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GATES foundation



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

For Third World, Water Is Still a Deadly Drink

By NICHOLAS D. KRISTOF

TRANE, India — Children like the Bhagwan boys scamper about barefoot on the narrow muddy paths that wind through the labyrinth of a slum here, squatting and relieving themselves as the wind arises, so casual about the filth as the bedraggled rats that nose about in the raw sewage trickling beside the paths.

Parents like Usha Bhagwan, a tall-thin 28-year-old housemaid, point out their children and fret about how to spend their rupees. Should they buy good food so that the children will get stronger? Or should they buy shoes so that the children will not get hookworms? Or should they send their sons and daughters to school? Or should they buy kerosene to boil the water?

There is not enough money for all of those needs, so parents must choose. It was to save money, as well as to save time, that Mrs. Bhagwan was serving unboiled water the other day to her 5- and 7-year-old boys in her one-room home. Her busy face and sharp eyes softened as she watched them take the white plastic cup and gulp the deadly drink.

The water has already killed two of her children, a 15-month-old lamash, a boy who died two years ago, and Shetal, a frail 3-month-old girl who died just a few months ago. But everyone in the slum drinks the water, usually without boiling, and water seems so natural and nurturing that Mrs. Bhagwan does not understand the menace it contains.

"I try to boil the water," Mrs. Bhagwan said pleasantly. "But the boys sometimes insist on drinking right away because they're thirsty."



Cambodian children get drinking water from creek used for bathing.

EVERYDAY KILLERS

Second of two articles.

To boil water consistently would cost about \$4 a month in kerosene, almost a third of Mrs. Bhagwan's savings. She could afford that, but then there would be less money for food.

The water comes from a pipe that runs into the slum where the Bhagwans live, in the city of Trane, near Bombay. The pipes are cracked and run in a ditch that is filled with sewage. Even if the water was properly treated at its origins, health workers say, sewage seeps into the water to produce one of the most deadly ailments in

(that kills some 2.1 million people annually, almost all of them children).

The larger issue is that the most fundamental health challenge in the world at the end of the 20th century may be the same as it apparently was four millennia ago: sanitation. To families like Mrs. Bhagwan's, perhaps nothing would make more difference than clean water and a toilet.

All in all, human wastes may be more menacing than nuclear wastes, for feces kill far more people than radioactive substances. A huge range of diseases and parasites infect people by the fecal-oral route, transmitted from one per-

“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

BILL & MELINDA
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VISITOR CENTER

ENTER
CURIOUS

OUR HISTORY



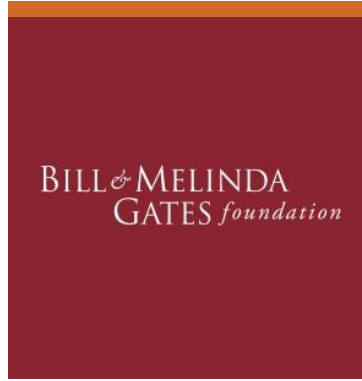
1994

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



\$40B

Trust endowment

1,500+

2015 active grantees

\$4.2B

2015 grant payments

1,300+

2015 employees worldwide

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



GLOBAL HEALTH

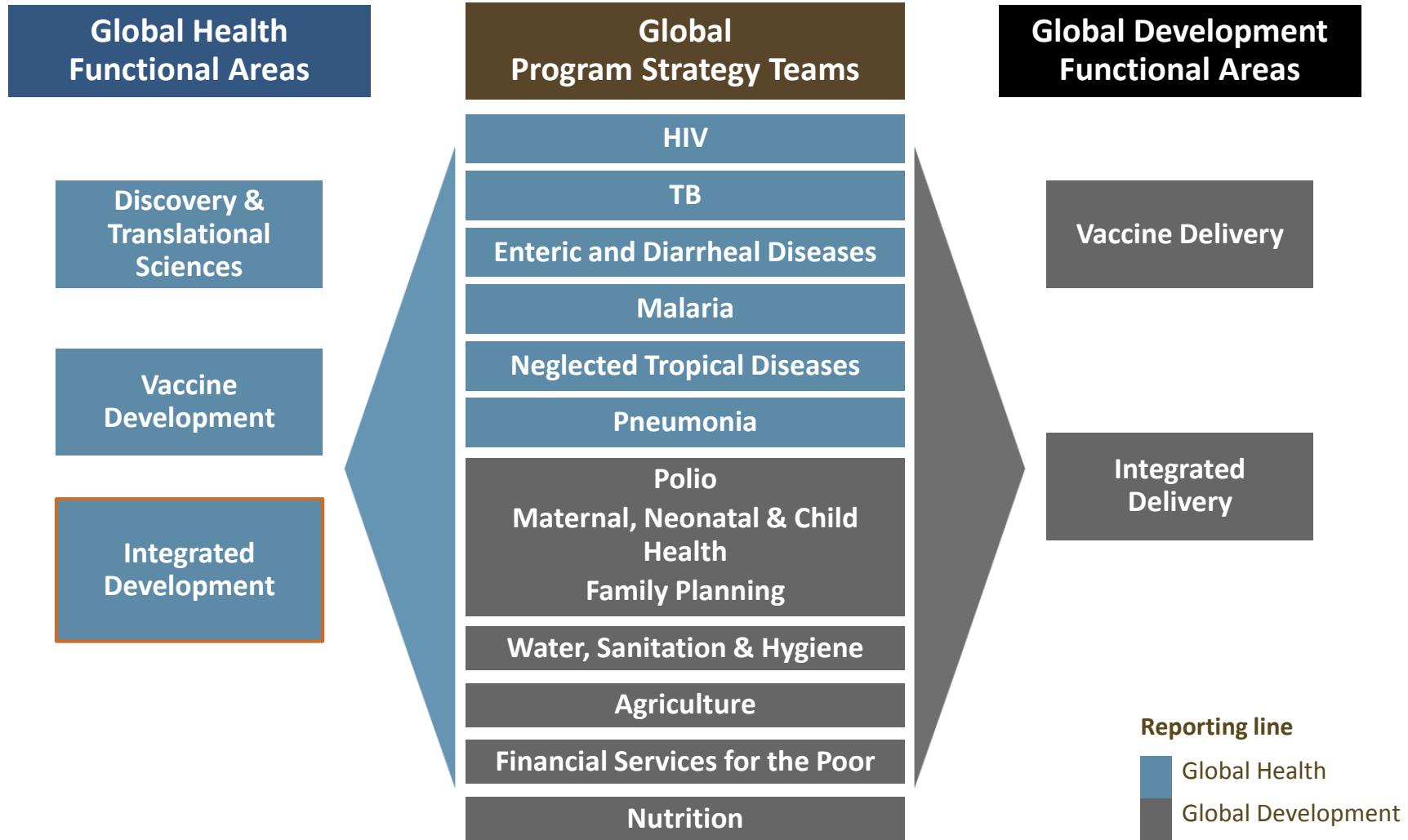
Discovering and developing affordable vaccines, drugs, and diagnostics for people in the developing world.

Programs:

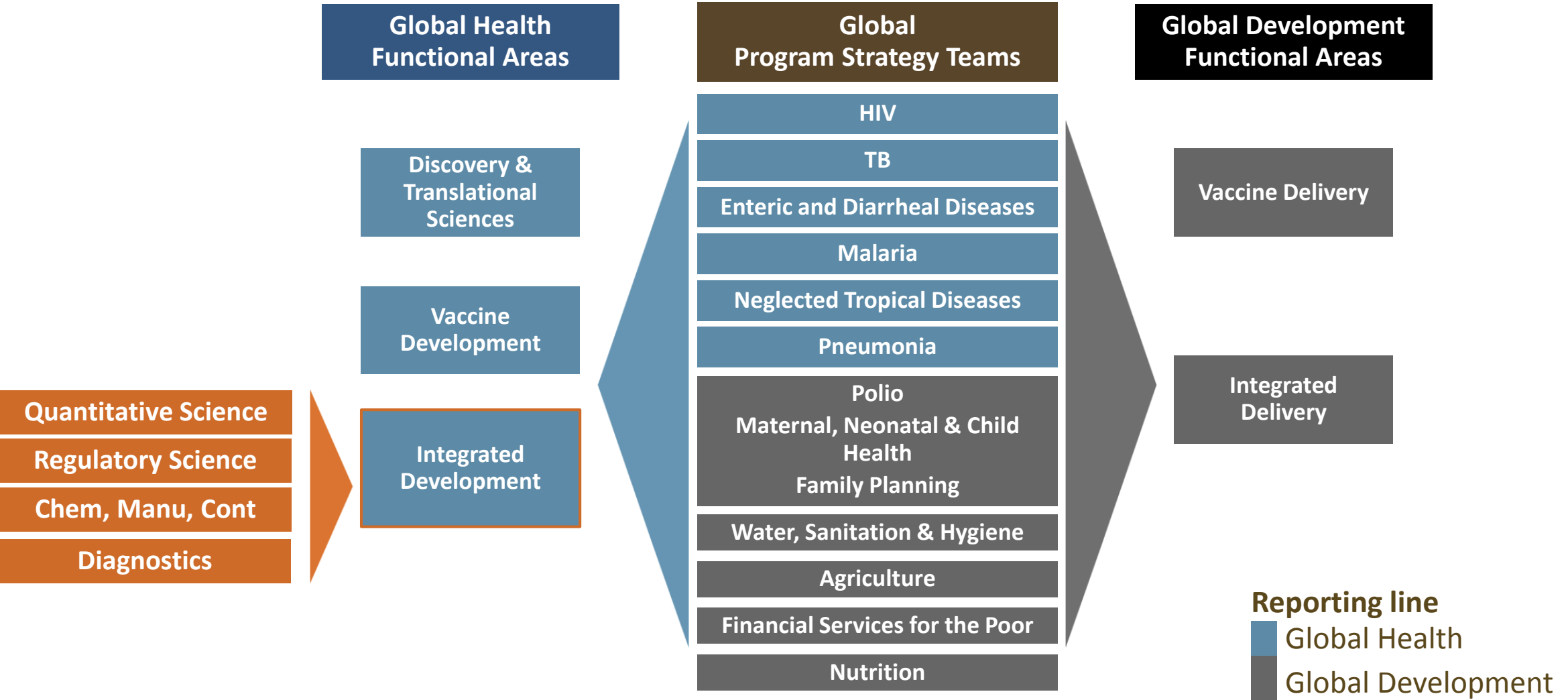
- Enteric and Diarrheal Diseases
- HIV
- Malaria
- Neglected Tropical Diseases
- Pneumonia
- Tuberculosis



BMGF Global Health/Development Organization



BMGF Global Health/Development Organization





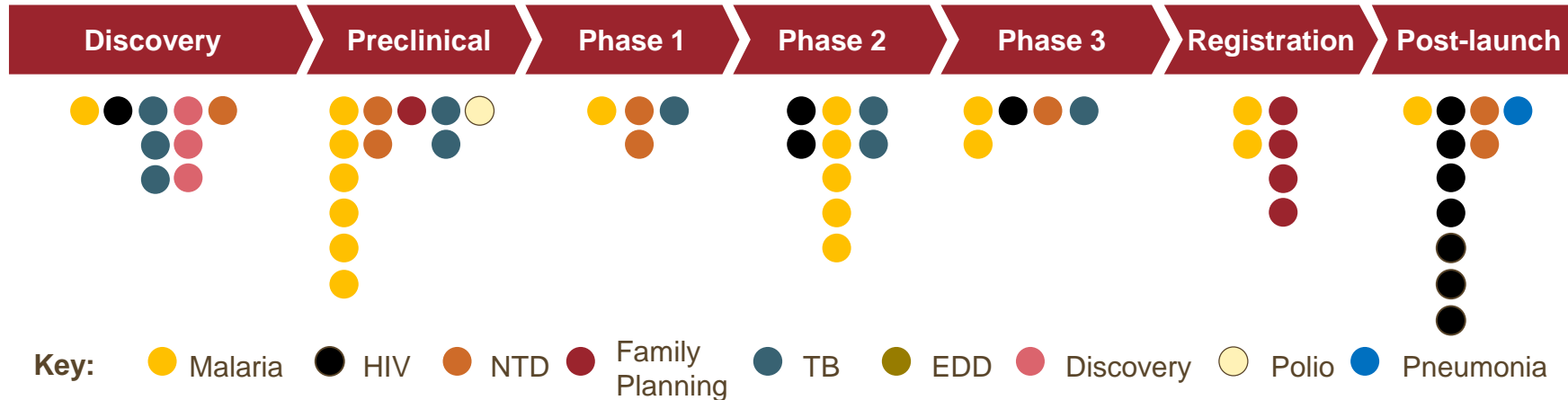
INTEGRATED DEVELOPMENT:

- 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

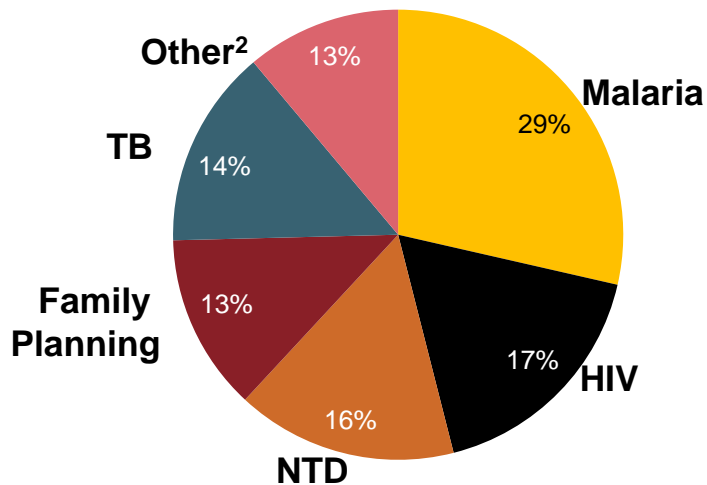
Portfolio summary¹



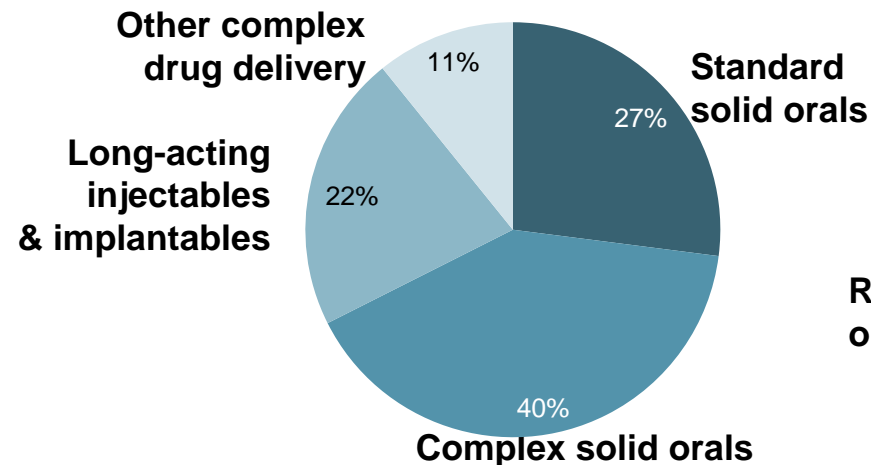
Portfolio highlights

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

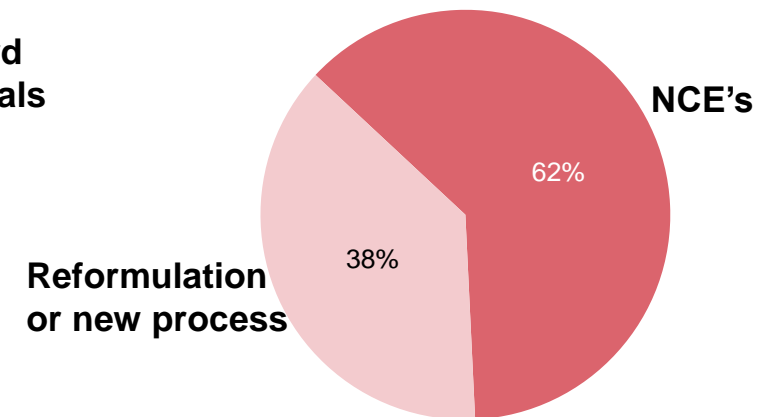
Portfolio by therapeutic area



Portfolio by technology



NCE's versus new dosage forms



¹ Product candidate bubble position represents only candidate stage of development and not progress within each respective stage; portfolio includes only therapeutics candidates (except Livestock) and excludes devices, diagnostics, and vector control candidates ² Other therapeutic areas are Discovery, EDD, Polio, Pneumonia

