UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Morning Brief :
Scientific Review

28 April 2020

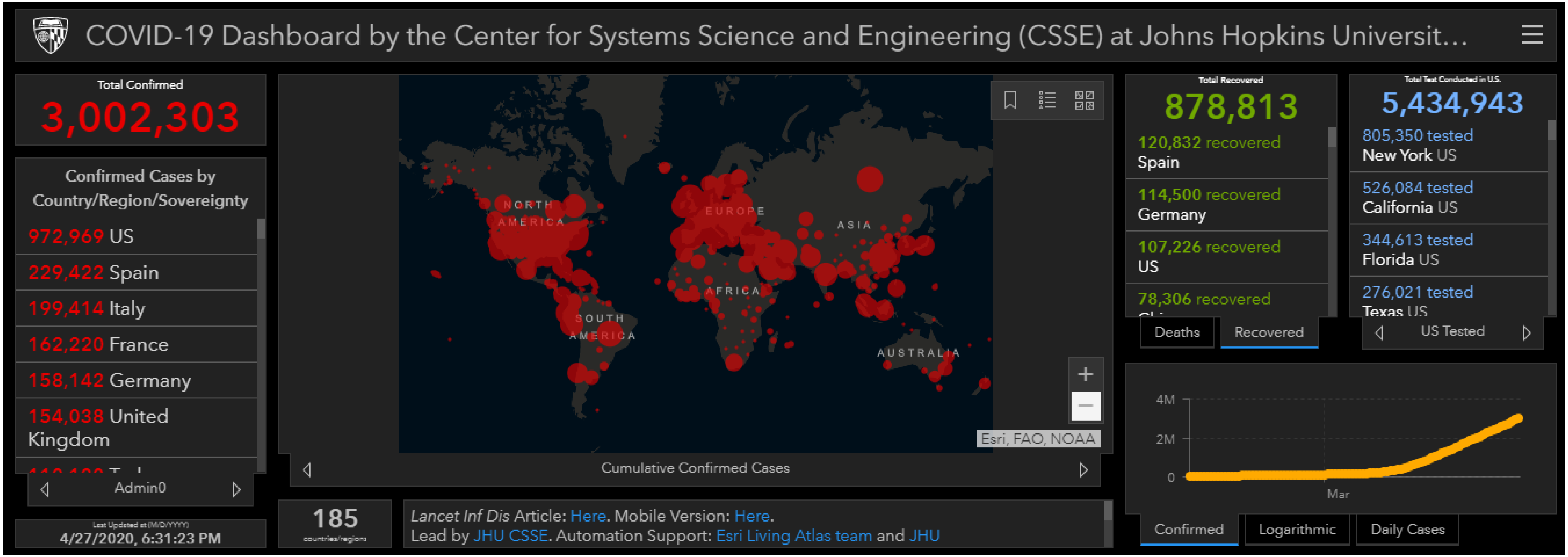
The purpose of the Morning Brief is to **summarise** and present key information, research articles and other relevant publications pertaining to critical care and COVID-19. We aim to prioritise information, articles and publications released in the preceding 24-48 hours.

Stellenbosch University Research Response Team

STELLENBOSCH UNIVERSITY
PULMONOLOGY

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Global Update



Accessed at 19:38 on 27 April 2020
Source: https://coronavirus.jhu.edu/map.html

South African Update

COVID-19 Statistics in South Africa

178470	4793	1473	90
Tests Conducted	Positive Cases Identified	Recoveries	Deaths

Accessed at 21:41 on 27 April 2020
Source: https://sacoronavirus.co.za/

BCG for COVID-19

<u>CONTENTS</u>

- BCG CORONA Protocol
- Immune system and non-specific effects on innate immunity
- BCG for trained immunity
- Retrospective epidemiological studies of BCG effect on COVID-19

TASK™

APPLIED SCIENCE

BCG CORONA Protocol

Title: Reducing morbidity and mortality in health care workers exposed to SARS-CoV-2 by enhancing non-specific immune responses through Bacillus Calmette-Guérin vaccination, a double-blinded, randomized controlled trial.

Hypothesis

- BCG vaccination reduces the morbidity and mortality of healthcare workers during the SARS-CoV-2 outbreak in South Africa.

Primary Objective:

- To compare the incidence of HCWs hospitalized due to SARS-CoV-2 infection per arm.

