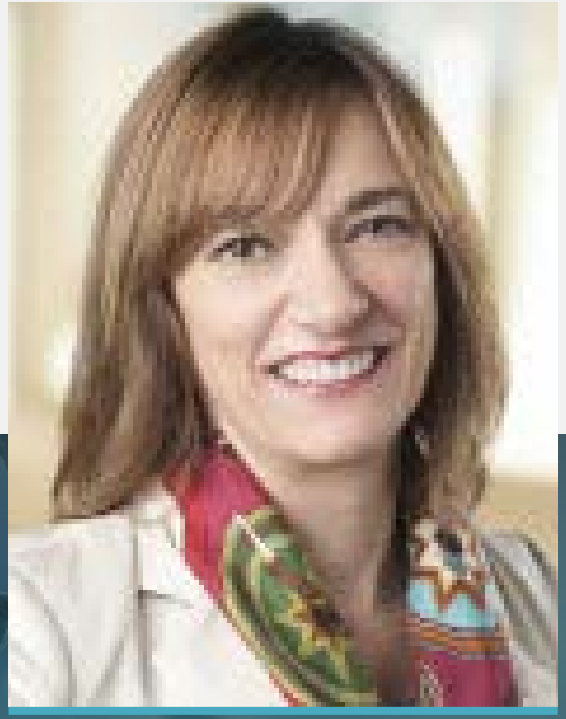

Bill & Melinda Gates
MEDICAL
RESEARCH
INSTITUTE
A NEW PARADIGM FOR TRANSLATIONAL VACCINE DEVELOPMENT
Introducing the Gates Medical Research Institute

MY JOURNEY

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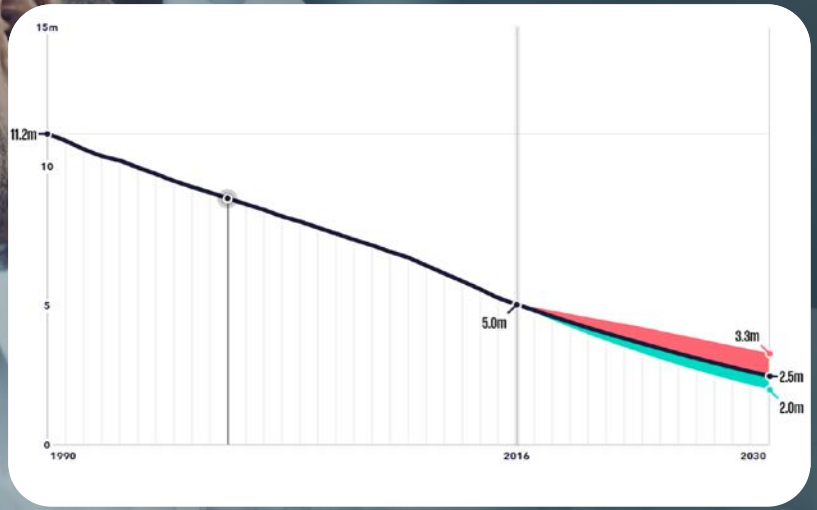
PROGRESS IN GLOBAL HEALTH

GLOBAL NUMBER OF DEATHS OF CHILDREN UNDER AGE 5 (IN MILLIONS)



“Wiping Out Polio: How The U.S. Snuffed Out A Killer”

NPR, 10/15/12

“Meningitis Vaccine Developed With Gates Foundation Drives Africa Cases to Lowest in Decade”

HuffPost, 6/6/13

“AIDS deaths halve as more get drugs”

BBC, 7/20/17

CHALLENGES REMAIN

525,000
CHILDREN UNDER AGE 5 KILLED BY ENTERIC AND DIARRHEAL DISEASES
each year[1]

430,000
DEATHS DUE TO MALARIA
in 2015[2]

1.4 Million
PEOPLE DIED FROM TUBERCULOSIS
in 2015[3]

1 WHO Diarrhoeal disease fact sheet, updated May 2017
2 WHO Global Malaria Report 2016
3 WHO Global Tuberculosis Report 2016


TOGETHER, THESE TOUGH DISEASES CAUSE OVER
4 DEATHS EVERY MINUTE


OUR MISSION

OUR MISSION

END DIARRHEAL DEATHS **IN CHILDREN**

ENTERIC AND DIARRHEAL DISEASES

A WORLD FREE OF MALARIA

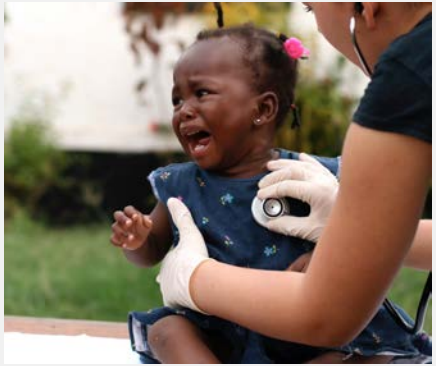
MALARIA

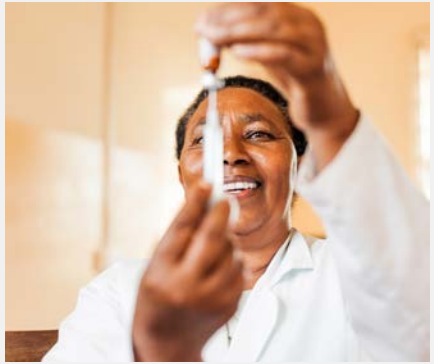
ACCELERATE THE END OF THE TUBERCULOSIS EPIDEMIC

TUBERCULOSIS


WHO WE ARE

OUR MANTRAS



URGENCY

Strive every day to do better than your last best accomplishment.

