Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

National surveillance of bacterial and fungal coinfection and secondary infection in COVID-19 patients in England: lessons from the first wave

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ABSTRACT

Objectives: The impact of bacterial/fungal infections on the morbidity and mortality of persons with coronavirus disease 2019 (COVID-19) remains unclear. We have investigated the incidence and impact of key bacterial/fungal infections in persons with COVID-19 in England.

Methods: We extracted laboratory-confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1st January 2020 to 2nd June 2020) and blood and lower-respiratory specimens positive for 24 genera/species of clinical relevance (1st January 2020 to 30th June 2020) from Public Health England's national laboratory surveillance system. We defined coinfection and secondary infection as a culture-positive key organism isolated within 1 day or 2–27 days, respectively, of the SARS-CoV-2-positive date. We described the incidence and timing of bacterial/fungal infections and compared characteristics of COVID-19 patients with and without bacterial/fungal infection.

Results: 1% of persons with COVID-19 (2279/223413) in England had coinfection/secondary infection, of which >65% were bloodstream infections. The most common causative organisms were *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumoniae*. Cases with coinfection/secondary infections were older than those without (median 70 years (IQR 58–81) versus 55 years (IQR 38–77)), and a higher percentage of cases with secondary infection were of Black or Asian ethnicity than cases without (6.7% versus 4.1%, and 9.9% versus 8.2%, respectively, $p < 0.001$). Age-sex-adjusted case fatality rates were higher in COVID-19 cases with a coinfection (23.0% (95%CI 18.8–27.6%)) or secondary infection (26.5% (95%CI 14.5–39.4%)) than in those without (7.6% (95%CI 7.5–7.7%)) ($p < 0.005$).

Conclusions: Coinfection/secondary bacterial/fungal infections were rare in non-hospitalized and hospitalized persons with COVID-19, varied by ethnicity and age, and were associated with higher mortality. However, the inclusion of non-hospitalized persons with asymptomatic/mild COVID-19 likely underestimated the rate of secondary bacterial/fungal infections. This should inform diagnostic testing and antibiotic prescribing strategy. **Sarah M. Gerver, Clin Microbiol Infect 2021;27:1658**

Introduction

With the second peak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, combined with the winter season in the northern hemisphere, there is an urgent need to better understand the effect of bacterial and fungal coinfections on the outcomes of COVID-19 patients. Given the potential for severe disease, hospitalization and mechanical ventilation [1], there is concern regarding the additional morbidity caused by coinfections amongst

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COVID-19 patients. Bacterial/fungal infections can be serious complications following influenza infection, with prevalence between 2% and 65% in influenza patients [2].

The prevalence of bacterial/fungal infections in patients with coronavirus disease 2019 (COVID-19) and associated morbidity and mortality are currently unclear. Early studies indicate a lower prevalence than for pandemic influenza, with a pooled prevalence of 7% from 18 studies (range 0–45%) [3]. To date, these studies have been small-scale, often in single-hospital settings. One study in two UK National Health Service (NHS) acute hospitals found 3.2% of COVID-19 patients (27/836) had a confirmed bacterial infection identified 0–5 days post hospital admission, increasing to 6.1% (51/836) over the entire admission [4]. Prevalence of bacterial/fungal infections in COVID-19 varies by setting and is higher in severe COVID-19 patients. A US study found that 11.9% of COVID-19 patients receiving invasive mechanical ventilation had bacteraemia versus 1.8% who did not [5], whilst a meta-analysis found that 14% of COVID-19 patients in intensive care units (ICUs) had bacterial coinfection versus 4% in mixed hospital settings [3]. There are also indications that coinfection increases mortality; one meta-analysis found odds of death in COVID-19 patients with bacterial/fungal infection to be 5.8 times higher than in those without [3].

During England's first wave of SARS-CoV-2, changes in antimicrobial prescribing in hospitals were observed; 23% of NHS Trusts (hospitals under the same management) changed their first-line treatment recommendations [6]. Globally, a high proportion of COVID-19 patients received empirical antibiotic treatment [7]. Whilst this precautionary approach is understandable in the wake of a global pandemic of a novel pathogen, reductions in antimicrobial stewardship programmes to maximize appropriate prescribing threaten efforts to curb antibiotic resistance. It is therefore important—particularly given England's second wave coinciding with seasonal increases in respiratory infections—to better characterize the frequency, profile and impact of bacterial/fungal infections in COVID-19 cases.

We have undertaken a national retrospective cohort study, using laboratory surveillance data, to describe bacterial/fungal infections in all persons with COVID-19 diagnosed in England up to the end of May 2020. This information should inform diagnostic testing, antibiotic prescribing, and infection prevention and control (IPC) precautionary strategies.

