The Tuberculosis Vaccine Pipeline

Mark Hatherill

South African Tuberculosis Vaccine Initiative
University of Cape Town, South Africa

WHO Global Tuberculosis Report 2022

Phase I	Phase IIa	Phase IIb	Phase III
AdHu5Ag85A[b] McMaster, CanSino	**ChAdOx185A-MVA85A**[b,i] University of Oxford	**BCG revaccination to prevent infection**[d,j] Gates MRI	**GamTBvac**[e] Ministry of Health, Russian Federation
TB/FLU-01L[b] **TB/FLU-04L**[b] RIBSP	**ID93 + GLA-SE(QTP101)**[e] Quratis U.S. NIH/NIAID	**DAR-901 booster**[f,j] Dartmouth	**MIP/Immuvac**[f,i,j] ICMR, Cadila Pharmaceuticals
BNT164[c] BioNTech SE	**AEC/BC02**[e] Anhui Zhifei Longcom	**H56: IC31**[e] SSI, Valneva, IAVI	**MTBVAC**[d,h] Biofabri, University of Zaragoza, IAVI, TBVI
		M72/AS01E[e,j] GSK, Gates MRI	**VPM1002**[d,g,i,j] SIIPL, VPM
		RUTI®[f] Archivel Farma, S.L.	**BCG vaccination to prevent infection (TIPI)**[d] HJF
Pending: **H107 (SSI) first-in-human**			**BCG revaccination in children and adolescents (BRiC)**[d,i,j] ICMR

14 candidates + BCG

3 viral vector
- Ad5Ag85A
- TB/FLU-01/4L
- ChadOx185A

5 subunit
- ID93+GLA-SE / QTP101
- AEC/BC02
- H56:1C31
- M72/AS01$_E$
- GamTBvac

3 inactivated mycobacterial
- 1 *M. obuense* (DAR-901)
- 1 *M. tuberculosis* (RUTI)
- 1 *M. indicus pranii* (Immuvac)

3 live mycobacterial
- 1 *M. tuberculosis* (MTBVAC)
- 1 rBCG (VPM1002)
- BCG revaccination

1 mRNA (BNT164)

https://www.who.int/teams/global-tuberculosis-programme/tb-reports

The TB vaccine pipeline 2012 vs 2022

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			BCG revaccination in children and adolescents (BRiC)[d,i,j] ICMR

2012
12 candidates
Phase 1 dominant

6 candidates no longer in development
6 candidates 2012 and 2022 (2 static)
8 new candidates

2022
14 candidates + BCG
Phase 2b-3 dominant

TB Vaccine Pipeline

Active clinical trials of TB vaccine candidates

There are 11 active clinical trials across nine candidates as of October 2022.

Platform

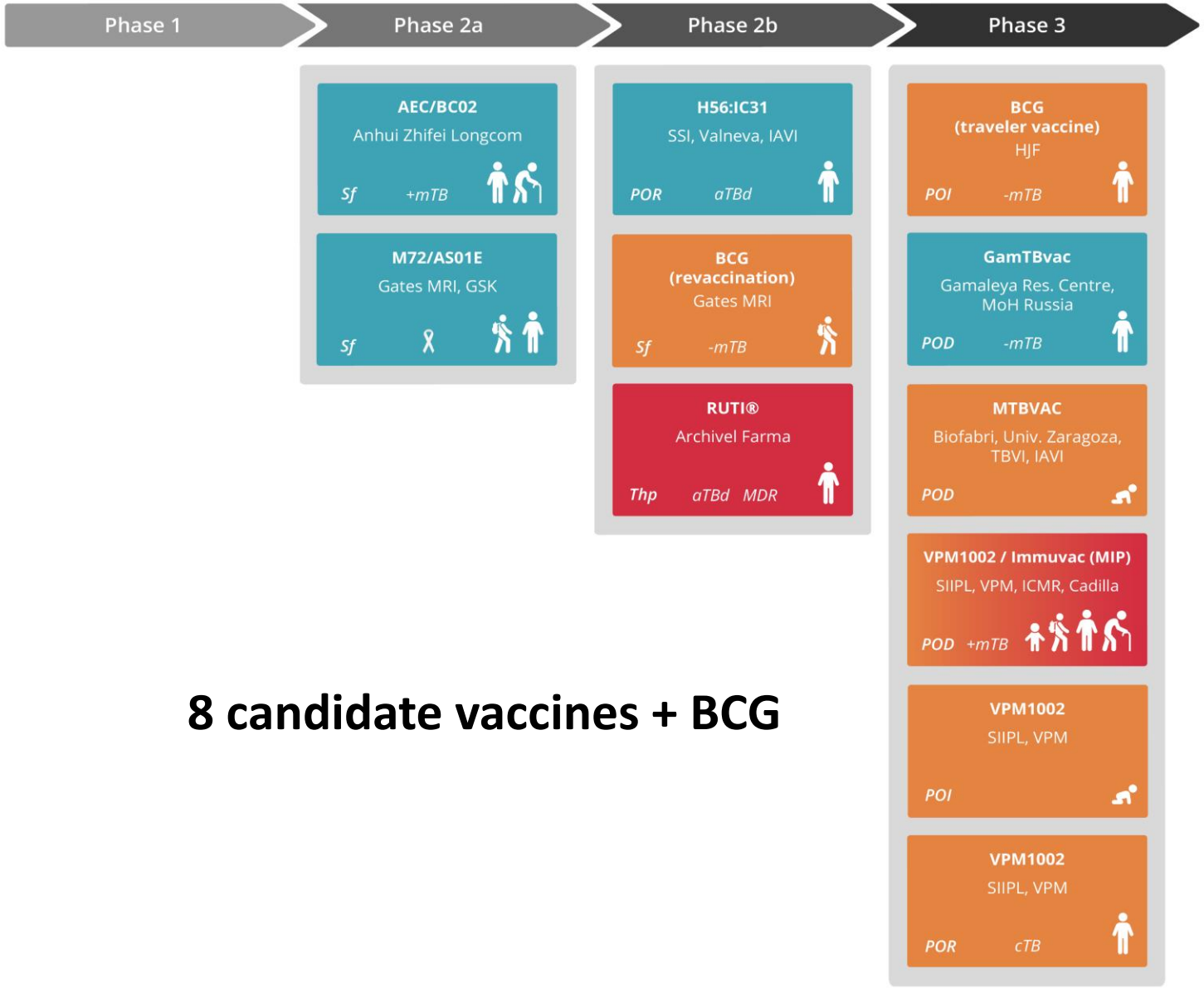
- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant

Trial target population

- Elderly
- Adults
- Adolescents
- Children
- Infants
- People living with HIV
- -mTB People without mTB infection
- +mTB People with mTB infection
- aTBd People with active TB disease
- MDR People with MDR-TB
- cTB People cured of active TB

Primary trial indication

- *Sf* Safety
- *POI* Prevention of Infection
- *POD* Prevention of Disease
- *POR* Prevention of Recurrence
- *Thp* Therapeutic



8 candidate vaccines + BCG

Stop TB Partnership
Working Group on New TB Vaccines

Information reported by vaccine sponsors or found in clinical trial registries or other public sources.

