Impact of the COVID-19 Pandemic on Invasive Pneumococcal Disease and Risk of Pneumococcal Coinfection with SARS-CoV-2: prospective national cohort study, England

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Summary: Invasive pneumococcal disease (IPD) and COVID-19 coinfections were rare in England, representing 0.025% of confirmed SARS-CoV-2 infections (40/160,886) and 3.5% of IPD cases (40/1,137) cases, but associated with higher case fatality compared to those with IPD alone or COVID-19 alone

ABSTRACT

Background

Streptococcus pneumoniae coinfection with influenza results in synergistic lethality, but there are limited data on pneumococcal coinfection with SARS-CoV-2.

Methods

Public Health England conducts invasive pneumococcal disease (IPD) and SARS-CoV-2 surveillance in England. IPD trends during 2000/01-2019/20 were analysed and cases between during February-June 2020 were linked with laboratory-confirmed SARS-CoV-2 infections. Multivariable logistic regression was used to assess risk factors for death.

Results: IPD incidence in 2019/20 (7.6/100,000; n=3,964) was 30% (IRR 0.70, 95%CI, 0.18-2.67) lower compared to 2018/19 (10.9/100,000; n=5,666) with large reductions observed across all age-groups during March-June 2020. The serotypes responsible for IPD during 2019/20 were similar to previous years. There were 160,886 SARS-CoV-2 and 1,137 IPD cases during February-June 2020, including 40 IPD/COVID-19 (0.025% [95%sCI, 0.018-0.034] of SARS-CoV-2 infections; 3.5% [95%CI, 2.5-4.8] of IPD cases), 21 with COVID-19 diagnosed 3-27 days after IPD and 27 who developed COVID-19 ≥28 days after IPD. Case-fatality rates (CFR) were 63.2% (25/40), 47.6% (10/21) and 33.3% (9/27), respectively (p<0.001). In addition to an independent association with increasing age and pneumococcal serotype group, CFR was 7.8-fold (95% CI, 3.8-15.8) higher in those with IPD/COVID-19 co-infection and 3.9-fold (95% CI, 1.4-10.7) higher in patients who developed COVID-19 3-27 days after IPD compared to patients with IPD only.

Conclusions: Large declines in IPD were observed following COVID-19 lockdown in England. IPD/COVID-19 confections were rare but associated with high CFR, mainly in older adults. The rarity, age distribution and serotype distribution of IPD/SARS-CoV-2 coinfections does not support wider extension of pneumococcal vaccination.

Key words: pneumococcal disease, bacterial co-infection, nosocomial infection, case fatality, risk factor

Introduction

Viral respiratory tract infections usually predispose to secondary bacterial infections which are associated with high morbidity and mortality, especially during pandemics [1, 2]. The association between *Streptococcus pneumoniae* and influenza, for example, is well-described, and has important implications because there are effective vaccines against the major pneumococcal serotypes causing invasive disease [3,4]. Coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, typically manifests as a respiratory tract infection and presents with fever and cough [5], which may progress to severe pneumonia, multi-organ failure and death, especially in older adults and those with underlying comorbidities [6-8]. Bacterial co-infection with COVID-19, however, appears to be uncommon [9-11]. A meta-analysis of mainly small case series estimated that 3.5% of COVID-19 patients had a bacterial co-infection and 14.3% had a secondary bacterial infection [12]. These infections occurred mainly intensive care patients, with no particular pathogen predominating [12].

In the United Kingdom, the first imported cases of COVID-19 were reported at the end of January 2020 and endemic transmission in late February, with cases increasing rapidly from early March and peaking in mid-April before declining [13]. In response, the UK implemented national lockdown measures on 23 March 2020 with a stay-at-home order for all but essential travel and work [14]. The reduced social mixing resulting from the lockdown is likely to have affected the incidence of many infectious diseases in addition to SARS-CoV-2 [15].

In England, Public Health England is responsible for enhanced national surveillance of invasive pneumococcal disease (IPD) and COVID-19. We used multiple national surveillance data sources to investigate the impact of the COVID-19 pandemic and the consequent lockdown on IPD, to estimate the risk of SARS-CoV-2 and IPD co-infection and to describe the demographics, responsible serotypes, comorbidity status, clinical features and outcomes of patients with IPD/COVID-19 co-infection during the first wave of COVID-19

pandemic in England. We also assessed the potential role of pneumococcal vaccines in reducing IPD morbidity and mortality during the COVID-19 pandemic.

Methods

The UK Pneumococcal Immunisation Programme

In the UK, the 13-valent pneumococcal conjugate vaccine (PCV13) replaced the 7-valent vaccine (PCV7) in 2010 and, until recently, was offered to infants at 8 and 16 weeks of age, with a booster at 1 year [16]. From 01 January 2020, a reduced infant 1+1 infant immunisation schedule at 12 weeks and 1 year was implemented in the UK [17]. In addition, children aged ≥2 years and adults with underlying comorbidities that predispose them to IPD and all adults aged ≥65 years are offered a single dose of 23-valent pneumococcal polysaccharide vaccine (PPV23) [18].

