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Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Invasive Pneumococcal Disease and Risk of Pneumococcal Coinfection With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Prospective National Cohort Study, England

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(See the Editorial Commentary by Howard on pages e76–8.)

Background. *Streptococcus pneumoniae* coinfection with influenza results in synergistic lethality, but there are limited data on pneumococcal coinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods. Public Health England conducts invasive pneumococcal disease (IPD) and SARS-CoV-2 surveillance in England. IPD trends during 2000/2001–2019/2020 epidemiological years were analyzed and cases during February–June 2020 linked with laboratory-confirmed SARS-CoV-2 infections. Multivariable logistic regression was used to assess risk factors for death.

Results. IPD incidence in 2019/2020 (7.6/100 000; n = 3964) was 30% (IRR, .70; 95% CI, .18–2.67) lower compared with 2018/2019 (10.9/100 000; n = 5666), with large reductions observed across all age groups during March–June 2020. There were 160 886 SARS-CoV-2 and 1137 IPD cases during February–June 2020, including 40 IPD/coronavirus disease 2019 (COVID-19) co-infections (.025% [95% CI, .018–.034] of SARS-CoV-2 infections; 3.5% [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 (CFRs) were 62.5 (25/40), 47.6% (10/21), and 33.3% (9/27), respectively ($P < .001$). In addition to an independent association with increasing age and serotype group, CFR was 7.8-fold (95% CI, 3.8–15.8) higher in those with IPD/COVID-19 coinfection and 3.9-fold (95% CI, 1.4–10.7) higher in patients who developed COVID-19 3–27 days after IPD compared with patients with IPD only.

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

Keywords. pneumococcal disease; bacterial coinfection; nosocomial infection; case fatality; risk factor.

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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), typically manifests as a respiratory tract infection and presents with fever and cough [5], which may progress to severe pneumonia, multiorgan failure, and death, especially in older adults and those with underlying comorbidities [6–8]. Bacterial coinfection with COVID-19, however, appears to be uncommon [9–11]. A meta-analysis of mainly small case series estimated that 3.5% of patients with COVID-19 had a bacterial coinfection and 14.3% had a secondary bacterial infection [12]. These infections occurred mainly in 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 United Kingdom implemented national lockdown

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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 (PHE) 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 coinfection and to describe the demographics, responsible serotypes, comorbidity status, clinical features, and outcomes of patients with IPD/COVID-19 coinfection during the first wave of the 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 Immunization Program

In the United Kingdom, 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 1 January 2020, a reduced infant 1 + 1 infant immunization schedule at 12 weeks and 1 year was implemented in the United Kingdom [17]. In addition, children aged 2 years or older and adults with underlying comorbidities that predispose them to IPD and all adults aged 65 years and older are offered a single dose of 23-valent pneumococcal polysaccharide vaccine (PPV23) [18].

National Surveillance

Public Health England 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 the general practitioner to complete a surveillance questionnaire on immunization history, comorbidities, clinical presentations, complications, and outcomes. A final reconciled database containing laboratory-confirmed IPD cases during the 2000/2001 to 2019/2020 epidemiological years (July to June, 20 years) was used for this analysis.

The SGSS also contains reports of laboratory-confirmed SARS-CoV-2 infections in England. In the United Kingdom, SARS-CoV-2 tests are performed through different routes called "Pillars" [20]. In Pillar 1, SARS-CoV-2 real-time reverse transcription–polymerase chain reaction (RT-PCR) tests are undertaken on respiratory swabs by PHE laboratories and National Health Service (NHS) hospitals for those with a clinical need and for healthcare and care workers. This group was prioritized 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 1 February to 30 June 2020 (5 months) using full name, sex, birth date, reporting hospital, and site and date of sample. The IPD and SARS-CoV-2 cases confirmed in June 2020 were linked with cases until 31 July 2020. Deaths were confirmed using the personal demographic service, an online national database that holds demographic data and death status for NHS patients.

