

# Protecting adults at risk of pneumococcal infection and influenza from exposure to SARS-CoV-2

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## ABSTRACT

There is a paucity of evidence linking pneumococcal infection and influenza with SARS-CoV-2 and COVID-19. There is circumstantial evidence of the possibility of an association between *S. pneumoniae* and SARS-CoV-2 such as the increased binding of *S. pneumoniae* to coronavirus-infected human airway epithelium, the frequent use of broad-spectrum antibiotics in the management of COVID-19 which could mask secondary bacterial infection, and the observation that pneumococcal vaccination is associated with decreased SARS-CoV-2 nasopharyngeal swab positivity. We performed a targeted literature review for the year 2020, using search terms *S. pneumoniae*, influenza, SARS-CoV-2, and found 25 relevant articles of a total of 291. Pneumococcal and influenza vaccinations have the potential to contribute toward efforts aimed at reducing the health burden of SARS-CoV-2, especially by reducing preventable admissions to hospital for pneumonia and the consequent risk of nosocomial SARS-CoV-2 transmission.

## ARTICLE HISTORY

Received 19 February 2021  
Revised 30 June 2021  
Accepted 15 July 2021

## KEYWORDS

*Streptococcus pneumoniae*; SARS-CoV-2; COVID-19; influenza; nosocomial infection; secondary bacterial infection; co-infection; vaccination

## Background and rationale

Pneumococcal infections historically have played a role in pandemics, namely influenza pandemics.<sup>1</sup> However, the evidence for the role of pneumococcal infections in SARS/MERS is equivocal.<sup>2</sup> There is laboratory experimental evidence that non-SARS coronaviruses can facilitate the binding of *S. pneumoniae* onto respiratory epithelium (Figure 1).<sup>3</sup> However, associations between pneumococcal infection and SARS-CoV-2 infections are thus far not clear. The use of antimicrobials may be “masking” underlying bacterial infections in SARS-CoV-2 and possibly the very population that is at risk of SARS-CoV-2/COVID-19 has a level of pneumococcal and influenza vaccination that may be contributing toward lowering the morbidity in SARS-CoV-2/COVID-19. Pneumococcal and influenza vaccination have the potential to contribute toward efforts aimed at reducing the health burden of SARS-CoV-2, especially by reducing preventable admissions to hospital for pneumonia and the consequent risk of nosocomial SARS-CoV-2 transmission. Performing a clinical trial to explore co-infections and the role of pneumococcal and influenza vaccination in SARS-CoV-2 morbidity would be impractical. We therefore sought to perform a targeted literature review with the following aims:

## Aims

- Explore the role of *S. pneumoniae* and influenza in the current SARS-CoV-2 pandemic

- Explore the role of pneumococcal and influenza vaccination in preventing hospital admissions for pneumonia in the current SARS-CoV-2 pandemic, and thereby the possibility of preventing subsequent morbidity and mortality
- Inform future and further research

