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REVIEW

Potential effects of vaccinations on the prevention of COVID-19: rationale, clinical evidence, risks, and public health considerations

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ABSTRACT

Introduction Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), has quickly spread around the world.

Areas covered This review will discuss the available immunologic and clinical evidence to support the benefit of the influenza, pneumococcal, and tuberculosis vaccines in the context of COVID-19 as well as to provide an overview on the COVID-19-specific vaccines that are in the development pipeline. In addition, implications for vaccination strategies from a public health perspective will be discussed.

Expert opinion Some vaccines are being considered for their potentially beneficial role in preventing or improving the prognosis of COVID-19: influenza, pneumococcal and tuberculosis vaccines. These vaccines may have either direct effect on COVID-19 via different types of immune responses or indirect effects by reducing the burden of viral and bacterial respiratory diseases on individual patients and national healthcare system and by facilitating differential diagnoses with other viral/bacterial respiratory disease. On the other hand, a large number of candidate vaccines against SARS-CoV-2 are currently in the pipeline and undergoing phase I, II, and III clinical studies. As SARS-CoV-2 vaccines are expected to be marketed through accelerated regulatory pathways, vaccinovigilance as well as planning of a successful vaccination campaign will play a major role in protecting public health.

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1. Introduction

Coronavirus disease (COVID-19) is an infectious disease first reported in the city of Wuhan (China) which quickly spread to the rest of the world [1]. COVID-19 is caused by the newly discovered severe acute respiratory syndrome coronavirus (SARS-CoV-2). Since the outbreak, more than 16.4 million cases of COVID-19 have been worldwide confirmed, with 653,862 deaths as of July 28th, 2020 [2]. The current lack of effective interventions to prevent or treat COVID-19 infection has turned clinicians' attention to repurpose already available treatments for off-label use of COVID-19, while waiting for the results of the many ongoing clinical studies of specific SARS-CoV-2 vaccines [3]. In addition, there is growing interest in some of the existing vaccines which prevent viral or bacterial respiratory diseases, specifically the influenza vaccine, the pneumococcal vaccine and tuberculosis Bacillus Calmette-Guérin (BCG) vaccine, as these may hypothetically play a role in COVID-19 prevention. This interest is triggered by evidence that live attenuated vaccines, such as the BCG vaccine, appear to protect against other seemingly unrelated pathogens [4]. In addition, the role of other vaccines concerning more common respiratory diseases, such as influenza and *Streptococcus pneumoniae*- respiratory infections, also came under scrutiny since contracting these diseases may make persons more vulnerable to COVID-19. It has therefore been suggested that the influenza, pneumococcal, and the BCG vaccines may have direct benefits concerning COVID-19 infection [5,6], but the underlying pre-clinical and clinical evidence has not been yet explored in detail. They may also have indirect benefits, such as reducing the burden of preventable super-infections among COVID-19 patients as well as facilitating differential diagnosis in patients with symptoms related to respiratory infections. The increased uptake of these three vaccines may have implications on vaccination campaigns addressing frail and elderly populations in the coming months [7]. On the other hand, a large number of candidate vaccines against SARS-CoV-2 are currently in the pipeline, undergoing phase 1, 2, and even 3 studies, as reported in clinicaltrials.gov, and emerging findings has been starting to be published [8,9]. As SARS-CoV-2 vaccines are expected to be marketed through accelerated regulatory pathways [10], vaccinovigilance as well as the planning of a successful vaccination campaign will play a major role in protecting public health. The aim of this review is to discuss the available immunologic and clinical evidence to support the benefit of the influenza, pneumococcal and tuberculosis vaccines to prevent or improve the prognosis of

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COVID-19; in addition, it provides an overview of the state of the art about the COVID-19 vaccines that are currently in the development pipeline. Finally, from a public health perspective, implications for vaccination strategies to be adopted in the next months will be discussed.

2. Immunologic mechanisms behind the usefulness of existing vaccines in COVID-19 infection

A vaccine, by definition, is a biological preparation that provides acquired immunity to a particular infectious disease [11]. This occurs by activating lymphocytes bearing receptors specific for the given disease-causing microorganism, its toxins or one of its surface proteins [12]. Because of this specificity, it can appear paradoxical that such a specific preparation might also protect against other microorganisms. Nevertheless, interference between the influenza vaccine and infections by other respiratory viruses has been reported [13,14]. More recently, a possible link between the BCG vaccine and increased immunity against COVID-19 infection has also been proposed [15–17]. The precise mechanism behind a non-SARS-CoV-2 vaccine evoking an increased or decreased response against SARS-CoV-2, a microorganism that is not related to any of the currently available vaccines, is still to be fully elucidated. To shed some light on the possible mechanisms of interference, at least three distinct mechanisms can be in general hypothesized: antigen mimicry, by-stander activation and trained immunity.

Antigen mimicry can occur when some antigens are shared between microorganisms or when there is sufficient similarity between molecules belonging to two different pathogens, thus giving rise to immunological mimicry with resulting activation and clonal expansion of lymphocytes specific to both vaccine antigens and other pathogens [18]. However, it is unlikely that this would occur between unrelated pathogens, because antigen mimicry is contingent on the degree of molecular similarity between different antigens [19]. For example, it is unlikely that a vaccine developed to protect against a specific bacterial infection would protect against viral infections not displaying sufficient structural similarity. By-stander activation occurs when there is antigen-independent activation of by-stander lymphocytes during human immune response [20]. This is believed to play an important role in several immunological phenomena, such as T and B cell memory [21,22] This putative mechanism of interference would likely rely on the magnitude of the immune response after vaccination, on vaccine adjuvant properties and, on the presence of an initial immune response against the pathogen, in this case SARS-CoV-2 [23]. Trained immunity is perhaps the most widely investigated mechanism among the possible mechanisms of vaccine interference [24]. It concerns an epigenetic reprogramming of cells of the immune system, mainly innate cells, after vaccination [25,26]. Such an event has been clearly described for the BCG vaccine in both murine and human studies, and has been found to promote the elimination of various non-mycobacterium infection including staphylococci, candidiasis, yellow fever, influenza [27]. The BCG vaccine led not only to a four- to seven-fold increase in IFN-γ production, but also to a two-fold enhanced release of monocyte-derived cytokines, such as TNF and IL-1β, in response to unrelated bacterial and fungal pathogens [27]. The increased presence of these cytokines in respiratory mucosal tissues, where monocyte-derived sentinel cells such as dendritic cells are present [28], can improve innate immune barrier functions, thus possibly protecting against viral invasion. This increased activity of circulating monocytes remained for up to 3 months after the BCG vaccine administration and co-occurred with a higher expression of the activation markers CD11b and Toll-like receptor 4. Such training effects were found to be mediated through the NOD2 receptor and increased levels of histone 3 lysine 4 trimethylation. The limited duration of this innate immunity activation following BCG administration might also justify, at least in part, the negative results obtained by a retrospective study analyzing childhood BCG vaccine and current COVID-19 in adults [29]. However, it should be emphasized that a direct effect of the existing vaccines to prevent COVID-19 is not yet fully corroborated by clinical data. It is likely that the main benefit of administering the BCG, pneumococcal and influenza vaccine is to prevent these diseases, and as a result, protect the respiratory airways, maintaining the mucosal respiratory tract healthy and effective. Although the lungs have been traditionally regarded as passive gas exchange organs, it is becoming evident that airway epithelial cells play a critical defense role in containing microorganism invasion [30]. They do not only act as a physical barrier, modulating their cell-to-cell junctions and maintaining a suitable muco-ciliar activity, but they also defend against pathogen invasion by signaling to leukocytes and by directly producing anti-microbial substances [31]. The protective arsenal of the respiratory mucosa includes a wide array of receptors able to sense invading pathogens [31]. As a whole, all these functions of the upper airway epithelium, which is the first point of contact for inhaled foreign organisms such as SARS-Cov-2, are complex responses that are part of the early innate immunity. Any inflammatory damage to the respiratory mucosal tissue, caused by common pathogens, such as *Streptococcus pneumoniae* and the influenza virus, could impair these protective defense mechanisms, paving the way for the invasion of other respiratory pathogens, including SARS-CoV-2, thus emphasizing the potential usefulness of vaccines to prevent common respiratory infections in the control of the current pandemic.