Methods

We undertook a national retrospective cohort study using the routine laboratory surveillance data of Public Health England (PHE). We defined our cohort as laboratory-confirmed COVID-19 cases reported to the PHE Second Generation Surveillance System (SGSS) Communicable Disease Reporting (CDR) module with a specimen date falling within weeks 1 to 22 of 2020 (1st January 2020 to 2nd June 2020). Of the testing pathways feeding into the SGSS, we used data from Pillar 1 (testing in NHS and PHE laboratories for hospitalized patients and healthcare workers) and Pillar 2 (commercially run laboratories testing the non-hospitalized public). Only the first laboratory-confirmed report of SARS-CoV-2 was used per person.

Our outcome variable was coinfection or secondary infection by bacteria or fungi, defined as a laboratory-confirmed blood or respiratory culture of one of 24 clinically relevant bacterial/fungal organisms (Supplementary Material Table S1), by timing of diagnosis relative to the SARS-CoV-2-positive sample date.

These clinically important organisms were identified through a pre-existing surveillance programme for key bacterial respiratory pathogens to inform antibiotic stockpiling for pandemic influenza preparedness, clinical and PHE Reference Laboratory reports of potential clusters among COVID-19 patients (particularly within ICUs), and a literature review. On 25th July 2020 we extracted all positive cultures of these 24 organisms in blood and lower respiratory samples reported to the SGSS between 1st January 2020 and 30th June 2020. Lower respiratory samples were defined as bronchial, lung, alveolar lavage, pleura, bronchoalveolar lavage, sputum, endotracheal aspirate and pleural fluid. For data on *Clostridioides difficile* infections (CDIs), we extracted all confirmed diagnoses in patients (≥2 years old) for the same time period from the Mandatory Surveillance of Healthcare Associated Infections (HCAI) Data Capture System (DCS) on 22nd July 2020.

Data for all bacterial/fungal organisms were grouped into rolling 14-day organism and site-specific (blood/respiratory) episodes, except for CDIs which due to their different data source were collected in static 28-day episodes. Further exceptions were *Mycoplasma* species identified from blood, where only culture results in patients aged <16 years were included.

The bacterial/fungal and SARS-CoV-2 datasets from the SGSS and the CDI dataset from the HCAI DCS were added to each other. Multiple observations from all data sources from individual patients were grouped together under a single unique identifier using a multistage algorithm (Supplementary Material Table S2).

Categorizing bacterial/fungal infections by timing of diagnosis

The first specimen date of each bacterial/fungal episode was used to determine when a coinfection/secondary infection occurred in relation to the SARS-CoV-2-positive specimen date. Categorization as coinfection or secondary infection was as described in Fig. 1. Episodes which started more than 1 day before the SARS-CoV-2 specimen date were excluded. Episodes were organism- and site-specific. For persons with multiple episodes, only the first was retained when presenting data at an individual level; however, all episodes were included when presenting data at species level.

Additional data sources

To assess associations between patient characteristics and coinfections/secondary infections, additional data were sourced via data linkage on unique patient identifiers. Ethnicity was obtained from the PHE National Incident Coordination Centre Epidemiology Cell [8], Index of Multiple Deprivation (IMD) data were obtained from the UK Office for National Statistics [9] and deaths were identified from the NHS Spine [10].

Statistical analysis

Case fatality rates (CFRs) were calculated among NHS-Spine-matched cases, stratified by coinfection/secondary infection status and site of infection. Age- and sex-adjusted CFRs were calculated using direct standardization and the mid-2019 population of England [11]. Pairwise comparisons were conducted on the standardized rates: difference in rates and the significance of any difference were obtained via Z-test. Analyses were completed in STATA^{TM15}.

Ethics

PHE have approval under Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002 to process patient-identifiable information without consent. This process considers the ethics and purpose of collecting and analysing the data, and as such ethical approval was not separately sought for this work.

