HOW PHARMACOLOGY AND QUANTITATIVE METHODOLOGIES ARE IMPACTING GLOBAL HEALTH: A PERSPECTIVE FROM THE BILL AND MELINDA GATES FOUNDATION

Dan Hartman, M.D.
Director, Integrated Development
“Dad, maybe we can do something about this.”

1997 note from Bill and Melinda Gates to Bill’s dad, William H gates
EVERY PERSON DESERVES THE CHANCE TO LIVE A HEALTHY, PRODUCTIVE LIFE
OUR HISTORY

1994
Bill Gates Sr. starts a small philanthropic foundation at his son’s request.

1997
Bill and Melinda read an article about rotavirus and are inspired to act.

2000
The Bill & Melinda Gates Foundation is created, with a focus on health, education, and libraries.

2006
Warren Buffett pledges Berkshire Hathaway stock valued at $31 billion.

2008
Bill joins Melinda full-time at the foundation.

2011
The foundation moves to its new permanent home in Seattle.
OUR GLOBAL REACH AND PRESENCE

- 1,500+ 2015 active grantees
- $4.2B 2015 grant payments
- 1,300+ 2015 employees worldwide
- $40B Trust endowment
WHAT WE DO

GLOBAL HEALTH

GLOBAL DEVELOPMENT

UNITED STATES PROGRAM

GLOBAL POLICY & ADVOCACY

COMMUNICATIONS
GLOBAL DEVELOPMENT

Delivering health and development solutions that help people lift themselves out of poverty.

Programs:
Agricultural Development
Emergency Response
Family Planning
Financial Services for the Poor
Global Libraries
Maternal, Neonatal & Child Health
Nutrition
Polio
Water, Sanitation & Hygiene
Discovering and developing affordable vaccines, drugs, and diagnostics for people in the developing world.

**Programs:**
- Enteric and Diarrheal Diseases
- HIV
- Malaria
- Neglected Tropical Diseases
- Pneumonia
- Tuberculosis
INTEGRATED DEVELOPMENT:

• 17 technical experts working with >50 external subject matter experts
• 73 products – 70% drugs, 25% diagnostics and 5 vector control

Aim to achieve greatest impact in the shortest period of time with the least amount of human and financial resources
THE FOUNDATION’S THERAPEUTICS PORTFOLIO IS DIVERSE WITH ~$1B IN ACTIVE INVESTMENTS

Portfolio summary

- **Approximately 60 programs** across all stages of development
- **Over 25 partners** with a wide range of technologies and experience
- **Funded by 9 disease areas** across the Foundation

**Portfolio by therapeutic area**

- Malaria: 29%
- HIV: 17%
- NTD: 16%
- TB: 14%
- Family Planning: 13%
- Other: 13%

**Portfolio by technology**

- Standard solid orals: 27%
- Long-acting injectables & implantables: 22%
- Complex solid orals: 40%
- Other complex drug delivery: 11%

**NCE’s versus new dosage forms**

- NCE’s: 62%
- Reformulation or new process: 38%
HOW WE DEVELOP OUR STRATEGIES

- Overall impact
- Cost effectiveness ($/DALY)
- Define what resources are needed (money/people)
- Understand the probability of technical and regulatory AND delivery success.
- Is it catalytic?
Where we work
TB causes more Disability Adjusted Life Years (DALYs) than Diabetes

- Only one new product approved in 40 years for TB – only in second line therapy and only as add on to other drugs
- In type II diabetes, 6 new products were approved in 2013 and 2014

### FACTS ABOUT THE GEOGRAPHIES WE WORK

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<td>111.8</td>
<td>88.8</td>
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</table>

¹ WHO World Health Statistics 2014; ² WB country data 2014; ³ WHO NCD report 2014; ⁴ UNICEF country statistics 2013
THE DEMOCRATIC REPUBLIC OF CONGO IS ABOUT 2/3 THE SIZE OF WESTERN EUROPE

- Last formal census: 1984
- Estimated population is 70-80 M
- 200 ethnic groups with major regional linguistic variation
- Life expectancy: 49.6 years
- Infant mortality: 73.15/1,000 live births
- 1400 miles of paved roads – ½ in “good” condition
The changing shape of global population

Population 2010

Mismatch between disease burden...malaria deaths

Source: http://www.worldmapper.org/
Mismatch between disease burden...HIV prevalence
Mismatch between disease burden...TB cases
Mismatch between disease burden...Diarrhea prevalence
Mismatch between disease burden... early neonate mortality
...and available medical care…

