



# Can BCG be useful to mitigate the COVID-19 pandemic? A Canadian perspective

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## Abstract

There is ample evidence from in vitro, animal and human studies that the Bacillus Calmette-Guerin (BCG) vaccine epigenetically reprograms innate immunity to provide “off target” protection against pathogens other than *mycobacteria*. This process has been termed “trained immunity”. Although recent ecological studies suggested an association between BCG policies and the frequency or severity of COVID-19 in different countries, the interpretation of these results is challenging. For this reason, a case-control study aiming to test this hypothesis has been initiated in Quebec. Several phase III clinical trials are underway, including one in Canada, to assess the efficacy of BCG against SARS-CoV-2 infection (results expected in 2021). In the past, BCG has been widely used in Canada but current indications are restricted to high-risk individuals and communities experiencing TB outbreaks as well as for the treatment of bladder cancer. The potential implication of BCG as an interim measure to mitigate COVID-19 is the subject of widespread discussion in the scientific community and can be considered for the vulnerable population in Canada. To conclude, BCG vaccination should be placed on the agenda of research funding agencies, scientific advisory committees on immunization and federal/provincial/territorial public health authorities.

## Résumé

Il existe de nombreuses preuves issues d'études in vitro, chez l'animal et chez l'humain qui montrent que le vaccin bacillaire de Calmette et Guérin (BCG) peut reprogrammer de manière épigénétique l'immunité naturelle et procurer ainsi une protection « hors-cible » contre des pathogènes autres que les mycobactéries. Ce processus a été appelé « immunité entraînée ». Bien que des études écologiques récentes aient suggéré l'existence d'une association entre les politiques d'utilisation du BCG et la fréquence ou sévérité de la COVID-19 dans différents pays, l'interprétation de leurs résultats est difficile. Pour cette raison, une étude cas-témoin a été entreprise au Québec en vue de tester cette hypothèse. Plusieurs essais cliniques de Phase III sont en cours, dont un au Canada, pour évaluer l'efficacité du BCG contre les infections causées par le SRAS-CoV-2 (résultats attendus en 2021). Dans le passé, le BCG a été utilisé à large échelle au Canada, mais actuellement, les indications sont limitées aux individus à haut risque et aux communautés dans lesquelles se produisent des éclosions de tuberculose, ainsi que pour le traitement du cancer de la vessie. L'intérêt potentiel du BCG en tant que mesure intérimaire pour contrôler la COVID-19 fait l'objet de discussions intenses dans la communauté scientifique et cela pourrait être envisagé pour des populations vulnérables au Canada. Pour conclure, la vaccination avec le BCG devrait être placée sur l'agenda des organismes de recherche, des comités scientifiques consultatifs et des autorités de santé publique fédérale, provinciales et territoriales.

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## Introduction

The ongoing COVID-19 pandemic is caused by a novel acute respiratory syndrome coronavirus (SARS-CoV-2), an RNA virus belonging to the *Coronaviridae* family. While the vast majority of SARS-CoV-2-infected, otherwise healthy individuals are asymptomatic or develop only mild disease, the infection may be severe and fatal in vulnerable populations (Wiersinga et al. 2020). SARS-CoV-2 infection triggers both innate and adaptive humoral and cellular immune mechanisms (Yuki et al. 2020; Rydyznski Moderbacher et al. 2020). Disease severity is associated with the failure of the initial immune response to control early viral replication that ultimately leads to cytokine storm and ARDS-like disease resulting in pulmonary edema, hypoxia and respiratory failure (Yuki et al. 2020; Rydyznski Moderbacher et al. 2020). While protection against SARS-CoV-2 appears to be associated with neutralizing antibodies, the longevity of these antibodies is still under investigation. Furthermore, both cellular innate (e.g., natural killer cells and macrophages) and adaptive immunity (e.g., CD4+ and CD8+) play a key protective role to SARS-CoV-2. It is critical to carefully analyze the kinetic and magnitude of the immune responses during early and late phases of the infection, as dysregulated immunity as well as subsequent immunopathology influence disease severity. Undoubtedly, an effective vaccine that improves the initial response to infection and prevents disease progression would be helpful to mitigate the burden of COVID-19.