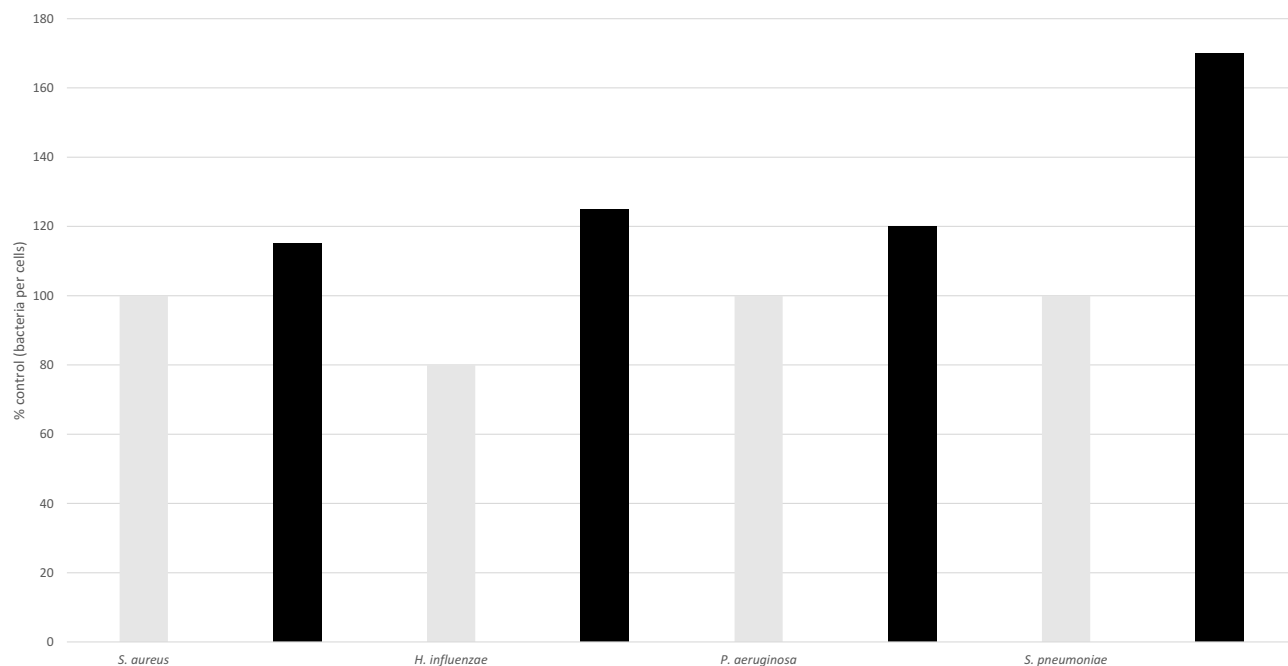
## Objectives

- Perform a targeted literature review (Medline/OVID and PubMed) using the search terms: *Streptococcus pneumoniae*, influenza, SARS-CoV-2
- Include all study designs peer-reviewed or in the process of being peer-reviewed, and performed from 1 January to 31 December 2020, published in English
- Inform future and further research in *S. pneumoniae*, influenza and SARS-CoV-2

## Methodology

We performed a targeted literature review using (Medline/OVID and PubMed) and using the following search terms for the period 1 January to 31 December 2020: *Streptococcus pneumoniae*, influenza, SARS-CoV-2. We included all study designs which were peer-reviewed or in the process of being peer-reviewed, performed in the year 2020. Our search yielded 291 articles of which 25 were relevant.

The review is structured as follows:



**Figure 1.** Number of bacteria that attached to mock (gray) or HCoV-NL63 infected LLC-MK2 (black) cells as a percentage of the control.<sup>3</sup> The differences for *S. aureus*, *H. influenzae* and *P. aeruginosa* are not significant; the difference for *S. pneumoniae* is significant.

- (1) Documentation of the extent to which nosocomial COVID-19 is a problem
- (2) The extent to which pneumococcal infections and influenza are problems in hospitalized COVID-19 patients, both those primarily admitted with COVID-19 and those with nosocomial COVID-19
- (3) The extent to which pneumococcal and influenza vaccination might diminish these problems

## The extent to which nosocomial COVID-19 is a problem

### Risk of nosocomial SARS-CoV-2 infection

Even with a safe and effective vaccine against SARS-CoV-2, it may be some time until there is sufficient community-wide protection for those at highest risk of contracting COVID-19 to be protected. In the meantime, avoiding unnecessary contact with the healthcare setting constitutes one way of decreasing exposure risk and preventing nosocomial infection.<sup>4-6</sup> In the 2020 UK study by Rickman *et al.* of 435 cases of PCR-positive COVID-19 inpatients over a six-week period, 47 (11%) had met the definition for definite hospital acquisition whilst a further 19 (4%) probably acquired the infection in hospital.<sup>6</sup> The median time from admission to symptom onset in these 66 hospital-acquired cases was 26 days (IQR 13 to 55 days) indicating that the patients were in hospital for a substantial amount of time before contracting COVID-19.