Definitions

Invasive pneumococcal disease 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 a hospital for any illness were routinely tested for SARS-CoV-2 infection at presentation and, if hospitalized, 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 analyzed using Stata v.15.0 (StataCorp, College Station, TX). Corrected annual IPD incidence by epidemiological year and serotype group (PCV13, PPV23, non-PPV23) were calculated as previously described, adjusting for missing proportion of isolates serotyped and missing age [19], using population denominators from the Office for National Statistics (www.statistics.gov.uk). We estimated the proportion of coinfections and secondary infections in individuals with IPD and SARS-CoV-2 infection between 1 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 (CFRs) 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 (CIs) and compared using the chi-square or Fisher's exact test as appropriate. A multivariable logistic regression model was fitted to assess risk factors associated with 30-day CFRs 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 2019/2020 in England (Figure 1). Most of the decline was observed between March and June 2020. The incidence of IPD in 2019/2020 (3964 cases, 7.6/100 000) was 30% (incidence rate ratio [IRR], .70; 95% CI, .18–2.67) lower compared with 2018/2019 (5666 cases, 10.9/100 000); this decline was seen across the individual age groups, including children aged less than 16 years (2.1/100 000; IRR, .71; 95% CI, .11–10.00), 16- to 64-year-olds (4.5/100 000; IRR, .65; 95% CI, .11–3.79), 65- to 84-year-olds (17.6/100 000; IRR, .72; 95% CI, .29–1.74), and individuals aged 85 years and older (54.9/100 000; IRR, .69; 95% CI, .42–1.76). The distribution of pneumococcal serotypes causing IPD during 2019/2020 was similar to previous years and, of the 3693 (93%) isolates with serotype information, included 19.7% PCV13 (n = 729), 56.0% PPV23 (n = 2068), and 24.1% non-PPV23 (n = 892) serotypes.

Invasive Pneumococcal Disease/COVID-19 Coinfections

Between 1 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 1137 laboratory-confirmed IPD cases, with 88 having both IPD and COVID-19 and including 40 IPD/COVID-19 coinfections predominantly during the early part of the pandemic (Table 1, Figure 3). The latter included 1 elderly patient who had visited the emergency department after a fall and who was asymptomatic but had screened positive for SARS-CoV-2. This patient was hospitalized 4 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 coinfection case since his initial SARS-CoV-2 swab result was an incidental finding.

Of the remaining 48 cases with IPD and COVID-19 diagnosed more than 2 days apart, an older adult with malignancy was first hospitalized 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 2 separate infections and was not included as an IPD/COVID-19 coinfection. 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 1 negative SARS-CoV-2 swab result since presenting to the 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 15–27 days after their IPD diagnosis and the remaining 27 tested positive for SARS-CoV-2 infection 28 days or later 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 was lowest in children during the 5-month surveillance and increased with age (Table 2). Coinfections with IPD/COVID-19 were identified in .025% (40/160 886; 95% CI, .018–.034%) of patients with confirmed SARS-CoV-2 infection and 3.5% of IPD (40/1137; 95% CI, 2.5–4.8%) cases. There were no IPD/COVID-19 coinfections in children. The risk of IPD/COVID-19 coinfection increased with age among patients with IPD but to a lesser extent than IPD alone or SARS-CoV-2 alone (Table 2). Hypertension and dementia were the 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 1 week of the latter infection (Figure 4). The CFR was highest in the coinfection group (25/40, 62.5%) compared with 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 or more apart (9/27 cases) (χ^2 for trend, $P < .001$). 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-fold) higher in patients who developed COVID-19 at 3–27 days after IPD and 7.75-fold (95% CI, 3.80–15.82-fold) higher in those with IPD/COVID-19 coinfection (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 or more after IPD. Those with IPD/COVID-19 coinfection had very high CFRs, which decreased with increasing interval between the 2 infections.