Source: http://www.worldmapper.org/
…or biomedical research
REGULATORY CHALLENGES AND ADVANCES IN LOW INCOME COUNTRIES
GENERAL PROCESS IN HIGH-INCOME COUNTRIES

“Closed”, linear highly regulated, proscribed system
Helps assure product quality, safety, efficacy and supply chain security
“Open”, loosely (if at all) regulated, multifaceted, complex system
Helps assure products of uncertain quality, safety, efficacy and supply chains that are insecure
### Key strategic axes

- **Promote “horizontal” integration**
  - focus on value-added activities
  - minimize redundancy
  - maximize **reliance**

- **Promote “vertical” efficiency**
  - process improvements
  - project management
  - enforcing PQ standards in mfg countries

### Medcines and Vaccines Registration Data

<table>
<thead>
<tr>
<th></th>
<th>1st RA approval time</th>
<th>PQ approval time</th>
<th>Spread in RA submissions</th>
<th>SSAfrica approval time</th>
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</thead>
<tbody>
<tr>
<td><strong>Medicines</strong></td>
<td></td>
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<tr>
<td>SRA</td>
<td>10 months</td>
<td>4</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>NRA</td>
<td>~12</td>
<td>27</td>
<td>~24</td>
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<td><strong>Vaccines</strong></td>
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<td>SRA</td>
<td>15</td>
<td>16</td>
<td>78</td>
<td>16</td>
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<tr>
<td>NRA</td>
<td>~12</td>
<td>16</td>
<td>N/A</td>
<td>N/A</td>
</tr>
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</table>

**SRA:** Stringent Regulatory Authority (e.g. US FDA, EMA); **NRA:** National Regulatory Authority (e.g. India CDSCO, China FDA)
AFRICAN REGULATORY HARMONIZATION VISION

55 countries → 6 regions → 1 continent
### Key Regulatory Systems Accomplishments 2014/15

<table>
<thead>
<tr>
<th>Major performance improvements in WHO-PQ for medicines and vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-35% reduction in vaccines PQ timelines (20-50% for WHO time) vs. &lt;2013 baseline</td>
</tr>
<tr>
<td>10-25% reduction in medicines PQ timelines (10-25% for WHO time)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major productivity improvement in WHO-PQ for diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 diagnostics PQed in 2015 vs. historical average of 9 products / year</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Achieved “new normal” for local registration of PQed medicines: &lt;90 days</th>
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<tbody>
<tr>
<td>120+ registrations performed under PQ collaborative procedure (27 countries enrolled)</td>
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</table>

<table>
<thead>
<tr>
<th>Regional product registration system established in East Africa*</th>
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<tbody>
<tr>
<td>Single dossier submission for all 6 regulatory authorities</td>
</tr>
<tr>
<td>First joint regional review of 8 dossiers (NCEs and generics) completed in Oct. 2015</td>
</tr>
<tr>
<td>Multiple joint reviews planned for 2016 (25+ products in the pipeline)</td>
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<tr>
<td>Currently expanding to <strong>West Africa</strong> and <strong>Southern Africa</strong></td>
</tr>
</tbody>
</table>

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*Includes Tanzania, Uganda, Kenya, Rwanda, Burundi, and Zanzibar*
One-third of the world’s population is estimated to have Latent TB Infection (LTBI):

- A state of persistent immune response to *Mtb*, without evidence of clinically active TB.
- ~5–10% convert to active disease, the majority within the first five years after initial infection.

9.0 million new cases of active TB in 2013

1.5 million deaths

- TB surpassed HIV and is #1 killer, death due to infectious agent
- HIV/TB co-infection is a problem, 25% of HIV deaths due to TB

Treatment effectiveness

- Drug sensitive - 85-90% with 6 months therapy
- Drug resistant – 50% with up to 20 months therapy

FEEDBACK SYSTEM CONTROL (FSC) APPROACH TO COMBINATION THERAPY

PRELIMINARY RESULTS

Acknowledgement:
Dr. Chih-Ming Ho, Director, Institute for Cell Mimetic Space Exploration, Professor of Mechanical and Aerospace Engineering
UCLA Associate Vice Chancellor for Research and Ben Rich-Lockheed Martin Chair Professor in School of Engineering

Dr. Marcus Horwitz, MD, Distinguished Professor of Medicine and Microbiology, Immunology, & Molecular Genetics- UCLA

Output-driven Feedback System Control platform optimizes combinatorial therapy of tuberculosis using a macrophage cell culture model.
The successful rate of combinatorial drug development from in vitro test to clinical trial is in single digit range. How do we de-risk and improve the successful rate?