Numerous studies have shown that vaccination with live-attenuated vaccines, the Bacillus Calmette-Guérin (BCG) vaccine mainly, is associated with lower rates or severity of diseases caused by unrelated pathogens (Netea et al. 2020a). In this line, the World Health Organization has recommended more investigations into “off target” effects of vaccines. Currently, there is a widespread discussion in the scientific community regarding BCG vaccination as an effective intervention to mitigate the COVID-19 pandemic (Aaby et al. 2020; Netea et al. 2020b). The objective of this short commentary is to briefly present the state of knowledge and perspectives regarding the potential of BCG studies and vaccination in the Canadian context.

## Immune mechanisms triggered by BCG vaccination

Conventionally, vaccine design involves the identification of an antigen that generates long-term adaptive T and B

cell memory responses providing protective immunity upon re-encounter with the same pathogen (Khader et al. 2019). However, this approach has not yet led to a successful vaccine against human coronaviruses (e.g., HCoV, HCoV-229E, SARS or MERS), although the development of vaccines against SARS-CoV-2 is rapidly progressing. The objective of vaccine development against SARS-CoV-2 remains the generation of neutralizing antibody against the viral S (Spike) protein (Speiser and Bachmann 2020). However, without a clear understanding of the immune response to SARS-CoV-2, these strategies risk increasing disease severity through a process called antibody-dependent enhancement and this is why phase 3 trials involving a very large number of participants are needed (Speiser and Bachmann 2020).

There is a growing body of literature indicating that live vaccines such as BCG, measles, smallpox and oral polio induce “off target” protection against other infectious diseases and this process has been termed “trained immunity” (Netea et al. 2020a). Immunological studies indicate that BCG protection in human challenges with yellow fever or malaria is associated with inflammatory monocytes (Arts et al. 2018; Walk et al. 2019) and that monocytes/macrophages from BCG-vaccinated individuals have a unique protective epigenetic imprinting (Kleinnijenhuis et al. 2012). In the context of live vaccination, there are three known factors that can impact the epigenetic programming of an immune cell: (1) direct infection; (2) pathogen-associated molecular patterns from the microorganisms; and (3) endogenous cytokines released during the induction of the host response. We have proposed that the impact of these factors on the duration of trained immunity occurs centrally, at the level of hematopoietic stem cells in the bone marrow and peripherally at the tissue-specific level (Divangahi 2018; Kaufmann et al. 2018; Netea et al. 2020a, 2020b). These studies provide a logical explanation of why short-lived innate immune cells can acquire memory and how trained immunity induced by a live vaccine like BCG can provide cross-protection against other infectious agents. Another, but less likely, protective mechanism could be through adaptive immune pathways resulting from a chemical homology between the SARS-CoV-2 E (Envelope) protein and the LytR protein C present in *mycobacteria* (Nuovo et al. 2020).

## Human studies on “off target” protection of BCG vaccination

In 1932, Carl Näslund reported that children who received BCG at birth in Sweden had a mortality rate that was threefold

lower than among unvaccinated children and this observation was not explained by a reduction in TB deaths (Näslund 1932). In experimental challenge trials in humans, BCG vaccination of healthy adults resulted in protection or attenuation of infection with a live-attenuated yellow fever virus or a low-virulence plasmodium (Arts et al. 2018; Walk et al. 2019). Results of randomized trials and observational studies pertaining to all-cause mortality and morbidity associated with BCG administration are shown in Table 1. While the nature of the BCG strains might, to some extent, explain differences between studies (Miyazaki et al. 2018; Curtis 2019), the majority of results suggest that BCG provides significant protection against non-mycobacterial infections. The most interesting of these studies is the recent RCT carried out in Greece and showing a significant 79% protection against all-cause non-TB infection over a 12-month period (Giamarellos-Bourboulis et al. 2020). The comparison of cumulative incidence curves in the experimental and control groups suggests a 6-week delay to observe some protection which is still present at the end of the 12-month follow-up period.