3. Clinical evidence of direct/indirect effects of existing vaccines on COVID-19

A multi-level approach was used to identify evidence about vaccines preventing or improving prognosis of COVID-19. First, a search in MEDLINE using a specific search query was carried out (see Appendix Box 1). Only articles reporting original research findings on the association between the three vaccines of interest and clinical outcomes (SARS-CoV-2 infection and COVID-19 relate hospitalization, length of hospital stay or mortality, etc.), published from 2019 onward and written in English were selected for inclusion. Secondly, clinicaltrials.gov was also searched for clinical trials which are being planned, conducted or already finalized, concerning the three vaccines of interest in the COVID-19 prevention as well as trials concerning specific COVID-19 vaccines. Thirdly, the EU PAS

Register, a register of post-authorization studies, set up by the European Medicine Agency, was queried to identify observational studies being conducted for the three vaccines of interest in the context of COVID-19. All these study repositories were searched on the 22nd July concerning the role of the influenza, pneumococcal and BCG vaccine in 2020.

3.1. Influenza vaccine

There are two types of influenza vaccines available to date: the inactivated influenza vaccine (IIV) and live attenuated influenza vaccines (LAIV). The IIV and LAIV are also referred to as trivalent vaccines because they protect against three different strains of seasonal flu virus, influenza A (H3N2), pandemic A (H1N1), and one of influenza B lineage virus [32]. Quadrivalent vaccines that protect against 4 strains of viruses, including both influenza B lineage viruses, have also been recently made available in some countries [33]. The influenza vaccine acts by inducing a humoral response to the influenza virus surface antigens [34] or inactivated split virions [35], contained in the vaccine, as antibodies are produced against haemagglutinins, thus neutralizing influenza viruses [36]. The live attenuated influenza vaccine, available as a nasal spray [37], elicits both a cellular and a humoral response [38].

A total of 167 papers were identified in MEDLINE, of which three original articles were considered to be of interest (Table 1). A letter to the editor concerning an observational research study conducted in Italy showed a modest negative correlation between the proportion of influenza vaccinated people >65 years and the number of deaths from COVID-19 (r: −0.59; p value: 0.005) [39]. Another observational study in the US, showed that a 10% increase in vaccine uptake may correspond to approximately a 30% reduction in mortality among COVID-19 patients, thus suggesting a potential protective role of the influenza vaccine on COVID-19 in this population [40]. However, these studies are limited by the fact that they used aggregated, rather than patient-level data, and did not report the number of patients included. A prospective, registry-based observational study was published which aimed to develop COVID-19 risk prediction models [5]. This study enrolled 11,672 persons who visited Cleveland Clinic, of whom 7% were SARS-CoV-2 positive persons. The authors concluded that the influenza vaccine may be associated with a lower risk of contracting COVID-19.

The search in clinicaltrials.gov yielded no clinical trials and only one observational study exploring the association of the influenza vaccine and COVID-19 (NCT04367883) through the recruitment of 2,574 patients admitted to the Terrassa Hospital in Barcelona and expected to be completed by August 2023. The aim of this observational study is to investigate if the patients admitted to hospital who had previously received the influenza vaccine had better clinical outcomes (shorter hospital stay and/or shorter intensive care unit stay) compared to persons who did not receive the vaccine. There are currently no registered studies in the EU PAS Register which are investigating the use, safety or effectiveness of the influenza vaccine in the context of the COVID-19 pandemic.

Although there is little clinical evidence concerning potential direct benefits or harms for COVID-19 treatment or prevention, a recent study has shown that influenza A virus can facilitate SARS-CoV-2 entry into lung epithelial cells and worsen clinical outcomes of COVID-19 infection [41]. Researchers have isolated SARS-CoV-2 from COVID-19 positive patients and compared its replication and viral tropism with SARS-CoV, MERS-CoV, H1N1, and H5N1 in ex vivo cultures of human bronchial and lung tissue [41]. They observed an overexpression of angiotensin-converting enzyme 2 (ACE2) receptors in alveolar epithelial cells following an influenza-like infection. This is important as ACE2 receptors facilitate the entry of SARS-CoV-2 into cells [41]. As such, a protective effect of influenza vaccine on COVID-19 can be speculated. In addition, the role of the influenza vaccine in reducing the burden of excess deaths due to COVID-19 should be emphasized. Indeed, it has been estimated that the influenza vaccine, by way of preventing influenza super-infection among COVID-19 patients, could reduce up to 36% of all preventable deaths among COVID-19 patients [42]. The indirect benefits of the influenza vaccine are therefore likely to be significant.

The WHO, the Australian Department of Health and the Italian Drug Agency suggest that the administration of the seasonal influenza vaccine may be useful to prevent influenza at a time where many persons are also at risk of COVID-19 [43–45]. Indeed, in a study conducted among 191 persons with COVID-19 from two hospitals in Wuhan, 15% of patients developed a secondary infection and 50% of non-survivors had a secondary infection, although the type of infection was not specified [46]. In another study conducted among 85 fatal COVID-19 cases in Wuhan, almost 10% of patients had influenza super-infection [47]. This highlights the importance of preventing secondary infection in persons infected with COVID-19. It has also been suggested that being protected against seasonal influenza makes the differential diagnosis of severe respiratory infections easier [43–45] and may reduce in general burden of viral respiratory diseases on national healthcare systems.

3.2. Pneumococcal vaccine

There are two types of pneumococcal vaccines: pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine [48]. Both types of vaccines contains pneumococcal capsular polysaccharide antigens that trigger an immune response, i.e. type-specific humoral antibodies; the main difference between the two vaccines is the number of polysaccharide types included and the presence or absence of conjugation: 13 in the conjugate vaccine, adsorbed onto an aluminum adjuvant and 23 in the non-conjugate vaccine [49]. These vaccines protect against pneumococcal disease, i.e. any type of illness caused by *Streptococcus pneumoniae* bacteria. These infections are associated with high mortality that can be prevented with pneumococcal vaccines [50].

A total of 13 studies were identified in MEDLINE, of which one original research article was found (Table 1). This observational study conducted in a cohort of 11,672 persons, of whom

Table 1. Observational studies concerning the influenza, pneumococcal and BCG vaccine in the context of the pandemic identified in MEDLINE on the 22 July 2020.