■ 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



FACTS ABOUT THE GEOGRAPHIES WE WORK

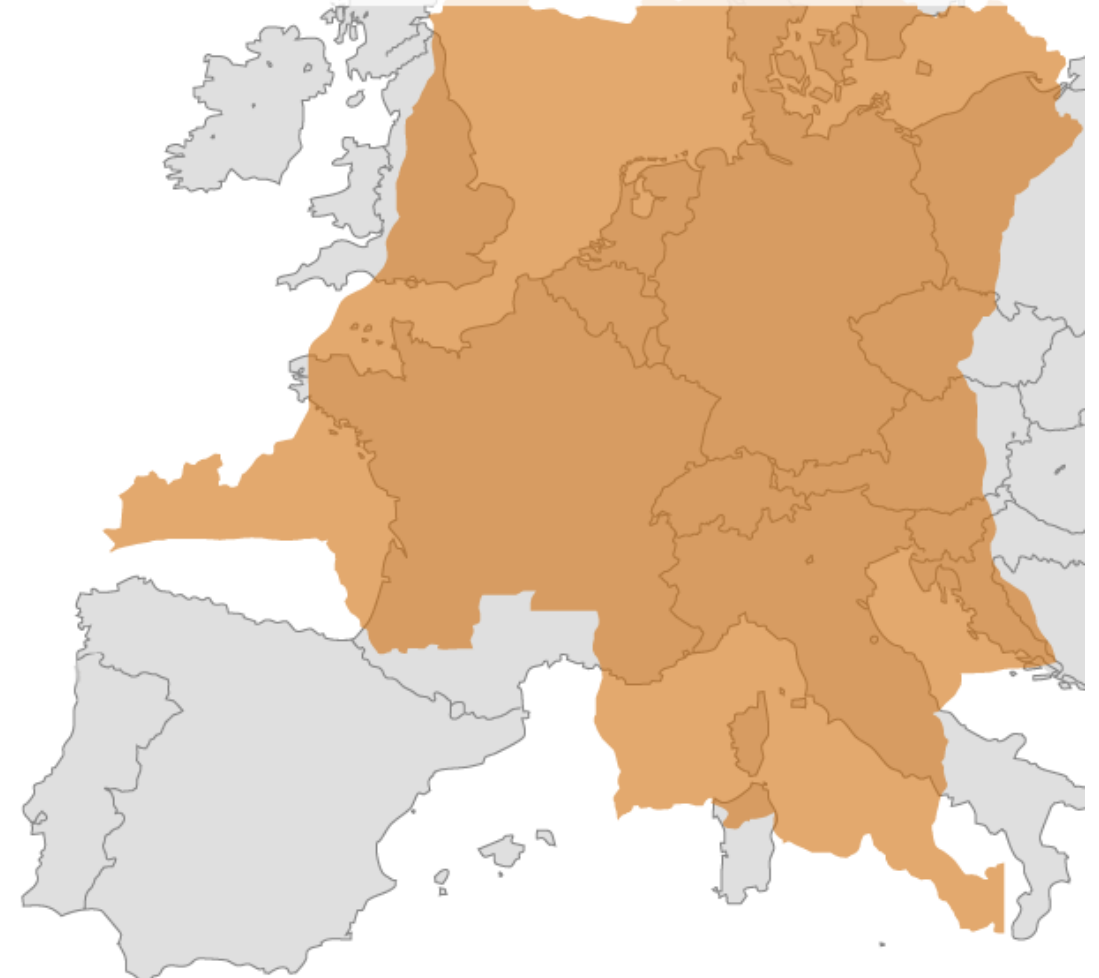
Country	Median Age (2012) ¹	<5 mortality rate per 1000 births (2012) ¹	No of births per mother ² (2012)	Deaths from TB per 100,000 (2012) ¹	Deaths from cardiovascular disease per 100,000 (both sexes) [2012] ³	% secondary school attendance Males (2008-2012) ⁴	% school attendance Females (2008-2012) ⁴
DRC	17	146	6.0	54	359.6	35.1	28.3
Kenya	19	124	4.5	22	205.0	39.5	41.6
Nigeria	18	73	6.0	16	266.5	54.2	54.3
UK	40	5	1.9	0.5	136	97.4	99.6
US	37	7	1.9	0.1	111.8	88.8	90.2

- **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

THE DEMOCRATIC REPUBLIC OF CONGO IS ABOUT 2/3 THE SIZE OF WESTERN EUROPE

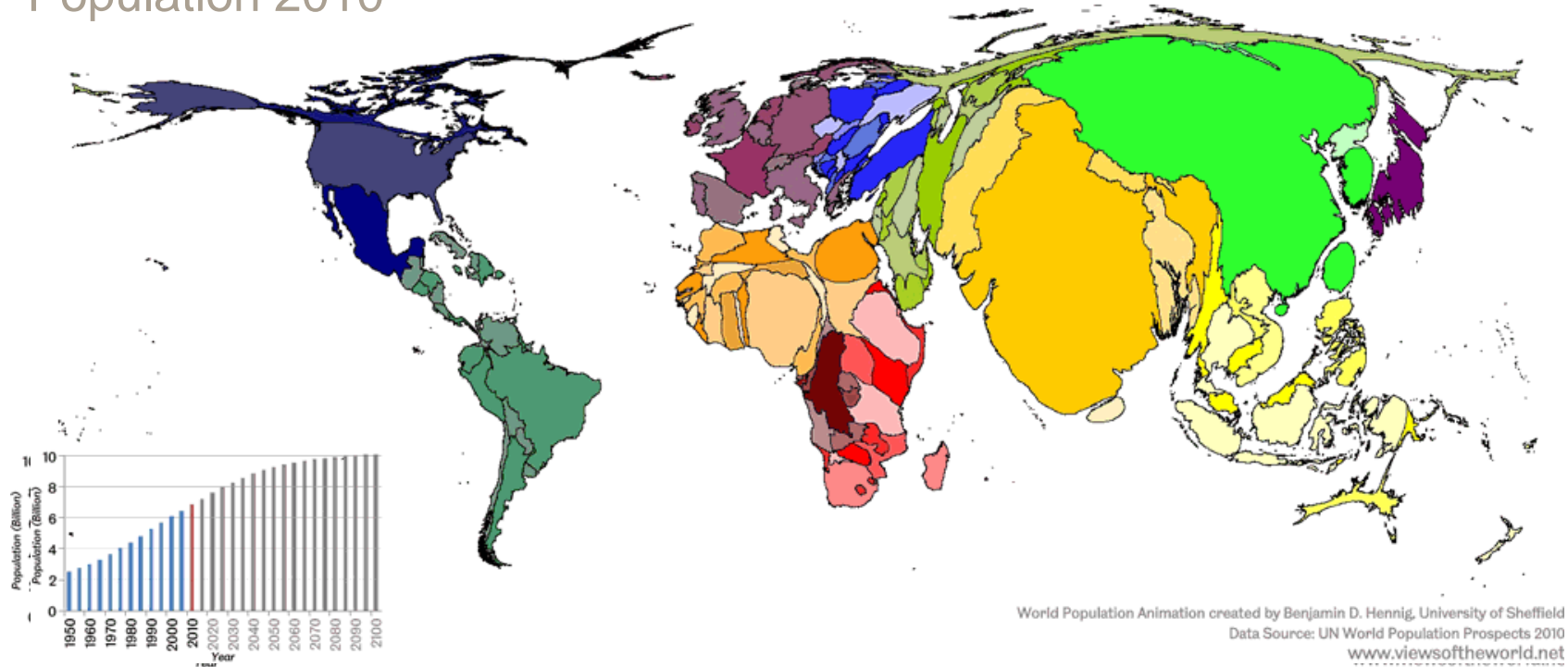
- Last formal census: 1984
- Estimated population is 70-80 M
- 200 ethnic groups with major regional linguistic variation
- Life expectancy: 49.6 years
- Infant mortality: 73.15/1,000 live births
- 1400 miles of paved roads – ½ in “good” condition

The Democratic Republic of Congo is a vast country around two thirds the size of Western Europe.

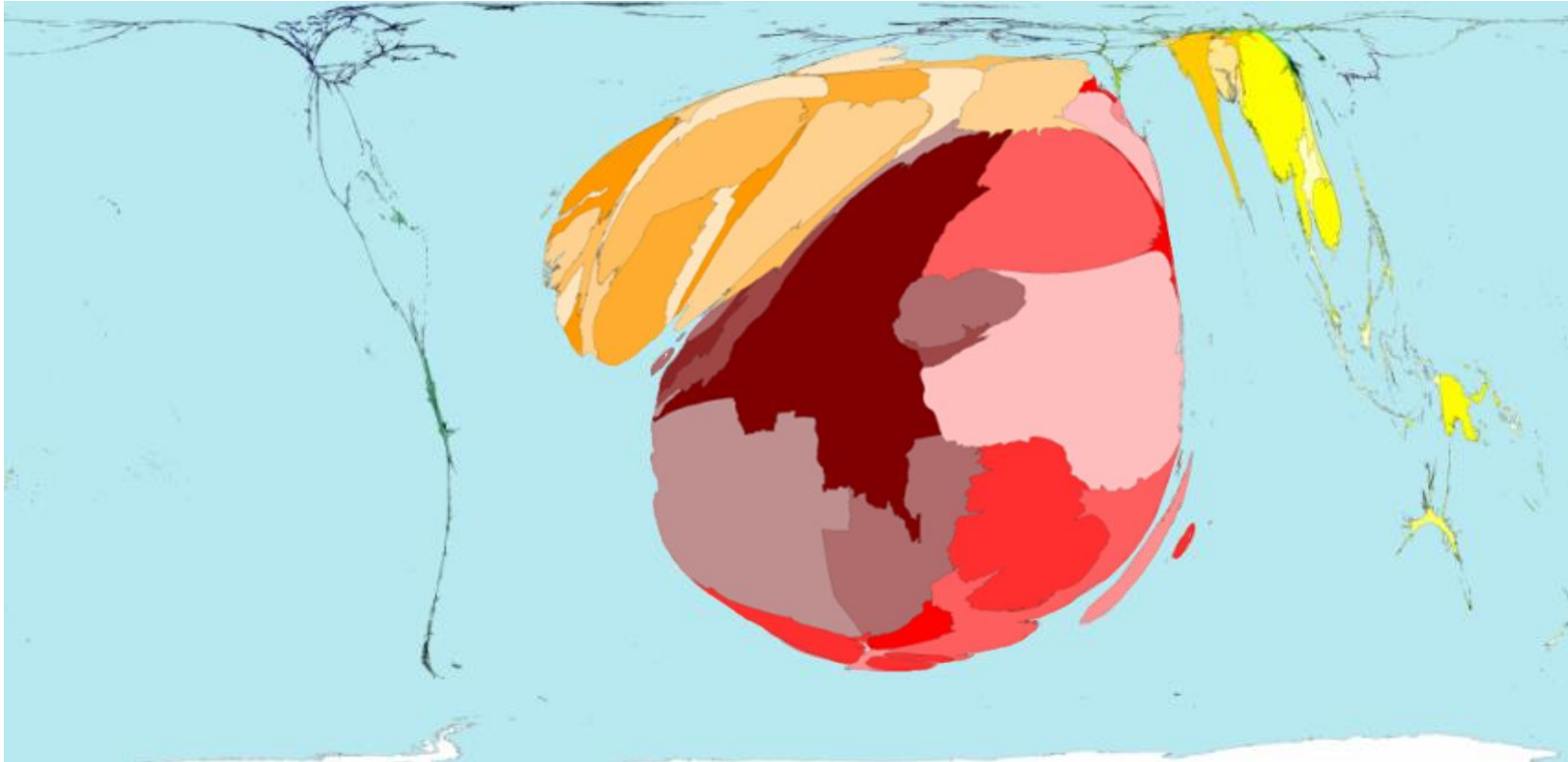


The changing shape of global population

Population 2010



Mismatch between disease burden...malaria deaths

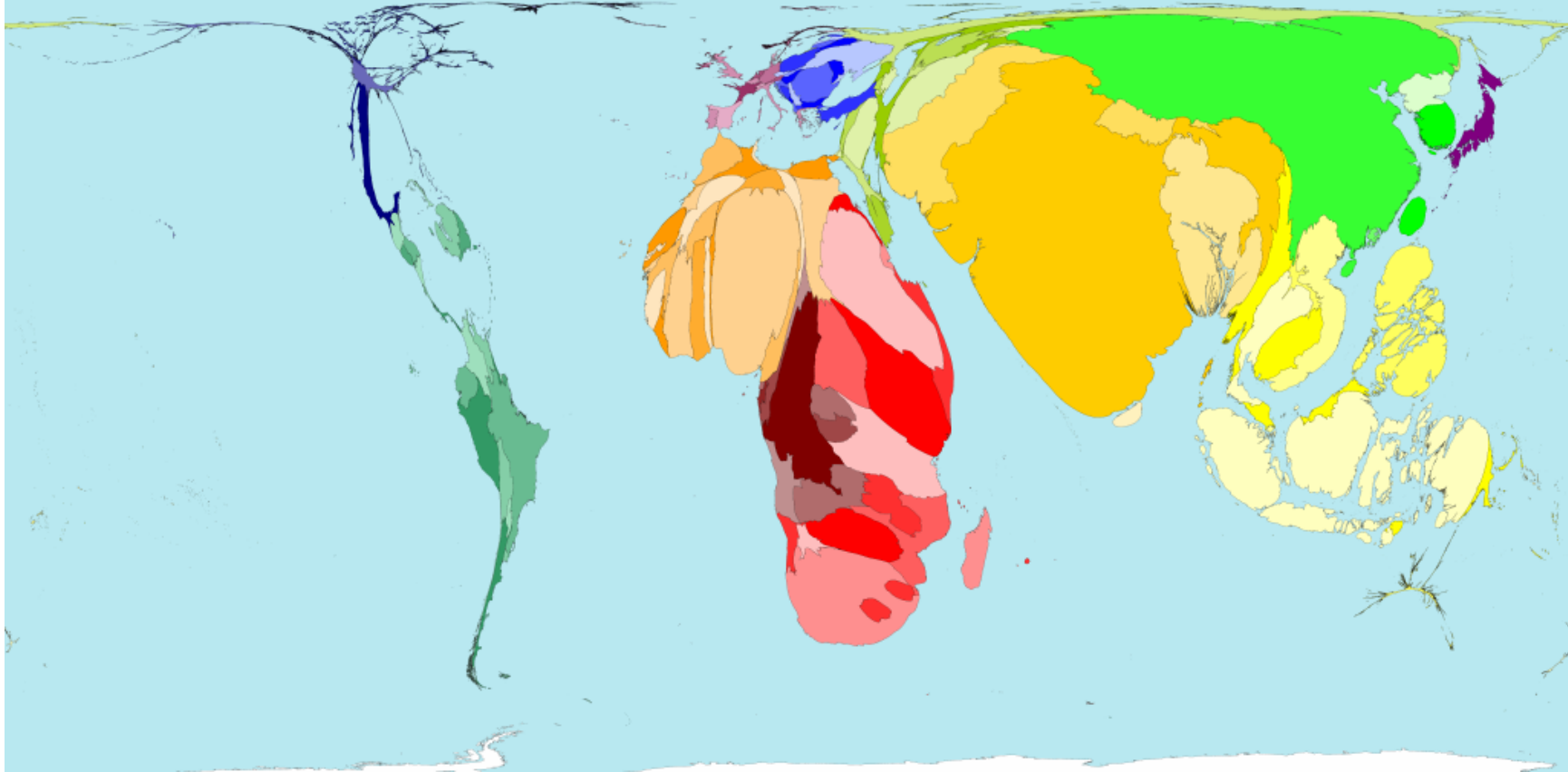


Source: <http://www.worldmapper.org/>

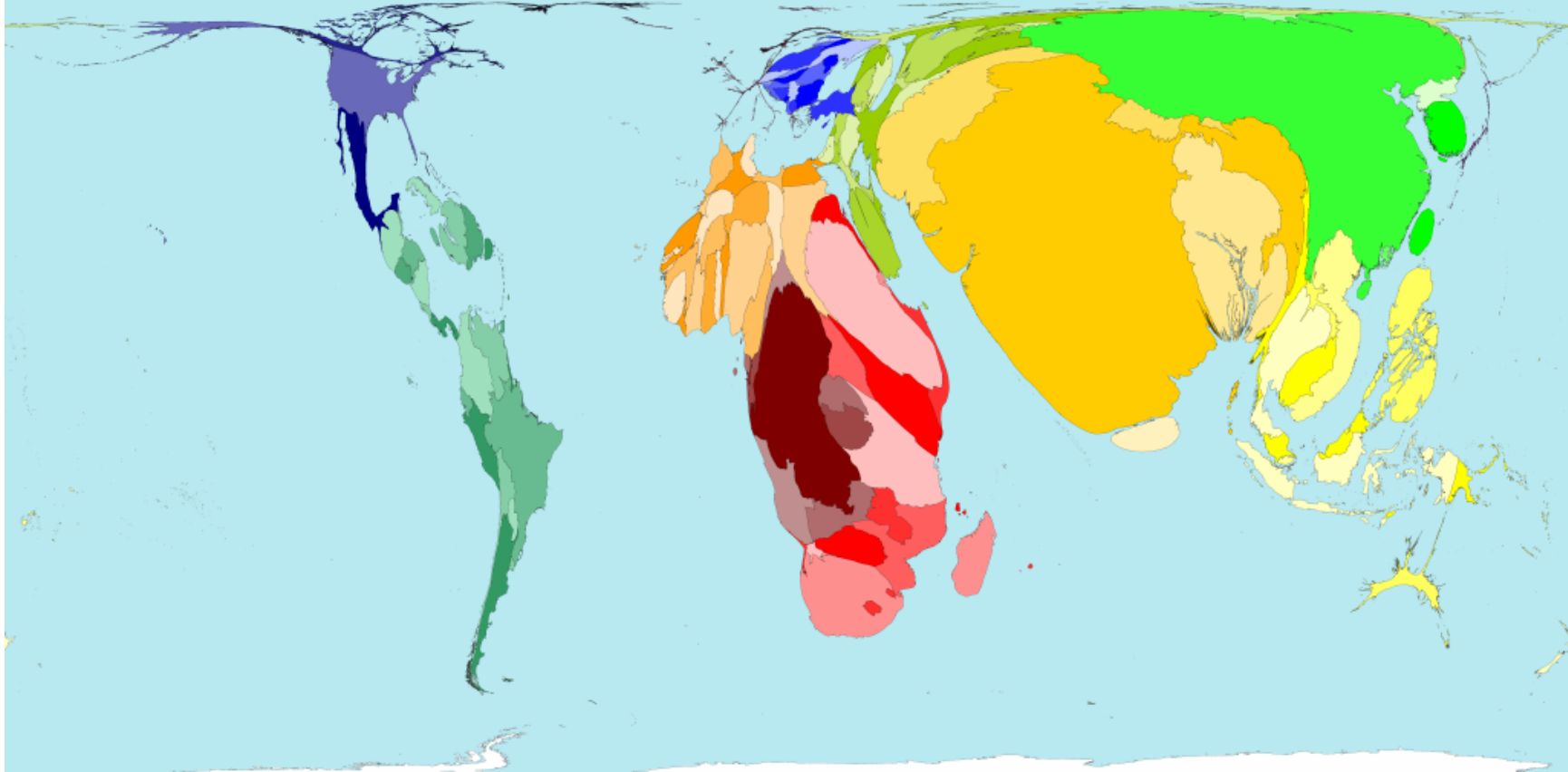
Mismatch between disease burden...HIV prevalence