- In single drug treatment, the efficacy (and toxicity) increase with dose.
- Due to synergetic or antagonist interactions in combinatorial drug, dose of each drug becomes an important parameter in determining the efficacy.
- \( Y \) drugs with \( X \) doses ends with \( X^Y \) combinations.
- 14 drugs were used for initial search. If 5 dose levels were used for optimization, 6 billion combinations needed to be tested by conventional method.

TB – FSC APPROACH

The successful rate of combinatorial drug development from in vitro test to clinical trial is in single digit range. How do we de-risk and improve the successful rate?

- In single drug treatment, the efficacy (and toxicity) increase with dose.
- Due to synergetic or antagonist interactions in combinatorial drug, dose of each drug becomes an important parameter in determining the efficacy.
- \( Y \) drugs with \( X \) doses ends with \( X^Y \) combinations.
- 14 drugs were used for initial search. If 5 dose levels were used for optimization, 6 billion combinations needed to be tested by conventional method.

Prior experimental studies with FSC demonstrated that the efficacy-dose response surface fits well with a second order algebraic equation, which can be represented by a parabolic response surface (PRS). With experimental tests equal to the number of the coefficients of the algebraic equation, the entire landscape of the parabolic response surface can be determined rapidly locating the optimal drug-dose combination without testing all $X^Y$ possible combinations.
In vitro test: 14 drugs were used in cell line search. The second order algebraic equation with 14 variables has 120 coefficients. With only 120 tests determine the entire landscape and locate the optimal combinations.

- Of all the three- or four-drug combinations only about 20 had high efficacies.
- The top two four-drug candidates for preclinical tests.
• Close to 1M people die from malaria annually and over 700,000 are less than 5 years old.
MALARIA PARASITE INFECTION LIFECYCLE

Figure: Alavi, et. al., Int J Parasitol. 2003 Aug;33(9):933-43.
DELIBERATELY INDUCED HUMAN MALARIA: EXPERIMENTAL MALARIA INFECTION WITH BLOOD STAGE PARASITES

*P falciparum* 3D7 gametocyte culture

*Anopheles stephensi*

9 infective bites

10-14 days

Initiate therapy after 7 days
## CLINICAL TRIAL DESIGN

**Day**

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- **Rx test drug**
- **Parasite Inoculation**
- **Clearance of asexual parasitemia over 48-96 hrs**
- **PCR (parasites)**
- **PCR (gametocytes)**
- **Rescue Drug Treatment as needed**
PCR CLEARANCE RATES

Slope of fitted curve for Artemether-lumefantrine: 1.44 (1.04-1.84)/day; PRR 759

Slope of fitted curve for Atovaquone-proguanil: 0.61 (0.42-0.80)/day; PRR 17
DOSE RANGING WITH MEFLOQUINE 5, 10, 15 MG/ML
DEFINING THE DOSE-RESPONSE IN HUMANS MIC DETERMINATION

Australian Volunteers
(100-500mg)

Thai Patients (100 mg)

1 month per cohort, 1 centre
All year round

6 months, 4 centres, seasonal
TRANSLATIONAL APPROACH REDUCES TIME AND COST

<table>
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<tr>
<th>Impact</th>
<th>Time (years)</th>
<th>Subject or patients</th>
<th>Cost saving ($M)</th>
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<tr>
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<td>Before</td>
<td>After</td>
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<tr>
<td>Earlier knowledge of PK/PD relationship</td>
<td>PoC</td>
<td>PoP</td>
<td>70</td>
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<td>Shorter/smaller PoP study</td>
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<tr>
<td>Shorter/smaller PoC</td>
<td>1.5</td>
<td>0.8</td>
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</table>
FAMILY PLANNING
220 million+ women in developing countries lack access to modern contraceptives leading to an estimated 80 million women with an unintended pregnancy.

