



## Short communication

## A new call for influenza and pneumococcal vaccinations during COVID-19 pandemic in Italy: A SIP/IRS (Italian Respiratory Society) and SITA (Italian Society of Antiinfective therapy) statement

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## ABSTRACT

Influenza and pneumococcal disease represent a well-known burden on healthcare systems worldwide, as well as they still have an attributed morbidity and mortality, especially in elderly individuals and vulnerable populations. In the context of the ongoing pandemic of COVID-19, a series of considerations in favor of extensive influenza and pneumococcal vaccination campaign are emerging, including a possible reduction of hospital extra burden and saving of sanitary resources. In addition, recent studies have suggested that prior vaccinations towards non SARS-CoV-2 pathogens might confer some protection against COVID-19. In this paper the authors consider all factors in support of these hypotheses and provide a consensus statement to encourage influenza and pneumococcal vaccinations in targeted populations.

## 1. Introduction

The coronavirus disease 2019 (COVID-19) was declared a pandemic on March 11, 2020, by the World Health Organization (WHO) [1]. Since then, COVID-19 has caused more than two million deaths and the overload of healthcare systems at a global level. Mortality and severe complications mainly occurred in vulnerable populations and older adults; hence, SARS-CoV-2 vaccination was recommended with priority in these subjects [2]. These vulnerable groups are also recommended to receive both influenza and pneumococcal vaccinations in view of the higher rate of influenza- and pneumococcal-related complications in

comparison to the general population [3]. Thus, immunization services were early reinstated and maintained in order to reduce the burden of vaccine-preventable respiratory syndromes in the context of the ongoing pandemic. Regarding this issue, recent studies have also speculated a potential protective effects of prior non SARS-CoV-2 vaccinations towards COVID-19 and its outcomes [4].

In this paper the authors consider this burden of evidence and provide a consensus statement on the role of influenza and pneumococcal vaccinations during COVID-19 pandemic in Italy.

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## 2. Risk of mortality for preventable respiratory infections

Although preventable, both seasonal influenza and pneumococcal diseases still cause a significant amount of severe cases and death each year [5–8].

Seasonal influenza epidemics implies a well-documented burden on healthcare systems during winter time and result in considerable mortality with estimates of 250,000–500,000 death annually [9]. Older age and comorbidities accounted as the most common risk factors for influenza-related complications including mortality [5,6].

*S. pneumoniae*-related disease is a relevant cause of mortality worldwide resulting in 1.6 million deaths each year [7]. Between 2007 and 2017, more than 10,000 invasive pneumococcal disease (IPD) cases were notified in Italy with the highest incidence and an increasing trend among individuals aged 65 years and over. Despite appropriate treatment, IPD-related mortality has been reported up to 10–25% of patients. On the other side, the burden of pneumococcal CAP is still significant across European countries with *Streptococcus pneumoniae* isolation in 38% of outpatients and 27% of in-hospital patients and mortality ranging from 7% to >40% following the severity of the disease [8].

It is finally worthy to note that co-infections of both influenza and common bacteria including *S. pneumoniae* accounted up to 10% of cases and resulted in a significant increase of the risk of unfavourable outcome, especially among older individuals [10].

## 3. Consideration of vaccine coverage

Despite proactive recommendations and public health policies on vaccinations worldwide, immunization for both influenza and pneumococcal disease are still far from acceptable rates in most countries [11,12].

A 2018 report edited by the European Centre for Disease Prevention and Control (ECDC) highlighted that, in front of the goal of vaccinating 75%, median vaccination coverage was only 47% and 45% for older individuals and patients with chronic medical conditions, respectively [12]. In Italy, among adults  $\geq 18$  years, vaccination coverage during the 2020–2021 season was 23.7%, while this percentage increased to 65.3% –but still under the threshold–across vulnerable populations [13].

Relating to *Streptococcus pneumoniae*, as a proof of effectiveness the prevalence of invasive and non-invasive pneumococcal disease has drastically decreased both in children and elderly population after the implementation of pneumococcal conjugate vaccines [14]. However, pneumococcal vaccination coverage still has low rates in many countries including Italy, where the cumulative total does not exceed 24–30% [15].

## 4. The impact of influenza and pneumococcal vaccinations on COVID-19 pandemic

In the context of COVID-19 pandemic, the role of viral and bacterial co-infections has gained increasing attention. First, translational data on MERS suggested that co-infections can enhance the infectivity of SARS-CoV-2, contributing to lung inflammation, evolution of pneumonia and disease severity throughout immunological response [16]. Regarding severe disease, the association between SARS-CoV-2 and other viruses was reported up to 35% of severe patients and included influenza viruses (mainly, influenza A), respiratory syncytial virus (RSV) and adenoviruses [17]. On the other side, bacterial co-infection was frequent among COVID-19 patients with *Streptococcus pneumoniae* as the most common, followed by *Klebsiella pneumoniae* and *Haemophilus influenzae* in a series of prospective observational studies across Europe [18]. Specifically, bacterial co-infections was more often observed in critically ill patients during hospitalization with predominance of gram-negative bacteria including *Pseudomonas aeruginosa* and *Escherichia coli*. COVID-19 patients suffering from hospital-acquired super-infections showed worse clinical outcomes compared to patients with no bacterial infection [19].