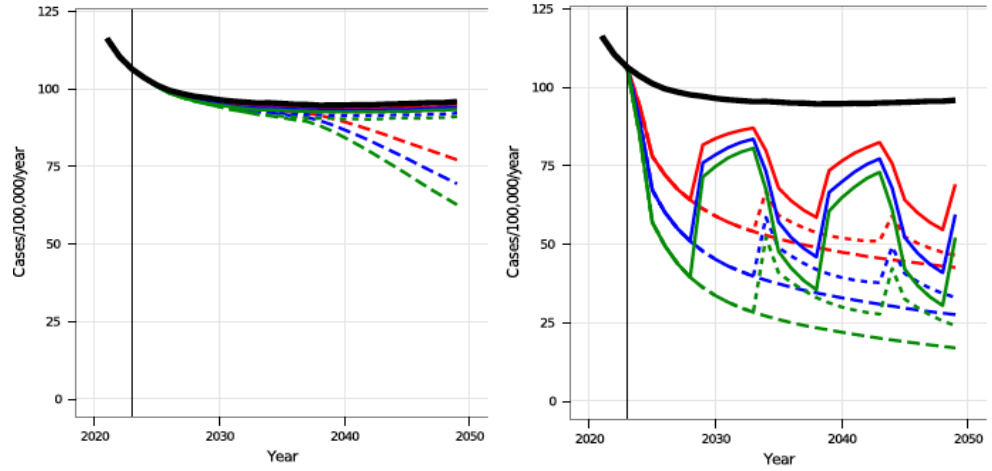
For the full list of completed trials for each candidate, visit www.newtbvaccines.org/tb-vaccine-pipeline/

Last update: 02 February 2023

New TB Vaccines for Infants or Adults?

Adult vaccine strategy with only 40% VE and 5-year protection (R)
more impact on TB incidence than by 2050 than
Infant vaccine strategy with 80% VE and lifelong protection (L)
– due to reduction in *M.tb* transmission

Modeled impact of an infant vs adult vaccine



PNAS

Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries

Gwenan M. Knight[a], Ulla K. Griffiths[b], Tom Sumner[a], Yoko V. Laurence[b], Adrian Gheorghe[b], Anna Vassall[b], Philippe Glaziou[c], and Richard G. White[a,1]

[a]TB Modelling Group, TB Centre, Centre for the Mathematical Modelling of Infectious Diseases, Faculty of Epidemiology and Population Health, and [b]Department of Global Health and Development, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom; and [c]Global Tuberculosis, World Health Organization, CH 1211 Geneva 27, Switzerland

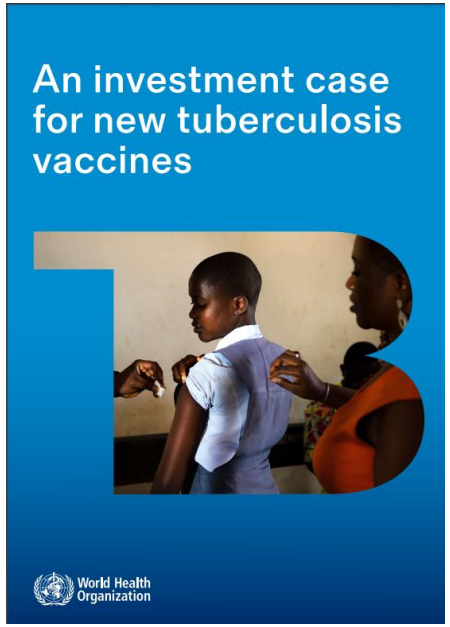
Edited* by Barry R. Bloom, Harvard School of Public Health, Boston, MA, and approved September 8, 2014 (received for review March 7, 2014)

PLOS MEDICINE

RESEARCH ARTICLE

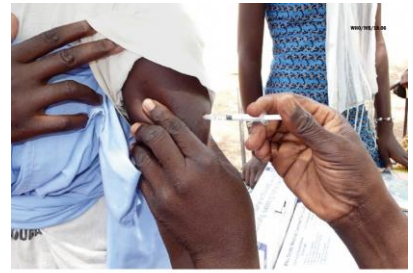
The cost and cost-effectiveness of novel tuberculosis vaccines in low- and middle-income countries: A modeling study

Allison Portnoy[1]*, Rebecca A. Clark[2,3,4], Matthew Quaife[2,3,4], Chathika K. Weerasuriya[2,3,4], Christinah Mukandavire[2,3,4], Roel Bakker[2,3,4,5], Arminder K. Deol[2,3,4,6], Shelly Malhotra[7,8], Nebiat Gebreselassie[9], Matteo Zignol[9], So Yoon Sim[10], Raymond C. W. Hutubessy[10], Inés Garcia Baena[9], Nobuyuki Nishikiori[9], Mark Jit[3,4,11], Richard G. White[2,3,4†], Nicolas A. Menzies[1,12‡]

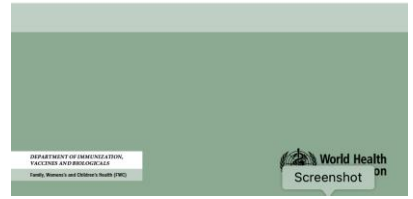


COSTS AND BUDGET IMPACT	VACCINE FOR INFANTS	VACCINE FOR ADOLESCENTS AND ADULTS
Timeline: 2025–2050 Vaccine price, US$ 4.60	(80% efficacy, 85% routine coverage, 10-year protection, base-case scenario)	(50% efficacy, 80% routine and 70% campaign coverage, 10-year protection, base-case scenario)
Global costs of vaccine introduction	US$ 11.8 (9.6–16.9) billion	US$ 50.5 (38.1–75.9) billion
Averted costs for drug-susceptible TB diagnosis and treatment	US$ 342 (223–489) million	US$ 3.5 (2.2–5.2) billion
Averted costs for drug-resistant TB diagnosis and treatment	US$ 299 (251–351) million	US$ 3.2 (2.6–3.8) billion

