# FROM MALARIA TO COVID-19: A GLOBAL HEALTH PERSPECTIVE

American Society of Clinical Pharmacology & Therapeutics

2019 Annual Meeting

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CEO, Gates Medical Research Institute

March 14, 2019

# / BEGIN WITH THE END IN MIND…OUR TARGET POPULATIONS

# / PROGRESS IN GLOBAL HEALTH

## The world has made substantial progress in child survival since 1990

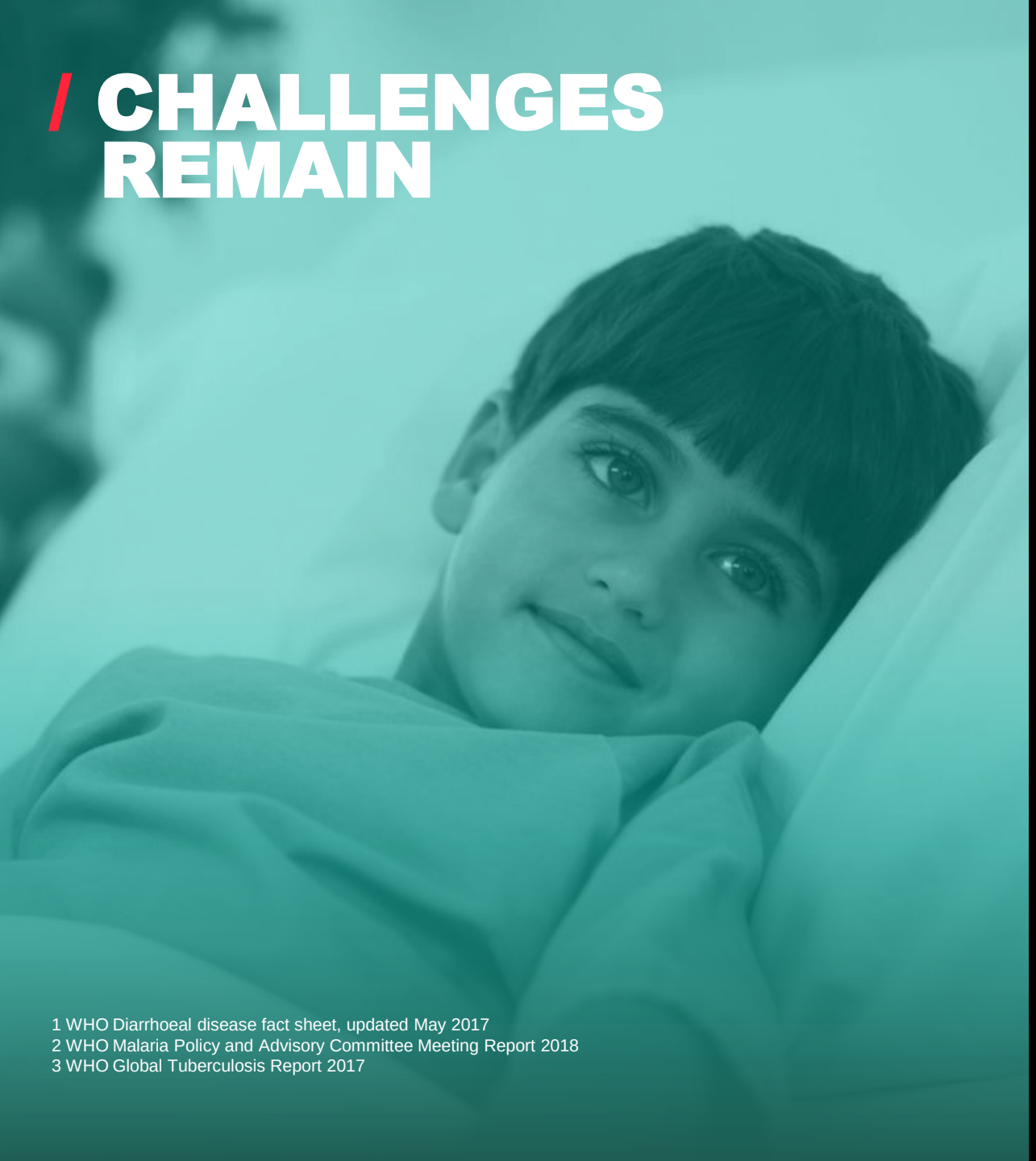

> 1.45 million children's lives saved by Hib and pneumococcal vaccines since 2000
> **SCIENCE DAILY 6/11/18**

> Is the end in sight for meningitis?
> **CNN 5/3/16**

> Polio: Closing in on zero
> **DEVEX 6/13/17**

* WHO Children: reducing mortality, October 2017

# / CHALLENGES REMAIN



**1.7 MILLION**

PEOPLE DIED FROM **TUBERCULOSIS**
in 2016[3]

**445,000**

DEATHS DUE TO **MALARIA**
in 2016[2]

**525,000**

CHILDREN UNDER AGE 5 KILLED
BY **ENTERIC AND DIARRHEAL DISEASES**
each year[1]

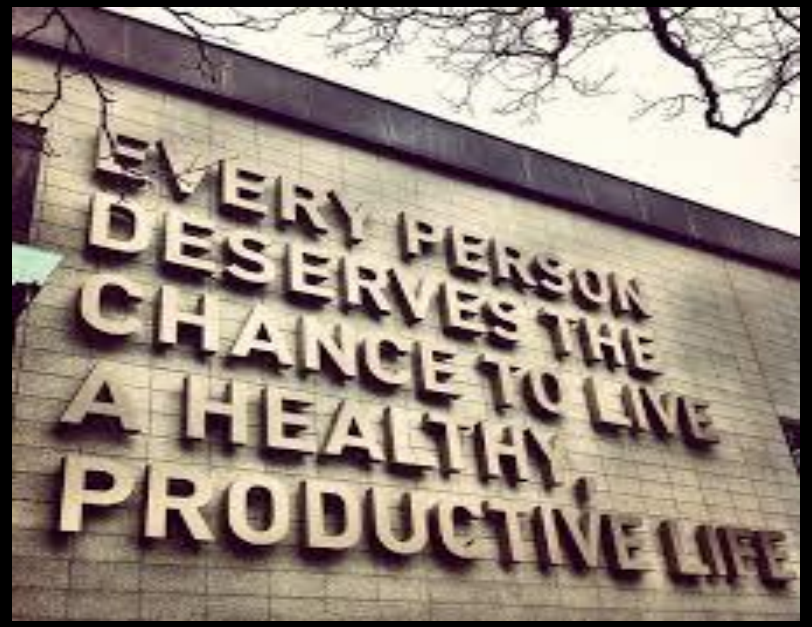
**2.5 MILLION**

CHILDREN DIE IN THE **FIRST MONTH OF LIFE**
1 MILLION FROM **PREMATURITY**[4]

1 WHO Diarrhoeal disease fact sheet, updated May 2017
2 WHO Malaria Policy and Advisory Committee Meeting Report 2018
3 WHO Global Tuberculosis Report 2017

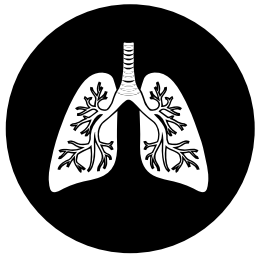
# TOGETHER, THESE DISEASES CAUSE TEN DEATHS EVERY MINUTE

# BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE



# GATES MRI MISSION

## DEVELOP PRODUCTS TO …



**TUBERCULOSIS**

Accelerate the end of the tuberculosis epidemic

**MALARIA**

Eradicate malaria

**ENTERIC AND DIARRHEAL DISEASES**

End diarrheal deaths in children

**MATERNAL NEONATAL & CHILD HEALTH**

Reduce adverse birth outcomes and mortality

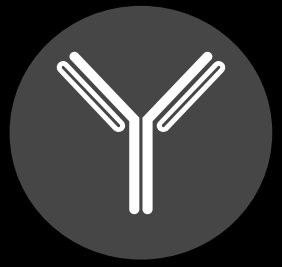
# GATES MRI OVERVIEW

# DISEASE AREA & MODALITIES

SMALL MOLECULE THERAPEUTICS

DIAGNOSTICS/ BIOMARKERS[1]

VACCINES



BIOLOGICS[2]

1 Biomarker optimization for early hand over to diagnostic companies
2 Includes mAbs and other non-small-molecule modalities, e.g., RNA, DNA, viral and cell platforms