National Surveillance

PHE conducts national IPD surveillance in England [19]. Briefly, hospital laboratories electronically report invasive pneumococcal infections to PHE using the Second-Generation Surveillance System (SGSS) and submit pneumococcal isolates to the PHE national reference laboratory for confirmation and serotyping. Confirmed cases are followed-up by requesting general practitioner to complete a surveillance questionnaire on immunisation history, comorbidities, clinical presentations, complications and outcomes. A final reconciled database containing laboratory-confirmed IPD cases during the 2000/01 to 2019/20 epidemiological years (July to June, 20 years) was used for this analysis.

SGSS also contains reports of laboratory-confirmed SARS-CoV-2 infections in England. In the UK, SARS-CoV-2 tests are performed through different routes called ‘Pillars’ [20]. In Pillar 1, SARS-CoV-2 RT-PCR tests are undertaken on respiratory swabs by PHE laboratories and NHS hospitals for those with a clinical need and for health and care workers. This group was prioritised for SARS-CoV-2 testing by RT-PCR during the first

pandemic wave, with minimal virus testing in the community. Positive results from Pillar 1 testing were linked with IPD cases from 01 February to 30 June 2020 (5 months) using full name, sex, birthdate, reporting hospital, site and date of sample. IPD and SARS-CoV-2 cases confirmed in June 2020 were linked with cases until 31 July 2020. Deaths were confirmed using the patient demographic service, an online national database which holds demographic data and death status for NHS patients.

Definitions

IPD was defined as isolation of *S. pneumoniae* from a normally sterile site. SARS-CoV-2 infection was confirmed by RT-PCR on an upper respiratory tract swab or a lower respiratory tract sample such as bronchioalveolar lavage (BAL). In England, blood cultures are invariably taken in hospital settings (emergency department or hospital ward) when a bacterial infection is suspected. During the first wave of the pandemic, patients attending hospital for any illness were routinely tested for SARS-CoV-2 infection at presentation and, if hospitalised, when COVID-19 was suspected. Coinfection was defined as a positive pneumococcal culture taken from a sterile site within 2 days of a positive SARS-CoV-2 RT-PCR result. Secondary infection was defined as a laboratory-confirmed infection in a sample taken 3-27 days after the first infection.

Statistical analysis

Data were analysed using Stata v.15.0 (StataCorp, Tx), Corrected annual IPD incidence by epidemiological year and serotype group (PCV13, PPV23, non-PPV23) was calculated as previously described, adjusting for missing proportion of isolates serotyped and missing age,[19] using population denominators from the Office for National Statistics (ONS; www.statistics.gov.uk). We estimated the proportion of coinfections and secondary infections in individuals with IPD and SARS-CoV-2 infection between 01 February and 30 June 2020 (with cases diagnosed until the end of July 2020) and compared the demographics, clinical features and outcomes of patients /who had separate episodes of IPD and COVID-19 (≥28

days apart). Case fatality rates (CFR) were calculated for deaths within 30 days of the last IPD or SARS-CoV-2 infection. Data that did not follow a normal distribution are presented as medians with interquartile range and compared using the Mann Whitney U test. Categorical variables are reported as proportions with binomial 95% confidence intervals and compared using the chi-squared or Fisher's Exact test as appropriate. A multivariable logistic regression model was fitted to assess risk factors associated with 30-day CFR and included age-group (<16, 16-64, 65-84 and ≥85 years), sex, ethnicity (White, Black, Asian, Other) and timing of infection (coinfection and secondary infection) comparing to the baseline group of IPD only cases during February-June 2020.

Results

There were large declines in IPD incidence across all age-groups during 2019/20 in England (Figure 1). Most of the decline was observed between March and June 2020. IPD incidence in 2019/20 (3,964 cases, 7.6/100,000) was 30% (IRR 0.70, 95%CI, 0.18-2.67) lower compared to 2018/19 (5,666 cases, 10.9/100,000); this decline was seen across the individual age groups, including children aged <16 years (2.1/100,000; IRR 0.71; 95%CI, 0.11-10.00), 16-64 year-olds (4.5/100,000; IRR 0.65; 95%CI, 0.11-3.79), 65-84 year-olds (17.6/100,000; IRR 0.72; 95%CI, 0.29-1.74) and ≥85 year-olds (54.9/100,000; IRR 0.69; 95%CI, 0.42-1.76). The distribution of pneumococcal serotypes causing IPD during 2019/20 was similar to previous years and, of the 3,693 (93%) isolates with serotype information, included 19.7% PCV13 (n=729), 56.0% PPV23 (n=2,068) and 24.1% non-PPV23 (n=892) serotypes.

IPD/COVID-19 coinfections

Between 01 February 2020 and 30 June 2020, there were 160,886 laboratory-confirmed SARS-CoV-2 infections reported through Pillar 1 testing in a healthcare setting (Figure 2) and 1,137 laboratory-confirmed IPD cases, with 88 having both IPD and COVID-19 and including 40 IPD/COVID-19 co-infections predominantly during the early part of the pandemic (Table 1; Figure 3). The latter included one elderly patient who had visited the emergency department with a fall, was asymptomatic but had screened positive for SARS-CoV-2. This patient was hospitalised four days later with a respiratory illness, had a positive blood culture for *S. pneumoniae* and was included in the analysis as an IPD/COVID-19 co-infection case since his initial SARS-CoV-2 swab result was an incidental finding.

