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Review

The role of trained immunity in COVID-19: Lessons for the next pandemic

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SUMMARY

Trained immunity is a long-term increase in responsiveness of innate immune cells, induced by certain infections and vaccines. During the last 3 years of the COVID-19 pandemic, vaccines that induce trained immunity, such as BCG, MMR, OPV, and others, have been investigated for their capacity to protect against COVID-19. Further, trained immunity-inducing vaccines have been shown to improve B and T cell responsiveness to both mRNA- and adenovirus-based anti-COVID-19 vaccines. Moreover, SARS-CoV-2 infection itself induces inappropriately strong programs of trained immunity in some individuals, which may contribute to the long-term inflammatory sequelae. In this review, we detail these and other aspects of the role of trained immunity in SARS-CoV-2 infection and COVID-19. We also examine the learnings from the trained immunity studies conducted in the context of this pandemic and discuss how they may help us in preparing for future infectious outbreaks.

BACKGROUND

At the end of 2019, a new form of pneumonia was identified in China, and in January 2020, a new viral pathogen from the coronaviruses family was discovered and termed SARS-CoV-2. The infection caused by the new coronavirus SARS-CoV-2 was named coronavirus disease-19 (or COVID-19) and caused a major pandemic. In the 3 years since the start of the pandemic, hundreds of millions of people were infected with the new virus, and more than 5 million people lost their lives (https://covid19.who.int).

Soon after the beginning of the pandemic, it became clear that dysregulation of immune responses played a very important role for the pathophysiology of COVID-19. Initially, most of the attention was centered on the clear hyperinflammatory profile that characterized many of the patients with severe forms of the disease.[1,2] An exaggerated production and release of proinflammatory cytokines, especially interleukin-1 (IL-1) and -6 (IL-6), has been hypothesized to induce systemic and local inflammation, local increase in immune cell recruitment in the lung, followed by endothelial cell activation, fluid extravasation, and impaired gas exchanges.[3] This chain of events can subsequently lead to respiratory insufficiency, the need for oxygen supplementation, sometimes artificial ventilation, and unfortunately, in a small but significant number of patients, to death. This hyperinflammation-centric view of the pathogenesis of COVID-19 led to large clinical trials in severely ill patients, which resulted in the successful identification of several important approaches for immunomodulatory treatments, such as the use of steroids, as well as blockers of IL-1 or IL-6 bioactivity.[4]

While hyperinflammation in the late stages of the disease clearly plays an important role in determining the patient's outcome, more in-depth studies during the pandemic showed that the immune dysregulation in COVID-19 is more complex and presents both defective and overreactive features, depending on the patient and especially the phase of the disease. In this respect, it has been shown that the overproduction of IL-6 can also have immunosuppressive effects on the antigen-presenting features of myeloid cells with decrease of HLA-DR expression,[2] while many patients with severe forms of the disease display defective T cell numbers and function.[5] Comprehensive transcriptomic studies of various immune cell populations have shown varying degrees of defective immune activation in patients with severe disease, both in lymphoid and myeloid cells.[6] These data argued therefore that immune defects are complex and variable in COVID-19 patients: on