THE OPPORTUNITY

- Reduction in unintended pregnancy by 70% (50M annually)
- Maternal deaths would drop by 67% (200,000 fewer deaths)
- New born deaths would drop by 77% (2.3M annually)
“Family planning and access to contraception—including information, supplies, and services—is an issue that I am passionate about, and it has become one of my personal priorities at the foundation. I believe it’s one of the most urgent issues of our time.”

—Melinda Gates
PROGRAMMABLE 15 YEAR CONTRACEPTIVE PRODUCT

**PTH Clinical Device**

- Size: 53 mm x 31 mm x 11 mm
- Drug Vol = 0.6 µg/mm³
- Device Vol

**Developed Device**

- Size: 28 mm x 22 mm x 7.5 mm
- Drug Vol = 87 µg/mm³
- 145x Improvement
- 5x longer life
- 725x Improvement
Lyndra’s products fit in a standard 00 capsule and are swallowed as a familiar pill.

The capsule dissolves and the system adopts its active configuration within the stomach; freely resides in the stomach without disrupting the mucosal barrier for a tunable period of time as drug is released from the system through controlled release technology.

Linkages within Lyndra’s products dissolve/break based on hydration, pH, and time-dependent factors to produce fragments that pass safely through the lower GI tract.
THE THREE COMPONENTS OF LYNDRA’S GASTRIC RESIDENCE PRODUCTS

- Drug-polymer blend
- time-dependent linker
- enteric safety linker
- thermoset rubber

Elastomer

Drug – Polymer Arm

Linkers

Linkers Dissolve in Time- and pH-Dependent Manners to Control Gastric Exit and Safety

pH 1.0 Stomach
Linkers intact

pH 7.0 Small Intestine
Linkers dissolved
PHARMACOKINETIC BENEFITS OF LYNDRA’S SYSTEM

**Continuous drug delivery to upper GI tract**
- Reduced $C_{\text{max}}$
- Potential for improved solubility, absorption, bioavailability
- Sustained PK
- Duration tunable from 1 day to > 7 days
SUSTAINING SERUM LEVELS WITH LYNDRA’S TECHNOLOGY

Serum Ivermectin (Stromectol) n=3 pigs

Serum doxycycline (100mg IR capsule) n=3 pigs

AUC: 85.9 ng/ml *day

Lyndra-Ivermectin n=3 pigs

AUC: 2180 ng/ml *day

Lyndra - Doxycycline n=3 pigs
TUNABLE RATE AND DURATION OF RELEASE

- In vitro release profiles tuned using standard excipients and methods
- Technology works with hydrophilic, hydrophobic, and lipophilic small molecule compounds
PIPELINE OF INNOVATIONS

• 3-12 month injectable ARV treatment and prevention
• Replace multiple dose vaccines with a single dose vaccines
• Injectable implants that can release drug for 6-24 months
• 11 essential micronutrients that are heat and humidity stable
• Inhaled surfactant
HEALTHY BIRTH, GROWTH & DEVELOPMENT

knowledge integration
BMGF MATERNAL & CHILD HEALTH STUDIES THROUGH 2013- ~US$500 MILLION

Legend
Population
Non-pregnant women of reproductive age
Pregnant women
Children (0-4 years)
Infants (0-24m)
Newborns (0-6m)
Non-pregnant women of reproductive age; Infants (0-24m)
Non-pregnant women; Newborns (0-6m)
Non-pregnant women of reproductive age; Newborns (0-6m)
Mixed cohort (3+ groups)
Outcomes
Anthropometry
Immune response; anthropometry
Immune response; morbidity
Morbidity; mortality
Mortality
Interventions
Therapeutic
Nutritional
Nutritional; behavioral; environmental
Nutritional; therapeutic; behavioral
None

The Americas (ex-US)
14 sites
10 studies
~$25M invested
~7k subjects

Europe / Middle East
5 sites
3 studies
~$10M invested
~3k subjects

Asia - Pacific
53 sites
33 studies
~$190M invested
~570k subjects

Africa
53 sites
34 studies
~$190M invested
~450k subjects

Note: 2 grants do not have sites listed, therefore not included in this slide

Random text added for padding
RESULTS FROM INVESTMENT: GROWTH & DEVELOPMENT NETWORK WEB