COLLABORATION

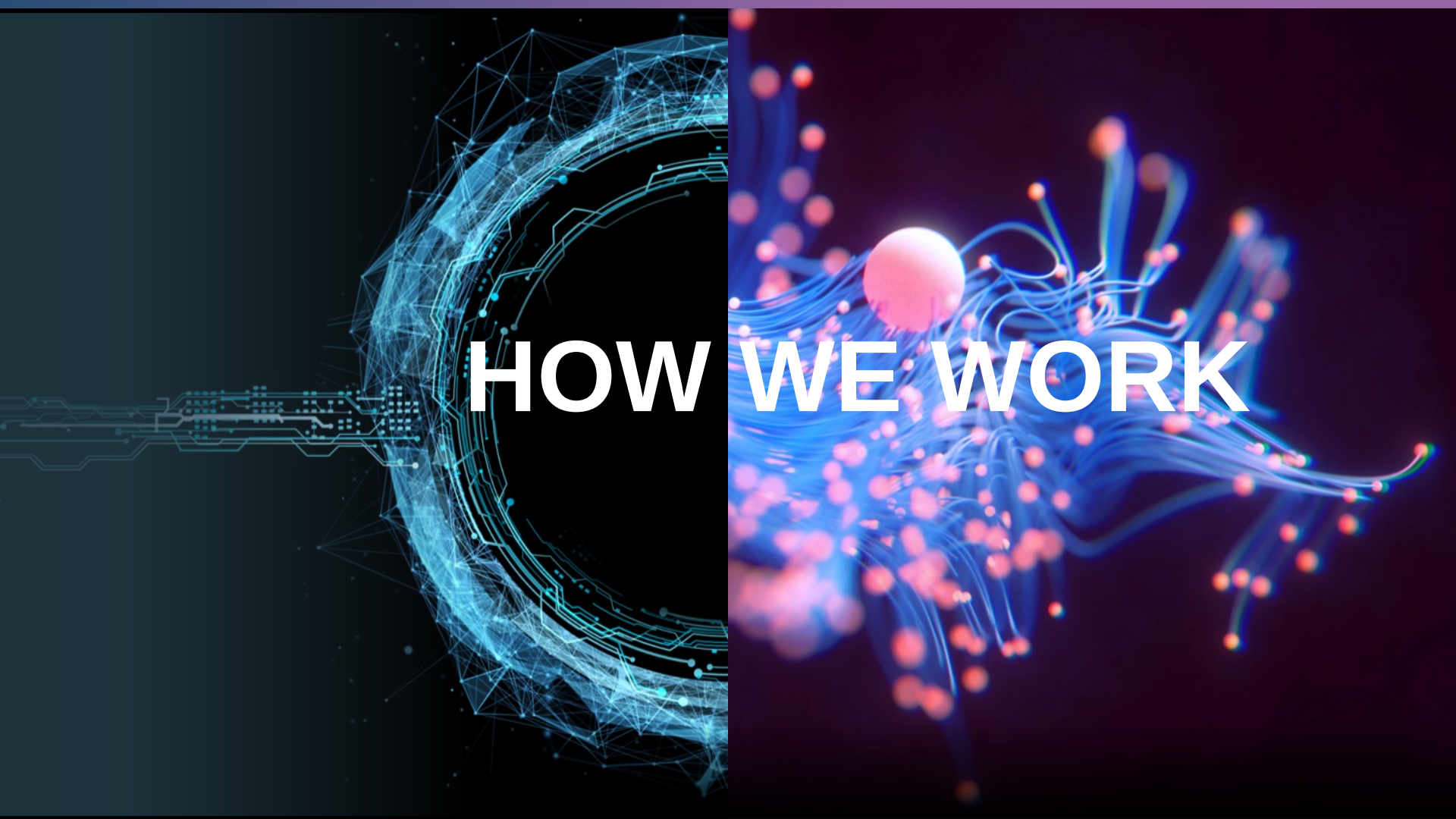
Solving the world's most complex disease burdens requires a convergence of creative genius.

INNOVATION

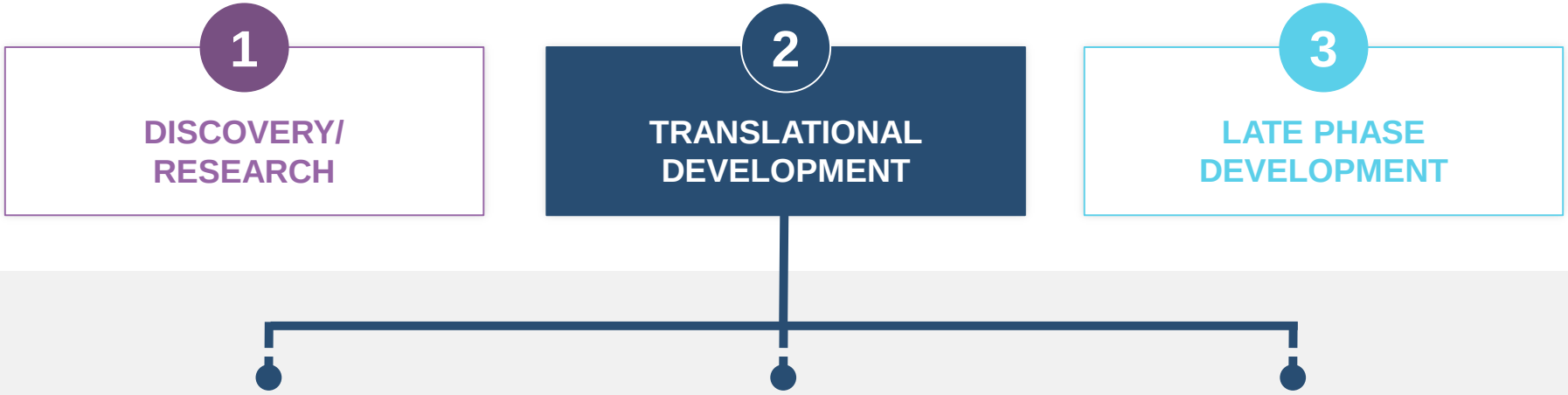
Uncover new methods, approaches, and solutions to achieve unprecedented results.