Of the remaining 48 cases with IPD and COVID-19 diagnosed >2 days apart, an older adult with malignancy was first hospitalised with mild, laboratory-confirmed COVID-19, recovered and then developed IPD as a separate episode 22 days later and survived. This patient was considered to have two separate infections and was not included as IPD/COVID-19 co-infection. The remaining 47 patients had their first positive SARS-CoV-2 test at least 3 days after their blood culture confirming IPD was taken. This group included 15 cases who tested positive for SARS-CoV-2 within 3-14 days after their blood culture confirming IPD was taken, of whom 11 had at least one negative SARS-CoV-2 swab result since presenting to hospital before subsequently testing positive for SARS-CoV-2; swab results were not available for the remaining 4 patients. Six other patients tested positive for SARS-CoV-2 at 14-27 days after their IPD diagnosis and the remaining 27 tested positive for SARS-CoV-2 infection ≥28 days after their IPD episode. The majority in the latter group had developed IPD during February and early March 2020, recovered from their illness and then developed SARS-CoV-2 infection during the peak of the epidemic in April 2020.

Both IPD and SARS-CoV-2 incidence were lowest in children during the 5-month surveillance and increased with age (Table 2). IPD/COVID-19 coinfections were identified in

0.025% (40/160,886; 95%CI, 0.018-0.034%) of patients with confirmed SARS-CoV-2 infection and 3.5% of IPD (40/1,137; 95%CI, 2.5-4.8%) cases. There were no IPD/COVID-19 co-infections in children. The risk of IPD/COVID-19 coinfection increased with age among IPD patients but to a lesser extent than IPD alone or SARS-CoV-2 alone (Table 2).. Hypertension and dementia were most commonly reported comorbidities.

There were 35 deaths within 28 days of the last infection in patients who developed IPD and COVID-19, with most deaths occurring within a week of latter infection (Figure 4). CFR was highest in the co-infection group (25/40, 63.2%) compared to 53.3% (8/15) in those with COVID-19 at 3-14 days after IPD, 33.3% for those with COVID-19 at 15-27 days after IPD (2/6 cases) and those with IPD and COVID-19 ≥28 days apart (9/27 cases) (χ^2 for trend, P<0.001). In addition to an independent association with increasing age and pneumococcal serotype group, death within 30 days was 3.88-fold (95% CI, 1.41-10.65) higher in patient who developed COVID-19 at 3-27 days after IPD and 7.75-fold (95% CI, 3.80-15.82) higher in those with IPD/COVID-19 co-infection (Table 3).

Discussion

The COVID-19 pandemic and subsequent lockdown measures were associated a large decline in IPD cases in England. The 30% decline in IPD incidence was observed across all age groups and for all pneumococcal serotype groups. Among 160,886 laboratory-confirmed SARS-CoV-2 infections confirmed in a healthcare setting, we found only 88 individuals who developed both IPD and COVID-19 during the first wave of the epidemic and only 40 IPD/COVID-19 coinfections. Contrary to our hypothesis that SARS-CoV-2 infection might predispose to secondary pneumococcal infection, we found that patients were more likely to develop COVID-19 after IPD or as a separate episode ≥28 days after IPD. Those with IPD/COVID-19 coinfection had very high CFR, which decreased with increasing interval between the two infections.

IPD decline

The decline in IPD incidence occurred during March-June 2020 when lockdown measures were implemented across the UK to control the spread of SARS-CoV-2, consistent with emerging reports of large reductions in bacterial and viral infections as a consequence of social distancing measures in countries that implemented lockdown during the COVID-19 pandemic [15]. Interestingly, we observed significant reductions in IPD cases in older adults, including ≥85 year-olds, at a time when large numbers of COVID-19 cases and deaths were reported in these age-groups [21]. The frail and elderly are at increased risk of both IPD and COVID-19 and both infections are individually associated with high CFR in this vulnerable age-group [18]. The inverse trend of decreasing IPD and increasing SARS-CoV-2 infections in older adults likely reflects differences in the source of infection and efficiency of transmission for the two pathogens. In particular, young children are considered to be the main reservoirs and source of pneumococcal infections [22], and it is likely the shielding of older adults, especially from children, during lockdown reduced their risk of IPD but not from COVID-19 which was mainly acquired from other adults, as evidenced in the extensive COVID-19 outbreaks in care homes which were driven mainly by cross-infection between residents and staff [23].

Risk of coinfection

We found very few pneumococcal coinfections associated with SARS-CoV-2 in our cohort. Interestingly, we did not identify any IPD/COVID-19 cases in children; since blood cultures are almost exclusively taken in hospital, children with IPD would have been tested for SARS-CoV-2 infection when they presented to hospital. This is consistent with the published case series, systematic reviews and meta-analyses which have so far not identified any patients with SARS-CoV-2 and pneumococcal co-infection [12]. There are limited data on bacterial coinfections with MERS or SARS [11], but reports of bacterial coinfections with influenza range between 2-65%, with *S. pneumoniae* being the most common co-infecting bacteria,

accounting for 35% (95%CI, 14%-56%) of infections in one systematic review [1]. During the influenza A(H1N1) pandemic, when there were no lockdown measures or school closures in England, data linkage similar to our current analysis identified pneumococcal co-infection rates of 8% (10/125) in <15 year-olds, 11% (33/305) in 15-44 year-olds, 4% (33/858) in ≥45 year-olds and 6% (76/1,288) of IPD cases [24]. There is currently sufficient evidence to strengthen and potentially expand pneumococcal vaccination to reduce the risk of secondary pneumococcal infections associated with influenza and particularly during influenza pandemics [3, 25]. In contrast, the very low risk, wide age range and distribution of pneumococcal serotypes causing IPD in patients with IPD/COVID-19 coinfections does not support wider immunisation with any of the currently available pneumococcal vaccines. It is, however, important to maintain high pneumococcal immunisation rates to continue to protect those who are at increased risk of pneumococcal disease after the lockdown is eased