In China, the proportion of nosocomial COVID-19 infection has been reported to be 44%.<sup>7</sup> The authors concluded: “A large proportion of confirmed cases of COVID-19 were infected within healthcare facilities.” However, another study which was designed to determine the frequency of nosocomially-acquired COVID-19 infection found that, over a 12-week

period and considering 9149 US patients suspected of having COVID-19 of which 697 were confirmed, only two cases were thought to be acquired nosocomially.<sup>8</sup>

All SARS-CoV-2 positive patients at a south-east London tertiary care facility, from 1 March to 18 April 2020, who developed symptoms >14 days after admission were classified as having hospital-associated COVID-19.<sup>9</sup> Approximately 5000 patients were tested for SARS-CoV-2 and of those 1729 tested positive. Of these, 865 (50%) were admitted to hospital within 14 days of testing. A total of 58 (7.1%) of COVID-19 cases in hospital were classified as having been acquired in hospital and a potential source patient was identified in 44 instances. Underlying risk factors for hospital-acquired infection included neurological, musculoskeletal, respiratory, renal, gastrointestinal, liver, cardiac, hematological and endocrine conditions, as well as dementia and HIV. Study results demonstrated that hospital transmission of SARS-CoV-2 could be initiated by “carriers” who may not have been showing symptoms and thus would not have been placed under respiratory precautions. In their conclusions, the authors recommended admission screening for all patients.

The risk of healthcare-associated acquisition of SARS-CoV-2 by healthcare workers has also been studied.<sup>10</sup> At the University Hospital Münster in Germany, from February to July 2020, 7760 healthcare workers, inpatients and outpatients were tested for SARS-CoV-2, of whom 357 were positive. Twenty-seven index cases of hospital-associated SARS-CoV-2 infection could be identified and were followed up to investigate any further transmission the hospital. Of these cases, 23 were healthcare workers and 4 were incidentally detected in patients who were asymptomatic on admission. In other words, healthcare workers played an important role as a link in the introduction of SARS-CoV-2 from the community to the hospital.

Another study of the potential for nosocomial transmission of SARS-CoV-2, performed at three hospitals in the south of The Netherlands in March 2020, involved the screening of 1,796 healthcare workers.<sup>11</sup> Of the 1,796 healthcare workers screened (15% of a population of 12,022 healthcare workers), 96 (5%) tested positive for SARS-CoV-2. Further, it was concluded that widespread nosocomial transmission as the source of infection in patients and healthcare workers was not occurring. Although nosocomial COVID-19 is definable, identifiable and measurable, the extent of the problem may not be extensive.

## The extent to which pneumococcal infections and influenza are problems in hospitalized COVID-19 patients

### Co-infections and SARS-CoV-2

In Wuhan, China, co-infections by other respiratory pathogens in patients with COVID-19 were found to be relatively common.<sup>12</sup> Of 250 patients hospitalized with COVID-19, 39 (15%) tested positive for at least one respiratory pathogen in addition to SARS-CoV-2. However, *Streptococcus pneumoniae* did not feature amongst these pathogens. Similarly, in 116 SARS-CoV-2 positive respiratory samples from California, 24 (20.7%) were positive for one or more additional pathogens with *Streptococcus pneumoniae* again not featured amongst them.<sup>13</sup>

In a retrospective, multicentre cohort study including all adult inpatients ( $\geq 18$  years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020, demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records and compared between survivors and non-survivors.<sup>14</sup> The investigators used univariate and multivariate logistic regression methods to explore the risk factors for death and reported that of 191 COVID-19 patients, 27 of 54 (50%) of patients that died had evidence of secondary bacterial infections (although the organisms were not documented).

Over a slightly longer time-course, 1 January to 17 April 2020, a systematic review and meta-analysis was designed to document the proportion of COVID-19 patients with bacterial, fungal or viral co-infections.<sup>15</sup> Patients of all ages in all settings were included. The majority of the 3834 patients included in the 30 studies were adults ( $n = 3748$ ) with a range of median ages from 42 to 63 years, but only three small studies reported data exclusively for children ( $n = 86$ ). Antibiotic use was reported in 17 of the 30 studies, with  $>90\%$  of patients in 10 studies receiving

empirical antibiotics. For hospitalized patients with COVID-19, the overall pooled proportion of patients who had laboratory-confirmed bacterial co-infections was 7% (95% confidence interval 3% to 12%). Specific co-infecting pathogens were identified in 17 studies but *S. pneumoniae* did not feature amongst these.

