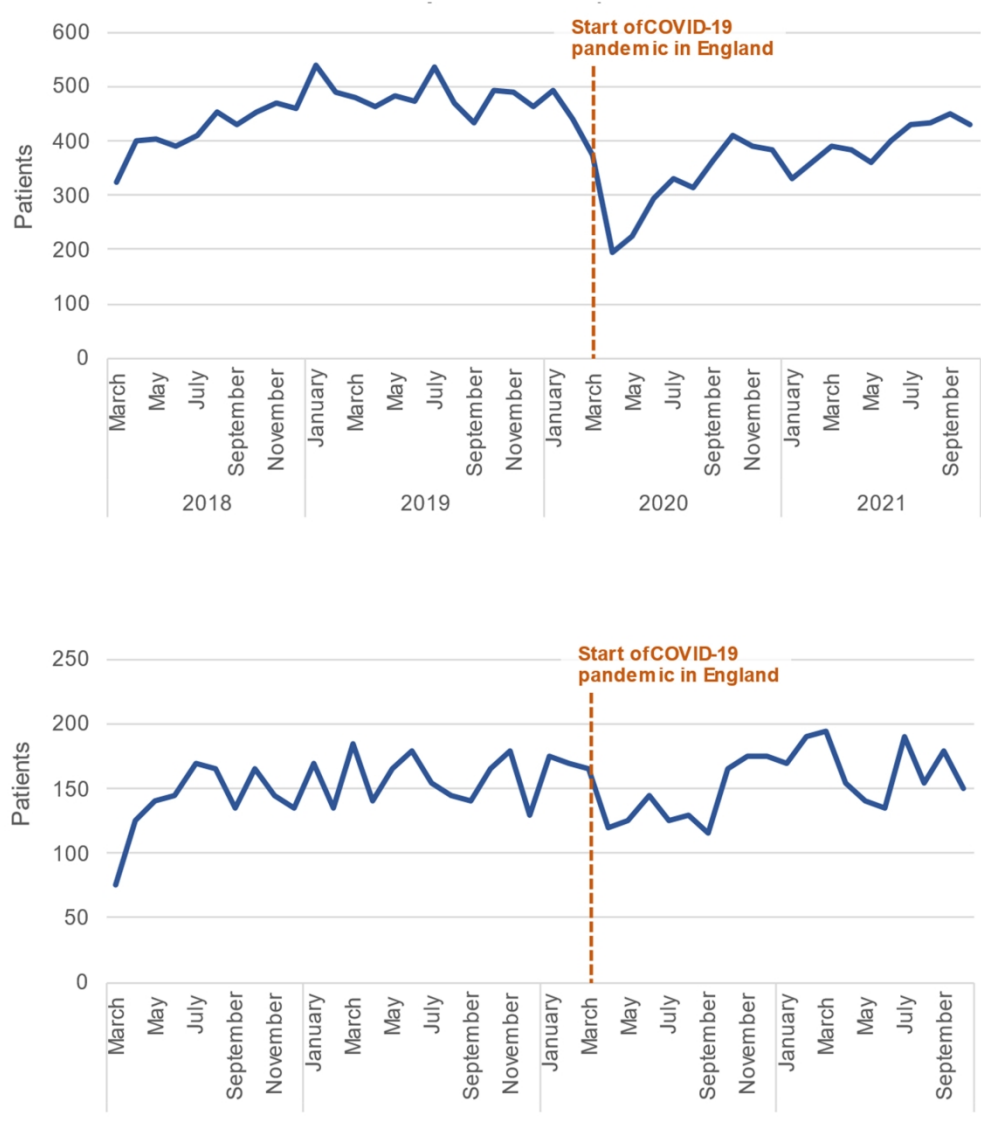51
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Figure 1