Additionally, the low overall risk of bacterial coinfections also predicates judicious use of empiric antimicrobials in patients hospitalised with COVID-19. Up to three-quarters of patients hospitalised with COVID-19 in England receive empiric antibiotics despite the low risk of bacterial coinfections [9]. Unnecessary and widespread empiric antibiotic overuse can predispose to hospital-acquired, potentially multidrug-resistant secondary Gram-negative bacterial as well as fungal infections, which significantly increasing the risk of a fatal outcome [26, 27].

In our cohort, CFR was 63.2% in patients with IPD/COVID-19 coinfection, which is significantly higher than that reported in older adults after IPD only [18] or COVID-19 only [28], and suggests a potential synergistic effect between the two pathogens, as has been described for pneumococcal/influenza coinfections [29]. Furthermore, in addition to the 40 coinfections, we also identified 21 other patients who developed COVID-19 3-27 days after being hospitalised with IPD and 10 (47.6%) died. It is possible that at least some of these patients had IPD/COOVID-19 coinfection but our finding that 11 of the 15 IPD patients with confirmed COVID-19 at 3-14 days after IPD had negative swabs for SARS-CoV-2 when they

were hospitalised for IPD supports secondary and potentially nosocomially-acquired SARS-CoV-2 infection. This highlights the importance of maintaining stringent infection control practices in hospital [30, 31], especially for frail and elderly adults, who may be hospitalised with a minor illness but could succumb to hospital-acquired COVID-19 [32, 33]. Finally, the finding that a third of patients who developed COVID-19 more than 14 days after their IPD episode died within 30 days of their subsequent SARS-CoV-2 infection highlights the vulnerability of this group of patients, most of whom were elderly and with multiple comorbidities.

Strengths and Limitations

The strength of this study lies in the availability and rapid cross-linking of multiple national data sources alongside long-term enhanced national surveillance of vaccine-preventable infections in England. In the UK, blood cultures are invariably performed in patients who attend hospital with suspected invasive bacterial infection. We, therefore, only linked IPD cases with Pillar 1 SARS-CoV-2 tests that were performed in a healthcare setting because we hypothesised that all IPD cases would have been hospitalised and tested for SARS-CoV-2 infection on admission. There was also very limited testing for SARS-CoV-2 in the community during the first wave of the epidemic in England. Additionally, since unwell individuals were more likely to have been referred directly to hospital instead of being assessed in primary care, they were unlikely to have been have been tested for SARS-CoV-2 outside the hospital setting or prescribed oral antibiotics that might have resulted in negative blood cultures on admission. A limitation of our analysis is that we only included patients with IPD and, therefore, cannot comment on the risk of non-invasive pneumococcal infections, such as pneumonia. IPD is, however, a reliable proxy for non-invasive pneumococcal disease [34]. To support this, case series reporting sputum cultures as well as deep tracheal cultures in ventilated patients have also not identified *S. pneumoniae* in COVID-19 patients [12], while radiological assessment of patients with severe respiratory presentations have rarely reported evidence of secondary bacterial pneumonia [35, 36].

Future studies using urine serotype-specific pneumococcal antigen testing could potentially help assess the risk of non-invasive pneumococcal pneumonia in patients with COVID-19 [37]. Another limitation is that it was not possible to distinguish between coinfection and secondary bacterial infection because the patients were only tested for the virus and had blood cultures taken when they first presented to hospital with their IPD episode. Finally, some patients, especially the frail and elderly, were not admitted to hospital and died at home or in a care home [38]. Early in the pandemic, these cases were also not tested for SARS-CoV-2 and, since they were not hospitalised, would not have been investigated for bacterial coinfections. In one case series, up to 50% of patients with COVID-19 who died had a secondary bacterial infection [26], although consistent with our findings, *S. pneumoniae* was not identified as a cause.

Conclusions

The COVID-19 pandemic and the lockdown that followed to stop the spread of SARS-CoV-2 was associated with large declines in IPD across all age groups. IPD/COVID-19 confections were rare but associated with high CFR mainly in older adults. Secondary COVID-19 in patients hospitalised with IPD was also associated with high CFR, highlighting the importance of enforcing stringent infection control practices in hospitals especially for vulnerable patients such as the frail and elderly. The rarity and broad age range of cases with IPD/COVID-19 coinfections as well as the wide range of responsible pneumococcal serotypes does not support extending current recommendations for any of the available pneumococcal vaccines during the COVID-19 pandemic. Eligible individuals should continue to receive pneumococcal vaccines according to local and national recommendations.

NOTES

Acknowledgement

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases. This includes PHE's responsibility to monitor the safety and effectiveness of vaccines, and as such, individual patient consent is not required.

