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The considerable impact of the SARS-CoV-2 pandemic and COVID-19 on the UK National Mycology Reference Laboratory activities and workload

Andrew M. Borman [1,2,*], Mark Fraser [1], Zoe Patterson [1], Sue McLachlan [1], Michael D. Palmer [1], Ciara Mann [1], Debra Oliver [1], Phillipa Brown [1], Christopher J. Linton [1], Agnieszka Dzietczyk [1], Michelle Hedley [1], Martin Gough [1] and Elizabeth M. Johnson [1,2]

[1]UK National Mycology Reference Laboratory, Public Health England South-West, Bristol BS10 5NB, United Kingdom and [2]Medical Research Council Centre for Medical Mycology (MRC CMM), University of Exeter, Exeter EX4 4QD, United Kingdom

*To whom correspondence should be addressed. Andrew M. Borman, PhD, UK National Mycology Reference Laboratory, PHE South-West, Science Quarter, Southmead Hospital, Bristol BS10 5NB, and Medical Research Council Centre for Medical Mycology (MRC CMM), University of Exeter, Exeter EX4 4QD, United Kingdom. Tel: (44) 117 414 6286; E-mail Andy.Borman@nbt.nhs.uk

COVID-19 impact on Mycology

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Abstract

Starting late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a devastating global pandemic of coronavirus-19 disease (COVID-19) with ~179 million cases and ~3.9 million deaths to date. COVID-19 ranges from asymptomatic infection to severe illness with acute respiratory distress requiring critical care in up to 40% of hospitalized patients. Numerous reports have identified COVID-19-associated pulmonary aspergillosis (CAPA) as an important infective complication of COVID-19. In the UK, the pandemic has had unprecedented impacts on the National Health Service (NHS'): each wave of infections required hospitals to reconfigure for large surges in patients requiring intensive care, to the detriment of most aspects of non-COVID care including planned operations, outpatient appointments, general practitioner consultations and referrals. The UK National Mycology Reference Laboratory (MRL) offers a comprehensive service for the diagnosis and management of fungal disease nationwide, with a test portfolio that includes: diagnosis of allergies to fungal and other respiratory allergens; diagnosis of superficial and invasive/systemic fungal infections using traditional mycological, serological and molecular approaches; identification and susceptibility testing of the causative fungi; therapeutic drug monitoring of patients receiving antifungal therapy. Here, we describe the impact of the first 14 months of the COVID-19 pandemic on MRL activities. Changes to MRL workload closely mirrored many of the NHS-wide challenges, with marked reductions in 'elective' mycological activities unrelated to the pandemic and dramatic surges in tests that contributed to the diagnosis and management of COVID-19-related secondary fungal infections, in particular CAPA and candidemia in COVID-19 patients in intensive care.

Lay summary

The COVID-19 pandemic has had an unprecedented impact on the UK National Health Service, with hospitals forced to repeatedly reconfigure to prepare for large surges in COVID-19 patients. Here we describe the impact of the first 14 months of the UK pandemic on the workload of the National Mycology Reference Laboratory.

Key words: COVID-19, SARS-CoV-2, invasive pulmonary aspergillosis, candidemia, diagnosis, Mycology Reference laboratory, impact.

Introduction

In a little over 12 months, the novel betacoronavirus SARS-CoV-2 has caused a global pandemic of coronavirus-19 disease (COVID-19) with over 179 million cases and in excess of 3.8 million deaths to date (as of 22nd June, 2021). Patients infected with SARS-CoV-2 experience a wide spectrum of clinical manifestations, ranging from asymptomatic infection, through mild flu-like illness to severe illness with acute respiratory distress syndrome (ARDS) that requires critical care in a subset of patients. It has been estimated that in approximately 5–10% of cases, symptoms are severe enough to necessitate hospitalization and up to 40% of hospitalized patients may develop ARDS.[1–4] Patients with underlying comorbidities, who are at elevated risk of progressing to severe COVID-19 and poor clinical outcomes, include those with pre-existing severe pulmonary conditions, cardiovascular disease, diabetes, and solid organ and stem cell transplant recipients. Additional risk factors for poor outcome include age 65 or over, obesity, and pregnancy.[1–4]