Author, year	Study type	Data source	Study population	Exposure of interest	Outcome	Main results
Influenza vaccine						
Marín-Hernández *et al.*, 2020	Observational cohort study using aggregate data	Not reported	People aged >65 years from each Italian region	Influenza vaccine	COVID-19 mortality	A moderate negative correlation between influenza vaccination and COVID-19 mortality was observed (r: −0.59; p value: 0.005)
Zanettini *et al.*, 2020	Observational study using aggregate data	- COVID-19 Data Repository by CSSE at Johns Hopkins University - New York Times COVID-19 data repository - Center of Medicare Disparity Office of Minority Health - Census Bureau - Homeland Infrastructure Foundation	Patients aged ≥ 65 years recruited from USA (across all the 50 states and the Washington D.C. district)	Influenza vaccine	COVID-19 mortality	A 10% increase in vaccination corresponded to a 28% reduction in COVID-19 mortality (MRR = 0.72; 95% CI: = 0.58–0.89)
Jehi *et al*, 2020	Observational study using patient-level data	Cleveland Clinic COVID-19 Registry	All patients who were tested for COVID-19 at Cleveland Clinic in Ohio and Florida.	Patients with influenza vaccine and/or other drugs or vaccines	Positive COVID-19 testing	5,940 (93.9%) COVID-19 negative persons received the influenza vaccine vs. 384 (6.1%) COVID-19 positive persons not receiving the influenza vaccine (p value: >0.01)
Pneumococcal vaccine						
Jehi *et al*., 2020	Observational study using patient-level data	Cleveland Clinic COVID-19 Registry	All patients who were tested for COVID-19 at Cleveland Clinic in Ohio and Florida.	Patients with pneumococcal vaccine and/or other drugs or vaccines	Positive COVID-19 testing	5,940 (93.9%) COVID-19 negative persons received the influenza vaccine vs. 384 (6.1%) COVID-19 positive persons not receiving the influenza vaccine (p value: >0.01)
BCG vaccine						
Hegarty *et al.*, 2020	Observational study using aggregate data	- The European Center for Disease Prevention and Control for the number of cases and deaths attributed to Covid-19 - The World Atlas of BCG - Worldometer.info for the population of all countries.	All indicated global cases and death of Covid-19	BCG vaccine	COVID-19 incidence and mortality	- COVID-19 incidence was 38.4 per million in countries with BCG vaccination program *vs.* 358.4 per million in countries without BCG vaccination program - The death rate was 4.28 per million persons in countries with BCG programs *vs.* 40 per million persons in countries BCG vaccination program
Hamiel *et al.*, 2020	Observational study using aggregate data	- Israeli Central Bureau of Statistics for specific birth years - Israeli Ministry of Health for COVID-19 tests	Israeli adults aged 39–41 and Israeli unvaccinated adults aged 35–37	BCG vaccine	COVID-19 case-fatality rate	Proportion of positive test results in the BCG vaccinated group (11.7%) compared to the unvaccinated group (10.4%) showed no statistically significant difference in case fatality rate (1.3%; 95% CI: −0.3% to 2.9%; p value: 0.09)
Escobar *et al.*, 2020	Observational study using aggregate data	Not reported	Population of countries with BCG vaccine program	BCG vaccine	COVID-19 mortality	A high correlation was observed between high BCG vaccine coverage and COVID-19 mortality (r^2 = 0.88; p value: <0.001)

(*Continued*)

Table 1. (Continued).

Author, year	Study type	Data source	Study population	Exposure of interest	Outcome	Main results
Klinger *et al.*, 2020	Observational study using aggregate data	- Worldometers website - World Bank data - UNESCO Institute of Statistics Dataset - Our World In Data (ourworldindata.org) - BCG world atlas	Population of countries with a BCG vaccine program	BCG vaccine	COVID-19 deaths per million	There was a moderate negative correlation between the number of years during which a mandatory BCG vaccine program was in place and the number of COVID-19 related deaths (r: −0.48; p value: <0.001). A similar trend was seen for number of COVID-19 cases.

Abbreviations: BCG: Bacillus Calmette-Guérin; COVID-19: Coronavirus Disease 2019; CSSE: Center for Systems Science and Engineering; MRR: Mortality rate ratio.

818 persons had COVID-19, already described in section 3.1, found that persons who had been administered a pneumococcal vaccine in the same year as the study was conducted had a significantly lower risk of contracting COVID-19 [5]. There are currently no registered studies in clinicaltrials.gov or in the EU PAS Register which are investigating use, safety or effectiveness of the pneumococcal vaccine in the context of the COVID-19 pandemic.

Streptococcus pneumoniae is one of the major bacterial causes of community-acquired pneumonia (CAP) and can also be a cause of super-infection in CAP patients [51,52]. Indeed, the American Thoracic Society and Infectious Diseases Society of North America recommends that the treatment of adults with community-acquired pneumonia should be based on antibiotic activity against *Streptococcus pneumoniae* [53]. Pneumococcal vaccines reduces the number of hospitalizations for pneumonia in adults older than 65 years [54]. This is important because elderly persons with COVID-19 infection are at highest risk of mortality [55]. It is therefore likely that the pneumococcal vaccine could mitigate the impact of COVID-19 on healthcare systems, reducing morbidity and mortality due to non-COVID-19 respiratory infections, especially in those people who present important risk factors, such as advanced age and multi-morbidity [56]. It has been estimated that there are 10% of COVID-19 deaths are due to pneumococcal super-infection and are therefore preventable as they could have potentially be avoided by prior vaccination [42]. The negative impact of respiratory pneumococcal infection as a secondary infection along with viral infection is widely acknowledged [57]. Secondary infection occurred commonly in a small cohort of Chinese COVID-19 patients who died, but the pathogens were not described [46].

The WHO and the Australian region of New South Wales have categorically stated in their advice to the public that the pneumococcal vaccine does not protect specifically against COVID-19 infection [58,59]. We argue that the value of the pneumococcal vaccine in reducing the burden of excess deaths among persons with COVID-19 is likely to be significant, as reported above [42].

3.3. BCG vaccine

The BCG vaccine is a live attenuated vaccine that has a protective effect against disseminated tuberculosis [60]. This vaccine triggers a cell-mediated immune response which provides a variable degree of protection against *Mycobacterium tuberculosis* [61]. The duration of this immunity is unknown [61].

The BCG vaccine was found to improve immunogenicity to the H1N1 vaccine in healthy volunteers in a randomized, placebo-controlled study enrolling 40 persons [62]. Based on this and similar findings in other viral infections [63], it is thought that the BCG vaccine may improve immunity to SARS-CoV-2 suggesting its potential role in preventing SARS-CoV-2 infection and/or reducing COVID-19 severity [64]. The BCG vaccine may activate trained innate immunity [4,16,65], leading to a massive release of interferon-gamma (IFN- γ), pro-inflammatory cytokines, including various interleukin (IL) types (IL-1 β, IL-2, IL-6, IL-8, IL-10, IL-12, IL-17) and tumor necrosis factor (TNF), thus protecting against respiratory tract infections [6,16,65,66]. There is however limited clinical evidence to support the direct usefulness of this vaccine in COVID-19 infection and the available evidence is generally of low quality. A total of 60 published articles were identified in MEDLINE, of which four were considered to be of interest. These studies, which indirectly correlated morbidity and mortality among COVID-19 cases with compulsory tuberculosis vaccination program [6,15,29,67], are limited by some serious methodological flaws. Three of the studies showed that there is a strong relationship between BCG vaccine and the reduction of COVID-19 mortality/morbidity; however, they are not sufficient to establish the protective role of BCG vaccine with certainty because data are not linked at the patient level and the criteria to establish casual inference are therefore not available.

The ongoing seventeen trials of BCG as preventive strategy for COVID-19 pandemic will shed light on the role of this vaccine in the context of the current pandemic (Table 1). Most of these trials aim to recruit healthcare workers with the earliest results likely to be available by May 2021 (NCT04417335). A total of 4 trials are in phase IV, while 12 are in phase III and all of them except for one are randomized. The median size of the study populations is 1,200 (interquartile range: 908–2,014). There are currently no registered observational studies in the EU PAS Register on BCG vaccine and COVID-19. The WHO does not recommend the use of the BCG vaccine to prevent COVID-19 specifically [68]. The ongoing clinical studies evaluating the benefit of the BCG vaccine in COVID-19 are presented in Table 2.

4. Development of SARS-CoV-2 vaccine: regulatory and clinical aspects

The high infection rate of the SARS-CoV-2, along with the high risk of negative outcomes among COVID-19 patients, has triggered intense research activity to develop a specific vaccine against SARS-CoV-2 [69]. The concern triggered by the pandemic is so significant that the first COVID-19 vaccine candidate entered human clinical studies with unprecedented rapidity on 16 March 2020 [69,70], only three months after the virus was isolated by Chinese scientists [8].