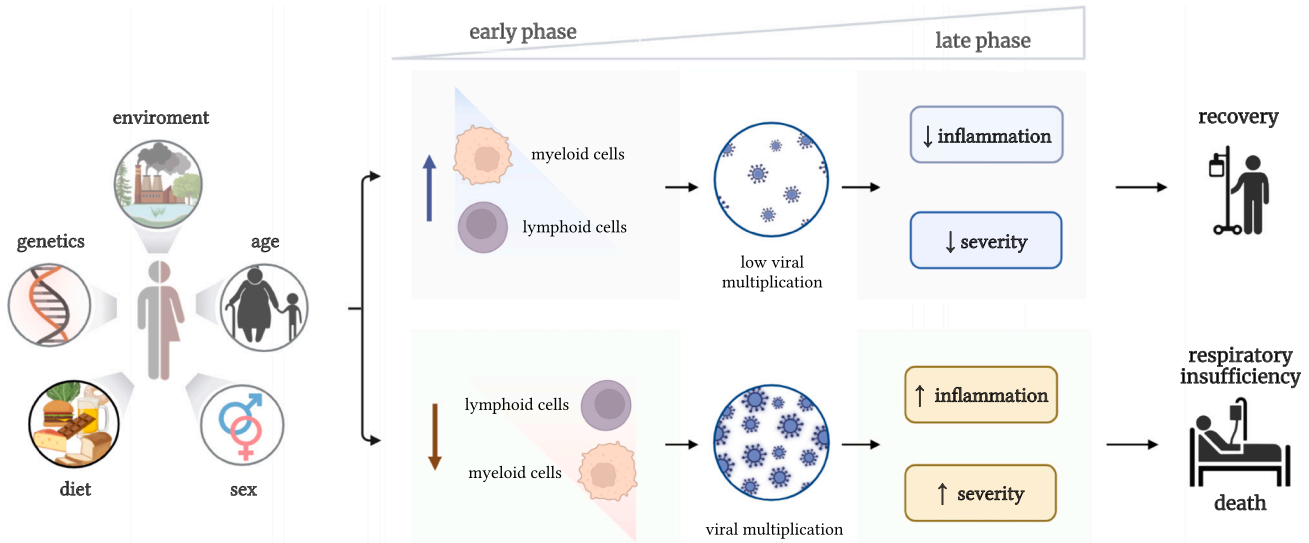

Figure 1. Immune system dysregulation in the pathophysiology of COVID-19
When the immune responses are effective in the beginning of the disease, they will inhibit multiplication of the virus, resulting in low viremia, low systemic inflammation, and survival. In case the host defense response is defective in the first stages of the infection (when the patient is still asymptomatic), this would allow the virus to multiply, spread systemically, and to induce ineffective hyperinflammation and a poor prognosis.

the one hand, if the immune responses are effective in the beginning of the disease, they would inhibit multiplication of the virus, resulting in low viremia, low systemic inflammation, and survival; on the other hand, if the host defense is defective in the first stages of the infection (when the patient is still asymptomatic), that would allow the virus to multiply, spread systemically, induce ineffective hyperinflammation, and have a poor prognosis (Figure 1). It has been therefore hypothesized that approaches that would boost innate immune responses from the beginning of the infection, even before antigen-specific T and B cell responses are activated, would likely improve the outcome of the patients.[7]

HETEROLOGOUS EFFECTS OF VACCINES: ACTIVATION OF TRAINED IMMUNITY RESPONSES

A large number of studies in the last century have shown that certain vaccines, especially with live attenuated microorganisms, are able to induce heterologous protection beyond the target disease.[8] The immunological mechanisms mediating these effects are likely multiple, including induction of cross-reactive T cell responses, as well as long-term increase in the function of innate immune cells, a process termed trained immunity.[9] Induction of trained immunity is antigen independent and can explain the broad protective effects induced by certain vaccines. The underlying molecular substrate is represented by epigenetic and metabolic rewiring of the cells: these processes lead to an increase in chromatin accessibility and an enhanced gene transcription for proteins that are necessary for host defense.[9] Among the vaccines shown to induce heterologous protection against infections and trained immunity responses are bacillus Calmette-Guerin (BCG), measles-containing vaccines such as measles-mumps-Rubella (MMR), oral polio vaccine (OPV), and lately also influenza vaccines.[10–12] Importantly, these vaccines do not all induce an identical transcriptional and functional trained immunity program. For example, BCG induces a trained immunity program biased toward myelopoiesis activation and enhancement of myeloid cell function,[13,14] whereas ASO3-adjuvanted influenza vaccination induces a more potent antiviral interferon response.[15]

Extensive studies investigating the mechanisms through which certain vaccines such as BCG induce heterologous protection have recently described monocyte-specific trained immunity transcriptional programs as an important component of this protection.[16] Importantly, single-cell sequencing technologies have shown that severe COVID-19 is characterized by defective trained immunity programs.[16] In addition, a number of recent randomized trials have shown that BCG vaccination protects against experimental infection models in humans,[17,18] as well as against respiratory tract infections in randomized trials in children[19,20] or adults.[2] These observations have led to the hypothesis that vaccines that can induce trained immunity may also protect against COVID-19.[21,22] As a result, a relatively large number of experimental studies, as well as epidemiological studies and clinical (phase III randomized) trials have been initiated to explore the capacity of trained immunity-inducing vaccines (especially BCG) to protect against susceptibility and severity of COVID-19. Thus, 3 years into the pandemic, much has been learned on the importance of trained immunity for COVID-19, and a number of important conclusions can be drawn that can be used for a better preparedness against future pandemics. In this review, we present a summary of the studies performed during the pandemic on the trained immunity-inducing vaccines and their effects against COVID-19, as well as an overview of the long-term effects of COVID-19 itself and the new COVID-19 vaccines on trained immunity. We examine what we have learned and discuss how this knowledge on trained immunity may help us in preparing for future infectious outbreaks.