In addition to the direct consequences of COVID-19 infection *per se*, COVID-19 associated pulmonary aspergillosis (CAPA) has been reported as a potential infective complication affecting critically ill patients with acute respiratory distress syndrome following SARS-CoV-2 infection. Depending on the individual study, widely variable incidence rates for CAPA of 1.0–39.1% of patients who are mechanically ventilated have been reported ([5–11]; reviewed in 12), with mortality rates in CAPA patients approximately double of those seen in equivalent patients with COVID-19 alone.[8,11,12] The variations in reported incidence rates likely stem from genuine geographical and seasonal differences in the prevalence of *Aspergillus* spores, coupled with the fact that definitive diagnosis of CAPA is challenging. Until recently,[10,13] standardized algorithms/definitions were lacking, many centers are reticent to perform aerosol-generating bronchoalveolar lavages (BALs) for *Aspergillus* antigen testing and conventional microscopic and cultural examination, and questions remain around the diagnostic utility of different serum biomarkers. Faced with such diagnostic challenges, current recommendations for the diagnosis of CAPA propose that serial screening for CAPA in intensive care unit (ICU) patients with deteriorating respiratory function should include regular *Aspergillus* galactomannan antigen (GM) and (1-3)-β-d-glucan antigen (BDG) testing of serum samples, GM testing of BAL fluids or other respiratory secretions, and *Aspergillus* PCR in conjunction with conventional mycological examination of such secretions if available.[6–10,13] Finally, in the first 6 months of 2021, COVID-19-associated mucoromycosis (CAM) has emerged as a further and particularly devastating infectious complication of COVID-19, especially in India and other parts of Southern Asia that have been ravaged by a second wave of COVID-19 disease driven by an emergent SARS-CoV-2 variant.[14,15]

Globally, the COVID-19 pandemic has had unprecedented impacts on local and national health systems. Healthcare centers and hospital trusts have been repeatedly required to reconfigure services to prepare for large surges in patients requiring intensive care with each wave of new infections,[16–18] in part by significantly reducing non-COVID care.[16–20] This, combined with fewer patients seeking healthcare due to fears of hospital-acquired infection, has resulted in significant reductions in elective procedures, urgent cancer referrals, outpatient appointments, and general practitioner (GP) consultations. In the UK, the British Medical Association[18] estimated that approximately 1.5 million elective procedures and 2.5 million outpatient appointments, coupled with over 270 000 urgent cancer referrals did not occur due to COVID-19 in the first 3 months of the pandemic alone (April–June, 2020). Given these unprecedented challenges and changes to the UK health system, here we have conducted a retrospective analysis of the direct impacts that the COVID-19 pandemic has had on the types and numbers of samples referred for testing to the UK National Mycology Reference Laboratory (MRL), which provides a comprehensive service for the diagnosis and management of fungal disease nationwide.

Methods

The portfolio of tests offered by the MRL includes testing for allergies to fungal and other respiratory allergens (*Aspergillus*, avian, and farmers lung precipitin tests), tests to aid the diagnosis of both superficial and invasive/systemic fungal infections including CAPA (cryptococcal, BDG, and GM antigen testing of serum samples and cerebrospinal fluid; microscopy and culture, GM, and *Aspergillus*-specific PCR testing of BAL fluids, other respiratory secretions and tissues where appropriate) identification and susceptibility testing of isolates of pathogenic yeast and molds (filamentous fungi), and therapeutic drug monitoring of serum drug concentrations in patients receiving antifungal therapy. Samples for testing are referred to the MRL from hospitals, GP services, and microbiology laboratories across the UK and the tests performed are those requested by the attending physician (where appropriate).

For the period 13th January 2020 (16 days before the first reported cases of COVID-19 in the UK) through 5th April, 2021, the Laboratory Information Management System (LIMS) used by the MRL was systematically searched on a weekly basis (at midnight on Sundays) and all tests received and entered onto the LIMS database for the preceding 7 day period were collated by test type and code. Baseline activity levels for each test type were calculated as the average weekly test number for the period 13th January 2020 to 2nd March 2020 (i.e., the 7 weeks prior to COVID-19 infections sustainably exceeding 1 infection/day based on 7 day average figures). Median baseline tests numbers (tests per week) were as follows: 204 (range 175–213, interquar-

Table 1. Peak and trough test numbers for key tests in the MRL portfolio.

	Test number (tests per week)		
Test	Pre-pandemic Baseline (median)[a]	UK wave 1 Peak/trough (date)[b]	UK wave 2 Peak/trough (date)[b]
ALL Tests	1227 (1185–1313)	605 (6 April 2020)[d] 1303 (20 April 2020)[d]	**2124** (1 February 2021)
BDG	331 (301–367)	**602** (20 April 2020)	**936** (1 February 2021)
GM	204 (175–213)	**284** (20 April 2020)	**546** (1 February 2021)
Voriconazole TDM	49 (36–52)	29 (6 April 2020)	**100** (22 February 2021)
Itraconazole + Posaconazole TDM	60 (43–80)	32 (6 April 2020)	54 (1 February 2021)
Precipitin tests (*Aspergillus* + avian + FL[c])	179 (152–183)	28 (6 April 2020)	95 (1 February 2021)
Yeast isolates for ID and susceptibility	96 (82–118)	29 (6 April 2020)	104 (1 February 2020)
Mould isolates for ID and susceptibility	50 (25–63)	12 (6 April 2020)	46 (1 February 2021)