There are several issues to consider in developing a reliable SARS-COV-2 vaccine candidate for mass manufacture and distribution. Firstly, it is still unclear what constitutes an optimal protective immune response against COVID-19. A study conducted among 285 patients with COVID-19 showed that SARS-CoV-2 infection led to a robust immune response [71]. However, there is very limited evidence about what level and type of immunity is required to prevent re-infection. Secondly, there is a need for both clinical endpoints (i.e. hospitalization and disease severity, evaluated as high-intensity medical care) and immunological endpoints (i.e. seroconversion) to assess the beneficial effects of a COVID-19 vaccine. This requires either a large number of enrolees, encompassing the wide variety of clinical symptoms affecting COVID-19 patients [72], or a multi-trial strategy with smaller homogeneous samples and the involvement of laboratories having comparable validated serologic assays. This is important to harmonize results among different vaccine products as well as among different vaccine trials. Thirdly, safety is a primary goal for vaccines that are given as preventive measure to healthy individuals, and there is also a risk that

Table 2. Clinical studies concerning the BCG vaccine in the context of the pandemic identified in clinicaltrials.gov on the 22 July 2020.

NCT number	Status	Study title	Conditions	Interventions	Number enrolled	Phase	Randomization	Study start	Study completion
BCG vaccine									
NCT04417335	Active, not recruiting	Reducing COVID-19 Related Hospital Admission in Elderly by BCG Vaccination	COVID-19	BCG vaccine Placebo	2014	IV	Yes	16 April 2020	May 2021
NCT04414267	Recruiting	BCG Vaccination to Prevent COVID-19	COVID-19	BCG vaccine Placebo	900	IV	Yes	26 May 2020	25 May 2021
NCT04369794	Not yet recruiting	COVID-19: BCG As Therapeutic Vaccine, Transmission Limitation, and Immunoglobulin Enhancement	COVID-19	BCG vaccine Placebo	1000	IV	Yes	June 2020	May 2022
NCT04348370	Recruiting	BCG Vaccine for Health Care Workers as Defense Against COVID-19	COVID-19	BGC vaccine Placebo	1800	IV	Yes	20 April 2020	November 2021
NCT04328441	Recruiting	Reducing Health Care Workers Absenteeism in Covid-19 Pandemic Through BCG Vaccine	COVID-19	BCG vaccine Placebo	1500	III	Yes	25 March 2020	25 December 2020
NCT04350931	Not yet recruiting	Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19	COVID-19	BCG vaccine Placebo	900	III	Yes	20 April 2020	1 December 2020
NCT04362124	Not yet recruiting	Performance Evaluation of BCG Vaccination in Healthcare Personnel to Reduce the Severity of SARS-CoV -2 Infection	COVID-19	BCG vaccine Placebo	1000	III	Yes	April 2020	November 2021
NCT04379336	Recruiting	BCG Vaccination for Healthcare Workers in COVID-19 Pandemic	COVID-19	BCG vaccine Placebo	500	III	Yes	4 May 2020	28 April 2021
NCT04475302	Recruiting	BCG Vaccine in Reducing Morbidity and Mortality in Elderly Individuals in COVID-19 Hotspots	COVID-19	BCG vaccine -	2175	III	No	1 July 2020	May 2021
NCT04327206	Recruiting	BCG Vaccination to Protect Healthcare Workers Against COVID-19	COVID-19	BCG vaccine Placebo	10,078	III	Yes	30 March 2020	30 March 2022
NCT04461379	Not yet recruiting	Prevention, Efficacy and Safety of BCG Vaccine in COVID-19 Among Healthcare Workers	COVID-19	BCG vaccine Placebo	908	III	Yes	6 July 2020	1 January 2021
NCT04373291	Not yet recruiting	Using BCG Vaccine to Protect Health Care Workers in the COVID-19 Pandemic	COVID-19	BCG vaccine Placebo	1500	III	Yes	May 2020	January 2021
NCT04384549	Not yet recruiting	Efficacy of BCG Vaccination in the Prevention of COVID19 Via the Strengthening of Innate Immunity in Health Care Workers	COVID-19	BCG vaccine Placebo	1120	III	Yes	11 May 2020	11 February 2021
NCT04439045	Not yet recruiting	Efficacy and Safety of VPM1002 in Reducing SARS-CoV-2 (COVID-19) Infection Rate and Severity	COVID-19	VPM1002 (recombinant BCG) Placebo	3626	III	Yes	14 June 2020	1 June 2021
NCT04387409	Recruiting	Study to Assess VPM1002 in Reducing Healthcare Professionals' Absenteeism in COVID-19 Pandemic	COVID-19	VPM1002 (recombinant BCG) Placebo	1200	III	Yes	25 May 2020	30 June 2021
NCT04435379	Recruiting	Study to Assess VPM1002 in Reducing Hospital Admissions and/or Severe Respiratory Infectious Diseases in Elderly in COVID-19 Pandemic	COVID-19	VPM1002 (recombinant BCG) Placebo	2038	III	Yes	18 June 2020	31 May 2021
NCT04453488	Not yet recruiting	Clinical Trial to Evaluate the Efficacy of RUTI® Against SARS- COV-2 Infection in Healthcare Workers	COVID-19	RUTI® vaccine Placebo	315	Not Applicable	Yes	10 July 2020	December 2020

Abbreviations: BCG: Bacillus Calmette-Guérin; COVID-19: Coronavirus Disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

vaccination could make subsequent SARS-CoV-2 infection more severe [73]. There are in fact two different vaccine-mediated syndromes (i.e., antibody-dependent enhancement and vaccine-associated enhanced respiratory disease) which are likely to occur when the antibody response fails to effectively neutralize the virus because of insufficient concentration or affinity or the wrong specificity [73].

With these aspects in mind, governmental authorities took important steps to help accelerating the development of prevention and treatment options for COVID-19. For example, the U.S. National Institutes of Health (NIH), along with the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are coordinating several biopharmaceutical companies in developing an international plan to promote a coordinated effort from research groups [74]. The planned Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership aims to build a collaborative platform to prioritize vaccine and drug candidates, streamline clinical trials, coordinate regulatory processes and/or leverage assets between consortium members to accelerate the response to the COVID-19 pandemics.

4.1. Overview of COVID-19 candidate vaccines already in clinical development phase

Several institutions have developed and currently update the overview of the global landscape of COVID-19 vaccine development by mostly using publicly available sources [75]. Heterogeneity across vaccine candidates at the preclinical development phase has been documented, and the number of vaccines entering the clinical phase is substantial. Based on the WHO list, US clinicaltrials.gov and the Chinese Clinical Trial Registry, 27 clinical trials for 23 corresponding vaccine candidates (4 RNA-based, 3 DNA-based, 5 viral vector-based, 5 inactivated virus-based vaccines, 4 with protein subunits, and 2 with virus-like particles or cells) have been currently identified as recruiting patients by 20 July 2020.

Table 3 shows the main characteristics of these trials: there are 11 phase I, 13 phase I/II, 2 phase II, and one phase II/III trials. However, the WHO website reports five phase III clinical trials: ISRCTN89951424, NCT04456595, ChiCTR2000034780, ChiCTR2000034780, NCT04470427 [76]. Among the reported trials, earliest results (i.e. by the end of December 2020) are expected for the following vaccines: BNT162 developed by BioNTech SE, an inactivated SARS-CoV-2 vaccine from Sinovac, and Gam-COVID-Vac Lyo from Gamaleya research. As far as phase II and III trials are concerned the following vaccines are at the most advanced stage of development: Ad5-nCoV from CanSino Biologics (China) actually recruiting 508 study participants, mRNA-1273 from the US National Institute of Allergy and Infectious Diseases with 600 enrolled subjects, and the ChAdOx1 nCoV-19 which will enroll 10,260 persons. Overall, most of the trials are claiming to provide results by the end of 2021.