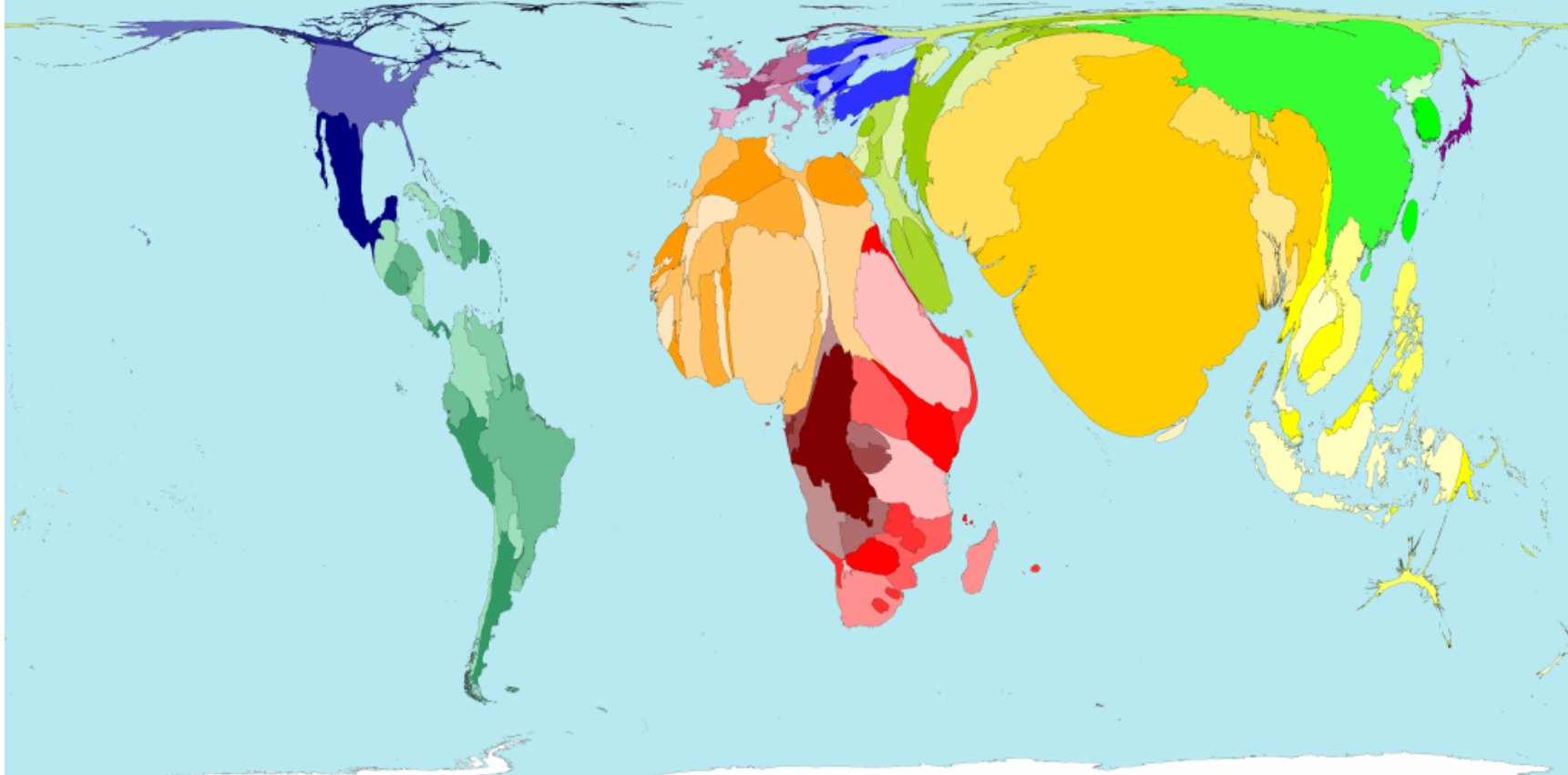
Mismatch between disease burden...TB cases



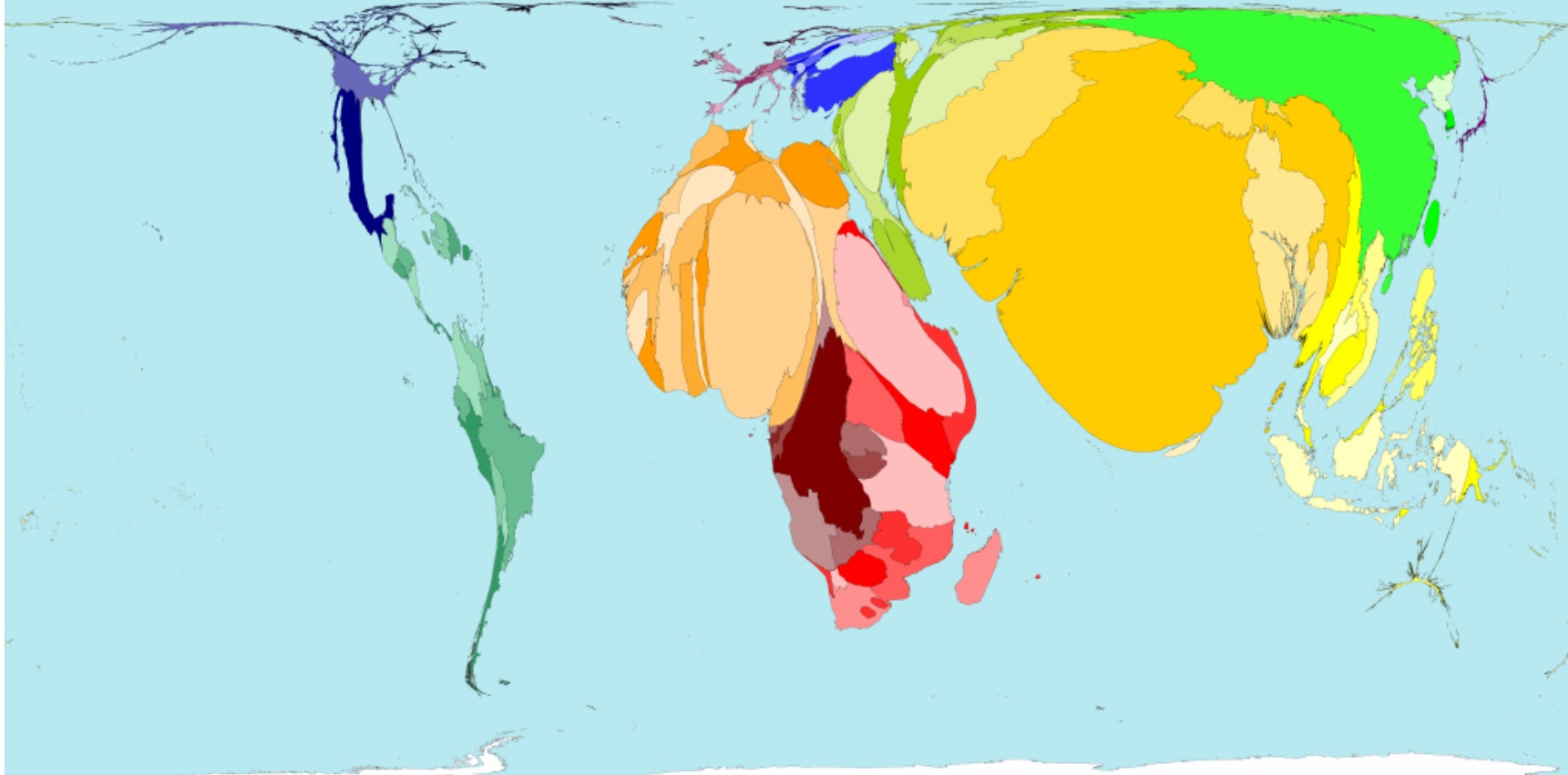
MALNUTRITION 2000



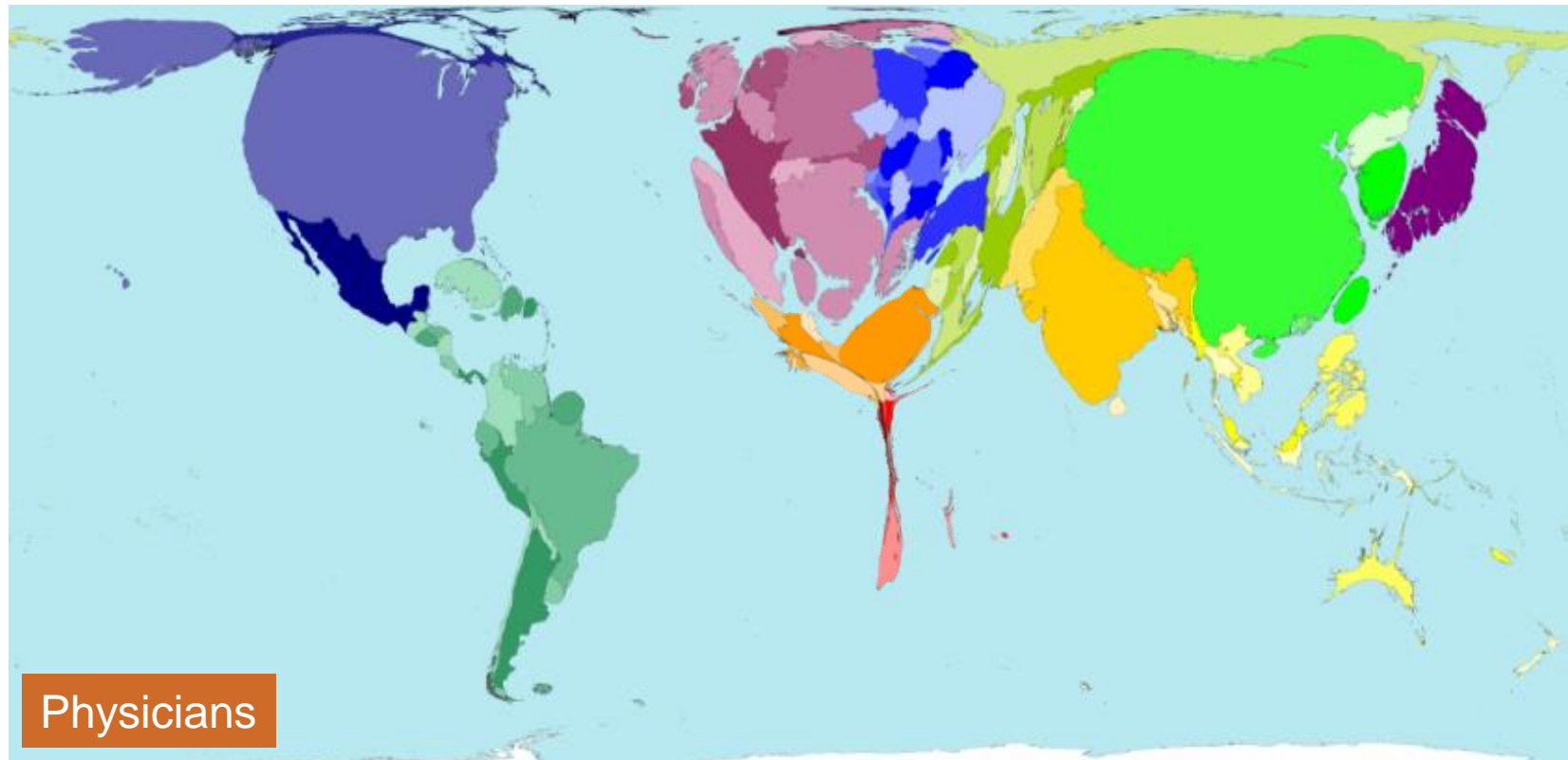
Mismatch between disease burden...Diarrhea prevalence



■ Mismatch between disease burden... early neonate mortality

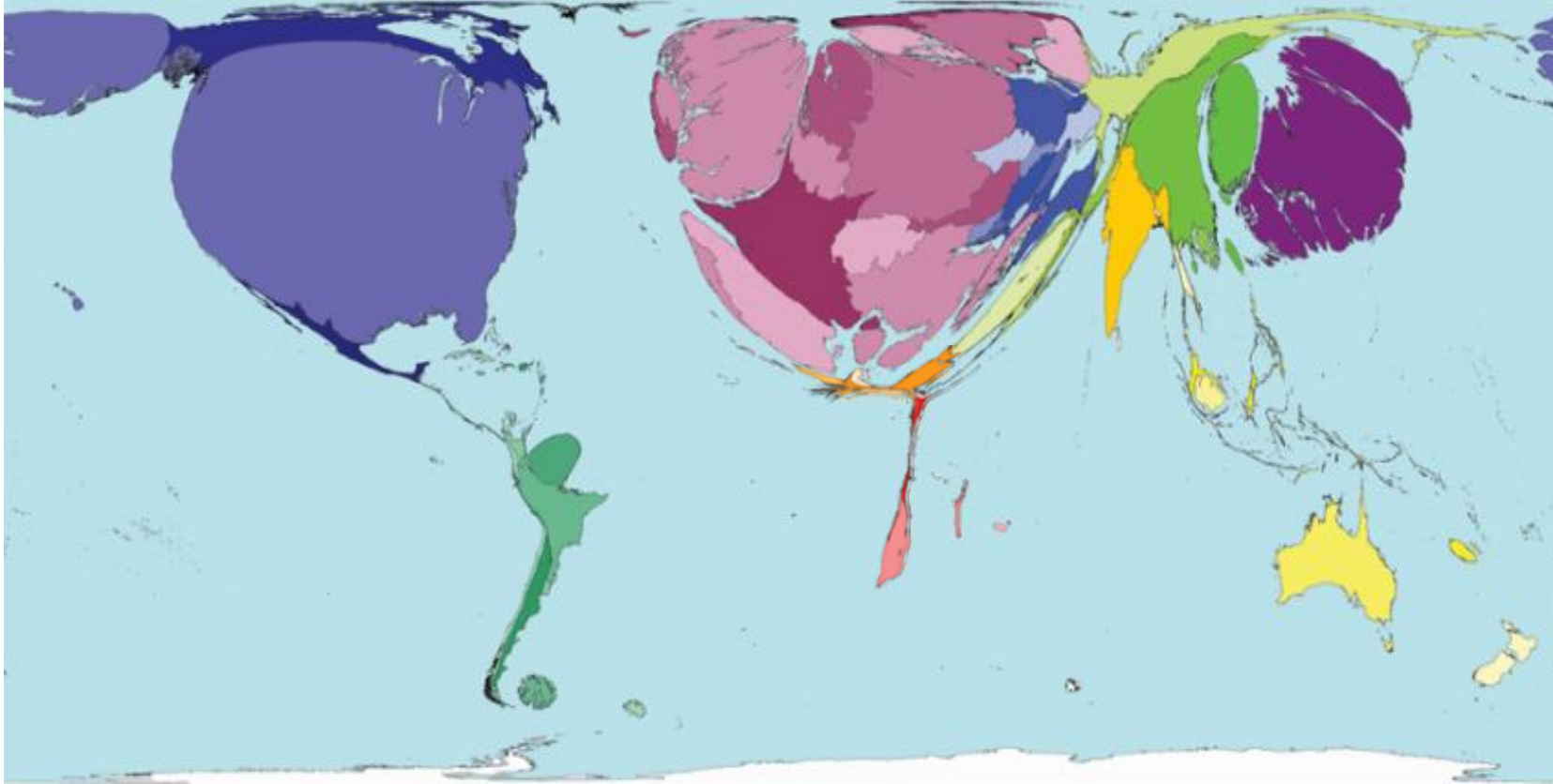


...and available medical care...