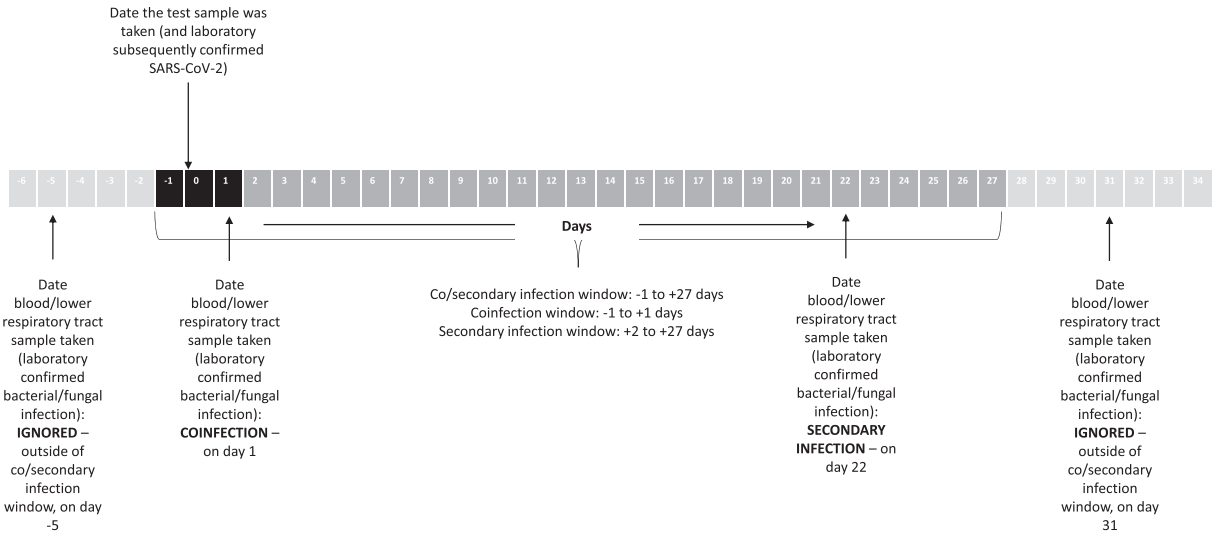

Fig. 1. Description of definitions used to categorize bacterial/fungal infections by timing of diagnosis.

Results

Frequency of key bacterial/fungal coinfections/secondary infections

During the study period 223413 persons had laboratory-confirmed SARS-CoV-2 infections. Among these, 2279 (1.0%, 95% CI 0.97–1.06%) had a coinfection or secondary infection with a key bacterial/fungal organism (Table 1). There were 879 (38.6%; 95%CI 36.56–40.60%) coinfections and 1400 (61.4%; 95%CI 59.40–63.44%) secondary infections. Most (66%) coinfections/secondary infections were bloodstream infections (BSIs), occurring in 0.7% of all COVID-19 cases (95%CI 0.64–0.71%). BSI coinfection were 6.5 times greater than respiratory coinfections, while BSI secondary infections were 2.0 times greater than respiratory secondary infections.

Time trends

The number of coinfections/secondary infections, by week of SARS-CoV-2-positive test, increased from weeks 10 to 14 (March 2020), following a trajectory similar to that of COVID-19 diagnoses (Fig. 2a). However, these trends diverged after week 14 when coinfections/secondary infections peaked and then rapidly declined, whereas diagnoses of COVID-19 cases continued to increase. However, Fig. 2b highlights the difference in incidence of coinfections/secondary infections in real time of the bacterial/fungal infection diagnoses rather than the SARS-CoV-2 specimen date; the incidence of secondary infections as a percentage of COVID-19 cases slowly increased, peaking at week 16, showing the time period for the burden of secondary infections for treatment and IPC purposes.

Characteristics of COVID-19 cases by coinfection/secondary infection status

COVID-19 cases without coinfection/secondary infection were younger (26% ≤40 years) and more likely to be female (55.8%) than COVID-19 cases with a coinfection/secondary infection (4–6% ≤40 years, ≤40% female, $p < 0.001$) (Table 2).

Differences also existed in ethnicity; while the majority were White/White British, a greater percentage of COVID-19 cases with coinfection were White/White British (78.8%) versus those

Table 1
Frequency of key bacterial and fungal infections diagnosed in blood and respiratory isolates reported to the Second Generation Surveillance System (SGSS), by timing of diagnosis, in 223 413 persons with coronavirus disease 2019 (COVID-19) diagnosed in England, January–May 2020[a]

Key bacterial/fungal infection by specimen type	COVID-19 cases without key bacterial/fungal infection		COVID-19 cases with key bacterial/fungal infection		Timing of bacterial/fungal diagnosis in relation to COVID-19 diagnosis					
	(n = 221134)[b]		(n = 2279)		Coinfection (n = 879)			Secondary infection (n = 1400)		
	n	% of COVID cases	n	% of COVID cases	n	% infections by site	% of COVID cases	n	% infections by site	% of COVID cases
Respiratory infection	—	—	508	0.2	111	21.9	0.0	397	78.1	0.2
Bloodstream infection	—	—	1509	0.7	727	48.2	0.3	782	51.8	0.4
Respiratory and bloodstream infection	—	—	59	0.0	1	1.7	0.0	58	98.3	0.0
CDI	—	—	199	0.1	39	19.6	0.0	160	80.4	0.1
CDI and bloodstream infection	—	—	4	0.0	1	25.0	0.0	3	75.0	0.0
CDI and respiratory	—	—	—	0.0	—	—	0.0	—	—	0.0
Any site	221134	99.0%	2279[c]	1.0	879	38.6	0.4	1400	61.4	0.6

CDI, *Clostridioides difficile* infection.
[a] Data are for weeks 1–22 inclusive, so incorporate COVID-19 diagnoses between 1st January 2020 and 2nd June 2020.
[b] Ten persons with COVID-19 did not have enough patient identifiers on their record for them to be matched to any SGSS bacterial/fungal data and are included in this subgroup (no coinfection/secondary infection).
[c] Of 2279 coinfections/secondary infections 404 were made up of multiple episodes. No persons with COVID-19 also had a respiratory, bloodstream *and C. difficile* infection.