5. Post-marketing vaccine safety surveillance during the COVID-19 epidemic

Every approved vaccine carries a certain risk of adverse reactions, just like every approved medication. Information on vaccine safety data is usually very limited in a pre-marketing setting, especially considering that the true risks and benefits of vaccines will play out in the long-term and in very large populations – often children or elderly, immunocompromized or otherwise vulnerable persons – as opposed to the small study population sizes and short observation periods in pre-marketing studies [77]. Nonetheless, in contrast to approved medications, which are generally used to treat a disease, vaccines are used to prevent disease in relatively healthy people. As a result, the threshold concerning acceptable vaccine risk is lower, in the sense that even a low risk may be considered unacceptable [78]. Moreover, potential adverse effects of vaccines are mainly immunologic, while adverse drug reactions are mostly dose- and mechanism-dependent effects, so more easily predictable [79]. Robust and proactive systems for vaccine post-marketing surveillance have been recently adopted to constantly monitor the quality, safety and efficacy of vaccines [80]. Several initiatives have been launched worldwide to perform post-authorization studies to rapidly investigate vaccine coverage, effectiveness, and safety throughout the vaccine life cycle using real-world data, such as healthcare claims data and electronic medical records. Nonetheless, vaccine post-marketing surveillance predominantly relies on spontaneous reporting systems (SRSs) [81].

Among the Good Pharmacovigilance Practices (GVP) drawn up by the EMA, there is a specific chapter concerning vaccines, aimed at strengthening and harmonizing the process of pharmacovigilance for vaccines in EU countries [79]. This chapter focuses on vaccine-specific aspects and challenges that should be considered when planning routine and additional pharmacovigilance activities for vaccines. Routine pharmacovigilance activities are based on the collection of Adverse Events Following Immunization (AEsFI) for the rapid monitoring of post-marketing vaccine safety. Besides routine or passive surveillance, EMA requires vaccine manufacturers to plan additional pharmacovigilance activities in their 'Risk minimization system' which may be needed for special situations or pandemics, such as detecting strain replacement phenomena for vaccines that may protect against only some types of organisms within a species. Other additional activities include assessing the evidence of safety for novel vaccines or for vaccines with a novel adjuvant, assessing vaccine effectiveness, especially where pre-marketing data are limited, investigating clusters of reported adverse events/reactions and finally, investigating whether there are higher than expected rates of vaccine failures and breakthrough infections in certain risk groups [82].

EudraVigilance is the system for collecting, managing and analyzing all Individual Case Safety Reports (ICSSs) related to adverse events to medicines or immunization authorized or being studied in clinical trials in the European Economic Area (EEA) [82]. ICSRs for AEsFI occurring after administration of the BCG vaccine, influenza vaccine, and pneumococcal vaccine collected in EudraVigilance

Table 3. Characteristics of clinical trials investigating COVID-19 vaccine candidates as of 20 July 2020.

Study ID#	Platform	Sponsor(s)	Clinical stage	Design*	Vaccine(s)	Study population	Primary outcomes	Estimated number of enrolled patients	Status**
NCT04445194	Recombinant CHO cells	Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.	Phase I	Randomized, placebo-controlled, dose-ranging, double blind trial	Recombinant new coronavirus vaccine (CHO cells) 2D regimen	Healthy volunteers (age 18–59 years)	[a]Number of adverse events after intramuscular injection up to one year post-vaccination	50	*Ongoing* Estimated end: September 2021
NCT04380701	RNA vaccine	Biontech RNA Pharmaceuticals GmbH	Phase I/ II	Non-randomized, dose-ranging, open-label trial	BNT162a1, BNT 162b1, BNT 162b2, BNT 162c2 (PB regimen, except SD for 162c2)	Healthy volunteers (age 18–55 years)	[a] Local and systemic solicited and unsolicited adverse reaction up to 28 days post-vaccination *Secondary endpoints: functional antibody response + titers + seroconversion*	200	*Ongoing* Estimated end: August 2020
NCT04368728	RNA vaccine	BioNTech SE	Phase I/ II	Randomized, placebo-controlled, dose-ranging, triple-blind trial	BNT162a1, BNT 162b1, BNT 162b2, BNT 162c2 (three escalating doses levels at SD and 2D regimen)	Healthy volunteers (age 18–85 years)	[a] Local and systemic adverse reaction up to 7 days post-vaccination [b] Serious adverse events up to 6 months post-vaccination [c] Grading shift and abnormal hematology and chemistry laboratory values up to 7 days post-vaccination	7,600	*Recruiting* Estimated end: March 2023
NCT04313127	Adenovirus vector	CanSino Biologics Inc.	Phase I	Non-randomized, dose-ranging, open-label trial	Ad5-nCoV (two escalating doses levels with SD regimen)	Healthy volunteers (age 18–60 years)	[a] Local and systemic adverse reaction up to 7 days post-vaccination	108	*Active, not recruiting* Estimated end: December 2022
NCT04341389	Adenovirus vector	CanSino Biologics Inc.	Phase II	Randomized, placebo-controlled, double-blind, crossover trial	Ad5-nCoV (two escalating doses levels with SD regimen)	Healthy adults (age 18 + years)	[a] Occurrence of adverse reactions up to 14 days post vaccination [b] Anti SARS-CoV-2 S IgG antibody response up to 28 days post vaccination [c] Neutralizing antibody response to SARS-CoV-2 up to 28 days post vaccination	508	*Active, not recruiting* Estimated end: January 2021
ChiCTR2000032459	Inactivated	Henan Provincial Center for Disease Control and Prevention	Phase I/ II	Randomized, placebo-controlled, dose ranging	Inactivated SARS-CoV-2 vaccine (Multiple doses)	Healthy adults (age 3+ years)	[a] Adverse reactions/events up to 7 days post-vaccination	NA	*Recruting* Estimated end: November 2021
NCT04336410	DNA vaccine	INOVIO	Phase I	Non-randomized, dose-ranging, open-label trial	INO-4800 (two escalating doses levels with SD and 2D regimen)	Healthy volunteers (age 18–50 years)	[a] Local and systemic adverse reaction up to 52 weeks post-vaccination [b] Functional antibody responses, change in antibody titers and Antigen-Specific Interferon-Gamma up to 52 weeks post-vaccination	40	*Recruiting* Estimated end: April 2021
NCT04283461	RNA vaccine	NIAID	Phase I	Non-randomized, dose-ranging, open-label trial	mRNA-1273 (three escalating doses levels with 2D regimen)	Healthy volunteers (age 18–99 years)	[a] Local and systemic adverse reaction up to 28 days post-vaccination [b] Serious or medically attended adverse events up to 394 days post-vaccination [c] New-onset chronic medical conditions up to 394 post-vaccination	120	*Recruiting* Estimated end: November 2021

(*Continued*)

Table 3. (Continued).