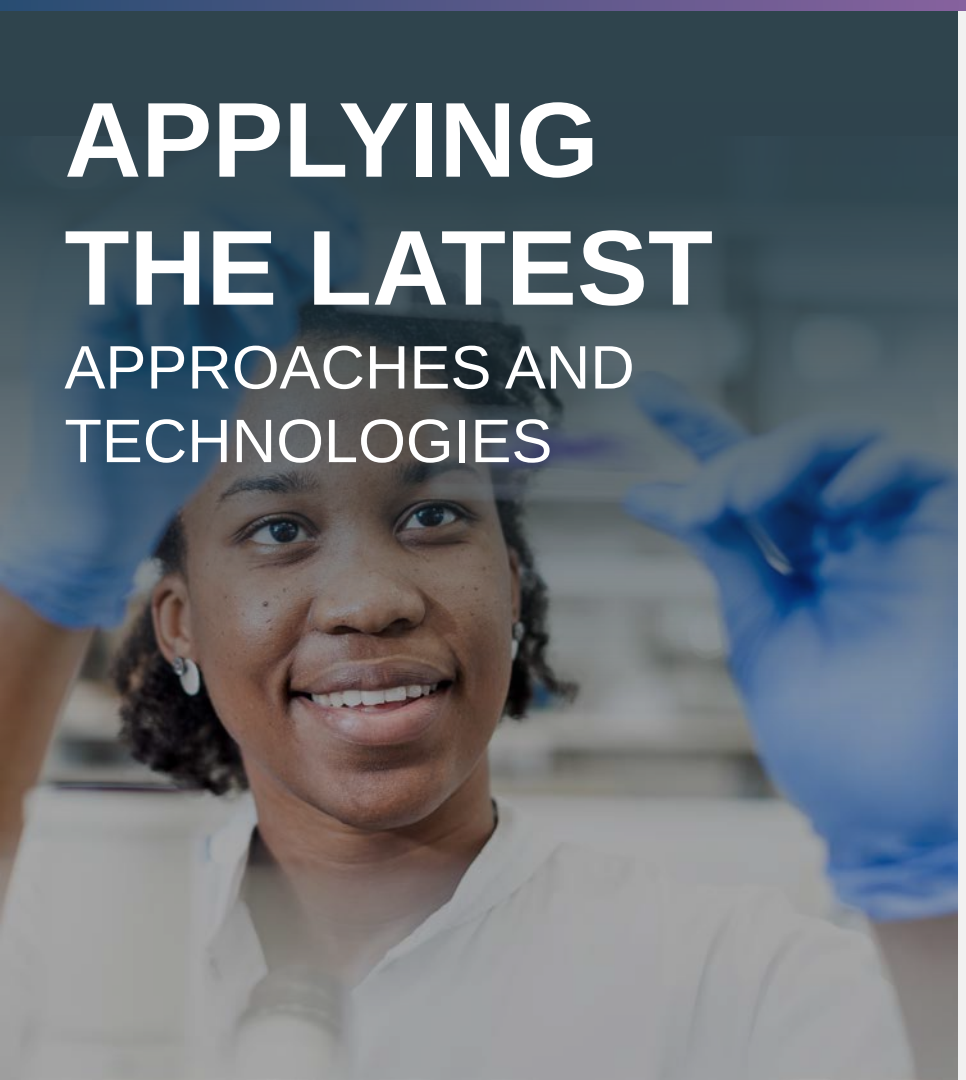
RIGOR

Follow the science with passion and perseverance.


HOW WE WORK

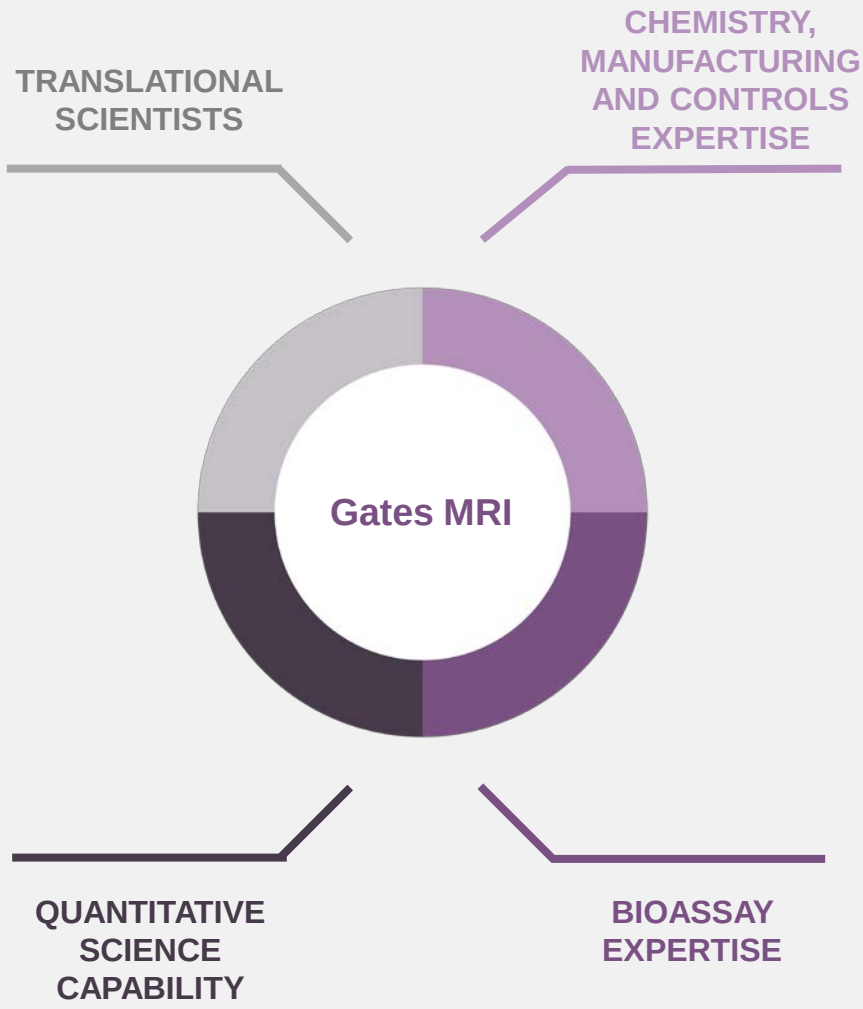
OUR PROCESS


1
DISCOVERY/
RESEARCH
2
TRANSLATIONAL
DEVELOPMENT
3
LATE PHASE
DEVELOPMENT
START
Optimization
for pre-clinical
development
MAIN
GxP studies enabling clinical
trials through ‘Proof of Concept’
in the target population
END
Effective “hand-off”
to late phase
development partners



APPLYING THE LATEST

APPROACHES AND TECHNOLOGIES



DISEASE AREA & MODALITIES

SMALL MOLECULE THERAPEUTICS

DIAGNOSTICS / BIOMARKERS[2]

VACCINES

BIOLOGICS[1]

