

BCG & COVID-19

This webinar, co-hosted by South African Immunology Society (SAIS) and Immunopaedia featured talks by Prof Christine Benn on “BCG for COVID-19 – hope or hype?” & Prof Gerhard Walz on “BCG trials for COVID-19 in SA – progress and promise.”

Studies have shown that in addition to BCG providing protection against Tuberculosis in children, it also have non-specific effects which are associated with a reduction in all-cause infant mortality* (Kristensen et al., 2020) and reduction in upper respiratory tract infections in revaccinated individuals (Nemes et al., 2019; Wardhana et al., 2020). These non-specific responses have been attributed to trained immunity# (Read more: [Have you heard of trained immunity?](#)) which are induced upon vaccination and contribute to a decrease in systemic inflammation.

Hope or hype?

Hypothesis 1: Weak data on BCG-at-birth and COVID, but some support from previous studies for long-term non-specific effects of BCG – jury still out – better studies needed.

Hypothesis 2: Strong evidence from previous epidemiological and immunological studies for recent BCG to protect against non-related infections – awaiting trials.

Important questions in relation to trials:

- First BCG or booster BCG?
- Non-COVID-19 infectious outcomes
- Effect modification by strain, sex, maternal BCG, etc.

Ethical aspect: Ensure BCG for babies

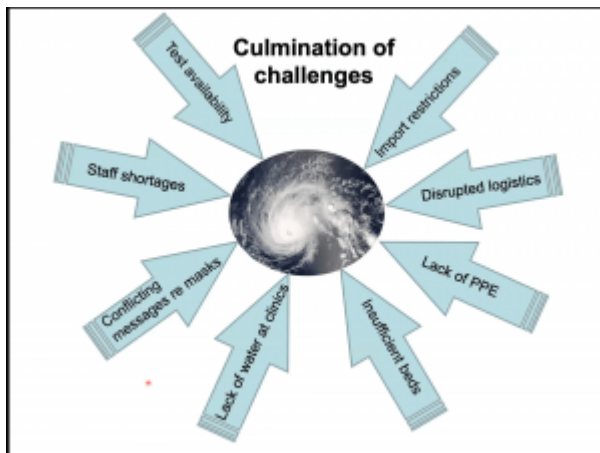
Trial	BCG early (1st 14 days) reduction	BCG later (1st 14 days) reduction
Trial 1	~100%	~50%
Trial 2	~100%	~50%
Trial 3	~100%	~50%
Combined analysis to the neonatal period	28% (CI: 12-42%) reduction (p=0.002)	

Prof Christine explained two main hypotheses around BCG & COVID-19: (1) BCG-at-birth protects against COVID-19 & Recent BCG protects against COVID-10. Currently, no direct evidence for either is available, however, a plethora of ecological studies have

suggested that the first hypothesis is responsible for low COVID-19 prevalence in some countries (Read: [BCG & COVID-19](#)). Realistically, this may not be possible because trained immunity is short lived < 2 years, suggesting that it may not be the sole reason for reduced burden in countries where BCG is still give. For hypothesis 2, trials are currently investigating are on-going, in the meantime observation studies provide evidence that recent BCG vaccination is associated with lower the risk of COVID-19 (Moorlag et al.,

2020; Amirlak et al., Pre-print)

Prof Gerhard Walzl then presented his talk on “*BCG trials for COVID-19 in SA: progress and promise*”. He highlighted challenges the SA healthcare system experiences which include high burden of TB, HIV and more recently non-communicable diseases like diabetes, and also inadequate intensive care facilities among others see below. He then described why BCG re-vaccination was “trailed”, and some challenges they experienced which included: funding challenges “poor buy in from govt”, PPE shortages, lockdown etc.



Why BCG and why revaccination?

- Dysregulated macrophages in CoV-2
- Innate immune training of CD14+ monocytes
- Transcriptomic myeloid bias on human HSPCs
- Enhanced cytokine responses in restimulation but reduced systemic inflammation
- Epidemiological evidence: 10.4% reduction in COVID-19 mortality for every 10% increase in BCG index (Escobar et al, PNAS, 2020)
- BCG efficacy wanes in adolescence (Steme et al., 1998)

...the trial

- Emergency trial started 4 May 2020: double blind, randomized, placebo controlled trial
- HCW and front line workers
- Baseline BCG vaccination or placebo
- Follow-up for one year
- Primary endpoint: CoV-19 hospitalization or death
- TASK: 1000 participants (780 enrolled)
- UCT: 500 participants (280 enrolled)

Can we still learn something from the trial?

- Emergency research not immune from politics (the good, the bad and the ugly of activism)
- Crises can bring competitors together
- Unprecedented rapid SAHPRA approval, WCGH and CoCT permissions and IRB approvals
- Opportunity to investigate the biology of BCG revaccination
 - Single cell ATACseq before and after BCG revaccination to assess chromatin accessibility

Notes:

- *: this is not only associated with BCG but also other live-attenuated vaccines such measles and polio
- #: Trained immunity is the non-specific resistance to infection that is conferred by innate immune cells. Mechanistic studies have attributed trained immunity to epigenetic re-programming that occurs when innate immune cells are activated by infection or vaccination (Netea et al., 2016).

Summary by Cheleka Mpande