Study ID#	Platform	Sponsor(s)	Clinical stage	Design*	Vaccine(s)	Study population	Primary outcomes	Estimated number of enrolled patients	Status**
NCT04405076	RNA vaccine	NIAID	Phase II	Randomized, placebo-controlled, dose-ranging, double blind trial	mRNA-1273 (two escalating doses levels with 2D regimen)	Healthy volunteers (age 18–54 years)	[a] Local and systemic adverse reaction up to 28 days post-vaccination [b] Serious or medically-attended adverse events up to 394 days post-vaccination [c] Immunogenicity of mRNA-1273 by titer of SARS-CoV-2-specific binding antibody (bAb)	600	*Active, not recruiting* *Estimated end: August 2021*
NCT04463472	DNA vaccine	Osaka University/ AnGes/Takara Bio	Phase I/ II	Non-randomized, dose-ranging, open label trial	AG0301-COVID19 (two escalating doses with 2D regimen)	Healthy volunteers (age 20–65 years)	[a] Incidence of Treatment-Emergent Adverse Events up to week 9 [b] Immunogenicity up to week 9	30	*Recruiting* Estimated end: July 2021
NCT04299724	Lentivirus vector	Shenzhen Geno-Immune Medical Institute	Phase I	Single group, open-label trial	Pathogen-specific artificial antigen presenting cells (aAPC) (SD regimen)	Healthy and Covid-19-positive volunteers (6 months – 80 years)	[a] (Serious) adverse events up to 28 days post-vaccination [b] Positive T cell response	100	*Recruiting* Estimated end: December 2024
NCT04276896	Lentivirus vector	Shenzhen Geno-Immune Medical Institute	Phase I/ II	Single group, open-label trial	LV-SMENP-DC vaccine and antigen-specific cytotoxic t cells (SD regimen)	Covid-19 positive volunteers (6 months – 80 years)	[a] Clinical improvement based on the 7-point scale [b] Murray lung injury score decrease	100	*Recruiting* Estimated end: December 2024
NCT04352608	Inactivated	Sinovac Research and Development Co., Ltd.	Phase I/ II	Randomized, placebo-controlled, dose-ranging, triple-blind trial	Inactivated SARS-CoV-2 vaccine (two escalating doses levels with 2D regimen)	Healthy adults (age 18–59 years)	[a] Adverse reactions up to 28 days post-vaccination [b] Seroconversion rates of neutralizing antibodies	744	*Recruiting* Estimated end: December 2020
NCT04324606	Adenovirus vector	University of Oxford	Phase I/ II	Randomized, active-controlled, single-blind trial	ChAdOx1 nCoV-19 (SD or SD plus boost regimen)	Healthy adults (age 18–55 years)	[a] Virologically confirmed symptomatic cases of COVID-19 up to 6 months post-vaccination (seroconversion rates, hospital and ICU admission, deaths) [b] Serious adverse events up to 6 months post-vaccination	1,090	*Active, not recruiting* Estimated end: May 2021
NCT04400838	Adenovirus vector	University of Oxford	Phase II/III	Randomized, active-controlled, single-blind trial	ChAdOx1 nCoV-19 (SD or SD plus boost regimen)	Healthy volunteers (age 5+ years)	[a] Virologically confirmed symptomatic cases of COVID-19 up to 6 months post-vaccination (seroconversion rates, hospital and ICU admission, deaths) [b] Serious adverse events up to 6 months post-vaccination	10,260	*Recruiting* Estimated end: August 2021
ChiCTR2000032459	Inactivated	Henan Provincial Center for Disease Control and Prevention	Phase I/ II	Randomized, placebo-controlled, double-blind trial	Vero cells (two escalating doses levels with 2D regimen)	Healthy volunteers (age 3+ years)	[a] Incidence of adverse reactions/ events up to 7 days after each dose	NA	*Recruiting* Estimated end: November 2021
CTRI/2020/07/026300	Inactivated	Bharat Biotech	Phase I/ II	Randomized, Active-controlled, Double-blind trial	BBV152 (three escalating doses levels with 2D regimen)	Healthy volunteers (age 12–65 years)	[a] Occurrence of Adverse throughout the study duration [b] immunogenicity up to day 194	1,125	*Recruiting* Estimated end: October 2021

(*Continued*)

Table 3. (Continued).

Study ID#	Platform	Sponsor(s)	Clinical stage	Design*	Vaccine(s)	Study population	Primary outcomes	Estimated number of enrolled patients	Status**
NCT04368988	Protein subunit	Novavax	Phase I/ II	Randomized, place-controlled, double-blind trial	SARS-CoV-2 rS (two escalating doses levels with 2D regimen)	Healthy volunteers (age 18–59 years)	[a] Subjects with solicited AEs up to 28 days [b]] Safety Laboratory Values up to 28 days [c] Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) up to 35 days	131	*Recruiting* Estimated end: July 2021
NCT04445389	DNA vaccine	Genexine, Inc.	Phase I/ II	Randomized, placebo-controlled, double-blind trial	GX-19 (two escalating doses levels with 2D regimen)	Healthy volunteers (age 18–50 years)	[a] Incidence of solicited, unsolicited, and serious adverse events up to 1 year post-vaccination	190	*Recruiting* Estimated end: June 2022
NCT04412538	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase I/ II	Randomized, placebo-controlled, double-blind trial	Inactivated vaccine (three escalating doses levels with 2D regimen)	Healthy volunteers (age 18–59 years)	[a] Adverse reactions/events rate up to day 28 [b] Seroconversion rate of Neutralizing, IgG antibodies against SARS-CoV-2 up to 28 days post-vaccination	942	*Recruiting* Estimated end: September 2021
NCT04437875	Adenovirus vector	Gamaleya Research, Health Ministry of the Russian Federation	Phase I/ II	Non-randomized, single group, open label trial	Gam-COVID-Vac Lyo (two components with a SD regimen)	Healthy volunteers (age 18–60 years)	[a] The changing of antibody levels against the SARS-CoV-2 glycoprotein S at 42 days [b] Number of Participants With Adverse Events through the whole study	38	*Active, not recruiting* Estimated end: August 2020
NCT04405908	Protein subunit	Clover Biopharmaceuticals AUS Pty Ltd	Phase I	Randomized, placebo-controlled, double-blind trial	SCB-2019 (two adjuvants with a 2D regimen)	Healthy volunteers (age 18–75 years)	[a] Incidence of solicited, unsolicited and serious adverse events (AEs) after vaccination up to 184 days post-vaccination [b] Immunogenicity(Anti-SCB-2019 Antibody Titers up to Day 184	150	*Recruiting* Estimated end: March 2021
NCT04453852	Protein subunit	Vaxine Pty Ltd	Phase I	Randomized, saline-controlled, double blind trial	COVAX-19 vaccine with adjuvant SD regimen	Healthy volunteers (age 18–65 years)	[a] Incidence of Adverse Events 1 weeks post-vaccination [b] COVID19 neutralizing antibody titers and T cell immunogenicity 2 weeks post-vaccination	40	*Recruiting* Estimated end: July 2021
ACTRN12620000674932	Protein subunit	University of Queensland	Phase I	Randomized, placebo-controlled, double-blind trial	SARS-CoV-2 Sclamp (four eascalating doses with 2D regimen)	Healthy volunteers (age 18–65 years)	Incidence of solicited and unsolicited AEs 28 post-vaccination [b] Anntibody immune responses and neutralizing responses elicited by SARS-CoV-2 Sclamp vaccine	120	*Recruiting* Estimated end: NA
2020–001646-20	RNA vaccine	Imperial College London	Phase I	Two stage randomized, placebo-controlled and open label dose escalation trial	LNP-nCoVsaRNA (three eascalating doses with 2D regimen)	Healthy volunteers (age 18–75 years)	[a] Solicited, unsolicited, and serious AEs up to 52 weeks [b] Serum neutralizing antibodies vaccine-induced serum IgG binding antibody responses at 2 week after 2 dose vaccination	320	*Recruiting* Estimated end: July 2021

(*Continued*)

Table 3. (Continued).