Invasive Pneumococcal Disease Decline

The decline in IPD incidence occurred during March–June 2020 when lockdown measures were implemented across the United Kingdom 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

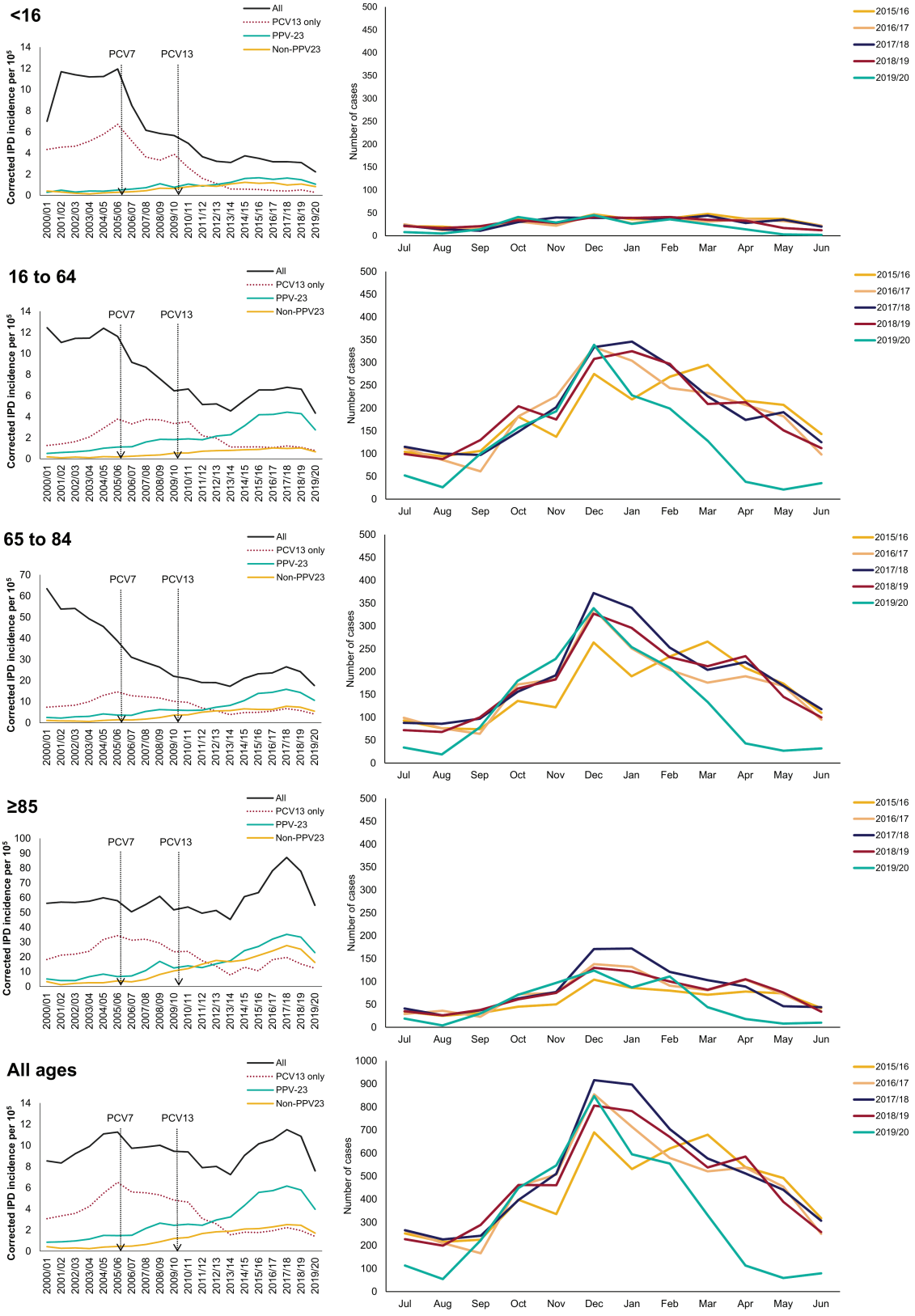

Figure 1. Corrected incidence of IPD in England by age group and serotype group, 2000–2020. The arrows indicate the timing of introduction of the 7-valent (PCV7) and the 13-valent (PCV13) pneumococcal conjugate vaccines. Abbreviations: IPD, invasive pneumococcal disease; PPV23, 23-valent pneumococcal polysaccharide vaccine.