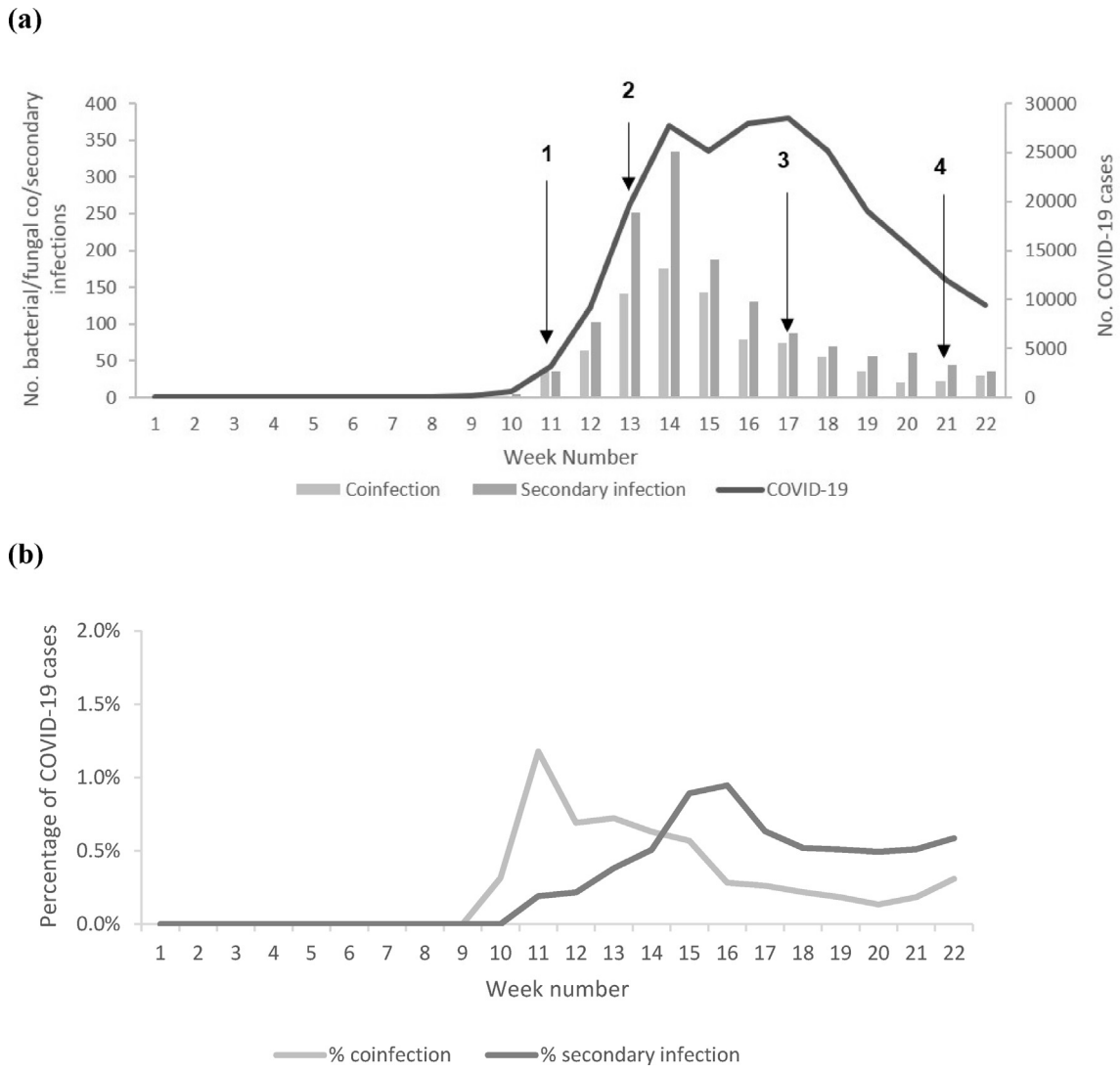

Fig. 2. Counts and percentage of coinfections/secondary infections in persons with coronavirus disease 2019 (COVID-19) diagnosed in England, January to May 2020[a], by week. (2a) Weekly totals of persons with COVID-19 also with a key bacterial/fungal coinfection or secondary infection, and weekly totals of COVID-19, by week of SARS-CoV-2 laboratory confirmation. (2b) Percentage of all persons with COVID-19 also with a key bacterial/fungal coinfection or secondary infection, by week of first coinfection/secondary infection diagnosis. **Fig 2a.** The count is of coinfection/secondary infection cases plotted against week of COVID-19 diagnosis and not the coinfection/secondary infection diagnosis. Arrows indicate timing of testing policy change: (1) reduced testing in the community; (2) testing available to front-line National Health Service (NHS) staff with symptoms; (3) testing available to all essential workers and members of their household with symptoms; (4) testing available to everyone in England (over the age of 5 years) with symptoms. **Fig 2b.** The percentage of persons with COVID-19 and a coinfection/secondary infection is plotted against the week of the first bacterial/fungal infection diagnosis and not the week of COVID-19 diagnosis. This is to show the distribution of secondary infections over time in the first wave of the COVID-19 pandemic in England, for consideration of infection prevention control/treatment processes over time. These data differ from those in (Fig. 2a). [a]Data are for weeks 1–22 inclusive, so incorporate COVID-19 diagnoses between 1st January 2020 and 2nd June 2020.

without coinfection/secondary infection or with secondary infection (<67%). Furthermore, more COVID-19 cases with secondary infection were of Black/Black British ethnicity (6.7%) or Asian/Asian British ethnicity (9.9%) compared to both those without coinfection/secondary infection (4.1% and 8.2%, respectively) or with coinfection (4.4% and 5.7%, respectively) (Table 2).

Case fatality rates (CFR)

The overall age–sex-adjusted CFR for COVID-19 cases without coinfection or secondary bacterial/fungal infection is 7.6% (95%CI 7.5–7.7%) versus 23.0% (95%CI 18.8–27.6%) among cases with coinfection and 26.6% (95%CI 14.5–39.5%) among cases with secondary infection (Table 2).

Organisms detected