[a]Weakly test numbers were compared against pre-pandemic median test numbers calculated for the period 13th January 2020 to 2nd March 2020 (i.e., the 7 weeks prior to COVID-19 infections sustainably exceeding 1 infection/day based on 7 day average figures). Pre-pandemic test number total ranges are shown in parentheses.
[b]Peak (bold) or trough (normal text) test numbers attained during waves 1 and 2 of the UK pandemic are given, with the peak or trough test date (week commencing) in parentheses.
[c]Total precipitin test numbers are shown, which include tests to detect antibodies to *Aspergillus*, avian, and Farmer's Lung (FL) antigens.
[d]For total test numbers during wave 1, two figures are given as a sharp decline in test numbers (week commencing 6th April 2020) was followed by a rapid recovery to pre-pandemic test numbers (week commencing 20th April 2020).

tile range 21) for *Aspergillus* antigen (GM), 331 (range 301–367, interquartile range 25) for BDG, 132 (range 114–139, interquartile range 11) for *Aspergillus* precipitin tests, 47 (range 38–54, interquartile range 5) for avian and farmers lung precipitin tests, 50 (range 25–63, interquartile range 23) for mold isolates for identification and susceptibility testing, 96 (range 82–118, interquartile range 17) for yeast isolates for identification and susceptibility testing, 29 (range 21–41, interquartile range 14) and 31 (range 22–39, interquartile range 14) for itraconazole and posaconazole therapeutic drug monitoring, respectively, and 49 (range 36–52, interquartile range 14) for voriconazole therapeutic drug monitoring. Baseline (pre-pandemic) test numbers are summarized in Table 1. Data for the numbers of new COVID-19 infections (by date of positive specimen, as 7 day averages for the whole UK, calculated on the Monday of each week) and numbers of patients in mechanical ventilation beds (7 day averages for the whole UK, calculated each Monday) were accessed and collated from https://coronavirus.data.gov.uk/details/cases and https://coronavirus.data.gov.uk/details/healthcare, respectively. Data for mechanical ventilation bed occupancy are only available for the UK from the week beginning the 6th April 2020.

Results

During the period 13th January 2020 to 5th April 2021, the MRL received and processed in excess of 88 000 samples covering the whole spectrum of diagnostic testing services offered by the laboratory, with a pre-pandemic median of 1227 tests per week (range 1185–1313, interquartile range 77; Table 1). Weekly activity followed three phases during the 14 months period examined: (i) a brief, sharp 50% reduction in total testing spanning the last 2 weeks in March 2020 and the first 2 weeks in April 2020 which coincided with the accelerative phase of the first wave of the COVID-19 pandemic in the UK and the first national lockdown, (ii) a rapid return to near baseline activity that then extended from the end of April 2020 through to the beginning of November, and (iii) a steady increase in overall activity that commenced the week beginning 9th November, 2020 and continued for the remainder of the study period, which coincided with the bi-phasic second wave of SARS-CoV-2 infections. By February 2021, test numbers had reached 175% of pre-pandemic levels (Fig. 1A and B; Table 1), before rapidly declining again towards baseline levels through late February and mid-March.

Test numbers for individual tests were significantly and differentially impacted throughout the different phases of the pandemic, with individual trends determined by whether the particular test was COVID/CAPA-related or part of non-COVID 'elective' mycology (Figs 1 and 2; Table 1). For the BDG and GM antigen tests, both of which form part of the overall algorithm for diagnosing CAPA,[6–10] serum sample numbers referred initially declined sharply for a brief period during the

