New Tuberculosis Vaccines: rising opportunities

Johan Vekemans

WHO Initiative for Vaccine Research

November 2019

La Miseria

Cristóbal Rojas

1886

STATUS OF THE TUBERCULOSIS EPIDEMIC

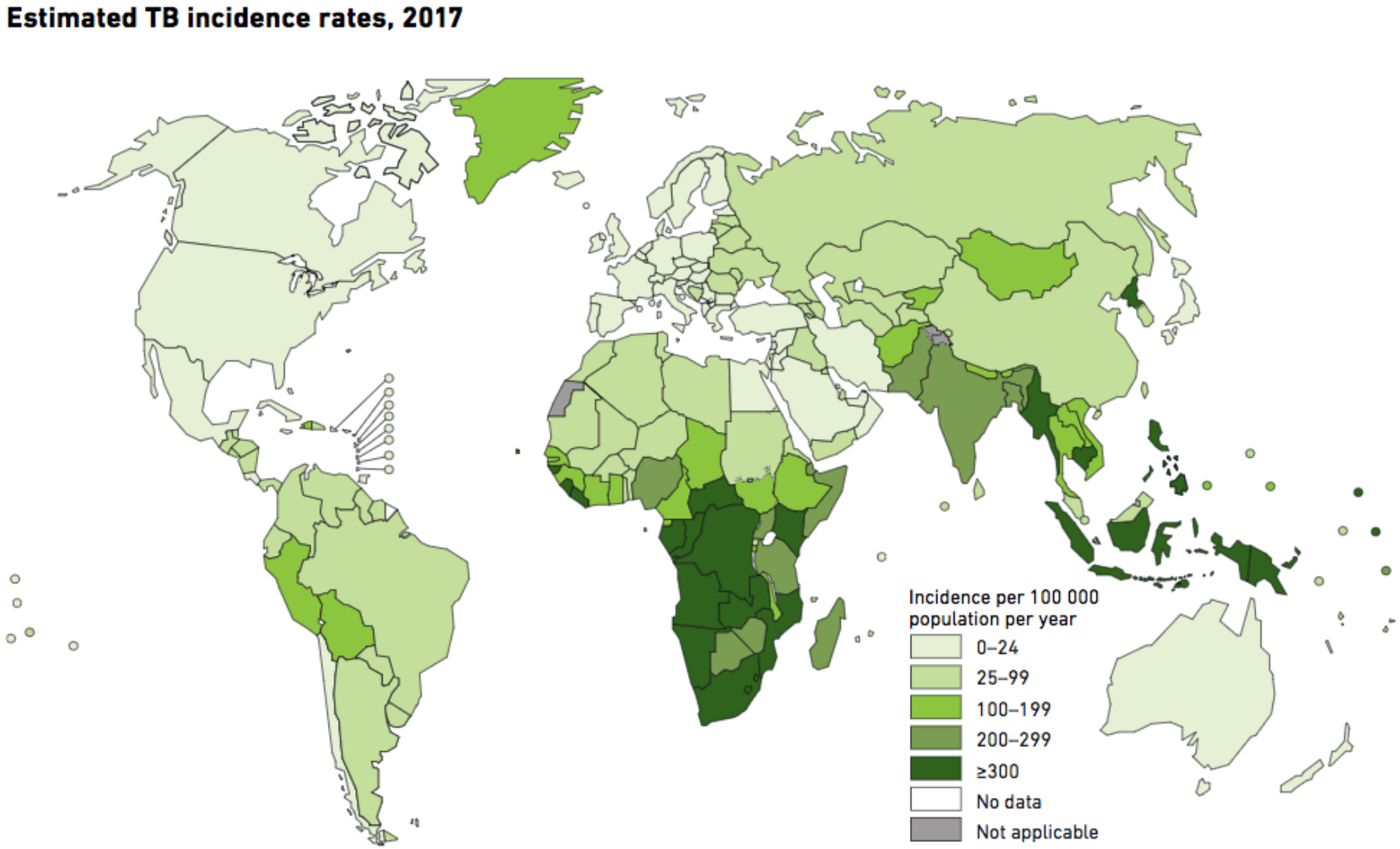
World Health Organization

Global Tuberculosis Report 2018

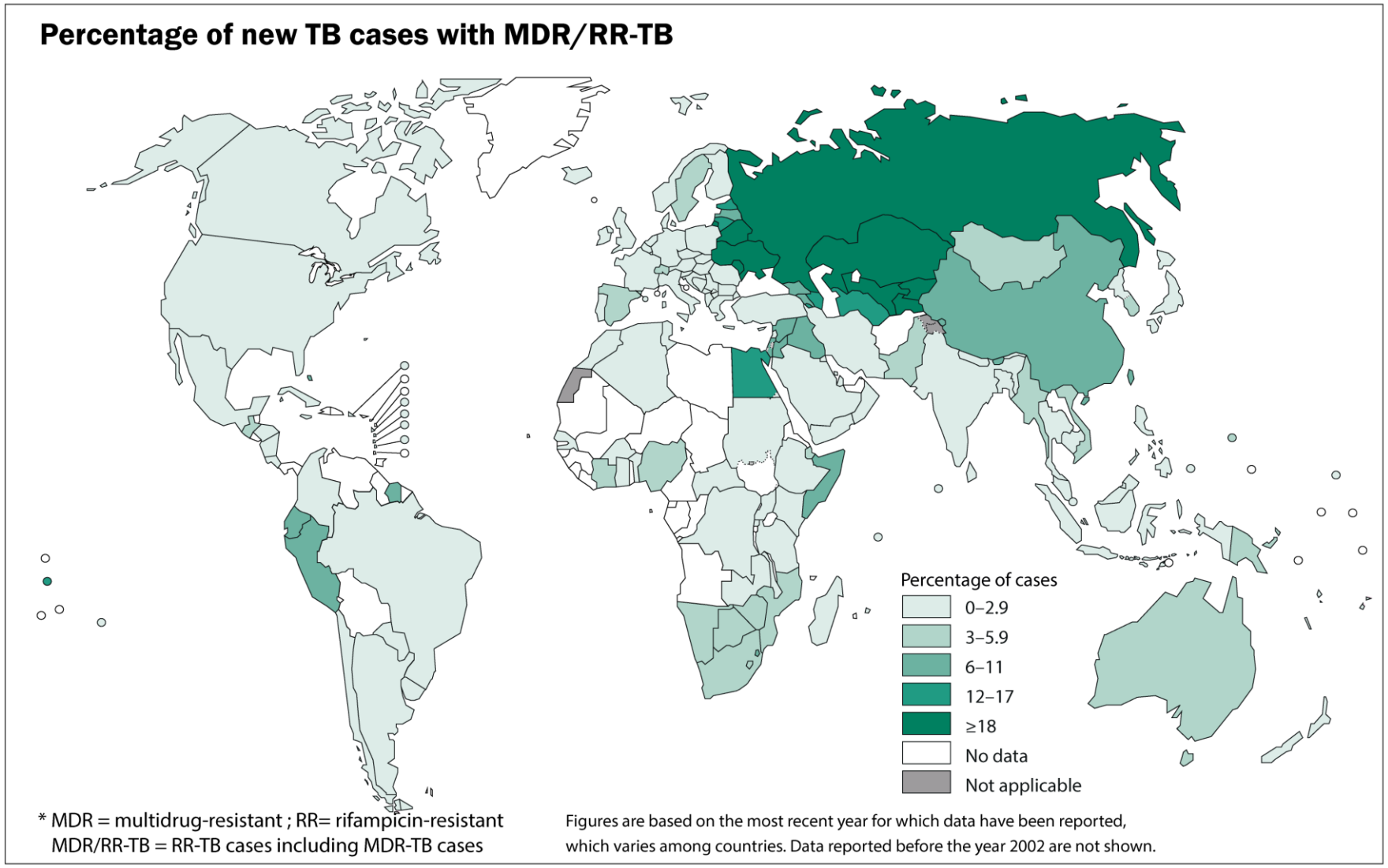
Geographic disparities

World Health Organization

- 1/3 of world population infected
- After infection, 10 % will develop TB



TB and AMR



any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2017*. WHO, 2017.

World Health Organization

BCG, the world's most widely used vaccine

World Health Organization

About one century old

Different strains used

Protective against pediatric TB ; durable protection in adolescence?