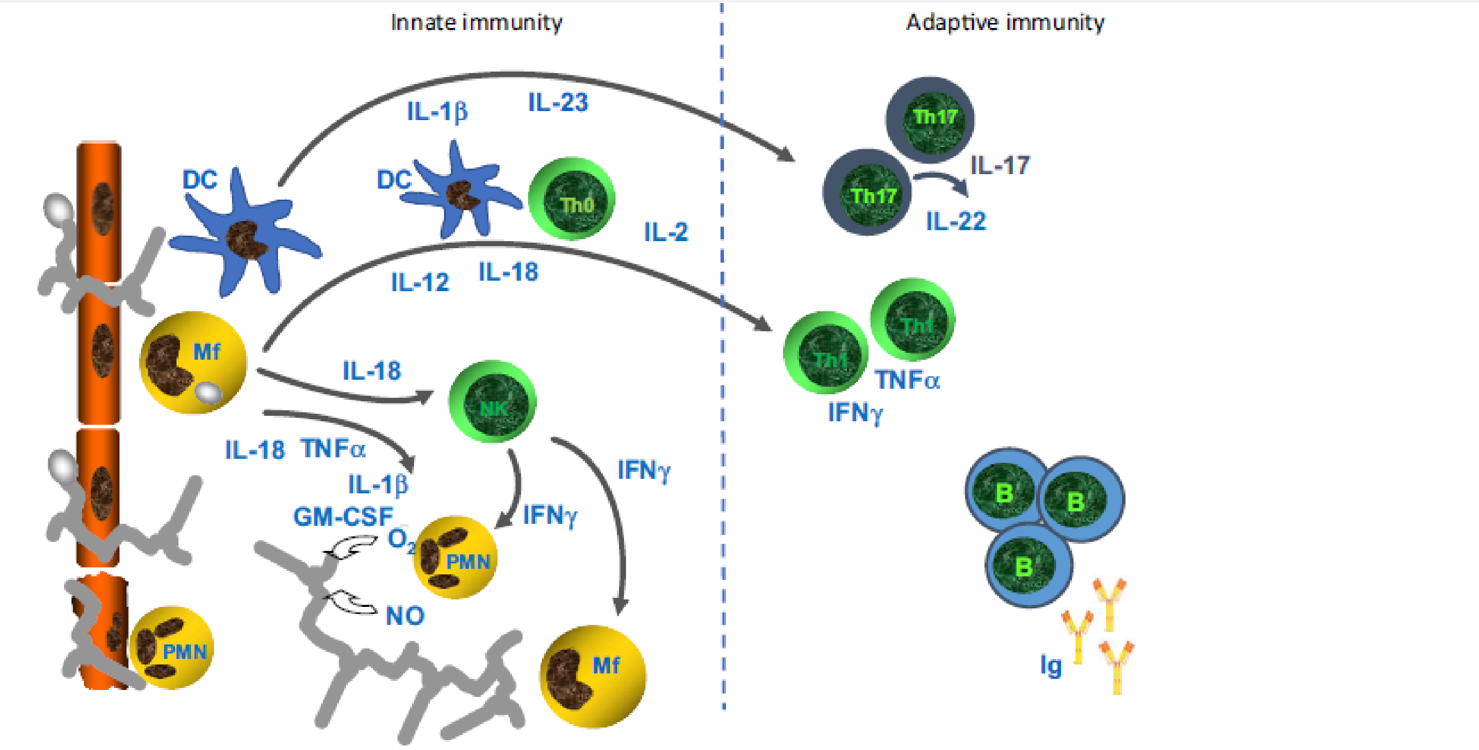
Immune System

INNATE IMMUNITY

Reacts rapidly

Non-specific

Previously thought to be static



ADAPTIVE IMMUNITY

Slower

Specific adaptive manner

Long-lived immunological memory

Non-specific trained immunity from vaccines

- Smallpox vaccine
  - In low-income countries a *Vaccinia* scar has been associated with >40% reductions in overall mortality among adults
- Measles vaccine
  - Infants who received measles vaccine at 4.5 months and again at 9 months had a <u>30% (95% CI = 6–48%) reduction in all-cause mortality</u> from 4.5–36.0 months of age compared with standard dosing at 9 months
- BCG vaccine
  - LBW neonates show that BCG at birth almost halves neonatal mortality, the combined estimate being a <u>48% (95% CI = 18–67%) reduction in mortality</u>.

The perceived lack of biological plausibility has been a major obstacle in recognizing and further investigating these effects.

Benn CS, Netea MG, Selin LK, Aaby P. A Small Jab - A Big Effect: Nonspecific Immunomodulation By Vaccines. Vol. 34, Trends in Immunology. 2013. p. 431–9.

Background – BCG

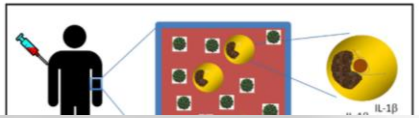
- Bacille Calmette Guerin – live attenuated vaccine
- Vaccine developed in 1920's
- Given at birth
  - Prevents severe forms of TB in children (TB meningitis)
  - Effect against TB wears off over 15 years
- Various revaccination strategies in countries globally discontinued
- WHO:
  - BCG revaccination is safe in TB unexposed and infected, and HIV uninfected people.
  - No evidence of any additional benefit of repeat BCG vaccination against TB

World Health Organization (WHO). BCG vaccines: WHO position paper – February 2018. Wkly Epidemiol Rec. 2018;(8):73–96.

Cell Host & Microbe

BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity

Graphical Abstract



Authors

Rob J.W. Arts, Simone J.C.F.M. Moorlag, Boris Novakovic, ..., Hendrik G. Stunnenberg, Reinout van Crevel, Mihai G. Netea

Long-Lasting Effects of BCG Vaccination on Both Heterologous Th1/Th17 Responses and Innate Trained Immunity

Johanneke Kleinnijenhuis[a, b] Jessica Quintin[a, b] Frank Preijers[c] Christine Stabell Benn[e] Leo A.B. Joosten[a, b] Cor Jacobs[a, b] Joke van Loenhout[d] Ramnik J. Xavier[f, g] Peter Aaby[e] Jos W.M. van der Meer[a, b] Reinout van Crevel[a, b] Mihai G. Netea[a, b]

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

ELSEVIER

CMI CLINICAL MICROBIOLOGY AND INFECTION

ESCMID

Narrative review

Trained innate immunity and resistance to *Mycobacterium tuberculosis* infection

Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes

Johanneke Kleinnijenhuis[a,b,1], Jessica Quintin[a,b,1], Frank Preijers[c], Leo A. B. Joosten[a,b], Daniela C. Ifrim[a,b], Sadia Saeed[d], Cor Jacobs[a,b], Joke van Loenhout[e], Dirk de Jong[f], Hendrik G. Stunnenberg[d], Ramnik J. Xavier[g,h], Jos W. M. van der Meer[a,b], Reinout van Crevel[a,b], and Mihai G. Netea[a,b,2]