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

ENTERIC AND DIARRHEAL DISEASES

MALARIA

TUBERCULOSIS

ROTAVIRUS VACCINES: A GIANT STEP FORWARD

END DIARRHEAL DEATHS **IN CHILDREN**

ENTERIC AND DIARRHEAL DISEASES

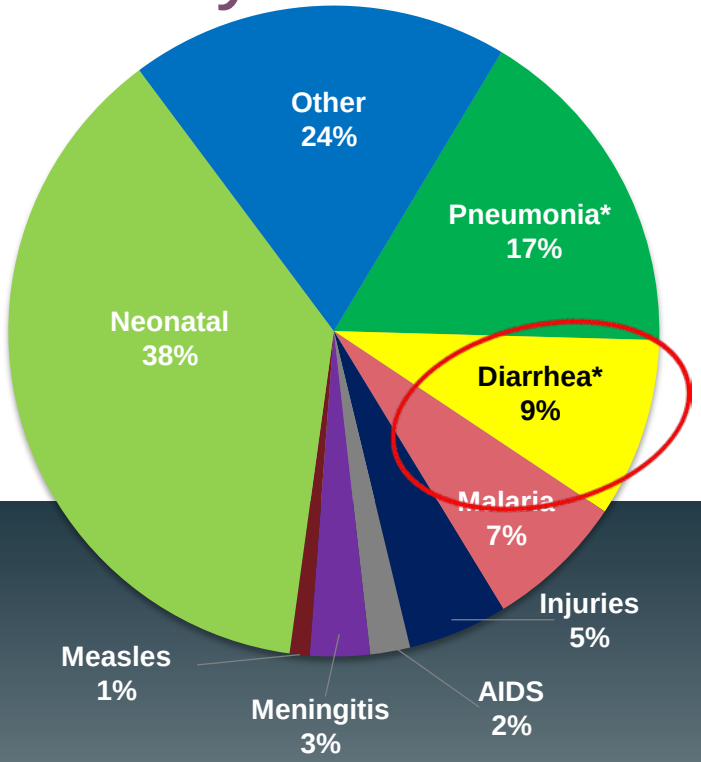
A WORLD FREE OF MALARIA

MALARIA

ACCELERATE THE END OF THE TUBERCULOSIS EPIDEMIC

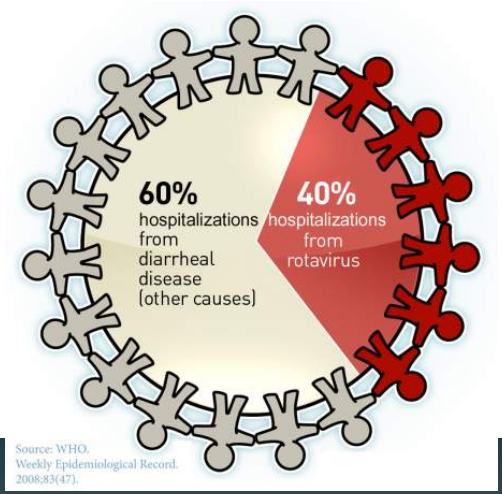
TUBERCULOSIS

Diarrhea is a leading cause of mortality in children <5

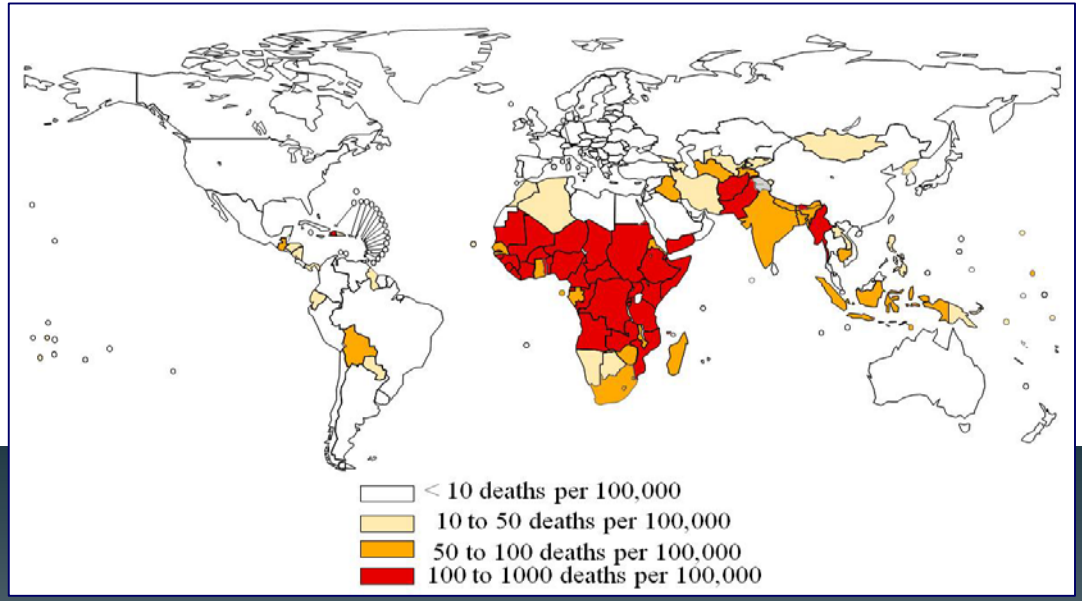


Source: CHERG 2013; *=includes neonatal deaths

Rotavirus is the most common cause of diarrhea-associated deaths in children <5



40% of all hospitalizations for diarrhea

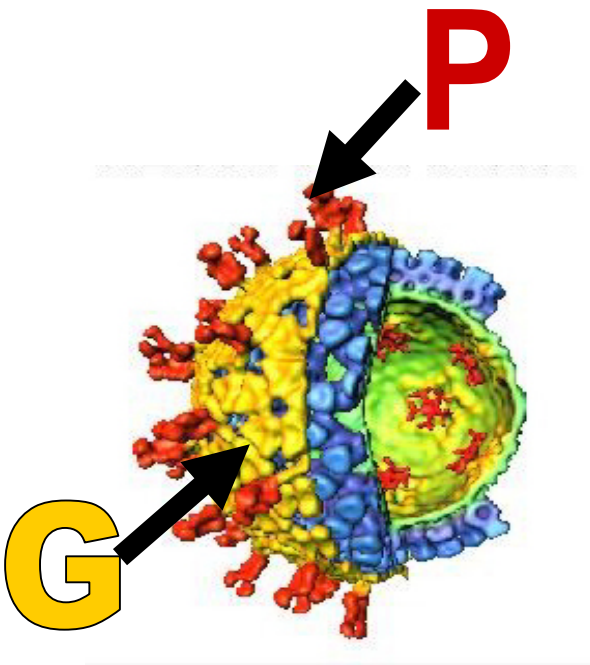


10 countries have ~85% of rotavirus-associated mortality

Tate JE, Burton AH, Boscho-Pinto C et al. Lancet Infect Dis 2010

Rotavirus Facts

- Two important antigens on outer surface that induce neutralizing antibody: Glycoprotein (G) and attachment protein (P)
- Naturally-occurring infection induces immunity against subsequent disease
- The exact mechanism responsible for immunity is still unclear