WHO Preferred Product Characteristics (PPC) for New TB Vaccines



WHO Preferred Product Characteristics
for New Tuberculosis Vaccines



Adolescents & Adults

50% or greater efficacy

Protect with/post- & without/pre- *Mtb* infection

Protect in diverse geographies

Safe in PLWHIV, elderly, pregnancy

10+ years protection

Infants

Superior efficacy vs BCG*

Superior safety vs BCG

Safe in HIV-infected infants

10+ years protection

*Infant BCG

VE 74% *Colditz, Pediatrics 1995*

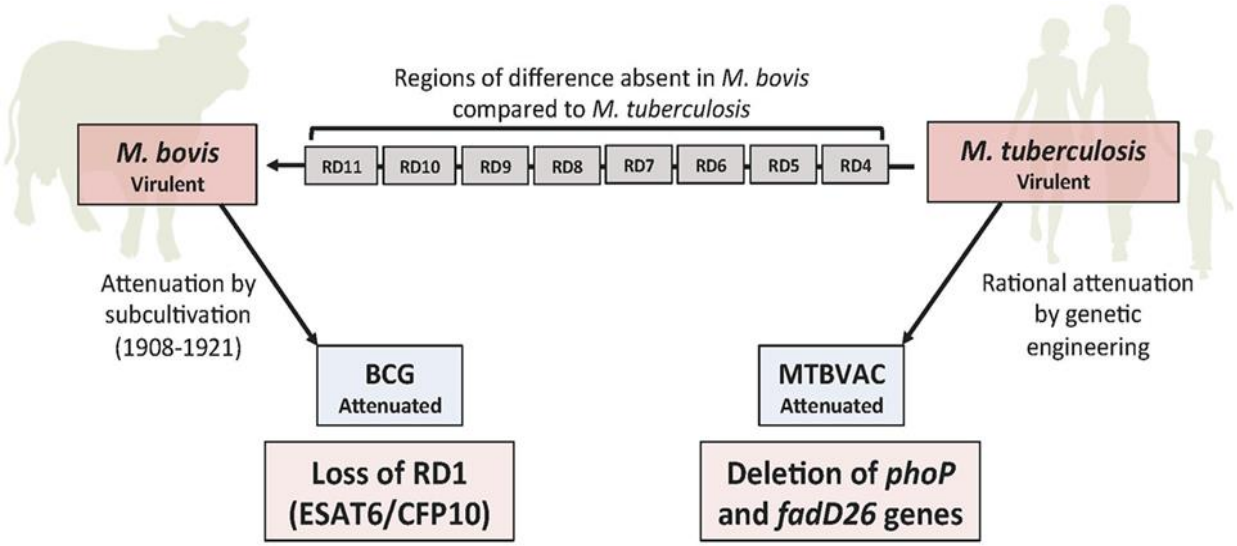
VE 59% *Mangtani, CID 2014*

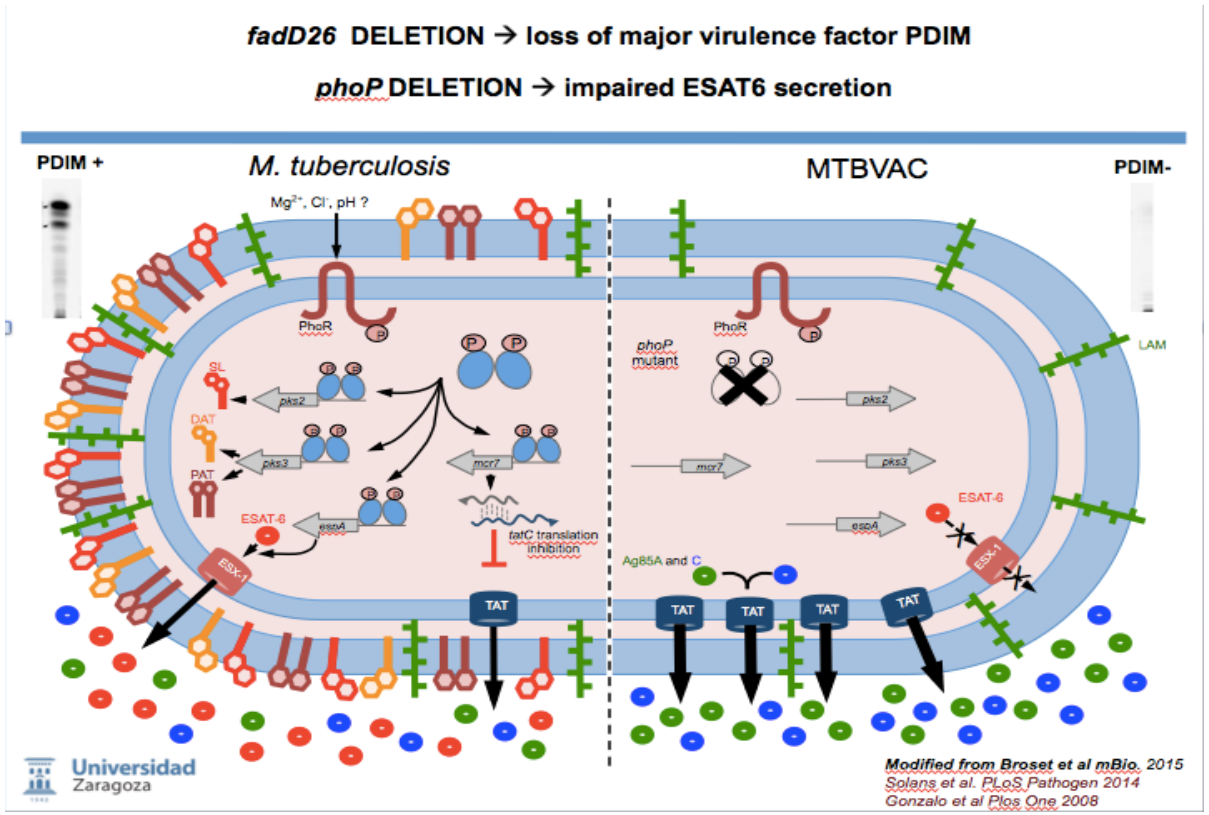
MTBVAC
Phase 3 POD (infants)

Live-attenuated *Mycobacterium tuberculosis* vaccine MTBVAC versus BCG in adults and neonates: a randomised controlled, double-blind dose-escalation trial

Michele Tameris*, Helen Mearns*, Adam Penn-Nicholson, Yolande Gregg, Nicole Bilek, Simbarashe Mabwe, Hennie Geldenhuys, Justin Shenje, Angelique Kany Kany Luabeya, Ingrid Murillo, Juana Doce, Nacho Aguilo, Dessislava Marinova, Eugenia Puentes, Esteban Rodríguez, Jesús Gonzalo-Asensio, Bernard Fritzell, Jelle Thole, Carlos Martin, Thomas J Scriba†, Mark Hatherill†, and the MTBVAC Clinical Trial Team

Lancet Respir Med 2019; 7:757–70





Started: Randomised, Double-blind Controlled Phase 3 Trial to evaluate the Efficacy, Safety and Immunogenicity of MTBVAC Administered in Healthy HIV unexposed and HIV exposed uninfected Newborns in Tuberculosis Endemic Regions of Sub-Saharan Africa (NCT04975178) >7,000 HIV-unexposed and HIV-exposed uninfected newborns, randomized BCG or MTBVAC, 72m FU for TB disease

Planned: Safety & immunogenicity (PLWH on ART)
Phase 3 safety & efficacy (adolescents & adults)

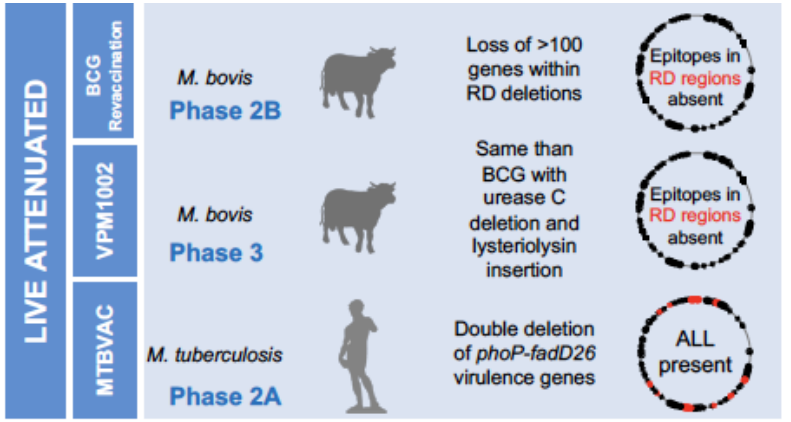
ClinicalTrials.gov Identifier: NCT04975178

Recruitment Status : Recruiting
First Posted : July 23, 2021
Last Update Posted : October 12, 2022

VPM1002

Phase 3 POI (Infants)
POD (Household Contacts >6 years)
POR (Adult TB patients)

VPM1002: recombinant urease C-deficient, listeriolysin-expressing BCG vaccine derived from the BCG Prague strain (minus RD1 and RD2 genes)



Completed: Study to Evaluate the Safety and Immunogenicity of VPM1002 in Comparison with BCG in HIV-exposed/-Unexposed Newborn Infants in South Africa (NCT02391415)

Cotton et al, Lancet Infect Dis 2022

VPM1002 less reactogenic than BCG (injection site ulceration, abscess, scarring)
Multifunctional CD4+ and CD8+ T cell responses higher in BCG vs VP1022

Safety and immunogenicity of VPM1002 versus BCG in South African newborn babies: a randomised, phase 2 non-inferiority double-blind controlled trial

Mark F Cotton, Shabir A Madhi, Angelique K Luabeya, Michele Tameris, Anneke C Hesseling, Justin Shenje, Elisma Schoeman, Mark Hatherill, Sajjad Desai, Dhananjay Kapse, Sina Brückner, Anthonet Koen, Lisa Jose, Andrew Moultrie, Sutika Bhikha, Gerhard Walzl, Andrea Gutschmidt, Leigh A Kotze, Devon L Allies, Andre G Loxton, Umesh Shaligram, Maria Abraham, Hilary Johnstone, Leander Grode, S H E Kaufmann, Prasad S Kulkarni

Follow-up: A multicenter, phase III, double-blind, randomized, active-controlled study to evaluate the efficacy and safety of VPM1002 in comparison to BCG in prevention of *Mycobacterium tuberculosis* infection in newborn infants (NCT04351685)