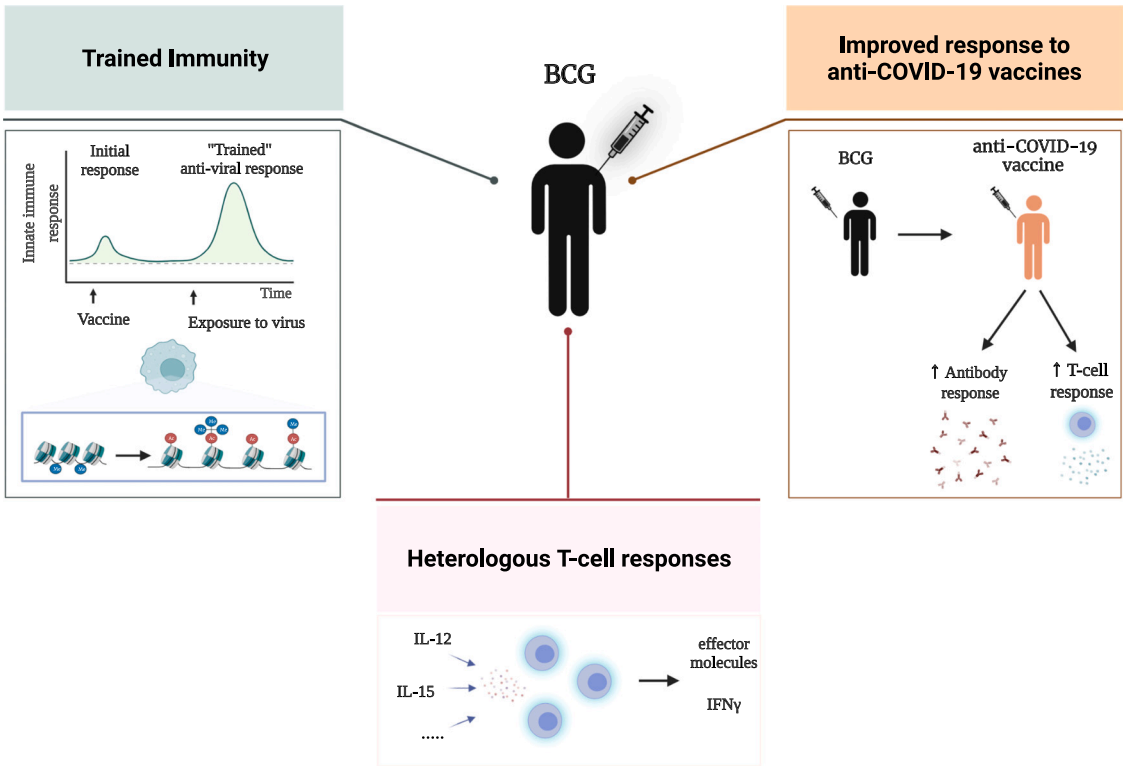

Figure 2. Immunological effects of BCG vaccination in SARS-CoV-2 infection: Direct antiviral effects through activation of trained immunity and T cell heterologous immunity, as well as improvement of the serological and T cell response of specific vaccines

BCG VACCINATION: EFFECTS ON COVID-19

Experimental animal models of SARS-CoV-2 infections developed early during the pandemic have proven useful in investigating the capacity of the BCG vaccine to protect against SARS-CoV-2 infection and mortality. In one study, it was reported that intravenous (i.v.) administration of BCG in mice induced protection of human-ACE2 transgenic mice against mortality in a model of SARS-CoV-2 infection, which was mediated by reduced viral loads, tissue pathology, inflammatory cell recruitment, and cytokine production.[23] This important observation showed the possibility to obtain heterologous protection against SARS-CoV-2. Importantly, however, subcutaneous (s.c.) administration of BCG did not show protective effects in this model, an observation that was also validated by a subsequent investigation.[24] These initial reports have been corroborated by two subsequent studies showing protective effects of i.v. BCG in either the K18-hACE2[25] or a hamster model[26] of SARS-CoV-2 infection, which was associated with induction of trained immunity responses such as myeloid cell differentiation, a transcriptional program in myeloid cells of antigen presentation and repair and activation of glycolysis. Not all studies were able to show protection against SARS-CoV-2 by BCG vaccination in rodent models, however, despite robust protection induced against influenza infection.[27] Interestingly, murine studies also suggested induction of cross-reactive antibodies against SARS-CoV-2 infection by BCG vaccination.[28,29] Finally, a non-human primate (NHP) model in rhesus macaques demonstrated rapid induction of innate immune cells such as monocytes and γδ-T cells by aerosol-administered BCG, but this did not result in overall protection of the animals.[30] All in all, these animal studies provide compelling arguments that trained immunity-mediated protection against SARS-CoV-2 infection can be induced (Figure 2), but the route of administration is very important—with i.v. administration of BCG being effective (in three of the four studies currently published), while s.c. administration fails to provide protection. Such a more potent protection induced by i.v. administration of BCG has been demonstrated in other infectious models as well.[31] The mechanisms behind the enhanced effective protection induced by i.v. as compared with s.c. administration need to be investigated in more detail. It can be hypothesized that i.v. BCG provides a more direct engagement of the bone marrow compartment and at the level required to induce trained immunity in immune cell progenitors, which may explain this stronger effect.