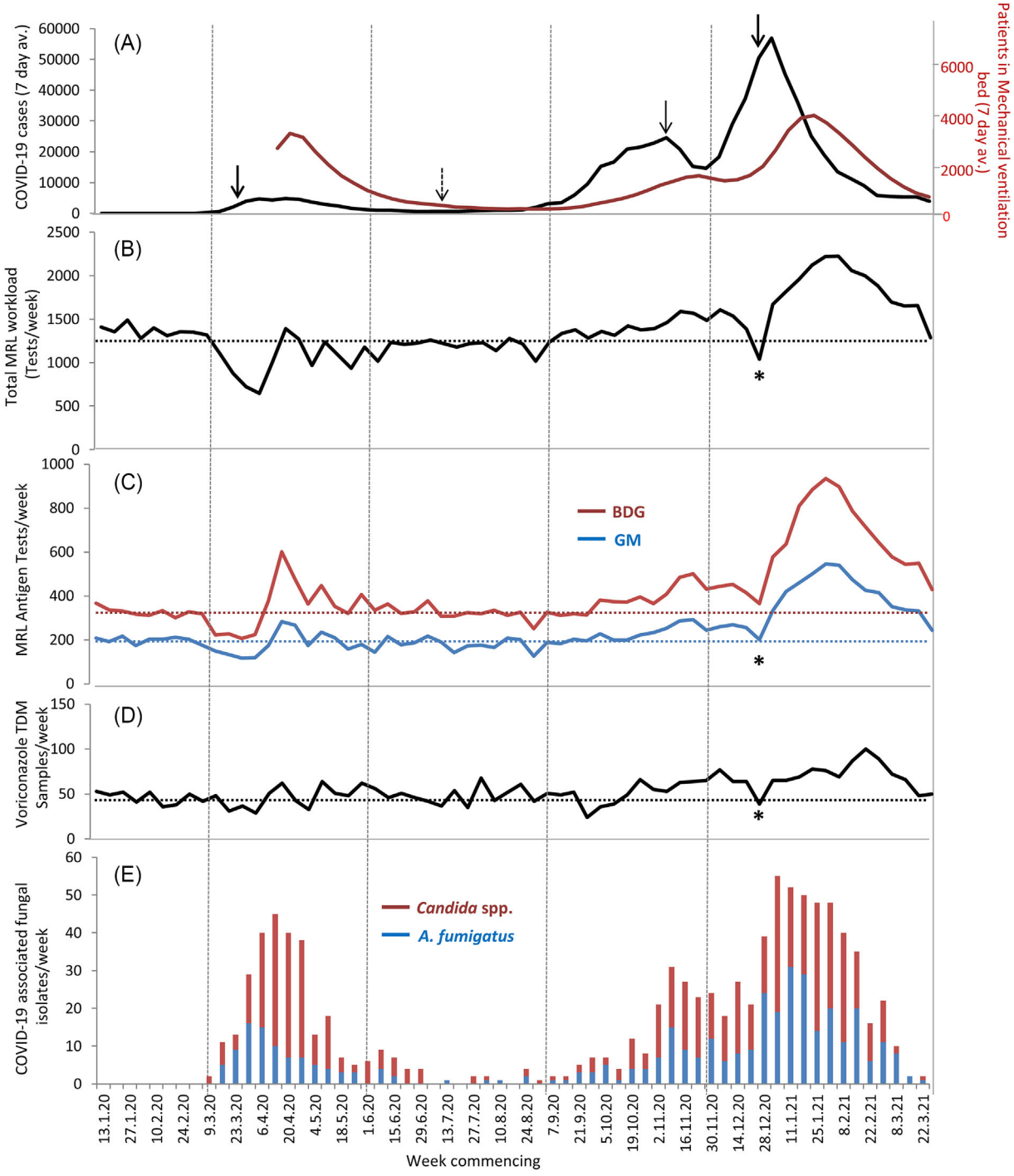

Figure 1. Impact of COVID-19 and CAPA/fungal co-infections on MRL test burden. (A) Data for the numbers of new COVID-19 infections (black line, left hand axis; cases stratified by date of positive specimen, 7 day averages for the UK, calculated on the Monday of each week) and numbers of patients in mechanical ventilation beds (red line, right hand axis; 7 day averages for the UK, calculated each Monday) were accessed and collated from https://coronavirus.data.gov.uk/details/cases and https://coronavirus.data.gov.uk/details/healthcare, respectively. Data for mechanical ventilation bed occupancy are only available for the UK from the week beginning the 6th April 2020. Dashed vertical lines delineate waves 1 and the bi-phasic nature of wave 2 of COVID-19 infections. Thick arrows mark nationwide lockdowns, thin arrow a partial lockdown, and the dashed arrow a relieving of lockdown measures after the first wave. (B) Total MRL activity (tests received per week) as compared to the pre-pandemic median activity (dashed horizontal line). (C) Weekly test activity for BDG (red curve) and GM (blue curve) as compared to the pre-pandemic median activities (red and blue dashed horizontal lines). (D) weekly voriconazole therapeutic drug monitoring activity as compared to the pre-pandemic median activity (dashed horizontal line). (E) Weekly numbers of isolates of *A. fumigatus* (blue bars) from respiratory specimens of COVID-19 patients and *Candida* spp. (red bars) from cases of candidemia in COVID-19 patients. Isolates were stratified by sample date and not by date of receipt at the MRL. Panels B through D: An asterisk denotes the reduced test numbers referred to the MRL over the Christmas/New Year period.