6,940 newborn infants (HIV unexposed and HIV-exposed uninfected) in Gabon, Kenya, South Africa, Tanzania, and Uganda, randomized BCG or VPM1002, FU 36m (POI, safety; 2^0 POD)

ClinicalTrials.gov Identifier: NCT04351685

Recruitment Status : Recruiting
First Posted : April 17, 2020
Last Update Posted : October 19, 2021

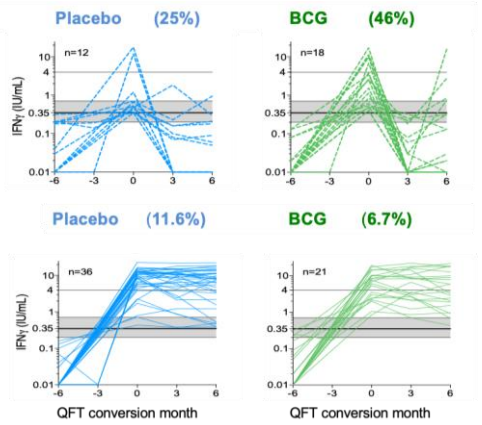
Next Steps…
BCG Revaccination PO(S)I

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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†



BCG 45% efficacy against sustained IGRA+ conversion

Sustained Mtb infection?

Follow-up: A Randomized, Placebo Controlled, Observer-Blind, Phase IIb Study to Evaluate the Efficacy, Safety, and Immunogenicity of BCG Revaccination in Healthy Adolescents for the Prevention of Sustained Infection With Mycobacterium Tuberculosis (BCG REVAX; Gates MRI-TBV01-201) (NCT04152161)

1,800 IGRA- SA adolescents (10-18 yr), randomized BCG revaccination or placebo
FU 48 months; primary endpoint sustained IGRA+ conversion 6 months
Results primary event-driven analysis expected end 2023…

ClinicalTrials.gov Identifier: NCT04152161

Recruitment Status : Active, not recruiting
First Posted : November 5, 2019
Last Update Posted : August 11, 2021

What would we do with positive PO(S)I findings?

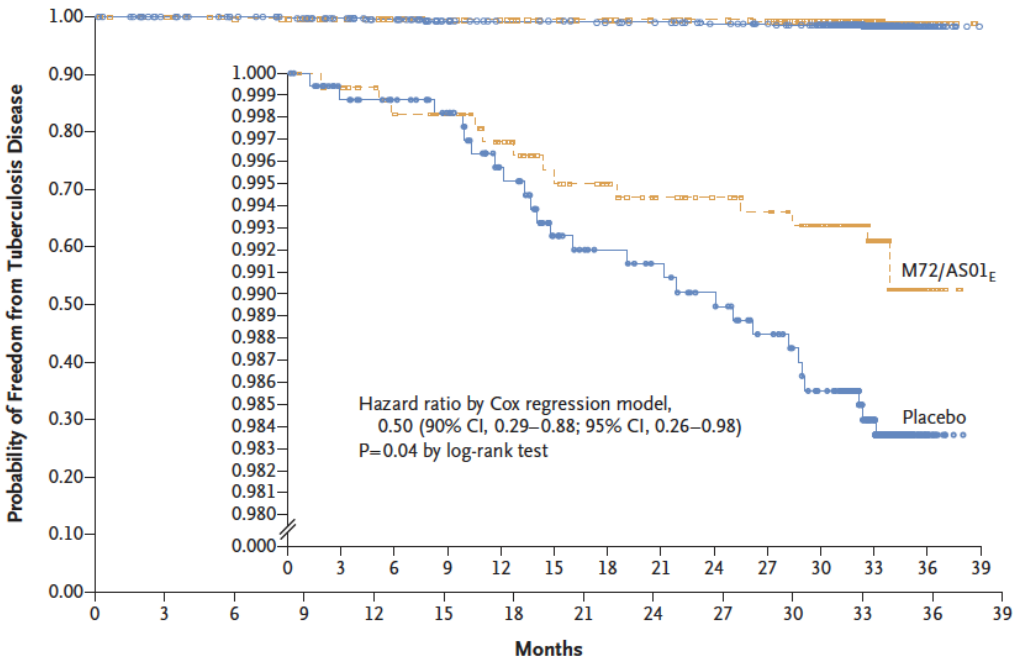
POD trial BCG revaccination in IGRA- adolescents?
TB incidence IGRA- lower, sample size +/- 60-70,000
Country-level interest in pragmatic trial with passive follow-up?

M72/AS01$_E$
POD (adolescents/adults)

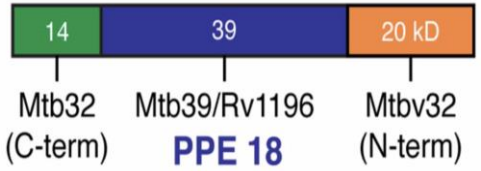
3,575 IGRA+ HIV- adults
Zambia, Kenya, SA

Randomized (1:1)
M72/AS01$_E$ or Placebo
2 doses, 1 month apart

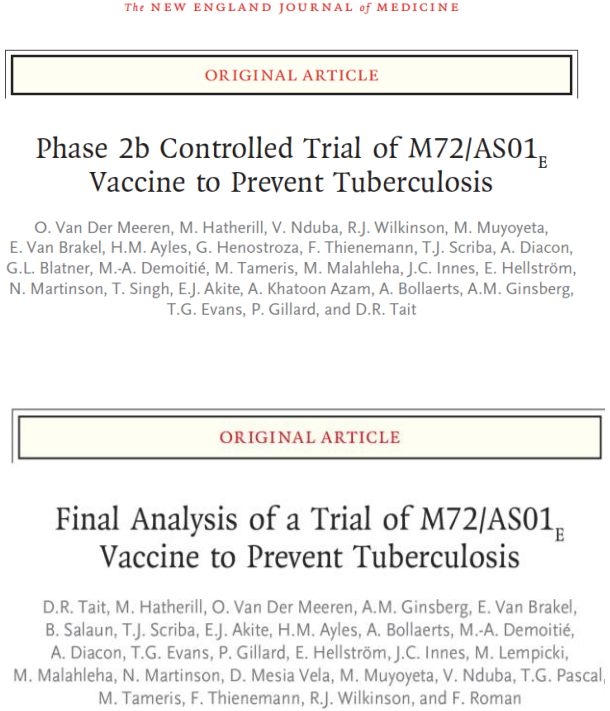
Subclinical TB excluded baseline
3-year follow-up
Micro+ symptomatic TB



Year 1	VE 27.4%	(95% CI −128.8 to 77.0)
Year 2	VE 55.2%	(95% CI −45.3 to 86.2)
Year 3	VE 60.2%	(95% CI−27.0 to 87.5)
Years 1-3	**VE 49.7%**	**(95% CI 2.1 to 74.2)**



Brennan, Infection & Immunity 2017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ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

ORIGINAL ARTICLE

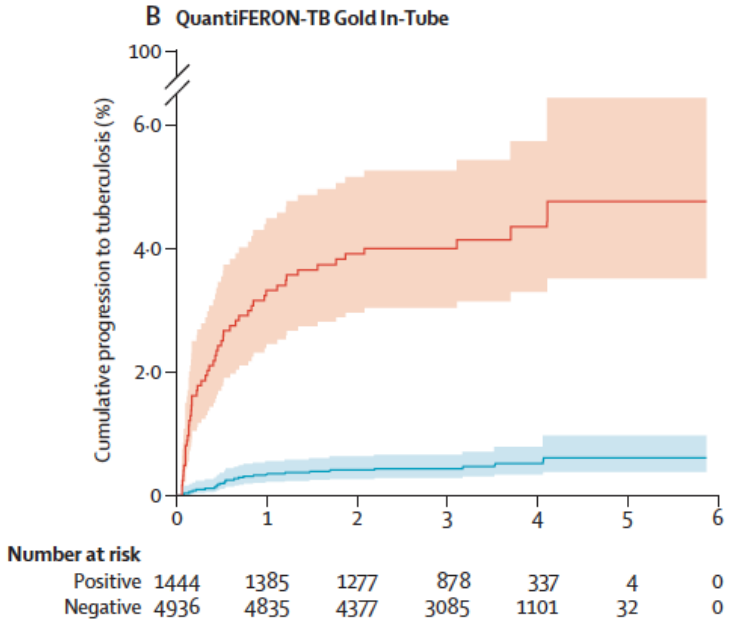
Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

