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Hypothetical Immunological and Immunogenetic Model of Heterogenous Effects of BCG Vaccination in SARS-CoV-2 Infections: BCG-induced Trained and Heterologous Immunity

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ABSTRACT

Though SARS-CoV-2 infections are yet to be completely characterised in a host-pathogen interaction context, some of the mechanisms governing the interaction between the novel betacoronavirus and the human host, have been brought to light in satisfactory detail. Among the emerging evidence, postulates regarding potential benefits of innate immune memory and heterologous immunity have been put under discussion. Innate immune memory entails epigenetic reprogramming of innate immune cells caused by vaccination or infections, whereas heterologous immunity denotes cross-reactivity of T cells with unrelated epitopes and bystander CD8+ activation. Familiarization of the host immune system with a certain pathogen, educates monocytes, macrophages and other innate cells into phenotypes competent for combating unrelated pathogens. Indeed, the resolution at which non-specific innate immune memory occurs, is predominant at the level of enhanced cytokine secretion as a result of epigenetic alterations. One vaccine whose non-specific effects have been documented and harnessed in treating infections, cancer and autoimmunity, is the Bacillus Calmette–Guérin (BCG) vaccine currently used for immunization against pulmonary tuberculosis (TB). The BCG vaccine induces a diverse cytokine secretion profile in immunized subjects, which in turn may stimulate epigenetic changes mediated by immunoreceptor signalling. Herein, we provide a concise summarization of previous findings regarding the effects of the BCG vaccine on innate immune memory and heterolo-

gous immunity, supplemented with clinical evidence of the non-specific effects of this vaccine on non-mycobacterial infections, cancer and autoimmunity. This interpretative synthesis aims at providing a plausible immunological and immunogenetic model by which BCG vaccination may, in fact, be beneficial for the current efforts in combating COVID-19.

Background

The COVID-19 pandemic is a rapidly evolving situation, with novel information emerging from the academic ether on a daily basis. Though the immunobiological details of SARS-CoV-2 infections continue to be uncovered in a rapid rate, a modest number of mechanisms governing the interaction between the novel betacoronavirus, have been brought to light at a satisfactory level of detail. Among the evidence that has emerged since the onset of the pandemic, postulates regarding the potential benefit of innate immune memory and heterologous immunity have been put forth and continue to be discussed. Innate immune memory entails epigenetic reprogramming of innate immune cells caused by vaccination, or viral and bacterial infections, whereas heterologous immunity colloquially denotes cross-reactivity of T cells with unrelated epitopes, along with bystander $CD8^+$ activation [1]–[11]. On the innate level, familiarization of the host immune system with a certain pathogen, may educate monocytes, macrophages and other innate cells into becoming more competent in combating non-related bacterial or viral pathogens [10], [12]. Interestingly, however, T cell cross reactivity likely stems from host genetic factors rather than pathogen-induced epigenetic reprogramming [13]–[19]. Indeed, the resolution at which bacteria, viruses and vaccines confer non-specific effects that lead to innate immune memory, is likely at the level of enhanced cytokine secretion as a result of epigenetic alterations [5], [9], [10], [20]–[27]. One vaccine whose non-specific effects have been documented and harnessed in treating infections, cancer and autoimmunity, is the Bacillus Calmette–Guérin (BCG) vaccine currently used for immunization against pulmonary tuberculosis (TB). The BCG vaccine induces a diverse cytokine secretion profile in immunized subjects, which in turn may stimulate potentially beneficial epigenetic changes mediated by immunoreceptor signalling [8], [28]–[31]. Additionally, the phenomenon of heterologous immunity has not only been observed in cases of BCG vaccination. The influenza vaccine may confer varying degrees of protection against severe forms of COVID-19 disease and presumably SARS-CoV-2 infection. This is reflected in studies where patients receiving the influenza vaccine within 120 days of a positive diagnosis were at a reduced risk of post-COVID-19 complications, further coupled with a decreased rate of COVID-19 positive cases among vaccinated populations [32]–[34]. However, much like in the case of BCG vaccination, more work is required to derive a definitive conclusion. Unsurprisingly, in a recently published preprint by Föhse et al. it was reported that the COVID-19 BNT162b2 mRNA vaccine likely induces complex innate immune system reprogramming at the level of cytokine regulation, offering protection against unrelated bacterial, fungal and viral stimuli [35].

A correlation between reduced COVID-19 morbidity and universal BCG vaccination has been implied since the early stages of the pandemic, though the immunobiological background and potential clinical significance of this remains to be substantiated [36]. Indeed, BCG vaccination leads to cellular memory at the level of both cytokines and cytokine-related transcription factors, some of which have been identified as potential targets of SARS-CoV-2 in order for the virus to establish immunosuppression [37]–[40]. The importance of this is reflected in the fact that SARS-CoV-2 dampens the adaptive immune response by acting directly on the transcriptional machinery of innate immune cells. Considering that the BCG vaccine leads to epigenetic changes that may be beneficial in preventing SARS-CoV-2-mediated immunosuppression or dissemination, this issue must be addressed in a methodical way that draws back to basic immunobiology, rather than mere statistical epidemiology. Herein, we provide a concise summarization of previous findings regarding the effects of the BCG vaccine

on innate immune memory and heterologous immunity, supplemented with clinical evidence of the non-specific effects of this vaccine on non-mycobacterial infections, cancer and autoimmunity. This interpretative synthesis aims at providing a plausible and unbiased immunological and immunogenetic model by which BCG vaccination may, in fact, be beneficial for the current efforts in combating COVID-19.

Cellular Entry of SARS-CoV-2

SARS-CoV-2 infections share similarities with the Middle East Respiratory Syndrome (MERS)-CoV and Severe Acute Respiratory Syndrome (SARS)-CoV in their mode of interaction with the human host. There is significant receptor binding domain (RBD) similarity between SARS-CoV and SARS-CoV-2 found on the spike