In parallel with the experimental studies, and due to the severity of the pandemic in 2020 and at the beginning of 2021, epidemiological studies and randomized trials with trained immunity-inducing vaccines were also initiated. Two hypotheses were under investigation: one that BCG given in childhood might protect against COVID-19 decades later and one that a recent BCG vaccination might protect against COVID-19. A number of initial epidemiological studies suggested that a program of BCG vaccination during childhood in particular geographical regions is associated with a low prevalence of COVID-19 and lower risk of severe COVID-19 in various countries.[32–34] However, such

Table 1. Randomized clinical trials with BCG vaccination and derivative vaccines during the COVID-19 pandemic

Trial	Country	Number and type volunteers[a]	Strain of BCG	Revaccination	Effect on susceptibility	Mortality placebo vs. BCG	Reference
BCG-CORONA	the Netherlands	1,600 HC	BCG-Denmark	no	no	0 vs. 1	Ten Doesschate et al.[41]
BCG-Elderly	the Netherlands	2,000 EL	BCG-Denmark	no	no	3 vs. 2	Moorlag et al.[42]
BCG-CORONA	South Africa	1,000 HC	BCG-Denmark	yes	no	4 vs. 0	Upton et al.[43]
ACTIVATE-2	Greece	300 EL	BCG-Moscow	yes	yes	3 vs. 0	Tsilika et al.[44]
BCG-PRIME	the Netherlands	6,000 EL	BCG-Denmark	no	no	18 vs. 13	Koekenbier et al.[45]
BCG-Brazil	Brazil	400 HC	BCG-Moscow	yes	yes	no mortality	Dos Anjos et al.[46]
BRACE	International	4,000 HC	BCG-Denmark	no/yes	no	no mortality	Pittet et al.[47]
BCG-Danish	Denmark	1,300 HC	BCG-Denmark	no/yes	no	no mortality	unpublished data
BCG-Poland	Poland	695 HC	BCG-10 vaccine (Biomed Lublin, Poland)	yes	no	no mortality	Faustman et al.[48]
BCG-India	India	1,450 EL	–	yes	unpublished	unpublished	unpublished data
Multiple BCG	USA	144 DM1	BCG-Japan	yes	yes	no mortality	Faustman et al.[49]
BCG-COVID	Brazil	300 COVID patients	–	yes	yes: effect on symptoms	no mortality	Jalalizadeh et al.[50]
BRIC	India	495 HRA	BCG-Moscow	yes	yes	1 vs. 0	Sinha et al.[51]
VPM1002	Germany	2,000 EL	VPM1002	no	yes	no mortality	Blossey et al.[52]
Mycobact-w	India	100 HC	–	yes	yes	no mortality	Jaiswal et al.[53]

[a]Approximate numbers of: HC, health-care providers; EL, elderly volunteers; DM1, type 1 diabetes; COVID, convalescent COVID-19 individuals; HRA, high-risk adults.

studies often suffer from inevitable biases. Specifically, most African and South American countries use BCG in childhood and also had a later start of the pandemic. Hence, later studies when the pandemic had picked up in these continents could not replicate the initial associations.[35–37] Moreover, the immunological effects during induction of trained immunity are believed to have a duration of several months and from 1 up to 2 years,[13,38] rather than the decades needed for the protection induced by neonatal BCG vaccination, although some epidemiological studies have found BCG in childhood to be associated with a decrease in all-cause mortality.[39] Interest therefore gathered around the hypothesis that a recent BCG would protect against COVID-19, and this hypothesis could be tested in randomized clinical trials providing solid advice regarding the capacity of BCG (and other vaccines) to protect against COVID-19.

Several randomized clinical trials investigating BCG vaccination effect on COVID-19 susceptibility have been initiated in 2020 and 2021. As severe COVID-19 patients are often characterized by hyperinflammation, a first important question was the safety of BCG vaccination (which can enhance innate immune responses). A retrospective study of recent BCG vaccination in healthy individuals demonstrated that BCG is safe with regard to COVID-19 severity,[40] which supported the decision to perform large clinical trials. Subsequently, a relatively large number of studies have been initiated in countries around the world, including Europe (the Netherlands, Greece, Denmark, Hungary, and Poland), the Americas (the United States and Brazil), Asia (India), Africa (Guinea-Bissau, Mozambique, and South Africa), and Australia (see Table 1). The results of the trials published so far were heterogeneous, but a number of broad patterns can be discerned.

First, the protection against susceptibility to COVID-19 differs in various populations. The majority of the larger studies performed in Europe, South Africa, or internationally do not show a protective effect of BCG vaccination against the susceptibility to COVID-19, both when the studies were conducted in health-care workers[41,43,47,48] and in individuals of older age with an increased susceptibility to severe infections.[42] However, a number of smaller studies from Greece,[44] Brazil,[46] India,[51] and the US[49] suggested beneficial effects of BCG.