BCG-vaccination enhances immunogenicity of subsequent influenza vaccination in healthy volunteers: a randomized placebo-controlled pilot study

Jenneke Leentjens[1,2], Matthijs Kox[2], Robin Stokman[2], Jelle Gerretsen[2], Dimitri A. Diavatopoulos[3], Reinout van Crevel[1], Guus F. Rimmelzwaan[4], Peter Pickkers[2], and Mihai G. Netea[1,*]

Cell Host & Microbe

Commentary

Trained Immunity: An Ancient Way of Remembering

Mihai G. Netea[1,*] and Jos W.M. van der Meer[1,*]

[1]Department of Internal Medicine, Radboud University Medical Centre, PO box 9101, 6500HB Nijmegen, the Netherlands

*Correspondence: mihai.netea@radboudumc.nl (M.G.N.), jos.vandermeer@radboudumc.nl (J.W.M.v.d.M.)

http://dx.doi.org/10.1016/j.chom.2017.02.003

The innate arm of the immune system has generally been regarded as primitive and non-specific and, in contrast to adaptive immunity, not to possess memory. Here we review the growing body of evidence that innate immunity has an important capacity to adapt, a de facto innate immune memory (also termed trained immunity), and this provides broad protection against infections.

BCG Re-vaccination of Adults with Latent *Mycobacterium tuberculosis* Infection Induces Long-lived BCG-Reactive Natural Killer Cell Responses[1]

Sara Suliman*, Hennie Geldenhuys*, John L. Johnson†, Jane E. Hughes*, Erica Smit*, Melissa Murphy*, Asma Toefy*, Lesedi Lerumo*, Christiaan Hopley*, Bernadette Pienaar*,§, Phalkun Chheng†, Elisa Nemes*, Daniel F. Hoft‡, Willem A. Hanekom*, W. Henry Boom†, Mark Hatherill#*, and Thomas J. Scriba#*,‖

*South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Disease and Molecular Medicine and Division of Immunology, Department of Pathology, University of Cape Town, Cape Town, South Africa

H4:IC31 Vaccine or BCG Revaccination for Tuberculosis

TO THE EDITOR: Nemes and colleagues (July 12 issue)[1] examined the effects of bacille Calmette–Guérin (BCG) revaccination on reducing the rate of sustained QuantiFERON-TB Gold In-tube assay (QFT) conversion among adolescents in a high-risk setting. One aspect that received relatively little attention in the trial regards the immuno-logic mechanisms responsible for these effects.

Charlotte de Bree, M.D.
Reinout van Crevel, M.D., Ph.D.
Mihai G. Netea, M.D., Ph.D.
Radboud University Medical Center
Nijmegen, the Netherlands
charlotte.debree@radboudumc.nl

No potential conflict of interest relevant to this letter was reported.

Published in final edited form as:
Science. 2016 April 22; 352(6284): aaf1098. doi:10.1126/science.aaf1098.

Trained immunity: a program of innate immune memory in health and disease

Mihai G. Netea[1,*], Leo A.B. Joosten[1], Eicke Latz[2,3,4], Kingston H.G. Mills[5], Gioacchino Natoli[6], Hendrik G. Stunnenberg[7], Luke A.J. O'Neill[5], and Ramnik J. Xavier[8,9]

[1]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands [2]Institute of Innate Immunity, Bonn University, Bonn, Germany [3]Department of Infectious Diseases and Immunology, UMass Medical School, Worcester, MA, USA [4]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany [5]School of Biochemistry and Immunology, Trinity College, Dublin, Ireland [6]Department of Experimental Oncology, European Institute of Oncology, Milan, Italy [7]Radboud University,

BCG and COVID-19

BCG trains your immune system

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

E. Nemes, H. Geldenhuys, V. Rozot, K.T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W.A. Hanekom, S.G. Self, L.-G. Bekker, R. Ryall,* S. Gurunathan, C.A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R.D. Ellis, B. Landry, D.A. Hokey, R. Hopkins, A.M. Ginsberg, T.J. Scriba, and M. Hatherill, for the C-040-404 Study Team†

ABSTRACT

BACKGROUND

Recent *Mycobacterium tuberculosis* infection confers a predisposition to the development of tuberculosis disease, the leading killer among global infectious diseases. H4:IC31, a candidate subunit vaccine, has shown protection against tuberculosis disease in pre-

BCG trains the innate immune system

- Monocytes can be functionally reprogrammed, or “trained,” to exhibit an enhanced and lasting phenotype after vaccination with BCG
- Protective effects not only against tuberculosis, but also against other infections.
- NOD2-mediated epigenetic change at the level of histone methylation (H3K4me3) is the mechanism through which BCG enhances innate immune responses.
- Epigenetics implies an inherited structural change without a genetic change
- Increased production of INFy, TNF and IL-1b.