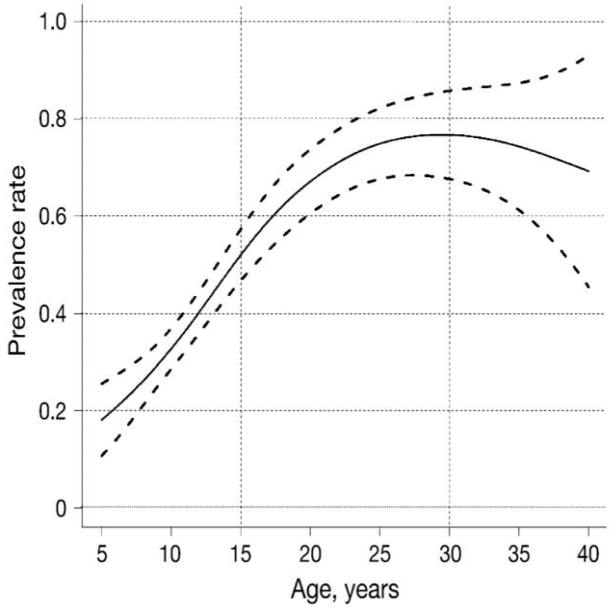
Planned: Phase 3 efficacy, safety, and immunogenicity licensure trial, multiple sites and countries, 2024
26,000 adolescents and adults aged 15-44 years, IGRA+(-); HIV-(+); (POD; 2^0 POI)
Site selection epi study (IGRA+ rates) multiple countries

Vaccinate before (IGRA-) or after (IGRA+) *M. tuberculosis* exposure?

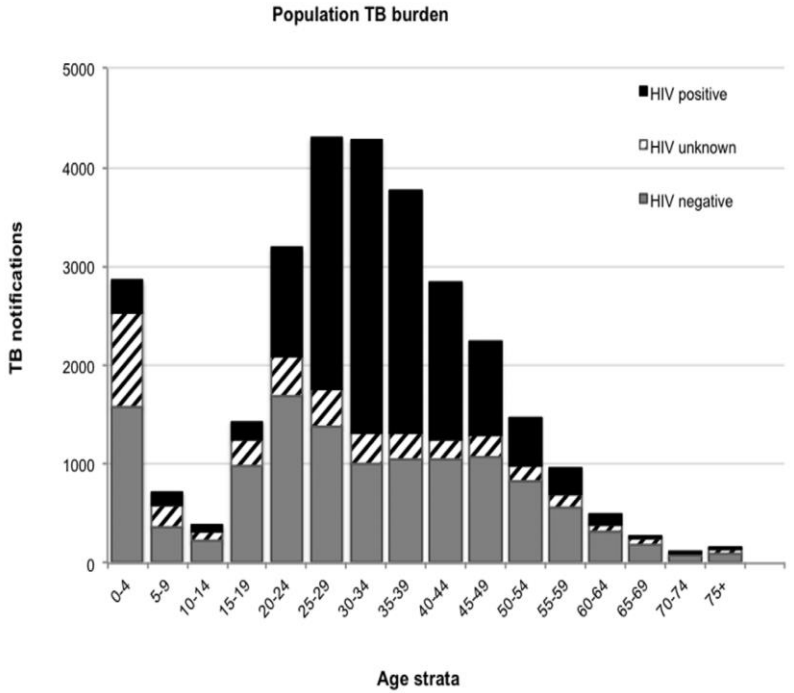
~23% global population (1.7 billion) Mtb-sensitized, ie. 77% not… *Houben, PloS Medicine 2016*



TB disease incidence after Mtb exposure
Abubakar Lancet ID 2018



TST (10mm+) prevalence rate by age
Wood et al, IJTLD 2010



TB Disease notifications (HIV-negative) by age
Wood et al, PLoS ONE 2011

Risk of TB disease highest within 2 years of exposure

***M.tb* infection and TB disease rates increase rapidly through adolescence into young adulthood**

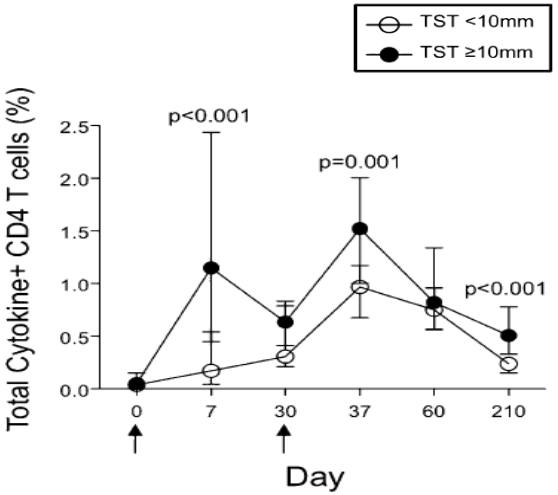
Target IGRA- pre-adolescents or IGRA+ adolescents and adults?

Can subunit vaccination protect Mtb-unsensitized (TST-/IGRA-) individuals against future exposure, infection, and progression to TB disease?

Induction and Regulation of T-Cell Immunity by the Novel Tuberculosis Vaccine M72/AS01 in South African Adults

Cheryl L. Day[1,2,3,*], Michele Tameris[1,*], Nazma Mansoor[1], Michele van Rooyen[1], Marwou de Kock[1], Hennie Geldenhuys[1], Mzwandile Erasmus[1], Lebohang Makhethe[1], E. Jane Hughes[1], Sebastian Gelderbloem[1,†], Anne Bollaerts[4], Patricia Bourguignon[4], Joe Cohen[4], Marie-Ange Demoitié[4], Pascal Mettens[4], Philippe Moris[4], Jerald C. Sadoff[5,§], Anthony Hawkridge[1], Gregory D. Hussey[1], Hassan Mahomed[1], Opokua Ofori-Anyinam[4,‖], and Willem A. Hanekom[1,‖]

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 188 2013

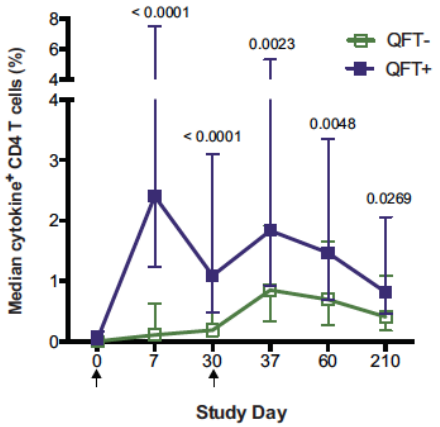


Adults: Total frequencies of M72-specific cytokine+ CD4 T cells were higher in TST+ vs TST-

Contents lists available at ScienceDirect
Vaccine
journal homepage: www.elsevier.com/locate/vaccine

Safety and immunogenicity of candidate vaccine M72/AS01$_E$ in adolescents in a TB endemic setting

Adam Penn-Nicholson[a,c,1], Hennie Geldenhuys[a,1], Wivine Burny[b], Robbert van der Most[b], Cheryl L. Day[a,c,d], Erik Jongert[b], Philippe Moris[b], Mark Hatherill[a], Opokua Ofori-Anyinam[b,2], Willem Hanekom[a,2], the Vaccine Study Team,