Role of the funding source:

This study was internally funded by PHE. The authors had sole responsibility for the study design, data collection, data analysis, data interpretation, and writing of the report. The authors are all employed by PHE, the study funder, which is a public body - an executive agency of the Department of Health. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Conflicts of interest

SNL performs contract research for vaccine manufacturers (including GSK, Pfizer, and Sanofi Pasteur) on behalf of St George's University of London and Public Health England but receives no personal remuneration. The Immunisation and Countermeasures Division at PHE has provided pharmaceutical companies with post-marketing surveillance reports on vaccine-preventable infections, which the companies are required to submit to the UK Licensing Authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. All other authors declare no competing interests.

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Table 1. Characteristics of patients with invasive pneumococcal disease (IPD) and COVID-19 by disease interval between February and June 2020 (5 months) in England.

	IPD/COVID-19 coinfection	COVID-19 3-27 days after IPD	Total (IPD and COVID-19 cases within 28 days of each other) ^	IPD and COVID-19 episodes ≥28 days apart	All cases with IPD and COVID-19 ^
	n=40	n=21	**n=62**	n=26	**n=88**
Age median, years (IQR)	79 (58-86)	77 (66-85)	**78 (58-85)**	80 (67-84)	**60 (42-85)**
Age group					
16-64y	15 (37.5%)	5 (23.8%)	**20 (32.3%)**	6 (23.1%)	**26 (29.5%)**
65-84y	14 (35.0%)	10 (47.6%)	**25 (40.3%)**	14 (53.8%)	**39 (44.3%)**
≥85y	11 (27.5%)	6 (28.6%)	**17 (27.4%)**	6 (23.1%)	**23 (26.1%)**
Sex					
Male	18 (45.0%)	7 (33.3%)	**26 (41.9%)**	10 (38.5%)	**36 (40.9%)**
Female	22 (55.0%)	14 (66.7%)	**36 (58.1%)**	16 (61.5%)	**52 (59.1%)**
Ethnic group					
White	33 (82.5%)	17 (81.0%)	**51 (82.3%)**	21 (80.8%)	**72 (81.8%)**
Black	1 (2.5%)	3 (14.3%)	**4 (6.5%)**	3 (11.5%)	**7 (8.0%)**
Asian	5 (12.5%)	1 (4.8%)	**6 (9.7%)**	1 (3.8%)	**7 (8.0%)**
Mixed	1 (2.5%)	0 (0.0%)	**1 (1.6%)**	1 (3.8%)	**2 (2.3%)**
Any comorbidity	n=40/40	n=21/21	**n=62/62**	n=26/26	**n=88/88**
Yes	29 (72.5%)	18 (85.7%)	**48 (77.4%)**	21 (80.8%)	**69 (78.4%)**
No	11 (27.5%)	3 (14.3%)	**14 (22.6%)**	5 (19.2%)	**19 (21.6%)**
Comorbidities $	n=40/40	n=21/21	**n=62/62**	n=26/26	**n=88/88**
Chronic heart disease	14 (48.3%)	7 (38.9%)	**21 (43.8%)**	10 (47.6%)	**31 (44.9%)**
Chronic respiratory disease	6 (20.7%)	4 (22.2%)	**7 (14.6%)**	10 (47.6%)	**20 (29.0%)**
Chronic liver disease	0 (0.0%)	4 (22.2%)	**3 (6.3%)**	1 (4.8%)	**5 (7.2%)**
Chronic renal disease	10 (34.5%)	5 (27.8%)	**13 (27.1%)**	6 (28.6%)	**21 (30.4%)**
Immunosuppressed/malignancy	5 (17.2%)	5 (27.8%)	**10 (20.8%)**	7 (33.3%)	**18 (26.1%)**
Diabetes mellitus	11 (37.9%)	7 (38.9%)	**17 (35.4%)**	5 (23.8%)	**23 (33.3%)**
Other	17 (58.6%)	11 (61.1%)	**28 (58.3%)**	13 (61.9%)	**41 (59.4%)**
Clinical presentation					
Meningitis	1 (2.5%)	0 (0.0%)	**1 (1.6%)**	1 (3.9%)	**2 (2.3%)**
Bacteraemic pneumonia	31 (77.5%)	15 (71.4%)	**47 (75.8%)**	16 (61.5%)	**63 (71.6%)**

Other/not reported	4 (10.0%)	4 (19.1%)	**8 (12.9%)**	4 (15.4%)	**12 (13.6%)**
Septicaemia	4 (10.0%)	2 (9.5%)	**6 (9.7%)**	5 (19.2%)	**11 (12.5%)**
ICU admission					
Yes	6 (15.0%)	0 (0.0%)	**6 (9.7%)**	4 (15.4%)	**10 (11.4%)**
No	34 (85.0%)	21 (100.0%)	**56 (90.3%)**	22 (84.6%)	**78 (88.6%)**
Died					
<28 days	25 (62.5%)	10 (47.6%)	**35 (56.5%)**	9 (33.3%)	**44 (50.0%)**
0-6 days	22 (88.0%)	4 (40.0%)	**26 (74.3%)**	7 (77.8%)	**33 (75.0%)**
7-13 days	2 (8.0%)	3 (30.0%)	**5 (14.3%)**	1 (11.1%)	**6 (13.6%)**
14-20 days	1 (4.0%)	1 (10.0%)	**2 (5.7%)**	1 (11.1%)	**3 (6.8%)**
21-27 days	0 (0.0%)	2 (20.0%)	**2 (5.7%)**	0 (0.0%)	**2 (4.5%)**
Serotype group					
Number of isolates serotyped	**n=38/40**	**n=18/21**	**n=57/62**	**n=23/26**	**n=80/88**
PCV13*	5 (13.2%)	2 (11.8%)	**8 (14.0%)**	5 (21.7%)	**13 (16.3%)**
Additional PPV23**	22 (57.9%)	9 (52.9%)	**31 (54.4%)**	12 (52.2%)	**43 (53.8%)**
Non-PPV23	11 (28.9%)	7 (41.2%)	**18 (31.6%)**	6 (26.1%)	**24 (30.0%)**