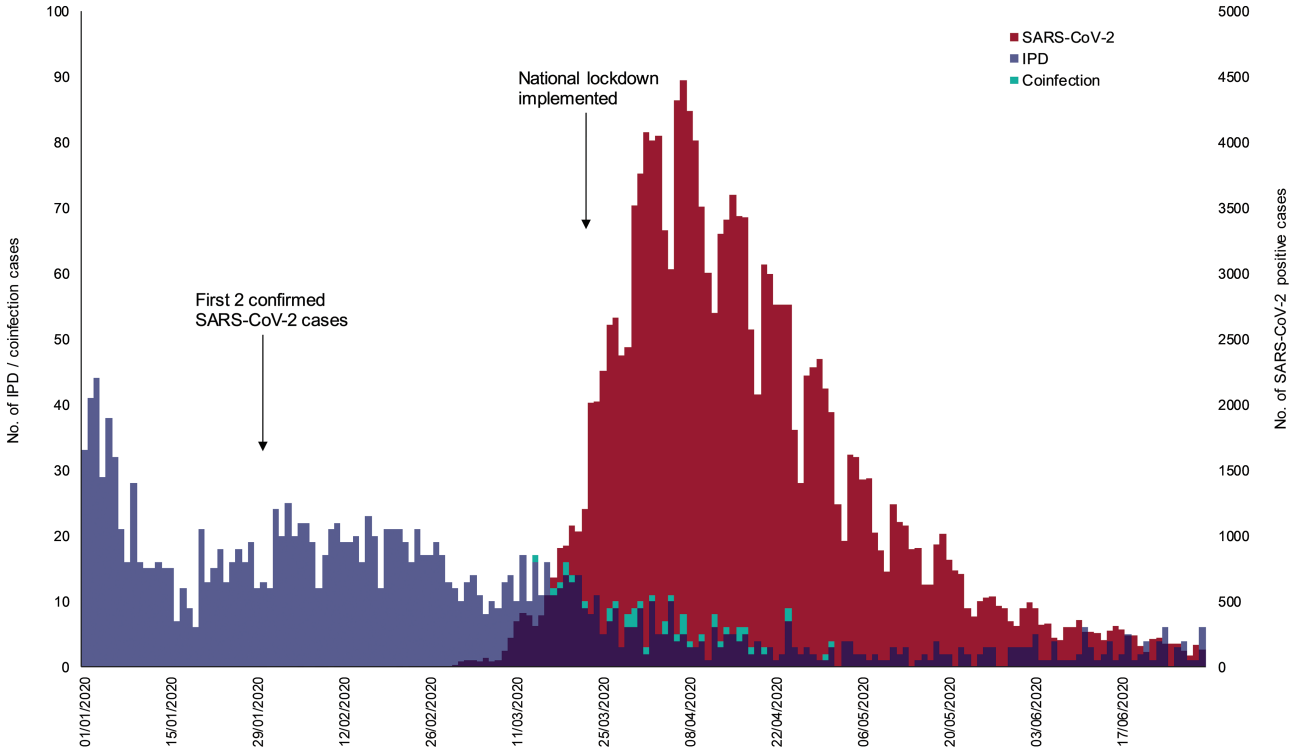

Figure 2. Number of cases of IPD, SARS-CoV-2, and coinfections during the first peak (1 February to 30 June 2020) of the COVID-19 pandemic in England. Abbreviations: COVID-19, coronavirus disease 2019; IPD, invasive pneumococcal disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

countries that implemented lockdown during the COVID-19 pandemic [15]. Interestingly, we observed significant reductions in IPD cases in older adults, including those aged 85 years and older, 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 CFRs 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 2 pathogens. In particular, young children are considered to be the main reservoirs and source of pneumococcal infections [22], and it is likely that 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 nursing homes that 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 the hospital, children with IPD would have been tested for SARS-CoV-2 infection when they presented to a hospital. This is consistent with the published case series, systematic reviews, and meta-analyses that have so far not identified any patients with SARS-CoV-2 and pneumococcal coinfection [12]. There are limited data on bacterial coinfections with Middle East respiratory syndrome (MERS) or severe acute respiratory syndrome (SARS) [11], but reports of bacterial coinfections with influenza range between 2% and 65%, with *S. pneumoniae* being the most common coinfecting bacteria, accounting for 35% (95% CI, 14–56%) of infections in 1 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 coinfection rates of 8% (10/125) in children younger than 15 years, 11% (33/305) in 15- to 44-year-olds, 4% (33/858) in those aged 45 years and older, and 6% (76/1288) 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 do not support wider immunization with any of the currently available pneumococcal vaccines. It is, however, important to maintain high pneumococcal