No evidence of impact against adult TB

Protection differs according to geographical settings

Not recommended for safety in HIV-infected

Some evidence of non-specific effects: needs better characterization

Albert CALMETTE and Camille GUERIN
Institut Pasteur, Lille

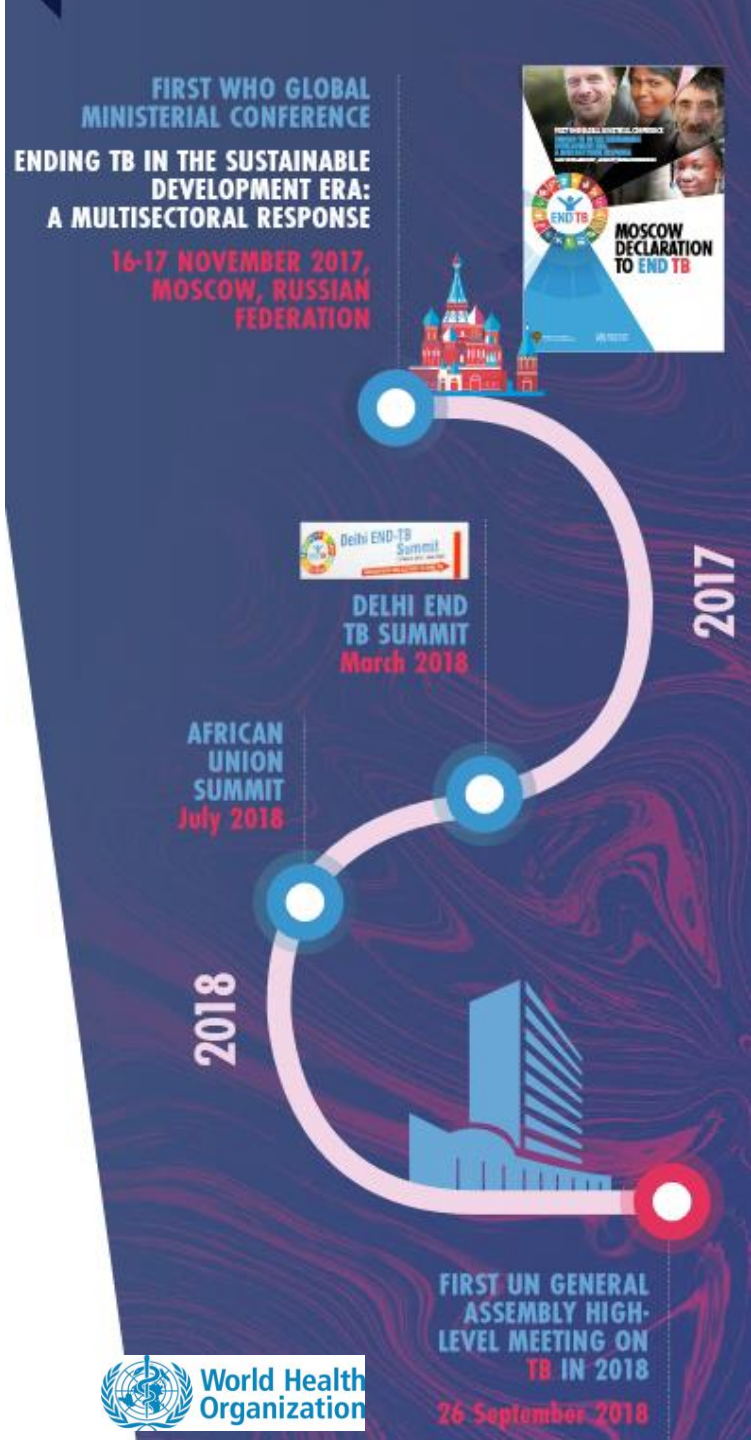
A better vaccine is needed

GLOBAL COMMITMENTS TO END TB

Vision: A world free of TB
Zero TB deaths, Zero TB disease, and Zero TB suffering

Goal: End the Global TB Epidemic (<10 cases/100,000 pyr)

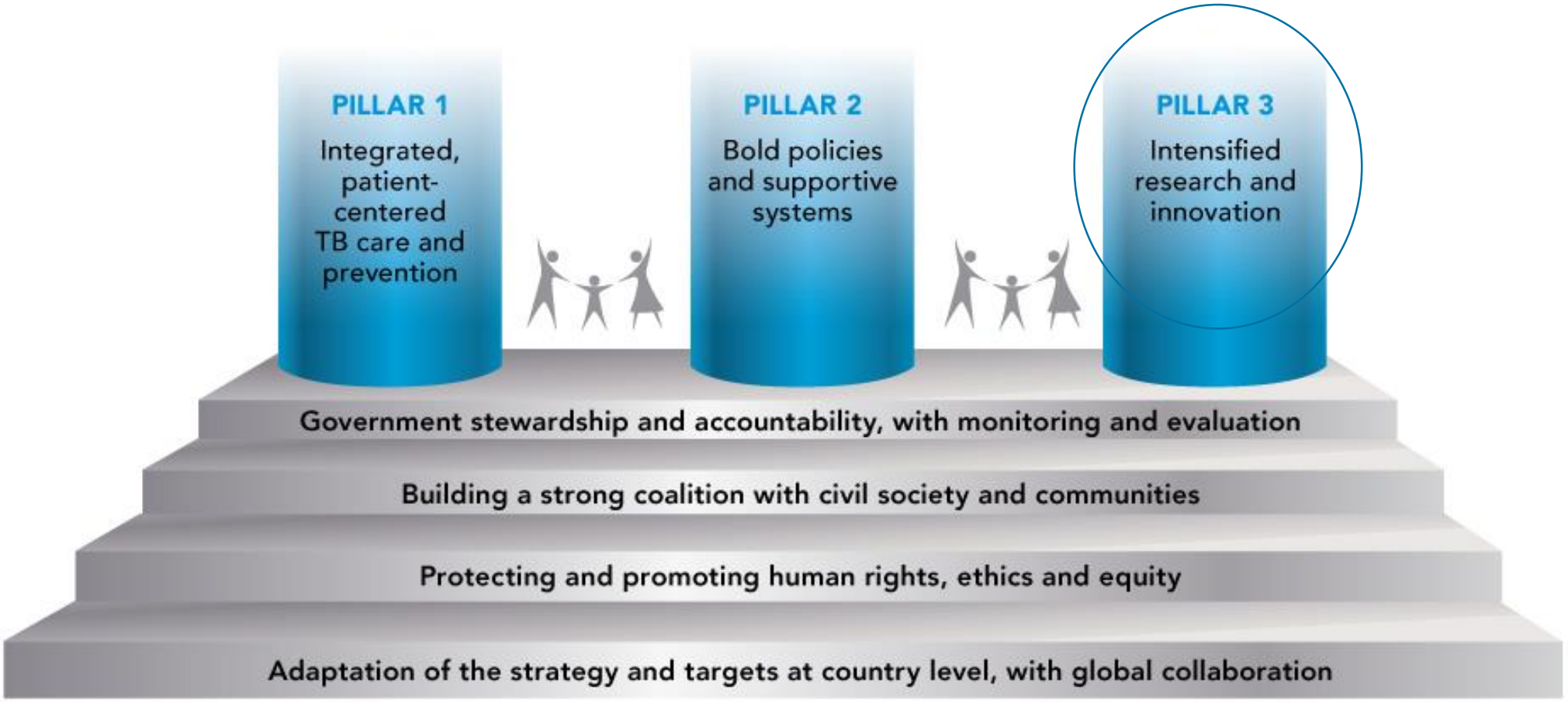
INDICATORS	MILESTONES		TARGETS
	2020	2025	2030
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	**90%**
Reduction in TB incidence rate compared with 2015 (%)	20%	50%	**80%**
TB-affected families facing catastrophic expenditures due to TB (%)	Zero	Zero	**Zero**