** PCV13 helps protect against the following pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, and 23F*

*** PPV23 helps protect against the following 11 serotypes in addition to PCV13: 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F.*

^ Total includes the single case who had COVID-19, recovered and then developed IPD as a separate episode 22 days later

$ Many patients had multiple comorbidities

Table 2. Incidence and incidence rate ratios of invasive pneumococcal disease (IPD) and COVID-19 between February and June 2020 (5 months) in England

a)

Age group	IPD Cases, February to June 2019		
	N (Incidence per 100,000)	**Incidence Rate Ratio [95%CI]**	**P-value**
<16	134 (1.25)	0.44 [0.37-0.53]	<0.001
16-64y	986 (2.81)	1.00 [Base]	
65-84y	923 (10.47)	3.72 [3.40-4.07]	<0.001
≥85y	397 (29.08)	10.34 [8.99-11.35]	<0.001
Total	2440 (4.36)	1.55 [1.44-1.67]	<0.001
	IPD Cases, February to June 2020		
	N (Incidence per 100,000)	**Incidence Rate Ratio [95%CI]**	**P-value**
<16	78 (0.72)	0.60 [0.47-0.76]	<0.001
16-64y	423 (1.20)	1.00 [Base]	
65-84y	445 (4.97)	4.12 [3.61-4.71]	<0.001
≥85y	191 (13.67)	11.35 [9.57-13.46]	<0.001
Total	1137 (2.02)	1.68 [1.50-1.88]	<0.001
	SARS-CoV-2 cases, February to June 2020		
	N (Incidence per 100,000)	**Incidence Rate Ratio [95%CI]**	**P-value**
<16	2252 (20.82)	0.09 [0.08-0.09]	<0.001
16-64y	82967 (236.26)	1.00 [Base]	
65-84y	46373 (517.75)	2.19 [2.16-2.21]	<0.001
≥85y	29294 (2096.85)	8.71 [8.60-8.83]	<0.001
Total	160886 (285.83)	1.21 [1.20-1.22]	<0.001

b)

Age group	IPD/COVID-19 coinfections in SARS-CoV-2 positive individuals		
	N (%)	**Rate Ratio [95%CI]**	**P-value**
<16	0 (0.00%)	-	-
16-64y	15 (0.018%)	1.00 [Base]	
65-84y	14 (0.030%)	1.67 [0.81-3.46]	0.16
≥85y	11 (0.038%)	2.08 [0.95-4.52]	0.06
Total	40 (0.025%)	1.38 [0.76-2.49]	0.29
	IPD/COVID-19 coinfections in patients with IPD		
	N (%)	**Rate Ratio [95%CI]**	**P-value**
<16	0 (-)	-	-
16-64y	15 (3.6%)	1.00 [Base]	
65-84y	14 (3.2%)	0.89 [0.43-1.82]	0.74
≥85y	11 (5.8%)	1.62 [0.76-3.47]	0.21
Total	40 (3.5%)	0.99 [0.55-1.78]	0.98

Table 3. Multivariable logistic regression to assess independent risk factors for death within 28 days of of the last infection in patients with invasive pneumococcal disease (IPD) and COVID-19 within 28 days of each other compared to those with IPD only. Patients who developed COVID-19 more than 28 days after IPD were not included in the analysis

	Baseline	IPD and COVID-19 within 28 days *	aOR [95% CI]	P-value
Age group (years)	n/N (%)	n/N (%)		
<16	77/1075 (7.2%)	0/61 (0.0%)	0.39 [0.13-1.12]	0.081
16-64	404/1075 (37.6%)	15/61 (32.8%)	Base	
65-84	420/1075 (39.1%)	14/61 (39.3%)	1.41 [0.96-2.07]	0.082
≥85	174/1075 (16.2%)	11/61 (27.9%)	3.61 [2.33-5.58]	<0.001
Serotype group				
PCV13	172/976 (17.6%)	7/55 (12.7%)	2.55 [1.70-3.83]	<0.001
Additional PPV23	558/976 (57.2%)	31/55 (56.4%)	Base	
Non-PPV23	246/976 (25.2%)	17/55 (30.9%)	1.76 [1.20-2.58]	0.004
Sex				
Male	517/1075 (48.1%)	25/61 (41.0%)	0.81 [0.58-1.12]	0.20
Female	558/1075 (51.9%)	36/61 (59.0%)	Base	
Infection type				
IPD only	N=1075	-	Base	
IPD/COVID-19 coinfection (within 2 days)	-	40/61 (65.6%)	7.75 [3.80-15.82]	<0.001
IPD followed by COVID-19 (3-27 days later)	-	21/61 (34.4%)	3.88 [1.41-10.65]	0.008