Table 1. Characteristics of Patients With Invasive Pneumococcal Disease and COVID-19 by Disease Interval Between February and June 2020 (5 Months) in England

	IPD/COVID-19 Coinfection (n = 40)	COVID-19 3–27 Days After IPD (n = 21)	Total (IPD and COVID-19 Cases Within 28 Days of Each Other)[a] (n = 62)	IPD and COVID-19 Episodes ≥28 Days Apart (n = 26)	All Cases With IPD and COVID-19[a] (n = 88)
Age, median (IQR), years	79 (58–86)	77 (66–85)	78 (58–85)	80 (67–84)	60 (42–85)
Age group, n (%)					
16–64 years	15 (37.5)	5 (23.8)	20 (32.3)	6 (23.1)	26 (29.5)
65–84 years	14 (35.0)	10 (47.6)	25 (40.3)	14 (53.8)	39 (44.3)
≥85 years	11 (27.5)	6 (28.6)	17 (27.4)	6 (23.1)	23 (26.1)
Sex, n (%)					
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, n (%)					
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 (%)	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[b]	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, n (%)					
Meningitis	1 (2.5)	0 (0.0)	1 (1.6)	1 (3.9)	2 (2.3)
Bacteremic 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, n (%)					
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, n (%)					
<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, n (%)					
Number of isolates serotyped	n = 38/40	n = 18/21	n = 57/62	n = 23/26	n = 80/88
PCV13[c]	5 (13.2)	2 (11.8)	8 (14.0)	5 (21.7)	13 (16.3)
Additional PPV23[d]	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)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IPD, invasive pneumococcal disease; IQR, interquartile range; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

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

[b]Many patients had multiple comorbidities.

[c]PCV13 helps protect against the following pneumococcal serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, and 23F.

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

immunization 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 hospitalized with COVID-19. Up to three-quarters of