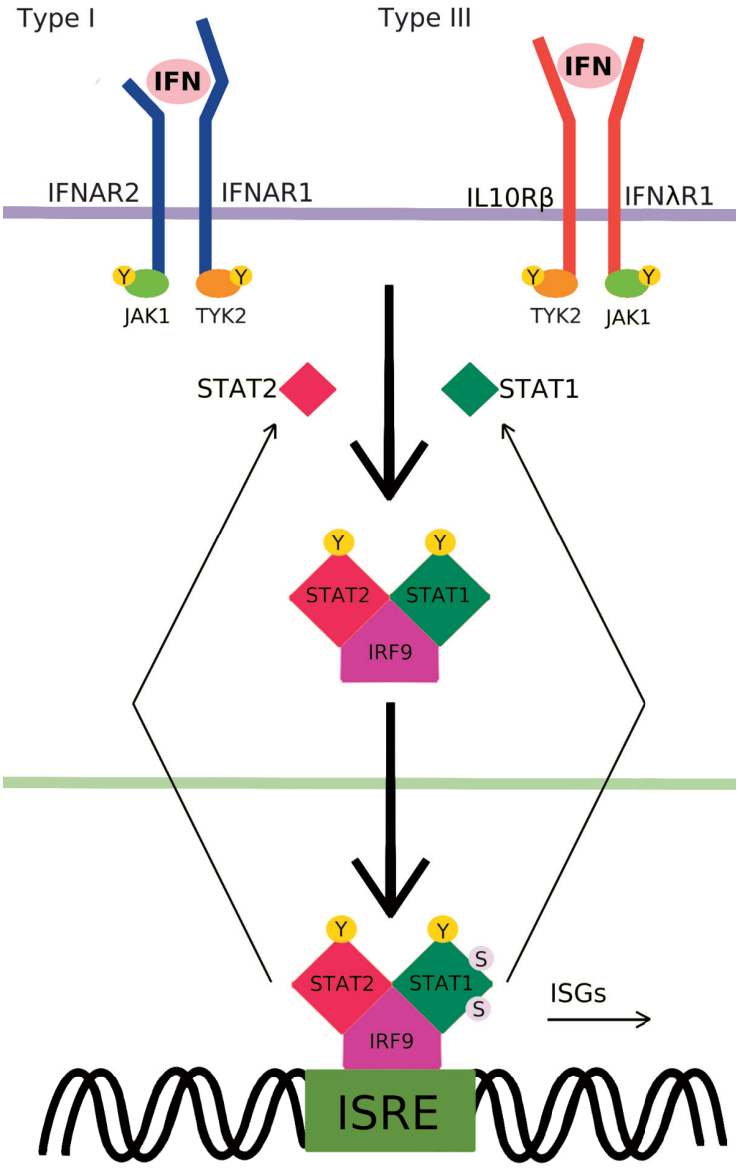


Figure 1. Type I and type III interferon responses are pivotal in the human innate antiviral response. Canonically, type I IFN signalling eventuates in the activation of the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) 2 proteins, whereas type III IFN responses recruits STAT1. Interferon regulatory factor (IRF) 9, particularly relevant in the antiviral response, associates with the JAK-STAT dimer, thereby creating the IRF9 transcription factor. IRF9 transcription factor is translocated into the nucleus, upon which it binds to the interferon stimulated response element (ISRE) located upstream of the interferon stimulated genes (ISG)

(S) protein of both viruses [41], [42]. SARS-CoV and SARS-CoV-2 infect cells expressing angiotensin converting enzyme 2 (ACE2), located in the lungs, the gastrointestinal tract, the renal tract and the heart [41], [43]–[45]. SARS-CoV-2, however, has overall higher binding affinity for ACE2 than SARS-CoV, and this is particularly pronounced for several clinically-relevant variants [39], [46], [47]. Once the S protein is bound to ACE2, ADAM metallopeptidase domain 17 (ADAM 17) and other sheddases cleave the extracellular domain as a method of preventing cellular entry. ADAM 17 further processes the membrane form of the interleukin (IL)-6 receptor (IL-6R)-α into a soluble form that will confer activation of signal transducer and activator of transcription 3 (STAT3) in non-immune cells, under the mediation of gp130. STAT3, in turn, activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, leading to potentially detrimental inflammatory responses [48].

It is possible that SARS-CoV-2, like MERS-CoV and SARS-CoV, binds to non-ACE2 receptors through carbohydrate binding, specifically various lectins and different glycoconjugates of different bacterial strains that comprise the lung microbiota [49]. Such findings offer clues for the immunosuppressive capabilities of SARS-CoV-2, particularly when discussing the notion that the viral RBD domain binds to C-type lectins such as CD209/DC-SIGN and CD209/L-SIGN, which would presumably allow the virus to infect innate and adaptive immune cells [38], [50], [51].

Immune Response to SARS-CoV-2

Innate Immune Response

Upon entry of the virus into the cell, cytosolic recognition of RNA viruses by innate immune cells occurs at the interface between the viral RNA or replication intermediates and the innate cytosolic RNA sensor, toll-like receptor (TLR) 3 and TLR7 and the cytosolic dsRNA sensor retinoic acid-inducible gene (RIG) I/ melanoma differentiation-associated protein (MDA) 5 [52]. Production of type I interferon (IFN) is triggered when viral pathogen-associated molecular patterns (PAMPs) are recognized by these receptors, activating NF-κB and interleukin regulatory factor (IRF) 3, which are then translocated into the nucleus to initiate transcription of pro-inflammatory cytokine genes, including IFN type I [53]. Successful secretion of IFN in the cytosol triggers the Janus kinase (JAK) - signal transducer and activator of transcription (STAT) 1 pathway, through the interferon-α/β receptor (IFNAR) (**Figure 1**) [53]. Although the role of DCs, and particularly resident respiratory DCs (rDCs) in SARS-CoV-2 infections warrants further research, the clinical presentation of COVID-19 is likely in part owed to altered DC function, thereby preventing their migration to the mediastinal and cervical lymph nodes in order to prime virus-specific T cells [54], [55]. *Per contra*, impaired rDC migration has been correlated with age, thereby offering another plausible explanation, or at least a relevant factor, to the discussion COVID-19 risk groups [55]. Since SARS-CoV-2 is particularly efficient at avoiding IFN-mediated innate immunity, this leads to massive immunopathology or extensive viral replication in the lungs and the respiratory tract, thereby often warranting a need for patient hospitalization in the confines of intensive care.

Adaptive Immunity in COVID-19

The issue of SARS-CoV-2 adaptive immunity, specifically protection longevity and its correlation to emerging viral variants, continues to be investigated and awaits definitive conclusions. Though certain studies have reported antibody longevity supported by long-lived bone marrow plasma cells (BMPCs), some evidence suggests that the neutralizing capability of these antibodies for SARS-Cov-2 variants is rendered unsatisfactory over time, at least for the S protein [56]–[58]. This is supported by studies reporting re-infections with genomically distinct SARS-Cov-2 variants [59], [60].

Secretion of cytokines and antigen presentation by antigen presenting cells (APCs) helps prime and direct the adaptive immune response to infections [61]. The Th1 immune response is the key player in response to viral agents, and was shown to be particularly relevant for resolving infections with SARS-CoV and MERS-CoV and, unsurprisingly, SARS-COV-2 [52], [62]. In the case of SARS-CoV infections, the specificity of B and T cell epitopes were mapped to the M, N, E and S viral proteins [63]. For SARS-Cov-2, however, these epitopes have thus far been mapped

to non-structural proteins (nsps), particularly nsp3, nsp5, the nucleocapsid (N) protein, the S protein and the open reading frame (ORF) 3a [64]. Interestingly, an IgM response targeting nsp3 and nsp5 have been correlated with a better prognosis of COVID-19, whereupon an IgG targeting S, N and ORF3a are associated with mortality and increased severity [64]. Namely, the serum of COVID-19 patients shows moderate cross-reactivity with SARS-CoV and no reactivity for other coronaviruses [65]. In terms of seroconversion, Zhao et al. found that, among 173 patients whose samples were analysed, seroconversion time for Ab, IgM and IgG was 93.1% (161/173), 82.7% (143/173) and 64.7% (112/173) respectively . Specifically, antibody presence was determined to be < 40%; however, after day 15, this significantly changed to 100.0%, 94.3% and 79.8% for Ab, IgM and IgG respectively, and relatively similar results were obtained in other studies [66]–[69]. Interestingly, long lasting IgG and neutralizing antibodies have been reported even 2 years upon initial diagnosis with SARS-CoV, and there is encouraging evidence that the same may be true for SARS-CoV-2 [70]. As evidence continues to emerge, it will be interesting to see whether the aforementioned long-lasting neutralizing antibodies following SARS-Cov-2 infection will carry sufficiently broad specificity for emerging variants in terms of the S protein and other immunogenic viral proteins.

Increase in serum Th2 cytokines were detected SARS-CoV, along with a higher frequency of polyfunctional $CD4^+$ T cells secreting tumour necrosis factor (TNF) α, IFN-γ and IL-2 in severely ill SARS-CoV patients; an overall increase in serum Th2 cytokines were present in patients that faced a fatal outcome [71]. However, it should be noted that $CD8^+$ cells dominate over $CD4^+$ in SARS-CoV, and strongly neutralizing Abs are present in convalescent patients [71]. As one may infer from the herein presented immunological data, severe lung immunopathology occurs at the delicate interface between the Th1 and Th2 immune response, yet commences at the level of innate immunity. Reducing IFN-mediated infection control allows SARS-CoV-2 to evade immune defences and delay the onset of adaptive immunity, which later results in rampant inflammation that damages the protective epithelial alveolar tissue comprised of ACE2-expressing type II alveolar cells [72], thus leaving the pulmonary tissue vulnerable to development of bacterial pneumonia [65]. Patients void of certain medical conditions generally fare better than those who are immunocompromised or who have previously been diagnosed with a condition that may be detrimental for competently combating viral infections [43].