GLOBAL TB PROGRAMME

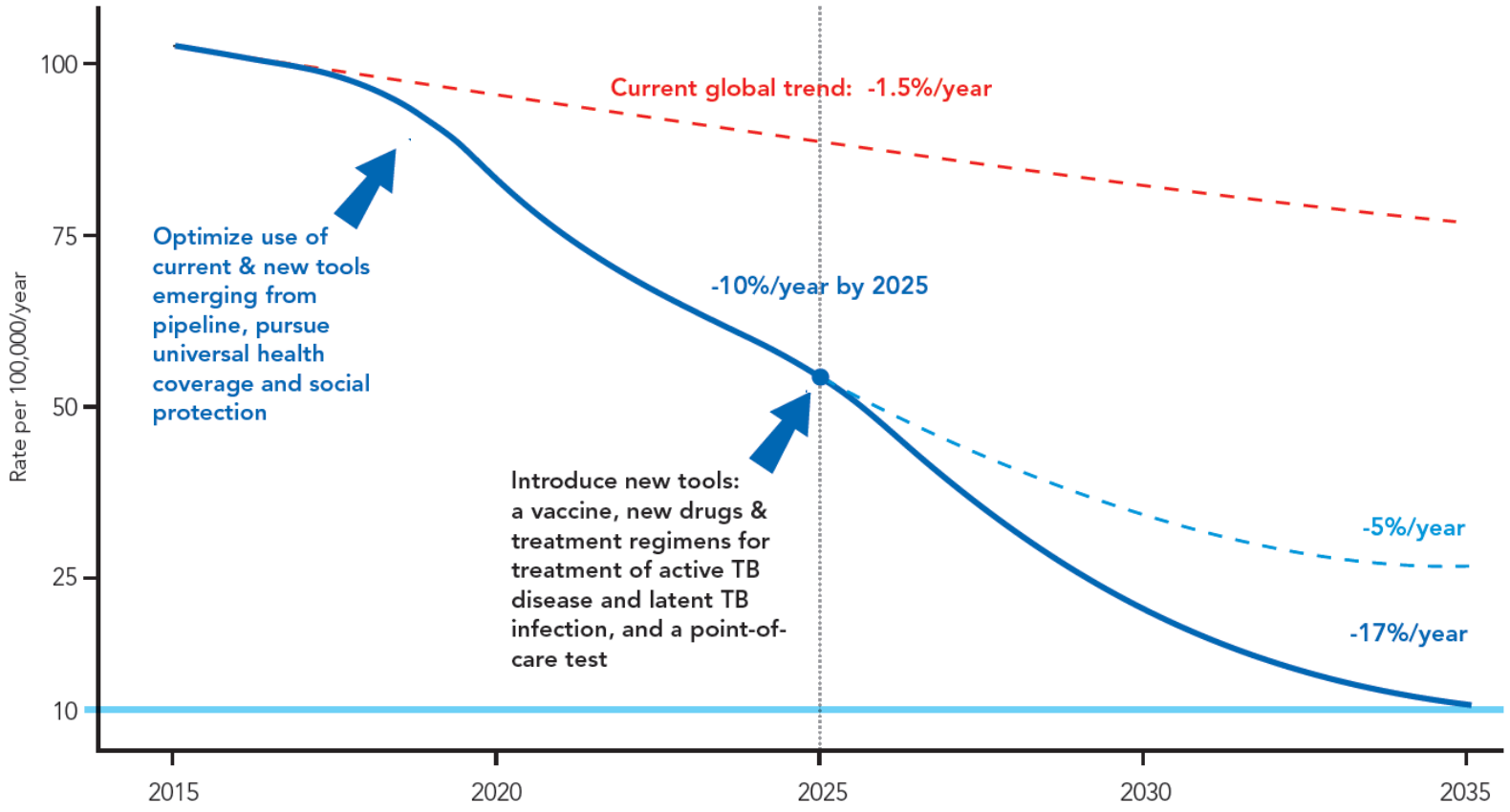
THE END TB STRATEGY

The End TB Strategy: 3 pillars and 4 Principles



Research is critical to
break the trajectory of the TB epidemic

World Health Organization



No new vaccine, no END TB

Is a new TB vaccine possible?

BCG protects neonates against pediatric TB

Following *Mycobacterium tuberculosis* infection, 90% people control infection

Immune correlates of risk are emerging

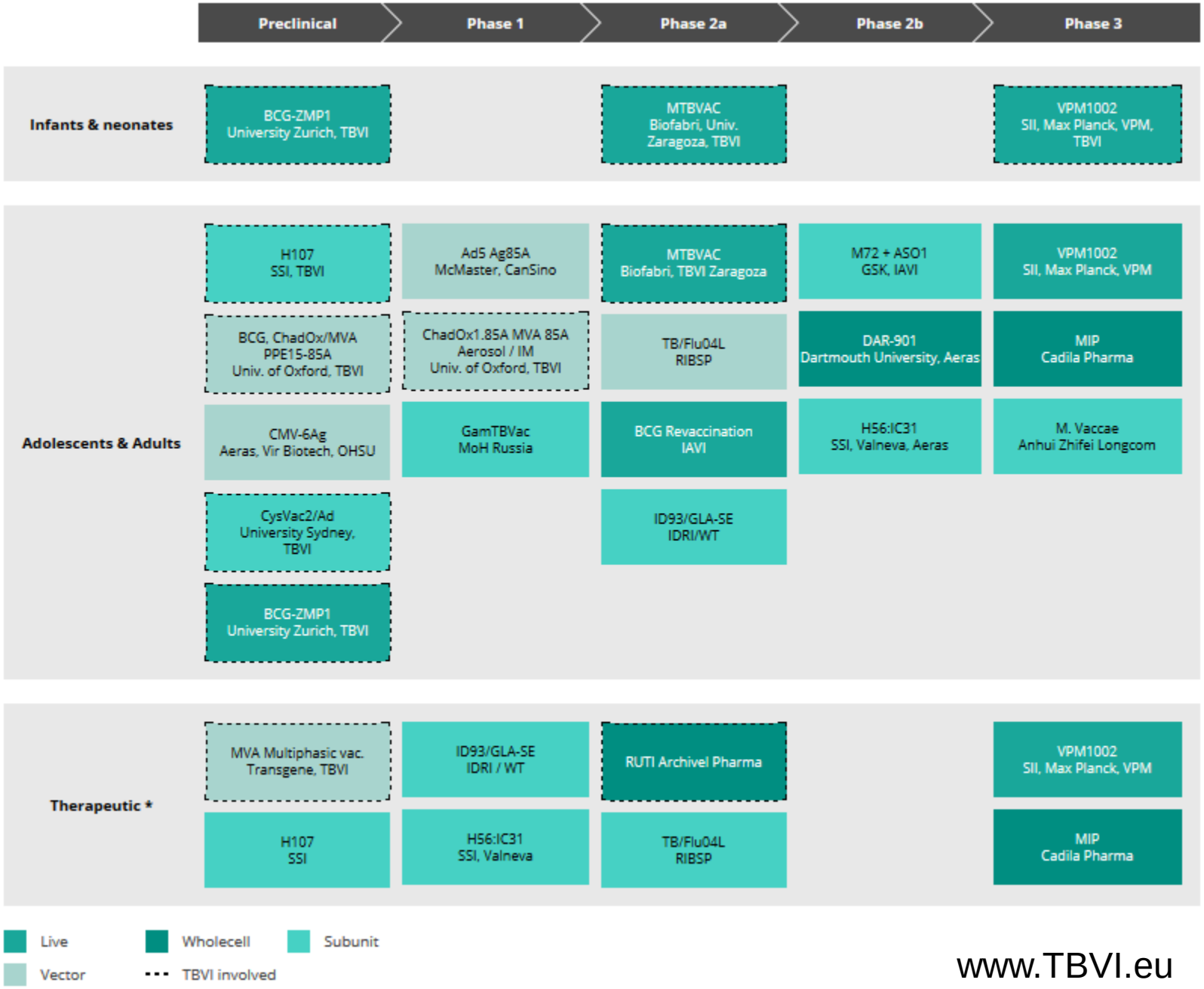
Recent evidence from clinical studies of candidate vaccines

Value of animal models as predictors of human results ?

Limited understanding of protective immunity (high heterogeneity)

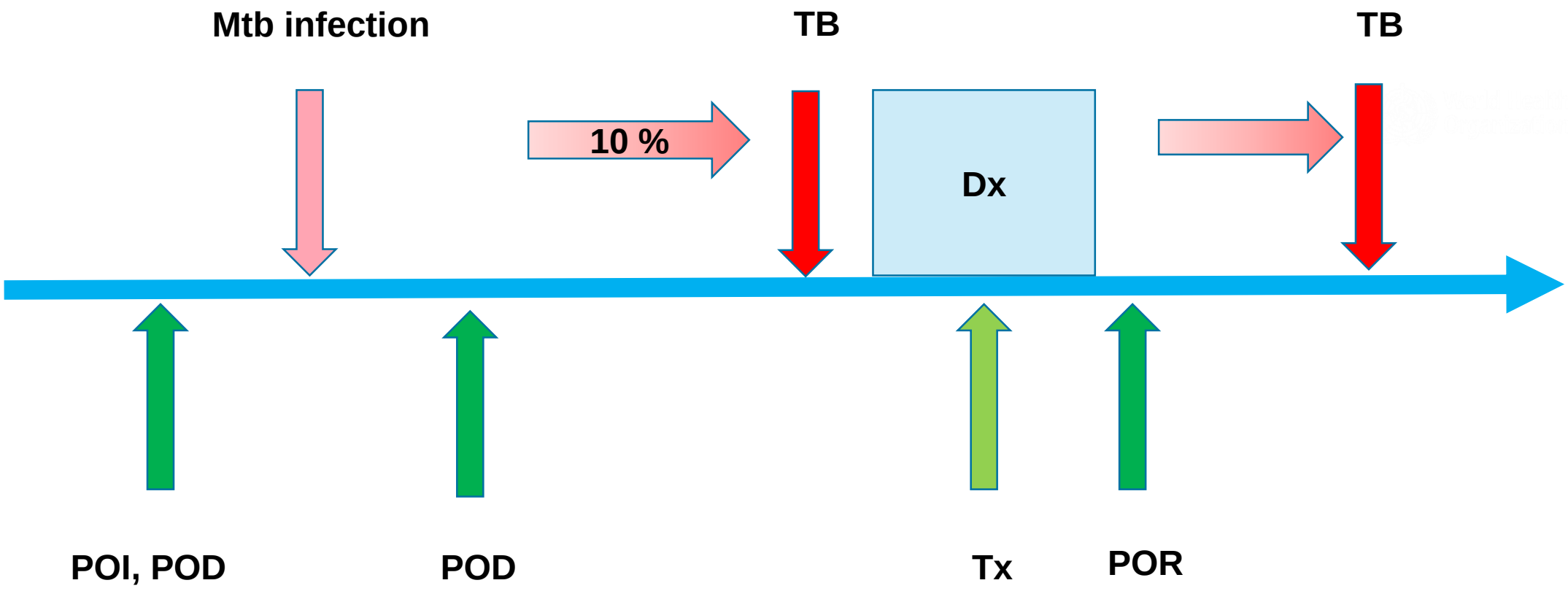
Failed business models to support product development and share financial risk

TB vaccine pipeline



www.TBVI.eu

Clinical efficacy trial endpoints



Prevention of Infection (POI), Disease (POD), Recurrence/re-infection (POR)

WHO strategic priorities

Developing a safe, effective and affordable TB vaccine for adolescents and adults