Neurocognitive Growth & Development

Child’s early experience at age 0-24 months

Motor development

Infant temperament

Breastfeeding status

Micronutrient intake

Iron status

Nutrient intake

Growth velocity

HAZ scores

Repetitive enteric infections

Reasoning skills

Depressive symptoms

Socioeconomic status

Environment

Home

Mother/caretaker

Somatic growth
HOW CAN WE MAXIMIZE THE UTILITY OF AVAILABLE DATA?
MECHANISTIC BIOLOGICAL CAUSES

- Reduced nutritional intake
- Reduced absorption and transfer
- Metabolism / physiological control of growth
- Increased demand
- Other / unknown

OVERARCHING: ECONOMIC – POLITICAL & INSTITUTIONAL – SOCIO-CULTURAL & BEHAVIORAL - ENVIRONMENTAL

IMMEDIATE:

- Preconception and pregnancy

FIRST 2 YEARS

- Suboptimal feeding
- Frequent infections
- Inadequate nutritional intake (quantity, quality of macro and micronutrients)
- Inadequate health or functioning of physiological processes

OUTCOMES

- Intergenerational cycle
- Child morbidity and mortality
- Cognitive development
- Immunity
- Chronic diseases in adulthood

UNDERNUTRITION
(stunting, wasting, micronut. defic., LBW/IUGR/SGA/PTB)
NO SINGLE MAGIC BULLET: THIS IS A COMPLEX MULTIFACTORIAL CHALLENGE REQUIRING COMBINATORIAL APPROACH

NUTRITION

VACCINES

SANITATION

VECTOR CONTROL

HEALTHY PREGNANCY, BIRTH, GROWTH & DEVELOPMENT
HBGDki GOAL: COMBINE THE RIGHT INTERVENTIONS IN THE RIGHT DOSAGE TO GET THE RIGHT RESPONSE AND AVOID THE ADVERSE OUTCOMES
THE HBGDki KNOWLEDGE BASE CONTAINS LMIC AND COUNTERFACTUAL HIC DATA AS NATURAL EXPERIMENTS

Reality: LMIC

- **53 studies:**
  - From most high stunting burden countries

- **~3.5M subjects data:**
  - 100s of covariates

- **DHS+:**
  - Dozens of prospective collaborations
  - $$$

Counterfactual: HIC

- **16 studies:**
  - Denmark, Netherlands, Singapore, US

- **+7.5M individual subject data:**
  - 1000s of covariates

- **DHS+:**
  - Dozens of prospective collaborations
  - $
WHAT IS DIFFERENT ABOUT HBGDki?

Leveraging accumulated data to estimate variance structure of multifactorial and highly nonlinear and time-varying pathway interactions

LEARN/EXECUTE

Model Uncertainty

CONFIRM/VALIDATE

UPDATE

Ensemble Bayesian and Super Learner modeling platforms

© Bill & Melinda Gates Foundation | 65
HBGDki 2016 Q1 Workshop

**Date**
- April 20-22

**Location**
- Seattle

**Attendees**
- N = +200 including Foundation representation + 7 technical Advisors involved in HBGDki

**Schedule of events**
- **Tuesday, April 19:** Arrival + evening reception
- **Wednesday & Friday, April 20, 22:** Full day workshops between data scientists and domain experts
- **Thursday, April 21:** Data, Digital Science day with Bill Gates, Global Good, Intellectual Ventures, IHME, UW START and HBGDki-Global

**Sponsors/Partners**
- Global Health and Global Development (including Discovery & Translational Sciences; Integrated Development; Integrated Delivery; Nutrition; Agriculture; Water, Sanitation & Hygiene; Maternal, Newborn & Child Health; Enteric & Diarrheal Diseases; and Pneumonia).

**Data Flash Highlights**
- Inference on the impact of fetal growth velocity on attained size, conditional risk of growth & development failure over the first 5 years of life
  - Demonstration of ultrasound-based predictive pregnancy and newborn outcome algorithms and potential application to Zika crisis
- Brain, gut, skeletal growth, maturation and maintenance dynamic energy-budget model
- Genome scale metabolic modeling of somatic growth sensitivity to variation in the different metabolites/components of breast milk, effects of mineral (Fe, Zn and Cu) on growth
SUMMARY

• We are promoting best practice product development including model based drug development in the developing world

• We are expanding our quantitative approach to many areas with the goal of creating the greatest impact in the shortest period of time with the least amount of human and financial resources

• We take risks where other won’t or can’t

• If we can imagine it, we can make it happen…
THE WORK IS COMPLICATED.
WHY WE DO IT IS NOT
THANK YOU