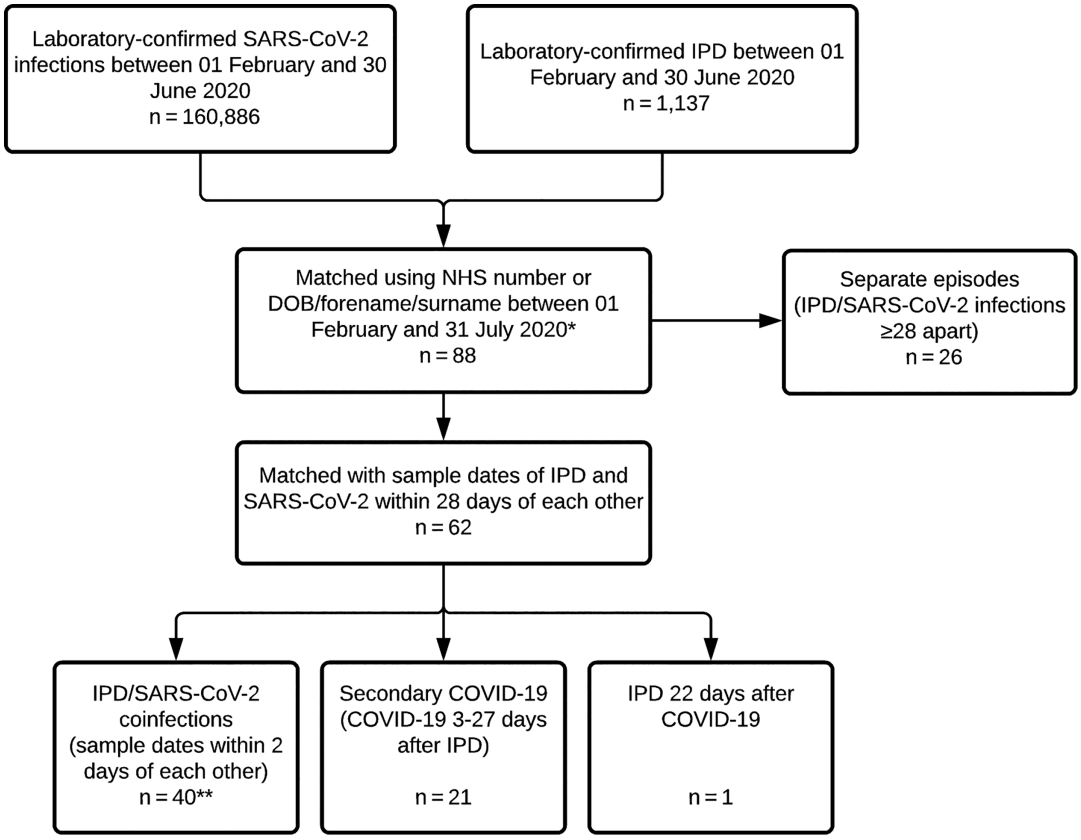

Figure 3. Flowchart of laboratory-confirmed cases with IPD and COVID-19 between 1 February and 30 June 2020 (5 months) in England. *IPD and SARS-CoV-2 cases were matched up to 31 July 2020 to confirm that there were no further coinfections for those initially infected with IPD/SARS-CoV-2 in June 2020. **Included 1 elderly patient who visited the emergency department after a fall, was asymptomatic, and had screened positive for SARS-CoV-2 but was hospitalized with a positive blood culture for *Streptococcus pneumoniae* 3 days later due to SARS-CoV-2 infection being an incidental finding. Abbreviations: COVID-19, coronavirus disease 2019; DOB, date of birth; IPD, invasive pneumococcal disease; NHS, National Health Service; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

patients hospitalized 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 increase the risk of a fatal outcome [26, 27].

In our cohort, the CFR was 62.5% 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 2 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 hospitalized with IPD and 10 (47.6%) died. It is possible that at least some of these patients had IPD/COVID-19 coinfection, but our finding that 11 of the 15 patients with IPD with confirmed COVID-19 at 3–14 days after IPD had negative swabs for SARS-CoV-2 when they were hospitalized for IPD supports secondary and potentially nosocomially acquired SARS-CoV-2 infection. This highlights the importance of maintaining stringent infection-control practices in the hospital [30, 31], especially for frail and elderly adults, who may be hospitalized with a minor illness but could succumb to hospital-acquired COVID-19 [32, 33]. Finally, the finding that one-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 United Kingdom, blood cultures are invariably performed in patients who present to a 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 hypothesized that all IPD cases would have been hospitalized and tested for SARS-CoV-2 infection on admission. There was also very limited testing for SARS-CoV-2 in the community during the

Table 2. Incidence and Incidence Rate Ratios of Invasive Pneumococcal Disease and COVID-19 Between February and June 2020 (5 Months) in England