One potential difference between the studies showing a beneficial effect of BCG vaccination and the other studies is the prior vaccination with BCG as infants in the individuals from the studies showing a protective effect: these individuals underwent revaccination during the trial, while the majority of participants in the European trials were BCG-naive at the beginning of the trials (Table 1). Indeed, BCG revaccination has been previously shown to be associated with reduced all-cause mortality[12] and enhanced protection also against tuberculosis (TB).[54] However, sub-group analysis of the BCG-PRIME participants with previous exposure to BCG, together with the negative results of the BCG-CORONA studies from South Africa and Poland, does not support the hypothesis of a beneficial effect of BCG revaccination over a first dose of BCG.[43,48] Genetic or environmental differences between the populations cannot be excluded, as geographical influence on BCG effects against TB has been documented in children,[55,56] but this remains to be further investigated. Another potential difference is the underlying vulnerability of participants. Three trials found a protective effect of BCG against COVID-19 incidence; these trials from Greece,[44] India,[51] and the US[49] were conducted in multi-morbid patients and in vulnerable type 1 diabetes patients, respectively. It may be

that BCG can improve a weak immune system but cannot improve on a well-functioning immune system as that of most healthcare workers. However, two studies in individuals of older age with co-morbidities but without hospitalizations from the Netherlands did not show protective effects (Table 1).

Second, none of the published trials to date had enough power to be able to draw conclusions regarding the effect of BCG on the severity of the disease. While all of the studies in healthcare workers did not observe any effect on severity, due to the low number of severe events in these relatively young populations, the incidence rate of hospitalization in BCG-PRIME study in elderly individuals with co-morbidities was 14% lower, although this was not statistically significant either.[45] Similarly, none of the studies had enough power to identify an effect of BCG vaccination on mortality. Interestingly however, in all four BCG-COVID19 studies in which mortality had been recorded (as well as the earlier published ACTIVATE trial)[2] mortality was smaller in the BCG-vaccinated group compared with the placebo group: summary statistics of these trials reported a 39% lower mortality in the BCG-vaccinated groups.[57] More studies as well as a broad meta-analysis of all studies currently reported or being completed is needed in order to be able to draw a firm conclusion regarding the effects of BCG vaccination on COVID-19 severity.

Third, the potential beneficial effects of BCG vaccination on the severity of COVID-19 may be explained by improvement of the immune responses in the vaccinated individuals. In this respect, both cellular and humoral immune responses were higher in BCG-vaccinated elderly who developed COVID-19, compared with unvaccinated individuals who were infected with SARS-CoV-2.[42] Furthermore, BCG vaccination reduced the concentration of inflammatory mediators in the circulation,[58] diminished the production of cytokines associated with severe COVID-19,[59] and enhanced the frequency of memory T cells[60] (Figure 2).

Finally, in addition to these studies that employed one standard dose of BCG vaccine, additional studies using different schedules or variants of BCG/mycobacterial vaccines also showed suggestive protective effects. In this respect, a randomized trial has been recently reported in which patients with type 1 diabetes received recent repeated BCG administrations. Interestingly, such multi-dose approach showed a very strong protection against COVID-19, with 92% less infections in the vaccinated individuals.[49] Although this is a small study, the magnitude of the effect warrants future investigations. Another interesting approach has investigated the effect of BCG administration in convalescent patients with COVID-19: improvements in the anosmia and ageusia in the BCG-vaccinated individuals has been reported.[50] A recent trial has also investigated the impact of VPM1002, a vaccine variant containing BCG expressing listeriolysin, and suggested consistent trends toward lower severity of the disease: a lower number of hospital and ICU admissions and decrease of disease duration from 14 to 9 days.[52] The total number of infections was not impacted by VPM1002 vaccination in this study. Another mycobacterial vaccine stimulant, *Mycobacterium*-w, activated NK cell responses with a gene expression profile that favors antibody-dependent cellular cytotoxicity (ADCC) and subsequently induced a very strong reduction in COVID-19 susceptibility by 85% in a small study.[53] More studies are needed to confirm the promising results of these alternative vaccination strategies.

OTHER VACCINES INDUCING TRAINED IMMUNITY EFFECTS

Although BCG was by far the most in-depth studied vaccine in the context of heterologous effects on COVID-19, other vaccines have also been previously reported to induce non-specific protection against infections. One of the most consistent inducers of protective effects against all-cause mortality in children are the measles-containing vaccines.[61] Though fewer studies have been performed with measles-containing vaccines, one randomized trial with MMR revaccination in Brazil reported a significant decrease in the severity (but not susceptibility) to COVID-19,[62] mirroring the effects reported for BCG. The results of a larger international study (CROWN-CORONATION) remain to be reported (ClinicalTrials.gov Identifier: NCT04333732).