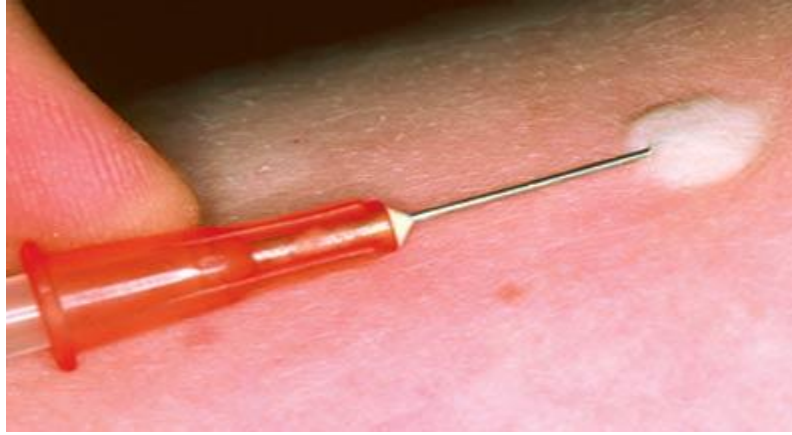
- 50% or greater efficacy in preventing confirmed pulmonary TB
- Protect both subjects with and without past *Mtb* infection
- Protective in different geographical regions and latitudes

Developing an affordable TB vaccine for neonates and infants

- with improved safety and efficacy as compared to BCG

WHO Preferred Product Characteristics for New Tuberculosis Vaccines

New TB Vaccines : Preferred Characteristics



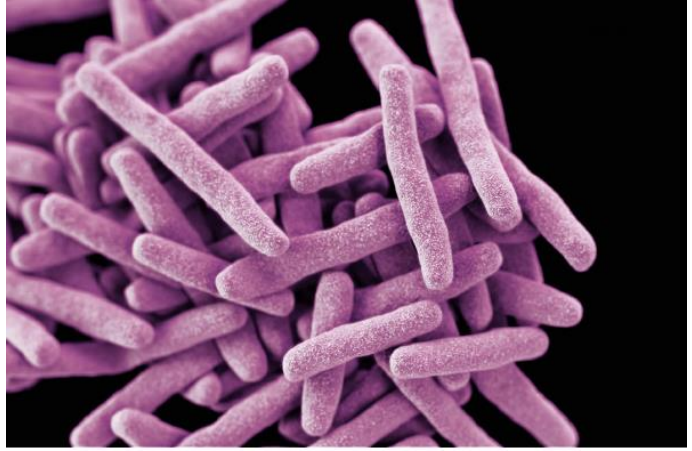
PROGRAMMATIC SUITABILITY

- Innovation related to ease of administration and thermostability
- Improved production process relative to current BCG

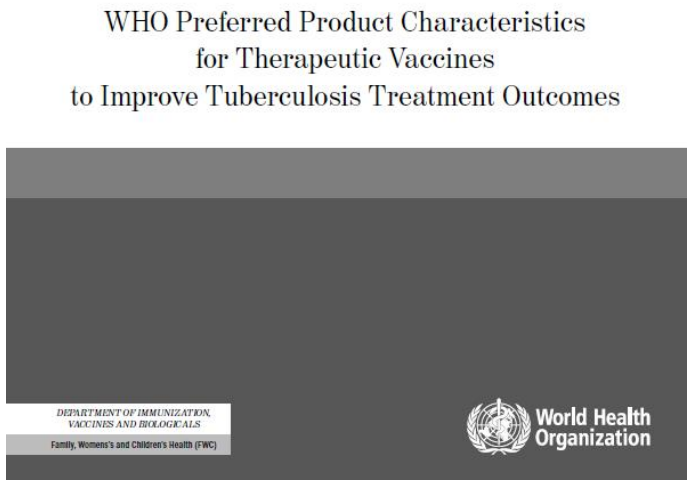
VALUE PROPOSITION

- The vaccine should be cost-effective and price should not be a barrier to access
- Evaluation of the vaccine impact on the TB epidemics in general, and on drug-resistant TB specifically, on co-morbidities (HIV), on health systems and the economy, is encouraged (role of modelling)

Vaccines for improvement of TB treatment outcome

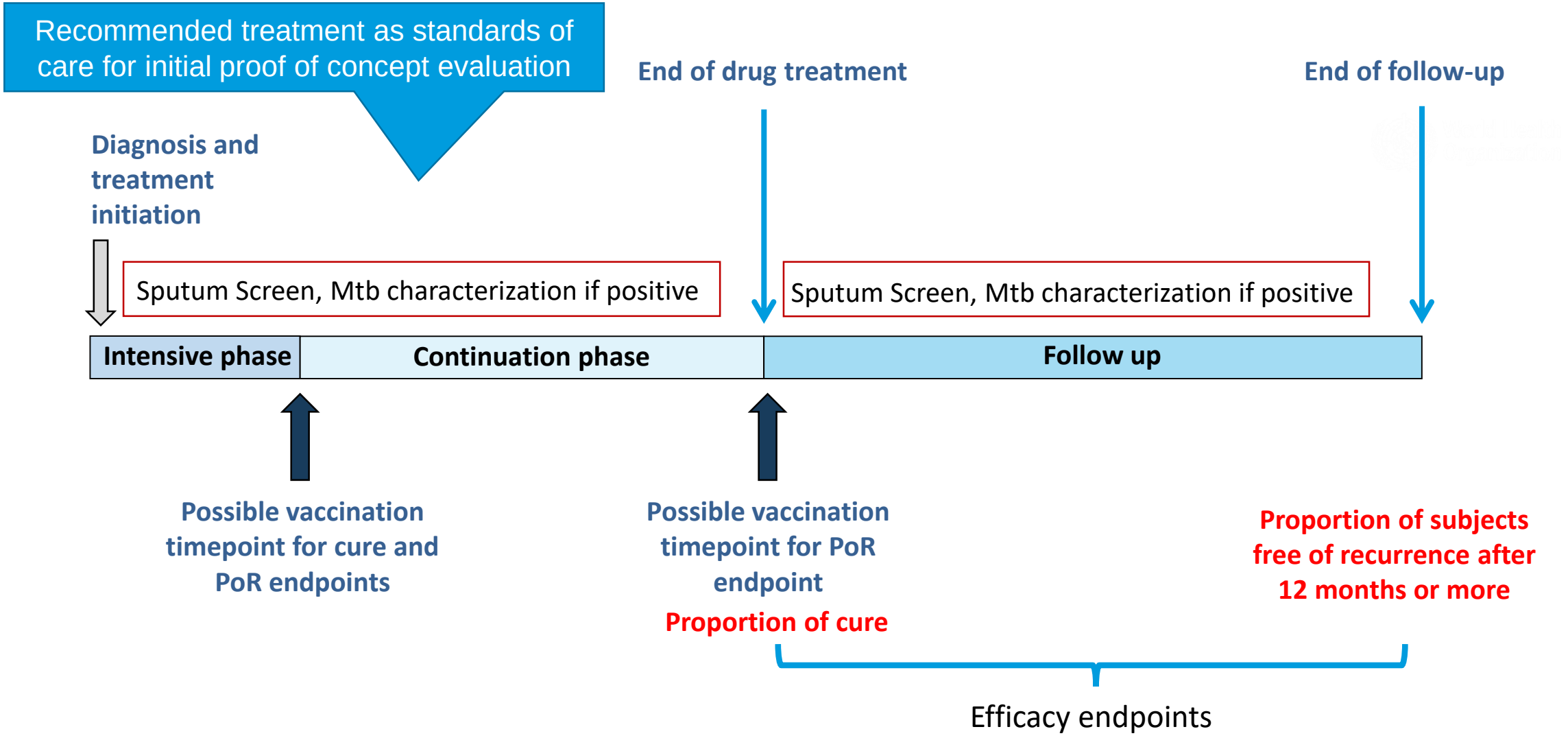


- Aim to reduce treatment failure (increase cure rates), reduce frequency of relapse, simplify and shorten treatment regimen
- Specific interest in drug-R TB



- Opportunity to also reduce progression to TB in recently exposed contacts, in TB infection test converters

Vaccines for improvement of TB treatment outcome



AERAS

SANOFI

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†

University of Cape Town · iYunivesithi yaseKapa · Universiteit van Kaapstad

DESMOND TUTU HIV FOUNDATION

BILL & MELINDA GATES foundation

satvi

Published 12th July 2018.
Slides courtesy Dr Nemes

The vaccines

BCG

- BCG has variable efficacy
- Routinely administered to newborns (here 2-8 x 10^5 CFU BCG SSI, ID)
- Never tested in a RCT for POI