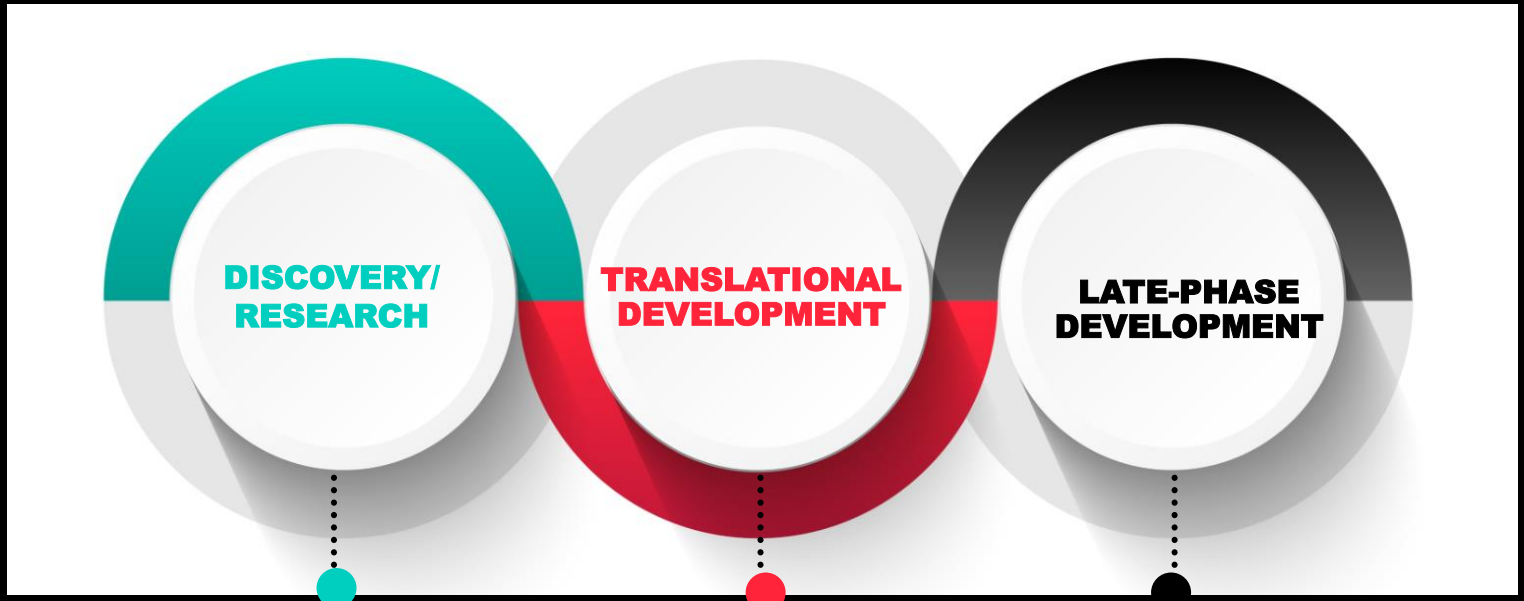
## ENTERIC AND DIARRHEAL DISEASES

## MALARIA

## TUBERCULOSIS

## MNCH

# GATES MRI AT A GLANCE



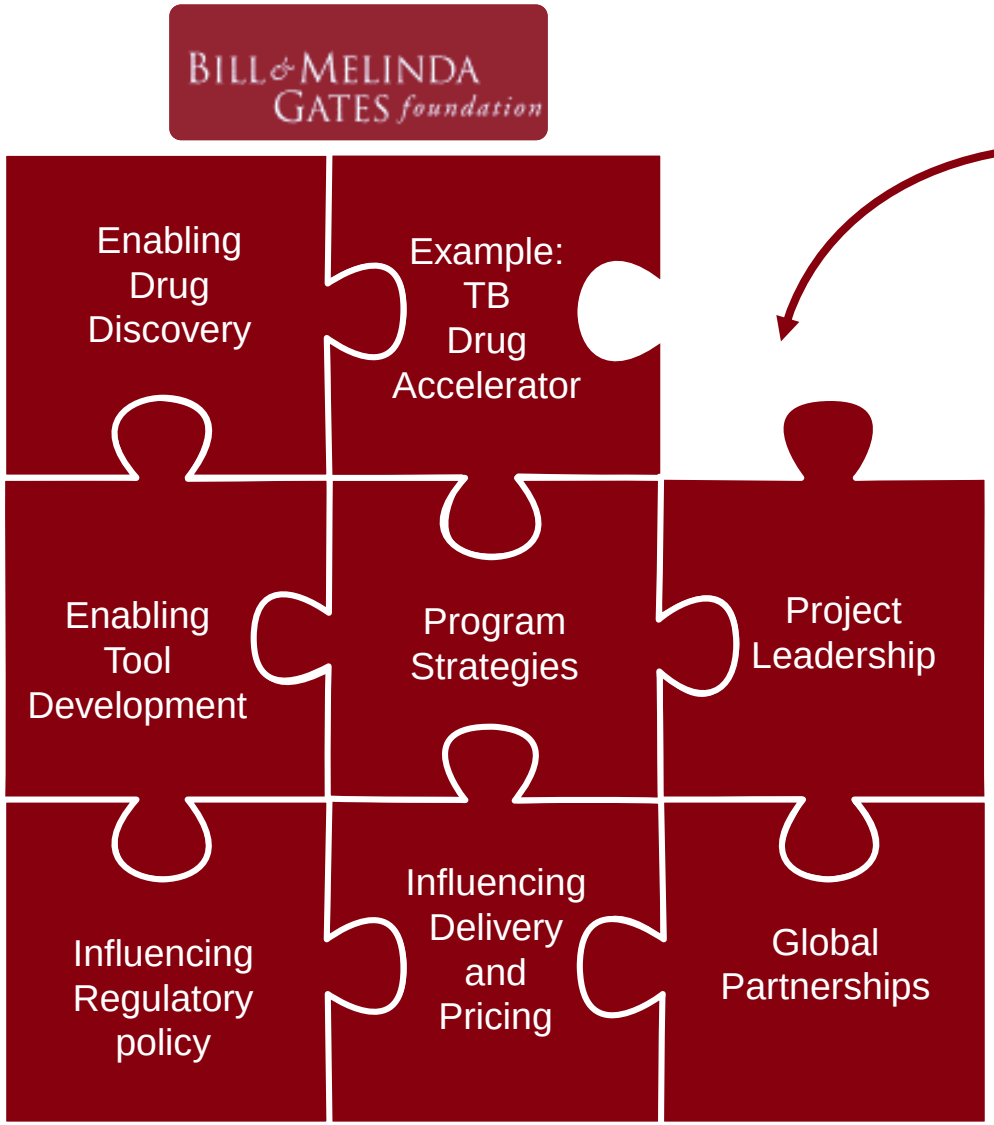

Lead optimization, working with early research partners

GxP studies through clinical POC in the target population, working with translational development partners

Effective handoff to late-phase development partners

| | |
|---|---|
| Location | Cambridge, MA (HQ), Seattle |
| Structure | Fully funded by a grant from the Gates Foundation |
| Portfolio | Initial focus on TB drugs, BCG booster, malaria vx with novel adjuvant, shigella vx, MNCH portfolio |
| Size | ~55 as of Feb, 2019 |
| Quality Management System | Quality and compliance systems implemented; first audit completed |

# RELATIONSHIP WITH THE FOUNDATION



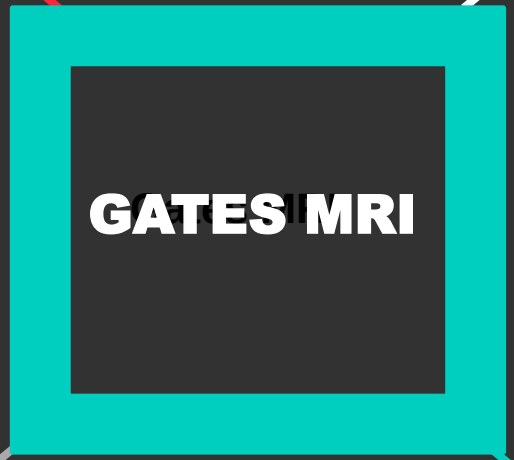

And many other capabilities…..

- **Wholly owned subsidiary of the Foundation**
- **Gates MRI is able to leverage the extensive skills and expertise of the Foundation and the long-standing relationships across academia and industry.**
- **We share a common belief:  all lives have equal value.**
- **We are committed to bringing the latest industry innovations to bear in our collective work.**

# INNOVATION FOR ACCELERATED TRANSLATIONAL DEVELOPMENT

DISCOVERY PORTFOLIO: RESEARCH DECISION SUPPORT AND ACCELERATION

CHEMISTRY, MANUFACTURING, AND CONTROLS




SYSTEMS BIOLOGY, QUANTITATIVE SCIENCES MODELING, QUANTITATIVE & SYSTEMS PHARMACOLOGY

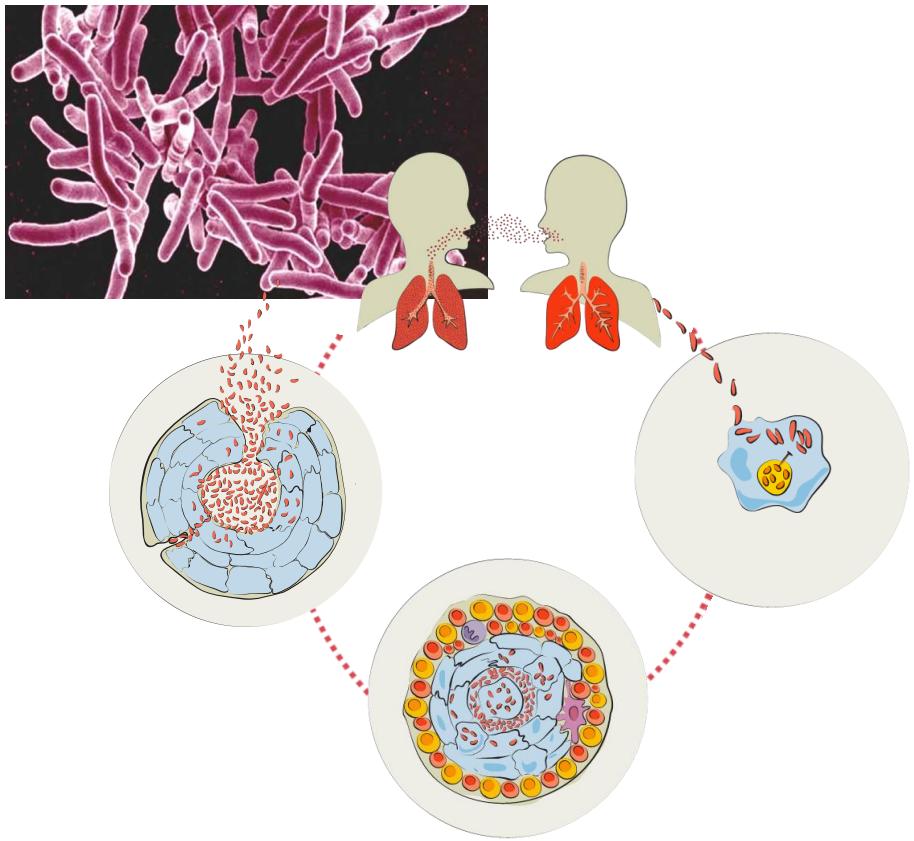
INNOVATIVE CLINICAL TRIALS (DESIGN AND EXECUTION)