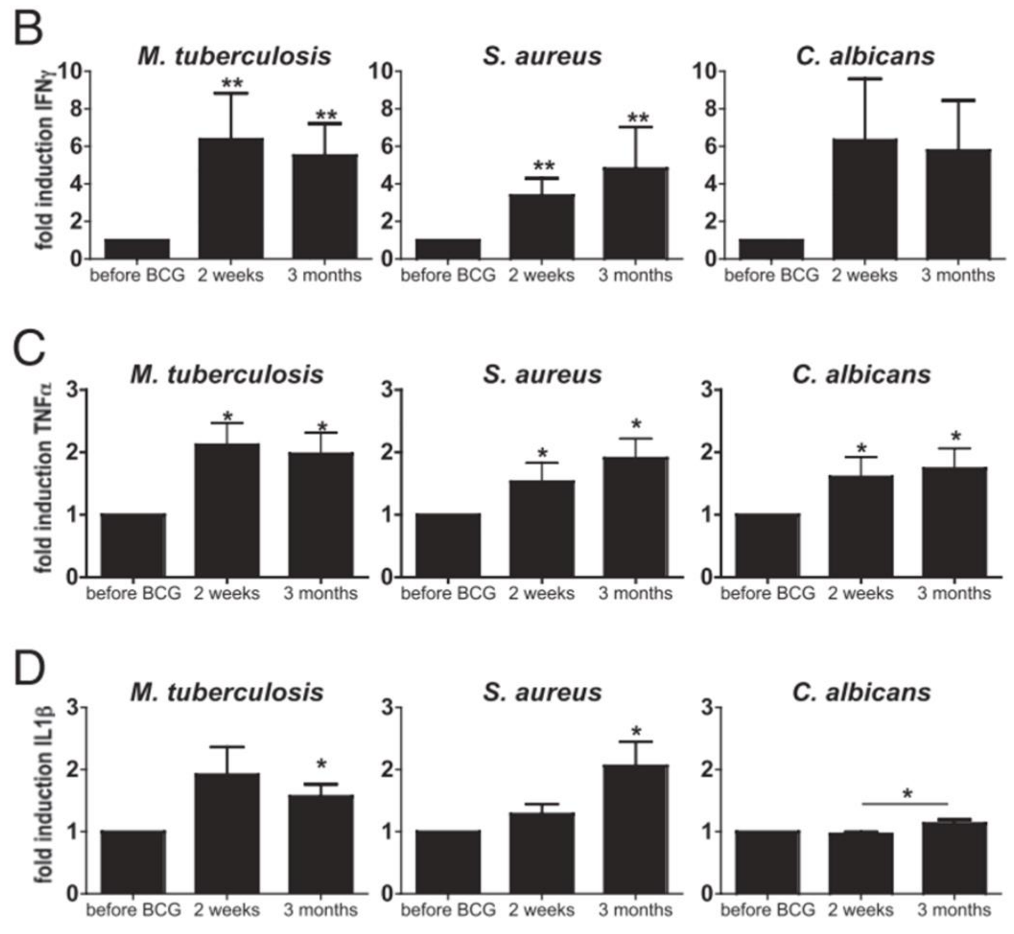


Fig. 1. BCG vaccination increased the nonspecific production of proinflammatory cytokines. (*A*) Diagram showing the course of the BCG vaccination trial. Blood was collected from 20 naïve (nonexposed) volunteers before and after (2 wk and 3 mo) vaccination with BCG. (*B–D*) PBMCs isolated from the 20 volunteers before and after (2 wk and 3 mo) vaccination were stimulated in vitro with sonicated *M. tuberculosis*, heat-killed *S. aureus*, and *C. albicans* blastoconidia. Proinflammatory cytokine production (INF-γ [*B*], TNF-α [*C*]), and IL-1β [*D*]) was assessed by ELISA in the supernatants. $^*P < 0.05$, $^{**}P < 0.01$.

Kleinnijenhuis J, Quintin J, Preijers F, Joosten LAB, Ifrim DC, Saeed S, et al. Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. Proc Natl Acad Sci U S A. 2012;109(43):17537–42.

Clinical studies - Aaby et al

- 1:1 Randomized trial of BCG vaccination at birth versus delayed vaccination in 2320 low-birth-weight children
- Neonatal mortality at 1 month was reduced by 45% (MRR=0.55) in the early vaccination group
- At 2, 6 and 12 months of age, the MRR for early BCG vs controls was 0.73, 0.78 and 0.83 respectively
- BCG had only a beneficial effect in the first month of life before controls received BCG
- Reduction in neonatal mortality was mainly due to fewer cases of neonatal sepsis, respiratory infection, and fever.