There was another interesting observation in a small-size trial: the antibody response against the 2009 pandemic influenza A (H1N1) vaccine was significantly enhanced in BCG-vaccinated adults compared with unvaccinated participants (Leentjens et al. 2015). This suggests that the effectiveness of a poorly immunogenic viral vaccine could be improved by BCG priming, an easily testable hypothesis in ongoing or planned vaccine trials.

Of note, intravesical BCG is a recognized and effective treatment for non-muscle invasive bladder cancer, clearly an “off target” indication of this vaccine, and a product is licensed for this use in Canada (Redelman-Sidi et al. 2014).

## BCG vaccine and COVID-19 in human studies

Recently, a series of ecological studies on the association between indicators of COVID-19 frequency or severity and BCG vaccination policies or uptake rates in different countries have been published or posted as pre-publications (De Wals et al. 2020). Results of these ecological studies should be interpreted very cautiously as the quality of exposure and outcome data is very heterogeneous, many potential confounders are not controlled for and inferences about individual risk that are based on inferences about the group to which they belong could be heavily biased, what is called the “ecological fallacy” (Wakefield 2008; Riccò et al. 2020).

Since the beginning of the COVID-19 pandemic, randomized clinical trials have been launched to assess BCG protection, targeting health care workers mainly. A total of 19 phase 3 trials in 13 countries were registered in *ClinicalTrials.gov* as of September 30, 2020, and first results are expected in early 2021. One of these trials is conducted by the University

Health Network in Toronto (NCT 04439045 2020). A total of 3626 frontline workers are to be recruited and randomized to receive or not a new-generation and not yet authorized recombinant BCG vaccine (VPM1002) having a better safety and immunogenicity profile than classical BCG vaccines (Nieuwenhuizen et al. 2017).

## BCG vaccination in Canada

The first BCG clinic on Canadian soil was established in Montreal in 1925 and vaccination started in First Nations reserves in the 1930s (Grzybowski and Allen 1999). Free provincial BCG programs for all children were implemented in Quebec and Newfoundland, whereas other provinces reserved its use for special high-risk groups. The BCG-Frappier strain was first used, followed by the BCG-Connaught after 1948. In Quebec, around 50% of persons in each birth cohort between 1949 and 1976 were vaccinated (Rousseau et al. 2017). Currently, BCG vaccination for TB prevention is only recommended in exceptional circumstances in Canada, such as for infants in high-risk communities, for persons at high risk of repeated exposure, for certain long-term travelers to high prevalence countries, and for infants born to mothers with infectious TB disease (PHAC 2020). At present, the vast majority of Canadians are not immunized against tuberculosis, with the exception of a proportion of adults in Quebec and Newfoundland and Labrador and residents in Nordic communities who were vaccinated thanks to provincial/territorial programs, as well as immigrants born in countries where BCG is routinely given to children.

In Nunavik, the most Northern region of Quebec with an Inuit population mainly, BCG vaccination at birth was discontinued in 2004 but TB clusters emerged and the vaccination of newborns was reintroduced in 6 of 14 villages in 2012–2018 with a catch-up for children under 2 years of age (Comité sur l’immunisation du Québec 2016). In this population with a very high rate of respiratory infections (De Wals 2020), the comparison of respiratory disease rates among BCG-vaccinated and BCG-unvaccinated cohorts of children would be an investigation of high scientific value.

## Perspectives

The use of BCG vaccine as an interim measure to mitigate COVID-19 in Canada faces several challenges, including:

- (i) the absence of high-quality evidence that BCG vaccine provides protection against COVID-19,
- (ii) uncertain vaccine supply since BCG is no longer produced domestically,
- (iii) identifying target groups, and
- (iv) promoting an “off-license” indication.