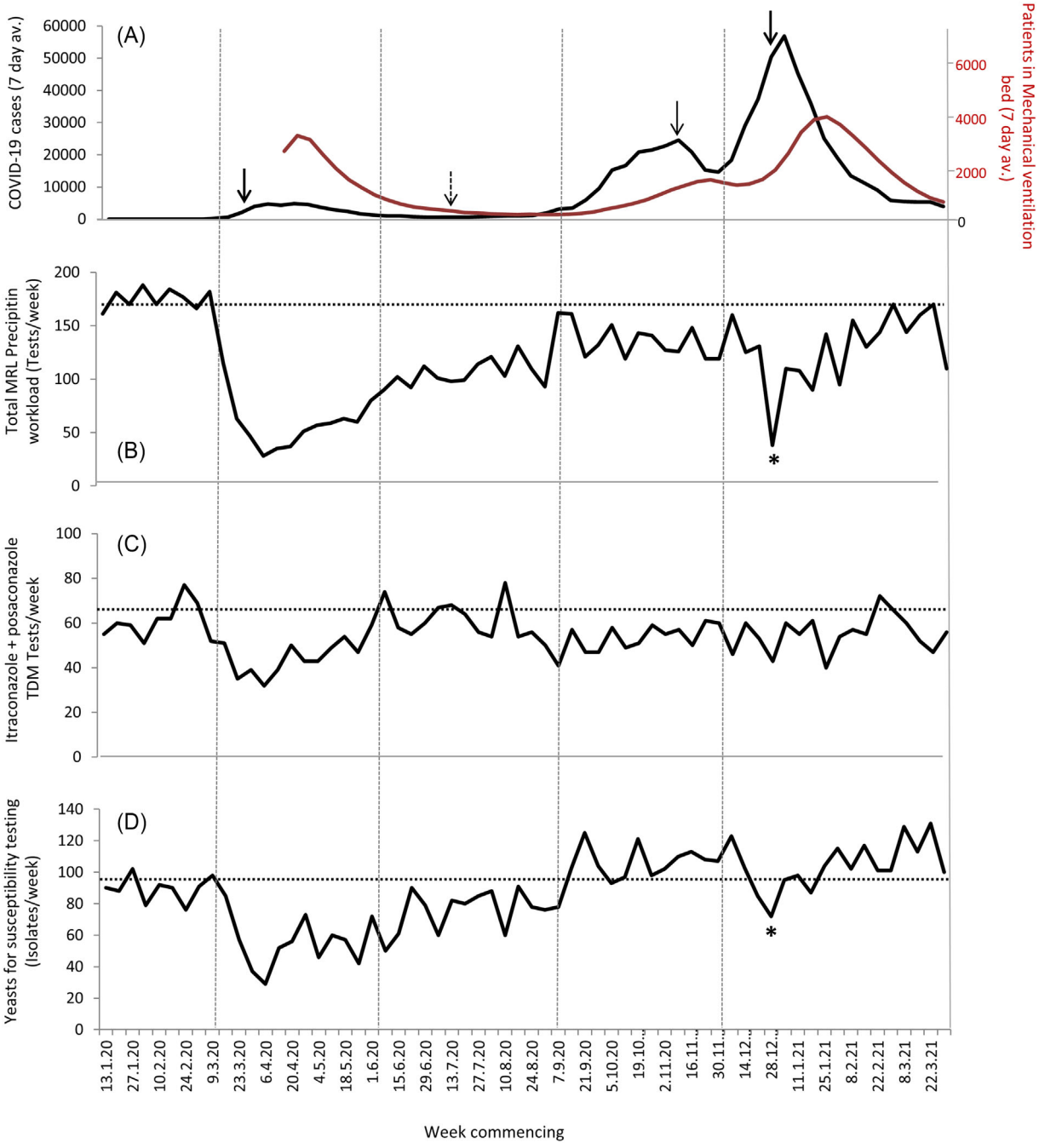

Figure 2. Impact of COVID-19 on non-pandemic related activity. (A) Is repeated from Fig. 1 with exactly the same conventions. (B) Combined weekly test numbers for *Aspergillus,* avian, and farmer's lung precipitin tests. (C) Combined weekly requests for itraconazole or posaconazole therapeutic drug monitoring. (D) weekly numbers of isolates of pathogenic yeast for identification and susceptibility testing. (B and D) An asterisk denotes the reduced test numbers referred to the MRL over the Christmas/New Year period. Dashed horizontal lines in panels B through D represent pre-pandemic median activity.

first national lockdown in March 2020, before increasing significantly through the second half of the first wave of the pandemic, returning to baseline levels throughout late spring and summer and then rising significantly again through the second wave of the pandemic (Fig. 1C). By early 2021, test numbers for both BDG and GM were ~300% of pre-pandemic levels. With the exception of the increase in test numbers during the first wave of the pandemic, subsequent increases followed the numbers of *de novo* diagnosed SARS-CoV-2 infections with a lag of 3–4 weeks (compare Figs 1A and 1C). This is reflective of the approximate time delay between diagnosis of SARS-CoV-2 infection and development of severe COVID-19 disease requiring protracted ICU stays, which is the principle risk factor for the development of CAPA. Indeed, the trends in BDG and GM test numbers over

this period map perfectly with changes in the numbers of patients in beds capable of delivery mechanical ventilation across the UK (Fig. 1A; red curve).