From 2279 COVID-19 cases with coinfection/secondary infection, 3448 organisms were cultured from respiratory and bloodstream specimens. The most common causative organisms of coinfection/secondary BSI were *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Enterococcus faecium* and non-pyogenic streptococci, while for respiratory coinfections/secondary infections *Pseudomonas aeruginosa* and *Haemophilus influenzae* replaced *E. faecium* and non-pyogenic streptococci in the top ranking (Table 3, all species, Supplementary Material Table S2).

E. coli, S. aureus and *K. pneumonia* were most common in both coinfections and secondary infections; however, streptococci were ranked top five amongst coinfections versus *E. faecium* and *P. aeruginosa* for secondary infections (Table 3).

Table 2
Characteristics of patients with coronavirus disease 2019 (COVID-19) by timing of diagnosis, diagnosed in England, January to May 2020[a]

Characteristic	COVID-19 patients without a key bacterial/fungal infection ($n = 221134$)		COVID-19 patients with a key bacterial/fungal coinfection ($n = 879$)		COVID-19 patients with a key bacterial/fungal secondary infection ($n = 1400$)	
	n	%	n	%	n	%
Age[b]						
0 to 9	2228	1.0	5	0.6	3	0.2
10 to 19	3918	1.8	1	0.1	3	0.2
20 to 29	23 859	10.8	8	0.9	10	0.7
30 to 39	28 058	12.7	20	2.3	70	5.0
40 to 49	30 740	13.9	37	4.2	144	10.3
50 to 59	36 307	16.4	80	9.1	276	19.7
60 to 69	22 666	10.2	116	13.2	359	25.6
70 to 79	23 626	10.7	216	24.6	263	18.8
80+	49 179	22.2	396	45.1	272	19.4
Unknown	553	0.3	0	0.0	0	0.0
Sex[b]						
Male	92 244	41.7	524	59.6	914	65.3
Female	123 414	55.8	355	40.4	486	34.7
Unknown	5476	2.5	0	0	0	0
Ethnicity[b]						
White/White British	147 210	66.6	693	78.8	909	64.9
Black/Black British	9058	4.1	39	4.4	94	6.7
Asian/Asian British	18 033	8.2	50	5.7	139	9.9
Mixed/multiple ethnic groups	2236	1.0	15	1.7	16	1.1
Any other ethnic group	6258	2.8	24	2.7	59	4.2
No ethnicity information	38 339	17.3	58	6.6	183	13.1
IMD quintile[b]						
1 (most deprived)	48 351	21.9	233	26.5	316	22.6
2	45 527	20.6	175	19.9	337	24.1
3	40 612	18.4	157	17.9	218	15.6
4	37 874	17.1	150	17.1	206	14.7
5 (least deprived)	32 063	14.5	117	13.3	164	11.7
Unknown	16 707	7.6	47	5.3	159	11.4
Crude all-cause 28-day case fatality rate [c,e]	$n = 195\ 219$[d]	CFR[c] (95%CI)	$n = 860$[f]	CFR (95%CI)	$n = 1376$[g]	CFR (95%CI)
Deaths	31 718	16.2 (16.1–16.4)	431	50.1 (46.7–53.5)	440	32.0 (29.5–34.5)
Adjusted all-cause 28-day case fatality rate[h,i]		7.6 (7.5–7.7)		23.0 (18.8–27.6)		26.5 (14.5–39.4)