Study ID#	Platform	Sponsor(s)	Clinical stage	Design*	Vaccine(s)	Study population	Primary outcomes	Estimated number of enrolled patients	Status**
NCT04449276	RNA vaccine	CureVac AG	Phase I	Randomized, place-controlled, dose-escalation, single blind trial	CVnCoV Vaccine (three eascalating doses with 2D regimen)	Healthy volunteers (age 18–60 years)	[a] Number of Participants With Grade 3 Adverse Reactions or any Serious Adverse Event up to 60 hours after last dose vaccination [b] Number of solicited, unsolicited, and serious adverse events up to day 394	168	*Recruiting* Estimated end: August 2021
NCT04450004	Virus Like particles	Medicago Inc.	Phase I	Randomized, dose-ranging, open label trial	Coronavirus-Like Particle COVID 19 Vaccine with adjuvants (two escalating doses with 2D regimen)	Healthy volunteers (age 18–55 years)	[a] Incidence of solicited, unsolicited and serious adverse events (AEs) after vaccination up to 21 days post-vaccination [b] Immunogenicity((neutralizing antibody and T cell immunity) up to 21 days	180	*Recruiting* Estimated end: April 2021

Abbreviations: SD: single dose; 2D: two doses; PB: prime/boost; NIAID: National Institute of Allergy and Infectious Diseases; LV: lentiviral vector system; SMENP: Spike, Membrane, Envelope, Nucleocapsid, and Protease; DC: dendritic cells

* Parallel cohorts unless otherwise stated; # Clinicaltrial.gov identified or Chinese clinical trial Identifier; ** As of 20th July May 2020

were extracted to investigate the impact of pandemic on vaccine surveillance. The number of ICSRs concerning the BCG, pneumococcal and influenza vaccine were extracted during the pandemic COVID-19 period (1st January–9th May 2020) and compared to the number of ICSRs during the corresponding quarter of 2019 (1st January–9th May 2019).

Compared to the January-May 2019 period, the number of ISCRs in the January–May 2020 period concerning the BCG vaccine was higher (N = 269 *vs*. 164). Reporting for the available pneumococcal vaccines was also slightly higher from January-May 2020 compared to January-May 2019 (N = 2,820 vs. 2,470). The frequency of ICSRs for the seasonal influenza vaccine were practically identical during the COVID-19 pandemic compared to before (N = 595 *vs*. 548).

The comparison of ICSRs for the three vaccines in a period before and during the COVID-19 pandemic showed no difference in reporting, suggesting that vaccine safety monitoring has not been neglected because of changing health priorities. The COVID-19 pandemic will also likely impact the ICSRs of the SARS-CoV-2 vaccines themselves. After approval of a COVID-19 vaccine, especially if through accelerated regulatory pathways, the detection of new potential safety signals should be as real-time as possible, to support regulatory decision-makers as the vaccine becomes more widely used. This is important as mass vaccination programs over a relatively short time period are expected. The quality of the rapidly generated vaccine safety data and the interpretation of this data will be critical.

6. Public health perspective on vaccination strategies to counteract COVID-19 pandemic

A recent paper on mortality data from 24 countries participating in the European mortality monitoring activity network, also known as EuroMOMO, estimated a notable all-cause excess mortality due to COVID-19 in people aged 65 years and older which accounted for over 90% of excess deaths [83]. The excess mortality greatly exceeded that observed in the past influenza seasons. Also, the report issued by the Italian National Institute of Statistics on the impact of COVID-19 pandemic on mortality in the first trimester of 2020 has shown a significant increase in all-cause mortality as compared to the 2015–2019 period. The report has correlated this excess mortality, among other causes, with the indirect effects of the COVID-19 pandemic, namely the health system crisis [84]. Furthermore, besides being a potential primary cause of death, COVID-19 can also play a role as a worsening factor of underlying comorbidities that might possibly accelerate death. This is also true for influenza, which has an average excess mortality rate of 1.9–-2.2 per 100,000 persons considering only influenza and pneumonia and 11.6–18.6 per 100,000 considering all causes [44]. Looking at the period from February 20th to 31st March 2020, the mortality rate in Italy has more than doubled in persons from 70 to 79 years of age as well as among those aged 80–89 [84]. Therefore, higher age is a risk factor for more severe disease. Similarly, the presence of comorbidities can increase the chance of infection and have a negative impact on infection outcome [85]. In fact, less than 4% of all patients who died in Italy from COVID-19 up to 14th May 2020 were free of any comorbidity [86]. All these aspects highlight the importance of shifting to a life-long vaccination approach [87] as it is known that infectious diseases can result in a worse clinical outcome as well as worse impact on quality of life in elderly and among people with comorbidities [88]. It goes without saying that these two target groups will be a priority once a vaccine against COVID-19 is available. Nonetheless, in order to promote healthy aging and protect healthcare systems from potential work overload during the next influenza season and the potential concurrent new wave of COVID-19 infection, it is also important to encourage pneumococcal and influenza vaccination. Indeed *Streptococcus pneumoniae* was identified as one of the most common pathogens responsible for severe infections, or even death, during the three influenza pandemics of the 20th century and the first influenza pandemic of the 21th century [89]. In line with this evidence, preventive measures against *S. pneumoniae* should be considered in the preparation of influenza pandemic policies [89].

Preparedness and response plans are already used to tackle potential influenza pandemics worldwide. The COVID-19 pandemic reminds us of the importance of preparedness as to ensure the 'availability of capacities and capabilities to detect, notify, respond to and recover from an emergency' [90]. The Italian National Pandemic Preparedness and Response Plan to an influenza pandemic addresses the importance of vaccination in all the pandemic phases [91]. In particular, during the interpandemic period, the organization of the seasonal influenza vaccination campaign makes it possible to lay the foundations for the collection of data during a pandemic period [91]. This aspect also highlights the importance of having the infrastructure, procedures and resources already available to deploy and administer a new vaccine in a short time to a large number of people. The planning of a vaccination campaign, such as that against influenza which recurs every year, includes decisions and instructions concerning the production, distribution, administration and monitoring of vaccines. The lack of existing national influenza vaccination programs has been shown to be an obstacle in the response to 2009 pandemic influenza in the WHO Western Pacific Region, for instance [92]. This is not the case of the WHO European Region, but it should be kept in mind that coverage of target groups is still low even in Europe and this might undermine influenza and pandemic preparedness [93]. The proper functioning of a nationwide vaccination campaign is essential to guarantee that adequate infrastructures are available [94]. Other activities are also important, namely the training of people involved in the management of the pandemic and a suitable communication strategy. These two actions are of utmost importance for a widespread and successful vaccination campaign. The challenge behind optimizing the various public health interventions during a pandemic is highlighted by the fact that during the 2009 influenza pandemic, the coverage of the pandemic influenza vaccine was as low as 4% of the target population, such as healthcare workers, blood donors, persons with at least one chronic condition and pregnant women [95]. In particular, an unambiguous, reliable, thorough and transparent communication should be provided to all the stakeholders also in the light of improving trust in health authorities [96]. These actions are also required to increase confidence in vaccines and counteract the potential effects of a pandemic on vaccination coverage. It is interesting to see that in France a decline in influenza vaccine coverage was observed after the 2009 pandemic influenza, probably due to disputes on mass vaccination campaigns that led to a loss of trust in French health authorities [97]. The COVID-19 pandemic has already led to a decline in childhood vaccination coverage. In Michigan, for

example, there was a decline in vaccination coverage in all childhood milestone age cohorts and the number of doses administered in the first quarter of 2020 to children less than 2 years old was 15.5% lower as compared to the previous two years [98]. Similarly, in England there was a decline in vaccination coverage as the number of first-dose measles-mumps-rubella vaccinations being 19.8% lower in 2020 compared with 2019 [99]. These trends were likely due to the lockdown with resulting limitations in both the delivery of vaccines and the access to vaccination services by the population. A reduction in routine immunizations during the pandemic was also observed in developing countries. For example, in a rural area of South Africa, a 50% drop in child visits for immunization has been observed immediately after the lockdown [100]. As a consequence, the return to normality may lead to possible outbreaks of some vaccine-preventable diseases [101]. In fact, the disruption of health services due to the COVID-19 pandemic is clearly visible and its consequences should be carefully addressed in as soon as possible.