Immune Evasion Tactics of SARS-CoV-2

SARS-CoV dampens the JAK-STAT pathway, which seems to be mechanism likely utilized by SARS-CoV-2 for immune evasion [52], [53]. This results in delayed onset of the INF-mediated anti-viral response by way of underexpression of genes containing interferon stimulated response element (ISRE), which has thus far been supported by *in vivo* and *ex vivo* studies on SARS-CoV and MERS-CoV [73]–[75]. SARS-CoV successfully interferes with induction with type I IFN by interfering with downstream signalling of cytosolic RNA sensors, through ubiquitination and subsequent degradation of their adaptor molecules, or by inhibiting the translocation of IRF3 into the nucleus by way of non-structural proteins PLpro and ORF3b [53], [76], [77]. Expressed both by MERS-CoV and SARS-CoV, PLpro has also been shown to inhibit dissociation of NF-κB from I-κB, which in turn inhibits the proper functioning NF- κB transcription factor [78]. By reducing the host's ability to control the infection, SARS-CoV-2 is able to freely replicate within the infected cell, and the mechanisms by which these evasion tactics eventuate leads to extensive inflammatory immunopathology. The reduced IFN-mediated viral control paves the way for viremia, as suppression of type I and III interferons leads to insufficient expression of interferon stimulated (ISG) genes [43]. These findings are in favour of the hypothesized pathogenesis discussed by Lin et al., who made the observation that acute respiratory distress syndrome (ARDS) is initiated somewhere around day 8 of disease onset, likely due to the overwhelming increase in pro-inflammatory cytokines, neutrophils and other immune cells which cause detrimental inflammatory damage to the host when excessively recruited [43]. Further supporting this hypothesis are data from

138 hospitalized COVID-19, where an increase in neutrophils, proinflammatory cytokines, D-Dimer and lymphopenia were detected in severely ill or deceased patients, contrasted with those who successfully recovered [79].

Dysregulation of functional T cells is particularly pronounced in SARS-CoV and likely SARS-CoV-2 infections, leading to overexpression of the programmed cell-death protein (PD)-1, T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) and T cell immunoreceptor with Ig and ITIM domains (TIGIT), as a consequence of excess production of IL-6, IL-6 and TNF-α [80]–[83]. Inducing overexpression of the aforementioned proteins is a sensical approach for SARS-CoV-2 to take. After all, even when minutely expressed on the surface of T cells, PD-1 negatively regulates T cell activity and sees elevated expression in exhausted T cells [84]. Furthermore, hierarchical T cell loss, along with T cell suppression and dysfunction are mediated by high expression levels of TIM-3 via impedance of cytokine production, particularly TNF and IFN-γ [85]. Expressed as a coinhibitory receptor on natural killer (NK) cells, memory T cells, follicular Th cells, and on a subset of regulatory T cells (Tregs), TIGIT engagement leads to inhibition of Th1 and Th17 cell response [86]–[90]. TIGIT ligation has been shown to directly suppress T cell proliferation and cytokine production of CD^{4+} T cells. Furthermore, TIGIT may indirectly inhibit T cell response through CD155 in DCs, leading to the production of the immunosuppressive cytokine IL-10 [90]. Though substantial work stands in the way of more comprehensive understanding, it is clear that SARS-CoV-2 likely utilizes similar immune evasion mechanisms as MERS-CoV and SARS-CoV in order to circumvent the human immune system.

The Bacillus Calmette-Guérin Vaccine

The Adaptive and Innate Immune Response to BCG Immunization

Despite it being the only approved vaccine for TB, the protection it offers is quite heterogenous in adults and adolescents (0 – 80%) [91]. This includes heterogenous efficacy in the context of its initial purpose, which is prevention of disseminated TB, tuberculous meningitis and severe forms of TB in children, where factors such as geographical location influence vaccine efficacy, though neonatal and postnatal administration of the vaccine offers decent protection against paediatric cases of disseminated TB and meningitis (60-80%) [92]–[94]. In spite of this, the current consensus is that there is an urgent need for a novel TB vaccine [95]. Even the induced cytokine profiles vary across populations. Evidence of the benefits of re-vaccination is relatively scarce and inconclusive, although it has been postulated that it does induce cellular and humoral immunity to an unclear extent [11], [91], [96], [97]. Administration routes may also play a role in the varying efficacy and limited protection [93]. Though most studies regarding discrepancies between BCG administration routes and their effects on efficacy stem from animal models, certain human studies have shed light on how different strains elicit distinct immune responses [98], [99]. This is reflected in differences between efficacy in the induction of specific IgG and IgA against various mycobacterial components such as lipoarabinomannan (LAM). The intranasal administration of BCG induces increased production of specific and non-specific IgG and IgA through IL-17 in mice [100], [101]. Studies on Rhesus monkeys and guinea pigs found that aerosol BCG administration increased protection to virulent *M. tuberculosis* challenge, although antibody production was never measured in human aerosol BCG studies [102]. Interestingly, an NHP-based study on intravenous (IV) BCG injections [103], revealed strikingly improved protection and precipitating antibodies post-vaccination, namely IgG, IgM and IgA. Currently the specific protective implications of these findings warrant further research, however such striking findings are native to IV BCG injections alone [91], [104]. Efficacy of the BCG vaccine presumably varies accordingly to the virulence of the BCG strain, however there is no sufficient data that clearly elucidates the true depth of the immunogenicity of different strains and how it confers protective immunity and non-specific effects [91], [105], [106].

Another layer of complexity is added to the topic of BCG strains by the presence of environmental mycobacteria that humans are exposed to in varying degrees across different geographies [107]–[110]. Limited data is available on the

antigens related to environmental mycobacteria, thus making the differentiation between different T-cell responses and various environmental mycobacteria, increasingly difficult, particularly in the context of BCG [93]. However, different B cell epitopes for different BCG strains were proposed as the plausible cause of heterogenous efficacy [111]. It should be noted that the overall topic of the humoral response to BCG vaccination has been modestly investigated. Regardless, the scarcity of comprehensive studies on this particular topic does not rule out the potentially significant effects that BCG vaccination has on humoral immunity.

Innate immune memory is not a novel concept, and has been previously explored to varying degrees of success in the context of BCG and other pathogens. Immunological memory of innate immune cells, though in defiance of the dogmatic classification of the innate immune system as void of permanent memory, has been compellingly challenged in recent years. It is known that exposure to PAMPs leads to improved innate immune response to bacterial and viral infections, though the underlying mechanisms behind this are poorly understood [6], [7]. Interactions between cell surface receptors of innate immune cells and their agonists, appear to be the driving force of these long-lived cellular memory. Despite there not being a comprehensive map displaying the ways in which BCG confers innate immune memory, numerous studies have validated the assumptions that BCG may effectively be used in non-mycobacterial infections for therapeutic purposes. Interestingly, BCG-induced training of the innate immune system seems to be completely independent of B and T cells.