A living rapid review and meta-analysis, which included 24 studies (of 1308 publications reviewed from December 2019 to March 2020) and 3338 patients (predominantly adult), to explore data on bacterial co-infection and secondary infection in patients with COVID-19 found that bacterial co-infection was evident in 3.5% of patients on presentation and that secondary bacterial infection occurred in 14.3% of the patients (although *S. pneumoniae* was not represented)<sup>16</sup>

In addition to the above there are case studies. For example, a female COVID-19 patient in her 80s with several underlying conditions had a positive urinary antigen test for *S. pneumoniae* and succumbed to respiratory infection despite antimicrobial treatment.<sup>17</sup>

In a review of laboratory results from inpatient and outpatient facilities in New York City, USA, 8990 (54.8%) of 16,408 patients tested positive for SARS-CoV-2.<sup>18</sup> Among a subset of 1204 who also tested positive by multiplex PCR, only 36 (3%) had concurrent influenza or RSV infection. The investigators did not determine whether those with co-infection had more severe illness. This question was addressed by UK investigators who found that patients infected with both influenza virus and SARS-CoV-2 were at greater risk of more severe illness.<sup>19</sup> Among 19,256 COVID-19 patients, the likelihood of those with COVID-19 was 58% lower among those with influenza compared with those without influenza. However, the 58 patients with co-infection had an increased risk of mortality compared to those with COVID-19 alone (OR = 5.92; 95% CI 3.32% to 10.91%). Among those with co-infection, 43.1% died compared with 26.9% of those with only SARS-CoV-2 infection. Mortality rates in co-infected patients rose in those 70–79 years of age and 80 years of age and older (57.1% and 66.7% respectively). In Turkey, the rate of influenza co-infection with COVID-19 in adult patients was reported to be 0.54%.<sup>20</sup>

Although *S. pneumoniae* is an infrequent cause of secondary or concomitant bacterial infection, cases of invasive pneumococcal disease (IPD) in England were 30% lower in 2019–202 compared with a year earlier (7.7 compared with 10.9 per 100,000; incidence ratio 0.7; 95% confidence interval 0.18 to 2.67 (Table 1).<sup>21</sup> Although IPD and COVID-19 co-infections were rare, they were associated with higher case fatality rates (CFRs)  $<28$  days (10/21, 47.6%) compared with  $\geq 28$  days after (9/27, 33.3%) the diagnosis of IPD ( $p < .001$ ). Causative serotypes were not documented. CFRs in co-infected patients

**Table 1.** Number of invasive pneumococcal disease (IPD) and COVID-19 cases in England (February to June 2020) along with the case fatality rates.<sup>21</sup>

	Number	Case-fatality rate	160,886 SARS-CoV-2 infections	95% confidence interval	1,137 IPD cases	95% confidence interval
IPD co-infection in COVID-19	40	25/40* (63.2%)	0.025%	0.018 to 0.034	3.5%	2.5 to 4.8
COVID-19 diagnosed 3 to 27 days after IPD	21	10/21* (47.6%)				
COVID-19 diagnosed $\geq 28$ days after IPD	27	9/27* (33.3%)				

\*  $p < .001$ .

were higher than average yearly CFRs in the UK (19%) during the period 2006–2016.<sup>22</sup>

From 12 March to 16 April 2020, 26 of 92(28%) adult ICU patients with severe COVID-19 in Argenteuil, France, who were cultured within 48 hours of admission were considered to have a co-infection with a pathogenic bacterium.<sup>23</sup> Among all 32 isolates, *S. pneumoniae* (6/32, 31%) ranked with MRSA (n = 10/32, 31%), *H. influenzae* (n = 7/32; 22%) and Enterobacteriaceae (n = 5/32; 16%) as the most common bacterial co-infections.