** excludes one case who had COVID-19, recovered and then developed IPD as a separate episode 22 days later*

LIST OF FIGURES

Figure 1

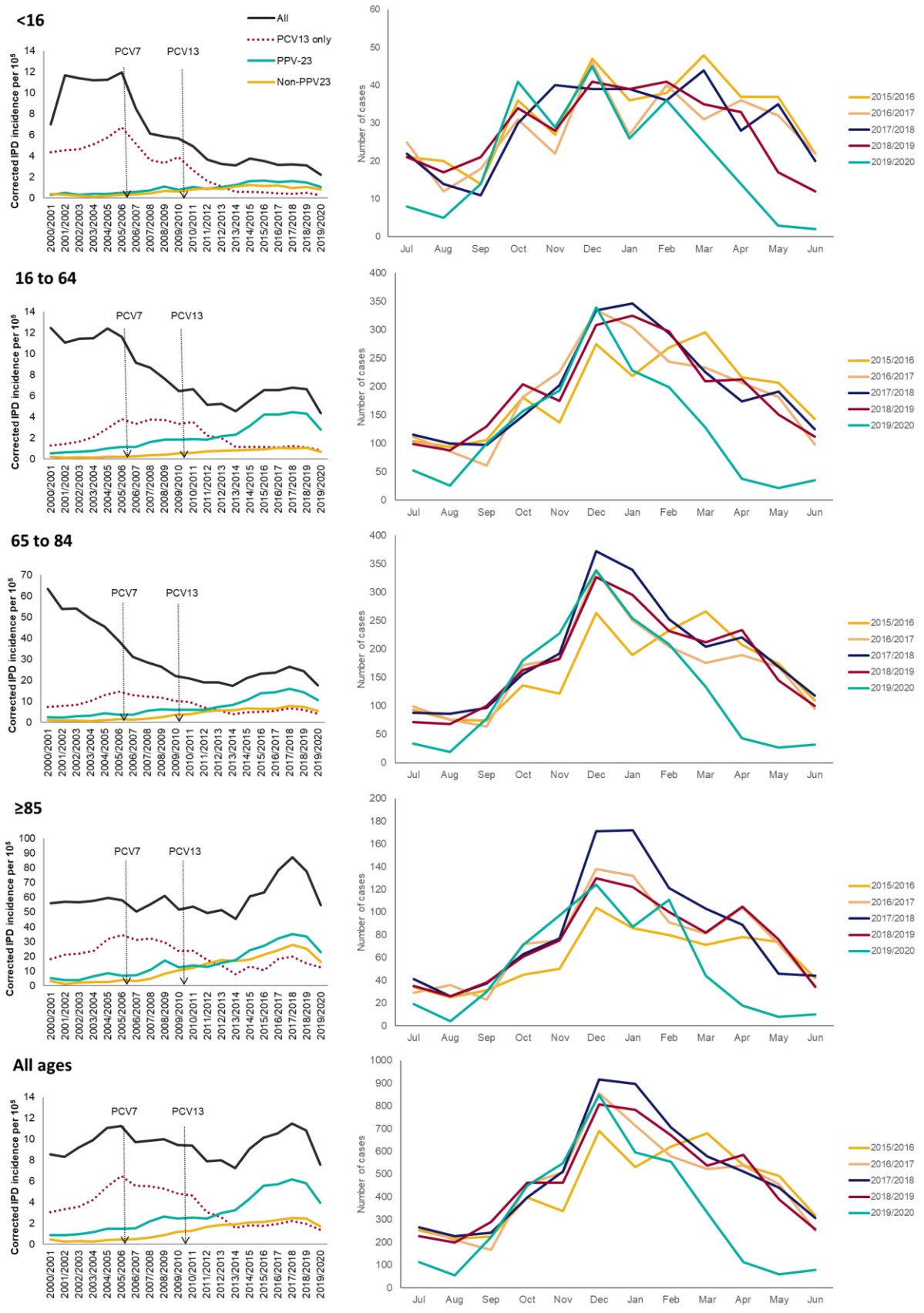
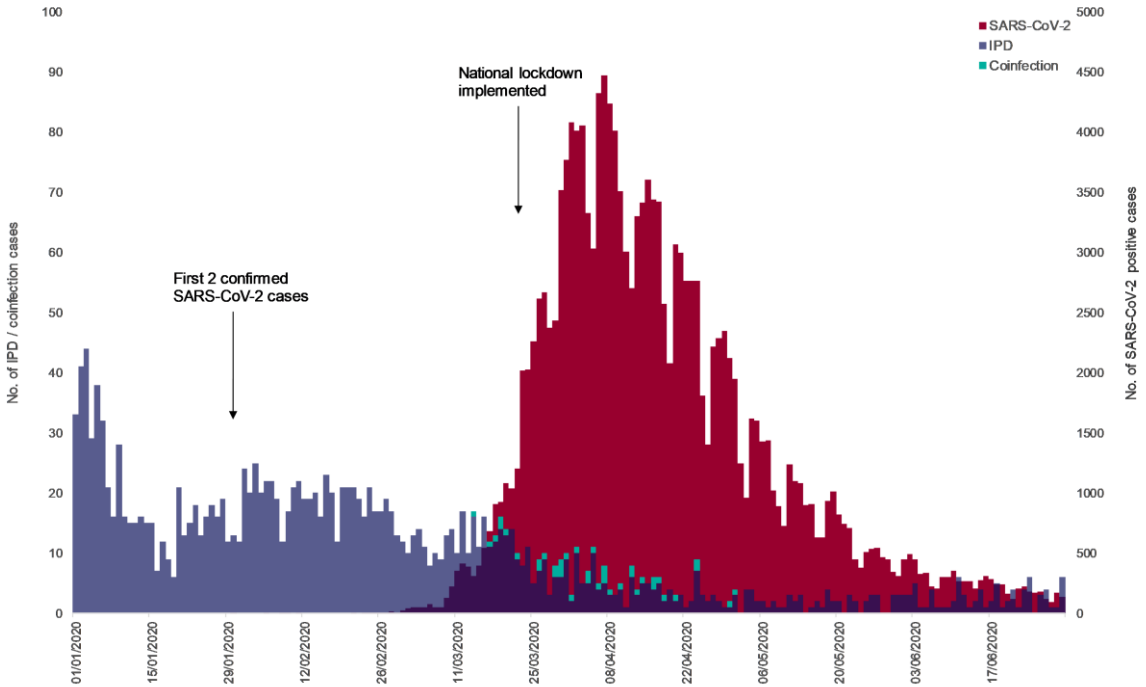