Source: <http://www.worldmapper.org/>

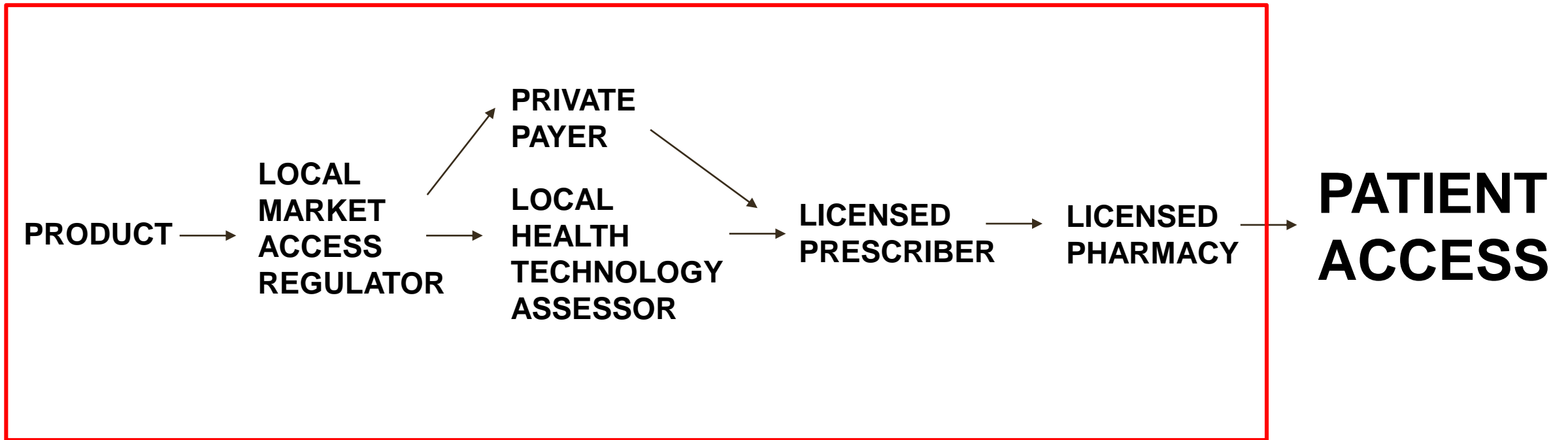
...or biomedical research



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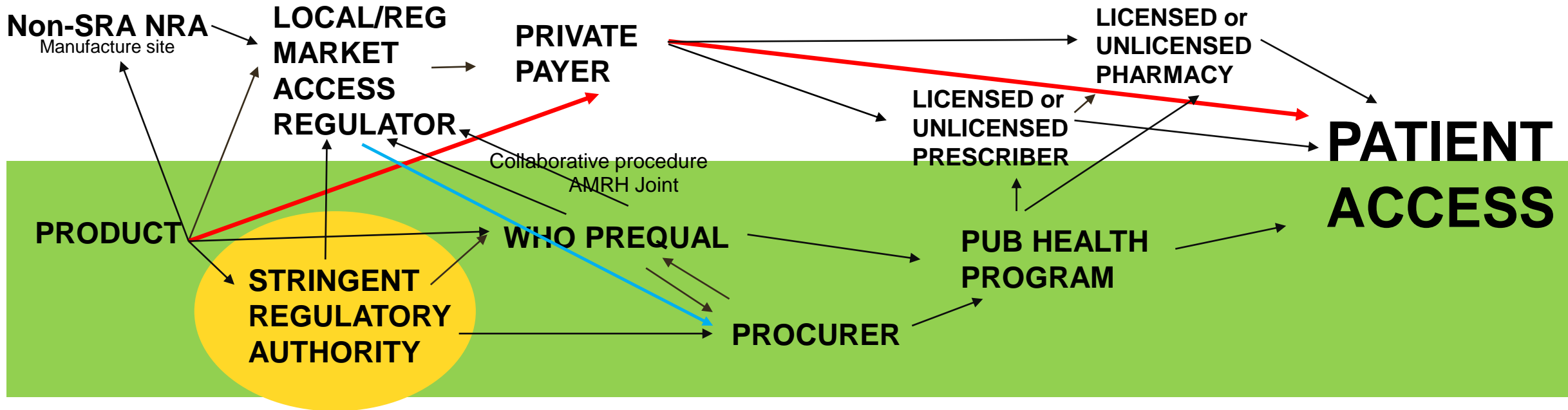
REGULATORY CHALLENGES AND ADVANCES IN LOW INCOME COUNTRIES

GENERAL PROCESS IN HIGH-INCOME COUNTRIES



“Closed”, linear highly regulated, proscribed system
Helps assure product quality, safety, efficacy and supply chain security

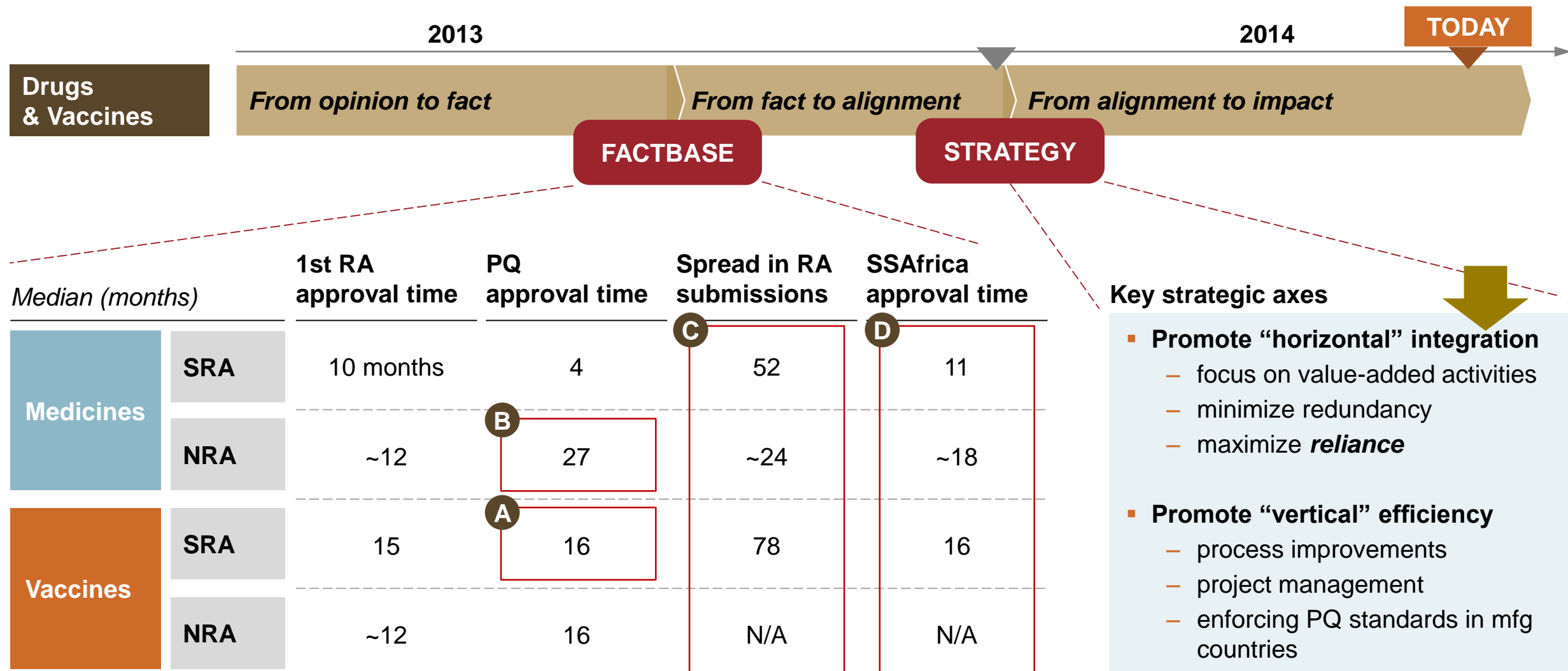
GENERAL PROCESS IN LOW-INCOME COUNTRIES



“Open”, loosely (if at all) regulated, multifaceted, complex system

Helps assure products of uncertain quality, safety, efficacy and supply chains that are insecure

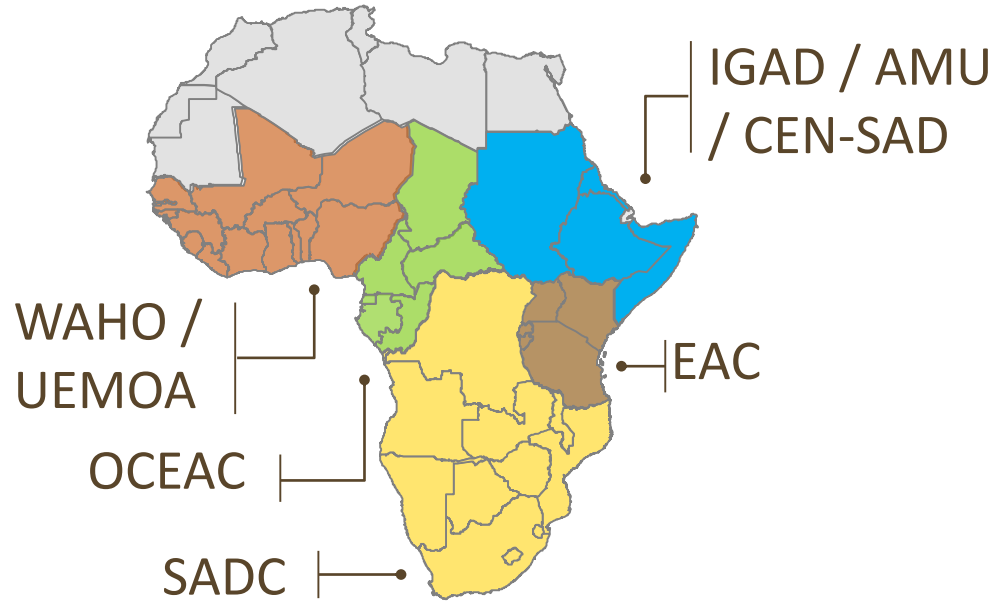
MEDICINES AND VACCINES REGISTRATION DATA



AFRICAN REGULATORY HARMONIZATION VISION



55 countries



6 regions



African Medicines Agency

KEY REGULATORY SYSTEMS ACCOMPLISHMENTS 2014/15

Major performance improvements in WHO-PQ for medicines and vaccines

- **20-35% reduction** in vaccines PQ timelines (20-50% for WHO time) vs. <2013 baseline
- **10-25% reduction** in medicines PQ timelines (10-25% for WHO time)

Major productivity improvement in WHO-PQ for diagnostics

- **23 diagnostics PQed** in 2015 vs. historical average of 9 products / year

Achieved “new normal” for local registration of PQed medicines: <90 days

- **120+ registrations** performed under PQ collaborative procedure (27 countries enrolled)

Regional product registration system established in East Africa*

- **Single dossier** submission for all 6 regulatory authorities
- **First joint regional review** of 8 dossiers (NCEs and generics) completed in Oct. 2015
- **Multiple joint reviews** planned for 2016 (25+ products in the pipeline)
- Currently expanding to **West Africa** and **Southern Africa**

*Includes Tanzania, Uganda, Kenya, Rwanda, Burundi, and Zanzibar

TB

- ❑ 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

Silva A., B-Y. Lee, D.L. Clemens, T. Kee, X. Ding, C-M Ho, and M.A. Horwitz. 2016.

Output-driven Feedback System Control platform optimizes combinatorial therapy of tuberculosis using a macrophage cell culture model.
Proc. Natl. Acad. Sci. USA. in press.

TB – FSC APPROACH

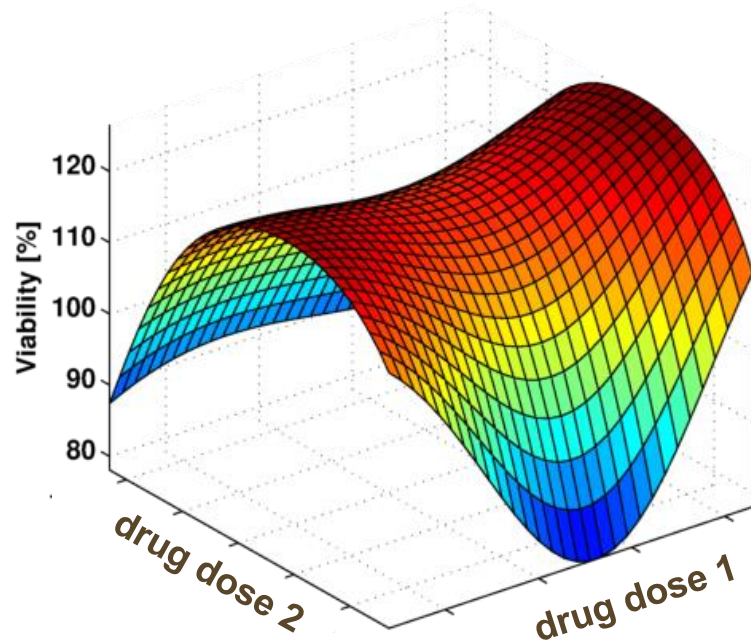
The successful rate of combinatorial drug development from in vitro test to clinical trial is in single digit range. How do we de-risk and improve the successful rate?

- 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.

TB – FSC APPROACH

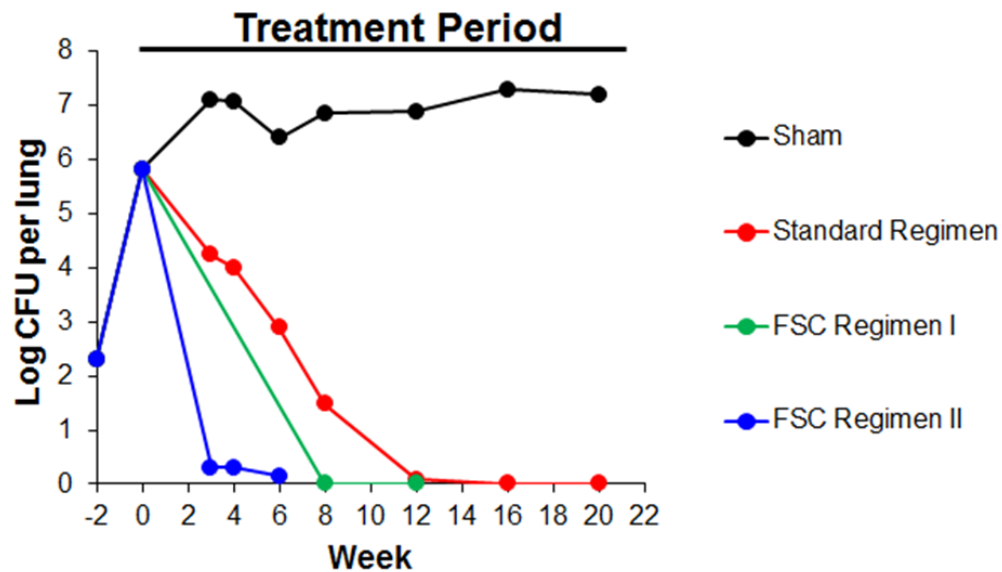
Prior experimental studies with FSC demonstrated that the efficacy-dose response surface fits well with a second order algebraic equation, which can be represented by a parabolic response surface (PRS).

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.