A virtually identical picture was seen with the evolution in the numbers of isolates of *Aspergillus fumigatus* referred to the MRL from COVID-19 patient respiratory secretions (Fig. 1E) and isolates of *Candida* species from episodes of candidemia in COVID-19 patients (Fig. 1E). In both cases, numbers increased synchronously with the first wave of COVID-19 in March–April, and again shortly after the bi-phasic second wave in November–February. The absence of a lag in test number increases for GM/BDG and isolate numbers for *Aspergillus/Candida* with the first wave in March–April is entirely consistent with the SARS-CoV-2 testing strategy that was employed in the UK during the early stages of the pandemic, where testing capacity was reserved for seriously ill patients who were already hospitalized, rather than wider scale community testing later during the year after testing capacity was expanded. The impact of potential fungal infections secondary to COVID-19 on MRL activity and on the wider NHS was also evident when numbers of serum samples referred for voriconazole therapeutic drug monitoring were examined (Fig. 1D), with moderately increased test activity that correlated well with the first wave and substantially increased referrals that continued throughout the subsequent waves of UK-wide COVID-19. It should be noted that voriconazole is the recommended first line treatment of choice for all forms of invasive aspergillosis.[21]

A completely different pattern was observed for those tests in the MRL portfolio that can be classified as non-pandemic related or 'elective mycology' (Table 1; Fig. 2). The numbers of serum samples received for testing for *Aspergillus fumigatus*, avian or farmer's lung precipitins (markers of allergic reactions to fungal or other environmental allergens): (i) declined precipitously in the week commencing 16th March 2020 (the week preceding the first total UK lockdown during the first wave of the pandemic), (ii) rebounded slowly over the next 6 months to briefly approach pre-pandemic levels in late September, and then (iii) declined once again during the second wave of UK coronavirus infections (Fig. 2B). Although overall sample numbers were lower, a similar pattern was seen with serum samples submitted for therapeutic drug monitoring of itraconazole and posaconazole levels (Fig. 2C), two antifungal agents that are predominantly employed either as antifungal prophylaxis in high risk, immunocompromised patients or to treat pulmonary exacerbations in patients with cystic fibrosis or dermatophytoses in otherwise healthy individuals (in the case of itraconazole). Requests for monitoring of itraconazole and posaconazole serum drug concentrations fell significantly during the first wave of the UK pandemic, briefly regained pre-pandemic levels in late summer/early autumn of 2020, and then fell slightly again during the second wave of infections. Finally, the numbers of isolates of pathogenic yeast referred to the MRL each week for identification and antifungal susceptibility testing have also varied significantly over the past 14 months (Fig. 2D). Following an initial sharp decline that coincided with the first wave of infections, test numbers gradually returned to pre-pandemic levels during summer 2020, and have increased to exceed pre-coronavirus levels during the second wave of infection. An examination of the isolation sites and accompanying clinical details for isolates received for susceptibility testing over the entire study period indicated that isolates of *Candida* spp. from cases of candidemia in COVID-19 ITU patients contributed only minimally to this recent workload exceedance, with the number of isolates from respiratory specimens from COVID-19 patients being significantly greater (data not shown).

Discussion

The current study has described the impact of the COVID-19 pandemic on the activities of the UK National Mycology Reference Laboratory, in particular on overall MRL workload and specific individual test burdens. The impact on MRL activity of the various phases of the COVID-19 pandemic in the UK was entirely dependent on whether individual tests in the MRL portfolio contributed towards the diagnosis and management of COVID-19- related fungal infections, in particular CAPA and candidemia in COVID-19 ITU patients. For serological diagnostic tests that are used to aid diagnosis of CAPA (serum BDG and GM testing), test numbers increased dramatically with each wave of COVID-19 infections and as could be predicted trended almost synchronously with the numbers of COVID-19 patients in mechanical ventilation beds. A similar pattern was observed with requests for therapeutic drug-monitoring of voriconazole, the first line treatment of choice for all forms of invasive aspergillosis[21] including CAPA.

The nationwide approach adopted by the UK to mitigate the impact of COVID-19 was to protect the most vulnerable patients from exposure to SARS-CoV-2, provide extra surge capacity in the NHS and prevent it from being overwhelmed, and to reduce community transmission in general.[16–20] In keeping with these principles, during the two waves of SARS-CoV-2 infections, the UK health service witnessed significant reductions in elective procedures, urgent cancer referrals, outpatient appointments and GP consultations, coupled with fewer patients seeking routine and emergency healthcare due to fears of hospital-acquired SARS-CoV-2 infection.[18,19] For MRL tests that were non-pandemic related, the evolution of test numbers was entirely consistent with the national pandemic response. Test numbers dropped precipitously with each new wave of COVID-19 infections and only slowly returned to pre-pandemic levels post-national lockdowns when SARS-CoV-2 infection numbers dwindled. Thus, requests for therapeutic drug monitoring of itraconazole and posaconazole (antifungal drugs employed predominantly for the treatment of dermatophyte infections, treatment of chronic