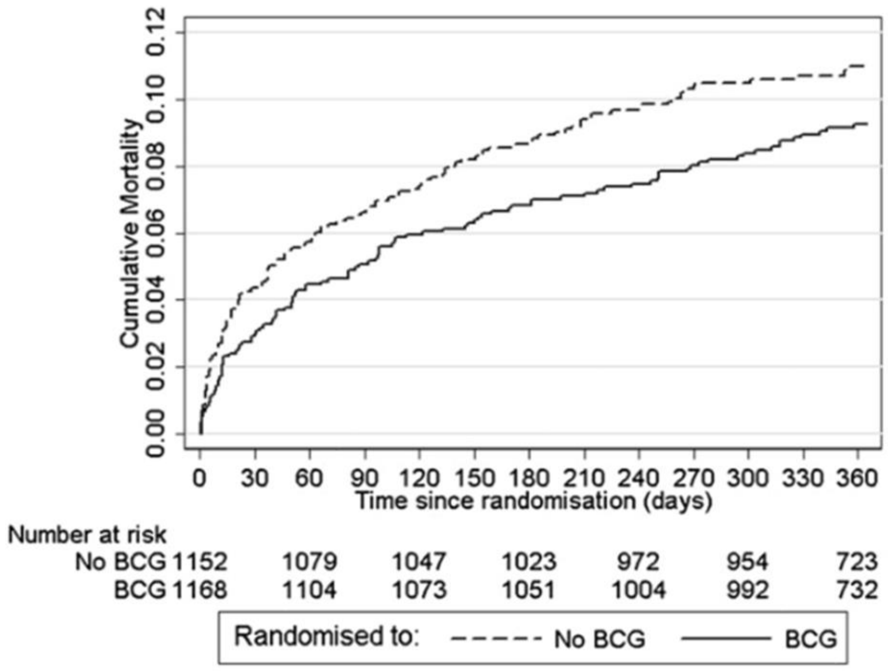
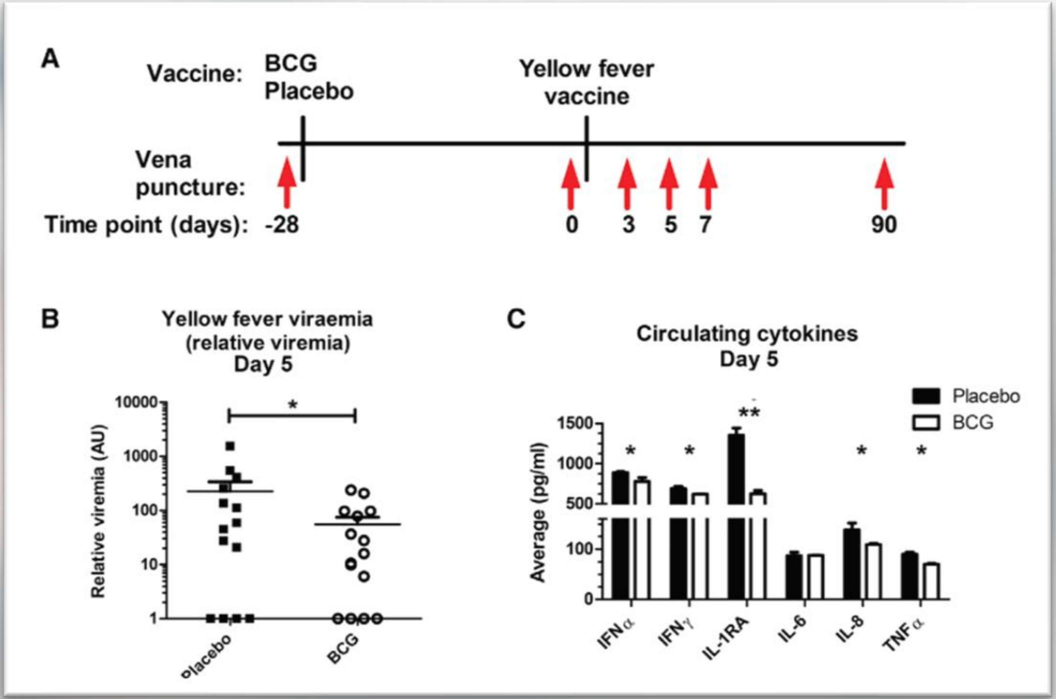


Figure 2. Cumulative mortality curves during the first year of life according to randomization group.

Aaby P, Roth A, Ravn H, Napirna BM, Rodrigues A, Lisse IM, et al. Randomized trial of BCG vaccination at birth to low-birth-weight children: Beneficial nonspecific effects in the neonatal period? J Infect Dis. 2011;204(2):245–52.

Clinical studies - Arts et al

- Randomized placebo-controlled study in healthy volunteers who randomly received BCG or placebo vaccination followed by yellow fever vaccine (live attenuated) at one month
- Significantly lower peak of viremia in BCG-vaccinated individuals
- Lower circulating inflammatory mediators
  - High cytokine production capacity from BCG vaccination leads to a rapid local antimicrobial response
  - Subsequent elimination of the pathogen, thereby preventing a systemic reaction and high levels of circulating cytokines



Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang SY, Oosting M, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host Microbe [Internet]. 2018;23(1):89-100.e5. Available from: https://doi.org/10.1016/j.chom.2017.12.010

Clinical studies - Wardhana et al

- Efficacy of 3 x monthly BCG vaccinations or placebo for the prevention of acute upper respiratory tract infection in the elderly
- 34 participants (17 per arm), 60-75 years old with 6 month follow up
- The prevalence of AURTI in the elderly
    - BCG vaccinations = 2/17 subjects
    - Placebo group = 10/17 subjects, 8 had repeated AURTI
    - $p<0.05$

Wardhana, Datau EA, Sultana A, Mandang V V., Jim E. The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper respiratory tract infection in the elderly. Acta Med Indones. 2011;43(3):185–90.

Clinical studies - Nemes et al

H4:IC31 Vaccine or BCG Revaccination for Tuberculosis

Bree C de, Crevel R van, Netea MG. H4:IC31 Vaccine or BCG Revaccination for Tuberculosis. N Engl J Med. 2018;379(20):1969.