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Figure 2

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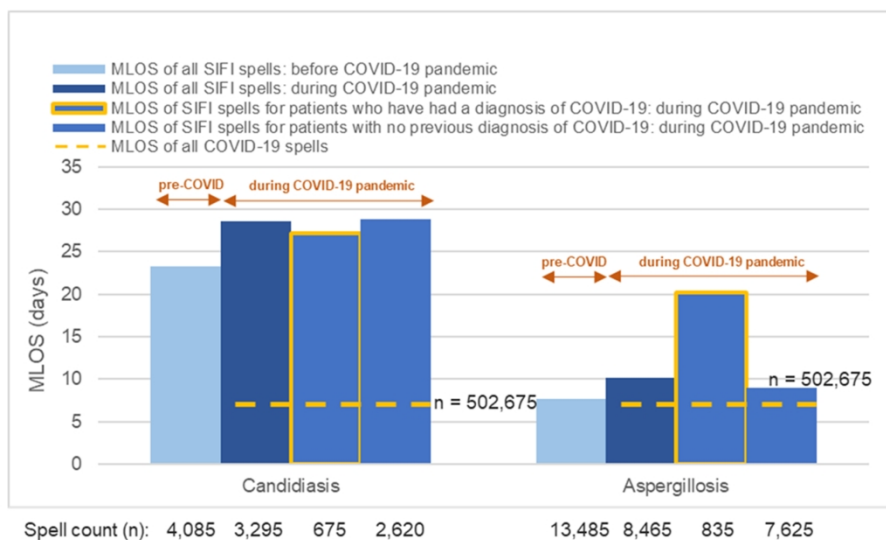51
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Figure 3

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Figure 4

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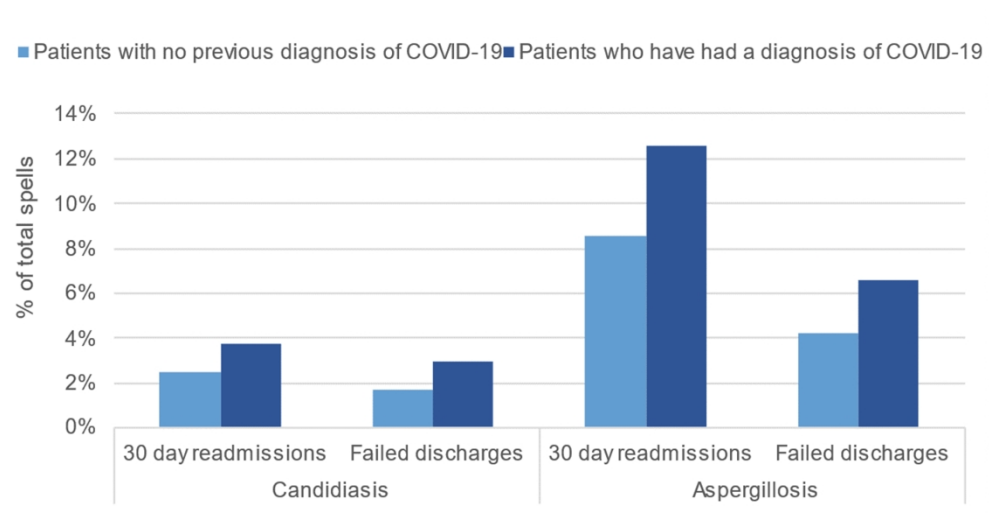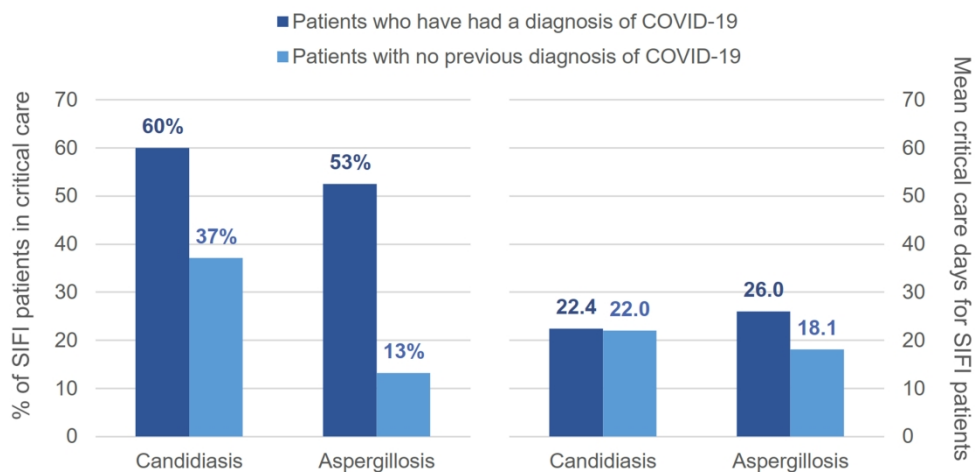41
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SUPPLEMENTARY MATERIALS

Appendix A: Study methods

Patient-level secondary care records were extracted from the Hospital Episode Statistics (HES) database for all patients diagnosed with either aspergillosis or candidiasis over the period March 2018 to October 2021; the diagnosis could be either a primary diagnosis or secondary diagnosis.