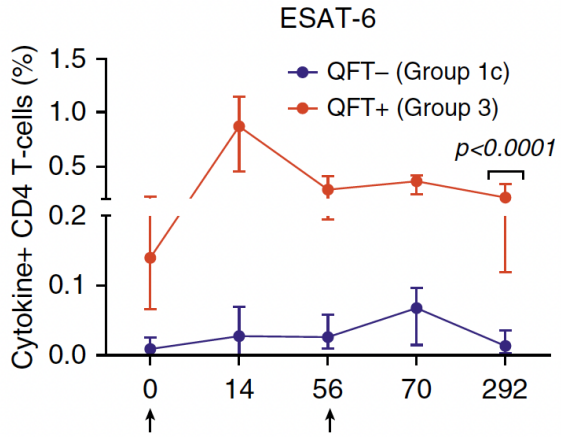


Adolescents: M72/AS01$_E$ induced higher median cytokine+ CD4 T cell responses in IGRA+ vs IGRA-

Dose Optimization of H56:IC31 Vaccine for Tuberculosis-Endemic Populations

A Double-Blind, Placebo-controlled, Dose-Selection Trial

Sara Suliman[1,2*], Angelique Kany Kany Luabeya[1,2*], Hennie Geldenhuys[1,2], Michele Tameris[1,2], Soren T. Hoff[3], Zhongkai Shi[4], Dereck Tait[5], Ingrid Kromann[3], Morten Ruhwald[3], Kathryn Tucker Rutkowski[4], Barbara Shepherd[4], David Hokey[4], Ann M. Ginsberg[4], Willem A. Hanekom[1,2], Peter Andersen[3], Thomas J. Scriba[1,2‡], Mark Hatherill[1,2‡], and the H56-035 Trial Group



Adults: Impact of Mycobacterium tuberculosis (M.tb) infection on immunogenicity of H56:IC31. Median frequency of ESAT-6-specific CD4 T cells.

Need an immune correlate of vaccine-mediated protection

Modelling studies

Vaccine efficacy in IGRA+ populations → greatest reduction in TB incidence by 2050
(IRR 51%, 52%, and 54% in China, South Africa, India)

Vaccine efficacy only in IGRA- populations → moderate reduction in TB incidence by 2050
(IRR 19, 36, and 51% in China, South Africa, India), greater impact in higher-transmission settings

Harris et al, Sci Transl Med 2020
*Assumptions: 10-year, 70% efficacy against disease

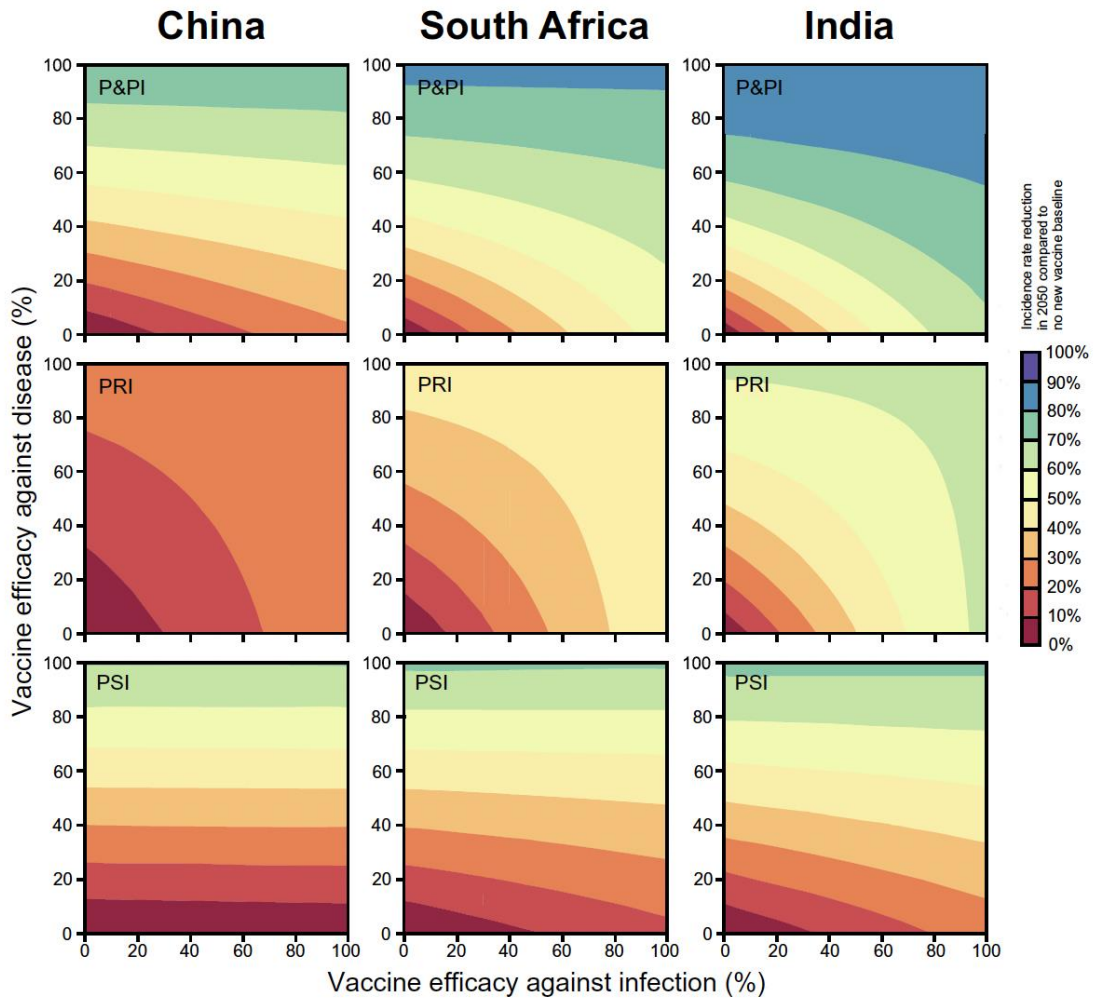


Fig. 3. Vaccine impact by prevention of infection and prevention of disease efficacy. IRR in 2050 by country from a vaccine with 10-year duration of protection for prevention of infection or disease or both, with efficacy in pre- and post-infection populations (P&PI; top row), pre-infection populations (PRI; middle row), or post-infection populations (PSI; bottom row), assumed safe and efficacious in HIV-positive populations, delivered from 2025 as routine vaccination of 9 year olds and as 10-yearly mass campaigns in China, South Africa, and India.

Optimal strategy?

Vaccine efficacy in both IGRA- and IGRA+

or

Combination pre- and post-exposure approaches

Why is TB vaccine development so slow?

Trial duration

Slow growing Mtb pathogen, slowly progressive TB disease, no epidemic waves, no immune correlates of vaccine-induced protection = long efficacy trials (5+ years)

"TB vaccine development is not a 100-day dash; it is an endurance marathon that requires an altogether different kind of stamina…" ***TAG TB Vaccine Pipeline Report 2022***

Trial-to-trial interval

Collective stakeholder inertia / lack of risk appetite

$M72/AS01_E$ Phase 2b trial completed 16th November 2018

Final efficacy results published 29th October 2019

Phase 3 trial expected to start in 2024…

Results expected…?