# OUR APPROACH TO ACCELERATING DRUG AND VACCINE DEVELOPMENT IN GLOBAL HEALTH

## CASE STUDIES IN TUBERCULOSIS

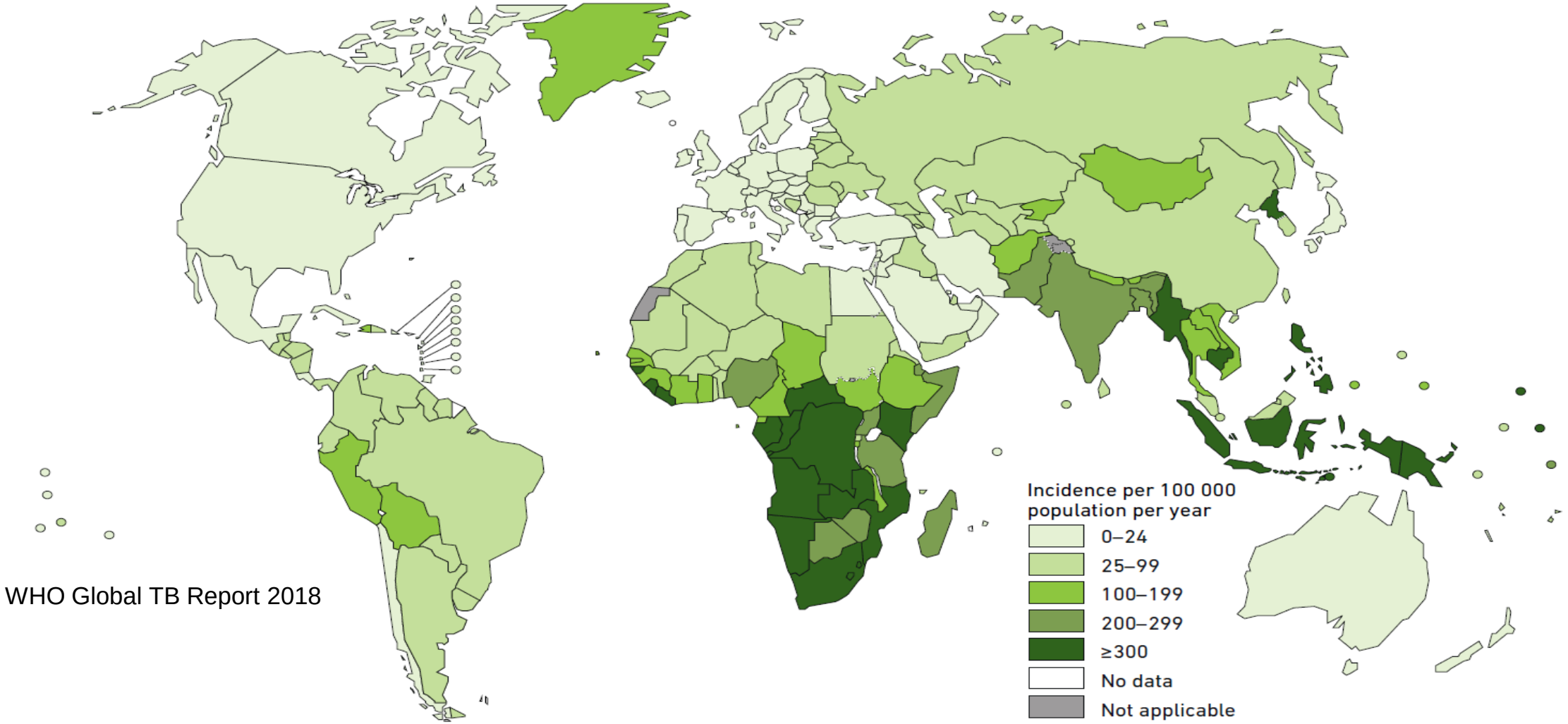
## BCG REVAX

# WHAT IS TUBERCULOSIS?



- Caused by a bacterium, *Mycobacterium tuberculosis* (Mtb)
- 25% of the world's population is infected with Mtb
- 90% of those infected are asymptomatic for life
- 10% will develop pulmonary disease
- In normal, healthy individuals, we can't predict who will get pulmonary disease (correlates of risk)
- We also don't understand immune mechanisms of protection (correlates of protection)
- Current treatment:  4 drugs for 6 to 9 months
- Current vaccine:  BCG for neonates/infants
  - Will soon have its 100$^{th}$ birthday

# TB CAUSES 1.7 MILLION DEATHS/YEAR NEARLY ALL ARE IN LOW INCOME COUNTRIES



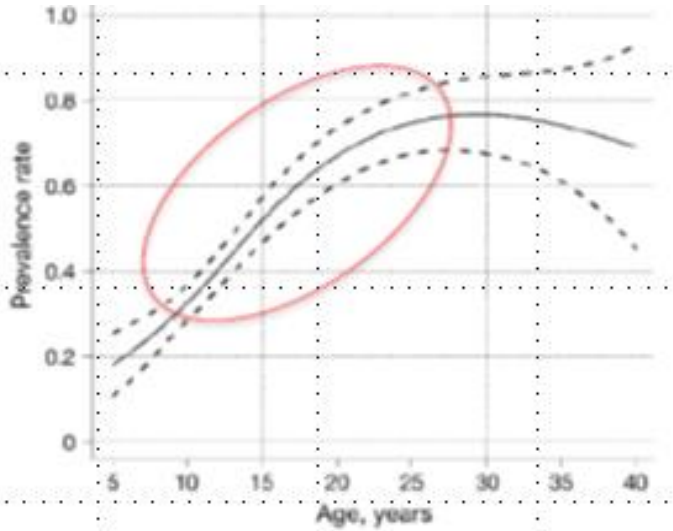

WHO Global TB Report 2018

# TB IS A DISEASE OF OLDER ADOLESCENTS AND YOUNG ADULTS IN LICS

**Cape Town, South Africa**

| | |
|---|---|
| **Infants** *Andrews LRM 2017* | **7%** |
| **Children (5-10 yr)** *Wood (TST) IJTLD 2010* | **28%** |
| **Adolescents (12-18 yr)** *Mahomed IJTLD 2011* *Nemes NEJM 2018* | **50%** |
| **Adults (25 yr)** | **75% (plateau)** |
| **Adults (31-35 yr)** | **88% (peak)** |

*Wood (TST) IJTLD 2010*




*M.tb* infection rates increase rapidly between age 10-25 years

Not feasible to implement pre-vaccination IGRA testing

New TB vaccine strategy may use age to target *M.tb*-infected/-uninfected populations

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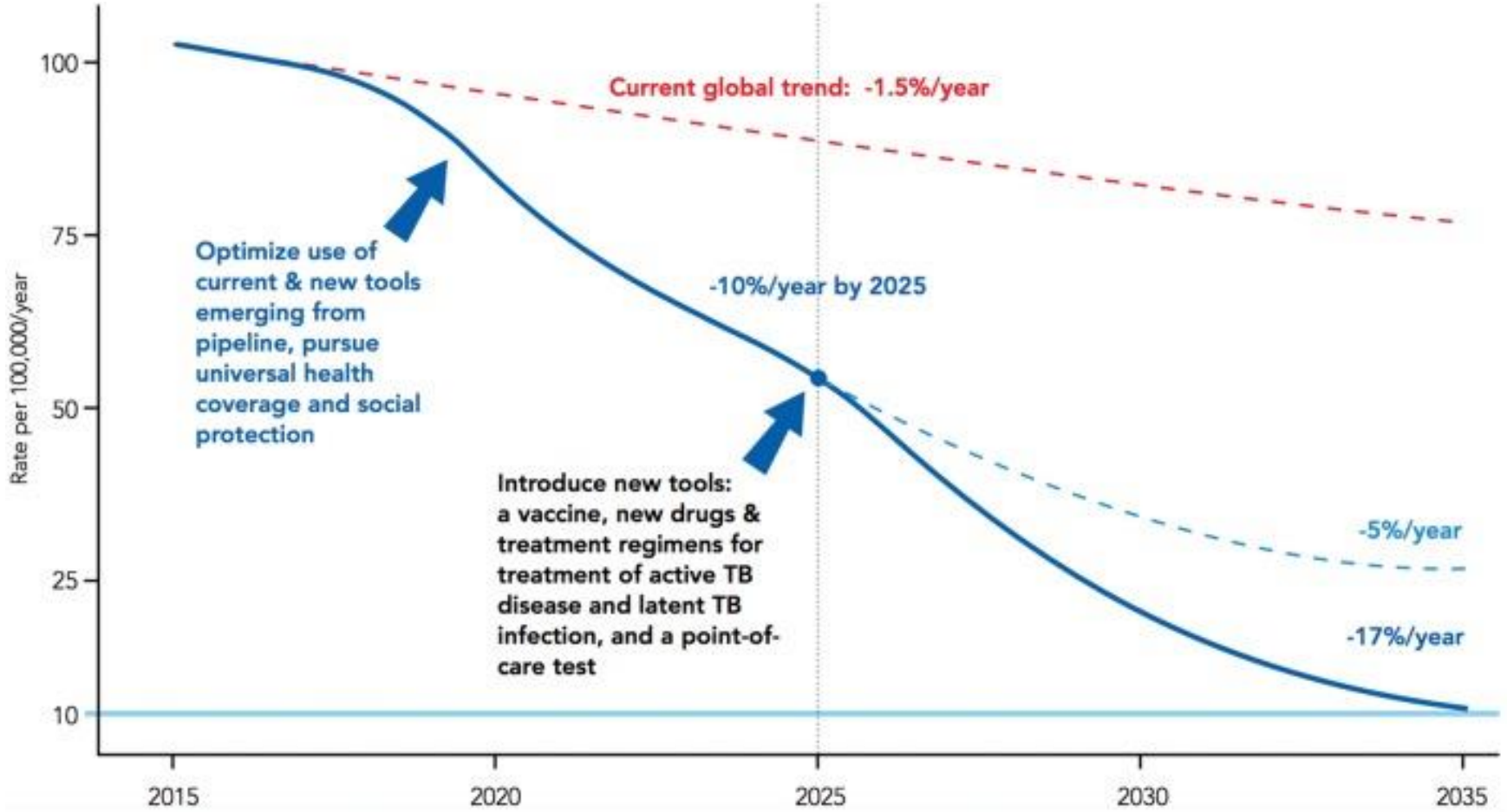
# NEW INTERVENTIONS ARE NEEDED TO HELP END THE TB EPIDEMIC




Source: Trans R Soc Trop Med Hyg. 2016 Apr; 110(4): 212-218

# 2018: A HISTORIC YEAR FOR TB VACCINES

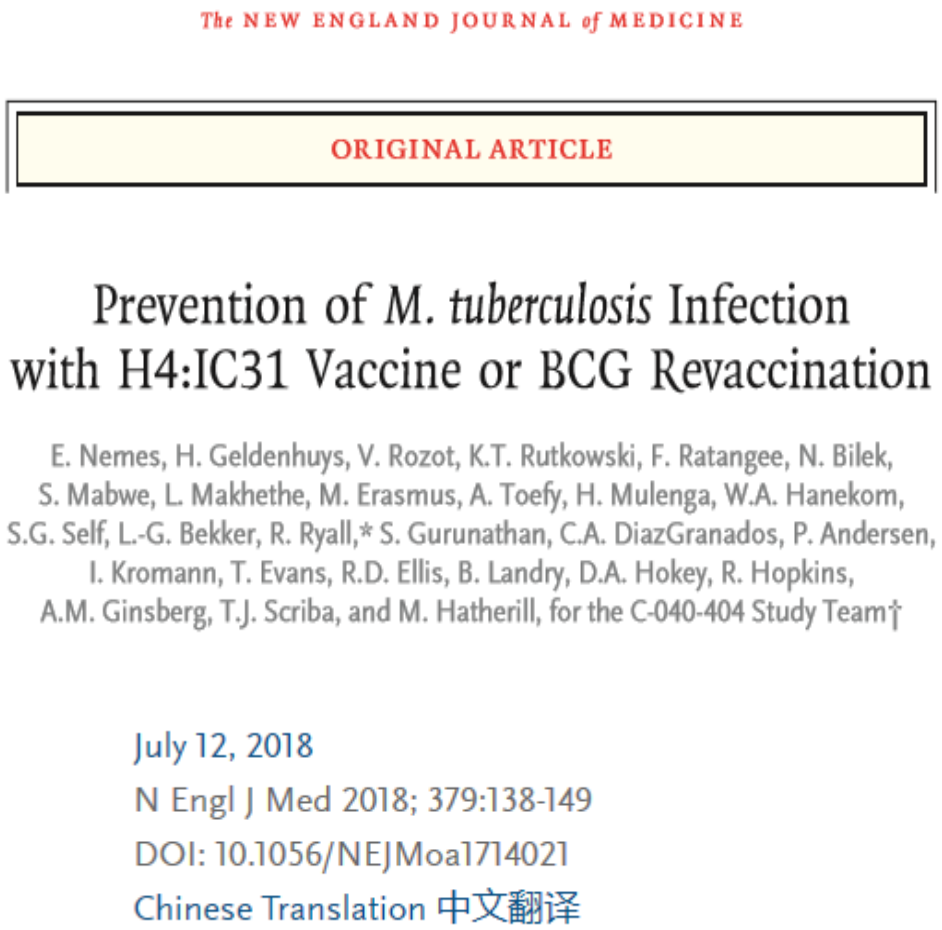
The NEW ENGLAND JOURNAL of MEDICINE

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. Diacc G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellstrò N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsbe T.G. Evans, P. Gillard, and D.R. Tait