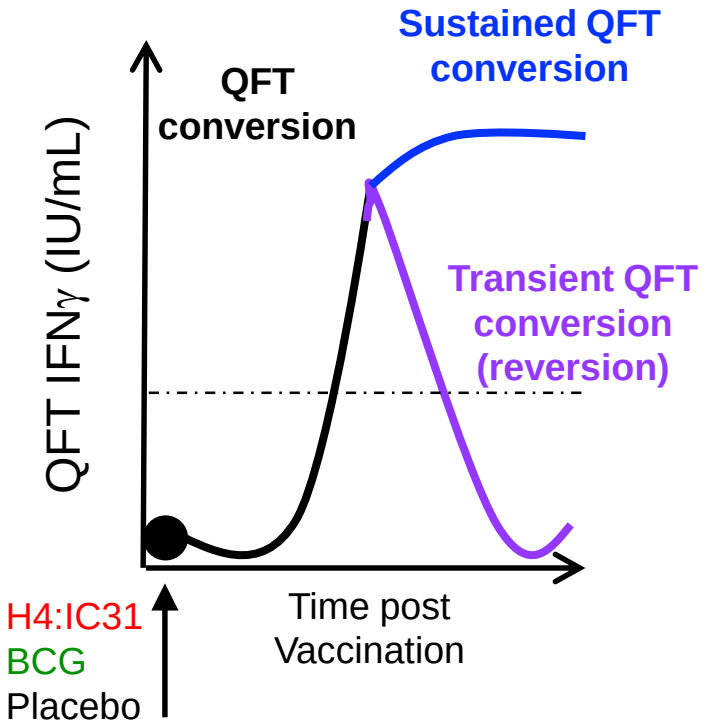
H4:IC31®

- H4:IC31® (SSI, Sanofi Pasteur): H4 (15mg fusion prot: Ag85B + TB10.4) + IC31 (500 nm, Valneva) IM.
- Designed as BCG boost vaccine
- H4:IC31® protective in animal models *(Aagaard 2009; Elvang 2009; Billeskov 2012)*, safe and immunogenic in humans *(Geldenhuys 2015; Norrby 2017)*
- Does not cross-react with QFT

Nemes, Geldenhuys, Rozot et al, NEJM 2018

H4 or BCG revaccination of M.tb-uninfected adolescents

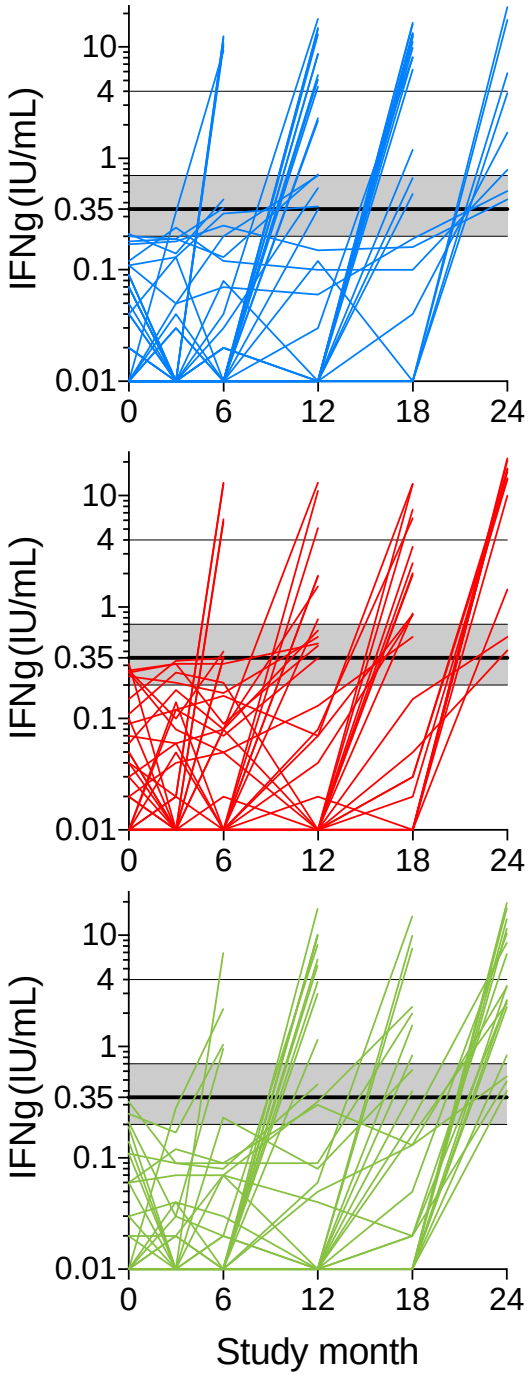
- **H4 + IC31**: fusion protein of Ag85B+TB10.4 in IC31
- **990 QFT- (HIV-) adolescents** randomized in RSA
- **QFT** every 6 months
- **2 years** follow-up
- **Primary endpoint:** QFN conversion



satvi DESMOND TUTU HIV FOUNDATION

Nemes, Geldenhuys, Rozot et al, NEJM 2018

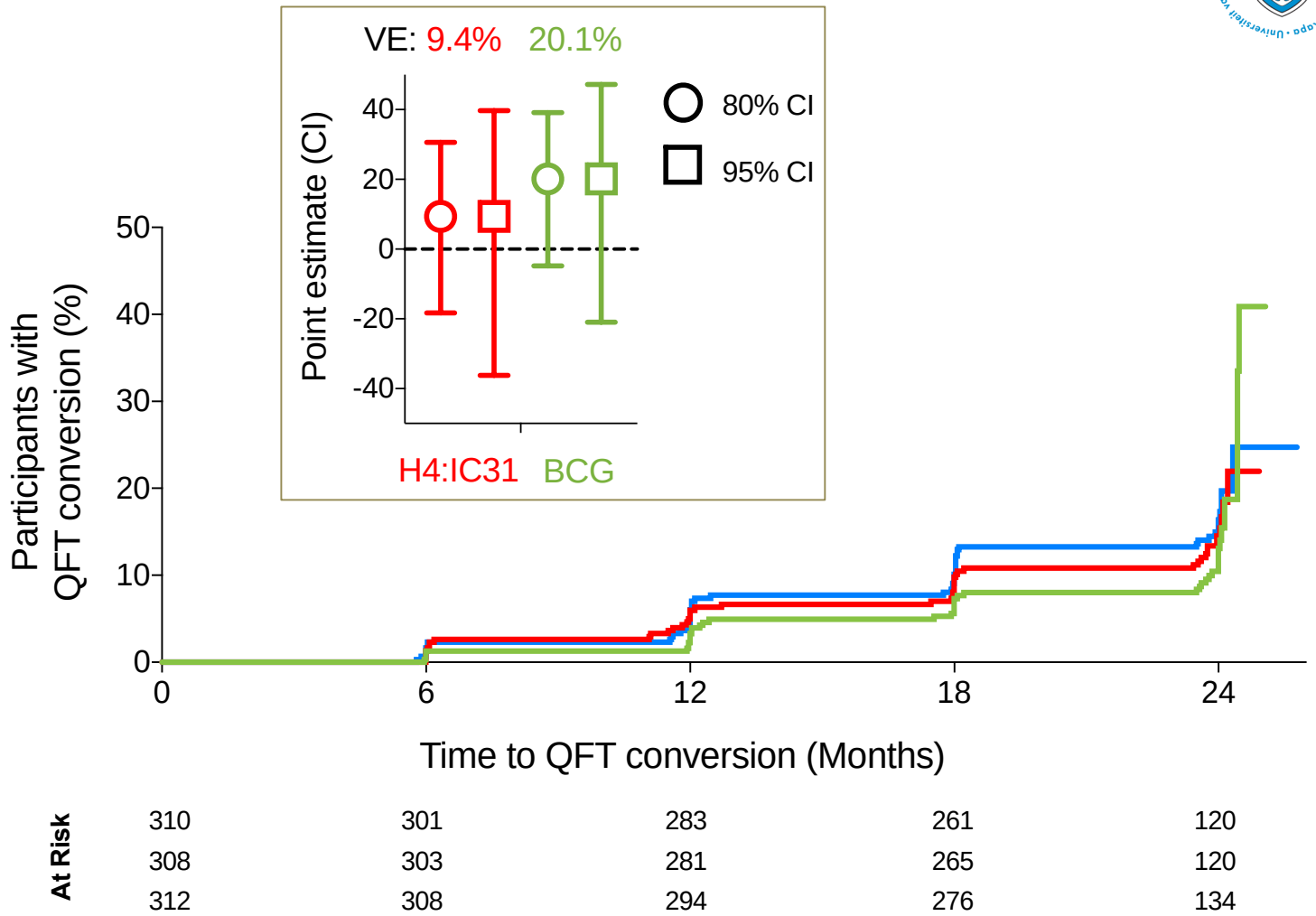
Efficacy: QFT conversion



Placebo
n=49/310
(16%)

H4:IC31
n=44/308
(14%)