- Trial was designed to
  - Test BCG revaccination vs a new vaccine (H4:IC31) vs placebo
  - Look at incidence of new and sustained TB infection by IGRA conversion (neg to pos)
  - 990 adolescents in a high-risk setting
- Incidental finding
  - BCG group had lower rate of upper respiratory tract infections
  - BCG vs H4:IC31 vs placebo group was 2.1%, 9.4% and 7.9% respectively.
  - (P<0.001 for both comparisons)

TO THE EDITOR: Nemes and colleagues (July 12 issue)[1] examined the effects of bacille Calmette–Guérin (BCG) revaccination on reducing the rate of sustained QuantiFERON-TB Gold In-tube assay (QFT) conversion among adolescents in a high-risk setting. One aspect that received relatively little attention in the trial regards the immunologic mechanisms responsible for these effects, which were assessed only by measurement of interferon-γ and interleukin-2 T-cell responses. Studies have shown a combination of improved long-term innate or trained immunity (through epigenetic reprogramming of myeloid cells) and adaptive responses after BCG vaccination, which leads to more effective control of mycobacterial and unrelated infections.[2-4] These mechanisms can also explain the decrease in unrelated respiratory tract infections after BCG revaccination that was observed by the authors. This decrease is consistent with the nonspecific beneficial effects after BCG vaccination that have been observed repeatedly in persons included in epidemiologic studies,[5] especially in infants, and warrants sustained attention in future investigations.

Nemes E, Geldenhuys H, Rozot V, Rutkowski KT, Ratangee F, Bilek N, et al. Prevention of M. Tuberculosis infection with H4:IC31 vaccine or BCG revaccination. N Engl J Med. 2018;379(2):138–49.