October 25, 2018
N Engl J Med 2018; 379:1621-1634
DOI: 10.1056/NEJMoa1803484



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†

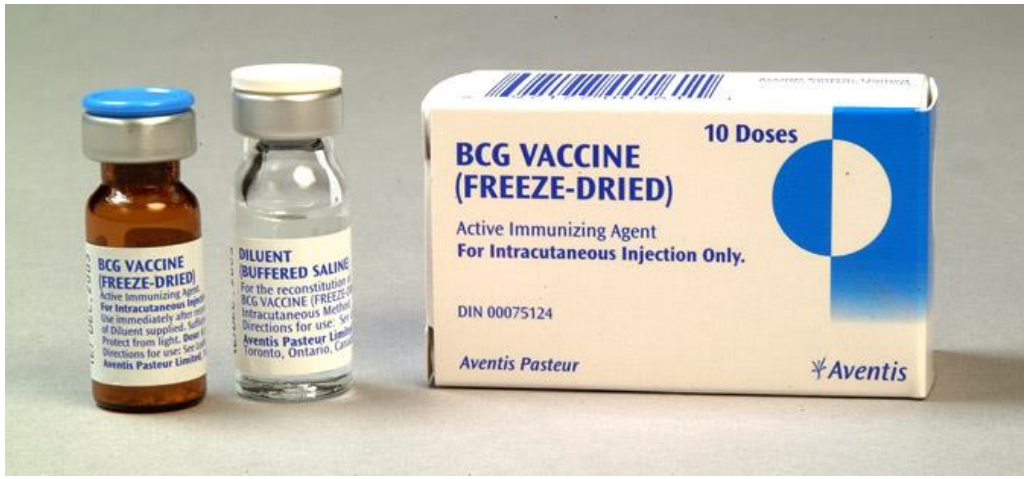
July 12, 2018
N Engl J Med 2018; 379:138-149
DOI: 10.1056/NEJMoa1714021
Chinese Translation 中文翻译

# BACILLUS CALMETTE-GUERIN (BCG) VACCINE

- Live, attenuated bovine tuberculosis strain (*Mycobacterium bovis)* that does not cause disease in humans but induces protective immunity
- Most widely used human vaccine
- First used in humans in 1921; more widely utilized after WWII
- Currently recommended for neonates and infants born in countries with high prevalence of TB
  - Prevents disseminated TB, TB meningitis
  - Efficacy ~50%
- There are six vaccines prequalified by the World Health Organization (WHO)

Albert Calmette
(1863-1933)

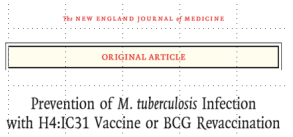
Camille Guerin
(1872-1961)



# EFFICACY OF BCG IN ADOLESCENTS AND ADULTS APPEARS HIGHLY VARIABLE

- Efficacy ranges from 0 to 80% and is lowest in areas with highest TB incidence
- Factors associated with low efficacy in adults are unclear
  - / Study designs
  - / Force of infection
  - / Latitude – those closer to the equator are exposed to other mycobacteria that may interfere with BCG immunity
  - / Other?

# H4:IC31 TB VACCINE PHASE II PREVENTION OF INFECTION STUDY




- Proof of Concept
  - Safety and Prevention of (established) Infection
- Population
  - QuantiFERON-negative, uninfected adolescents (aged 12-17 years)
  - Received BCG at birth
  - Western Cape, South Africa (SATVI)
  - High risk of infection (~10% per year)
- Sample size=990 subjects
- 3 Study Arms:
  - H4:IC31 vaccine (n=331)
  - BCG revaccination (n=330)
  - Placebo (saline) (n=329)
- Primary Efficacy Endpoint:
  - QuantiFERON conversion from negative to positive Day ≥84

DESMOND TUTU HIV FOUNDATION

AERAS

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

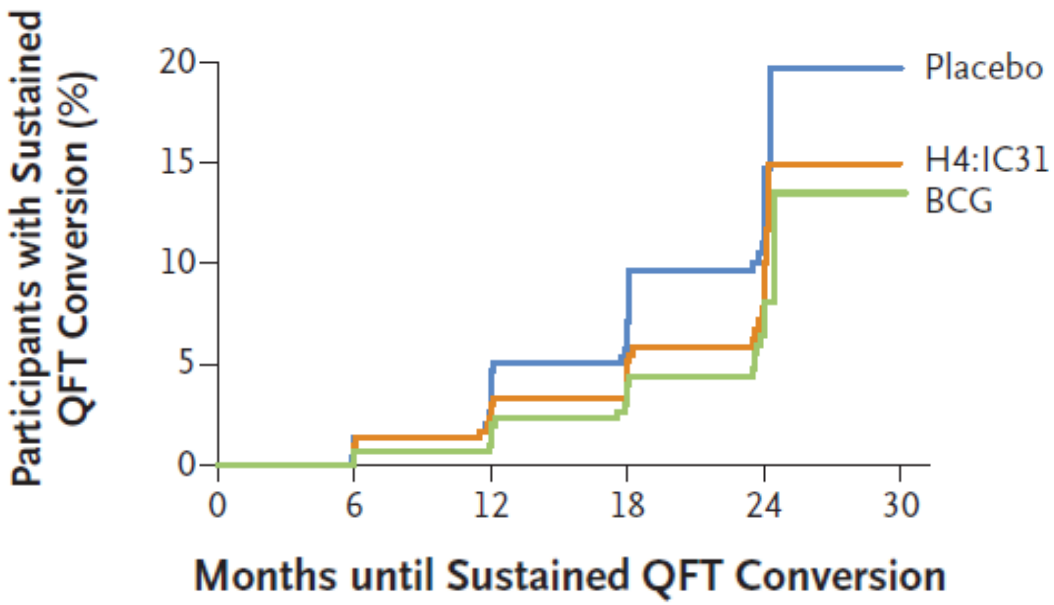
SANOFI PASTEUR

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

# BCG REVACCINATION OF ADOLESCENTS APPEARS TO PROVIDE PROTECTION AGAINST SUSTAINED *Mtb* INFECTION (POSI)

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

- **Primary endpoint not met**: No efficacy of BCG or H4:IC31 for the prevention of primary QFT conversion (≥Day 84)
- **Secondary endpoint met**: 45% efficacy for BCG and 30% efficacy for H4 at preventing sustained (≥6 mos) QFT conversion
- **Exploratory endpoint met**: Both vaccines showed efficacy against primary conversion to >4.0 IU/mL



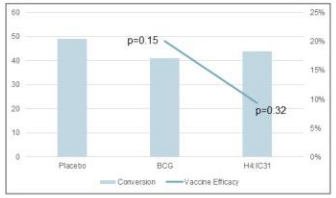
# WHERE TO FROM HERE?

# GATES MRI – OUR APPROACH TO BCG REVAX

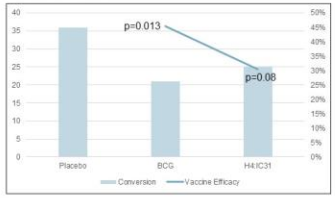
## H4:IC31: PHASE II SAFETY AND EFFICACY RESULTS

**Safety**
- Both vaccines safe and immunogenic
- No vaccine-related serious adverse events
- Most common vaccine-related adverse event was injection site swelling in BCG revaccinated participants

**Primary Efficacy Endpoint: Initial QFT Conversion**
- No statistically significant efficacy



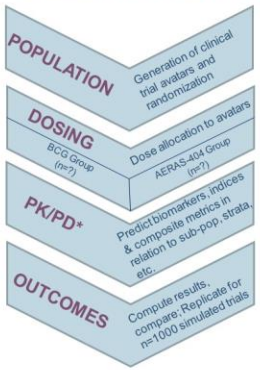

**Secondary Efficacy Endpoint: Sustained QFT Conversion**
- >45% Efficacy for BCG
- Efficacy statistically significant at nominal p-value of 0.05




## KEY QUESTIONS FOR A REPEAT ADOLESCENT BCG PREVENTION OF INFECTION TRIAL:

- Can we repeat the initial observation in the same population, with statistical rigor?
- How generalizable are the findings? Is the prevention of infection effect specific to the studied population, or can it be seen in other populations?
- Differences in force of infection, exposure to environmental mycobacteria, other variables
- What is the durability of the prevention of infection effect?
- What are the immune correlates of protection?
- How can biological observations made in this study impact the broader TB vaccine development effort?