Second, in the light of a possible resurgence of influenza infection in the next winter season, a proactive approach to immunization can reduce influenza and pneumococcal related medical visits and Emergency Room admissions, thus alleviating the burden for healthcare systems, sparing medical resources and enabling better COVID-19 diagnosis and surveillance [5,20]. Recent studies revealed that influenza and pneumococcal immunizations had a significant implication in mitigating both COVID-19 infection and clinical outcomes [21–23]. A cornerstone meta-analysis of observational studies involving more than 290,327 participants found that prior exposure to influenza vaccination represented an independent protective factor against risk of SARS-CoV-2 infection, especially in patients older than 60 years. The same analysis did not show significant associations with clinical outcomes including hospitalization, admission to intensive care unit and mortality [5]. Among the possible explanations, the authors suggested that individuals who had routinely received influenza vaccine in the previous years were more likely to have a better adherence to COVID-19 prevention measures. In addition, immunized people might have had less exposure to high-risk areas, including medical facilities and hospitals. However, a possible effect of viral vaccines in the induction of a non-specific activation of innate immunity cannot be excluded. Pneumococcal vaccination was associated to a reduction in the risk of SARS-CoV-2 infection, as well as rates of pneumococcal vaccination were reported to inversely correlate with prevalence and mortality from COVID-19 [24]. The analysis of US and Italian regional data confirmed these previous results demonstrating positive correlations between IPD prevalence and COVID-19 rates, as well as negative correlation between pneumococcal vaccination and COVID-19 rates [4]. Bernstein and colleagues analysed international data on both influenza and pneumococcal vaccination rates and reported that the influenza vaccination rate in adults  $\geq 65$  years, in combination with pneumococcal vaccination rate, provided significantly higher protection against the risk of COVID-19 compared to individual vaccines [4]. Therefore, the authors hypothesized a possible protective synergism between pneumococcal and influenza vaccines in preventing the acquisition of SARS-CoV-2.

## 5. The SIP/SITA statement

Considering the following factors:

- 1 influenza and pneumococcal disease are preventable diseases that are still affected by residual attributable mortality;
- 2 co-infections with either influenza viruses or *Streptococcus pneumoniae* are reported in COVID-19 patients and might have a negative impact on clinical outcome;
- 3 prevention of both influenza and pneumococcal-related hospital admissions might help to reduce extra burden for healthcare systems and save sanitary resources;
- 4 on the base of recent evidence, it is possible to speculate that prior immunization with non SARS-CoV-2 vaccines might lower the risk of COVID-19 infection and adverse clinical outcomes;

The authors recommend a proactive effort to provide influenza vaccination to the general population with special attention to high-risk groups and elderly individuals paralleled by a strong improvement in pneumococcal vaccination coverage for these same groups of patients. National and regional authorities and stakeholders should promote extensive vaccination campaigns and ensure adequate availability as well as suitable facilities for vaccine administration.

## 6. Future research

The speculations that prior immunizations with non SARS-CoV-2 vaccines might have a protective effect against COVID-19 open new questions in both epidemiological reports and translational research. First, we lack data estimating the real occurrence of bacterial as well as

viral co-infection during COVID-19. In this context, we have reasons to suspect that co-infections are more common than reported and that we are missing them during routine surveillance. Large scale epidemiological studies should be implemented especially in prevision of future SARS-CoV-2 epidemics across European countries. Second, there is still little information concerning the phenomenon called 'viral interference', defined as the protective effect of a previous viral immunization toward a secondary infection from a different virus. A clear notion is not yet available on the extent to which post-vaccination immunity can also protect against other respiratory viruses including SARS-CoV-2; what are the immunological mechanisms underlying this phenomenon and whether they are temporary or not; whether this mechanism is also shared by other events such as pneumococcal vaccination and if they combine each other with a synergistic effect. Overall, it is still necessary to acquire a full understanding of the mechanisms by which a specific immunization affects susceptibility or resistance to other circulating pathogens.

### Author Contributions

FB, MdP, AG, PV, CI, AG, MT, SE, LR, MB contributed equally to the manuscript. All authors participated in the design or implementation or analysis, and interpretation of the literature review and in the development of this manuscript and in its critical review with important intellectual contributions.

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