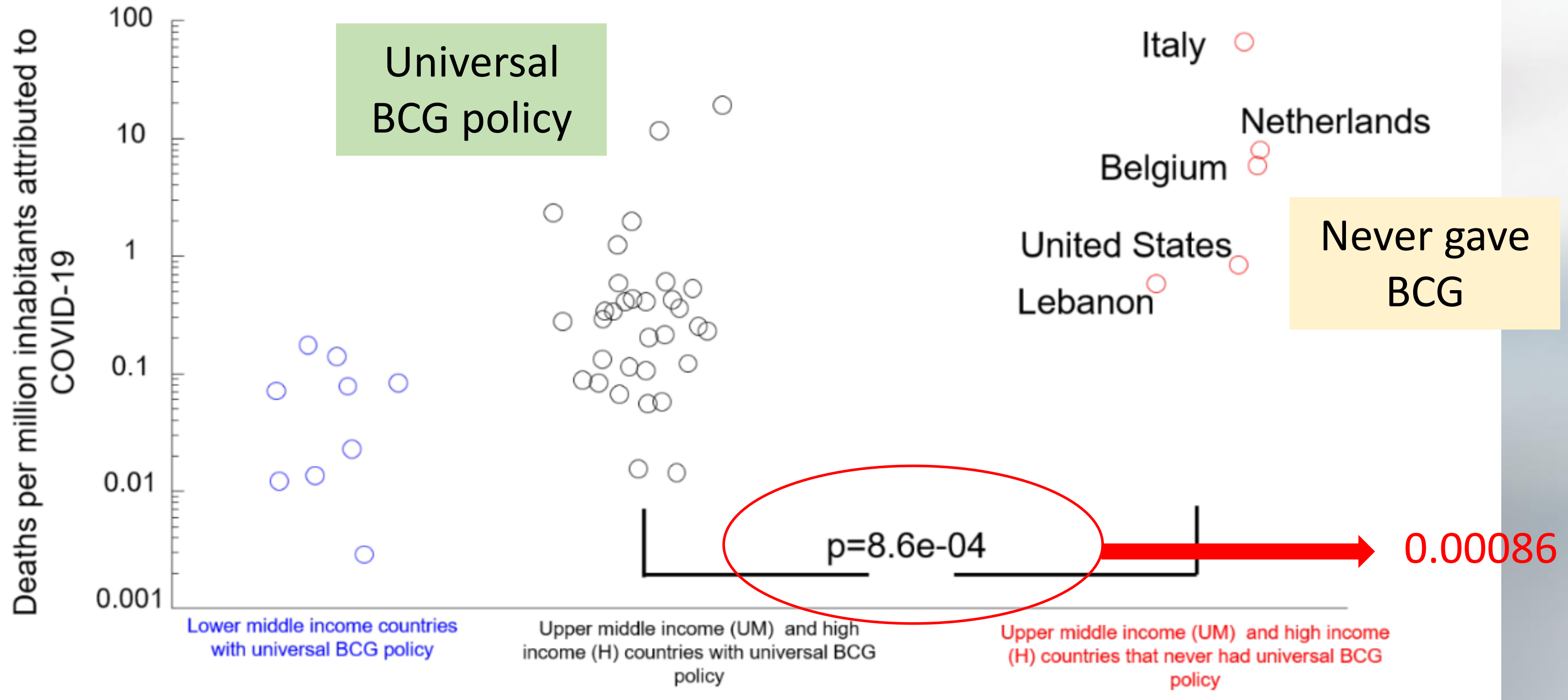


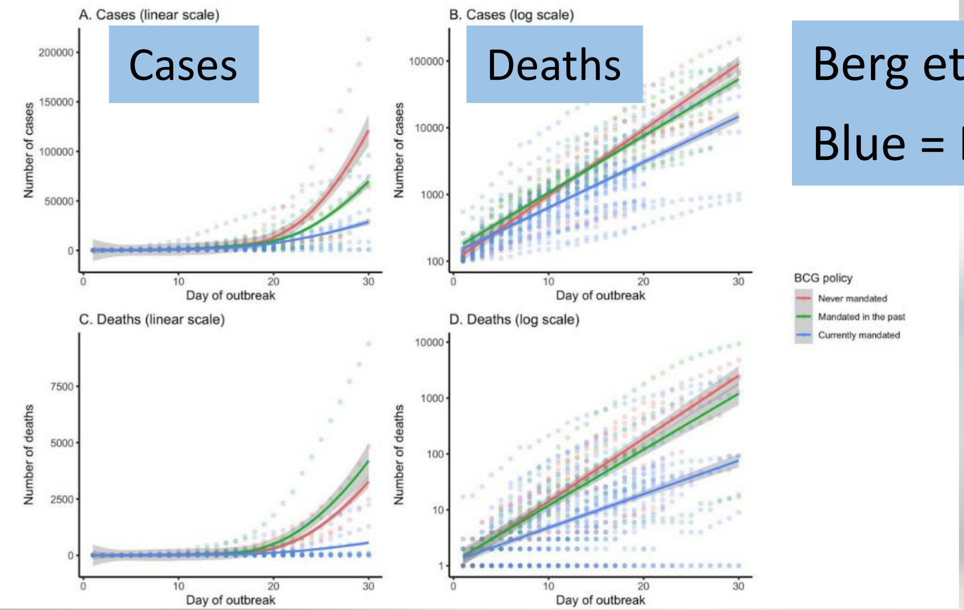
Figure 1: Higher death rates were presented in countries that never implemented a universal BCG vaccination policy.

BCG and COVID-19

BCG vaccination at birth may confer *some* level of protection against COVID-19

Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv. 2020;1–9.

Figure 1. Growth curves by country BCG policy for (A-B) cases and (C-D) deaths, presented on linear (A & C) and logarithmic (B & D) scales.



Cases

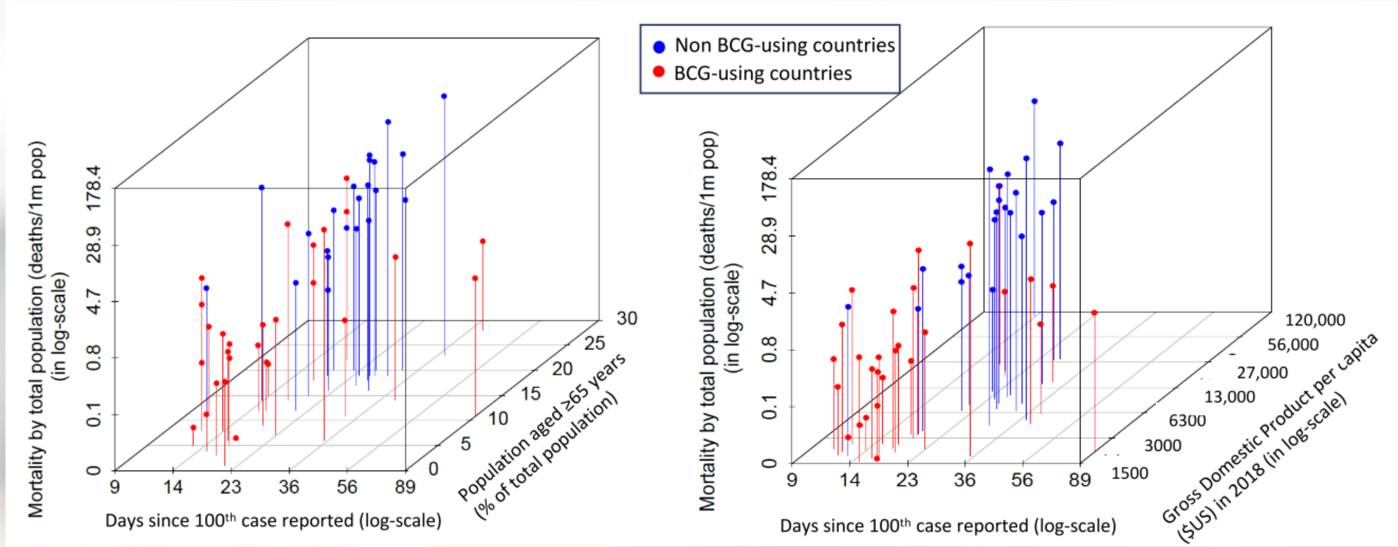
Deaths

Berg et al

Blue = BCG

Martha K. Berg, Yu Q, Salvador CE, Melani I, Kitayama S, Berg MK, et al. Mandated Bacillus Calmette-Guérin (BCG) vaccination predicts flattened curves for the spread of COVID-19. medRxiv. 2020;1–10.

Shet A, Ray D, Malavige N, Santosham M, Bar-Zeev N. Differential COVID-19-attributable mortality and BCG vaccine use in countries. medRxiv. 2020;2020.04.01.20049478.