## CLINICAL TRIAL SIMULATIONS

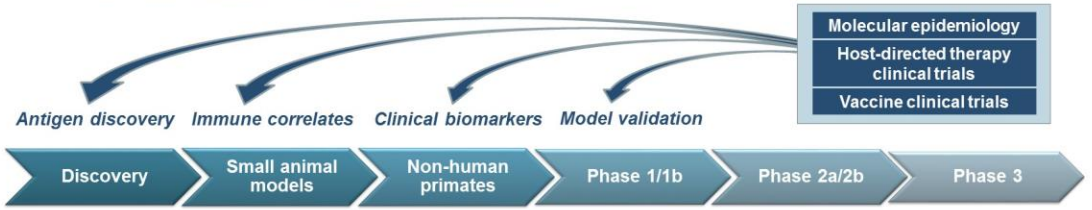



* Actually reflects Immunostimulation/ Immunodynamic modelling

- **Define virtual population characteristics that mimic what we expect to encounter in the revaccination study** (demographics, TB burden disease comorbidities (e.g., HIV co-infection), assay performance / correlation with outcomes)
- **Avatars capture patient-level, target population in line with the enrollment strata**.
- **Create a sampling distribution algorithm** to assign response attributes in line with predefined functional relationships and the protocol event schedule.
- **Construct treatment-response algorithms** for all responses of interest
  - *Mtb* Infection = fn (TRT, TB burden, comorbidities, assay, age, biomarker baseline)
  - AEs= fn (TRT, TB burden, comorbidities, age, biomarker baseline)
  - Therapeutic Window Composite metric = TBD
- **Define** covariate relationships that may alter response(s) and be considered as **simulation scenarios**
  - Assay threshold windows and variability
  - TB burden
  - Inclusion / exclusion criteria
  - Stratification
  - Sample size

## INNOVATION FOR TB VACCINES

**APPLY HUMAN BIOLOGY TO OVERCOME ROADBLOCKS**

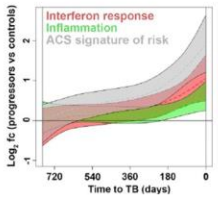


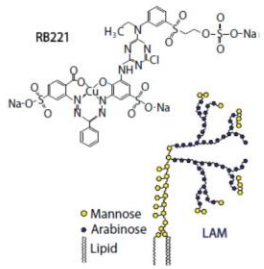

**ROADBLOCKS**

| | | | | |
|---|---|---|---|---|
| •Antigenic determinants of protection unknown<br>•Key immune cell subsets not well correlated with protection | •Small animal and non-human primate models not always predictive of clinical outcome | •No human challenge model<br>•Lack of standardization for immune correlates | •Surrogate endpoints for prevention of infection need refinement | •10K+ subjects needed for prevention of disease studies |

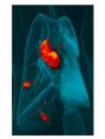
## INNOVATIONS TO IMPROVE INTERROGATION OF VACCINE-ELICTED IMMUNITY AND PROTECTION

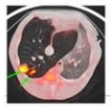
- **Can be applied broadly across the entire study (3000+ participants)**
  - Blood transcriptomics
  - Blood flow cytometry
  - Urine LAM

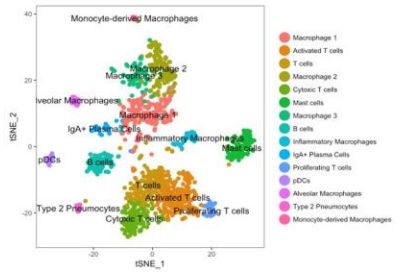



- **Can be applied in an experimental medicine sub-study**
  - PET/CT Imaging
  - Pulmonary immunity (BAL)
  - Blood CyToF and single-cell transcriptomics







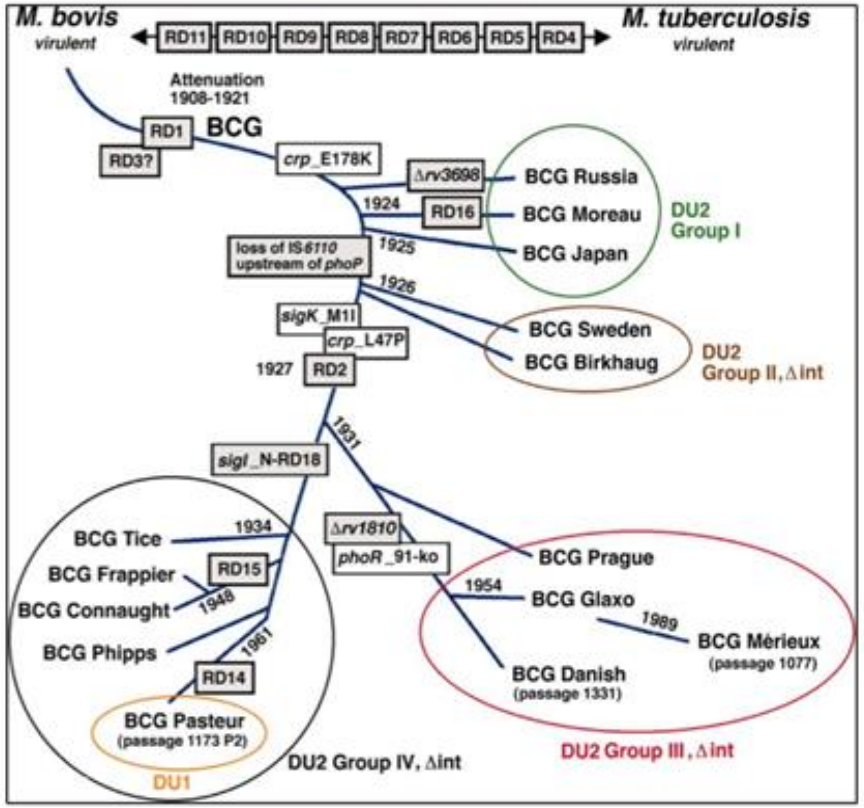

# BCG REVAX PATH FORWARD

- Key questions identified i.e., factors most likely to confound study
  - Study population, force-of-infection, latitude (exposure to other mycobacteria)

- Confirming the initial findings of POSI in a “high force-of-infection” country
  - Randomized (1:1), placebo controlled, observer-blind Phase 2b study in ~1800 subjects in South Africa

- Biomarkers and quantitative sciences
  - Further validate the QuantiFERON biomarker assay
  - Deep immuno-profiling for correlates of risk and correlates of protection

- CMC
  - Reviewed lineages of different vaccine strains from 1921 to present day
  - Utilizing additional assays to better characterize vaccine potency for clinical trial



# POTENTIAL TO ACCELERATE IMPACT

- What data are needed for a policy recommendation for a booster dose of BCG?

- Will prevention of sustained infection translate to prevention of pulmonary disease?
  - 90% of those with naturally occurring infection never develop symptoms
  - A meta-analysis of studies conducted in children shows that BCG prevents infection AND disease, in a pattern similar to other vaccines
  - How can we show the same is true for adolescents/adults?

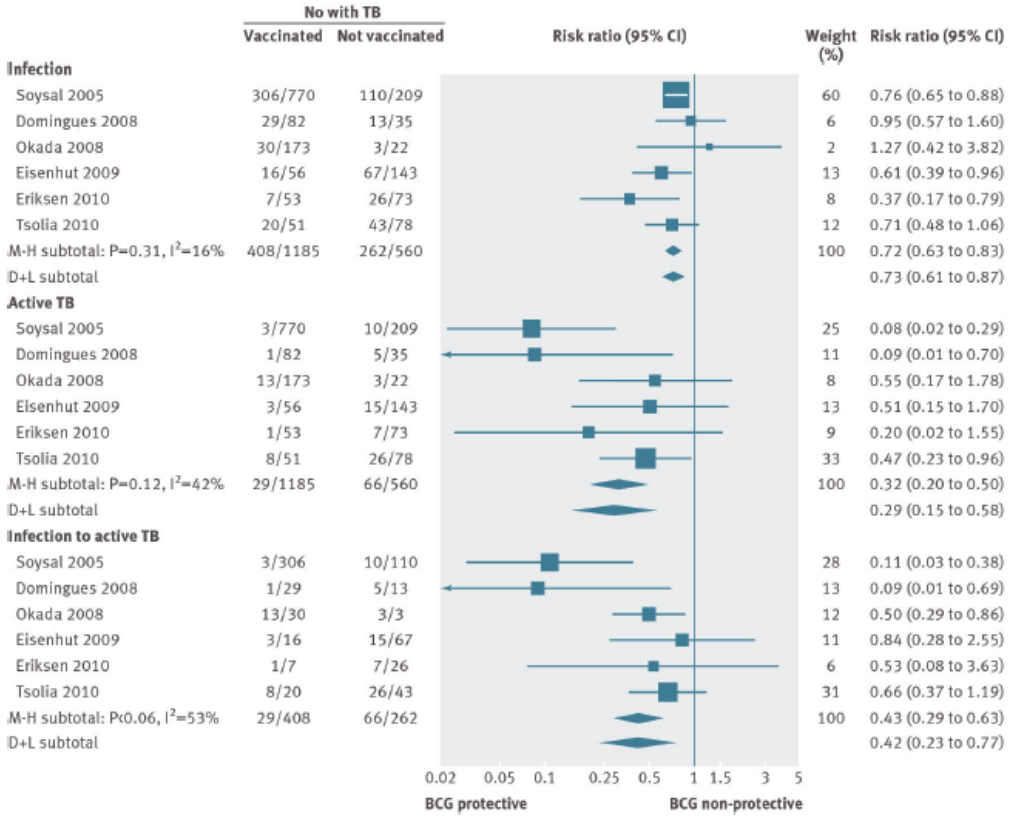



**Fig 7** Types of protection against *Mycobacterium tuberculosis* (TB) in children vaccinated with BCG: protection against infection (irrespective of whether they went on to develop active TB); overall protection against active TB; protection against progression from infection to active TB during screening. D+L=DerSimonian and Laird method; M-H=Mantel-Haenszel method