Age Group	n (Incidence per 100 000)	Incidence Rate Ratio [95% CI]	*P*
IPD cases, February to June 2019			
<16 years	134 (1.25)	.44 [.37–.53]	<.001
16–64 years	986 (2.81)	1.00 [Base]	
65–84 years	923 (10.47)	3.72 [3.40–4.07]	<.001
≥85 years	397 (29.08)	10.34 [8.99–11.35]	<.001
Total	2440 (4.36)	…	
IPD cases, February to June 2020			
<16 years	78 (0.72)	.60 [.47–.76]	<.001
16–64 years	423 (1.20)	1.00 [Base]	
65–84 years	445 (4.97)	4.12 [3.61–4.71]	<.001
≥85 years	191 (13.67)	11.35 [9.57–13.46]	<.001
Total	1137 (2.02)	…	
SARS-CoV-2 cases, February to June 2020			
<16 years	2252 (20.82)	.09 [.08–.09]	<.001
16–64 years	82 967 (236.26)	1.00 [Base]	
65–84 years	46 373 (517.75)	2.19 [2.16–2.21]	<.001
≥85 years	29 294 (2096.85)	8.71 [8.60–8.83]	
Total	160 886 (285.83)	…	
	n (%)	Rate Ratio [95% CI]	
IPD/COVID-19 coinfections in SARS-CoV-2–positive individuals			
<16 years	0 (—)	…	
16–64 years	15 (0.018)	1.00 [Base]	
65–84 years	14 (0.030)	1.67 [0.81–3.46]	.16
≥85 years	11 (0.038)	2.08 [0.95–4.52]	.06
Total	40 (0.025)	…	
IPD/COVID-19 coinfections in patients with IPD			
<16 years	0 (—)	…	
16–64 years	15 (3.6)	1.00 [Base]	
65–84 years	14 (3.2)	0.89 [0.43–1.82]	.74
≥85 years	11 (5.8)	1.62 [0.76–3.47]	.21
Total	40 (3.5)	…	

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; IPD, invasive pneumococcal disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

first wave of the epidemic in England. Additionally, since unwell individuals were more likely to have been referred directly to the hospital instead of being assessed in primary care, they were unlikely to 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 noninvasive pneumococcal infections, such as pneumonia. Invasive pneumococcal disease is, however, a reliable proxy for noninvasive 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 patients with COVID-19 [12], while radiological assessments 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 noninvasive 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 the hospital with their IPD episode. Finally, some patients, especially the frail and elderly, were not admitted to the 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 hospitalized, would not have been investigated for bacterial coinfections. In 1 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. Invasive pneumococcal disease/COVID-19 coinfections were rare but associated with high CFRs, mainly in older adults. Secondary COVID-19 in