Epidemiological studies have also earlier reported beneficial heterologous pan-viral effect of the OPV,[63,64] and observational studies suggest an effect on COVID-19 as well. In this respect, mothers of children vaccinated with OPV also displayed decreased susceptibility to SARS-CoV-2 infection, compared with age-matched women.[65] In this case, the protection of the mothers would likely be provided by their exposure to the OPV through fecal viral shedding from the infants. The hypothesis of a beneficial effect of OPV on COVID-19 was subsequently strengthened by a randomized trial in 1,000 individuals that reported a significant reduction of COVID-19 incidence in the OPV-vaccinated individuals compared with controls,[66] and a randomized trial in 3,700 individuals aged 50 or above in Guinea-Bissau recently showed that OPV was associated with a reduced risk of all-cause morbidity in males (but not females) during the pandemic.[67] These data are complemented by experimental studies showing that OPV-defective viral genomes can induce non-specific protection against a number of infections, including with SARS-CoV-2.[68] This effect of the defective OPV genomes may be induced either through interference with viral replication or through activation of innate immune responses and potential induction of an interferon activation program. These data warrant increased efforts to determine the beneficial heterologous effects of OPV and the mechanisms that mediate them in more detail.

Recent immunological studies have also reported induction of a strong antiviral trained immunity program by ASO3 adjuvanted influenza vaccination.[15] This has been independently validated in immunological studies showing a more regulated immune response against SARS-CoV-2 in humans,[69] which was accompanied by lower incidence and severity of COVID-19 in influenza-vaccinated individuals.[70–72] Randomized trials are necessary to confirm these beneficial effects. The same is true for the anti-zoster vaccine Shingrix, which was also reported to induce a significant reduction of both COVID-19 incidence (16% lower) and hospitalization (32% lower) in a large epidemiological study.[73]

Finally, one of the most intriguing possibilities regarding the role of trained immunity in the vaccination against COVID-19 is that the novel specific vaccines currently in use may also exert trained immunity effects that could contribute to their efficacy. While the mRNA-based platform, which is at the basis of one of the most successful anti-COVID-19 vaccines, is known to

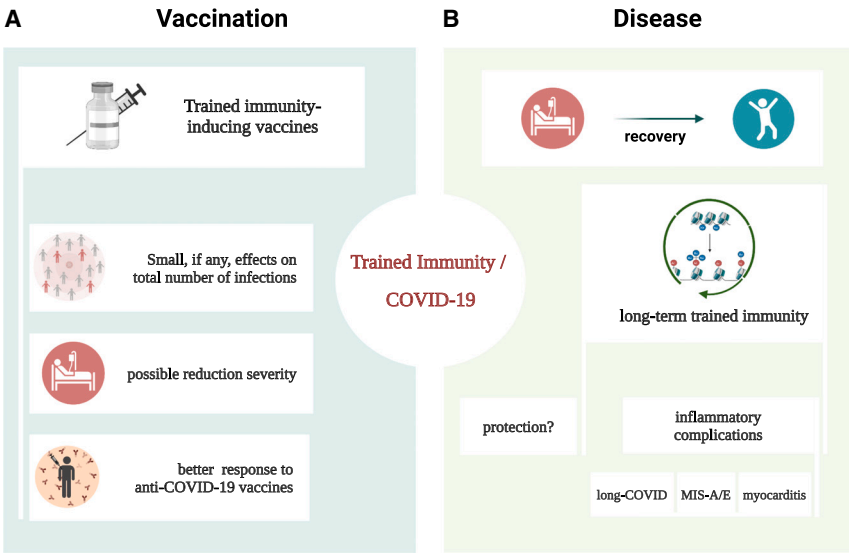

Figure 3. Trained immunity impacts on COVID-19

(A) Vaccines with trained immunity-inducing capacity: effects of single-dose administrations are very limited against total number of infections, with possible exceptions in some populations. Multiple dose administrations may be better, but more trials are needed.

(B) COVID-19 itself inappropriately induces long-term trained immunity programs that may play a role in the pathophysiology of long-COVID.

induce strong inflammation,[74] very recent studies have shown that the mRNA vaccines also induce long-term transcriptional reprogramming of myeloid cells.[75] This results in functional changes of both innate and adaptive immune cells, and the former can be considered a *de facto* induction of trained immunity.[76] Whether the mRNA vaccines can thus induce also cross-protection against other infections and whether these properties affect their effects against COVID-19 remain to be investigated. Interestingly, a very recent study reported that vaccination of Hong Kong residents with either the BNT162b2 mRNA vaccine or the inactivated virus vaccine CoronaVac indeed may have enhanced resistance to TB.[77] On the other hand, the role of such effects in mediating some of the rare but severe inflammatory complications of vaccination (such as myocarditis and pericarditis)[78] needs to be investigated.