## The extent to which pneumococcal and influenza vaccination might diminish these problems

### Role of pneumococcal vaccine in preventing hospitalization and pneumonia

In a Japanese study of hospitalized patients  $\geq 65$  years of age during 2014–2018, 1355 patients were retrospectively enrolled including 1045 who had not been vaccinated against *S. pneumoniae* and 315 who had.<sup>24</sup> Prior pneumococcal vaccination was associated with shorter all-cause hospital stays (adjusted RR = 0.66, 95% CI 0.57 to 0.76) and with reduced all-cause in-hospital mortality (adjusted OR = 0.42, 95% CI 0.22 to 0.83).

In a US study of 62,918 consecutive adults hospitalized with community-acquired pneumonia from 1999 to 2003 at 109 community and teaching hospitals, 7390 (12%) had a record of prior pneumococcal vaccination.<sup>25</sup> Pneumococcal vaccinees were less likely to die of any cause during hospitalization when compared with those with no vaccination (adjusted OR 0.50, 95% CI 0.43 to 0.59). Another important finding was that pneumococcal vaccination reduced the median length of hospital stay by two days compared with no vaccination ( $p < .001$ ).

A Spanish study evaluated the effectiveness of 23-valent pneumococcal polysaccharide vaccine (PPSV23) in preventing hospital admission for community-acquired pneumonia (CAP) in adults  $\geq 65$  years of age over the period 1 May 2005 to 31 January 2007.<sup>26</sup> Cases with CAP were matched with three age- and sex-matched controls. Among 489 cases and 1,467 controls, the overall adjusted effectiveness of PPSV23 was 23.6% (95% CI 0.9% to 41.0%).

### Potential role of pneumococcal vaccination in preventing SARS-CoV-2

A national Italian web-based survey was established in April 2020 using the European Commission's open-source official EUSurvey management tool to collect data about behaviors and vaccination history.<sup>27</sup> The inclusion criteria were:

- 18 years of age or older
- Having access to a mobile phone, computer or tablet with internet connectivity
- Giving informed consent on-line to participate in the study

The self-administered questionnaire covered socio-demographic variables, clinical factors including chronic conditions and medications, vaccinations (including unspecified pneumococcal vaccines and unspecified influenza vaccines in the preceding 12 months), lifestyle and behaviors, including behaviors during lockdowns. From April to June 2020 there were 198,828 respondents with a mean age of 48 years, a standard deviation of 14.7 years and of whom 59.7% were female; 170,731 were aged between 18 and 64 years whilst 28,097 were aged from 65 to 104 years. Of those aged 18 to 64 years of age, 16% had received influenza vaccination and 2% pneumococcal vaccination, whilst 53% and 13% respectively of those aged 65 to 104 years had received influenza vaccination and pneumococcal vaccination. Table 2 shows the characteristics of study participants associated with positive versus negative SARS-CoV-2 nasopharyngeal swab results (disease not specified).<sup>27</sup>

The study reported that the EPICOV19 respondents who had received a pneumococcal vaccination in the previous year had a lower probability of having a positive SARS-CoV-2 test in comparison with their non-vaccinated counterparts. History of pneumococcal vaccination in the preceding 5 years was not included in the questionnaire. Such a question may have revealed higher rates of pneumococcal vaccination. What cannot be excluded, however, is the possibility that there had been an increasing vaccination coverage with pneumococcal conjugate vaccine in children resulting in a decline in adult pneumococcal infection through indirect protection. The “healthy user” effect may also have been a potential confounder (*vide infra*). Whilst the findings need to be confirmed in further studies such as a propensity score matched case-control study, pneumococcal vaccination was associated with a 39% and 44% lower probability of a positive SARS-CoV-2 nasopharyngeal swab in younger and older participants respectively.