CFR, case fatality rate; CI, confidence interval; IMD, index of multiple deprivation.
The percentage without any ethnicity information in the COVID-19 patients without a key bacterial/fungal co/secondary infection and patients with a secondary infection was more than double that observed in the coinfection group.
[a] Data are for weeks 1–22 inclusive, so incorporate COVID-19 diagnoses between 1st January 2020 and 2nd June 2020.
[b] Age, sex, ethnic group and IMD quintile comparisons across all three patient groups, by a χ-square test, were found to have a p-value <0.001.
[c] Calculated as the number of deaths divided by the number of reports with complete NHS number, multiplied by 100.
[d] Excludes 25 909 reports which failed to link to the NHS Spine; additionally, excludes six reports where the date of death was recorded as >82 days before the specimen date. Up to 82 days was allowed as post-mortem samples may have been tested substantially after date of death, but these were all within a realistic time frame with respect to date of death and the start of the COVID-19 epidemic.
[e] Mortality information obtained by linking reports with a complete NHS number and date of birth to the NHS Spine.
[f] Excludes 19 reports which failed to link to the NHS Spine.
[g] Excludes 24 reports which failed to link to the NHS Spine.
[h] Age–sex direct standardized CFR to the England mid-2019 population estimate.
[i] Age–sex directly standardized CFRs compared in a pairwise manner between patients without a coinfection or secondary infection and those with either a coinfection or a secondary infection, with a p-value <0.005. There was no difference between those with a coinfection versus a secondary infection.

Polymicrobial bacterial/fungal infections occurred in 18% of COVID-19 cases with coinfections/secondary infections (404/2279), accounting for 914 species (*E. faecium*, *S. aureus* and *E. coli* accounted for $\geq$10% each).

The majority of key bacterial/fungal species were predominantly secondary infections; however, the majority of reported *Streptococcus pneumoniae,* non-pyogenic and pyogenic streptococci were coinfections (66.7%, 62.6% and 84.1%, respectively).

The median age varied by organism and coinfection/secondary infection status (Table 3).

Of all secondary infection episodes, the median time to onset of bacterial/fungal infections is 13 days (IQR 8–18). However, *S. pneumoniae* and *H. influenzae* have shorter times to onset: 4 (IQR 2–7) and 6 (IQR 3–8) days, respectively.

Discussion

This study found that just 1% of COVID-19 cases had a coinfection or secondary infection, which is often lower than has been found in other studies (0–45.4% for bacterial and 0–6.9% for fungal coinfections) [3–5]. Furthermore, our profile of causative organisms differs from that reported to date in other COVID-19 coinfection studies [3]. The lower incidence identified in our study may reflect our inclusion of all persons with COVID-19, whereas other studies have been restricted to hospitalized patients. Data in the SGSS does not provide details of hospital admission; therefore, linkage with additional datasets would be required to limit our COVID-19 population to hospitalized patients only. People diagnosed with COVID-19 in the community, who did not require

Table 3
Characteristics of patient episodes of the top key bacterial and fungal infections diagnosed in blood and respiratory isolates reported to the Second Generation Surveillance System (SGSS) by species, presented by ranking of overall coinfections/secondary infections, diagnosed in England, January to May 2020[a]