Upon administration of the vaccine via intradermal injection, a pro-inflammatory response is elicited at the injection site, which includes IL-1β, TNFα, monocyte chemoattractant protein-1 (MCP-1/CCL2), and IL-8, the source of which are local innate immune cells [112], [113]. Stimulation of monocytes/macrophages with these and other cytokines have been correlated with trained immunity. Interestingly, BCG-enhanced IL-1β production has been strongly correlated with human trained immunity that offers protection against the Yellow fever Virus (YFV) [114], [115]. Innate immune cells migrate to the injection site around day 9 post-vaccination. Adult humans that have been BCG vaccinated for the first time have lingering BCG at the injection site for approximately 4 weeks, eventuating in a cellular infiltrate comprised of mostly of $CD15^+$ neutrophils, although $CD3^+$ lymphocytes and $CD14^+$ monocytes may also be found [93], [106], [116]. Migration of APCs carrying live mycobacteria or mycobacterial antigens to proximal lymph nodes, under the mediation of type I polarizing cytokines and IFN-γ, results in education of naïve T-cells into $CD4^+$ and CD^{8+} cells [107], [117], [118]. Presence of IFN-γ further propagates antimycobacterial activity of macrophages and mediates enhanced antibody production by plasma cells [119], [120]. A pool of mycobacteria-specific CD^{8+} cells that secrete IFN-γ and express granzymes and perforins, are detectable in peripheral blood up to 10 weeks post-vaccination in human newborns [121], [122]. Furthermore, large amounts of TNF-α, IL-2 and IFN-γ are produced by Th1 $CD4^+$ cells, which were also detectable in *ex vivo* studies investigating BCG-immunized newborns [123]–[125]. Enhancement of the T-cell response to BCG administration is conferred by neutrophils ingesting live BCG [126], [127]. Although macrophages, NK cells and monocytes have been given the most attention in studies regarding innate immune memory, DCs may also garner phenotypic changes that favour long-lived immunological memory [128], [129]. 4-8 weeks upon BCG immunization, a long-lived B cell response is induced, eventuating in an increase in secretion of IgG [119], [130] .

A Model of Innate Immune Memory

Epigenetic Modifications of Cellular Memory and Response Genes in Innate Phagocytic Cells: TLR Signalling

Exposure to the mannose-capped lipoarabinomannan (ManLAM) found on the cell walls of *M. tuberculosis*, BCG and other mycobacteria, promote IL-8 secretion specifically by macrophages, which further stimulates recruitment and activation of neutrophils [27], [131]–[134]. However, other BCG molecular patterns may also be involved. Stimulated neutrophils prime macrophages into phenotypes that confer protection against a wide variety of pathogens, and such phenotypes demonstrate longevity both upon BCG vaccination and stimulation by non-mycobacterial PAMPs [112], [113], [134]. The root of this longevity may

indeed be found in the epigenetic reprograming of innate immune cells, as such phenotypes evidently extend towards myeloid progenitor cells, with TLR signalling being heavily implicated in the process [24].

Generally, TLR-associated macrophage inflammatory genes may be differentiated into primary response genes (PRGs) and secondary response genes (SRGs), with PRGs being induced within approximately one hour upon stimulation [24]. TLR ligation confers permissive chromatin regions as a result of histone H3 lysine residue 4 trimethylation (H3K4me3) and H3 acetylation (H3A) (**Figure 2**) [24]. Such epigenetic modifications lead to transcriptionally engaged RNA polymerase II (RNA pol. II) being bound to the promoter proximal regions of stimulus-responsive PRG, even after stimulus-induced signalling. Under homeostatic conditions, certain PRGs have higher basal transcriptional activity even in the absence of stimulus due to higher levels of H3K4me3 within their transcription start sites (TSS) [24]. Of course, TLR signalling enhances the transcriptional activity of such genes. These basal epigenetic modifications have been heavily correlated with the binding of the specificity protein (Sp1) transcription factor to GC-abundant CpG elements found within the PRG promoters [23], [113].

An emphasis to extend of this epigenetic programming, are findings pertaining to the presence of protective BCG-trained monocytes 3 months following vaccination, and the underlying mechanism was associated with H3K4me3 and H3A on promoters associated with PRG [22]. BCG vaccination significantly increases trimethylation of PRG promoters by way of TLR4 and IFN-γ-mediated signalling in macrophages, though other TLRs are very likely involved at least on a monocyte differentiation level [135]. Considering that monocytes express each type of TLR, BCG vaccination could induce their epigenetic reprogramming via TLR signalling, thereby causing their differentiation into phenotypes of trained immunity [136]. These phenotypes may show increased potency for the clearance of viral infections, as the aforementioned cells are the first ones to encounter viral and bacterial pathogens.

Interferons and Epigenetic Modification of Interferon-stimulated Genes

BCG vaccination induces an IFN-γ response through stimulation with numerous mycobacterial antigens [28], [93]. Though BCG-induced innate immune cell memory phenotypes are increasingly studied in the context of protection against bacteria and fungi, it may render the innate immune system better equipped for viral infections with

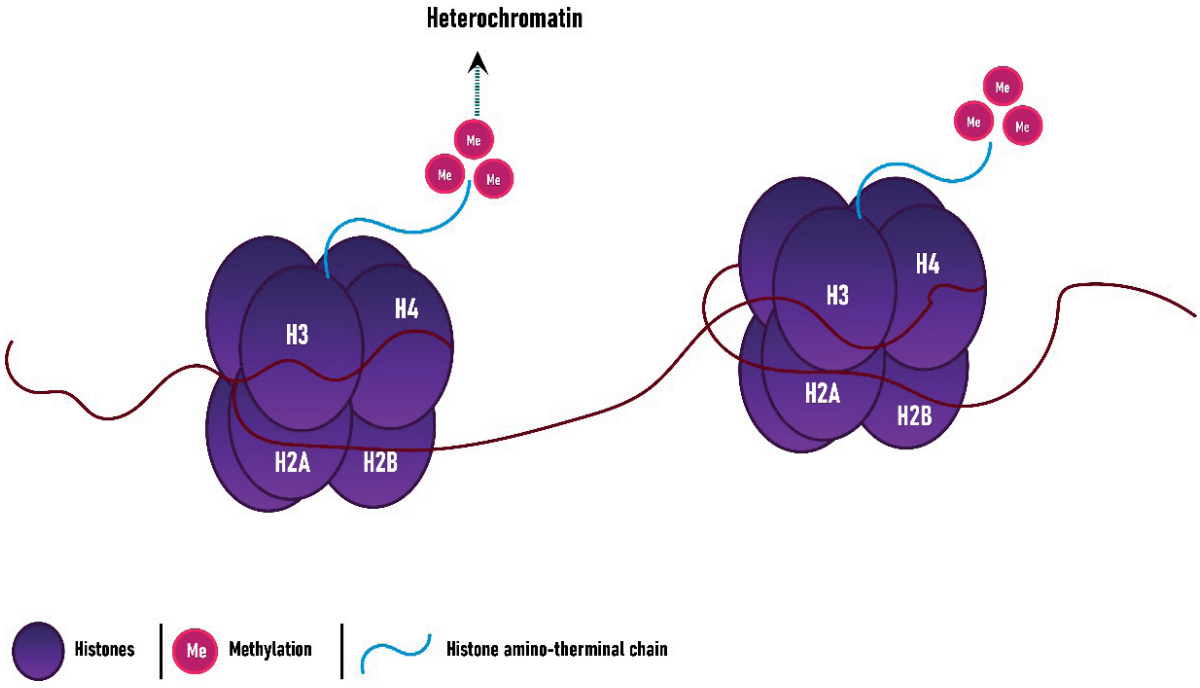


Figure 2. Histone H3 trimethylation at lysine residue 4 at promoter-associated GC-abundant CpG elements, is an epigenetic modification associated with trained immunity

RNA viruses such as SARS-CoV-2. Epigenetic modifications committed to cellular memory upon IFN exposure open some interesting questions with regards to SARS-CoV-2 immune evasion tactics, the answers to which are gradually emerging. BCG vaccination leads to increased production of IFNs, such as IFN-β and IFN-γ, therefore creating optimal conditions for epigenetic modifications [25], [26], [137], [138]. Whether this holds any merit for COVID-19 prophylaxis or treatment remains to be determined.