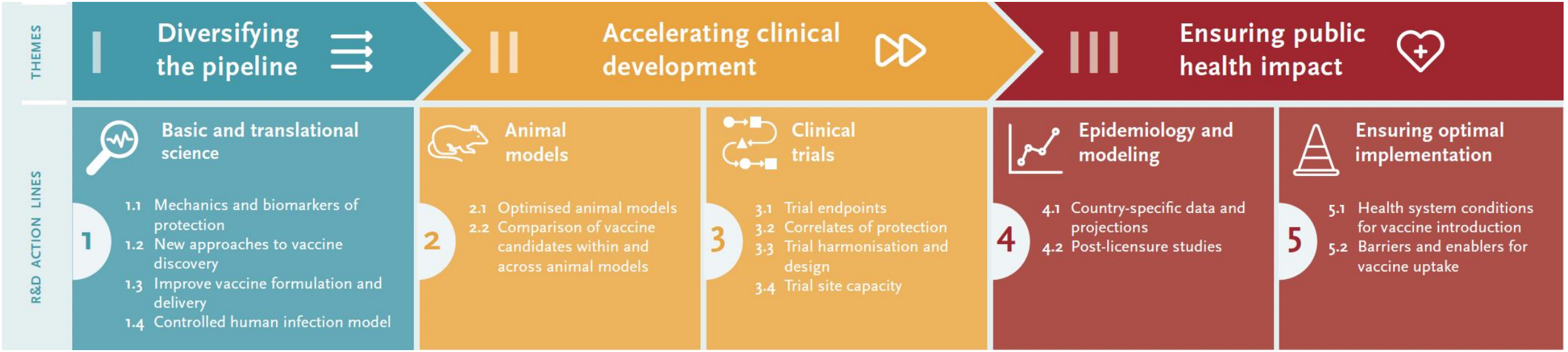
THE GLOBAL TB VACCINE R&D ROADMAP

Accelerating research and development of new vaccines against tuberculosis: a global roadmap

*Frank Cobelens, Rajinder Kumar Suri, Michelle Helinski, Michael Makanga, Ana Lúcia Weinberg, Britta Schaffmeister, Frank Deege, Mark Hatherill, on behalf of the TB Vaccine Roadmap Stakeholder Group**

Cobelens et al, Lancet Infect Dis 2022

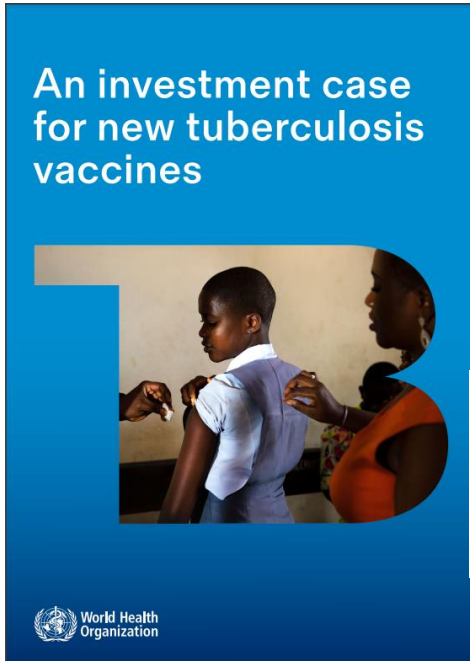
Supported by EDCTP through a grant to the Amsterdam Institute of Global Health and Development in collaboration with WHO



Priorities: diversity of vaccine design and delivery; validated preclinical models; more efficient clinical trials; discovery of immune correlates of protection; understanding of cost-effectiveness, demand and integration into existing programmes

Access new funding streams, reduce financial risk

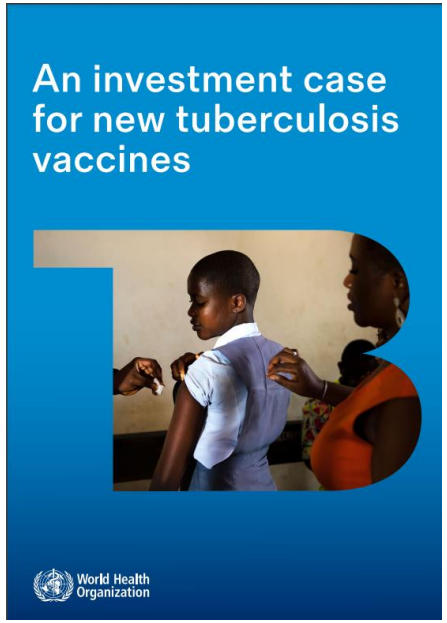
COSTS AND BUDGET IMPACT	VACCINE FOR INFANTS	VACCINE FOR ADOLESCENTS AND ADULTS
Timeline: 2025–2050 Vaccine price, US$ 4.60	(80% efficacy, 85% routine coverage, 10-year protection, base-case scenario)	(50% efficacy, 80% routine and 70% campaign coverage, 10-year protection, base-case scenario)
Global costs of vaccine introduction	US$ 11.8 (9.6–16.9) billion	US$ 50.5 (38.1–75.9) billion
Averted costs for drug-susceptible TB diagnosis and treatment	US$ 342 (223–489) million	US$ 3.5 (2.2–5.2) billion
Averted costs for drug-resistant TB diagnosis and treatment	US$ 299 (251–351) million	US$ 3.2 (2.6–3.8) billion

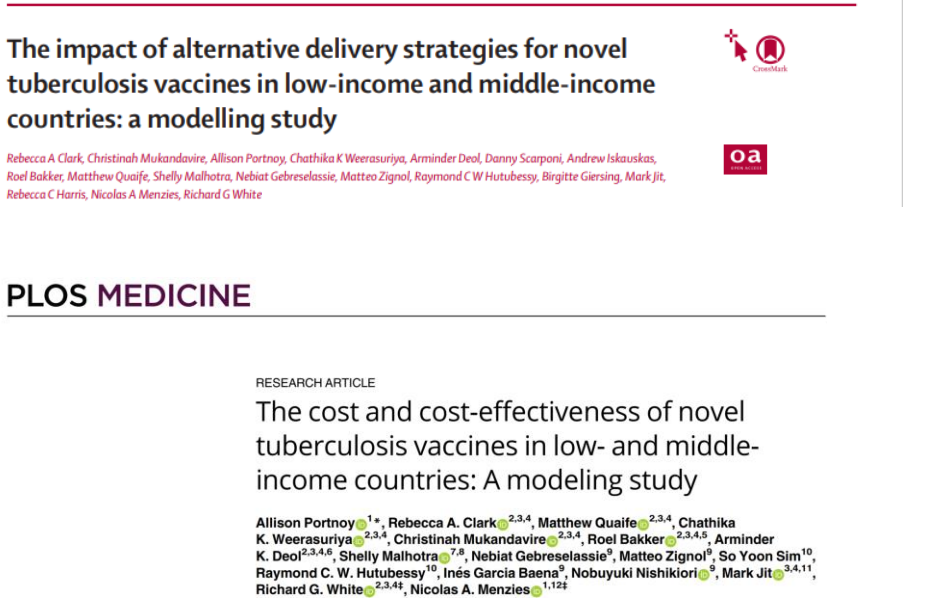


The case for increased investment in TB vaccine R&D is compelling

TB vaccine with 50% efficacy for adolescents/adults:

- Prevent 37 million TB cases and 4.6 million deaths (2025–2050)
- Avert US$ 3.5 billion DS-TB costs
- Cost-effective in all high TB burden countries
- Cost-saving in 58 of 105 (55%) LMIC





Ongoing

Assessment of full value of new TB vaccines

Development of Evidence Considerations for Vaccine Policy (ECVP)

Development of a Global Framework for Countries to achieve Rapid Introduction and Impact of New TB Vaccines for Adults and Adolescents