THE IMPACT OF BCG ON THE SPECIFIC IMMUNE RESPONSES INDUCED BY THE NOVEL ANTI-COVID-19 VACCINES

As mentioned earlier, BCG enhanced cellular and humoral immune responses in individuals infected with SARS-CoV-2,[42] which raises the possibility that it may improve the specific responses induced by the novel anti-COVID-19 vaccines as well. Indeed, BCG has been previously shown to improve vaccination responses in children,[79,80] while in adults it potentiates the responses to influenza and *Salmonella* vaccines.[81,82] Moreover, approaches of using BCG as the "prime" in prime-boost strategies for TB vaccination have also been tested.[83,84] A number of proof-of-principle studies have subsequently assessed whether BCG can also improve immune responses after vaccination with the novel mRNA and adenovirus-based anti-COVID-19 vaccines. Indeed, BCG revaccination 30 days before the Pfizer-BioNTech anti-COVID-19 vaccines induced significantly higher titers of neutralizing anti-SARS-CoV2 antibodies, compared with individuals who received placebo before the COVID-19 vaccine.[85] Similarly, BCG revaccination qualitatively and quantitatively enhanced SARS-CoV-2 neutralizing antibodies and T cell responses induced by the Oxford/AstraZeneca adenovirus-based vaccine in SARS-CoV-2 seronegative young Indian adults.[86]

Altogether, mounting evidence suggests that BCG vaccination can act as an amplifier of specific immune responses induced by the novel COVID-19 vaccines and could thus improve the quality and durability of their effects (Figure 2). Whether this can lead to an improved clinical efficacy remains to be investigated.

COVID-19 INDUCES LONG-TERM CHANGES IN MYELOID CELL COMPARTMENT

The consequences of trained immunity as an immunological process for COVID-19 have been most intensively studied from the point of view of vaccination (Figure 3). However, SARS-CoV-2 infection itself is also accompanied by strong and complex immunological effects, and an increasing number of studies have investigated the long-term effects of the infection on innate immune cells. In line with this, a recent study using single-cell sequence technologies has shown the establishment of trained immunity in a newly described population of T-bet-enriched $CD16^+$ and IRF1-enriched $CD14^+$ monocytes with sequential trained and activated epigenomic states.[87] Moreover, epigenetic memory was induced not only in the peripheral innate immune cell populations but in their progenitors as well,[88] a hallmark of the induction of central trained immunity in the bone marrow.[9]

An important question relates to the clinical consequences of such trained immunity programs induced by COVID-19 (Figure 3). One possibility would be that such a program may contribute to the protection against re-infection or the severity of a secondary viral infection, although this remains to be formally demonstrated. It is interesting to observe that patients with COVID-19 are generally accompanied by less co-infections compared with other viral infections such as influenza. Another possibility is that an inappropriately strong induction of trained immunity may contribute to the long-term inflammatory complications of COVID-19. Indeed, long-COVID-19 patients display transcriptional dysregulation in their innate immune cells,[89] as well as immunological dysfunction characterized by highly activated innate immune cells with high expression of type I and III interferons that persists for more than half a year following COVID-19.[90] Interestingly, single-cell profiling identified a population of $CD9^+$ monocytes persisting for at least 3–4 months after COVID-19, which showed trained immunity characteristics with

Box 1. Conclusions on the role of trained immunity in COVID-19

1. Experimental studies in animals showed protection induced by i.v. administration of BCG against SARS-CoV-2 infection.
2. Trained immunity-inducing vaccines (BCG, MMR, Shingrix) do not protect against total number of SARS-CoV-2 infections, with the possible exception of OPV, influenza, and multiple BCG vaccinations in some populations.
3. Trained immunity-inducing vaccines are likely to decrease the clinical severity of COVID-19 and overall mortality, but large randomized trials with enough statistical power are needed to be able to draw definitive conclusions.
4. BCG vaccination improves B and T cell responsiveness to both mRNA- and adenovirus-based anti-COVID-19 vaccines.
5. The novel anti-COVID-19 vaccines induce long-term trained immunity programs.
6. SARS-CoV-2 infection can induce inappropriately strong induction of trained immunity in some individuals, which can contribute to the long-term inflammatory complications.

enhanced production of chemokines (IL-8 and MCP-1).[91] Aberrant innate immune cell populations, but also cytotoxic T cells, were observed in the airways of patients with ongoing respiratory complications after COVID-19.[92]

Post-COVID-19 long-term dysregulation of the innate immune cell function could also play a role in the severely exaggerated inflammation in pediatric or adult patients with multisystem inflammatory syndrome (MIS-C and MIS-A). Severe forms of MIS-C are characterized by a monocyte/dendritic cell signature with higher production of both cytokines and chemokines.[93,94] Other important pathophysiological components are likely to involve superantigen-induced immune activation.[95] In addition, the pathophysiology of MIS-A is also characterized by inappropriate activation of the innate immune cells and inflammation and has been shown to respond to anti-cytokine therapies in small studies.[96,97] More studies are needed to understand the involvement of trained immunity in these long-term complications of COVID-19.