In addition, during the COVID-19 period (March 2020–October 2021) patients with a previous diagnosis of COVID-19 were identified by analysing all previous secondary care records for patients admitted to hospital with a diagnosis of aspergillosis or candidiasis (a patient is deemed to have had a diagnosis of COVID-19 if it occurs within the same spell as their aspergillosis or candidiasis diagnosis or in a previous spell).

These records were subsequently aggregated in order to produce an analysis around the impact of COVID-19 on serious and invasive fungal infections in England. Patient data from the pre-COVID-19 period has been compared to patient data in the COVID-19 period; and within the COVID-19 period itself, the data of patients with a previous diagnosis of COVID-19 has been compared to those with no previous diagnosis of COVID-19.

For the purposes of the study, the pre-COVID-19 period has been defined as March 2018–February 2020 and the COVID-19 period as March 2020–October 2021.

In order to identify patients with a relevant diagnosis of aspergillosis or candidiasis, the following ICD-10 codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision were used:

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Diagnosis group	ICD-10 code	Diagnosis description
Aspergillosis	B44.0	Invasive pulmonary aspergillosis
	B44.1	Other pulmonary aspergillosis
	B44.7	Disseminated aspergillosis
	B44.8	Other forms of aspergillosis
	B44.9	Aspergillosis, unspecified
Candidiasis	B37.1	Pulmonary candidiasis
	B37.5	Candidal meningitis
	B37.6	Candidal endocarditis
	B37.7	Candidal sepsis

In order to identify patients with a relevant diagnosis of COVID-19, the following ICD-10 codes

from the International Statistical Classification of Diseases and Related Health Problems, 10th

Revision were used:

ICD-10 code	Diagnosis description
U07.1	COVID-19, virus identified
U07.2	COVID-19, virus not identified

Data access

Secondary care data is taken from the English Hospital Episode Statistics (HES) database

produced by NHS Digital, the new trading name for the Health and Social Care Information

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Appendix B: HES disclaimer

1. Secondary care data is taken from the English Hospital Episode Statistics (HES) database produced by NHS Digital, the new trading name for the Health and Social Care Information Centre (HSCIC) Copyright © 2023, the Health and Social Care Information Centre. Re-used with the permission of the Health and Social Care Information Centre. All rights reserved.

2. HES Data must be used within the licencing restrictions set by NHS Digital, which are summarised below. Wilmington Healthcare accept no responsibility for the inappropriate use of HES data by your organisation.

   2.1. One of the basic principles for the release and use of HES data is to protect the privacy and confidentiality of individuals. All users of HES data must consider the risk of identifying individuals in their analyses prior to publication/release.

      2.1.1. Data should always be released at a high enough level of aggregation to prevent others being able to 'recognise' a particular individual. To protect the privacy and confidentiality of individuals, Wilmington Healthcare have applied suppression to the HES data - '*' or '-1' represents a figure between 1 and 7. All other potentially identifiable figures (e.g. patient numbers, spell counts) have been rounded to the nearest 5.

      2.1.2. On no account should an attempt be made to decipher the process of creating anonymised data items.

   2.2. You should be on the alert for any rare and unintentional breach of confidence, such as responding to a query relating to a news item that may add more information to that already in the public domain. If you recognise an individual while carrying out any analysis you must exercise professionalism and respect their confidentiality.

   2.3. If you believe this identification could easily be made by others you should alert a member of the Wilmington Healthcare team using the contact details below. While

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appropriate handling of an accidental recognition is acceptable, the consequences of deliberately breaching confidentiality could be severe.

2.4. HES data must only be used exclusively for the provision of outputs to assist health and social care organisations.

2.5. HES data must not be used principally for commercial activities. The same aggregated HES data outputs must be made available, if requested, to all health and social care organisations, irrespective of their value to the company.