The judicious and rational planning of future vaccination campaigns against influenza and COVID-19 is required now more than ever as there is also evidence suggesting that the increase in influenza vaccination coverage could help to contain the spread of COVID-19 [102]. Similarly, a timely and efficient uptake of routine vaccinations, including that against *Streptococcus pneumoniae* in high risk groups, should be a priority. Eventually, the regular collection of data on the efficacy and safety of SARS-CoV-2 vaccines will be essential for both the decision-making process as well as for the additional and continuous systematic data collection on the role of influenza and *Streptococcus pneumoniae* co-infections and vaccinations against them on COVID-19 outcomes.

7. Conclusions

There are immunologic mechanisms by which existing vaccines, such as the BCG vaccine, the pneumococcal vaccine and the influenza vaccine, may hypothetically directly prevent COVID-19 prevention. However, the major contribution of these vaccines, in particular pneumococcal and influenza vaccines, probably mainly remains that of preventing specific respiratory diseases co-occurring with COVID-19 and leading to worse prognoses, thus also reducing the burden on national healthcare systems. An additional contribution of these vaccines is likely to be that of aiding the differential diagnosis of COVID-19. As such, vaccination campaigns concerning existing vaccines addressing frailer population should be implemented. On the other hand, there are several specific SARS-CoV-2 vaccine candidates in the pipeline which have entered the clinical development phase at an unprecedented rate. Past experience has shown that for the pandemic vaccine to have a high uptake level, concerted public health interventions and communication strategies will be needed.

8. Expert opinion

The pressure to identify drugs or vaccines that can be rapidly used in the COVID-19 pandemic has led to the hypothesis that three existing vaccines may be beneficial, namely the BCG vaccine, the pneumococcal vaccine and the influenza vaccine. All three vaccines are widely considered to be effective and safe to prevent the diseases they were originally intended to prevent tuberculosis, thereby improving public health considerably. There is limited evidence of a direct benefit of these vaccines specifically on the prevention of COVID-19 although there are plausible immunologic mechanisms by which these vaccines may improve the immune response to SARS-CoV-2. The hypothesis that they may also prevent COVID-19 arises from a series of observations, which allow us to envision the mechanisms of action through which this putative protection might occur, namely antigen mimicry, by-stander activation and trained immunity. In this context, it appears reasonable to distinguish between live/attenuated vaccine and inactivated or second/third generation vaccines, the latter including preparation by genetic engineering which contain subsections as protein forms or recombinant vector vaccines. Live/attenuated vaccine, such as BCG, are clearly more likely to result in putative trained immunity, which hardly can be envisaged by administration of non-live/attenuated viral proteins contained in influenza vaccines or bacteria polysaccharides of pneumococcal vaccines. Similarly influenza vaccines, which are mainly composed of viral subparticles, are unlikely to result in a trained innate immunity, although a nasal spray of live attenuated influenza vaccine (LAIV, Q/LAIV), which contains the live but attenuated form of the virus, is also currently available in Europe [37] and America [103] may potentially lead to trained innate immunity. There is no information currently available regarding the possible interference of the influenza LAIV/QLAIV with other diseases. Finally, it is worth noting that the role of the distinct adjuvants of above-mentioned vaccines in both by-stander and trained immunity mechanisms of vaccine interference remains to be elucidated. In addition to these strictly immunological mechanisms, as we reported above, it has been recently observed that influenza virus can induce the in vitro upregulation of mRNA for ACE2, the main human cell receptor for SARS-CoV-2. Interestingly, the increase of ACE2 mRNA in the presence of the influenza virus occurred in alveolar epithelial cells, but not in macrophages [41]. It remains to be elucidated whether this increased expression of ACE2 correlates with a higher risk of either SARSR-CoV-2 infection or COVID-19 severity.

Based on the number of ongoing experimental studies identified, the BCG vaccine seems to have been by far the most commonly investigated vaccine in the context of COVID-19. However, the safety of administering an additional vaccination during the early phases of a challenging infection, such as COVID-19, should carefully be weighed against the expected benefit. The timing and sequence of vaccine administration might even be detrimental to an effective immune response against the invading SARS-CoV-2 pathogen.

However, the main role of the vaccines in question is likely to concern the prevention of respiratory super-infections which can potentially increase the risk of morbidity and mortality in persons affected with COVID-19. Indeed, super-infections have been commonly reported among persons affected with COVID-19 [46,47,104,105,106,107]. Studies comparing the overall reduction in morbidity/mortality among COVID-19 patients who have received routine influenza, BCG and pneumococcal vaccines are likely to be a useful addition to what is known about these vaccines, as there is currently no published epidemiological large-scale study [42]. In this case, the comparison group might consist of persons affected with COVID-19 who were eligible

for the BCG, influenza and pneumococcal vaccine (i.e. not having any medical contraindications) but elected not to take this vaccination. The main study group might be persons with COVID-19 who took their routine vaccines as indicated. The secondary use of previously collected data is ideal to address the question of whether routine vaccinations reduce the morbidity and mortality among COVID-19 infected patients. There are several databases which could be used to conduct such a study. For example, Italian regional claims databases contain information on vaccinations along with a very good temporal and geographic coverage [108]. There are also electronic medical record database, such as The Health Improvement Network database in the UK, also known as THIN [109], the Integrated Primary Care Information database in the Netherlands, also known as IPCI [110] and Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria in Spain, also known as BIFAP [111], which also have information on vaccinations and good temporal and geographic coverage. Electronic healthcare data from different countries has also been used to conduct multi-country studies on vaccine use [112,113]. Such databases have immense potential, particularly in the context of a pandemic because they can leverage data which has already been collected. As a result, studies can be conducted very rapidly.

The race to develop a vaccine specific to SARS-CoV-2 has led to several potential vaccine candidates which are expected to be launched in the coming months. The global scale of the pandemic has brought together several international regulatory and scientific bodies to produce and share key safety and efficacy data for the novel vaccines in parallel. Such international collaboration will certainly accelerate the marketing and distribution of vaccines against COVID-19. Even here, observational studies have a lot of potential, particularly in vaccine safety monitoring once the vaccine is launched. The public perception of vaccine safety is of great importance because it may limit vaccine uptake. The value of having high-quality transparent research in countering public distrust while providing high-quality evidence was implicitly recognized in the Accelerated development of vaccine benefit-risk collaboration in Europe (ADVANCE) project, funded by the Innovative Medicines Initiative and conducted in collaboration between the European Centre for Disease Prevention and Control and the European Medicines Agency, and national public health and regulatory bodies, vaccine manufacturers, and academic centers [114]. Accordingly, EMA has commissioned a large independent study for the rapid and accurate monitoring of the SARS-CoV-2 vaccine safety as soon as this is marketed [115].

Declaration of interest

No potential conflict of interest was reported by the authors.

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Appendix Box 1: Search queries applied to MEDLINE on 22 July 2020

Vaccine	Search query applied to MEDLINE
Influenza vaccine	COVID-19 OR SARS-CoV-2 OR severe acute respiratory syndrome coronavirus 2 OR coronavirus di Wuhan OR coronavirus OR MERS-CoV OR middle east respiratory syndrome coronavirus AND influenza vaccine OR influenza vaccination OR flu shots OR flu vaccine OR flu vaccination OR flu jabs
Pneumococcal vaccine	COVID-19 OR SARS-CoV-2 OR severe acute respiratory syndrome coronavirus 2 OR coronavirus di Wuhan OR coronavirus OR MERS-CoV OR middle east respiratory syndrome coronavirus AND pneumococcal vaccine OR pneumococcal vaccination OR PCV OR pneumococcal conjugate vaccine OR PPSV OR pneumococcal polysaccharide vaccine
BCG vaccine	COVID-19 OR SARS-CoV-2 OR severe acute respiratory syndrome coronavirus 2 OR coronavirus di Wuhan OR coronavirus OR MERS-CoV OR middle east respiratory syndrome coronavirus AND BCG vaccine OR Bacillus Calmette–Guérin vaccine OR TB vaccine OR tuberculosis vaccine

Abbreviations: BCG: Bacillus Calmette–Guérin