Organism	Number of coinfections		Number of secondary infections		Respiratory infections		Bloodstream infections		Coinfections				Secondary Infections					
									Age (years)		Male		Timing of onset		Age (years)		Male	
	n	%	*n*	%	*n*	%	*n*	%	Median	IQR	*n*	%	Median	IQR	Median	IQR	*n*	%
Escherichia coli[b]	267	47.0	301	53.0	66	12	502	88.4	79	69–87	145	54.3	14	8-19	71	60–80	192	63.8
Staphylococcus aureus[b]	209	41.0	301	59.0	262	51.4	248	9.7	73	59–83	132	63.2	12	6-19	58	49–68	201	66.8
Klebsiella pneumoniae[b]	65	20.6	250	79.4	73	23.2	242	76.8	77	63–84	45	69.2	13	9-18	61	52–68	169	67.6
Enterococcus faecium[b]	43	15.4	237	84.6	13	4.6	267	95.4	77	65–86	26	60.5	13	9-18	60	51–69	182	76.8
Non-pyogenic *Streptococci*[b]	147	62.6	88	37.4	23	9.8	212	90.2	79	66–87	105	71.4	11	6-15	61	54–74	66	75.0
Pseudomonas aeruginosa[b]	40	18.7	174	81.3	124	57.9	90	42.1	73	63–83	30	75.0	15	9-20	59	52–68	110	63.2
Clostridioides difficile[b]	41	19.7	167	80.3	NA	NA	NA	NA	81	72–88	20	48.8	11	5-18	81	66–87	87	52.1
Klebsiella aerogenes[b]	6	4.3	134	95.7	59	42.1	81	57.9	70	64–86	5	83.3	13	8-18	58	50–66	109	81.3
Haemophilus influenzae[b]	41	35.7	74	64.3	112	97.4	3	2.6	74	62–80	27	65.9	6	3-8	63	56–73	52	70.3
Enterobacter cloacae[b]	18	16.7	90	83.3	37	34.3	71	65.7	71	60–88	13	72.2	11	8-17	61	53–67	67	74.4
Enterococcus faecalis[c]	26	26.0	74	74.0	10	10.0	90	90.0	77	67–83	15	57.7	14	7-18	63	53–67	59	79.7
Serratia marcescens[d]	9	11.3	71	88.8	35	43.8	45	56.3	78	71–80	7	77.8	11	8-17	60	48–68	55	77.5
Candida albicans[c]	6	8.1	68	91.9	—	—	74	100	82	76–84	3	50.0	15	12-18	62	52–66	48	70.6
Streptococcus pneumoniae[e]	42	66.7	21	33.3	24	38.1	39	61.9	75	52–83	23	54.8	4	2-7	54	46–65	11	52.4
Pyogenic *Streptococci*[e]	53	84.1	10	15.9	5	7.9	58	92.1	79	61–86	33	62.3	13	3-21	60	38–75	7	70.0
Enterococcus other [e,f]	10	18.2	45	81.8	2	3.6	53	96.4	74	69–83	8	80.0	13	10-18	61	56–71	35	77.8
Klebsiella oxytoca[e]	7	14.6	41	85.4	19	39.6	29	60.4	69	56–87	4	57.1	15	10-21	61	47–66	32	78.0
Stenotrophomonas maltophilia[d]	1	2.3	43	97.7	35	79.5	7	15.9	i	i	—	—	13	8-16	64	53–70	32	74.4
Pseudomonas other[e,g]	13	32.5	27	67.5	22	55.0	18	45.0	71	61–85	6	46.2	12	7-19	63	51–75	17	63.0
Klebsiella other[e,h]	4	10.8	33	89.2	19	51.4	18	48.6	61	47–69	3	75.0	13	7-18	62	54–65	29	87.9
Aspergillus fumigatus [d]	1	3.6	27	96.4	28	100	—	—	i	i	1	100	10	6-14	61	54–68	17	63.0

NA, not applicable; IQR, interquartile range (25th and 75th percentiles). Medians and IQR rounded to 0 decimal places. i can be found in place of for median and IQR calculated where there was only one value, i.e. median and IQR was the value for that individual patient-episode.

Table 3 is a count of all patient episodes of coinfection/secondary infection with bacterial/fungal pathogens and not per patient; therefore, numbers will differ between patient-episodes of bacterial/fungal pathogens and the number of COVID-19 patients.

The full list of species and genera can be found in Supplementary Material Table S2. These top 21 organisms were selected for inclusion in this highlights table by cross-referencing the top ten organisms causing respiratory infections and the top ten organisms causing bloodstream infection; these were compared to the overall list of organisms and their placement found in the overall ranking of all bacterial/fungal pathogens causing coinfection/secondary infection among COVID-19 patients. Any organism found in the overall list between the top ten organisms causing either/or respiratory and bloodstream infections were included.

[a] Data are for weeks 1–22 inclusive, so incorporates COVID-19 diagnoses between 1st January 2020 and 2nd June 2020.

[b] Top ten overall, regardless of site.

[c] Top ten bloodstream infections but not top ten overall.

[d] Top ten respiratory infections but not top ten overall.

[e] Organism counts in overall list fall between those selected for in top ten organisms causing either respiratory or bloodstream infections.

[g] *Pseudomonas* other species includes: *P. fluorescens, P. luteola, P. monteilli, P. oryzihabitans, P. stutzeri* and *Pseudomonas* unspeciated.

[h] *Klebsiella* other species includes: *K. ornithinolytica, K. variicola, Klebsiella* unspeciated.

[f] *Enterococcus* other species includes*: E. avium, E. cassilifavlus, E. gallinarum, E. raffinosus* and *Enterococcus* unspeciated.

hospital admission, would likely not have been tested for other bacterial/fungal infections, resulting in an under-detection of coinfections and secondary infections in our cohort. That said, our cohort was determined by testing eligibility, which changed rapidly in the early months of the epidemic. Between 5th and 27th March 2020 testing was restricted to hospitalized patients only [12], which coincides with the higher incidence of coinfections and secondary infections detected. However, even this incidence, when largely restricted to hospitalized patients, is considerably lower than that reported from hospital-based studies.