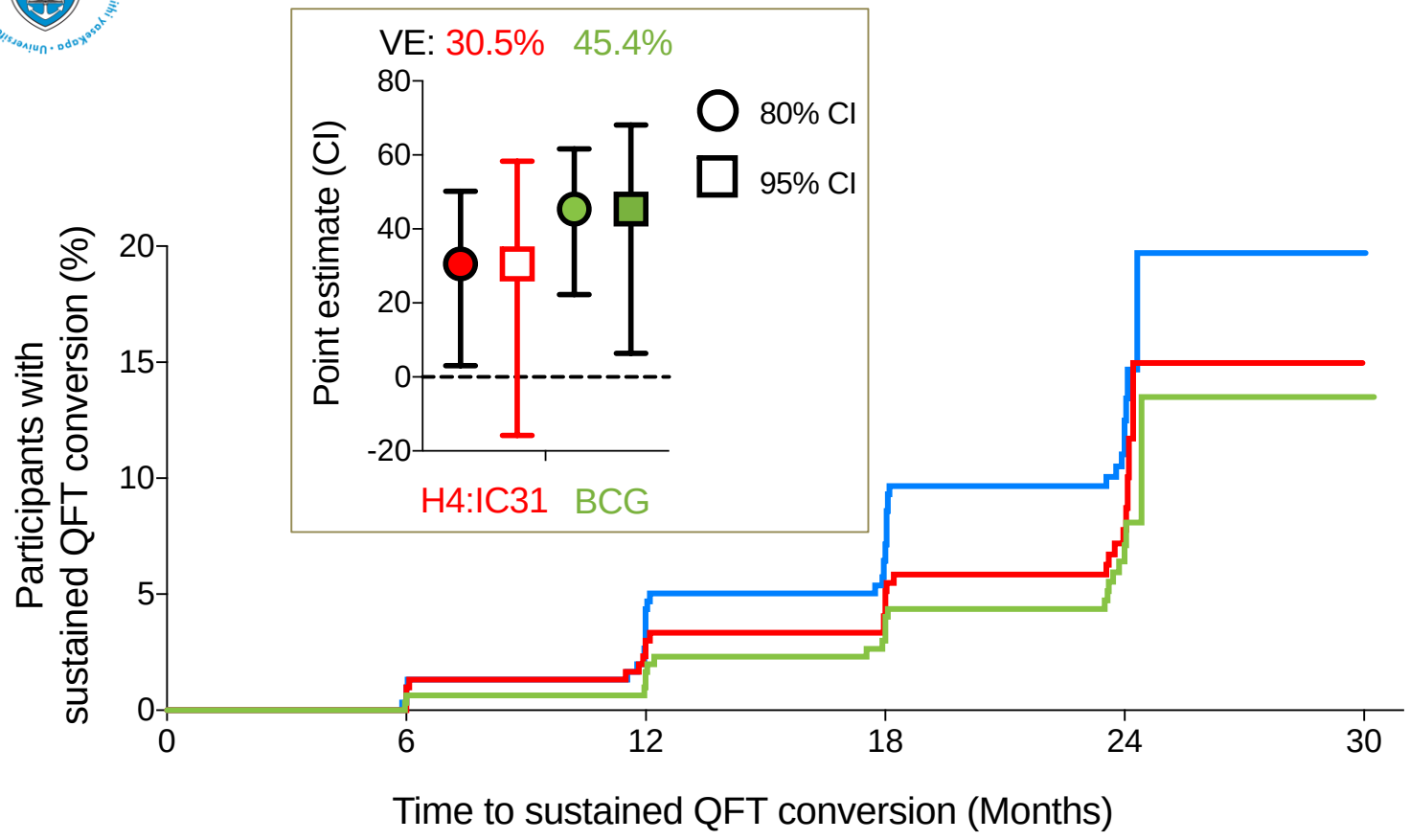
BCG
n=41/312
(13%)



At Risk				
310	301	283	261	120
308	303	281	265	120
312	308	294	276	134

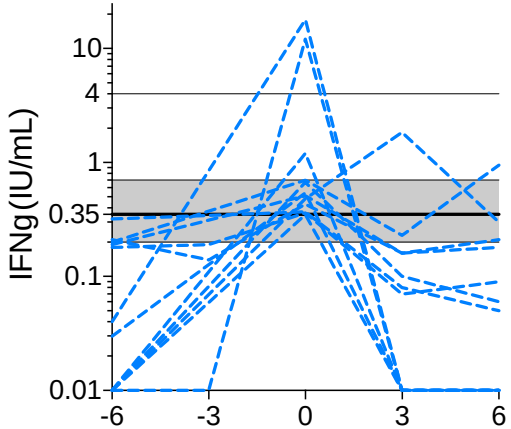
Nemes, Geldenhuys, Rozot et al, NEJM 2018

Efficacy: Sustained QFT conversion

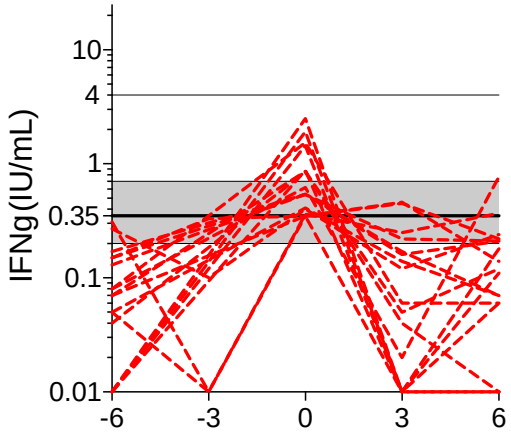


At Risk					
	310	302	287	263	122
	308	303	288	268	124
	312	308	297	281	136

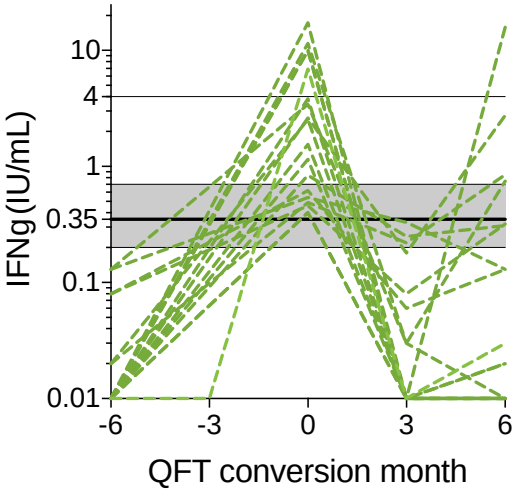
Placebo
n=12/48
(25%)



H4:IC31
n=17/42
(40%)



BCG
n=18/39
(46%)

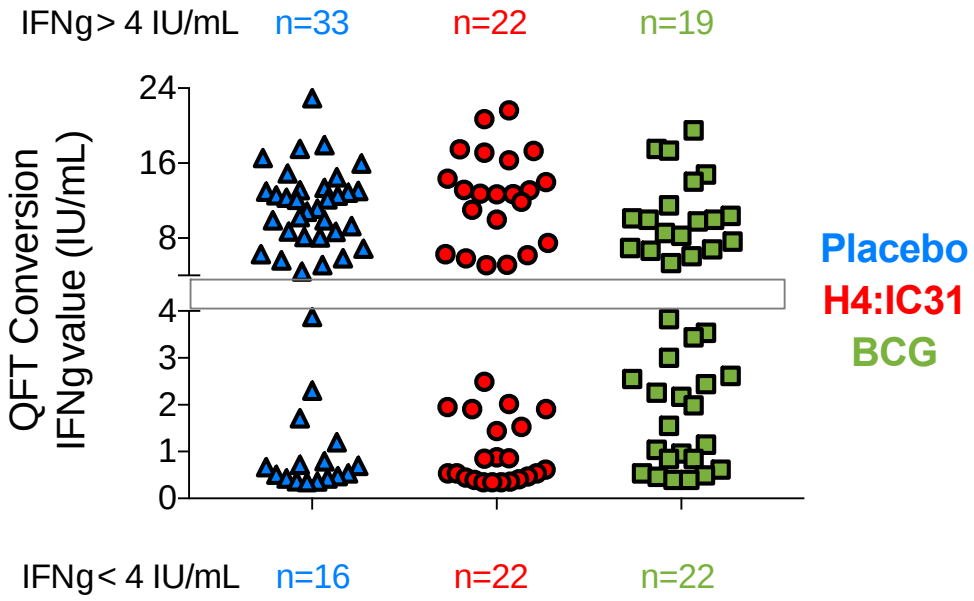


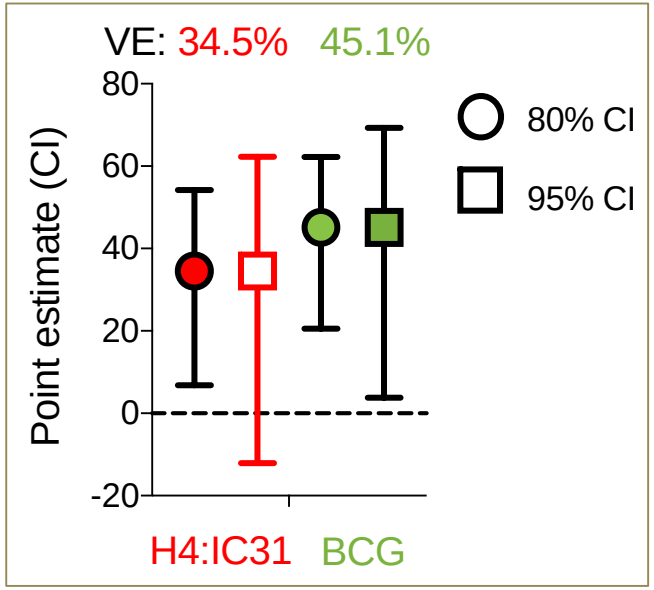
Nemes, Geldenhuys, Rozot et al, NEJM 2018

Efficacy exploratory endpoint: QFT conversion > 4 IU/mL

Higher risk of TB in children and adults converting QFT > 4.0 IU/mL

Andrews et al, Lancet Resp Med 2017
Winje et al., Thorax 2018





Rates of participants with QFT conversions > 4 IU/mL

Nemes, Geldenhuys, Rozot et al, NEJM 2018

BCG Revaccination: future prospects ?