Rotavirus Vaccines: At least 4 licensed worldwide; 3 WHO Pre-qualified

- Attenuated human G1P[8] strain
- Two different human-bovine reassortant with G1, G2, G3, G4, and P1 human surface proteins
- Naturally occurring human-bovine reassortant G9P[11]

All licensed rotavirus vaccines are live viral vaccines administered orally

A Rotavirus Vaccine Story: WC3 Bovine-Human Reassortant

1981:
WC3 bovine rotavirus identified

1980's:
Safety data looked favorable but inconsistent efficacy of bovine vaccine leads to development of reassortants with human surface proteins

1991:
Licensed to Merck

1992-4:
Proof of concept (efficacy)
75% all RV GE
100% severe RV GE

1994-6:
Program stopped because of non-liquid formulation (desired presentation)

1997-1998:
Program restarted with breakthrough on liquid formulation. Immunogenicity study to identify final formulation.

To accelerate, a Phase 2b dose-ranging study of non-liquid also initiated to identify lowest efficacious dose.

1998:
RotaShield (Wyeth) licensed and recommended

1999:
RotaShield (Wyeth) withdrawn because of intussusception

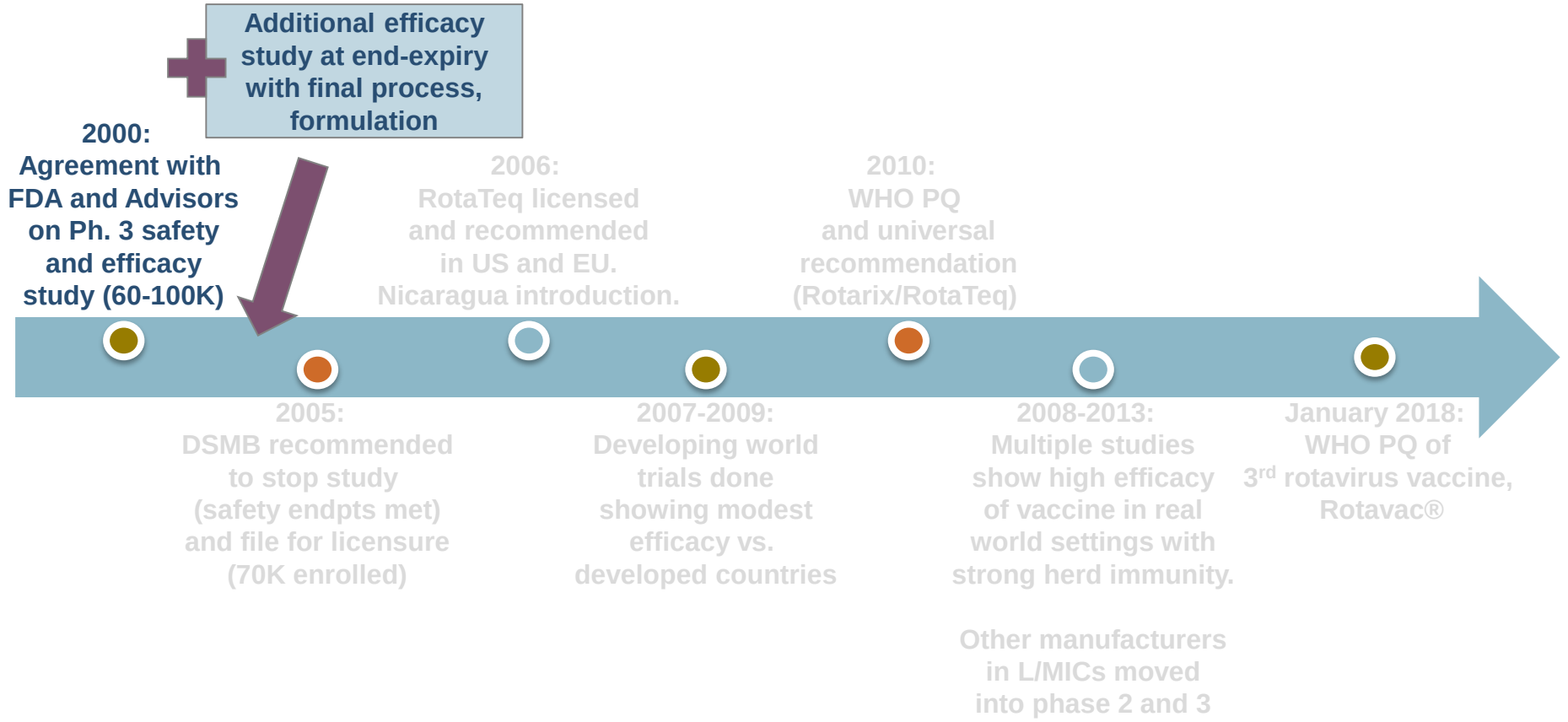
A Rotavirus Vaccine Story (Cont.)
Recap of the state of affairs in 1999-2000

- Two **efficacy studies** with favorable data **BUT** both conducted with the non-liquid formulation (~100% efficacy against severe RV GE; safety data favorable)
- A new **formulation** that showed good immunogenicity **BUT** correlation with efficacy was unknown
- A **bioprocess** nearing lock **BUT** still at small scale
- An **evolving potency assay** from plaque to MQPA
- Discussions with FDA/EMA and Scientific Advisors to begin a **large-scale Phase 3 safety study BUT** with a sample size of 60,000 to 100,000 infants
  - Intussusception is uncommon (1/2000 infant yrs)