### Potential role of influenza vaccination in preventing SARS-CoV-2

The EPICOV19 study showed that individuals 65 years of age and older appeared not to have been protected against SARS-CoV-2 infection through influenza vaccination although there was a marginal protection in those less than 65 years of

**Table 2.** Probability of a SARS-CoV-2 positive nasopharyngeal swab according to influenza and pneumococcal vaccination status.<sup>27</sup>

	All			18 to 64 years of age			65 to 104 years of age		
	OR	95% CI	p-Value	OR	95% CI	p-Value	OR	95% CI	p-Value
<b>(a) Not adjusted model</b>									
Flu vaccine during previous autumn	1.02	0.91–1.15	0.7387	0.86	0.75–0.99	0.0301	0.83	0.60–1.14	0.2440
Pneumococcal vaccination	0.77	0.58–1.02	0.0635	0.67	0.46–0.97	0.0342	0.42	0.26–0.66	0.0002
<b>(b) Adjusted model*</b>									
Flu vaccine during previous autumn	0.89	0.78–1.01	0.1408	0.85	0.74–0.98	0.0235	0.87	0.59–1.28	0.4826
Pneumococcal vaccination in previous 12 months	0.56	0.41–0.75	0.0001	0.61	0.41–0.91	0.0156	0.56	0.33–0.95	0.0313



age (Table 2).<sup>27</sup> However, it is not clear from the study whether or not the influenza vaccine was well-matched with the circulating influenza virus strains.

By contrast, a US study of 27,201 patients tested for SARS-CoV-2 found that the odds of testing positive for SARS-CoV-2 were reduced by 24% in patients who had received influenza vaccine compared with those who had not (Odds Ratio of 0.76 with a 95% confidence interval 0.68 to 0.86,  $p < .001$ ).<sup>28</sup> Those receiving influenza vaccination had higher rates of comorbidities, such as chronic pulmonary disease, than those who were unvaccinated. However, the authors note that the observed protective association may have been confounded by differences in behavior, response to social distancing and mask orders, and by socioeconomic factors. There are subtle ways, such as dysregulation of the innate immune response, that the influenza virus may increase the susceptibility to SARS-CoV-2 virus infection at the level of the receptors in the lower respiratory tract.<sup>29</sup> There are also possible immunological mechanisms, such as the “bystander” effect, by which influenza vaccination could at least decrease the severity of COVID-19.<sup>30</sup>

## Discussion

Pneumococcal infection has historically contributed to morbidity and mortality associated with pandemic respiratory viruses. However, its contribution to COVID-19 morbidity and mortality through co-infection has thus far not been clearly elucidated, based upon the available evidence. Although it has been previously concluded that the majority of deaths associated with the 1918–19 influenza pandemic were the direct result of secondary bacterial pneumonia, it has not yet been explained why children who were infected with the same influenza virus and colonized with the same bacteria as adults had relatively few deaths.<sup>1</sup> Then and now with COVID-19, it could well be the host response and not the bacterial infection or the virus itself that is more directly responsible for mortality. There needs to improved data confirming or not confirming the roles of pneumococcal infection and influenza as risk factors for COVID-19 hospitalization and nosocomial COVID-19. This is especially important for influenza because the COVID-19 pandemic has been associated with a low occurrence of influenza in both the Southern and Northern hemispheres.<sup>31</sup> Whether influenza virus infection returns to its usual seasonal pattern in countries with high SARS-CoV-2 vaccination rates remains to be seen.

It should be noted that definitive pathogen identification was not available in several cited studies that reported suspected bacterial co-infection. Whilst co-infection results are equivocal, our review suggests that preventing pneumococcal disease and influenza may reduce morbidity and perhaps mortality arising from COVID-19 by reducing the risk for hospital-acquired infection and the severity of COVID-19.