**Table 1** Results of studies on all-cause mortality and morbidity associated with BCG vaccination

Country	Design	Main results	Reference
USA and UK	Meta-analysis of 6 randomized trials in 1940–1959.	Mortality rate ratio for BCG versus control for diseases other than tuberculosis = 0.75 (95% CI: 0.59–0.94)	Shann (2013)
Low-income countries	Meta-analysis of 5 clinical trials.	Receipt of BCG vaccine was associated with a reduction in all-cause mortality: average relative risk = 0.70 (95% CI: 0.49–1.01).	Higgins et al. (2016)
Low-income countries	Meta-analysis of 9 observational studies.	Receipt of BCG vaccine was associated with a reduction in all-cause mortality: average relative risk = 0.47 (95% CI: 0.32–0.69).	Higgins et al. (2016)
Denmark	Cohort study of 5316 children born in 1965–1976.	Compared with individuals who had not received BCG, those who had received BCG had an adjusted hazard ratio of 0.58 (95% CI: 0.39–0.85).	Rieckmann et al. (2017)
Spain	Comparison of hospitalization rates in different regions in 1992–2011.	Hospitalization rates due to respiratory infection not attributable to tuberculosis in BCG-vaccinated children was lower compared to non-BCG-vaccinated children for all age groups 0–14 years: total preventive fraction = 41.4% (95% CI: 40.3–42.5; $p < 0.001$ ).	De Castro et al. (2015)
Kenya	Case-control study in hospitalized patients 15–54 years of age.	Presence of a BCG scar was associated with protection (OR 0.51; 95% CI: 0.32–0.82) against community-acquired pneumonia.	Muthumbi et al. (2017)
Guinea-Bissau	Prospective study of children <5 years in 2009–2011.	Presence of a BCG scar was associated with reduced risk of mortality for respiratory infections: relative risk = 0.20 (95% CI: 0.07–0.55).	Storgaard et al. (2015)
Uganda	Prospective study of 819 pregnancies in 2006–2014.	BCG vaccination was associated with a lower rate of death among children between 1 and 5 years of age: adjusted hazard ratio 0.26 (95% CI: 0.14–0.48).	Nankabirwa et al. (2015)
Denmark	Randomized trial in 3 hospitals.	4184 pregnant women were randomized and their 4262 children allocated to BCG or no intervention and there was no difference in risk of hospitalization for infection up to 15 months of age: relative risk = 1.05; 95% CI: 0.93–1.18).	Stensballe et al. (2017)
Greenland	Cohort study among 19,363 children (66% BCG vaccinated) followed up to 3 years of age.	Relative risk in BCG-vaccinated as compared with BCG-unvaccinated children = 1.07 (95% CI: 0.96–1.20) for infectious diseases overall, and specifically 1.10 (95% CI: 0.98–1.24) for respiratory tract infections.	Haahr et al. (2016)
India	Randomized clinical trial in low-birth weight infants.	BCG administration had no effect on neonatal mortality: 15.6% of 1537 in the BCG group and 16.1% of 1535 in the control group; adjusted hazard ratio = 0.95 (95% CI: 0.80–1.13).	Jayaraman et al. (2019)
Greece	Phase 3 double-blind randomized clinical trial: 198 persons 65 years of age or more discharged after hospitalization for medical reason and vaccinated with BCG or saline placebo.	Interim analysis after 12 months: BCG vaccination significantly increased median time to first non-TB infection, 16 weeks in BCG group compared to 11 weeks in placebo group; incidence of new infections = 42.3% (95% CI: 31.9–53.4) after placebo vaccination versus 25.0% (95% CI: 16.4–36.2) after BCG vaccination; most of the protection was against respiratory tract infections of probable viral origin (hazard ratio 0.21, $p = 0.013$ ).	Giamarellos-Bourboulis et al. (2020)

Traditionally, recommendations for vaccine use in Canada are based on best scientific evidence ideally derived from randomized clinical trials (Ismail et al. 2010). The implementation of immunization programs is a provincial/territorial responsibility (with a few exceptions) and each jurisdiction is free to decide which vaccine to use, to buy them, to define target groups and vaccination schedules (De Wals 2011). Although many trials are underway on the efficacy of BCG to prevent/mitigate COVID-19, the decreasing circulation of SARS-CoV-2 in some communities and the effectiveness of personal protection to reduce exposure, especially among health care workers (HCWs), might delay the completion of

these trials and also reduce their power. Evidence derived from observational studies may be helpful in this context.