TB – FSC APPROACH

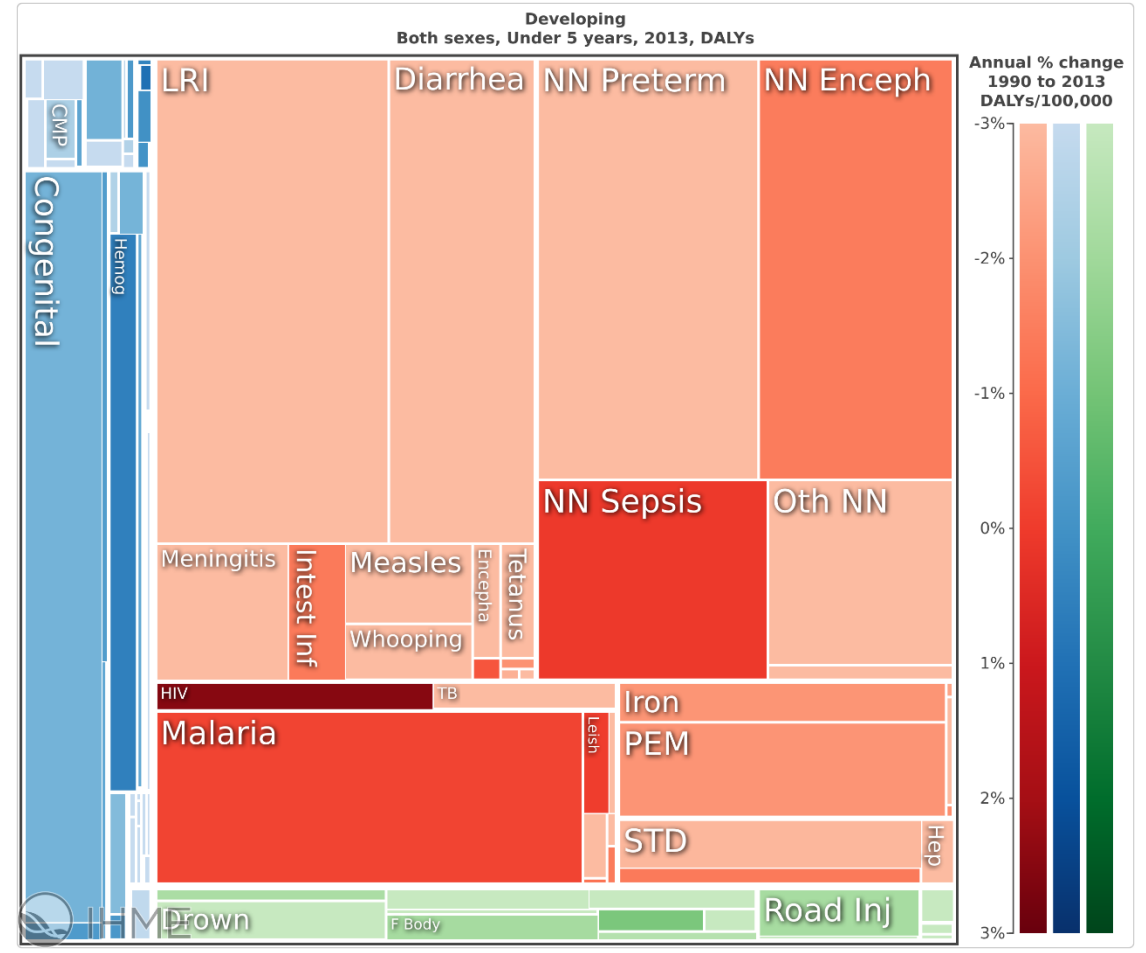
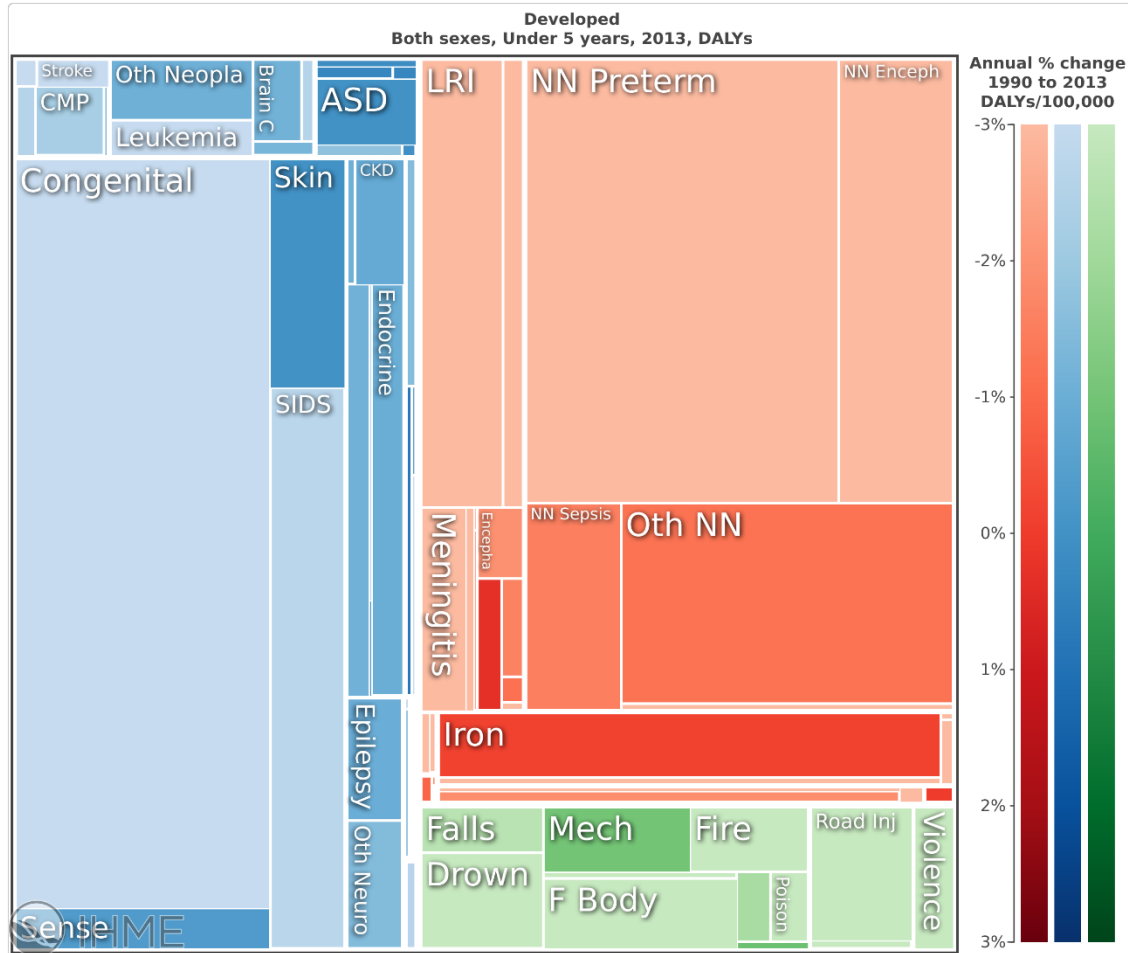
- **In vitro test:** 14 drugs were used in cell line search. The second order algebraic equation with 14 variables has 120 coefficients. With only 120 tests determine the entire landscape and locate the optimal combinations.
- Of all the three- or four-drug combinations only about 20 had high efficacies.
- The top two four-drug candidates for preclinical tests.



Time to Relapse-Free Cure		
Drug Regimen	80% Relapse-Free Cure (weeks)	100% Relapse-Free Cure (weeks)
Standard Regimen	12	16
FSC Regimen I	8	12
FSC Regimen II	3	4

MALARIA

- Close to 1M people die from malaria annually and over 700,000 are less than 5 years old.



MALARIA PARASITE INFECTION LIFECYCLE

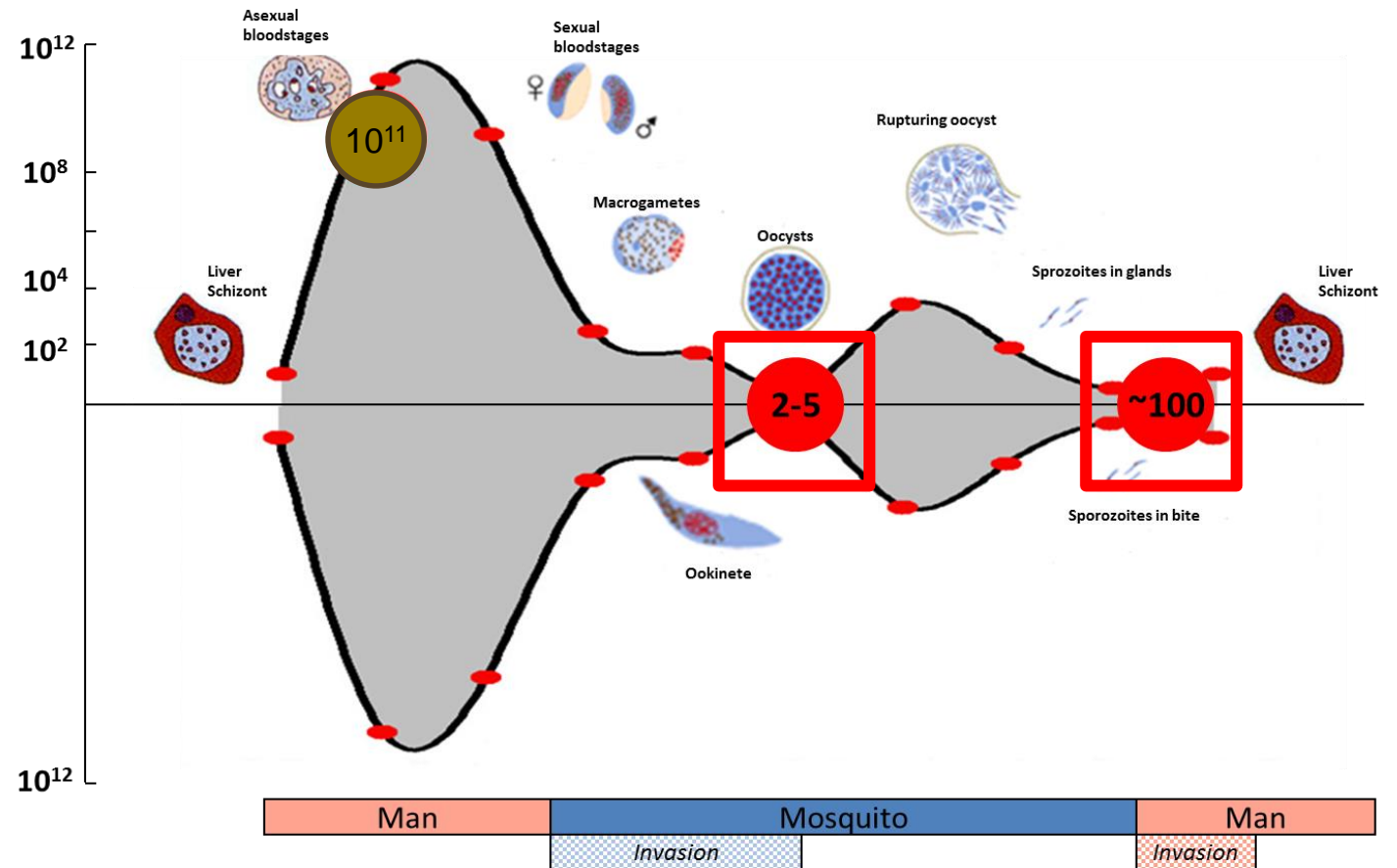
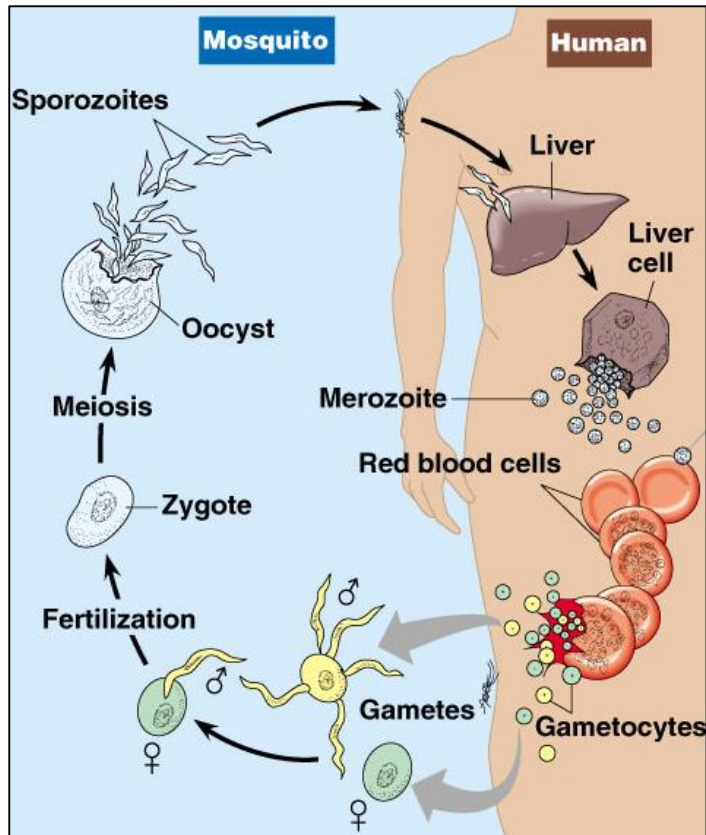


Figure: Alavi, et. al., Int J Parasitol. 2003 Aug;33(9):933-43.