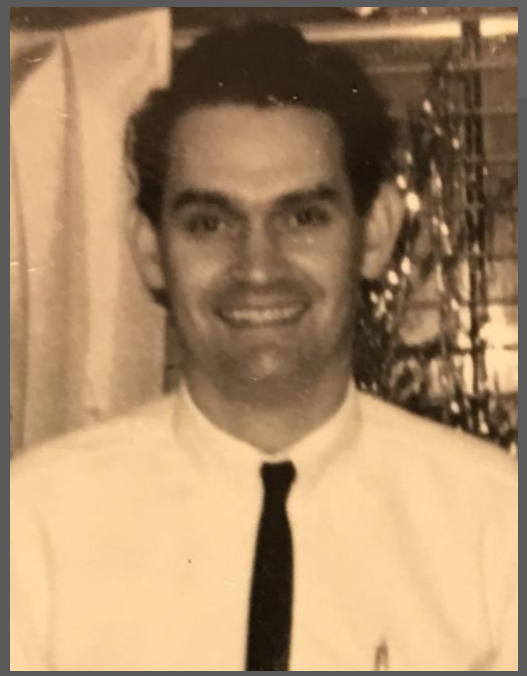
Source: *BMJ* 2014;349:g4643

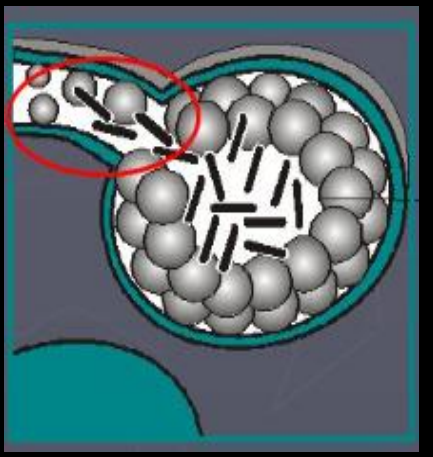
# OUR APPROACH TO ACCELERATING DRUG AND VACCINE DEVELOPMENT IN GLOBAL HEALTH

## CASE STUDIES IN TUBERCULOSIS

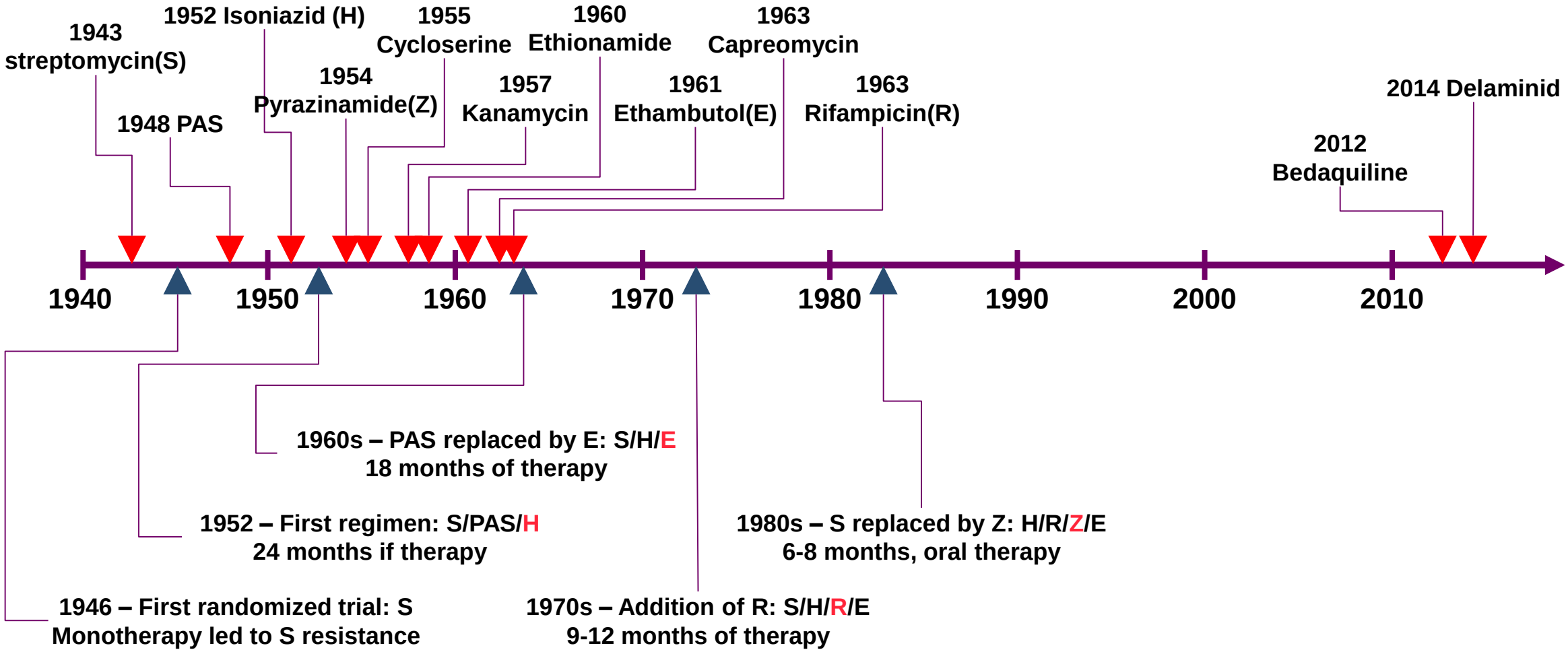
## NEW TB DRUG REGIMENS

# / BEGIN WITH THE END IN MIND…





# HISTORY OF TB DRUG APPROVALS



# STANDARD OF CARE (SOC)

- **Drug Susceptible:  6 to 9mos (Isoniazid, Rifampin, Pyrazinamide, Ethambutol or HRZE)**
  - HRZE for 2mos then HR for 4mos
  - 92% cure rate in trial setting; ~55–85% in field*
  - ~20% Grade 3 to 4 AEs
  - ~20-25% with AE of hepatotoxicity
  - Rifampin – prototype CYP inducer, DDI liability
  - Inexpensive - ~$50/course

- **Multi-drug Resistant:  9 to 24mos**
  - Newer Short Course Regimen: 7 drugs for 9 to 12mos (Kanamycin; Moxifloxacin; Prothionamide; Clofazimine; Pyrazinamide; Isoniazid; Ethambutol)
  - 80% cure rate in trial setting; Older SoC 20-24mos ~50% in field**
  - Middle income countries, treatment and medical costs ~$6,000***

*Drug Dev Res. 2011 Sep; 72(6): 501–508

** http://guadalajara.worldlunghealth.org/media/conference-news/updates/stream-clinical-trial-results-provide-vital-insight-into-nine-month-treatment-regimen-for-multidrug-resistant-tuberculosis

***Laurence et al. Pharmacoeconomics, May 2015

# A SHORTER, SAFER, SIMPLER TB DRUG REGIMEN IS NEEDED

## Current Standard of Care

*Drug Sensitive*

- 4 drugs for 2 mos; 2 drugs for 4 mos
- 92% cure rate in trials; 55-85% in field*
- ~20% Grade 3-4 adverse events including hepatoxicity
- Inexpensive ~$50/course

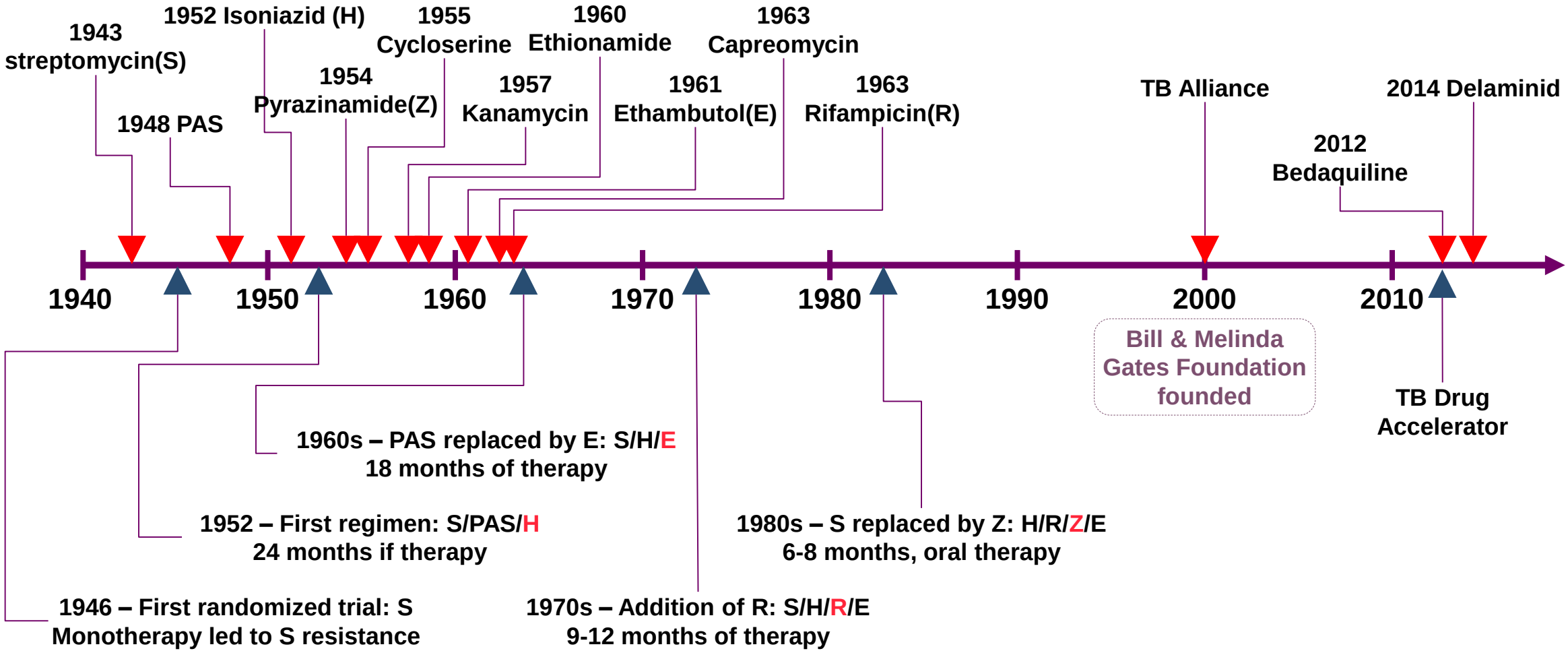
*Multi-Drug Resistant:*

- Short Course Regimen: 7 drugs 9-12mos
- 80% cure rate in trials; ~50% in field**
- Middle income countries, treatment and medical costs ~$6,000***

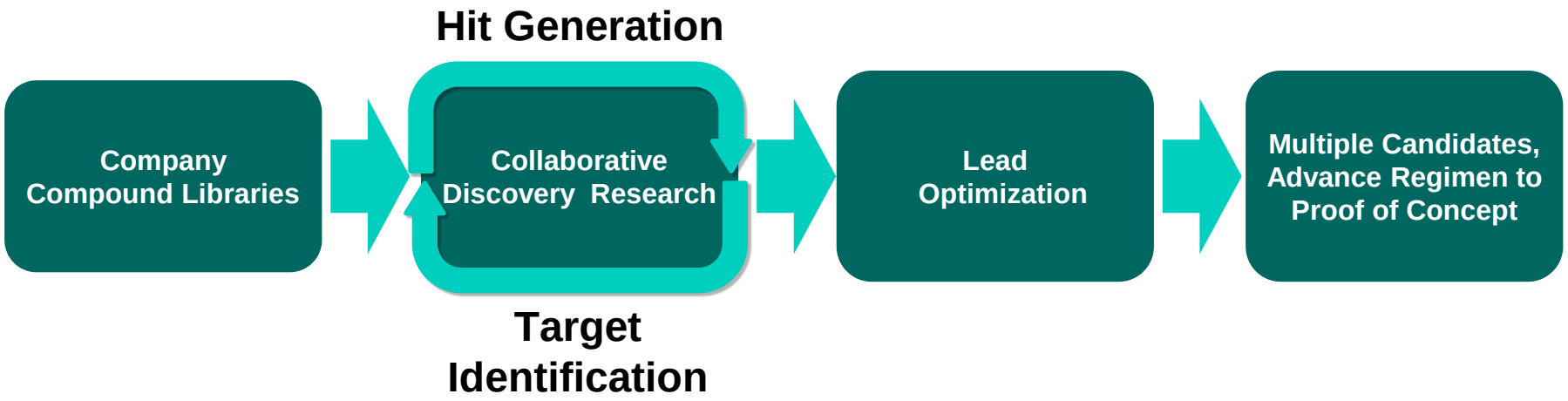
## Desired: Universal/Pan TB Regimen

- 3 or 4 drugs regardless of resistance
- Shorter - <2 months
- Safer - No safety lab or ECG monitoring
- Simpler
  - No sensitivity testing
  - All oral; fixed dose combination
  - No interactions with other drugs; no need to modify dosing with anti-retrovirals
- Affordable