THE LANCET

Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi

Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial

Laura C Rodrigues, Susan M Pereira, Sergio S Cunha, Bernd Genser, Maria Yury Ichihara, Silvana C de Brito, Miguel A Hijjar, Ines Dourado, Alvaro A Cruz, Clemax Sant'Anna, Ana Luiza Bierrenbach, Mauricio L Barreto

Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: Second report of the BCG-REVAC cluster-randomised trial

Mauricio L. Barreto[a,*], Susan M. Pereira[a], Daniel Pilger[b], Alvaro A. Cruz[c], Sergio S. Cunha[d], Clemax Sant'Anna[e], Maria Y. Ichihara[a], Bernd Genser[a,f], Laura C. Rodrigues[b]

Large RCT showed no efficacy of BCG revaccination

Karonga BCG trial, Malawi
BCG-REVAC, Brazil

No assessment TST/IGRA status at vaccination
Unable to stratify VE by IGRA-

BMGF-funded repeat trial in RSA

M72/AS01$_E$ vaccine candidate

World Health Organization

The NEW ENGLAND JOURNAL of MEDICINE

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

The NEW ENGLAND JOURNAL of MEDICINE

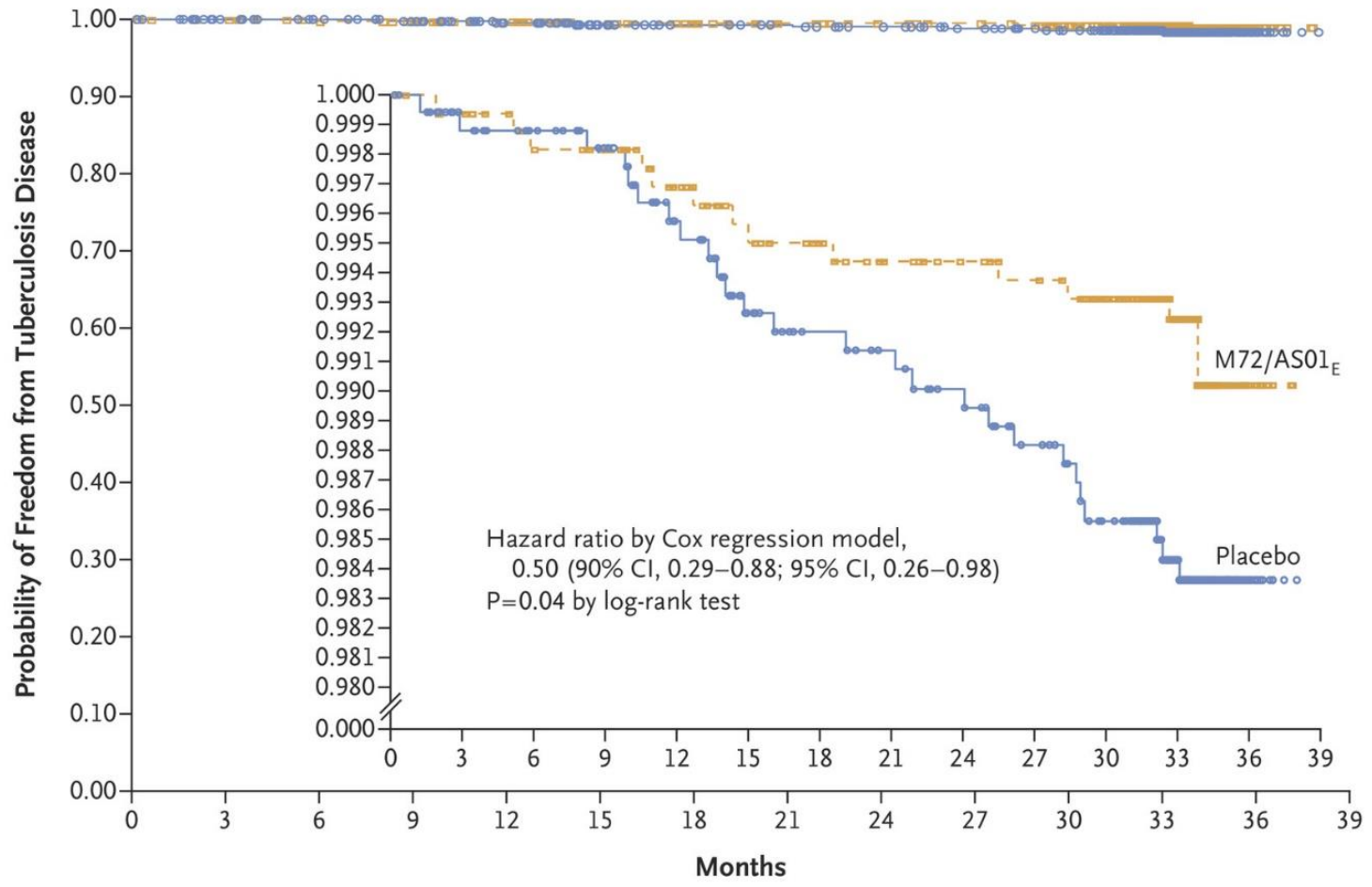
ORIGINAL ARTICLE

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

- HIV negative healthy adults (18-50 yrs)
- 3,573 vaccinated from South Africa, Kenya and Zambia
- MTB infected: positive by QuantiFERON but negative at Xpert MTB/RIF
- design: double-blind, randomized (1:1)
- 2 doses 1 month apart

M72/AS01 protection against pulmonary TB



No. at Risk													
M72/AS01E	1626	1621	1614	1609	1592	1580	1573	1566	1561	1557	1542	1468	12
Placebo	1663	1650	1642	1632	1610	1586	1576	1571	1564	1553	1539	1460	19

Over 3 years follow-up:

VE 50% (90% CI 12-74%)

Trend towards higher point estimate of VE with increasing endpoint specificity, more advanced disease

No evidence of waning protection

WHO consultation on M72/AS01 pathway forward

World Health Organization

- GSK is seeking a partner/s to take license of M72 from GSK to develop, license, manufacture, be liable for, and supply M72 for the 'developing world'. Limited number of doses currently available. Process improvement needed for Phase 3 material

- Major risk of undue delays

- WHO preference:

  - Progression to Phase 3 trial in a population of teenagers/young adults in settings with high incidence
  - Accelerated licensure with narrow indication (prevention of pulmonary TB in young adults in high endemic settings)
  - Parallel proof-of-concept evaluation for other indications (HIV+, pediatric, contacts, PoR) and schedule optimization ; generate evidence in LTBI /-/
  - Post-licensure investigations, country-led

- Need for innovative financing, informed by full public value assessment

World Health Organization

LANCET INFECT DIS 2019

A new tuberculosis vaccine: breakthrough, challenges, and a call for collaboration

Johan Vekemans, Nebiat Gebreselassie, Matteo Zignol, Martin Friede, Tereza Kasaeva, Soumya Swaminathan
Immunization, Vaccines and Biologicals (JV, MF), and Global Tuberculosis Programme (NG, MZ, TK), World Health Organization, 1211 Geneva, Switzerland
vekemansj@who.int

Tuberculosis is the deadliest infectious disease in human history, and remains the leading cause of death from a single infectious agent globally. WHO estimates that tuberculosis caused illness in 10 million people and claimed 1·6 million lives in 2017 alone.[1,2] Currently, tuberculosis is responsible for a quarter of annual deaths due to antimicrobial resistance, and remains the primary cause of death among people with HIV.[1,3] Overcoming the disease's destructive potential will require a mix of incremental progress and giant leaps forward. The End TB Strategy, developed by WHO in 2014, set out ambitious goals and milestones to end the epidemic by reducing incidence by 80% and mortality by 90% by 2030, relative to 2015, in the context of the Sustainable humans—coupled with the need for a large sample size to show vaccine efficacy during later stages of vaccine development have served as additional disincentives for researchers and study sponsors.[8]

