A NEW PARADIGM FOR TRANSLATIONAL VACCINE DEVELOPMENT

Introducing the Gates Medical Research Institute
MY JOURNEY
A NEW PARADIGM FOR TRANSLATIONAL VACCINE DEVELOPMENT

Introducing the Gates Medical Research Institute
PROGRESS IN GLOBAL HEALTH

“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

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

1. 525,000 children under age 5 killed by enteric and diarrheal diseases each year¹

2. 430,000 deaths due to malaria in 2015²

3. 1.4 Million people died from tuberculosis in 2015³

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
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
   - Optimization for pre-clinical development

2. TRANSLATIONAL DEVELOPMENT
   - GxP studies enabling clinical trials through ‘Proof of Concept’ in the target population

3. LATE PHASE DEVELOPMENT
   - Effective “hand-off” to late phase development partners
APPLYING THE LATEST APPROACHES AND TECHNOLOGIES

TRANSLATIONAL SCIENTISTS

CHEMISTRY, MANUFACTURING AND CONTROLS EXPERTISE

QUANTITATIVE SCIENCE CAPABILITY

BIOASSAY EXPERTISE

Gates MRI
**DISEASE AREA & MODALITIES**

- **SMALL MOLECULE THERAPEUTICS**
- **DIAGNOSTICS / BIOMARKERS**
- **VACCINES**
- **BIOLOGICS**

**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

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**ENTERIC AND DIARRHEAL DISEASES**

**MALARIA**

**TUBERCULOSIS**
ROTAVIRUS VACCINES: A GIANT STEP FORWARD

- End diarrheal deaths in children
- A world free of malaria
- Accelerate the end of the tuberculosis epidemic

Enteric and diarrheal diseases
Malaria
Tuberculosis
Diarrhea is a leading cause of mortality in children <5

- Diarrhea*: 9%
- Neonatal: 38%
- Other: 24%
- Pneumonia*: 17%
- Malaria: 7%
- Measles: 1%
- Meningitis: 3%
- Injuries: 5%
- AIDS: 2%
- Other: 24%

* = includes neonatal deaths

Source: CHERG 2013
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
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)


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 immunogenicity 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.)**

- **2000:** Agreement with FDA and Advisors on Ph. 3 safety and efficacy study (60-100K)
- **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
- **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.
- **January 2018:** WHO PQ of 3rd rotavirus vaccine, Rotavac®

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

![Graph showing potency vs storage time with release window and variability](image-url)
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- **2008-2013:** WHO PQ of 3rd rotavirus vaccine, Rotavac®
- **January 2018:** GAVI forms Rotavirus Vaccine Program (PATH)
- **Additional efficacy study at end-expiry with final process, formulation**
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

Impact of Rotavirus Vaccine on rotavirus disease in Australia

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
The Rotavirus Vaccine (Cont.)

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2018:
- January 2018: WHO PQ of 3rd rotavirus vaccine, Rotavac®
Opportunities for innovation in enteric vaccines?

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

Nearly real-time safety monitoring

What if an immunologic correlate of protection had been identified?

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
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<th><strong>ABOUT THE GATES MRI</strong></th>
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<td>Boston / Cambridge</td>
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OUR ONLY BOTTOM LINE IS THE NUMBER OF LIVES SAVED
Thank You
Rotavirus: 500K deaths in children <5

Each dot represents 1000 deaths