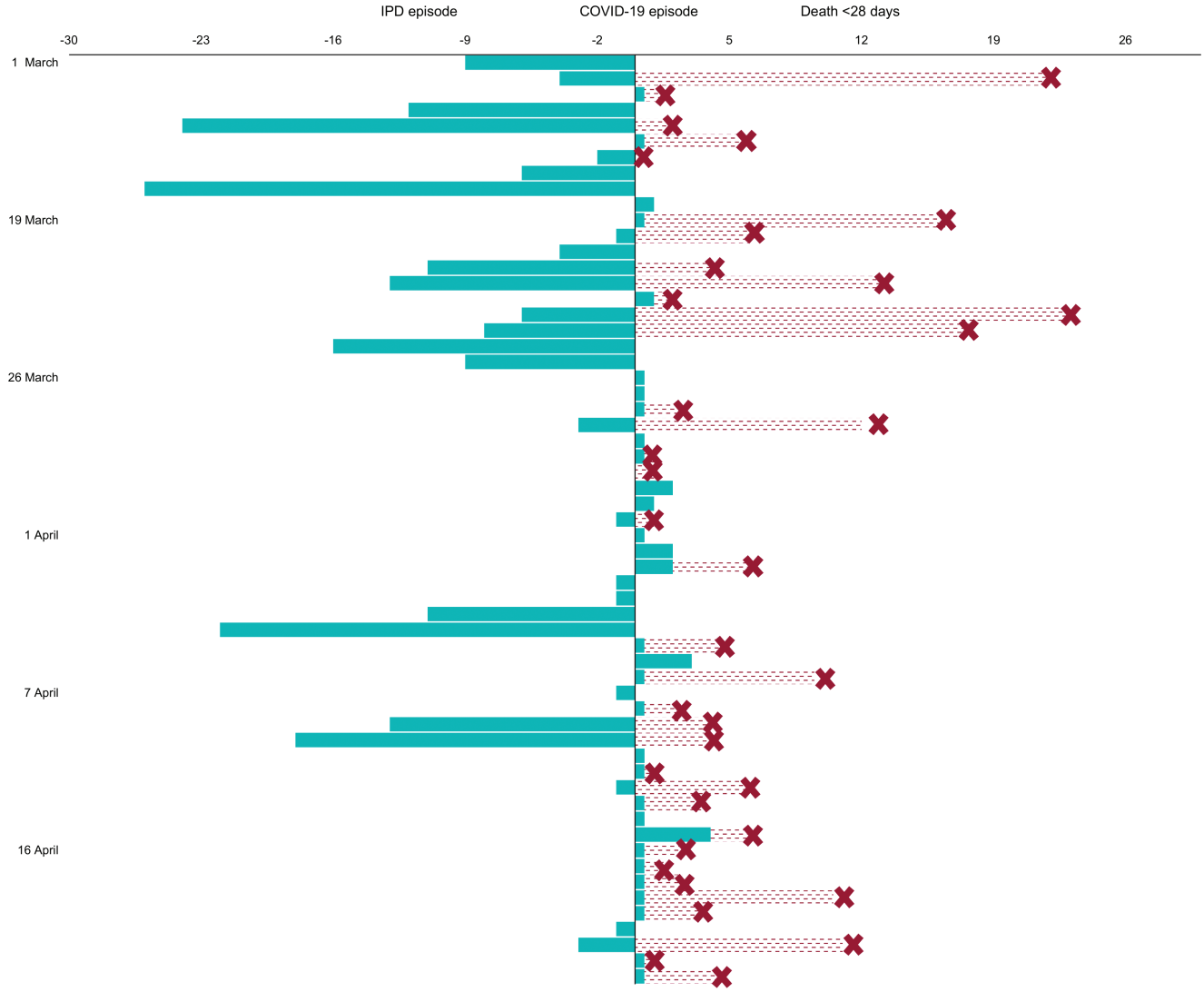

Figure 4. Timeline of IPD and COVID-19 infections in patients who developed both infections within 28 days between 1 February and 30 June 2020 (5 months) in England. The teal bars on the left of the vertical line (day 0) depict the interval in days between IPD and COVID-19 diagnosis, while the teal bars on the right of the vertical line (day 0) depict the interval in days between COVID-19 and IPD diagnosis (those within 2 days of each other were considered IPD/COVID-19 coinfections). The dashed red lines followed by the symbol "X" represent time to death for fatal cases. Abbreviations: COVID-19, coronavirus disease 2019; IPD, invasive pneumococcal disease.

patients hospitalized with IPD was also associated with high CFRs, 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 do 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

Acknowledgments. Public Health England (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.

Disclaimer. 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 Public Health England, 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.

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Potential conflicts of interest. S. N. L. 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 (PHE) but receives no personal remuneration. The Immunisation and Countermeasures Division at PHE has provided pharmaceutical companies with postmarketing surveillance reports on vaccine-preventable infections, which the companies are required to submit to the UK Licensing Authority

Table 3. Multivariable Logistic Regression to Assess Independent Risk Factors for Death Within 28 Days of the Last Infection in Patients With Invasive Pneumococcal Disease (IPD) and COVID-19 Within 28 Days of Each Other Compared With Those With IPD Only

	Baseline, n/N (%)	IPD and COVID-19 Within 28 Days,[a] n/N (%)	aOR [95% CI]	*P*
Age group				
<16 years	77/1075 (7.2)	0/61 (0.0)	.39 [.13–1.12]	.081
16–64 years	404/1075 (37.6)	15/61 (32.8)	Base	
65–84 years	420/1075 (39.1)	14/61 (39.3)	1.41 [.96–2.07]	.082
≥85 years	174/1075 (16.2)	11/61 (27.9)	3.61 [2.33–5.58]	<.001
Serotype group				
PCV13	172/976 (17.6)	7/55 (12.7)	2.55 [1.70–3.83]	<.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]	.004
Sex				
Male	517/1075 (48.1)	25/61 (41.0)	.81 [.58–1.12]	.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]	<.001
IPD followed by COVID-19 (3–27 days later)	…	21/61 (34.4)	3.88 [1.41–10.65]	.008

Patients who developed COVID-19 more than 28 days after IPD were not included in the analysis. Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

[a]Excludes 1 case who had COVID-19, recovered, and then developed IPD as a separate episode 22 days later.

in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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