



Revising the model for vaccine development: a step towards tuberculosis immunity

Amy Dagenais¹

¹University of Ottawa, Ottawa, Ontario, Canada

Date Published: August 26, 2021

DOI: <https://doi.org/10.18192/UOJM.V11i1S1.5929>

Keywords: *Tuberculosis, COVID-19, vaccines*

Thanks to accelerated vaccine development, the first COVID-19 vaccine was approved for use by Health Canada only nine months after the disease was declared a pandemic by the World Health Organization.¹ This unprecedented feat was made possible by three critical factors: a stressed sense of urgency, substantial funding, and parallel pre-clinical and clinical trials. Such a concerted effort not only led to the development of multiple effective vaccines, but also bred innovation as mRNA technology bloomed despite its limited use in the past. This success story paves the way for the accelerated development of vaccines for other diseases, such as tuberculosis—the deadliest infectious disease of modern times before COVID-19 emerged.

AN URGENT NEED FOR A TUBERCULOSIS VACCINE

Tuberculosis (TB) is an infectious bacterial disease

with the largest infectious disease burden in the world, tolling 10 million new infections and 1.2 million deaths in 2019 alone.² Indeed, tuberculosis is one of the top 10 causes of death worldwide—but the situation remains underdiscussed as most cases are recorded in developing areas, such as South-East Asia (44%) and Africa (25%), or in underserved populations such as the Inuit in Canada.^{2,3} Approximately one-quarter of the world population is infected by the etiological agent of tuberculosis: the bacterium *Mycobacterium tuberculosis* (Mtb), known as the most successful human pathogen.²

The intracellular pathogen has co-evolved with humans to evade host immune defenses, rendering TB treatment particularly difficult. Well-followed treatment regimens generally take approximately six months to complete, but patient non-compliance and heavy antibiotic exposure have given rise to multi-drug and extensively-drug resistant

strains of Mtb^{2,4} Hope for TB treatment has largely turned towards host-directed therapies as most pharmaceutical companies no longer invest in antibiotics in virtue of the rapid onset of resistance and ensuing financial loss.^{5,6} A vaccine is desperately needed to quench the problem at its source.

There is an existing vaccine for TB known as the Bacille Calmette-Guérin (BCG) vaccine, but its inefficacy in adults has driven many countries, including Canada, to discontinue its use—partially or fully—in infants and international travelers.⁷ In turn, there were 14 new TB vaccines in the pipeline as of March 2020 dispersed across live attenuated, whole cell inactivated/fragmented, protein/adjuvant, and viral vectored platforms. Each of these 14 vaccines have been or will be subject to the sequential 10+ year pre-clinical and clinical trial timeline to test for safety and efficacy, even though TB represents an immediate public health threat.⁸

With a TB vaccine, disease development could be decelerated to lighten the global health and economic burden of TB, preserve existing antibiotics, and save millions of lives. Vaccines are of utmost importance for vulnerable populations. For instance, there is an over-representation of damaging respiratory disease in Inuit populations, rendering individuals more susceptible to TB later on.⁹ Paired with inadequate access to healthcare and other social determinants, the rate of TB in Inuit populations is 290x higher than Canadian-born non-indigenous populations.¹⁰

MIRRORING COVID-19 VACCINE DEVELOPMENT FOR TB

A primary driving force for the rapid development of COVID-19 vaccines was the immediate sense of urgency stressed by the WHO and international governments, which is critically lacking from the TB dialogue. Though the WHO has had a TB action plan since 1997, progress has been painfully slow compared to the COVID-19 response. Secondly, once the COVID-19 genome sequence was determined, massive amounts of resources were mobilized for vaccine development, including financial support, laboratory equipment, and staff.¹¹ For instance, the Canadian government alone has invested or pledged over two billion dollars related to COVID-19 vaccines and

therapeutics since the pandemic started.¹² Contrarily, the Canadian government invested less than 25 million dollars towards TB research in 2019—24% less than the minimum fair share funding target established by the United Nations.¹³ A third massive push for COVID-19 vaccine development came in the form of parallel pre-clinical and clinical trials, paired with earlier development of manufacturing facilities. This modification reduced the vaccine development timeline from 10+ years to less than one.¹¹

If these same three steps are taken towards the development of a TB vaccine, a vaccine could be theoretically approved in less than one year. At the very least, if vaccine development stages were made parallel rather than sequential for the TB vaccines currently in clinical trial phases I and II, a successful candidate could be identified much sooner. This approach could also reveal whether any of the current candidates hold promise—and, if not, these clinical trials could cease. Funding could then be transferred to support new pre-clinical studies.