An alternative possibility is that the lower incidence of coinfections and secondary infections in our cohort may due to under-detection. It is possible that early in the COVID-19 epidemic, acute service pressures reduced testing for other organisms [13]. This may partially explain the reduction in laboratory reports on hospital respiratory and blood samples of a wide range of organisms to the SGSS detected in weeks 11 and 12 (Supplementary Material Fig. S1a, b). For COVID-19 cases specifically, the continued microbiological investigation for other organisms, particularly respiratory pathogens, may have often ceased following a positive SARS-CoV-2 result. One study in two English acute hospitals reported that whilst 77% of their COVID-19 patients had blood samples taken, only 15% had respiratory samples taken [4]; this may explain our finding that >65% of coinfections were bacteraemias.

Whilst recognizing that our study design may have underestimated the true incidence, given the comprehensive scale of our study, we have shown that laboratory-confirmed bacterial/fungal infections in COVID-19 cases in England's first wave was considerably lower than feared, and much lower than observed in seasonal and pandemic influenza [2]. This could have resulted from social distancing and lockdown measures which interrupted community transmission of a range of seasonal pathogens [14,15]. This is supported by the reduction in laboratory reports of common pathogens identified in blood and respiratory samples (Supplementary Material Fig. S1a,b).

The implications of our study for antibiotic prescribing is nuanced. There are indications that, in response to the COVID-19 epidemic, English hospitals changed their antibiotic prescribing recommendations [6]; a high proportion of COVID-19 patients globally received empirical broad-spectrum antibiotic treatment, including on hospital admission [7]. The low incidence of detected bacterial/fungal infections in COVID-19 cases may indicate that these strategies were not required. Conversely, this low incidence may have resulted from widespread empirical antimicrobial use, averting bacterial/fungal infections.

The peak incidence of bacterial/fungal infections was detected in week 15 (early April), then subsequently reduced. This may indicate infection control issues that were present as the number of COVID-19 infections started to increase rapidly, but were then largely resolved as procedures and staff adapted [16]. The early peak in coinfections may have resulted from delayed healthcare-seeking, with patients anxious about attending healthcare services early in the pandemic managing symptoms at home [17].

Limitations

We were restricted to using routine surveillance data for this study, and this has inherent limitations. The SGSS does not include clinical information or prescribed medications; thus we cannot determine what importance the timing/presence of antimicrobial or immunomodulatory therapy may have had. Our outcome variable is dependent on which COVID-19 cases received additional microbiological testing, and for what, and when this testing was undertaken. This bias may have led to an underestimation of the incidence. The data on bacterial/fungal disease is also from voluntary surveillance, dependent on hospital laboratories reporting to the SGSS. Whilst this data source has very high completion [18], it is possible that some testing and reporting was reduced during the COVID-19 response, partially explaining the reduction in laboratory reports detected and leading to missed reports of bacterial/fungal infections in COVID-19 cases. A more robust study design would be to conduct screening for these organisms in a cohort of COVID-19 patients.

Furthermore, this national-level cohort included all laboratory-confirmed cases of COVID-19, including the full range of syndromes, from asymptomatic cases in the community to severely unwell patients on ventilators with prolonged hospitalization. The likelihood of bacterial/fungal infections is likely to differ among these patient groups. We did not have access to additional information on hospital admission, including to intensive care, or the use of ventilators or antimicrobials during this analysis, but further work utilizing data linkage will address some of these limitations and allow us to determine which bacterial/fungal infections were likely to be healthcare-associated.

Finally, whilst we included age/sex-adjusted 28-day all-cause CFR as an outcome and found higher CFRs in patients with coinfection/secondary infection, these data should be treated with caution. It may still reflect the differences in patient characteristics, such as comorbidities, in the different subgroups, and as such acts as a signal warranting more sophisticated analysis.

Conclusion

During the first wave of COVID-19 in England, the overall incidence of key bacterial/fungal coinfections/secondary infections was low. Incidence of coinfections/secondary infections peaked early in the pandemic, potentially stemming from delays in healthcare seeking and temporary disruption to IPC measures. We recommend that clinicians note the profile of the leading causative organisms of coinfections/secondary infections in England in the first wave, to inform microbiological investigations, IPC measures, and prudent prescribing strategies for COVID-19 patients.

Author contributions

SMG: figures, data analysis, data interpretation, writing (original draft), project administration, methodology. RG: data analysis, methodology, writing (review and editing). KW: data analysis, methodology, writing (review and editing), figures. ST: methodology, writing (review and editing). ON: data analysis, writing (review and editing). GR: data analysis, writing (review and editing). CSB: conceptualization, methodology, writing (review and editing). BM-P: conceptualization, methodology, writing (review and editing). RH: conceptualization, methodology, supervision, writing (review and editing). VH: methodology, supervision, writing (review and editing).

Transparency declaration

The authors declare no competing interests. No funding was received for this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.05.040.

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