DELIBERATELY INDUCED HUMAN MALARIA: EXPERIMENTAL MALARIA INFECTION WITH BLOOD STAGE PARASITES



P. falciparum 3D7
gametocyte culture



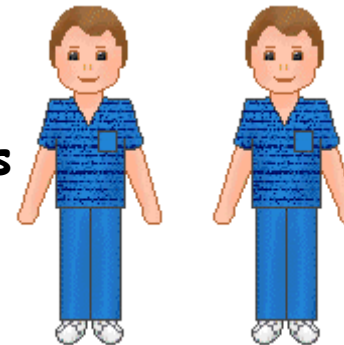
*Anopheles
stephensi*



10 -14 days

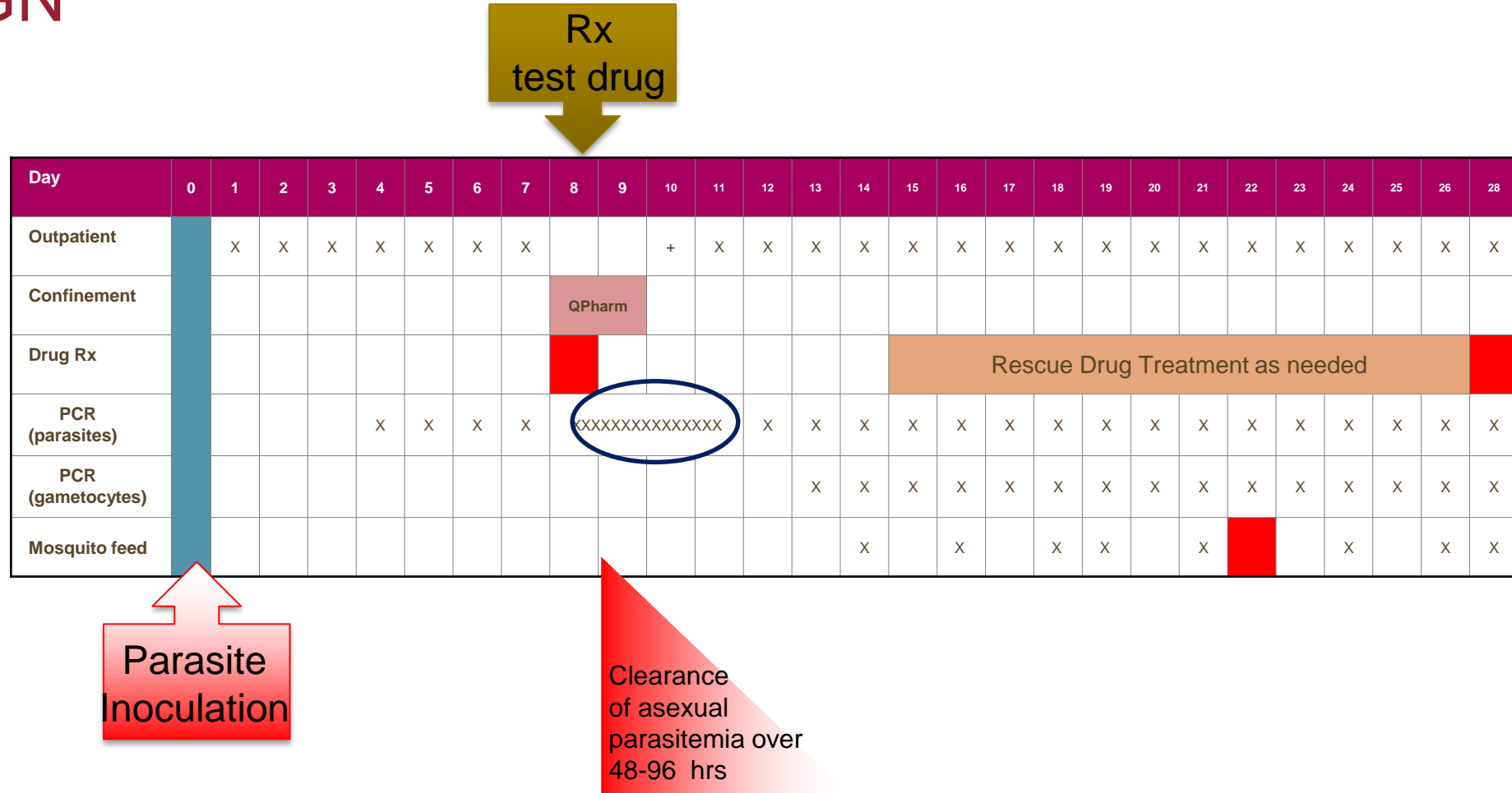


9 infective bites



Initiate therapy
after 7 days

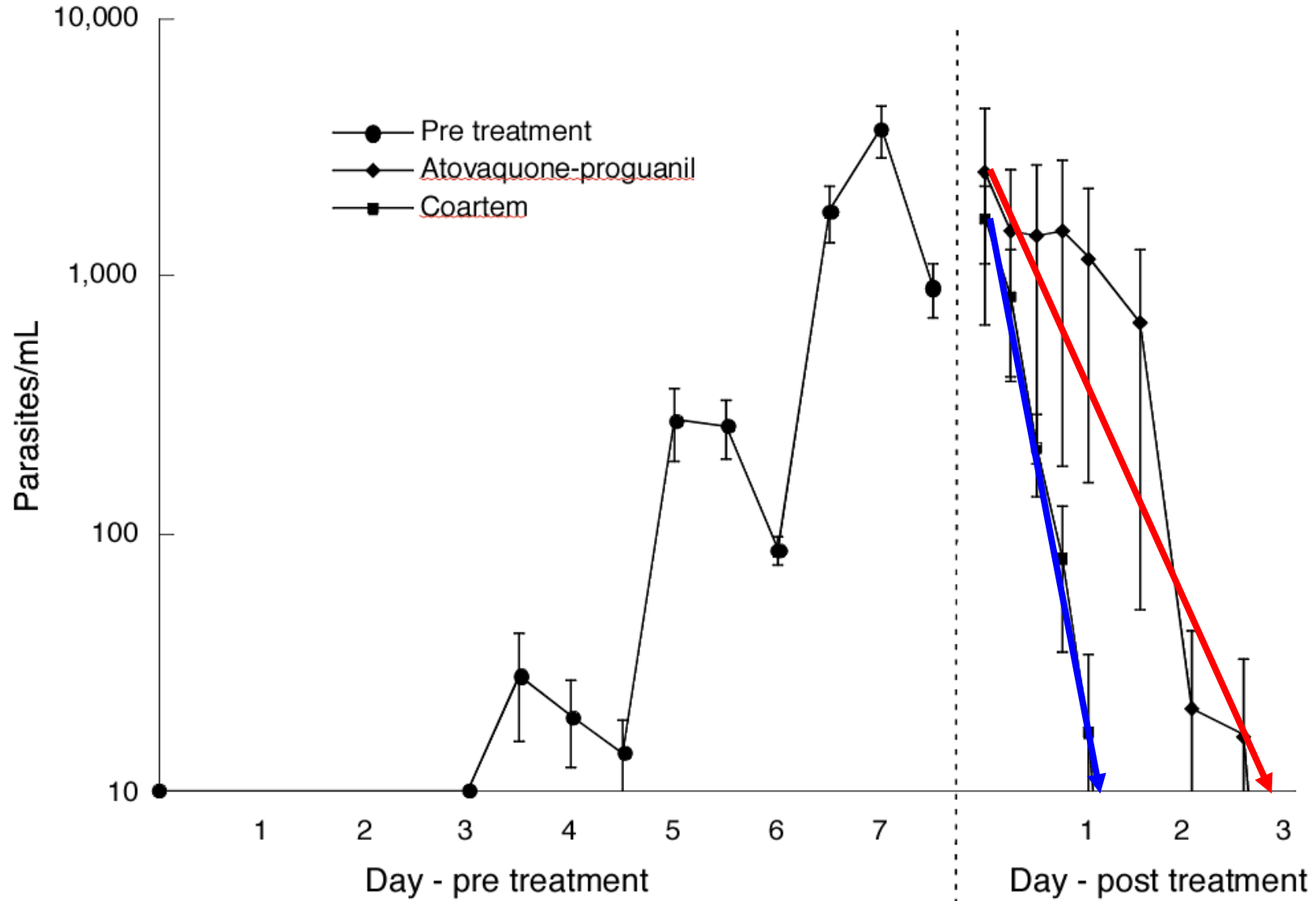
CLINICAL TRIAL DESIGN



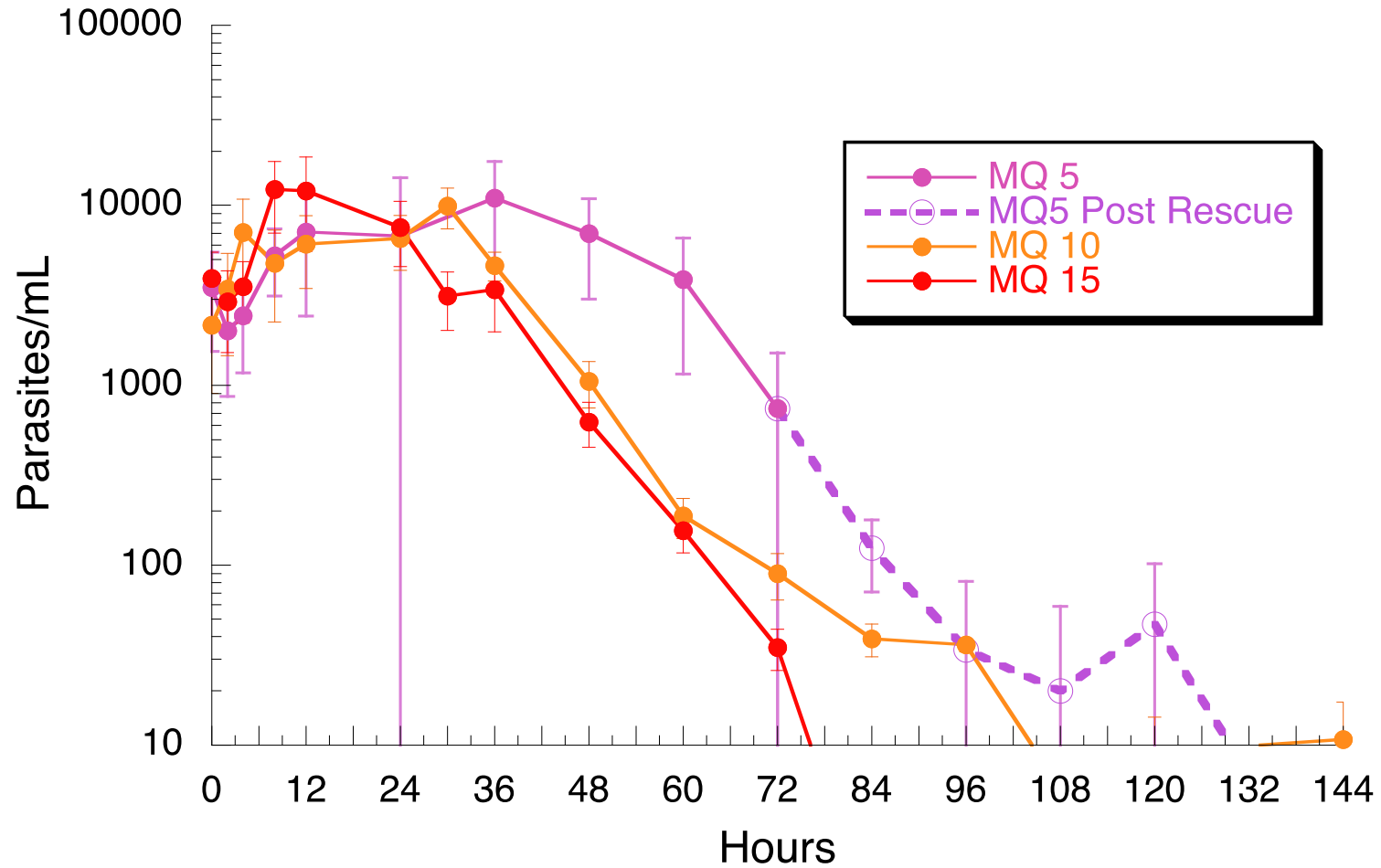
PCR CLEARANCE RATES

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

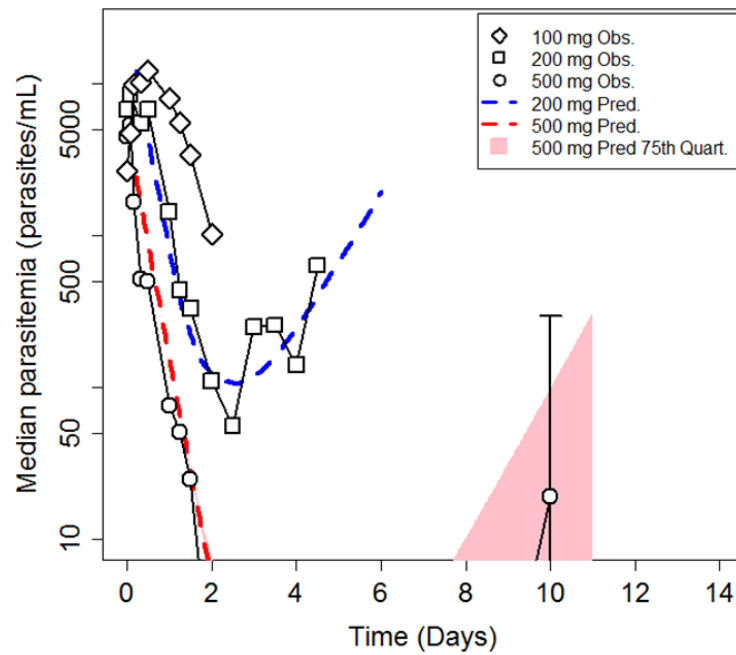


DOSE RANGING WITH MEFLOQUINE 5, 10,15 MG/ML



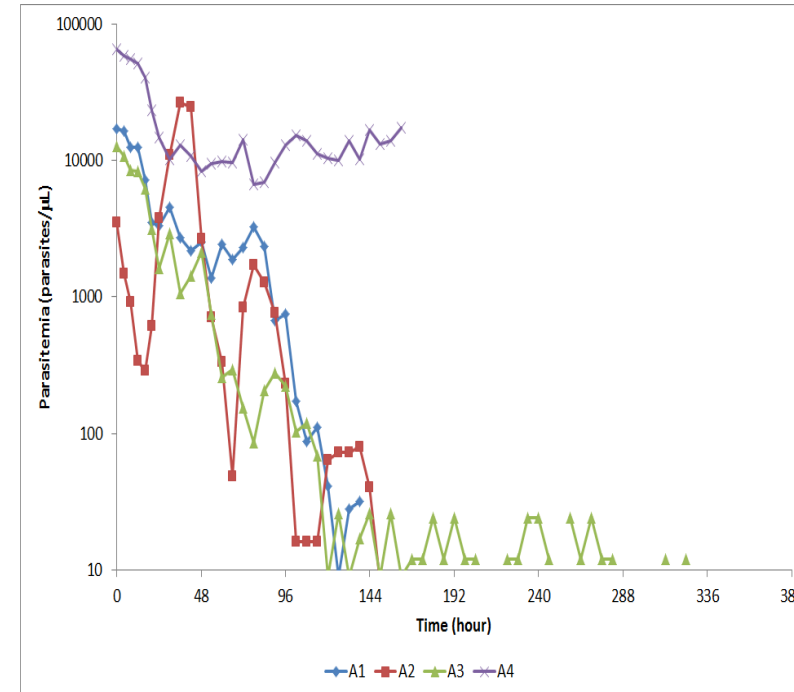
DEFINING THE DOSE-RESPONSE IN HUMANS MIC DETERMINATION

Australian Volunteers (100-500mg)



1 month per cohort, 1 centre
All year round

Thai Patients (100 mg)



6 months, 4 centres,
seasonal

TRANSLATIONAL APPROACH REDUCES TIME AND COST

Impact	Time (years)		Subject or patients		Cost saving (\$M)	
	Before	After	Before	After	Before	After
Earlier knowledge of PK/PD relationship	PoC	PoP	70	44	2.7	1.25
Shorter/smaller PoP study	1.5	0.25	>30	24	1.5	0.75
Shorter/smaller PoC	1.5	0.8	40	10 – 20	1.2	0.5

FAMILY PLANNING



THE CHALLENGE

- 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)



A photograph of Melinda Gates, a woman with brown hair tied back, wearing a teal button-down shirt and sunglasses on her head. She is looking towards the right of the frame. She is surrounded by a diverse group of women, many wearing colorful headwraps and traditional African attire. The background is slightly blurred, suggesting an outdoor setting with many people.

“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

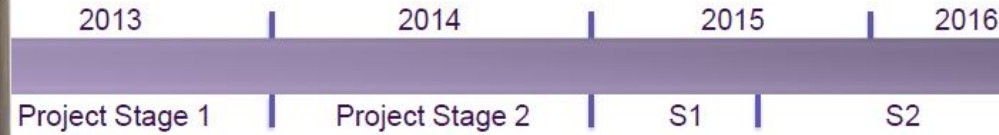
PROGRAMMABLE 15 YEAR CONTRACEPTIVE PRODUCT

PTH Clinical Device

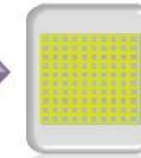


53 mm x 31 mm x 11mm

$$\frac{\text{Drug Vol}}{\text{Device Vol}} = 0.6 \mu\text{g}/\text{mm}^3$$



Developed Device



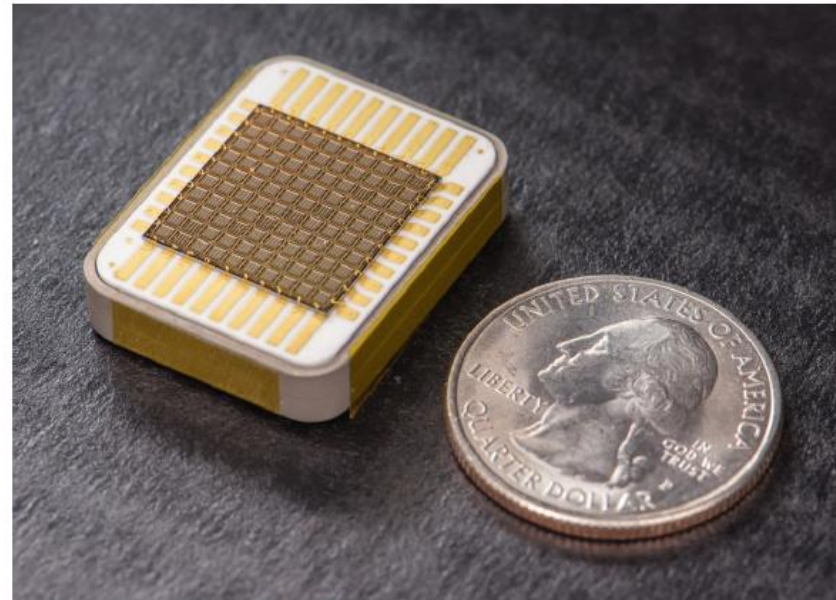
28 mm x 22 mm x 7.5 mm

$$\frac{\text{Drug Vol}}{\text{Device Vol}} = 87 \mu\text{g}/\text{mm}^3$$

145x Improvement

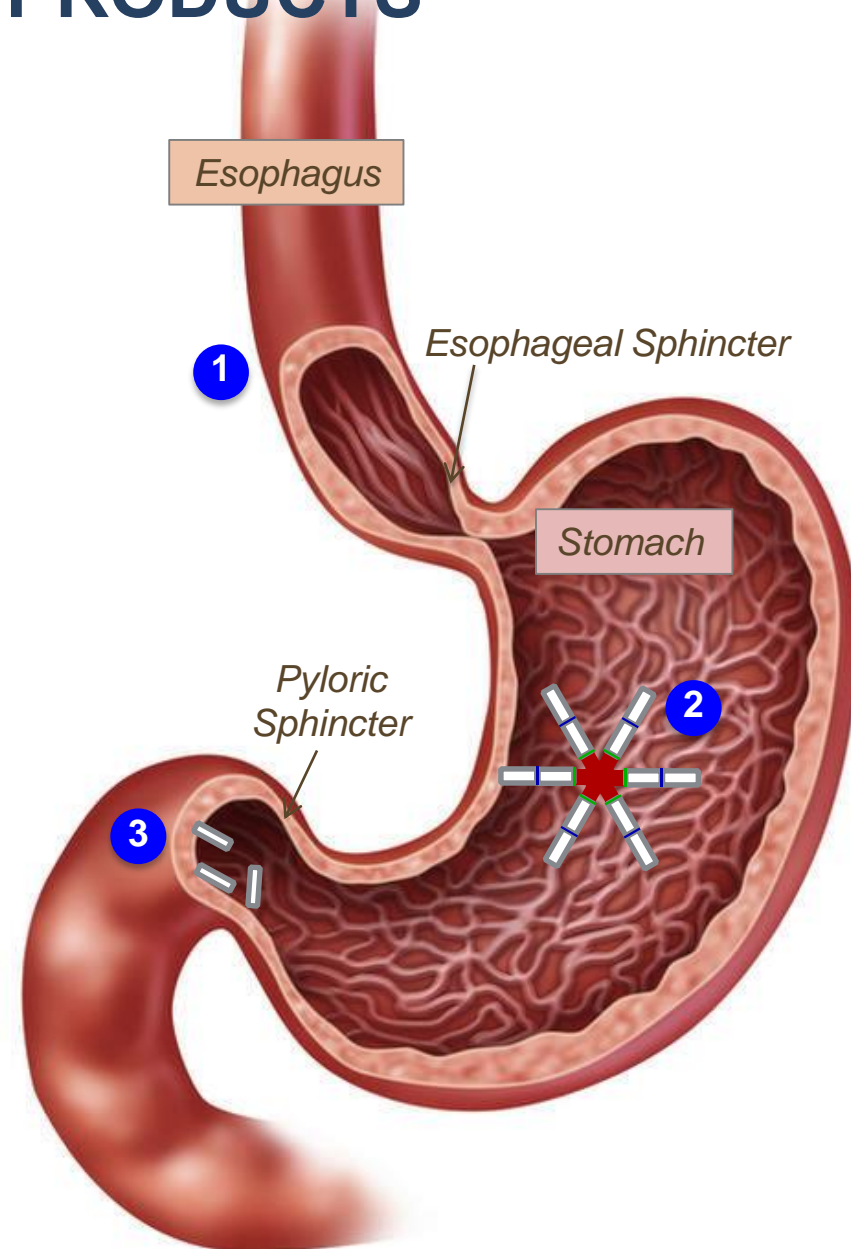
5x longer life

725x Improvement







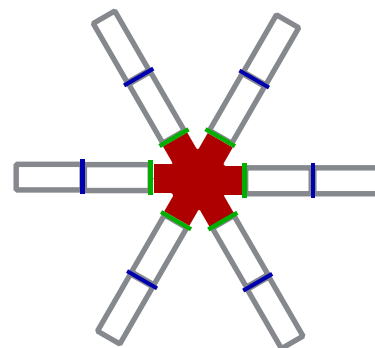
LYNDRA'S GASTRIC RESIDENCE PRODUCTS

- 1 Lyndra's products fit in a standard 00 capsule and are swallowed as a familiar pill
- 2 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.
- 3 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