pulmonary aspergillosis infections, or pulmonary exacerbations in patients with cystic fibrosis [itraconazole], or antifungal prophylaxis in high risk hematology/oncology patients [itraconazole or posaconazole], and precipitin tests (sensitization to fungal or other environmental allergens) all reduced synchronously with the first wave of COVID-19 in Spring 2020 and only briefly returned to near pre-pandemic levels between the first and second waves of infection (Fig. 2). This might have been due to a risk-benefit analysis of routinely monitoring levels of these drugs in a lockdown situation in patients receiving them for prophylaxis or treatment of chronic infections. The numbers of isolates of pathogenic yeast referred for identification and susceptibility testing followed a similar trend except that test levels during the second wave of COVID-19 (November 2020 through March 2021) have consistently exceed pre-pandemic levels. As mentioned above, a significant proportion of this excess workload is constituted by organisms isolated from respiratory specimens (sputum samples, tracheal aspirates, bronchoalveolar lavages) from COVID-19 patients. It is worth emphasizing here that most international guidelines for the diagnosis and treatment of candidiasis agree that recovery of *Candida* spp. from respiratory secretions usually indicates colonization rather than deep infection, and rarely requires treatment with antifungal drugs.[22] We would suggest that this is also likely to be the case in patients with COVID-19.

The current study does have several limitations. The principal one is that the test numbers analyzed were 'total test numbers' rather than those tests specifically submitted with clinical details specifying COVID-19, since supporting clinical information for samples referred to the MRL is frustratingly and frequently absent or incomplete. However, we believe that it is safe to assume that excess workloads (GM, BDG, voriconazole therapeutic drug monitoring) during this period can be directly attributed to COVID-19 cases given the absolute agreement seen between workload and epidemiological trends, including the 3–4 week lag between new diagnoses and ITU admissions/BDG and GM testing which represents the time delay between a positive COVID-19 diagnosis and ITU admission for those most seriously affected (Fig. 1). Indeed, it is likely that the impact of COVID-19 cases on BDG and GM test numbers will have been significantly greater than simply the excess tests compared to pre-pandemic levels. Effectively, the vast majority of BDG and GM test requests pre-pandemic correspond to hematology/oncology patients who are at elevated risk of invasive fungal infections, a patient group with particularly elevated risk of poor COVID-19 outcomes for whom hospital visits and admissions were dramatically reduced during the pandemic.[20] The substantial rise in biomarker testing during the pandemic certainly reflects clinical acceptance that isolation of *A. fumigatus* from respiratory samples is far from proof of invasive disease and CAPA.

A second limitation is that the COVID-19 testing capacity and strategy evolved across the study period: positive case numbers during the first (March–June 2020) wave were principally restricted to those COVID-19 patients who were already hospitalized as compared to more widespread community testing that ensued as the year progressed. These changes in testing strategy potentially complicate direct comparisons between the first and second waves of COVID-19 infections in the UK. However, official numbers for mechanical ventilated bed occupancy across the UK are available from 2nd April 2020 onwards (before the peak of the first wave of infections), together with daily counts of patients hospitalized with COVID-19 (peak numbers of daily hospitalizations for the first wave of 3565 on 1st April 2020, and second wave of 4576 on 12th January 2021; Healthcare | Coronavirus in the UK (data.gov.uk), which are reasonable metrics by which to compare waves 1 and 2. On that basis, it is clear that clinical awareness of CAPA and the need for regular diagnostic testing has increased substantially during the first 13 months of the UK pandemic. First, BDG and GM test requests fell significantly below baseline in the early stages of the first wave of the pandemic (Fig. 1) before rebounding to approximately 2-fold higher than pre-pandemic levels during the second half of wave 1, suggesting limited awareness of the risk of fungal co-infections and the utility of fungal biomarker testing early in the pandemic. Second, although the number of patients hospitalized daily with COVID-19 or occupying mechanical ventilation beds during wave 2 was never more than double those at the peak of wave 1, BDG and GM test requests during wave 2 exceeded those during wave 1 by approximately 6-fold, implying that clinicians were testing a greater proportion of hospitalized patients and/or employing serial biomarker testing in particularly at-risk COVID-19 patients. Given the deleterious impacts of fungal co-infections on outcome in COVID-19 patients reported elsewhere,[8,11,23] this raised awareness due to alerts and publications addressing this issue can only benefit patient care. Finally, the current data represents tests referred specifically to the MRL, the UK National Mycology Reference Laboratory. The COVID-related workload trends identified here cannot automatically be extrapolated to local and regional mycology laboratories across the UK as many of the diagnostic tests in our repertoire are not available elsewhere. However, anecdotal conversations with colleagues in several regional mycology laboratories would suggest that they have also had to manage requests for surge fungal antigen testing aimed to facilitate the diagnosis of COVID-19-associated fungal infections (data not shown).