The relevance of type I and II IFN in antiviral response has been fastidiously substantiated, thereby making these IFN classes integral in the discussion of SARS-CoV-2 immunopathology [26]. IFN stimulation of macrophages eventuates in the creation of chromatin marks for transcriptional memory via histone trimethylation of histone H3.3 and H3K36me3 [113]. The ISGs that take part in macrophage cellular memory have been thoroughly studied, though distinct sets of genes of other innate immune cells may undergo similar modification when adequately stimulated. Interestingly, IFN memory evidently depends on functional STAT1, whereas STAT3 appears to be redundant for induction of IFN memory phenotypes [26]. Contextually to innate immune memory, ISGs may be divided into refractory (108), memory (66) and non-memory (251) ISGs, and this was elegantly demonstrated by Kamada and others in their work on IFN-induced macrophage memory [26]. Marks of permissive chromatin are most prominent in the memory-associated genes, with increased RNA pol. II binding status in contrast to refractory and non-memory ISGs [139]. Though BCG vaccination induces IFN-γ, thereby conferring epigenetic modifications of ISGs, it is likely that this represents only a component of innate immune memory, rather than the underlying mechanism.

BCG-induced Epigenetic Modifications Through NOD2 Signalling

BCG-induced trained immunity likely depends on a large number of host-specific, environmental and vaccine-related factors, with modest progress in identifying PAMPs that promote epigenetic modifications (**Figure 3**). Progress made in recent years, however, points to host receptors playing a particularly relevant role in acquiring phenotypic traits of trained immunity, coupled with a miniscule number of identified antigens. For instance, muramyl dipeptide (MDP) found in mycobacteria, including BCG, has been shown to confer viral protection in a nucleotide-binding oligomerization domain-containing protein 2 (NOD2) and IFN-β-mediated fashion [37], [140]. MDP treatment of cell lines before or after infection induces NF-κB and mitogen-activated protein kinase (MAPK) cascades, with potential relevance with immunosuppressive infections with pathogens such as SARS-CoV-2 [139], [141]. In fact, *in vitro* pre-treatment of fibroblasts with MDP leads to human cytomegalovirus (HCMV) suppression upon NOD2 ligation; an outcome that is IFN-β dependent and suggestive of the relevance of NOD2 in viral infections [142], [143]. Considering that both DNA and RNA viruses and their corresponding PAMPs are NOD2 agonists, modifications of genes associated with NOD2 signalling may be particularly relevant for the innate immune response to SARS-CoV-2, assuming *a priori* acquisition of trained phenotypes [140]. Furthermore, basal expression levels of NOD2 are higher in macrophages and monocytes in contrast to fibroblast, therefore NOD2 mediated signalling is likely more pronounced in these cells. Of course, this increased potency may translate to increase efficiency with regards to trained immunity.

NOD2 signalling leads to IκB kinase complex (IKK) activation in order to degrade the inhibitory IκBα protein. Synergic IFN-γ and MDP signalling leads to increased IKK activation, thereby significantly reducing IκBα levels in a STAT1 independent fashion [144]. Though understanding of IKK regulation is incomplete, it is known that TNF-α negatively regulates IKK activity by C-terminus phosphorylation of the IKKβ subunit [28]. Taking this into consideration, it is not difficult to infer that BCG-induced TNF-α may render the BCG vaccine inadequate for therapeutic purposes in COVID-19. A possible way out of this conundrum may lie in the heterogenous BCG-induced cytokine profiles across different populations, which opens the possibility of tailoring different BCG strains in accordance to the populational response [113]. Evidence supporting this suggestion may be extrapolated from the work of Kleinnijenhuis and others, where BCG-induced trained immunity of human monocytes was achieved in a NOD2 and Rip2 dependent manner [115], [145],

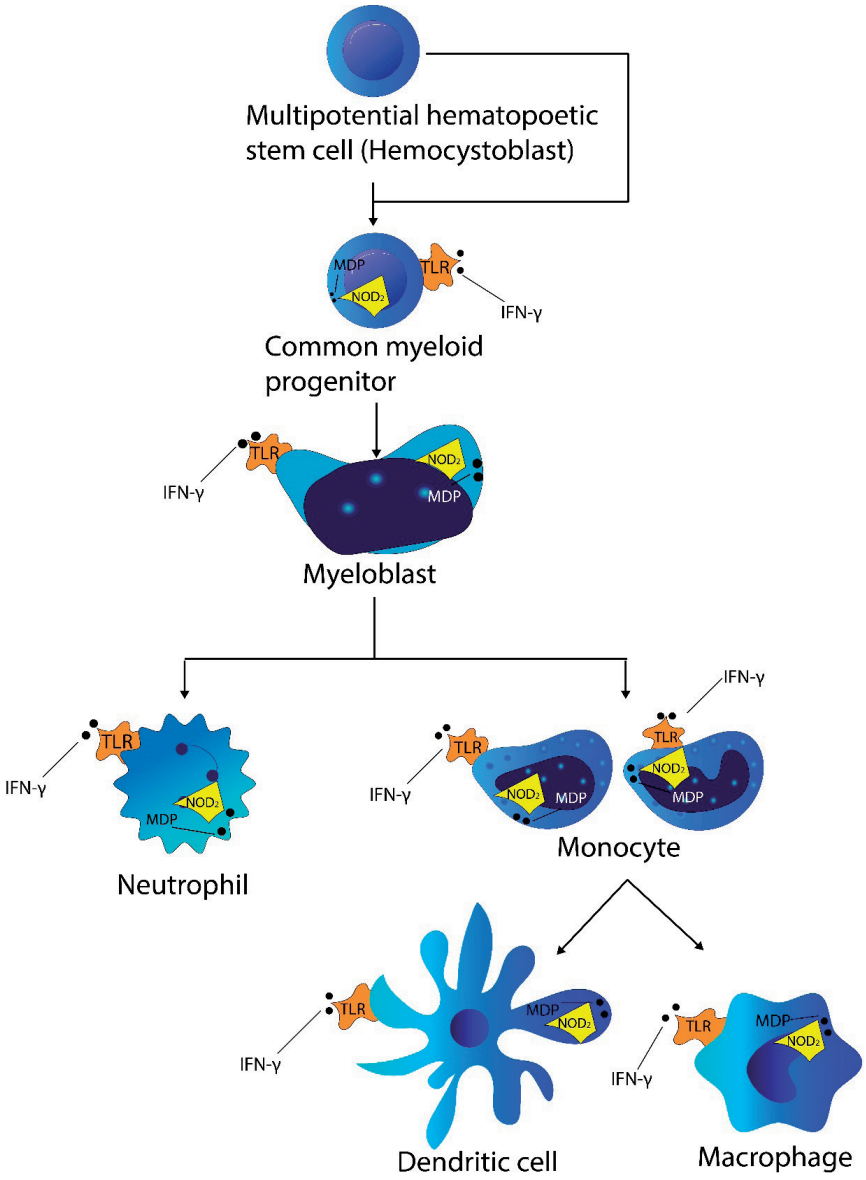


Figure 3. Different cells of the innate immune system can undergo cytokine/antigen-stimulated epigenetic changes that may induced trained immunity. Common myeloid progenitor cells may also be stimulated, thereby differentiating into trained phenotypes. Abbreviations: MDP – muramyl dipeptide, IFN-γ – Interferon Gamma, TLR – Toll Like Receptor, NOD2 – Nucleotide-binding oligomerization domain-containing protein 2

[146]. Strikingly, their work demonstrated redundancy of TLR2 and TLR4 in this process, though it is likely that other mechanisms take part in this process that were simply not considered in the work. Considering that SARS-CoV-2 likely blocks IκB dissociation from NF-κB, it would be interesting to see whether NOD2-dependent trained immunity entails phenotypes that are more resilient to this tactic. Redundancy of TLR2 and TLR4 does not exclude the roll of TLRs in trained immunity, but rather emphasize the complexity and heterogeny of the mechanisms behind it.