<16
All
PCV13 only
PPV-23
Non-PPV23
PCV7
PCV13
Corrected IPD incidence per 10⁵
Number of cases
2015/2016
2016/2017
2017/2018
2018/2019
2019/2020
Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun
16 to 64
65 to 84
≥85
All ages

Figure 2


SARS-CoV-2
IPD
Coinfection
National lockdown implemented
First 2 confirmed SARS-CoV-2 cases
No. of IPD / coinfection cases
No. of SARS-CoV-2 positive cases
0
10
20
30
40
50
60
70
80
90
100
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
01/01/2020
15/01/2020
29/01/2020
12/02/2020
26/02/2020
11/03/2020
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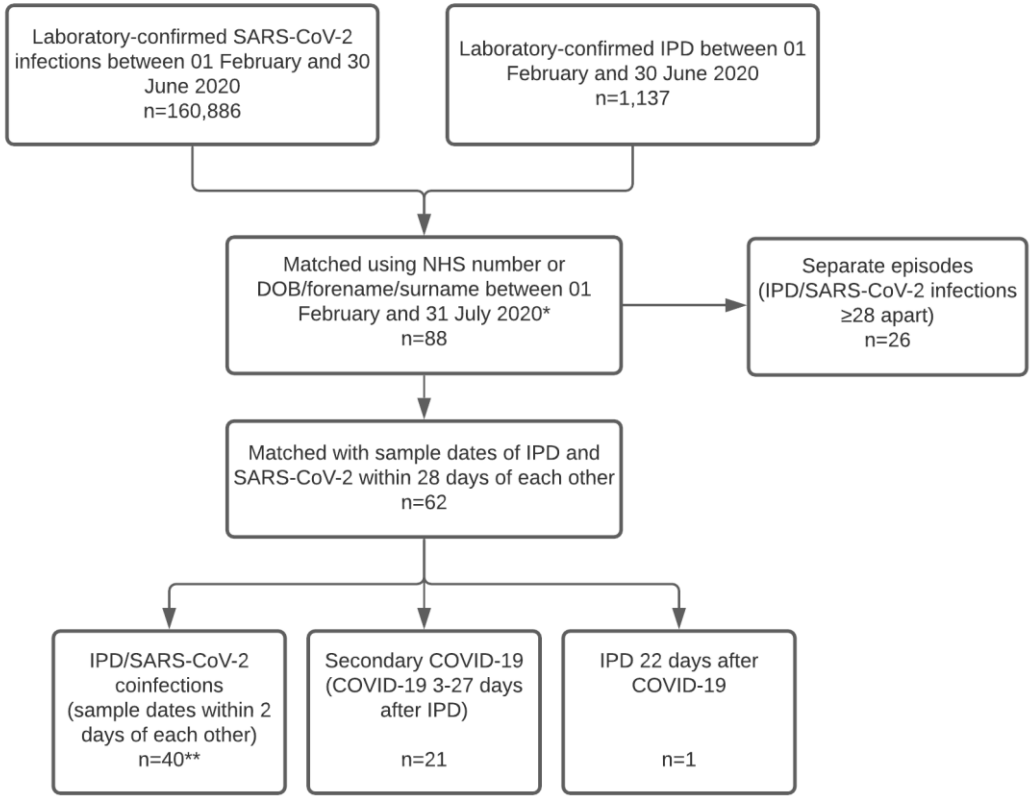
06/05/2020
20/05/2020
03/06/2020
17/06/2020

Figure 3



*IPD and SARS-CoV-2 cases were matched up to 31 July 2020 to confirm that there were no further coinfections for those initially infected with IPD/SARS-CoV-2 in June 2020.
**Included 1 elderly patient who visited the emergency department with a fall was asymptomatic and had screened positive for SARS-CoV-2 but hospitalised with a positive blood culture for *S. pnuemoniae* 4 days later due to SARS-CoV-2 infection being an incidental finding.

Figure 4