A case-control study is underway in Quebec to determine whether BCG administered during infancy/childhood decreases the risk/severity of SARS-CoV-2 infection in adulthood, based on COVID-19 cases diagnosed in two regions (Montreal and Eastern Townships) and patients hospitalized for other conditions are selected as controls, whereas provincial BCG registry data are used to assess BCG exposure (Alex Carignan, written communication). Quebec is one of the few places in the world where such study could be performed.



Currently, 22 pharmaceutical companies are producing BCG vaccines and production facilities are mostly situated in low-income countries (Cernuschi et al. 2018). The overall global supply capacity is around 500 million doses per year and annual purchase is around 350 million doses. Extending the indication of BCG for the control of the COVID-19 pandemic would be an interesting avenue for low- and middle-income countries unable to rapidly acquire specific SARS-CoV-2 vaccines in a context of advance purchase by high-income countries, including Canada.

Production of the BCG-Connaught on Canadian soil officially ended in 2016. Thereafter, the BCG-Japan vaccine based on the Tokyo-172 strain was distributed through the Health Canada Special Access Program as this product was never submitted for authorization and there is no hope that another product will be submitted, even under a fast-track free process. Decisions to increase BCG supply and stockpiling for COVID-19 mitigation would be under the control of provincial and territorial public health authorities unless a federal strategy is proposed.

Although frontline health care workers exposed both to COVID-19 patients and community transmission is a group that could eventually benefit from BCG vaccination, the acceptability of an “off target” indication may be problematic. The size of this group is another issue as there are approximately 1.4 million HCWs in Canada (Canadian Institute for Health Information 2020). Isolated First Nations and Inuit communities living in Nordic regions are another group of much smaller size to consider. For example, the Inuit population in Canada totalled approximately 65,000 people as of the 2016 census (StatCan 2020). Up to now, Nordic communities have been relatively spared in the pandemic thanks to the implementation of strict protective measures. The introduction of the SARS-CoV-2 virus in these vulnerable communities could have devastating effects. BCG is already used in many of these communities and acceptability is high, BCG vaccination or revaccination of adults is safe when contraindications are respected (SAGE Working Group on BCG Vaccines and WHO Secretariat 2017), BCG could provide some additional protection against TB (Redelman-Sidi et al. 2014), extended protection against all viral infections (Giamarellos-Bourboulis et al. 2020) and an enhancement of the immune response to a SARS-CoV-2 vaccine with limited potency (Leentjens et al. 2015).

To conclude, BCG vaccination as an interim measure to mitigate the burden of COVID-19 in Canada should be placed on the agenda of scientific advisory committees and federal/provincial/territorial public health authorities.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