# HISTORY OF TB DRUGS



# TB DRUG ACCELERATOR




**PHARMACEUTICAL COMPANIES:**

Bayer, Lilly, Eisai, AstraZeneca, MERCK, SANOFI, abbvie, GlaxoSmithKline

**RESEARCH INSTITUTIONS:**

Cornell University, Texas A&M, NIH National Institute of Allergy and Infectious Diseases, Drug Discovery Unit, Rutgers Biomedical and Health Sciences, IDRI Infectious Disease Research Institute, University of Cape Town, Colorado State University, Calibr California Institute for Biomedical Research, TB ALLIANCE Global Alliance for TB Drug Development

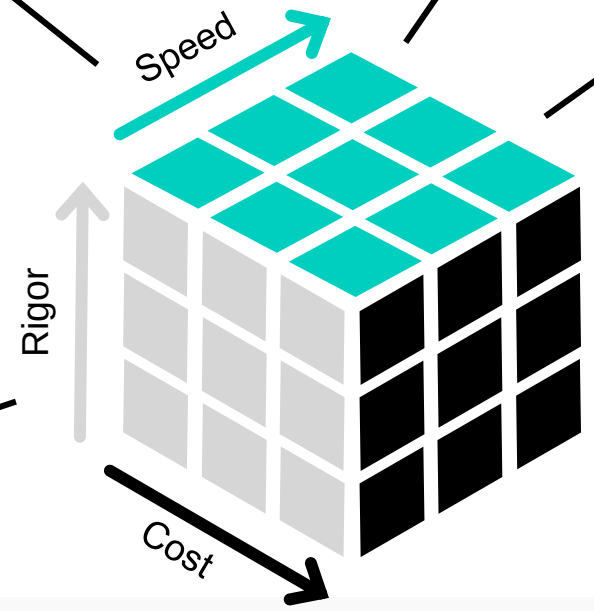
# CHALLENGES IN GLOBAL HEALTH TB DRUG REGIMEN DEVELOPMENT

Individual drugs in the regimen will **originate from different partners;** Robust governance needed

**Mouse models** are time- and resource-intensive

Predicting the long term outcome of short regimens requires **novel biomarkers**

Adaptive trials needed for efficient development; introduce **regulatory complexity**




20 drug candidates would present ~**5000 possible 4- drug combinations**

Quantitative science models are not yet integrated with experimental tools to aid in **regimen prioritization**

**Drug supply logistics** from multiple partners are complex

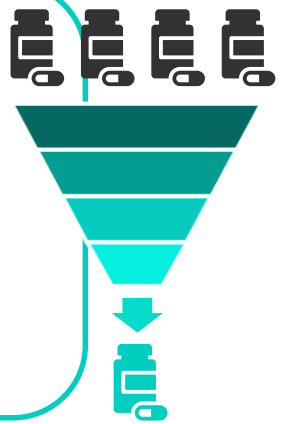
# PRECLINICAL: INTEGRATED EXPERIMENTAL QS APPROACH TO REGIMEN PRIORITIZATION

## Challenges

- Mouse models are time- and resource-intensive
- Recent clinical failures have cast doubt on the translatability of mouse-derived regimens
- 20 drug candidates would present about 5000 possible 4-drug combinations

## Opportunities

- Use *ex vivo* experiments and *in silico* tools to explore a wider range of potential combinations
- Perform mechanistic and predictive modelling to refine understanding of combination synergy
- Industrialize throughput and speed of physiologic *in vivo* models for final down-selection and prioritization of regimens



## Ongoing Activities

**Map existing data and execute gap-filling experiments**

**Adapt the relapsing mouse model to regimens**

**Evaluate novel endpoints (TB RNA, fluorescent biomarkers, imaging)**

**Operationalize predictive and mechanistic models from academic partners**

# BIOMARKERS: OPTIMIZING DECISION-MAKING

## Challenge

Current sputum mycobacterial biomarkers are not validated to predict cure from short term regimens; readouts are delayed

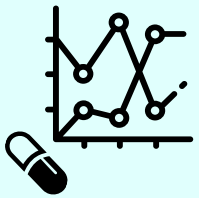
## Opportunities

Gates MRI biomarker, statistics and QS experts are contributing to an experimental framework for the assessment and validation of novel TB drug biomarkers, while building the underlying operational capabilities and infrastructure needed.

### Validated Clinical Biomarkers

- Formal biomarker validation including assessment of preanalytical, analytical and biomarker variability
- Iterative hypothesis testing and refinement to clinically validate biomarkers

### Regulated Bioanalysis



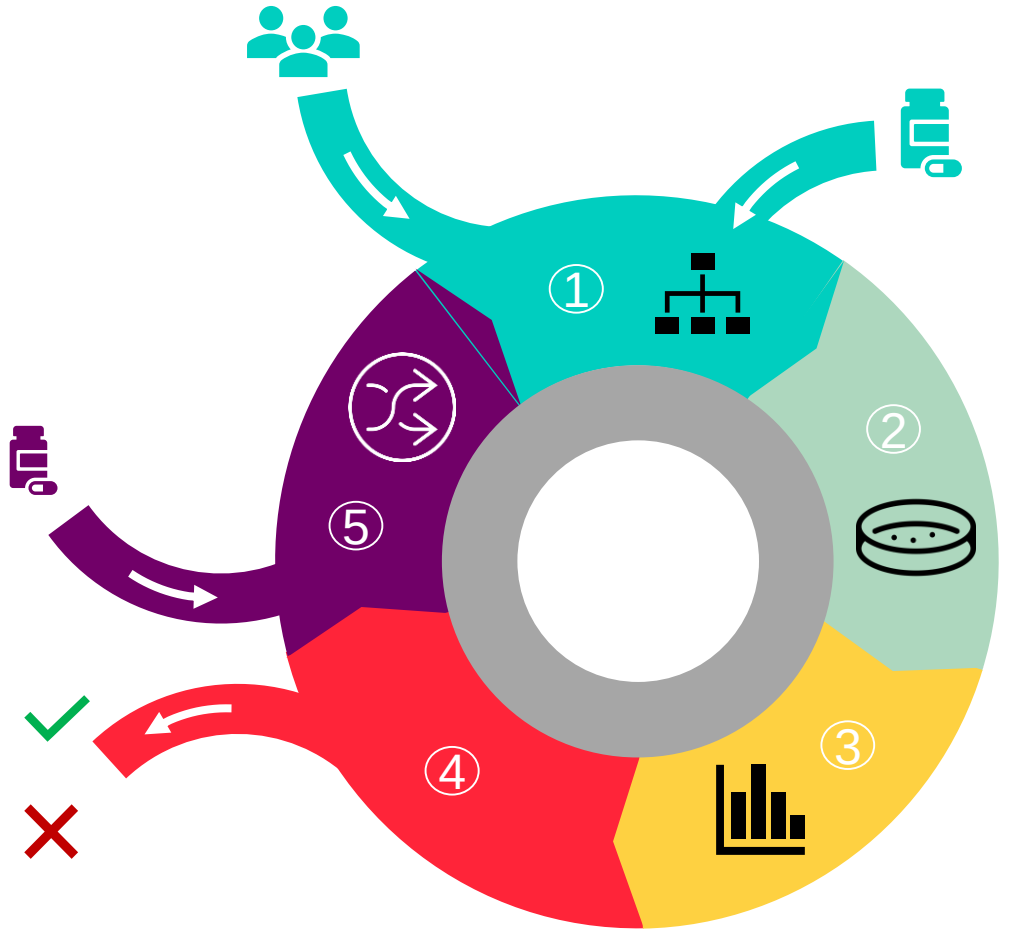
- Establishing a network of bioanalytical labs using the innovator's method and bioanalytical CRO where possible

### Biorepository & Sample Tracking

- Working with a well established clinical biorepository; implementing 2Q2019
- Implementing a cloud-based SAS solution for sample tracking and management

# APPROACH TO ADAPTIVE PLATFORM TRIAL DESIGN FOR TB DRUG REGIMENS

1. Assign patients to control or experimental arm
2. Assess serum sputum culture conversion (SSCC) and novel biomarkers
3. Predict/assess relapse free cure rates at 12 months based on short-course regimens
4. Define and evolve quantitative go/no-go criteria for failure vs success based on ongoing data collection
5. If graduated or futile, introduce new combination therapy and update randomization



# QUANTITATIVE SCIENCE IS INTEGRAL TO EVERYTHING WE DO

**Pick the Best Combinations**

Response surface modeling (RSM) and other predictive models coupled with patient-level TB data (AI/ML approach) and mechanistic QSP modeling

**Pick the Right Doses**

PK, PK/PD, Population PK/PD modeling, DDI simulation

**Pick the Right Biomarkers**

Computational/statistical framework for biomarker ID and validation

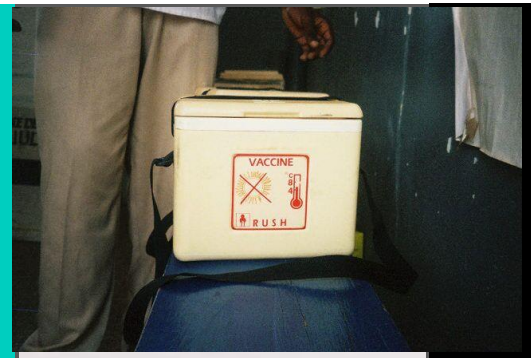
**Inform Adaptive Trial Design and Execution**

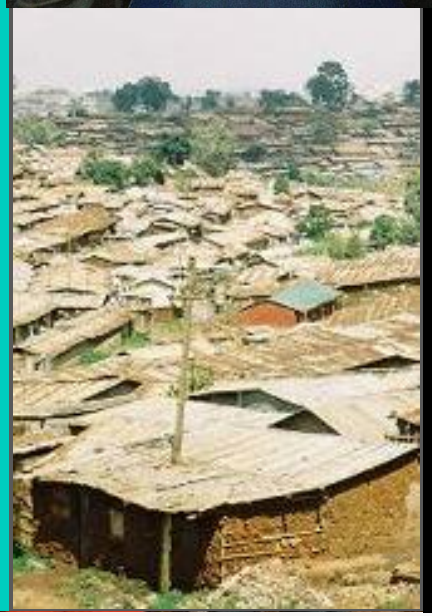
Clinical trial simulations, Bayesian statistics, decision rules, response-adaptive randomization