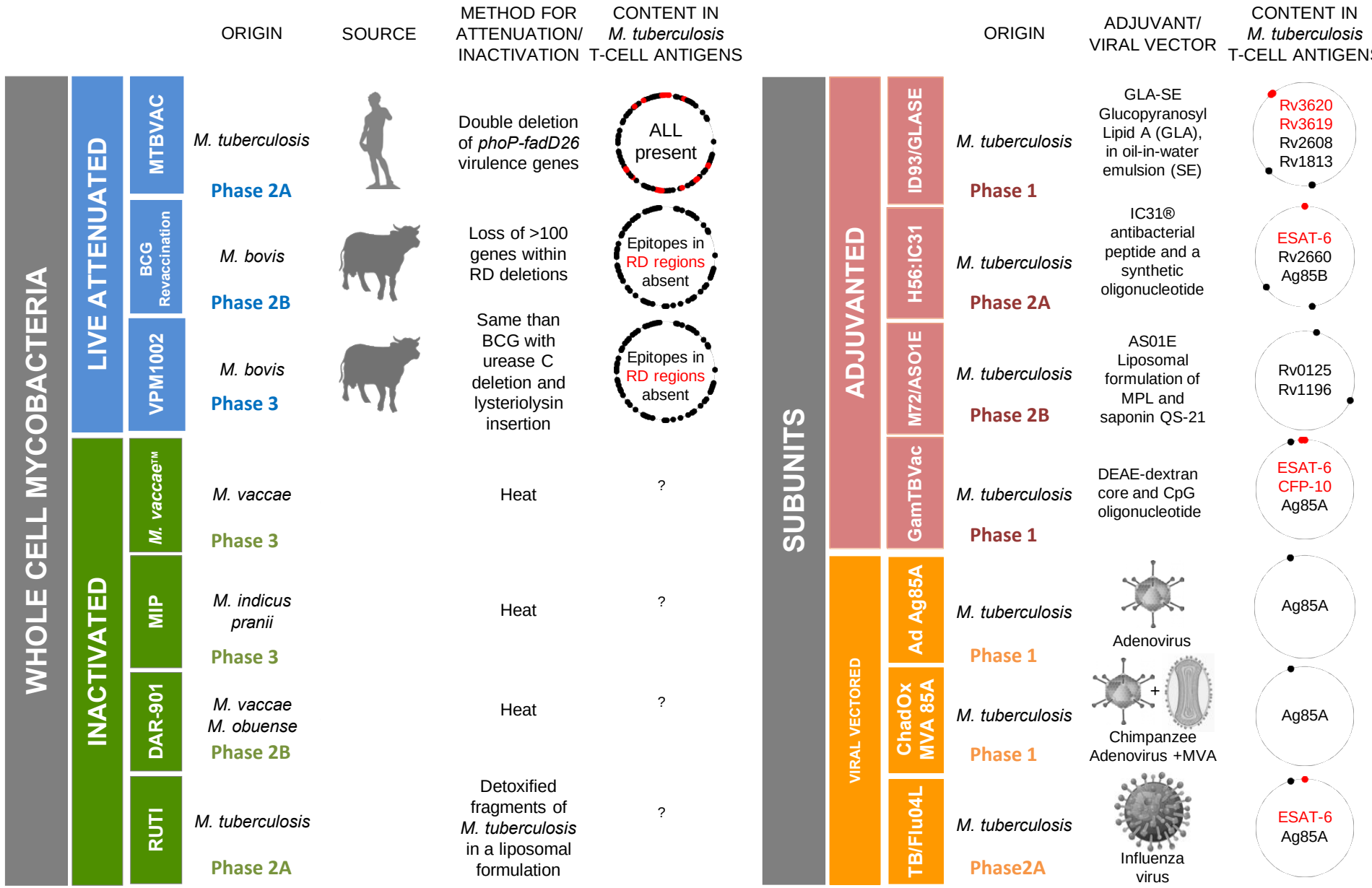
Global advocacy efforts

→ drive demand, funding, implementation and uptake of a new, effective TB vaccine

Study participants and their communities
Investigators and study teams
Sponsors and funders
Collaborators

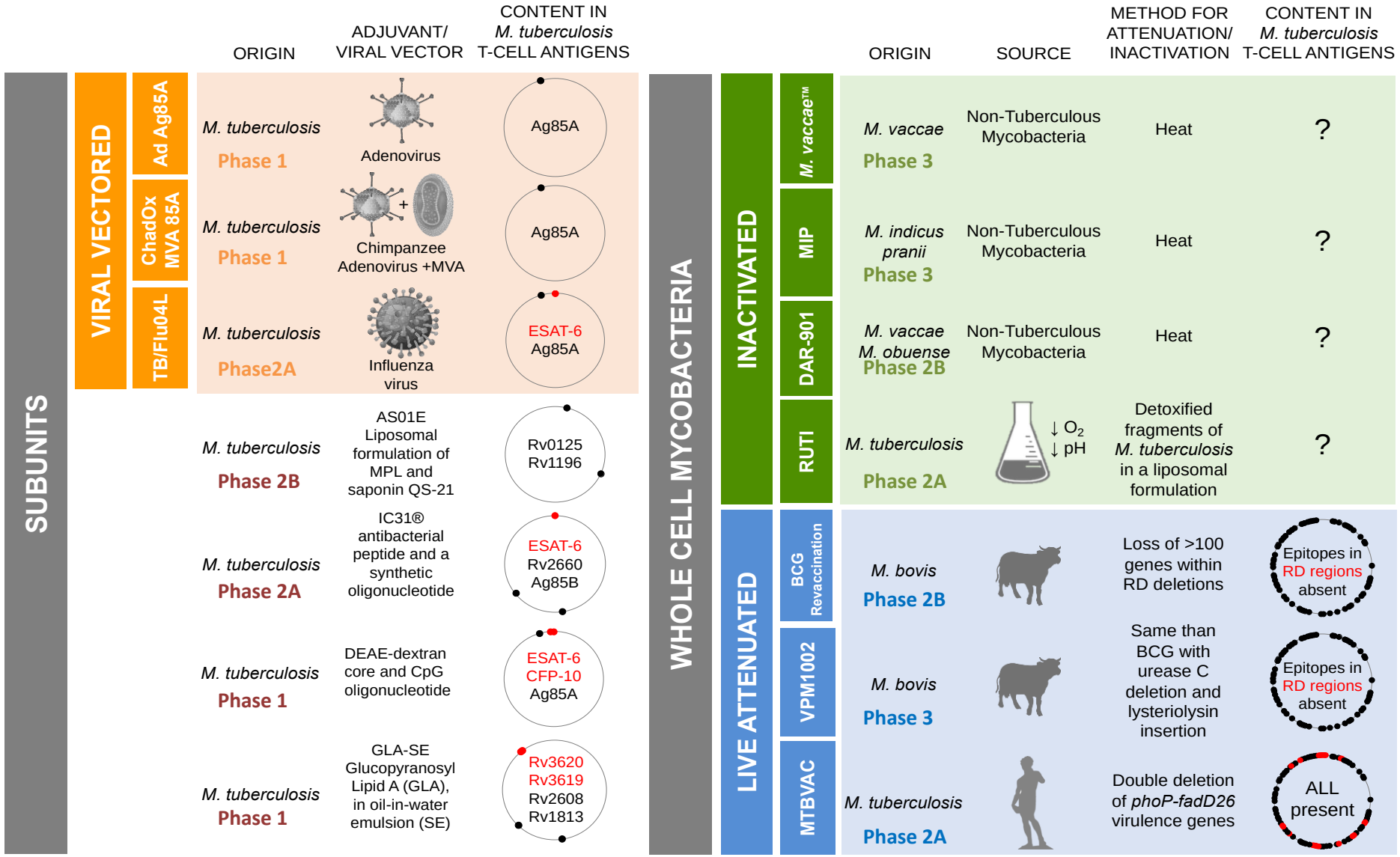
EXTRA SLIDES

DIVERSITY OF THE PIPE LINE OF TB VACCINE CANDIDATES IN CLINICAL TRIALS



Slide courtesy Carlos Martin, Update on TB Vaccine Pipeline, Applied Sciences April 2020

DIVERSITY OF CANDIDATES IN CLINICAL TRIALS



Courtesy Carlos Martin
Update on TB Vaccine Pipeline , Applied Sciences 2020