- Aaby, P., Stabell Benn, C., Flanagan, K.L., Klein SL, Kollmann TB, Lynn DL, et al. (2020). The non-specific and sex-differential effects of vaccines. *Nature Rev Immunol*. Available at: <https://www.nature.com/articles/s41577-020-0338-x.pdf>. Accessed 30 Sept 2020.
- Arts, R. J. W., Moorlag, S. J. C. F. M., Novakovic, B., Wang, S. Y., Oosting, M., Kumar, V., et al. (2018). BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. *Cell Host & Microbe*, 23, 89–100.e5.
- Canadian Institute for Health Information. (2020). Health workforce 2018. Available at : <https://www.cihi.ca/en/health-workforce>. Accessed 30 Sept 2020.
- Cernuschi, T., Malvolti, S., Nickels, E., Friede, M., et al. (2018). Bacillus Calmette-Guérin (BCG) vaccine: A global assessment of demand and supply balance. *Vaccine*, 36, 498–506.
- CIQ - Comité sur l'immunisation du Québec. (2016). *Avis sur la pertinence de la réintroduction du vaccin bacille Calmette-Guérin (BCG) au Nunavik dans le contexte d'une recrudescence de la tuberculose*. Québec, Institut national de santé publique. Available at : [https://www.inspq.qc.ca/sites/default/files/publications/2179\\_pertinence\\_reintroduction\\_vaccin\\_tuberculose\\_nunavik.pdf](https://www.inspq.qc.ca/sites/default/files/publications/2179_pertinence_reintroduction_vaccin_tuberculose_nunavik.pdf). Accessed 30 Sept 2020.
- Curtis, N. (2019). BCG vaccination and all-cause neonatal mortality. *The Pediatric Infectious Disease Journal*, 38, 195–197.
- de Castro, M. J., Pardo-Seco, J., & Martínón-Torres, F. (2015). Nonspecific (heterologous) protection of neonatal BCG vaccination against hospitalization due to respiratory infection and sepsis. *Clinical Infectious Diseases*, 60, 1611–1619.
- De Wals, P., Rousseau, M. C., Menzie, D., & Divangahi, M. (2020). *Le vaccin BCG pourrait-il apporter une protection contre la COVID-19 ?* Québec: Institut national de santé publique du Québec. Available at: <https://www.inspq.qc.ca/publications/2993-vaccin-bcg-protection-contre-covid19>. Accessed 30 Sept 2020.
- De Wals, P. (2020). *Fardeau des infections respiratoires et des otites et impact du programme d'immunisation contre le pneumocoque dans la population du Nunavik*. Québec: Institut national de santé publique. Available at: [https://www.inspq.qc.ca/sites/default/files/publications/2677\\_fardeau\\_infections\\_respiratoire\\_population\\_nunavik.pdf](https://www.inspq.qc.ca/sites/default/files/publications/2677_fardeau_infections_respiratoire_population_nunavik.pdf). Accessed 30 Sept 2020.
- De Wals, P. (2011). Optimizing the acceptability, effectiveness and costs of immunization programs: The Quebec experience. *Expert Review of Vaccines*, 10, 55–62.
- Divangahi, M. (2018). Are tolerance and training required to end TB? *Nature Reviews. Immunology*, 18, 661–663.
- Giamarellos-Bourboulis, E. J., Tsilika, M., Moorlag, S., Antonakos, N., Kotsaki, A., Domínguez-Andrés, J., et al. (2020). Inactivate: Randomized clinical trial of BCG vaccination against infection in the elderly. *Cell*, S0092-8674(20), 31139–31139. <https://doi.org/10.1016/j.cell.2020.08.051>.
- Grzybowski, S., & Allen, E. A. (1999). Tuberculosis: 2. History of the disease in Canada. *CMAJ*, 160, 1025–1028.
- Haahr, S., Michelsen, S. W., Andersson, M., Bjorn-Mortensen, K., Soborg, B., Wohlfahrt, J., et al. (2016). Non-specific effects of BCG vaccination on morbidity among children in Greenland: a population-based cohort study. *International Journal of Epidemiology*, 45, 2122–2130.
- Higgins, J. P., Soares-Weiser, K., López-López, J. A., Kakourou, A., Chaplin, K., Christensen, H., et al. (2016). Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ*, 355, i5170.
- Ismail, S. J., Langley, J. M., Harris, T. M., Warshawsky, B. F., Desai, S., & FarhangMehr, M. (2010). Canada's National Advisory Committee on Immunization (NACI): evidence-based decision-