2.6. HES data must not be used for, including (but not limited to), the following activities:

2.6.1. Relating HES data outputs to the use of commercially available products. An example being the prescribing of pharmaceutical products

2.6.2. Any analysis of the impact of commercially available products. An example being pharmaceutical products

2.6.3. Targeting and marketing activity

2.7. HES data must be accessed, processed and used within England or Wales only. HES data outputs must not be shared outside of England or Wales without the prior written consent of Wilmington Healthcare.

2.8. If HES data are subject to a request under the Freedom of Information Act, then Wilmington Healthcare and NHS Digital must be consulted and must approve any response before a response is provided.

3. 2022/23 HES data are provisional and may be incomplete or contain errors for which no adjustments have yet been made. Counts produced from provisional data are likely to be lower than those generated for the same period in the final dataset. This shortfall will be most pronounced in the final month of the latest period, e.g. September from the April to September extract. It is also probable that clinical data are not complete, which may in particular affect the last two months of any given period. There may also be errors due to coding inconsistencies that have not yet been investigated and corrected.

4. ICD-10 codes, terms and text © World Health Organization, 1992-2023

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9. You can contact Wilmington Healthcare by telephoning 0845 121 3686, by e-mailing client.services@wilmingtonhealthcare.com or by visiting www.wilmingtonhealthcare.com

Supplementary Table A. *Candida*-related codes excluded from the analysis

ICD-10 code	Diagnosis description
B37.0	Candial stomatitis • Oral thrush
B37.2	Candidiasis of skin and nail • Candidal onychia • Candidal paronychia
B37.3	Candidasis of vulva and vagina • Candidal vulvovaginitis • Monilial vulvovaginitis • Vaginal thrush
B37.4	Candidiasis of other urogenital sites • Candidal balanitis • Candidal urethritis
B37.8	Candidiasis of other sites • Candidal cheilitis • Candidal enteritis
B37.9	Candidiasis, unspecified • Thrush not otherwise specified

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Supplementary Table B. Outcomes in patients with aspergillosis and candidiasis before COVID-19 (2 years between March 2018–February 2020) and during the COVID-19 period (18 months between March 2020 to October 2021).

Outcome	Aspergillosis	Candidiasis
Patients with SIFI before COVID-19	6,255	3,445
Patients with SIFI during COVID-19 period	4,880	2,990
All admitted patients with no previous COVID-19 diagnosis, n	4,350	2,385
Of all admitted patients with no previous COVID-19 diagnosis, those admitted to CCU, n (%)	575 (13.2)	885 (37.1)
All admitted patients who had had a diagnosis of COVID-19, n	600	600
Of all admitted patients who had a diagnosis of COVID-19, those admitted to CCU, n (%)*	315 (52.5)	360 (60.0)
Mean length of stay for SIFI before COVID-19, days	7.7	23.3
Mean length of stay for SIFI during COVID-19 period, days	10.2	28.6
All spells for SIFI for patients who had had a diagnosis of COVID-19, days	20.2	27.2
All spells for SIFI for patients with no previous COVID-19 diagnosis, days	9.0	28.8
All COVID-19 spells, days	11.9	11.9
Mean length of stay in CCU during COVID-19 period		
Patients with SIFI in CCU who had had a diagnosis of COVID-19, days	26.0	22.4
Patients with SIFI in CCU with no previous COVID-19 diagnosis, days	18.1	22.0
All COVID-19 spells in CCU, days	10.8	10.8
30-day readmission during COVID-19 period		
Patients who had had a diagnosis of COVID-19, %	12.6	3.7
Patients with no previous diagnosis of COVID-19, %	8.6	2.5
Failed discharge during COVID-19 period		