An interesting new avenue for TB vaccine development is the mRNA platform as none of the vaccines in the current pipeline utilize this technology. Indeed, mRNA vaccines have shown promise for bacterial pathogens, such as group A and B Streptococcus.¹⁴ Though COVID-19 is a virus and Mtb is a bacterium, both exhibit intracellular lifestyles and characteristic surface proteins that could be potential immune targets. For instance, the membrane proteins Rv0232 and Rv1115 on Mtb are known to be antigenic in vivo,¹⁵ just like the infamous spike protein on the etiological agent of COVID-19, SARS-CoV-2. Indeed, mRNA technology is an attractive avenue for vaccine development and worthy of investment.

LESSONS TO TAKE AWAY FROM COVID-19 ACCELERATED VACCINE DEVELOPMENT

The path towards global TB immunity is clear: the same importance and resources devoted to COVID-19 accelerated vaccine development need to be applied to TB vaccine development. This effort requires: 1) a properly communicated sense of urgency, 2) financial investment in research, training, and infrastructure, and 3) a modified vaccine development timeline. This would allow for new

vaccine candidates, like mRNA-based vaccines, or existing candidates to be developed more quickly. In the future, accelerated vaccine development could equally be utilized for other infectious agents, such as *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*, creating a world in which infectious disease and antimicrobial resistance are far less burdensome.

15. Li H, Liu L, Zhang W, Zhang X, Zheng J, Li L, et al. Analysis of the antigenic properties of membrane proteins of *Mycobacterium tuberculosis*. *Sci Rep*. 2019 Dec;9(1):3042.

REFERENCES

1. Government of Canada. Pfizer-BioNTech COVID-19 Vaccine (tozinameran) [Internet]. Government of Canada; [updated 2021 Mar 26; cited 2021 Mar 26]. Available from: <https://covid-vaccine.canada.ca/pfizer-biontech-covid-19-vaccine/product-details>
2. World Health Organization. Global tuberculosis report 2020. Geneva (CH): WHO Press; 2020. 232 p. Licence: CC BY-NC-SA 3.0 IGO.
3. Vachon J, Gallant V, Siu W. Tuberculosis in Canada, 2016. *CCDR*. 2018 Mar 1;44(3/4):75–81.
4. World Health Organization. Global tuberculosis control 2009: epidemiology, strategy, financing. WHO Press; 2009. 314 p. ISBN 978 92 4 156380 2
5. Young C, Walzl G, Du Plessis N. Therapeutic host-directed strategies to improve outcome in tuberculosis. *Mucosal Immunol*. 2020 Mar;13(2):190–204.
6. World Health Organization. Lack of new antibiotics threatens global efforts to contain drug-resistant infections [Internet]. World Health Organization; 2020 Jan 17 [cited 2021 Mar 26]. Available from: <https://www.who.int/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections#:~:text=Declining%20private%20investment%20and%20lack,weak%20pipeline%20for%20antibiotic%20agents>
7. Public Health Agency of Canada. Canadian Tuberculosis Standards 7th Edition. Ontario (CA): Government of Canada; 2014. Chapter 16: Bacille Calmette-Guérin (BCG) vaccination in Canada; p. 405.
8. Martin C, Aguilo N, Marinova D, Gonzalo-Asensio J. Update on TB Vaccine Pipeline. *Applied Sciences*. 2020 Apr 10;10(7):2632.
9. Kovesi T. Respiratory disease in Canadian First Nations and Inuit children. *Paediatr Child Health*. 2012 Aug 1;17(7):376–380.
10. Patterson M, Flinn S, Barker K. Addressing tuberculosis among Inuit in Canada. *CCDR*. 2018 Mar 1;44(3/4):82–5.
11. World Health Organization. Coronavirus update 45: Update on COVID-19 vaccine development [Internet]. World Health Organization; [updated 2020 Dec 21; cited 2021 Mar 26]. Available from: https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update45-vaccines-developement.pdf?sfvrsn=13098bfc_5
12. Government of Canada. Backgrounder – Government of Canada investments in COVID-19 vaccines, therapeutics and biomanufacturing capacity [Internet]. Government of Canada; 2021 Feb 2 [cited 2021 Mar 26]. Available from: <https://www.canada.ca/en/innovation-science-economic-development/news/2021/02/backgrounder--government-of-canada-investments-in-covid-19-vaccines-and-biomanufacturing-capacity.html>
13. Treatment Action Group. Tuberculosis research funding trends 2005-2019. New York (US); 2020. 62 p.
14. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines — a new era in vaccinology. *Nat Rev Drug Discov*. 2018 Apr;17(4):261–79.