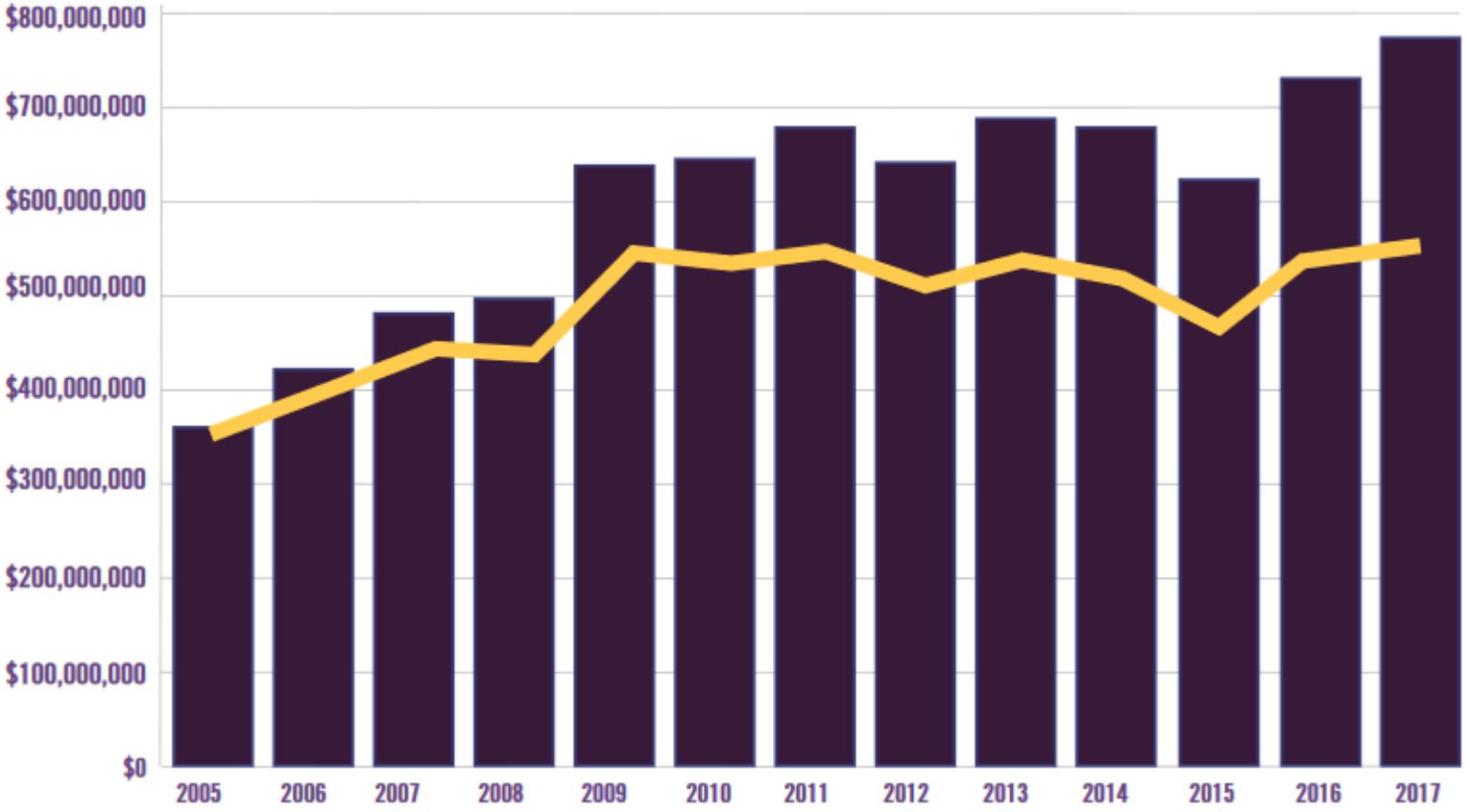
A phase 2b trial conducted in Kenya, South Africa, and Zambia,[9] and published in 2018, showed that M72/AS01$_E$, an experimental tuberculosis vaccine developed by GlaxoSmithKline and Aeras, was significantly protective against tuberculosis disease. Two doses of M72/AS01$_E$, administered 1 month apart to HIV-negative adults with evidence of latent *Mycobacterium tuberculosis* infection, provided 54% protection (90% CI 13·9–75·4; 95% CI 2·9–78·2; p=0·04) against pulmonary tuberculosis, over about 2 years of follow-up. The study, still blinded at an

Downstream pathway success: listen to the community. Build-in country perspectives

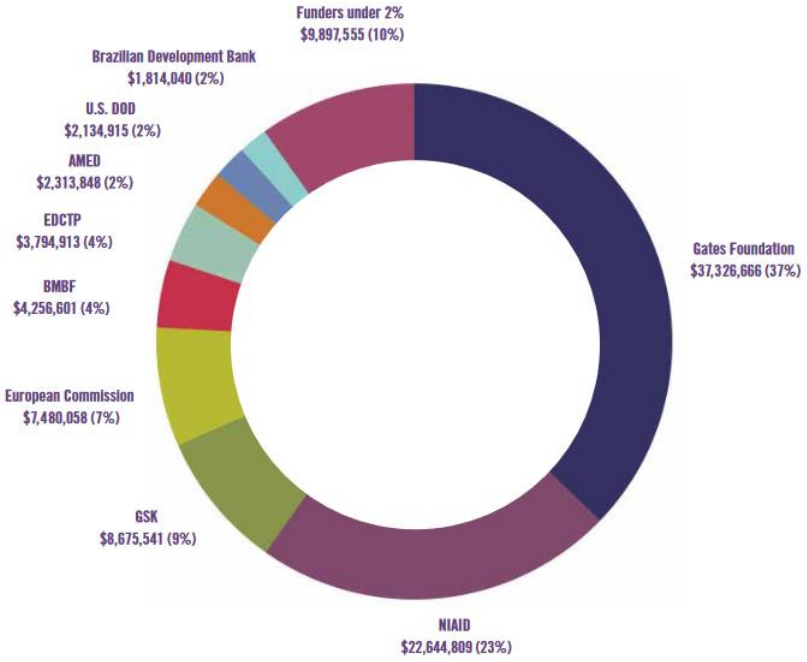
TB research funding trends: the 1.3 billion gap

World Health Organization

Total TB R&D Funding, 2005–2017



Vaccines: $100,338,945



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†

Published 12th July 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

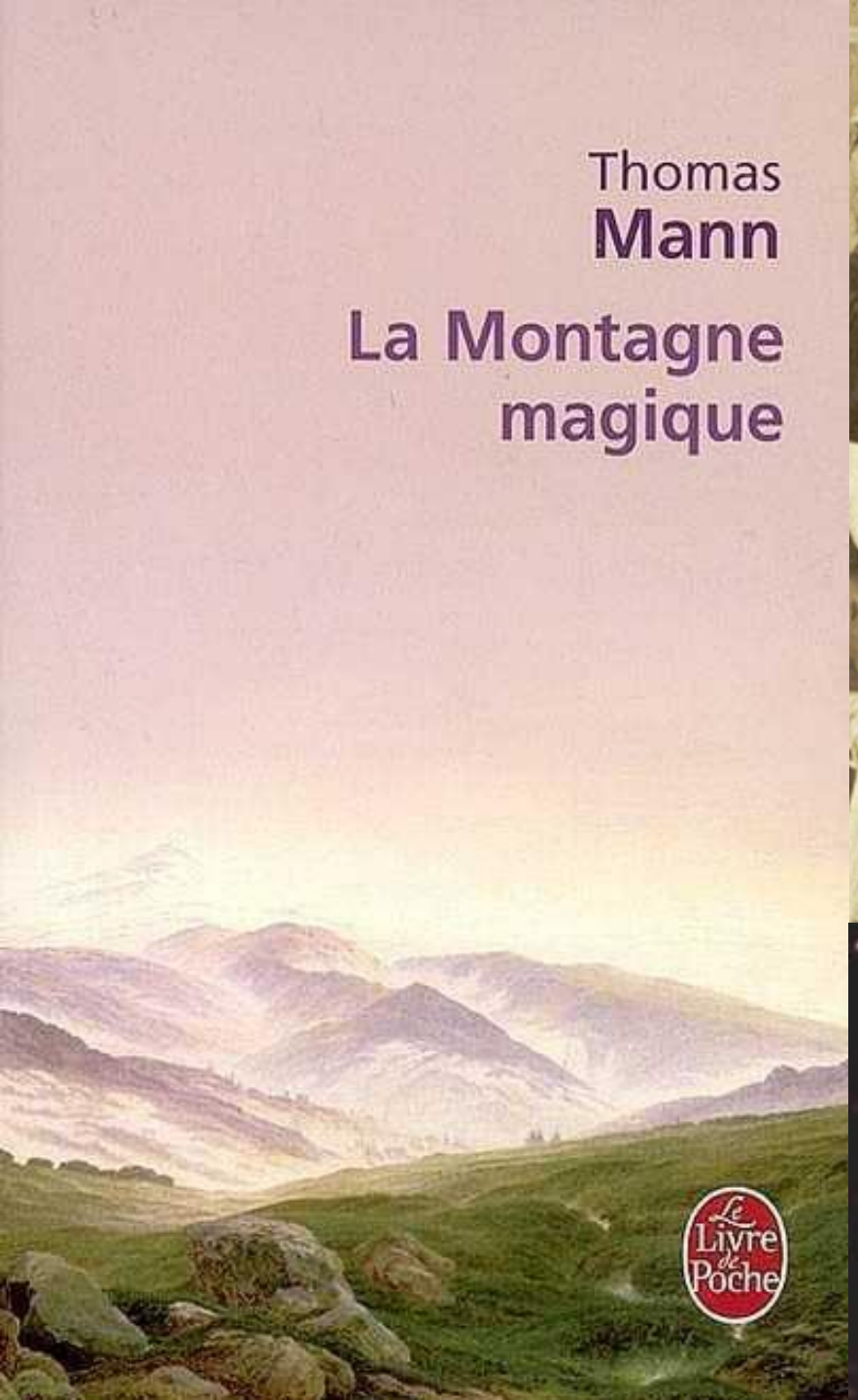
O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts,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

Published 25th September 2018

7 million people got TB

>1 million people died from TB

satvi


Thomas
Mann
La Montagne
magique
Le Livre de Poche

Thank you

World Health Organization