Questions and Comments

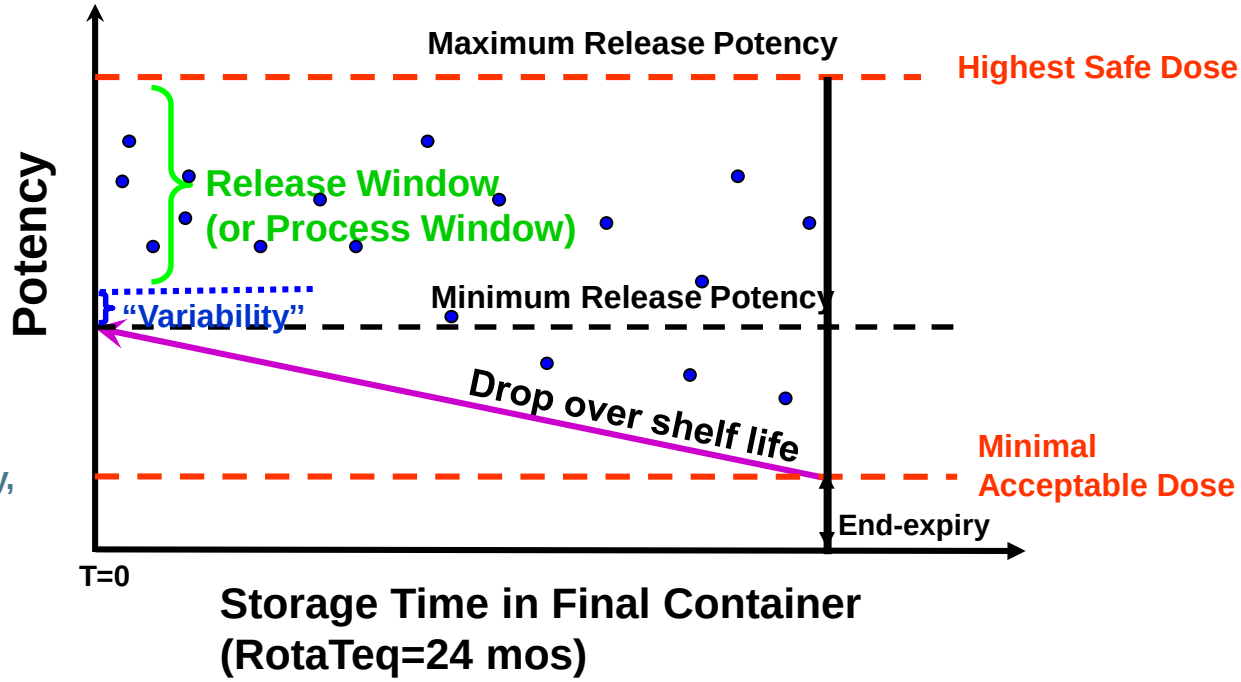
1. **For efficacy, is it possible to bridge using analytical and clinical immuno-genicity data or is another efficacy study needed?**
2. **For the large-scale safety study, what dose / dose range should be targeted?**
3. **The vaccine is a live virus**

The Rotavirus Vaccine (Cont.)



Clinical data informed target dose of vaccine campaigns for large-scale trial and ultimately informed the potency spec for commercial vaccine

- For the safety trial, we targeted doses that were anticipated to be within the range of release for the commercial vaccine
- We continuously monitored blinded safety data and increased the target dose of new vaccine campaigns over the course of the study
  - Confirmed vaccine safety over a range of doses and widened the release window
- The efficacy data from the repeat study, stability data and safety data informed the potency specifications for the commercial vaccine



The Rotavirus Vaccine (Cont.)

Additional efficacy study at end-expiry with final process, formulation

2000: Agreemen… FDA and A… on Ph. 3 … and efficacy study (60-100K)

GAVI forms Rotavirus Vaccine Program (PATH)

2005: DSMB recommended to stop study (safety endpts met) and file for licensure (70K enrolled)

2006: RotaTeq licensed and recommended in US and EU. Nicaragua introduction.

2007-2009: Developing world trials done showing modest efficacy vs. developed countries


World Health Organization
Weekly epidemiological record
Relevé épidémiologique hebdomadaire

2010: WHO PQ and universal recommendation (Rotarix/RotaTeq)

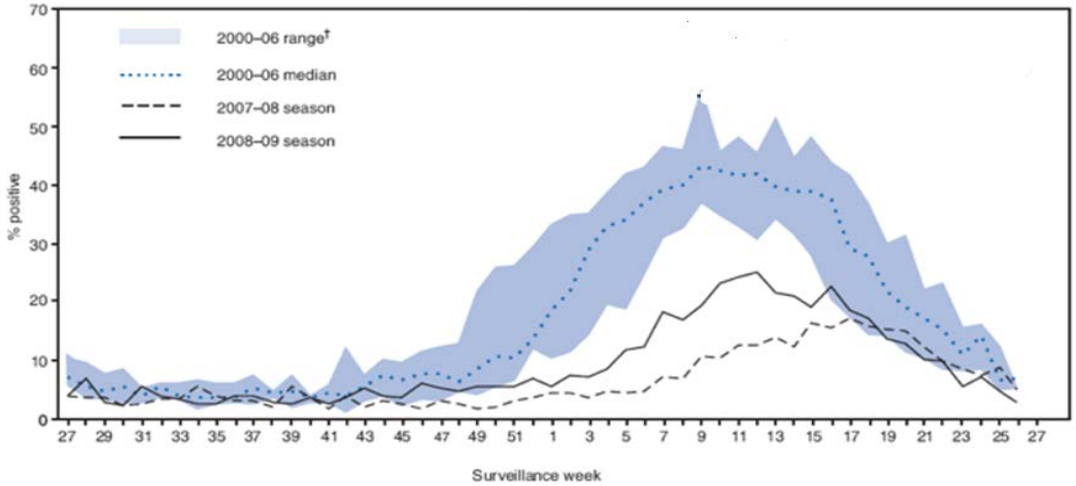
2008-2013: Multiple studies show high efficacy of vaccine in real world settings with strong herd immunity.