A Model of Heterologous Adaptive Immunity for SARS-CoV-2 Infections

Vaccines were initially considered to eventuate in immune responses precisely tailored towards the pathogen-associated antigen contained within the vaccine. Canonically, once the phagocytic cells engulf an antigen/pathogen, they migrate to proximal lymph nodes and present pathogen-associated peptides (epitopes) to naïve T cells via the type I/II major histocompatibility complex (MHC I/II). In turn, this leads to T and B cell priming, followed by their clonal expansion. The

traditional interpretation of adaptive immune memory infers that educated lymphocytes are specific only for the epitopes presented by way of MHC molecules. Whilst this specificity, indeed, is predominantly present in the human immune system, a closer inspection of T cell reactivity reveals evidence of heterogenicity, colloquially termed "heterologous immunity". The "off target" vaccine effects that give rise to heterologous immunity lead improved responses to unrelated pathogens and immunological tolerance in autoimmune conditions, though negative effects have also been documented [145], [147]–[151]. Specific mechanisms behind heterologous immunity are poorly understood, however epigenetic programming, cross-reactivity between epitopes and changes in metabolic profiles of lymphocytes, likely play major roles [152]–[155].

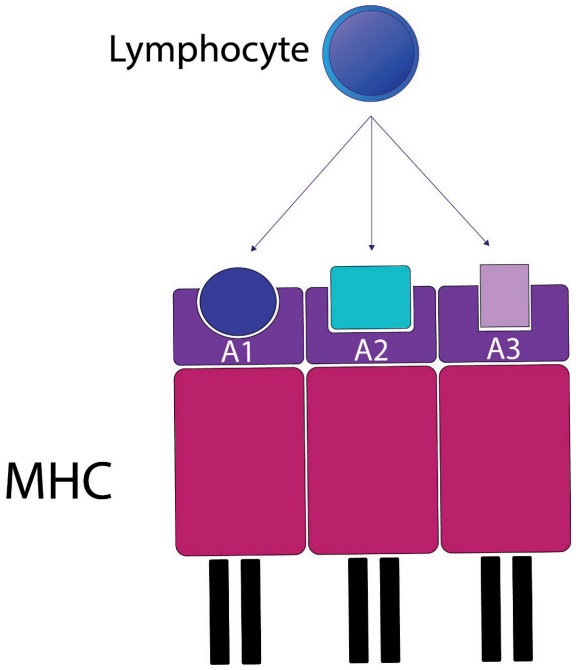


Figure 4. Cross-reactive lymphocytes can respond to different antigen determinants presented on the MHC grooves. Though T cells are most prominently known for cross-reactivity, B cells may also be cross reactive [158]. Abbreviations: MHC – Major Histocompatibility Complex

Immunological Cross-reactivity of T Cells

APCs present pathogen-associated epitopes by way of MHC I and II to $CD8^+$ and $CD4^+$ T cells respectively, in the form of short amino acid sequences (MHC I: 8-11, MHC II: 13-17). Hitherto proposed to depend on the presentation of such conserved linear sequences by clonal selection theory, T cell reactivity evidently extends towards completely unrelated antigenic determinants presented from the MHC antigen-binding groove [152]–[155] (**Figure 4**). Considering that the amino acid sequences that garner heterologous T cell reactivity are modestly homologous, regular immunological cross-reactivity may be possible not only for unrelated infections, but detrimental in the context of autoimmunity [156], [157]. The root of this heterology is poorly understood, though several plausible mechanisms have been suggested, all of which may, singularly or synergistically, share responsibility for this phenomenon. Though heterologous immunity has thus far been documented in the context of viral infections, BCG vaccination may indirectly lead to heterology through induction of cytokine secretion.

Phenotypic alterations that are to be observed when discussing cross-reactivity, are at the resolution of the T cell receptor (TCR). TCRs are heterodimers comprised of subunits TCRα and TCRβ, though approximately 5% of human TCRs are comprised of TCRγ and TCRδ. Expression of TCRs and Ig chains on the surface of T cells is controlled by a mechanism known as allelic exclusion, with their expression corresponding to a single allelic copy [16]. This ensures that the *modus operandi* of T and B cell priming is that of clonal selection, the benefit of which entails avoidance of autoimmunity by way of high specificity [13]. However, biallelic expression of TRC and Ig kappa (κ) chain (Igκ) has been documented in T cells, and correlated with affinity for a broader spectrum of antigens [13], [159]. Of course, this alone cannot be attributed to cross-reactivity, as heterogenicity in T and B cell ligand receptor binding is now understood as putative [17]. Interestingly, incomplete allelic exclusion of the TCRα chain can lead to expression of two distinct TCRs, thereby increasing the likelihood of cross-reactivity [18].

Permissive and repressive epigenetic control of T cells, though an integral part of the canonical adaptive response, very likely extend towards the facilitation of heterologous immunity in the context of TCRs and surface Ig [147], [151], [160]–[166]. Though trained immunity is independent from T and B cells, heterologous immunity relies on the canonical relationship between the two components of the immune system. Perhaps characterised with heterogeny, BCG-induced cytokine

expression profiles predominantly include IFN-γ, which in turn stimulates macrophages and monocytes to secrete numerous cytokines, including IL-15. This cytokine regulates survival of T cells in the absence of antigens, either through induction of apoptosis or division [167]. It is possible that epigenetic alterations that occur upon BCG vaccination may influence permissiveness of the chromatin regions that corresponds to regulatory regions of the IL-15 gene, though this remains to be determined. In any case, the influence of BCG on heterologous immunity is likely predominantly mediated via innate immune cells. The threshold for TCR activation is lowered in effector/memory $CD8^+$ cells through the expression of TLR 1/2/6 and 6 are respectively. Considering that TLRs are important receptors in BCG recognition, this opens the possibility of epigenetic reprogramming as a result of TLR signalling.

Mycobacterial Activation of Bystander $CD8^+$ Cells

Activation of bystander $CD8^+$ cells, interestingly enough, is independent of TCRs, yet heavily dependent on secretion of IL-15, which BCG vaccination may indirectly induce [4]. Bystander activation of $CD8^+$ have been documented as the main sources of IFN-γ along with stimulated NK cells in melioidosis caused by *Burkholderia pseudomallei* [2]. Furthermore, enhanced expression of IFN-γ mRNA was documented in mouse models, however the study that reports this used and experimental *M. avium* model [3]. In spite of this, homologies between BCG and *M. avium* antigens may evoke similar, if not identical, T cell responses. Interestingly, virally activated $CD8^+$ exhibit strong affinity towards granulomas induced by BCG, though this has thus far only been documented for immunodeficient mice, and it is unclear whether BCG activation of T cells would have the same effect on viral infections [1]. In the absence of more comprehensive studies to draw a conclusion from, it may only be cautiously proposed that BCG-induced IL-15 secretion likely influences bystander $CD8^+$ T cell activation.