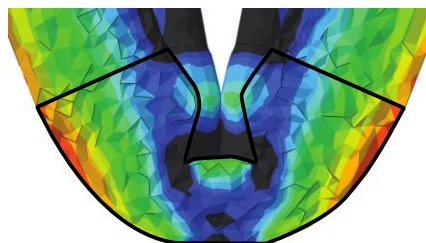


THE THREE COMPONENTS OF LYNDRA'S GASTRIC RESIDENCE PRODUCTS

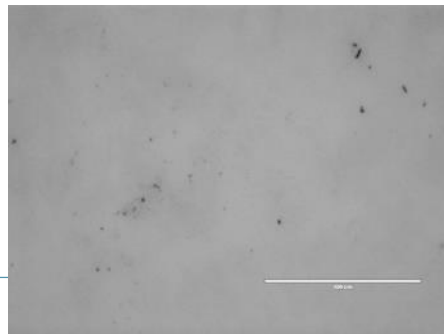
-  Drug-polymer blend
-  time-dependent linker
-  enteric safety linker
-  thermoset rubber



Elastomer

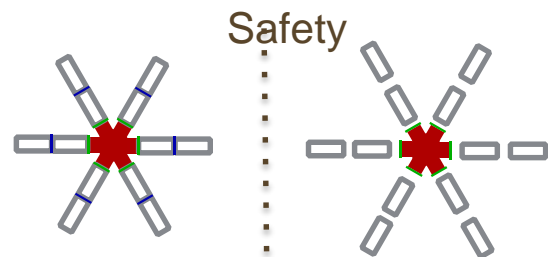


Drug – Polymer Arm



Linkers

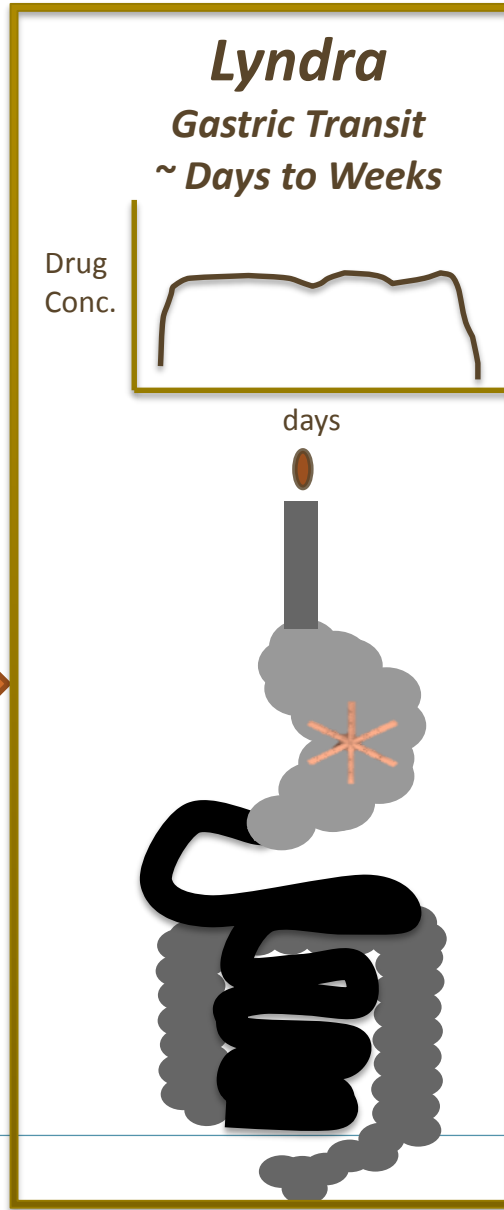
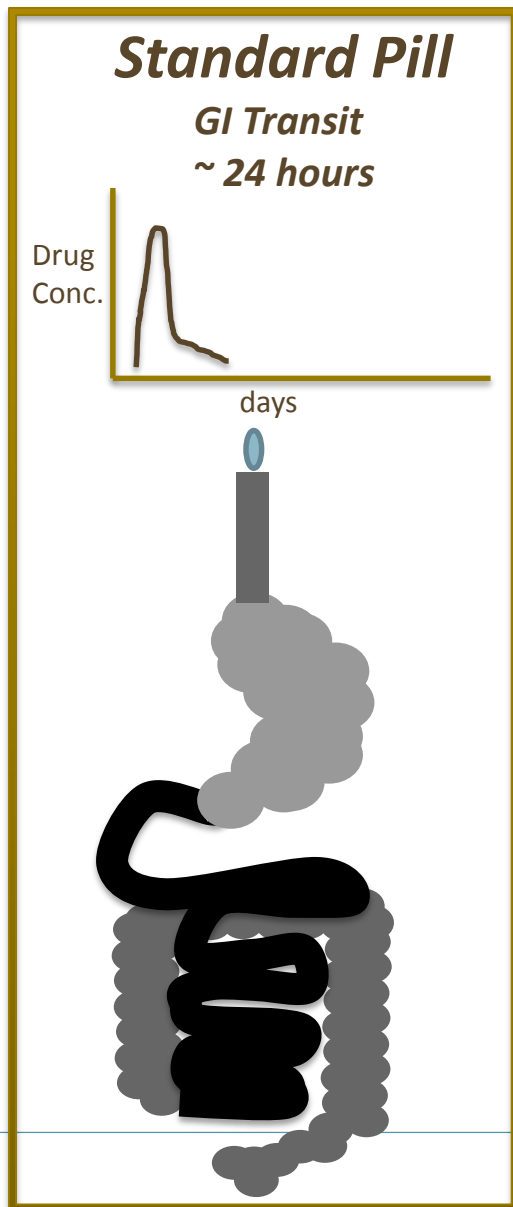
Linkers Dissolve in Time- and pH-Dependent Manners to Control Gastric Exit and Safety



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

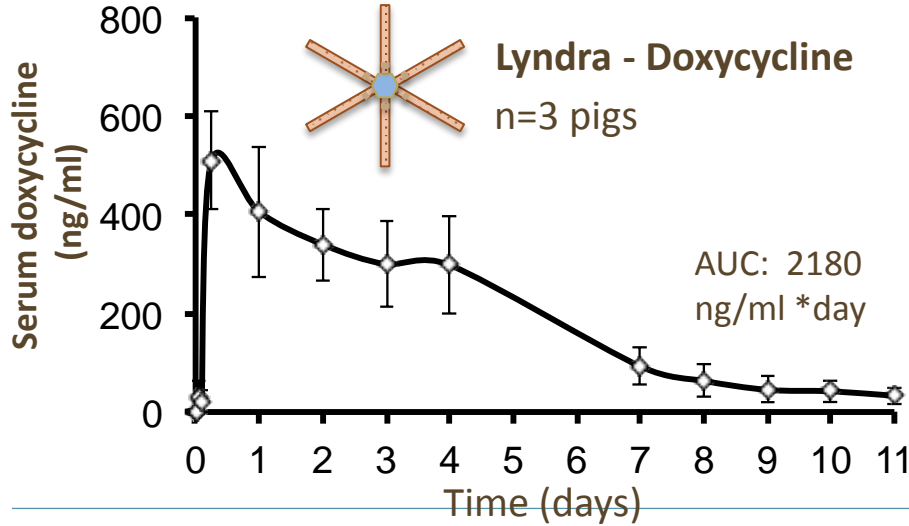
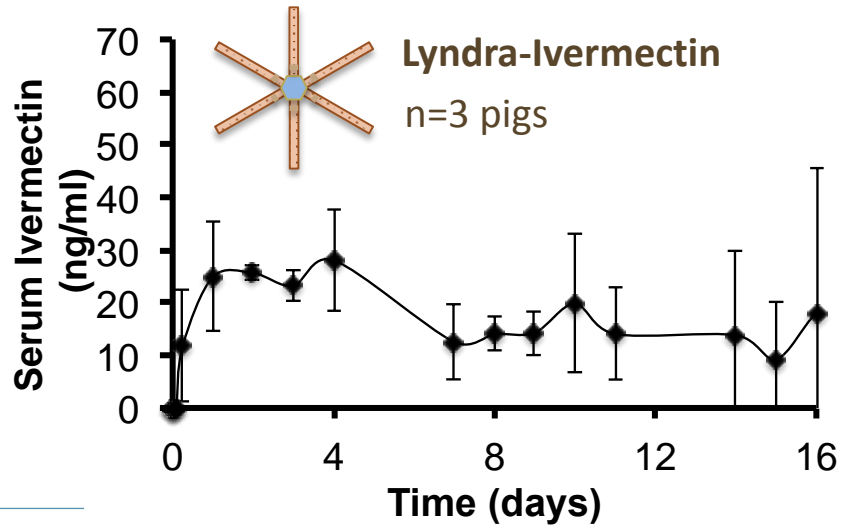
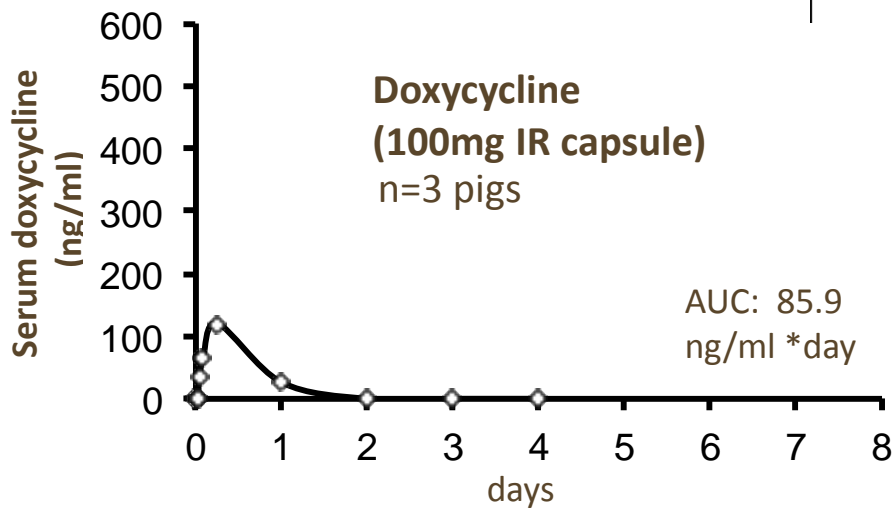
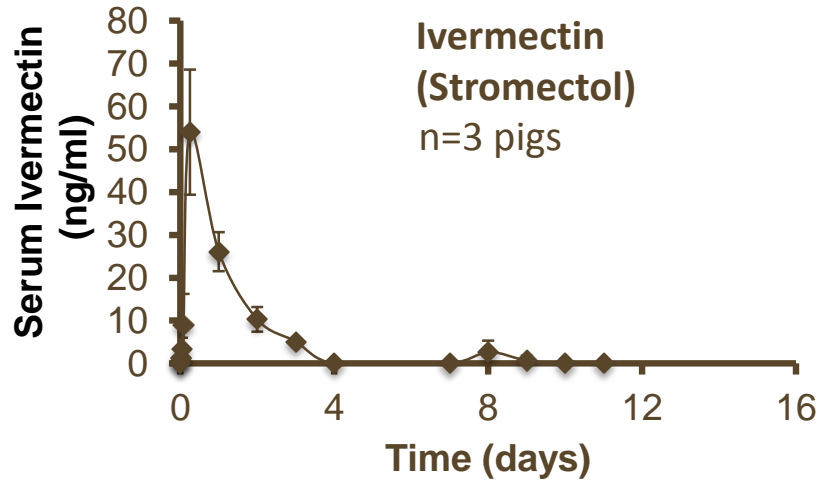
Reduced C_{max}

Potential for improved
solubility,
absorption,
bioavailability

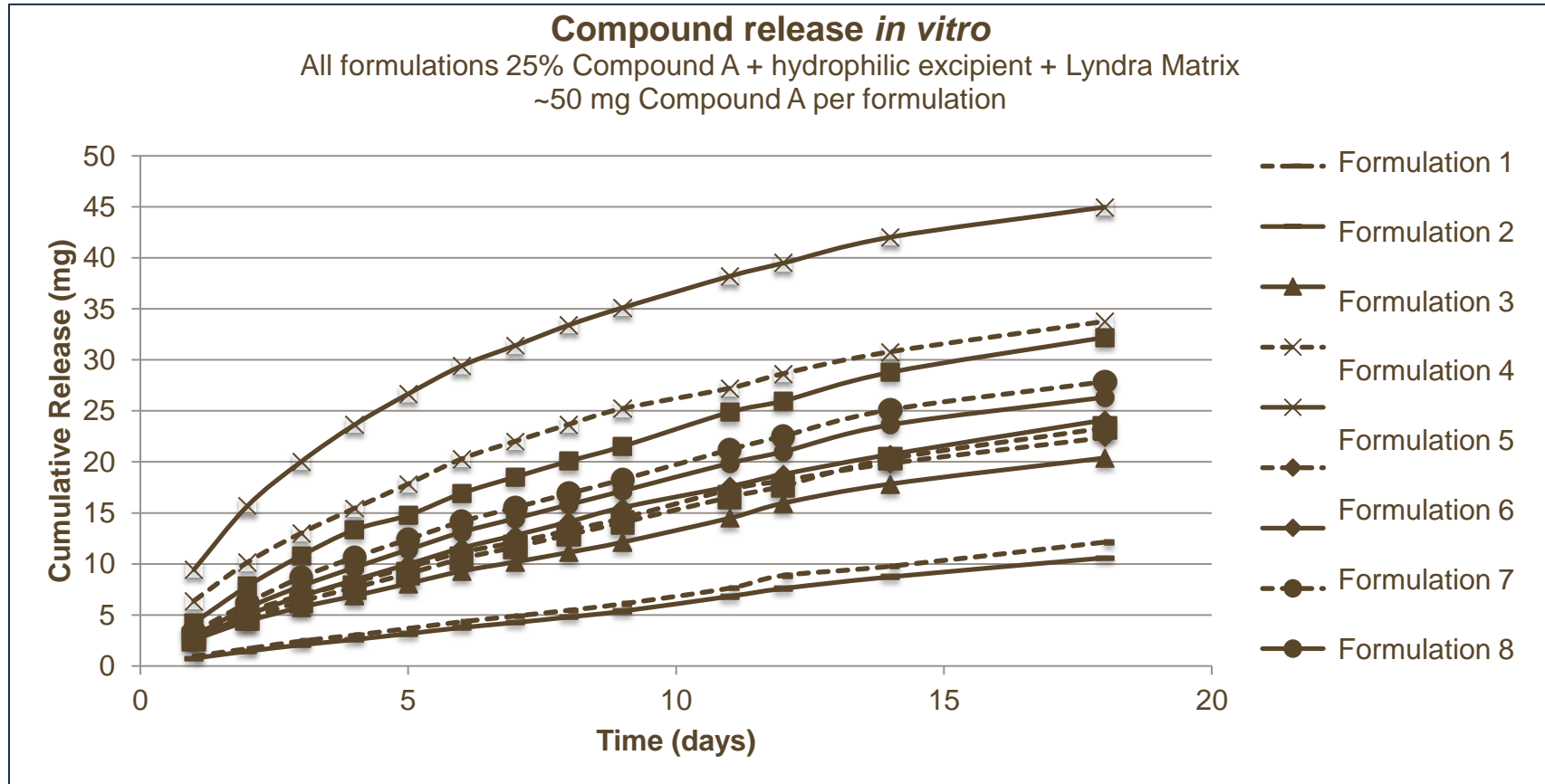
Sustained PK

Duration tunable from
1 day to > 7 days

SUSTAINING SERUM LEVELS WITH LYNDRA'S TECHNOLOGY



TUNABLE RATE AND DURATION OF RELEASE



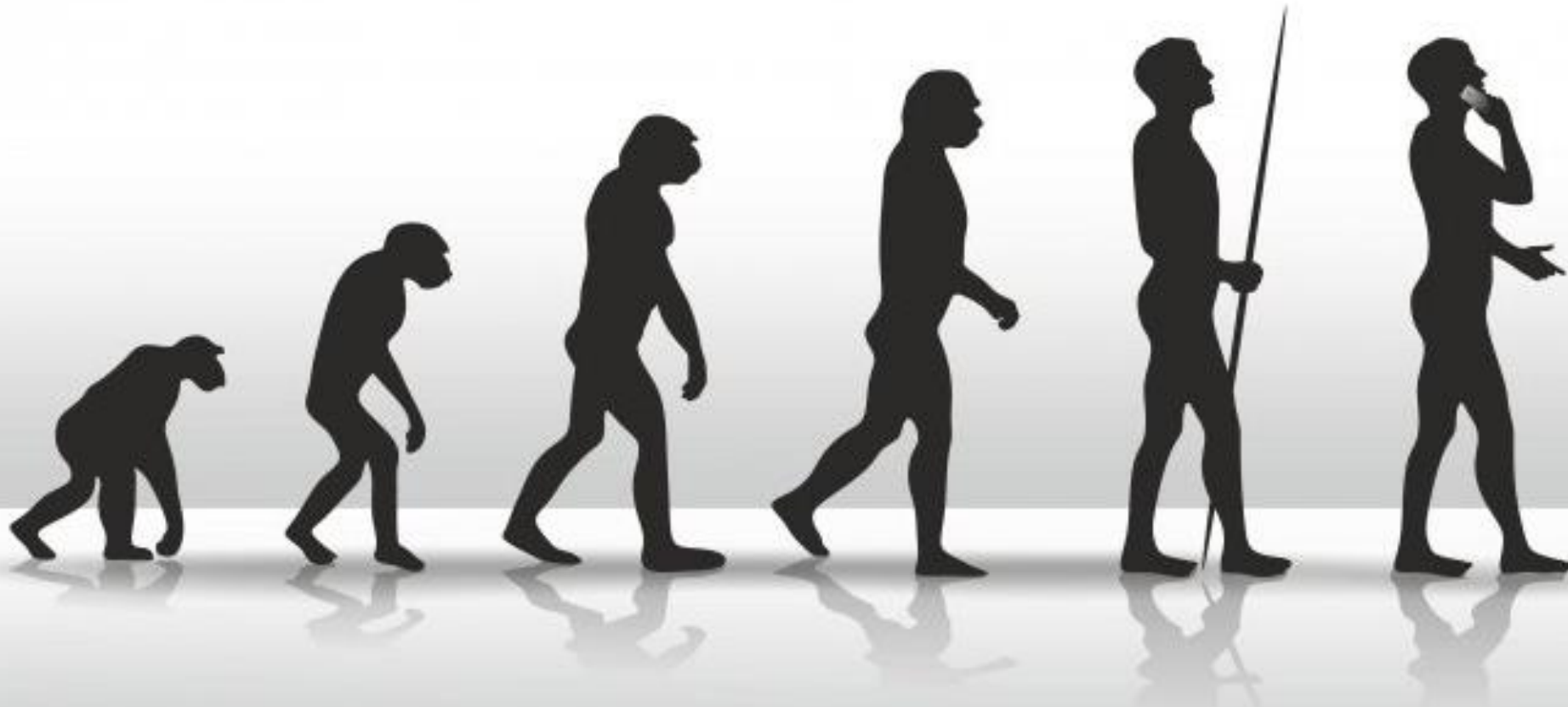
- In vitro release profiles tuned using standard excipients and methods
- Technology works with hydrophilic, hydrophobic, and lipophilic small molecule compounds