Other manufacturers in L/MICs moved into phase 2 and 3

January 2018: WHO PQ of 3rd rotavirus vaccine, Rotavac®

Impact of Rotavirus Vaccine on rotavirus disease in the United States

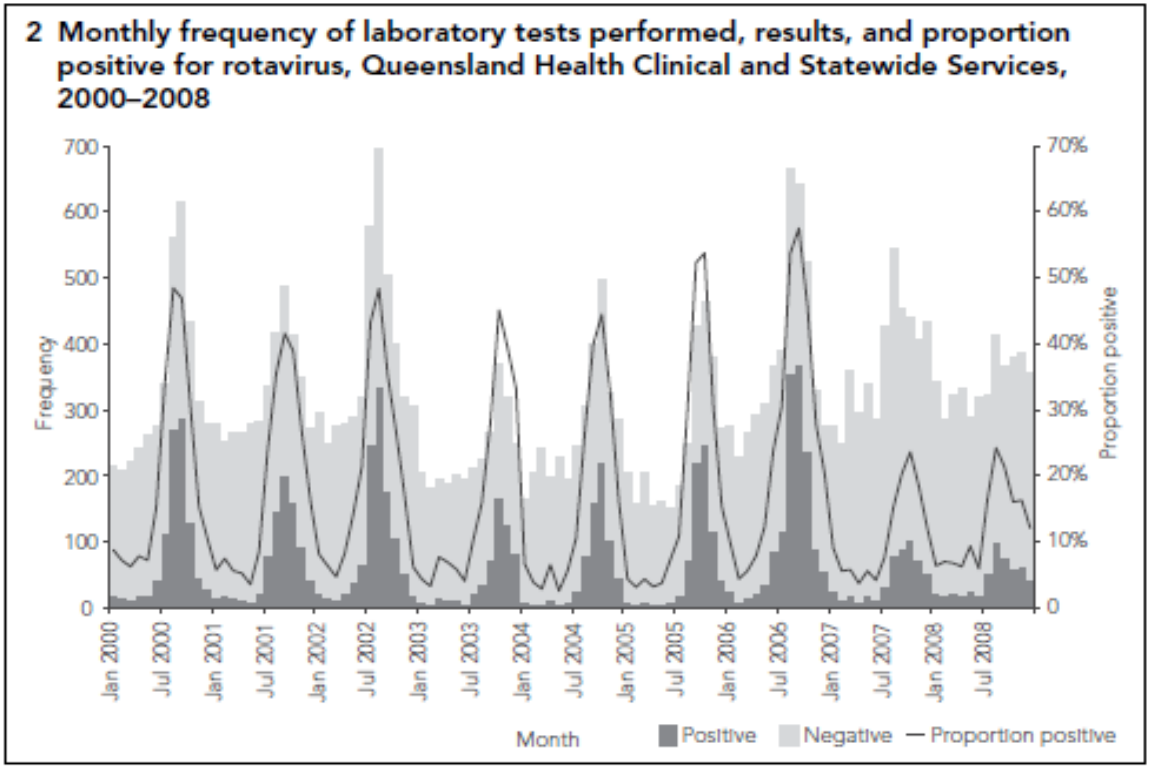
Hospitalizations for gastroenteritis have been significantly reduced among individuals 0 to ≤44 years of age in the post- vs. pre-vaccine era



From 2008-2013, rotavirus vaccines reduced the number of acute gastroenteritis-related hospitalizations by 382K, saving $1.228 billion

Gastanaduy PA, Curns AT, Parashar UD, et al JAMA 2013;310: 851-53
CDC data. MMWR 2009 (58)41: 1146-49; Leshem E, et al. *J Pediatric Infect Dis Soc*. 2017. doi:10.1093/jpids/pix057

Impact of Rotavirus Vaccine on rotavirus disease in Australia



Lambert SB, Faux CE, Hall L et al, Med J Aus 2009; 191:157-60

Reduction in diarrheal disease deaths after introduction of Rotavirus Vaccine in Mexico

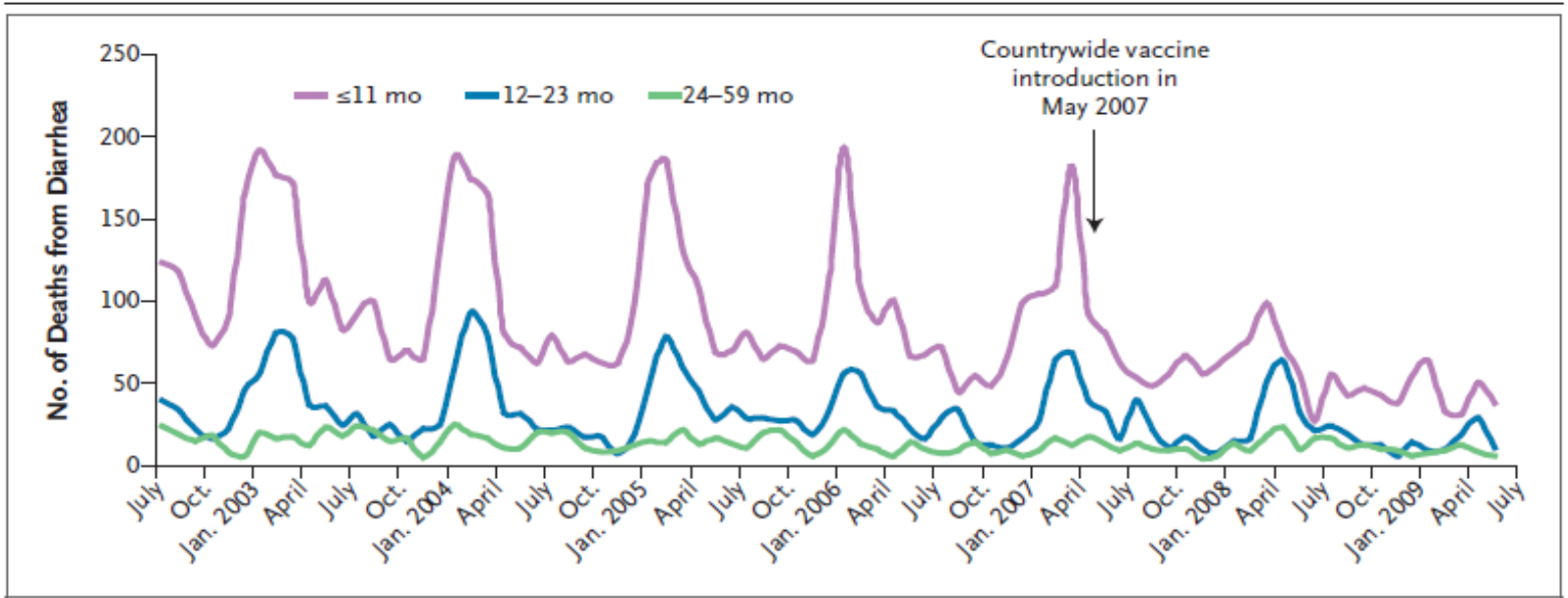
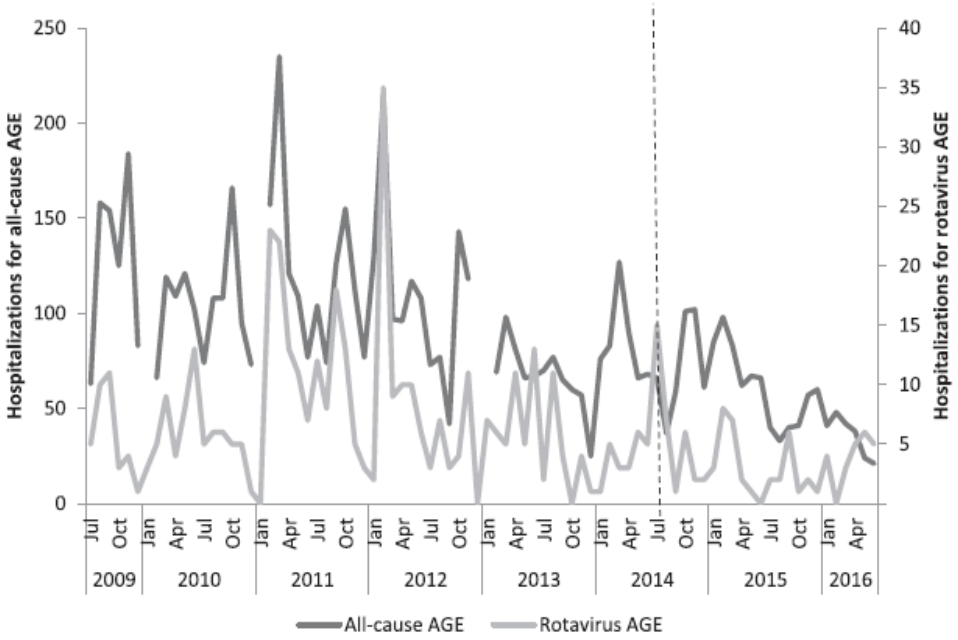