Though currently available evidence is somewhat suggestive of a relationship between non-specific T cell activation and BCG immunization, comprehensive work lies ahead in determining whether the vaccine may induce a $CD8^+$ cell phenotype that could contribute to better outcome with SARS-CoV-2. Considering that BCG contains a large number of highly diverse antigens, it is not surprising that T cells induced by BCG vaccination are quite broad in epitope specificity [110], [115], [168]. *Per contra*, excessive T cell cross-reactivity may lead to autoimmunity, thereby making the heterologous immunity narrative a double-edged sword [13]–[16], [18], [19]. Recently $CD4^+$ T cells cross-reactive to SARS-CoV-2 have been detected in COVID-19 patients, though the exact implications of this remain unclear, and are likely population-specific [169]. However, it has been proposed that their presence could potentially reduce viral loads in both the lungs and the upper respiratory tract upon infection.

Non-specific Immunomodulatory Effects of the BCG Vaccine

Reports of non-specific benefits of BCG vaccination on other infectious diseases has seen a steady increase in recent years, correlating the vaccine with reduced mortality rate among infants, along with adjuvant-like effects on other unrelated childhood vaccines [170]. Beneficial effects of BCG on non-mycobacterial infections is colloquially thought to be mediated by innate immune memory or heterologous lymphocyte activation [30], [171], due the absence pathogen-specific antibody epitopes in mouse studies where the vaccine conferred a better outcome in infections with *Salmonella typhimurium* and challenges with *Plasmodium spp.* and *Babesia* [172]. Perhaps the most striking evidence regarding non-specific BCG benefit is the improved antibody response to oral polio vaccine boosting detected in patients who were also given BCG at the time of booster administration [173], [174]. Thus, it is likely that the beneficial effects of the BCG vaccine vary concordantly to the strain of BCG and the immunogenetic background of the host. For instance, an Australian study conducted on 56 BCG-vaccinated and 52 BCG nonvaccinated infants, uncovered higher titters of IgG with epitopes for *Haemophilus influenzae* type B polysaccharides, pneumococcal capsular polysaccharide PAMPs and tetanus toxoid (TT) [175]. *Per contra*, a randomized study on new-borns in Denmark found that a reduction in infant hospitalizations was only for cases where the mothers were also BCG vaccinated [176], [177].

Non-specific BCG effects do not shy away from the domain of respiratory viral infections,

where beneficial effects of BCG continue to be reported, however comprehensive understanding of this puzzling occurrence is modest at best [8], [31], [120]. Although a number of different BCG strains exist and continue to be regularly used, there is very limited work on the efficacy conferred by each different strain, both in tuberculosis prophylaxis and non-specific effects in non-

Table 1. Some currently ongoing clinical trials regarding the correlation of the BCG vaccine and reduced risk of COVID-19 (https://clinicaltrials.gov/)

Title	Status	Interventions	Locations
Reducing Health Care Workers Absenteeism in Covid-19 Pandemic Through BCG Vaccine	Active, not recruiting	– Drug: BCG Vaccine – Drug: Placebo	– Jeroen Bosch ziekenhuis, Den Bosch, Brabant, Netherlands – Canisius Wilhelmina Ziekenhuis, Nijmegen, Gelderland, Netherlands – Radboud UMC, Nijmegen, Gelderland, Netherlands – Sint Maartenskliniek, Nijmegen, Gelderland, Netherlands – Noordwest Ziekenhuisgroep locatie Alkmaar, Alkmaar, Noord Holland, Netherlands – Hagaziekenhuis, Den Haag, Zuid-Holland, Netherlands – Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands – Erasmus Medical Center, Rotterdam, Zuid-Holland, Netherlands – University Medical Center Utrecht, Utrecht, Netherlands
Reducing COVID-19 Related Hospital Admission in Elderly by BCG Vaccination	Active, not recruiting	– Biological: BCG vaccine – Biological: Placebo	– Radboud University, Nijmegen, Gelderland, Netherlands – UMC Utrecht, Utrecht, Netherlands
BCG Vaccination for Healthcare Workers in COVID-19 Pandemic	Active, not recruiting	– Biological: Bacille Calmette-Guérin (BCG) – Other: Placebo Comparator	– TASK Foundation, Cape Town, Western Cape, South Africa
BCG Vaccination to Protect Healthcare Workers Against COVID-19	Active, not recruiting	– Drug: BCG Vaccine – Drug: 0.9%NaCl	– St Vincent's Hospital, Sydney, Sydney, New South Wales, Australia – Prince of Wales Hospital, Sydney, New South Wales, Australia – Sydney Children's Hospital, Randwick, Sydney, New South Wales, Australia – The Children's Hospital at Westmead, Sydney, New South Wales, Australia – Westmead Hospital, Sydney, New South Wales, Australia – Royal Adelaide Hospital, Adelaide, South Australia, Australia – Women's and Children's Hospital, North Adelaide, South Australia, Australia – Royal Children's Hospital, Melbourne, Victoria, Australia – Epworth Richmond, Melbourne, Victoria, Australia – Monash Health- Monash Medical Centre, Melbourne, Victoria, Australia – and 26 more
Prevention, Efficacy and Safety of BCG Vaccine in COVID-19 Among Healthcare Workers	Active, not recruiting	– Biological: BCG vaccine – Other: Placebo	– Hospital Universitario "José E. González", Monterrey, Nuevo León, Mexico
BCG Vaccine in Reducing Morbidity and Mortality in Elderly Individuals in COVID-19 Hotspots	Active, not recruiting	– Biological: BCG vaccine (Freeze-dried)	– Tuberculosis Research Centre, Chennai, Tamilnadu, India
Efficacy and Safety of VPM1002 in Reducing SARS-CoV-2 (COVID-19) Infection Rate and Severity	Active, not recruiting	– Biological: VPM1002 – Other: Placebo	– University Health Network, Toronto, Ontario, Canada

mycobacterial infectious diseases. There is some evidence indicating that BCG decreases the morbidity of acute lower respiratory tract infections caused by respiratory syncytial virus (RSV); this effect was observed in young children in Guinea-Bissau and in a study that included elderly people, where a decrease in incidence of acute upper respiratory tract infections was reported [178]. However, it should be noted that the study on elderly people, which did yield positive results in favour of the non-specific protection of BCG against viral infections, was conducted by administering the vaccine once a month for three months, thereby warranting cautious interpretation. A significant reduction in respiratory tract infections was also reported in a study of BCG-vaccinated adolescents in the South-African population [179]–[181]. Although the results of these studies are in favour of non-specific prophylactic BCG effects in viral infections, therapeutic effects of the vaccine have also been reported, specifically regarding patients infected with the human papilloma virus (HPV) [182].