- making on vaccines and immunization. *Vaccine*, 28(Suppl 1), A58–A63.
- Jayaraman, K., Adhisivam, B., Nallasivan, S., Krishnan, R. G., Kamalarathnam, C., Bharathi, M., et al. (2019). Two randomized trials of the effect of the Russian strain of Bacillus Calmette-Guérin alone or with oral polio vaccine on neonatal mortality in infants weighing <2000 g in India. *The Pediatric Infectious Disease Journal*, 38, 198–202.
- Kaufmann, E., Sanz, J., Dunn, J. L., Khan, N., Mendonça, L. E., Pacis, A., et al. (2018). BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis. *Cell*, 172, 176–190. e19.
- Khader, S. A., Divangahi, M., Hanekom, W., Hill, P. C., Maeurer, M., Makar, K. W., et al. (2019). Targeting innate immunity for tuberculosis vaccination. *The Journal of Clinical Investigation*, 129, 3482–3491.
- Kleinnijenhuis, J., Quintin, J., Preijers, F., Joosten, L. A., Iffrim, D. C., Saeed, S., et al. (2012). Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proceedings of the National Academy of Sciences of the United States of America*, 109, 17537–17542.
- Leentjens, J., Kox, M., Stokman, R., Gerretsen, J., Diavatopoulos, D. A., van Crevel, R., et al. (2015). BCG vaccination enhances the immunogenicity of subsequent influenza vaccination in healthy volunteers: A randomized, placebo-controlled pilot study. *The Journal of Infectious Diseases*, 212, 1930–1938.
- Miyazaki, J., Onozawa, M., Takaoka, E., & Yano, I. (2018). Bacillus Calmette-Guérin strain differences as the basis for immunotherapies against bladder cancer. *International Journal of Urology*, 25, 405–413.
- Muthumbi, E., Lowe, B. S., Muyodi, C., Getambu, E., Gleeson, F., & Scott, J. A. G. (2017). Risk factors for community-acquired pneumonia among adults in Kenya: A case-control study. *Pneumonia*, 9, 17.
- Nankabirwa, V., Tumwine, J. K., Mugaba, P. M., Tylleskär, T., Sommerfelt, H., & PROMISE-EBF Study Group. (2015). Child survival and BCG vaccination: A community based prospective cohort study in Uganda. *BMC Public Health*, 15, 175.
- Näslund, C. (1932). *Resultats des expériences de vaccination par le BCG poursuivies dans le Norrbotten (Suède) (Septembre 1927–Décembre 1931)*. Vaccination Préventive de Tuberculose. Paris: Institut Pasteur, Rapports et Documents.
- NCT 04439045. (2020). Efficacy and safety of VPM1002 in reducing SARS-CoV-2 (COVID-19) infection rate and severity (COBRA). Washington, DC: ClinicalTrials.gov, US National Library of Medicine. Available at: <https://clinicaltrials.gov/ct2/show/NCT04439045>. Accessed 30 Sept 2020.
- Netea, M. G., Domínguez-Andrés, J., Barreiro, L. B., Chavakis, T., Divangahi, M., Fuchs, E., et al. (2020a). Defining trained immunity and its role in health and disease. *Nature Reviews Immunology*, 4, 1–14. <https://doi.org/10.1038/s41577-020-0285-6> Online ahead of print.
- Netea, M. G., Giamarellos-Bourboulis, E. J., Domínguez-Andrés, J., Curtis, N., van Crevel, R., van de Veerdonk, F. L., et al. (2020b). Trained immunity: a tool for reducing susceptibility to and the severity of SARS-CoV-2 infection. *Cell*, 181, 969–977.
- Nieuwenhuizen, N. E., Kulkarni, P. S., Shaligram, U., Cotton, M. F., Rentsch, C. A., Eisele, B., et al. (2017). The recombinant Bacille Calmette-Guérin vaccine VPM1002: Ready for clinical efficacy testing. *Frontiers in Immunology*, 8, 1147.
- Nuovo, G., Tili, E., Suster, D., Matys, E., Hupp, L., & Magro, C. (2020). Strong homology between SARS-CoV-2 envelope protein and a Mycobacterium sp. antigen allows rapid diagnosis of mycobacterial infections and may provide specific anti-SARS-CoV-2 immunity via the BCG vaccine. *Annals of Diagnostic Pathology*, 48, 151600. <https://doi.org/10.1016/j.anndiagpath.2020.151600>.