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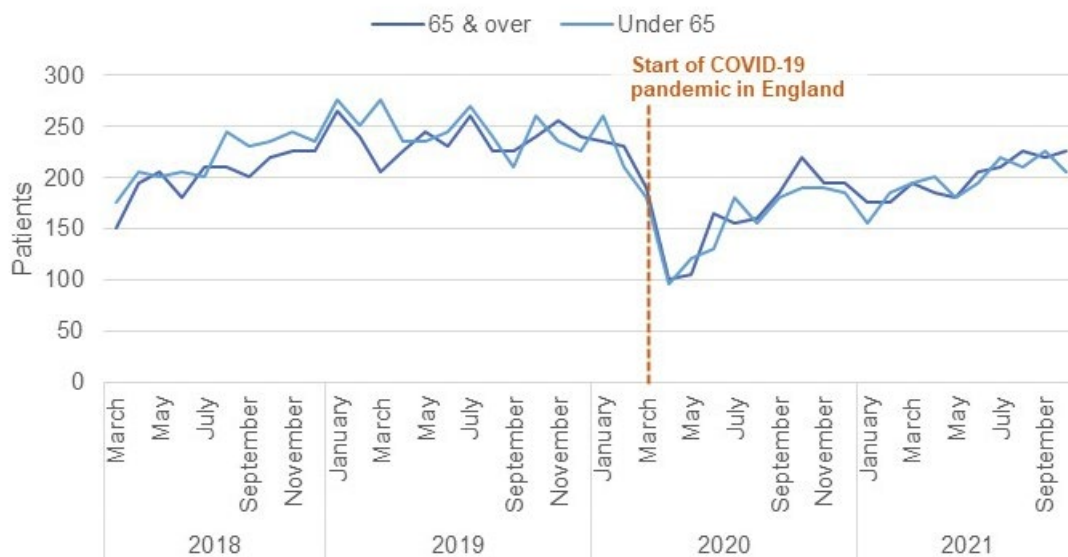|		
Patients who had had a diagnosis of COVID-19, %	6.6	3.0
Patients with no previous diagnosis of COVID-19, %	4.2	1.7

CCU, critical care unit.

*If a patient had COVID and SIFI within the same spell, they are part of the 'had had a diagnosis of
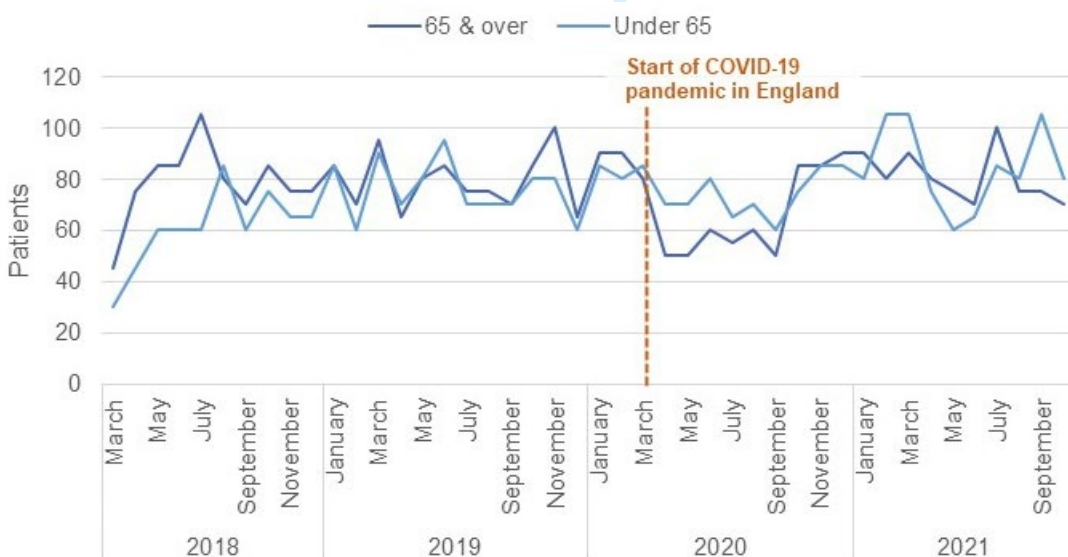
COVID' group.

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Supplementary Figure A. Monthly trend in serious invasive fungal infection (SIFI) patient count by broad age group, March 2018 to October 2021: aspergillosis (a) and candidiasis (b).

(a)

(b)

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2–3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4–6
Objectives	3	State specific objectives, including any prespecified hypotheses	2, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6–8, Supplementary materials 2–3,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6–7, Supplementary materials 2–3,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6–7, Supplementary materials 2–3,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7, Supplementary materials 2–3,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6–8, Supplementary materials 2–3,7
Bias	9	Describe any efforts to address potential sources of bias	3,6–8, Supplementary materials 2–3
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6–8, Supplementary materials 2–3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6–8, Supplementary materials 2–3
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Supplementary materials 10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8–13, Supplementary materials 8–10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8–13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8–13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14–15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	3,15–16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14–16
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.