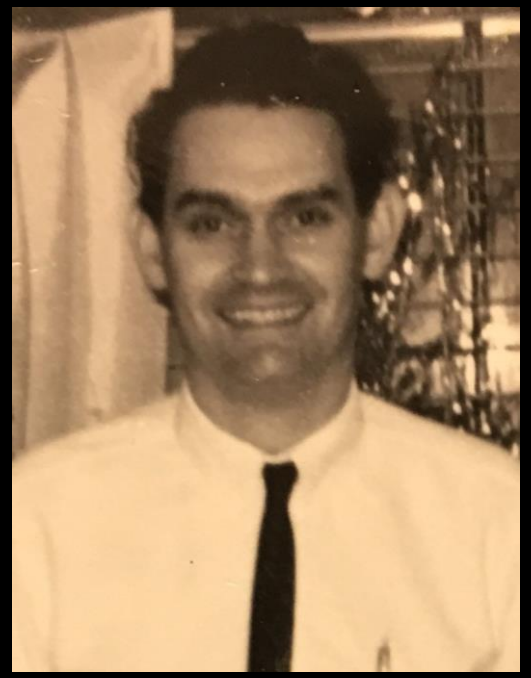
**Support Downstream Registrations**

Coordination of modeling deliverables with regulators (e.g. FDA)

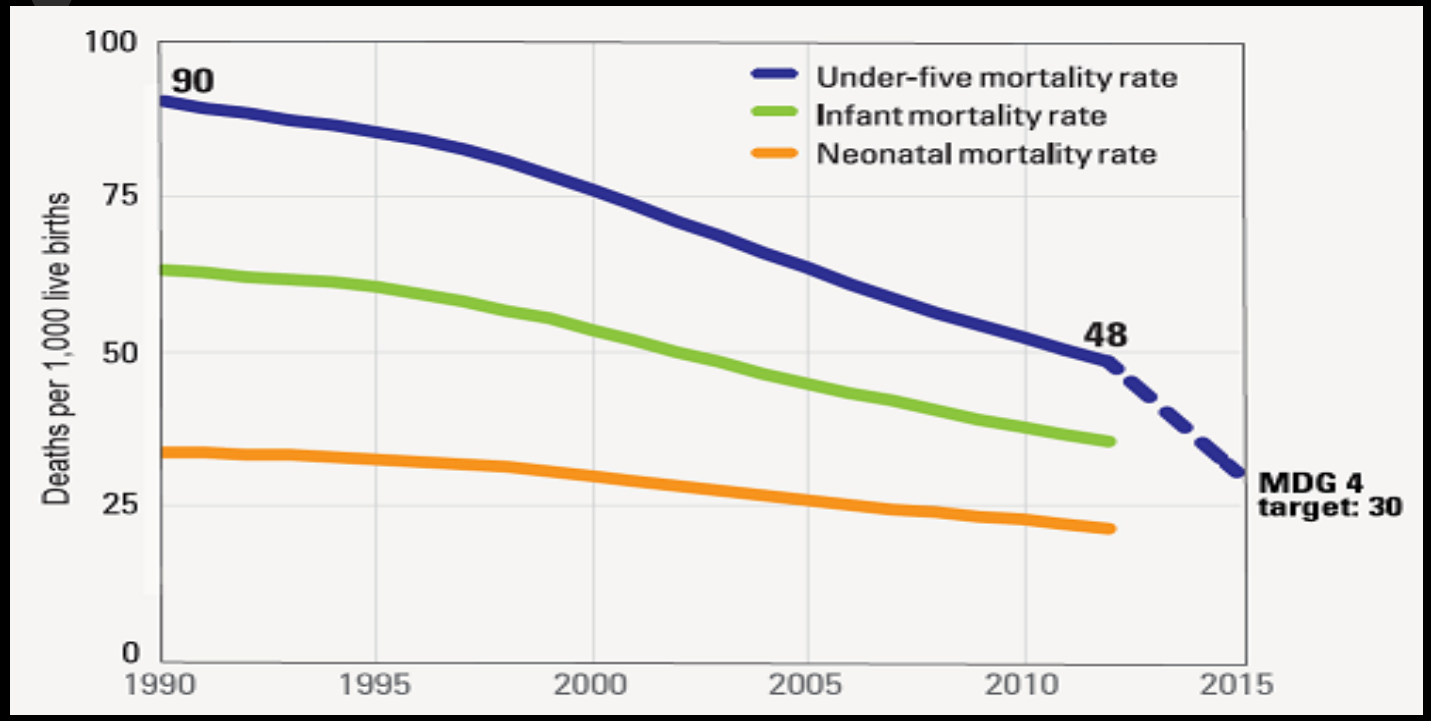
# / FROM PATIENT TO MOLECULE… BEGINNING WITH THE END IN MIND



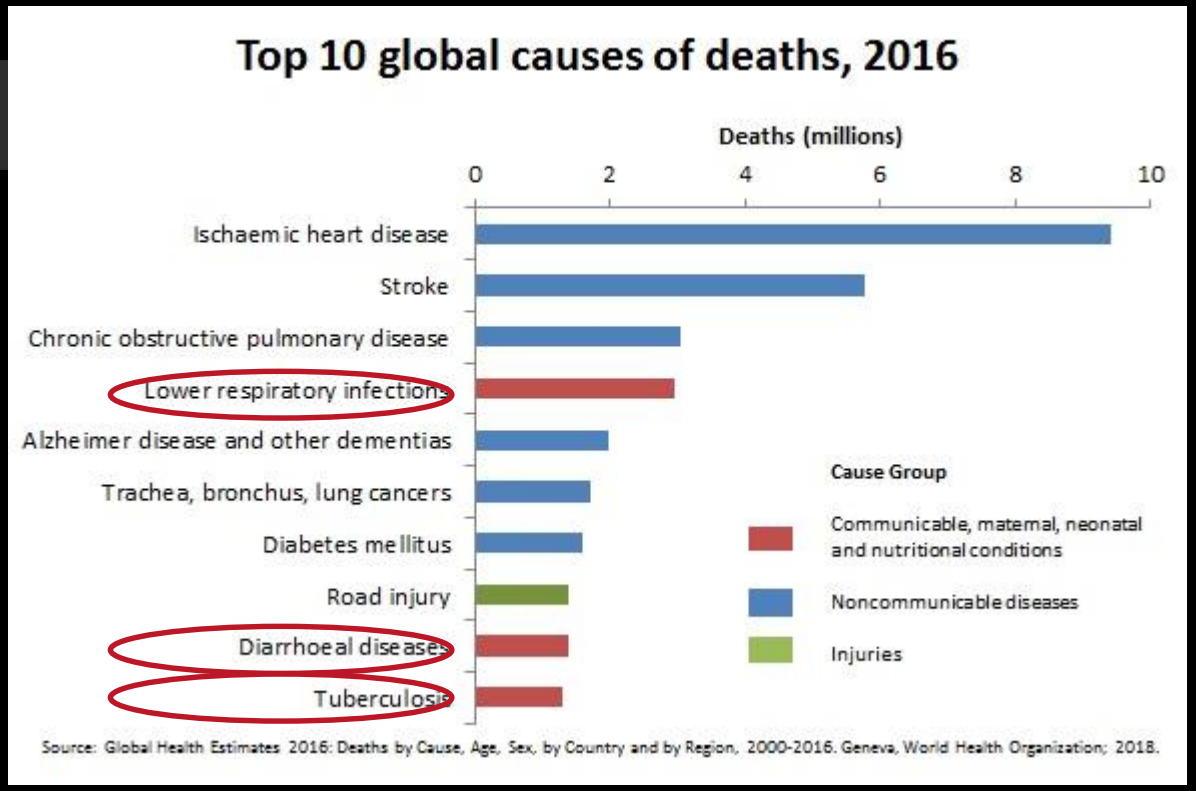


# / BEGIN WITH THE END IN MIND…




**Source: The World Bank**

# / BEGIN WITH THE END IN MIND…

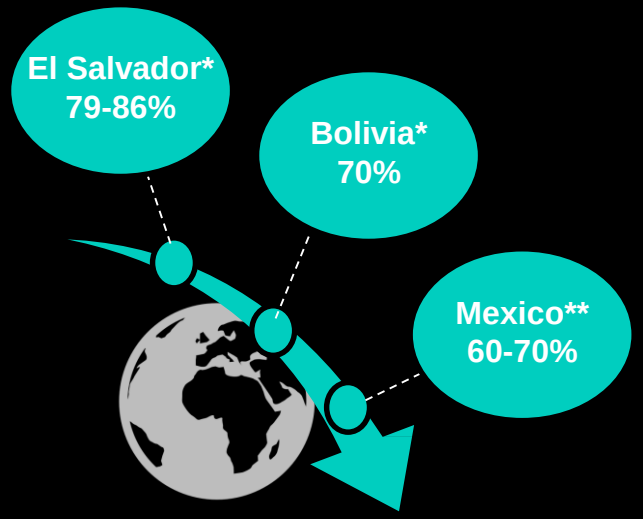



**Source: WHO**

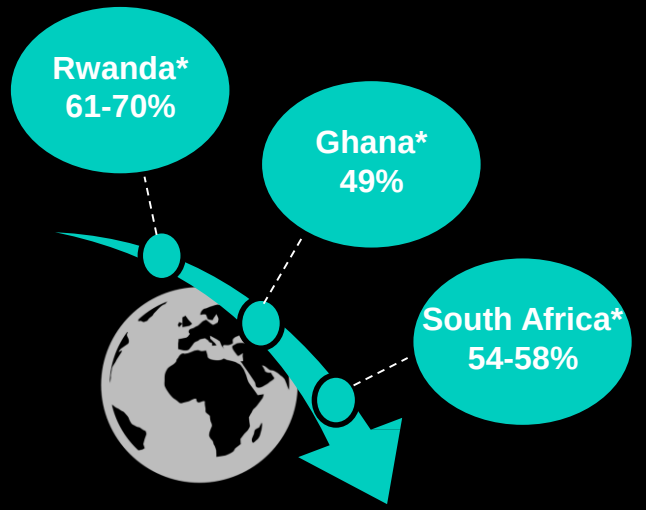
# / GLOBAL IMPACT

## Reduction in Diarrheal Hospitalizations Associated with Rotavirus Vaccines

### South & Central America




### Africa




*Rotavirus hospitalizations
**All-cause diarrhea hospitalizations

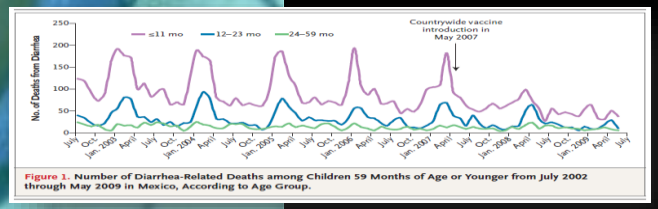



Figure 1. Number of Diarrhea-Related Deaths among Children 59 Months of Age or Younger from July 2002 through May 2009 in Mexico, According to Age Group.

Richardson V, Pichardo JH, Solares MQ et al. NEJM; 2010: 362: 358-360

**Rotavirus hospitalizations**
documented
**reductions of more than 50%**
in children