In summary, here we have analyzed the impact of the COVID-19 pandemic on the overall MRL workload and specific individual test burdens during the first 14 months of the pandemic in the UK. The trends in workload mirror very closely the overall UK response to mitigating the impact of COVID-19 on both the NHS and on the clinically most vulnerable patient groups. Moreover, our data suggest that national awareness of COVID-19-associated fungal co- and secondary infections and

their diagnosis has increased substantially as the UK pandemic has progressed.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

References

1. Xu Z, Li S, Tian S, Li H, Kong LQ. Full spectrum of COVID-19 severity still being depicted. *Lancet*. 2020; 395: 947–948.
2. Wu C, Chen X, Cai Y et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020; 180: 1–11.
3. Clinical Spectrum | COVID-19 Treatment Guidelines (nih.gov).
4. CDC. *Coronavirus disease 2019 (COVID-19)*. 2020. http://web.archive.org/web/20200709001525/https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html.
5. Arastehfar A, Carvalho A, van de Veerdonk FL et al. COVID-19 associated pulmonary aspergillosis (CAPA)-From immunology to treatment. *J Fungi*. 2020; 6: 91.
6. Verweij PE, Gangneux J-P, Bassetti M et al. Diagnosing COVID-19-associated pulmonary aspergillosis. *Lancet Microbe*. 2020; 1: e53–e55. doi:10.1016/S2666-5247(20)30027-6.
7. Boch T, Reinwald M, Spiess B et al. Detection of invasive pulmonary aspergillosis in critically ill patients by combined use of conventional culture, galactomannan, 1-3-beta-D-glucan and *Aspergillus* specific nested polymerase chain reaction in a prospective pilot study. *J Crit Care*. 2018; 47: 198–203.
8. White PL, Dhillon R, Cordey A et al. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. *Clin Infect Dis*. 2020; ciaa1298. 10.1093/cid/ciaa1298.
9. Borman AM, Palmer MD, Fraser M et al. COVID-19-associated invasive aspergillosis: data from the UK National Mycology Reference Laboratory. *J Clin Microbiol*. 2020; 59: e02136–20.
10. Armstrong-James D, Youngs J, Bicanic T et al. Confronting and mitigating the risk of COVID-19 associated pulmonary aspergillosis. *Eur Respir J*. 2020; 56: 2002554.
11. Bartoletti M, Pascale R, Cricca M et al. PREDICO study group. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. *Clin Infect Dis*. 2020:ciaa1065. doi:10.1093/cid/ciaa1065.
12. Salmanton-García J, Sprute R, Stemler J et al. FungiScope European Confederation of Medical Mycology/The International Society for Human and Animal Mycology Working Group. COVID-19-Associated Pulmonary Aspergillosis, March-August 2020. *Emerg Infect Dis*. 2021; 27: 1077–1086.
13. Koehler P, Bassetti M, Chakrabarti A et al. European Confederation of Medical Mycology; International Society for Human Animal Mycology; Asia Fungal Working Group; INFOCUS LATAM/ISHAM Working Group; ISHAM Pan Africa Mycology Working Group; European Society for Clinical Microbiology; Infectious Diseases Fungal Infection Study Group; ESCMID Study Group for Infections in Critically Ill Patients; Interregional Association of Clinical Microbiology and Antimicrobial Chemotherapy; Medical Mycology Society of Nigeria; Medical Mycology Society of China Medicine Education Association; Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology; Association of Medical Microbiology; Infectious Disease Canada. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis*. 2021; 21: e149–e162.
14. Chandra S, Rawal R. The surge in covid related mucormycosis. *J Infect*. 2021; S0163-4453(21)00288-7. doi:10.1016/j.jinf.2021.06.008.
15. Raut A, Huy NT. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? *Lancet Respir Med*. 2021; S2213-2600(21)00265-4. doi:10.1016/S2213–2600(21)00265–4.
16. Carroll WD, Strenger V, Eber E et al. European and United Kingdom COVID-19 pandemic experience: the same but different. *Paediatr Respir Rev*. 2020; 35: 50–56.
17. Aziz S, Arabi YM, Alhazzani W et al. Managing ICU surge during the COVID-19 crisis: rapid guidelines. *Intensive Care Med*. 2020; 46: 1303–1325.
18. https://www.bma.org.uk/media/2840/the-hidden-impact-of-covid_web-pdf.pdf
19. Ibrahim LS, Venables ZC, Levell NJ. The impact of COVID-19 on dermatology outpatient services in England in 2020. *Clin Exp Dermatol*. 2020; doi:10.1111/ced.14547.
20. van de Haar J, Hoes LR, Coles CE et al. Caring for patients with cancer in the COVID-19 era. *Nat Med*. 2020; 26: 665–671.
21. Patterson TF, Thompson GR, 3rd, Denning DW et al. Executive Summary: Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; 63: 433–442.
22. Pappas PG, Kauffman CA, Andes DR et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; 62: e1–e50.
23. Mitaka H, Kuno T, Takagi H, Patrawalla P. Incidence and mortality of COVID-19-associated pulmonary sspergillosis: a systematic review and meta-analysis. *Mycoses*. 2021; doi:10.1111/myc.13292.