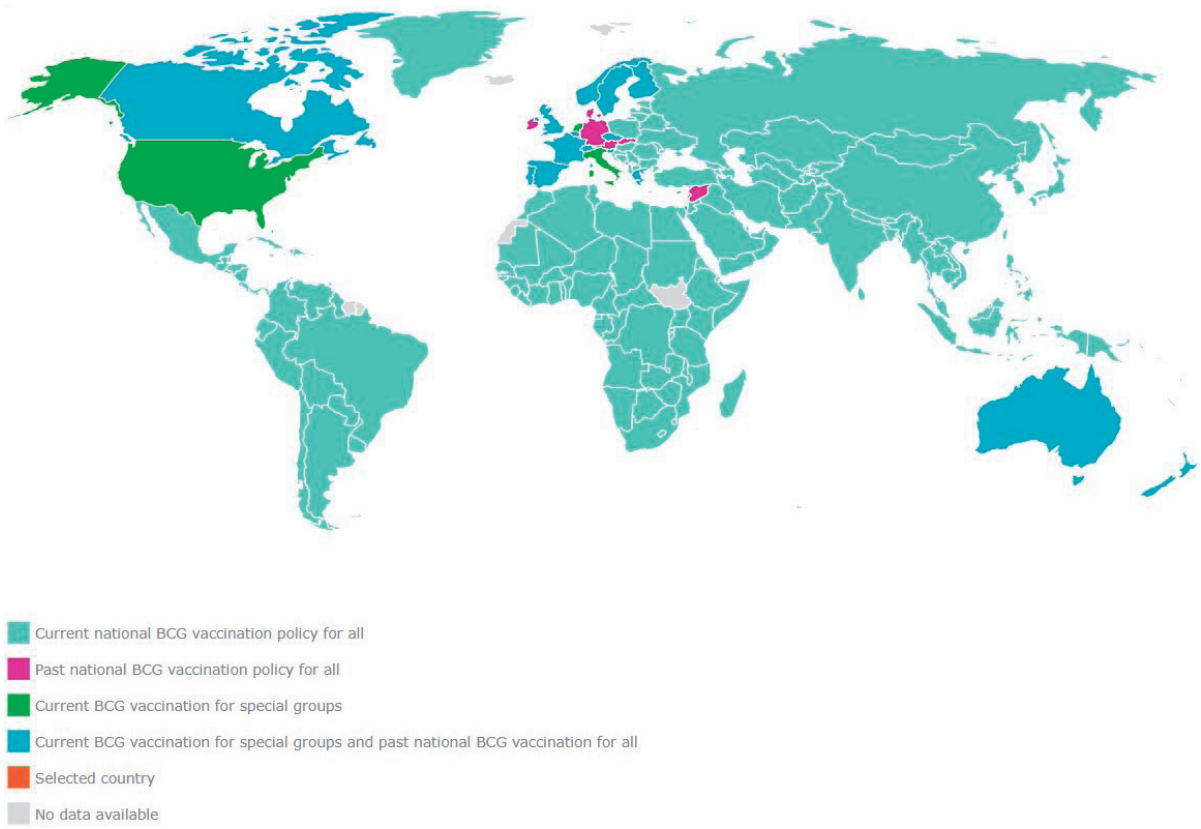
Perhaps most interesting for the COVID-19 pandemic is a study that reported improved antibody titters for the influenza A strain (H1N1) that caused the 2009 "swine flu" epidemic, when BCG was administered prior to the H1N1 vaccine. The enhanced protection was hallmarked by an improved production of IFN-γ for the H1N1 study [183], contrasted with another study that reported that BCG-induced IL-1β production is the likely mechanism of conferred protection during viral infections [151]. However, the same IFN-γ-mediated protection was observed for the vaccinia virus in infected mice upon BCG vaccination, which promoted the secretion of this cytokine by $CD4^+$ T cells [184]–[186]. IL-1β plays a role in inflammatory responses, apoptosis, cell differentiation and proliferation, and has shown to play an important role in viral immunity [187]. Improvement of non-specific Th1 and Th17 immune responses, along with enhanced innate trained immunity, has also been reported in BCG-immunized patients, with satisfactory durations [188].

Implications for the COVID-19 Pandemic

At the present moment, there are a number of clinical trials aimed at evaluating the presumed protective effects of the BCG vaccine towards COVID-19, some of which are summarized in **Table 1**. It is likely, however, that BCG strain will have an impact on its effects on COVID-19 and infections with SARS-CoV-2, and trials are currently underway for the purpose of assessing which strain, if any, is adequate for implementation in the battle against COVID-19. Thus far, the candidates of interest are the Danish and Tokyo strain, although it currently remains utterly unclear what the immunological basis for their difference in efficacy might be [106]. Frequently used BCG strained along with their characteristics are summarized in **Table 2** [189], [190]. Virulence of the BCG strain was hypothesized to play a role in protection against *Mycobacterium tuberculosis*, potentiating the assumption that the trials will eventuate in varying efficacy across BCG strains for COVID-19 [43]. There is an obvi-

Table 2. Summarization of frequently used BCG vaccines and their characteristics. Abbreviations: CRR, complete response rate; NA, not applicable

Strain	Mean CRR	Weight (mg)	Recommended dose (cfu)±	Secretion of lipid virulence factors	Secretion of MPB64/ MPB70 and MPB8
RIVM/1	60	80	2-30 x 10^8	NT	Unknown
Romanian	64	NA	NA	NT	Unknown
Copenhagen	67	NA	NA	Yes	Absent/Present
S. African	69	NA	NA	NT	Unknown
A. Frappier	60 (39–100)	NA	NA	Yes	Absent/Present
Glaxo	65 (53–88)	NA	NA	No	Absent/Present
Tice	71 (56–82)	12.5	2-8 x 10^8	Yes	Absent/Present
Pasteur	74 (40–80)	NA	NA	Yes	Absent/Present
Tokyo	77 (63–84)	80	0.4-0.5 x 10^8	No	Present/High
Connaught	79 (70–92)	81	1.8-15.9 x 10^8	NT	Unknown
Moreau RdJ	90	80	0.04 x 10^8	No	Present/High
Moscow	90.5	120	3-57 x 10^8	Yes	Present/High



ous need to bridge the gap between findings in basic immunobiology and clinical application, which will hopefully occur upon the conclusion of these clinical trials. Since COVID-19 vaccines are still not internationally widely available to all countries, the potential for utilization of existing vaccine technologies in mitigating some of the fallout caused by COVID-19, could significantly improve patient care in countries where COVID-19 vaccines are scarcely available.

Concluding Remarks

Although the mechanisms of action remain unclear, non-specific effects of BCG have been reported to confer a degree of protection against viral infections and non-mycobacterial bacterial infections. It is likely that BCG predominantly influences innate immune memory, causing epigenetic modulation of monocytes and macrophages, and inducing secretion immunomodulating cytokines. Effects on heterologous immunity, however, can currently only be described as indirect, particularly through induction of IL-15 secretion. Though heterologous immunity does, indeed, depend on adequate pathogen processing by the innate immune system, BCG-induced bystander $CD8^+$ activation may boost the innate immune response through enhanced IFN-γ production.

Although recent studies have shown that BCG promotes the Th1 and Th17 immune response, further studies should be directed at uncovering whether such effects are dependent on BCG strain and the immunogenetic background of patients. Considering that BCG has been shown to increase titters of polysaccharide-specific IgG in bacterial infections, it is possible that the same might be true in the case of SARS-CoV-2 spike glycoprotein, which the virus uses to bind to cells expressing ACE2 and C-type lectins. Substantial evidence has mounted over the years in favour of non-specific benefits of BCG vaccination in a variety of other infectious and oncologic diseases, further solidifying the plausibility of this model. However, the effects of this vaccine vary in accordance to BCG strain and likely a plethora of host-derived factors, most of which are incompletely understood. In essence, trained and heterologous immunity are incredibly complex and multifaceted phenomena with proven therapeutic potential, and could possibly confer improved outcome in asymptomatic SARS-CoV-2 infec-

tions, or COVID19 disease. It is encouraging to see the number of clinical trials that are currently underway, tasked with resolving a lot of unclarity regarding the issue of BCG-induced heterologous immunity. Though this work is concerned with providing a hypothetical model by which the BCG vaccine may induce non-specific protection against SARS-Cov-2 – based on studies concerning other pathogens – we recognize the limitations of all previous studies pertaining to this topic. Firstly, though this is a plausible immunobiological model, it largely based on *in vitro* and animal studies, with several prominent examples derived from human test subjects. Human studies concerning heterologous immunity tend to suffer from the issue of bias, and the potentially relevant host-derived intricacies influencing the ability of a vaccine to influence innate immune cell memory, is difficult to control for. Though our model holds plausibility, it should be understood as suggestive rather than definitive, and more work is definitely needed – one that bridges clinical relevance and basic immunobiological studies – in order to derive a definitive conclusion.

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Availability of supporting data
This is a review; therefore, this is not applicable. Each of the studies that this manuscript is based on are publicly available.

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