Figure 1. Number of Diarrhea-Related Deaths among Children 59 Months of Age or Younger from July 2002 through May 2009 in Mexico, According to Age Group.

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

Reduction in hospitalizations for rotavirus and all-cause acute gastroenteritis in children <5 in Kenya



http://dx.doi.org/10.1016/j.vaccine.2017.07.096

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Opportunities for innovation in enteric vaccines?

What if there had been a "good" animal model for intussusception? A feasible model for rotavirus disease?

What if an immunologic correlate of protection had been identified?

Nearly real-time safety monitoring

Group sequential (adaptive) design feasible because of diagnostic clarity for intussusception


LOOKING AHEAD

PROGRESS THROUGH PARTNERSHIP

1

DISCOVERY/ RESEARCH

EARLY RESEARCH PARTNERS

Academic centers/Institutes
Pharma industry
Product development partnerships

2

TRANSLATIONAL DEVELOPMENT

TRANSLATIONAL DEVELOPMENT PARTNERS

Academic, clinical, industry, and community partners

3

LATE PHASE DEVELOPMENT

LATE DEVELOPMENT PARTNERS

Pharma industry
Product development partnerships

Benefits applied across the whole of the global health ecosystem

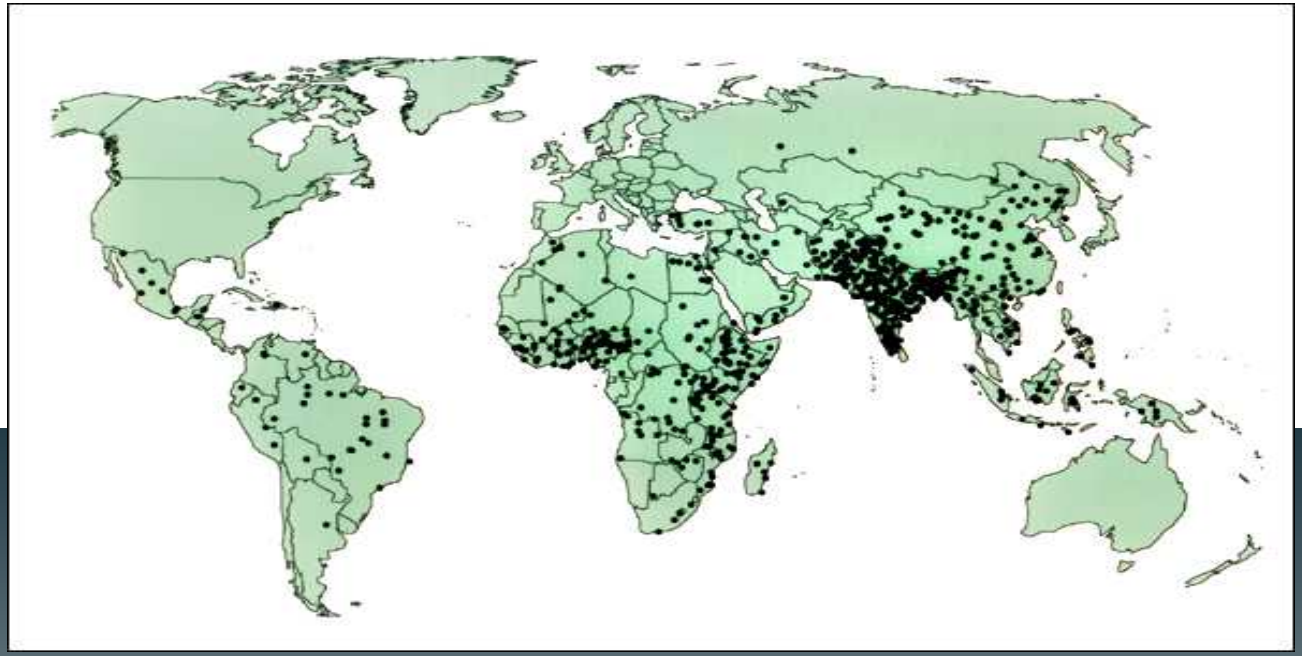
ABOUT THE GATES MRI

Location	**Boston / Cambridge** **Seattle**
Structure	**Funded by a grant from the Gates Foundation**
Portfolio	**Initial focus on EDD, TB, and malaria, with initial candidates in Y1 pipeline**
Size	**~50 FTEs, including support functions, in Y1, scaling up as portfolio grows**
Quality Management System	**Working with experts to develop quality and compliance systems**


OUR ONLY BOTTOM LINE IS THE
NUMBER OF LIVES SAVED


Thank You

Rotavirus: 500K deaths in children <5



Each dot represents 1000 deaths