CONCLUSIONS FROM THE PANDEMIC: THE IMPACT OF TRAINED IMMUNITY FOR COVID-19

Trained immunity has emerged as an important immunological process in which innate immune cells undergo long-term epigenetic and functional changes after infections or vaccinations. Because of the capacity of certain vaccines, especially those consisting of live attenuated microorganisms, to induce broad heterologous protection against infections, an increased interest had emerged at the beginning of the COVID-19 pandemic to assess the impact of these vaccines and trained immunity induction on SARS-CoV-2 infection.[21] After experimental, epidemiological, and clinical studies performed in the last 3 years, a number of important conclusions can be drawn regarding the role of trained immunity (Box 1). Briefly, most of the studies in healthy individuals do not demonstrate an overall protection against total number of COVID-19 infections, whereas some smaller studies in vulnerable groups found protective effects. A decrease of disease severity was suggested, but not formally demonstrated, to be induced by several of these vaccines.

What could be the lessons for future pandemics with new pathogens? While the data till now mainly suggest an impact of trained immunity-inducing vaccines on disease severity, this could still have important beneficial effects in reducing the effects of a pandemic. Indeed, mathematical modeling of the use of trained immunity-inducing vaccines shows an important impact on mortality and morbidity during a pandemic, even at very low efficacy of 5%–15%.[98,99] The rapid development of specific and effective vaccines against SARS-CoV-2 represented one of the major successes of biomedical research during this pandemic. Moreover, the protection offered by these vaccines against severe COVID-19 makes the direct deployment of trained immunity-inducing vaccines unnecessary for the current pandemic. Nevertheless, the research done on trained immunity during COVID-19 has been extremely valuable at several levels.

First, these studies provide the proof-of-principle for the potential deployment of trained immunity-inducing vaccines against novel pathogens in the future. Such deployment may well become extremely important in a future pandemic, until specific vaccines can be developed and tested. Trained immunity-inducing vaccines that are already approved and shown to be safe can thus become a tool for ''bridge vaccination'' to mitigate the consequences for health care and the economy in the beginning of a future pandemic (Figure 4). Second, they suggest that induction of trained immunity may improve the quality of current specific COVID-19 vaccines for which durability of the response is a major weakness. Third, the novel platforms used for the design of the novel anti-COVID-19 vaccines (mRNA, adenovirus-based) are strongly proinflammatory and are likely to induce trained immunity programs. It is important to study their non-specific effects on other infections and on overall health and to harness their potential capacity for inducing both trained immunity as well as specific immune responses.

Finally, the current trained immunity-inducing vaccines are not ideal: in fact, only approximately 50% individuals are good responders after BCG vaccination.[17] Efforts should be made for the development of better trained immunity-inducing vaccines as a component of pandemic preparedness for the future. Designing novel anti-COVID-19 vaccines that induce both adaptive immunity and trained immunity responses and improved efficacy and safety should be encouraged, as recently shown in experimental studies.[100] Only then the entire potential of the immune system would be truly harnessed to protect us against new and dangerous pathogens.

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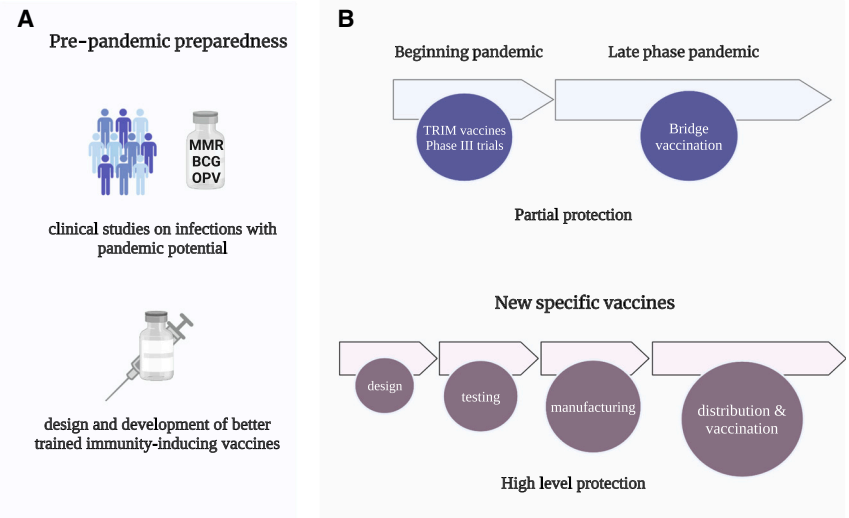

Figure 4. A framework for using trained immunity-based vaccines in future pandemics

(A) Development of improved vaccines with trained immunity-inducing capacity for pandemic preparedness.

(B) Rapid phase III trials using vaccines with trained immunity-inducing capacity in the beginning of a pandemic with a new pathogen will identify those that can partially protect against infections and/or severity. Such vaccines can be quickly used to diminish the impact of the new pathogen, in parallel with the design, testing, manufacturing, and distribution of specific vaccines that will induce higher levels of protection.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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