Whilst the Rickman *et al.* 2020 study suggests that a substantial period of time in hospital may need to elapse before nosocomial acquisition of SARS-CoV-2 occurs, nevertheless decreasing contact with the healthcare system in general and hospitalizations in particular are documented benefits of pneumococcal vaccination.<sup>6</sup> There is thus the potential for pneumococcal vaccination to decrease the likelihood of the

nosocomial acquisition of SARS-CoV-2, especially those at highest risk with underlying conditions and/or immunosuppression. However, whilst pneumococcal vaccination may be associated with fewer cases of fatal COVID-19 in hospitalized patients, it is unclear whether potential confounding variables such as the “healthy user” effect have been ruled out.

Secondly, pneumococcal vaccination by potentially reducing the circulation of resistant *S. pneumoniae* could assist in the rationalization of antimicrobial chemotherapy in COVID-19 patients and in efforts to institute antimicrobial stewardship.

Thirdly, there are both theoretical immunological explanations and circumstantial evidence which point to the potential protective effect of influenza vaccination against SARS-CoV-2.

Our approach does have limitations and may not exhaustively represent all available evidence that is continuing rapidly to evolve over the course of the SARS-CoV-2 pandemic, for example a report from Spain that pneumococcal pneumonia had occurred in 3% of COVID-19 patients.<sup>32</sup> There may also be studies in languages other than English which address these questions but which we have not included. We were unable to find any randomized controlled trials which address the interrelationships between *S. pneumoniae*, influenza and SARS-CoV-2 nor such trials comparing vaccination versus non-vaccination and outcomes such as co-infection or nosocomial SARS-CoV-2 infection. Lastly, our approach may have missed salient search terms which could have inserted bias into our search results.

Targeted interventions other than population-based pneumococcal and influenza vaccination are likely to have a greater impact on COVID-19, for example, active treatment of PCR-positive individuals that reduce symptomatic and severe COVID-19, and of course SARS-CoV-2 vaccination itself.

Further research is required, including the use of indirect and molecular methods for diagnosis, to document the likely burden of pneumococcal infection in those exposed to SARS-CoV-2 and, in turn, those with COVID-19. Comparative studies, comparing jurisdictions with relatively high adult pneumococcal and influenza vaccination coverage with those with relatively low coverage, and yet similar overall exposure to SARS-CoV-2, could elucidate any links as could case-control studies.

More basic research at the microbiome level could confirm whether or not *S. pneumoniae* is more adherent to the human respiratory epithelium infected with SARS-CoV-2 and what are the interactions of influenza and SARS-CoV-2 at the receptor level. More widespread use of the EUSurvey management tool could confirm the finding from Italy that pneumococcal vaccination is associated with a lower probability of a positive SARS-CoV-2 nasopharyngeal swab.<sup>27</sup>

Another interesting avenue of research is to explore the possibility that cross-reactivity between SARS-CoV-2 proteins, the carrier protein CRM<sub>197</sub> and proteins in pneumococcal vaccines could deliver some degree of protection against SARS-CoV-2.<sup>33</sup>

Finally, the need for more widespread use of pneumococcal and influenza vaccination does not need to be justified by the presence of a SARS-CoV-2 pandemic. By a systematic review of coverage and factors associated with uptake of these vaccines, as was undertaken in Australia for example, improved

programs can be designed which include official national vaccination coverage targets, incentives, key performance indicators and better coverage in highly at-risk and vulnerable populations.<sup>34</sup>

## Conclusions

National and international guidelines on adult pneumococcal and influenza vaccination are already in place, noting at the same time that pediatric pneumococcal and influenza vaccination can impact rates of adult disease by means of reducing transmission. Pneumococcal and influenza vaccination also have the potential to decrease the nosocomial transmission of SARS-CoV-2 by decreasing hospitalizations for pneumonia and decreasing the severity of COVID-19. With a safe and effective SARS-CoV-2 vaccine, the co-administration of such a vaccine with pneumococcal and influenza vaccines needs to be explored.

## Acknowledgments

We would like to thank Karyn Davis of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA for editorial assistance.

## Disclosure of potential conflicts of interest

EDGM and KF are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own stock or stock options in Merck & Co., Inc., Kenilworth, NJ, USA, a company that develops and manufactures pneumococcal vaccines, and which is developing vaccines against SARS-CoV-2

## Funding

Funding provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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