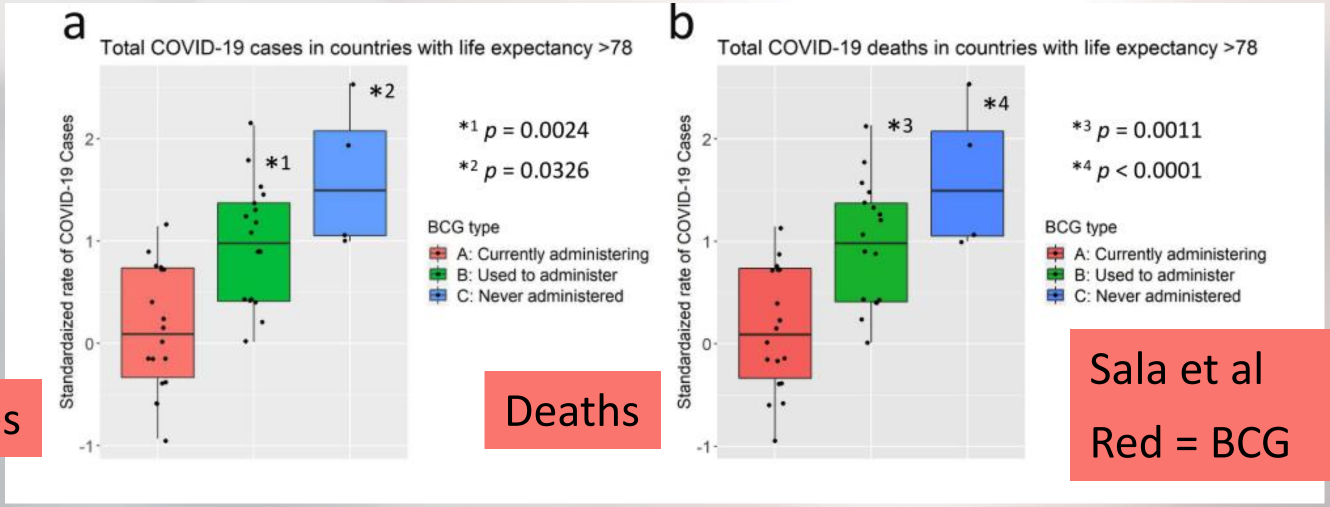


Deaths

Shet et al

Red = BCG

Height of line = deaths



Cases

Deaths

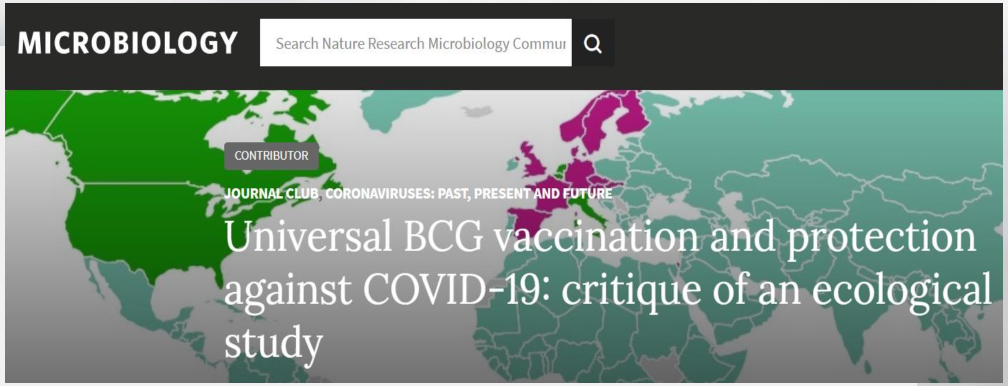
Sala et al

Red = BCG

BCG and COVID-19

Sala G, Miyakawa T. Association of BCG vaccination policy with prevalence and mortality of COVID-19. medRxiv. 2020;1–16.

Critique of Miller et al



- A critique of the study
  - Study Design:
    - Low quality evidence observed at the population level
    - Sweeping inferences about BCG's effectiveness
    - Ecological studies
      - Strictly hypothesis-generating queries
      - Should not be stretched beyond this purpose
  - Timing matters:
    - Findings may change epidemic progress.
    - Drawing premature conclusions from rapidly changing data in a pandemic is problematic.
  - Lack of testing:
    - Shortages of diagnostic tests, and a country's specific testing algorithm.
  - Correlation is not causation:
    - Under-funded health systems in low income countries have low COVID-19 testing capacity
    - Falsely low numbers of reported cases and deaths.
    - These countries are more likely to have universal BCG vaccination policies in place

Available at: https://naturemicrobiologycommunity.nature.com/users/36050-emily-maclean/posts/64892-universal-bcg-vaccination-and-protection-against-covid-19-critique-of-an-ecological-study

New preprint with contradictory results

The effect of BCG vaccination on COVID-19 examined by a statistical approach: no positive results from the Diamond Princess and cross-national differences previously reported by world-wide comparisons are flawed in several ways

Masakazu Asahara, Ph. D.[1]
[1]Division of Liberal Arts and Sciences, Aichi Gakuin University, Nisshin, Aichi 470-0195, Japan
Contact: kamono.mana@gmail.com

- Three objectives
  - Reviewing the infection and mortality ratio on Diamond Princess
    - no significant difference in infections in BCG vs. non-BCG nations
  - Comparing the number of mortalities among nations
    - After correcting for arrival time of COVID-19 in a country, previously reported effect of BCG vaccination on decreasing total mortality disappeared
  - Comparing the maximum daily increase rate of mortalities among nations
    - showed no significant difference among BCG vaccination policies
- Some results showed statistically significant differences - confounders
  - national infection-control policies,
  - social distancing,
  - behavioral changes of people,
  - possible previous local epidemics of closely related viruses,
  - inter-population differences in ACE2 or other genetic polymorphism.

Asahara M. The effect of BCG vaccination on COVID-19 examined by a statistical approach : no positive results from the Diamond Princess and cross-national differences previously reported by world-wide comparisons are flawed in several ways. medRxiv. 2020;1–29.

Summary

- BCG can train the innate immune system
  - Reacts more quickly to a pathogen
  - prevents a systemic inflammatory reaction
  - driven by the NOD-2 receptor mediated epigenetic changes
  - Duration of this trained immunity unknown
- Poor and contradictory evidence that BCG at birth is protective in the COVID-19 pandemic
- Limited supportive evidence for widespread use as an immunity booster in the COVID-19 pandemic
  - This warrants further research through well designed randomized trials