- Public Health Agency of Canada. (2020). *Canadian Immunization Guide*. Ottawa: Government of Canada. Available at: <https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html>. Accessed 30 Sept 2020.
- Redelman-Sidi, G., Glickman, M. S., & Bochner, B. H. (2014). The mechanism of action of BCG therapy for bladder cancer—a current perspective. *Nature Reviews Urology*, 11, 153–162.
- Riccò, M., Gualerzi, G., Ranzieri, S., & Bragazzi, N. L. (2020). Stop playing with data: There is no sound evidence that Bacille Calmette-Guérin may avoid SARS-CoV-2 infection (for now). *Acta Biomed*, 91, 207–213.
- Rieckmann, A., Villumsen, M., Sørup, S., Haugaard, L. K., Ravn, H., Roth, A., et al. (2017). Vaccinations against smallpox and tuberculosis are associated with better long-term survival: A Danish case-cohort study 1971–2010. *International Journal of Epidemiology*, 46, 695–705.
- Rousseau, M. C., Conus, F., Kâ, K., El-Zein, M., Parent, M. É., & Menzies, D. (2017). Bacillus Calmette-Guérin (BCG) vaccination patterns in the province of Québec, Canada, 1956–1974. *Vaccine*, 35, 4777–4784.
- Rydzynski Moderbacher, C., Ramirez, S. I., Dan, J. M., Grifoni, A., Hastie, K. M., Weiskopf, D., et al. (2020). Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. *Cell*, S0092-8674(20), 31235–31236. <https://doi.org/10.1016/j.cell.2020.09.038>.
- SAGE Working Group on BCG Vaccines and WHO Secretariat. (2017). *Report on BCG vaccine use for protection against mycobacterial infections including tuberculosis, leprosy, and other nontuberculosis mycobacteria (NTM) infections*. Geneva: WHO. Available at: [https://www.who.int/immunization/sage/meetings/2017/october/1\\_BCG\\_report\\_revised\\_version\\_online.pdf?ua=1a](https://www.who.int/immunization/sage/meetings/2017/october/1_BCG_report_revised_version_online.pdf?ua=1a). Accessed 30 Sept 2020.
- Shann, F. (2013). Nonspecific effects of vaccines and the reduction of mortality in children. *Clinical Therapeutics*, 35, 109–114.
- Speiser, D. E., & Bachmann, M. F. (2020). COVID-19: Mechanisms of vaccination and immunity. *Vaccines (Basel)*, 8, E404. <https://doi.org/10.3390/vaccines8030404>.
- StatCan. (2020). *Statistics on indigenous people*. Ottawa: Government of Canada. Available at: [https://www.statcan.gc.ca/eng/subjects-start/indigenous\\_peoples](https://www.statcan.gc.ca/eng/subjects-start/indigenous_peoples). Accessed 30 Sept 2020.
- Stensballe, L. G., Sørup, S., Aaby, P., Benn, C. S., Greisen, G., Jeppesen, D. L., et al. (2017). BCG vaccination at birth and early childhood hospitalisation: a randomised clinical multicentre trial. *Archives of Disease in Childhood*, 102, 224–231.
- Storgaard, L., Rodrigues, A., Martins, C., Nielsen, B. U., Ravn, H., Benn, C. S., et al. (2015). Development of BCG scar and subsequent morbidity and mortality in rural Guinea-Bissau. *Clinical Infectious Diseases*, 61, 950–959.
- Wakefield, J. (2008). Ecological studies revisited. *Annual Review of Public Health*, 29, 75–90. <https://doi.org/10.1146/annurev.publhealth.29.020907.090821>.
- Walk, J., de Bree, L. C. J., Graumans, W., Stoter, R., van Gemert, G. J., van de Vegte-Bolmer, M., et al. (2019). Outcomes of controlled human malaria infection after BCG vaccination. *Nature Communications*, 10, 874.
- Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J., & Prescott, H. C. (2020). Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. *JAMA*, 324, 782–793.
- Yuki, K., Fujiogi, M., & Koutsogiannaki, S. (2020). COVID-19 pathophysiology: A review. *Clinical Immunology*, 215, 108427. <https://doi.org/10.1016/j.clim.2020.108427>.

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