PIPELINE OF INNOVATIONS

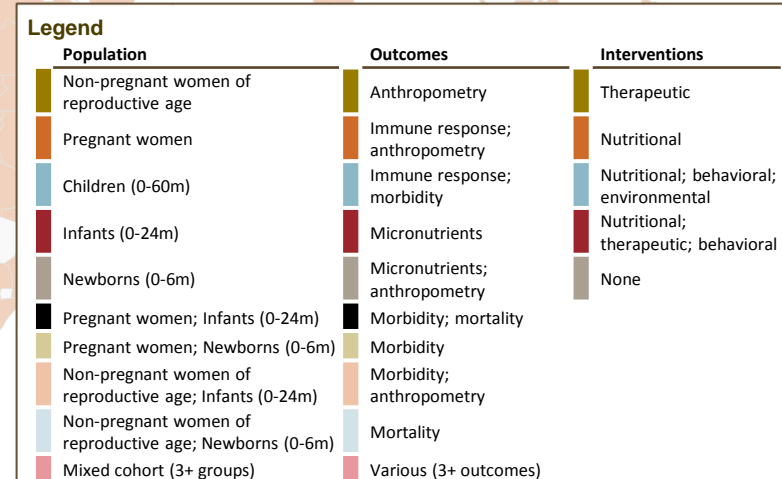
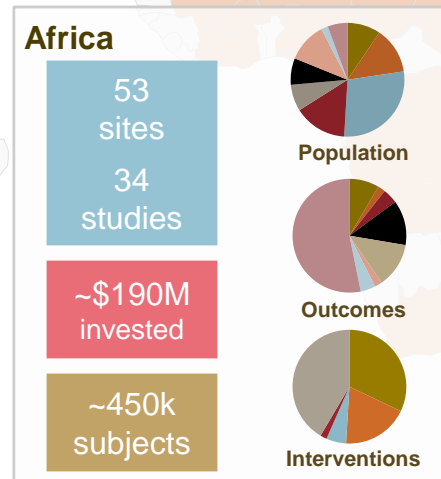
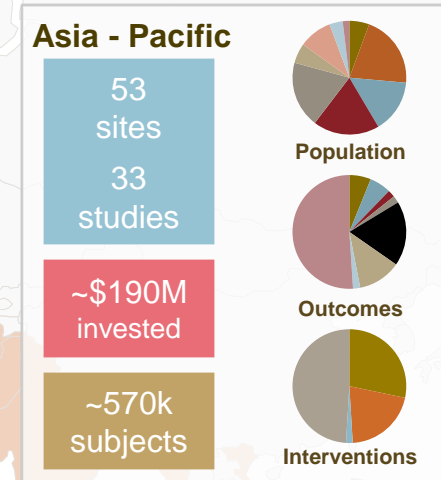
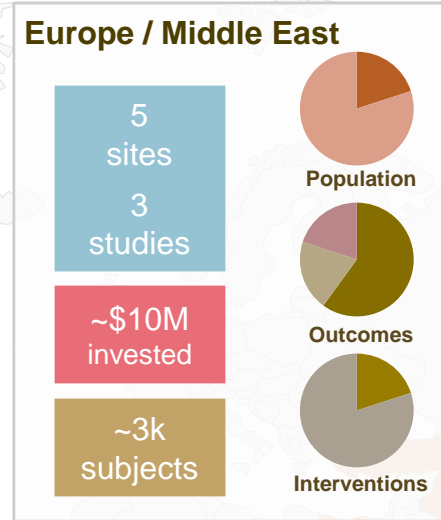
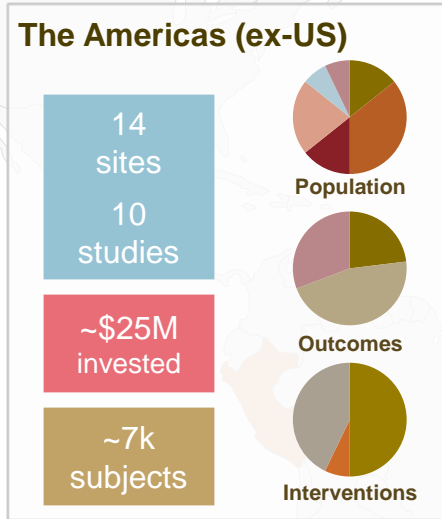
- 3-12 month injectable ARV treatment and prevention
- Replace multiple dose vaccines with a single dose vaccines
- Injectable implants that can release drug for 6-24 months
- 11 essential micronutrients that are heat and humidity stable
- Inhaled surfactant

HEALTHY BIRTH, GROWTH & DEVELOPMENT

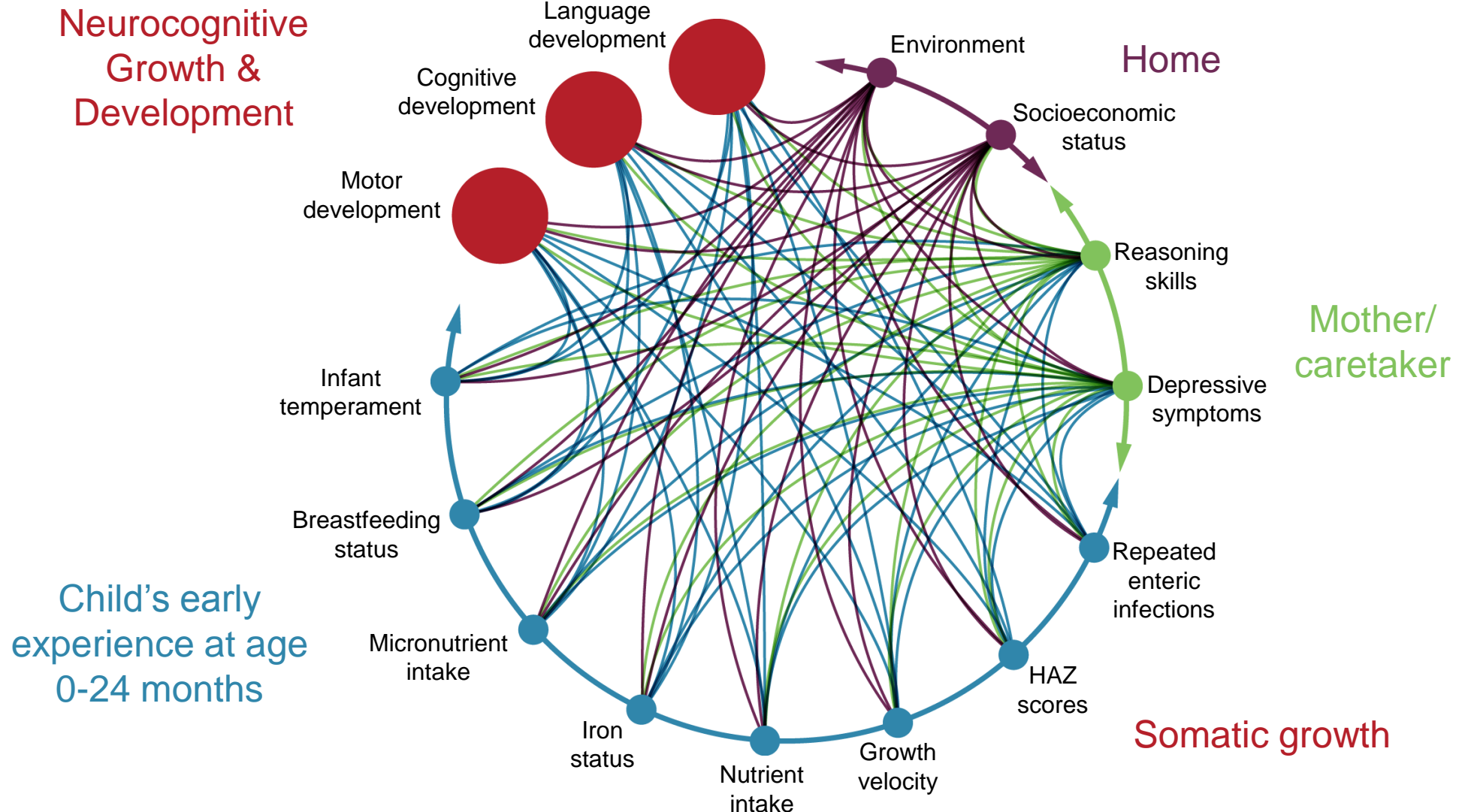
knowledge integration



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



RESULTS FROM INVESTMENT: GROWTH & DEVELOPMENT NETWORK WEB



Neurocognitive
Growth &
Development

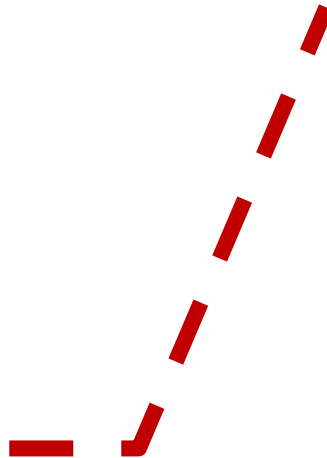
Home

Mother/
caretaker

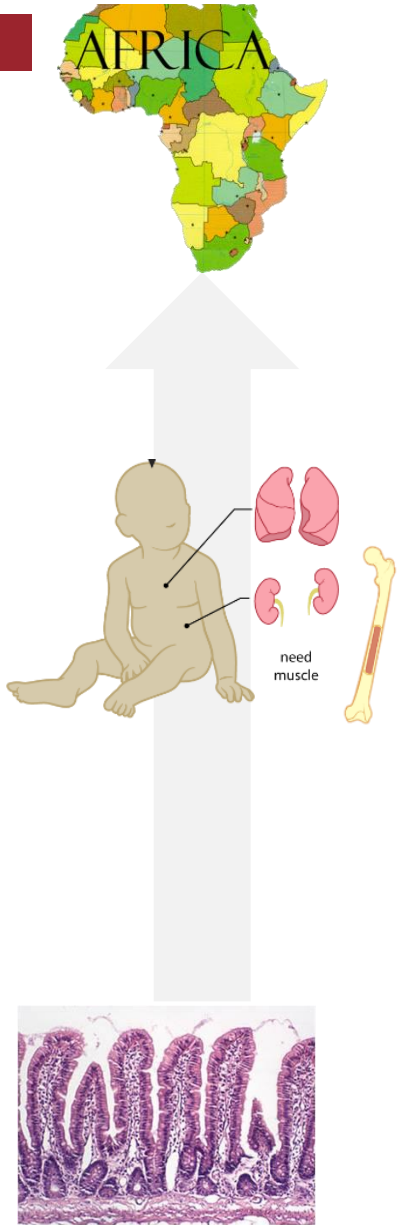
Child's early
experience at age
0-24 months

Somatic growth

HOW CAN WE MAXIMIZE THE UTILITY OF AVAILABLE DATA?



THE BIOLOGICAL AND GLOBAL HEALTH PROBLEM TRAVERSES 11 ORDERS OF MAGNITUDE **HBGDki**



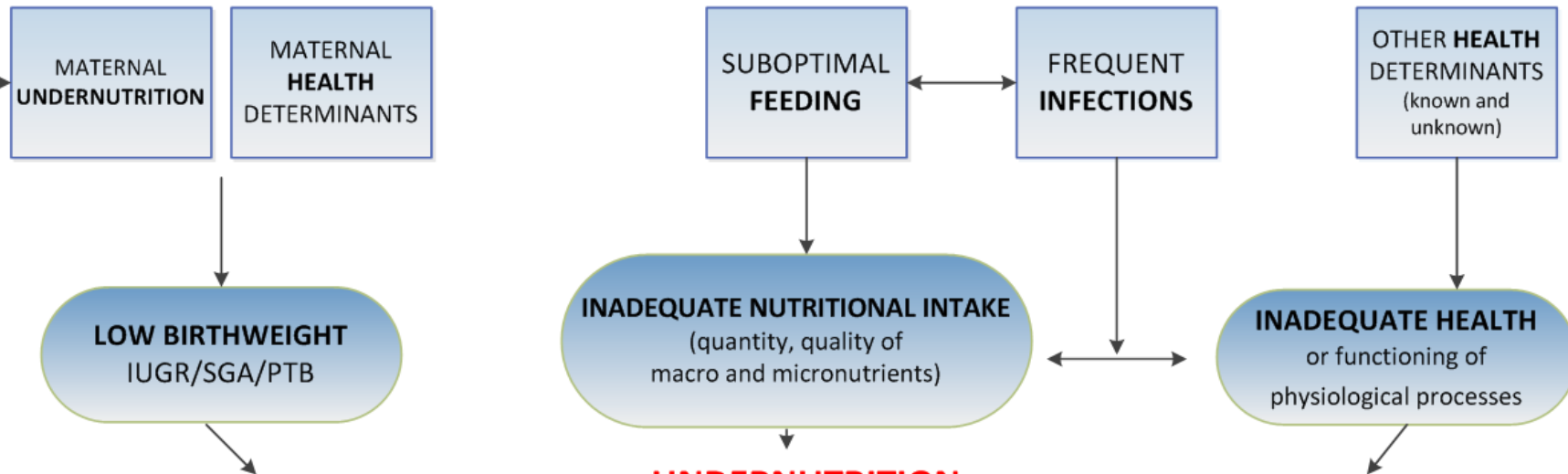
DETERMINANTS

Overarching: *ECONOMIC – POLITICAL & INSTITUTIONAL – SOCIO-CULTURAL & BEHAVIORAL - ENVIRONMENTAL*

Immediate:

Preconception and pregnancy

First 2 years

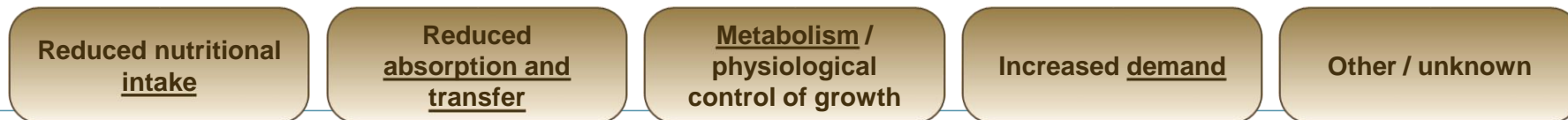


UNDERNUTRITION
(stunting, wasting, micronut. defic., LBW/IUGR/SGA/PTB)

OUTCOMES



MECHANISTIC BIOLOGICAL CAUSES



NO SINGLE MAGIC BULLET: THIS IS A COMPLEX MULTIFACTORIAL CHALLENGE REQUIRING COMBINATORIAL APPROACH

NUTRITION



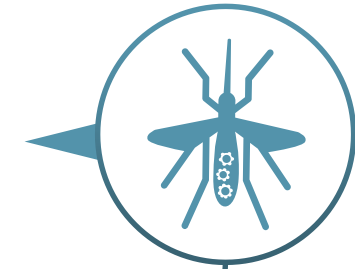
VACCINES



SANITATION



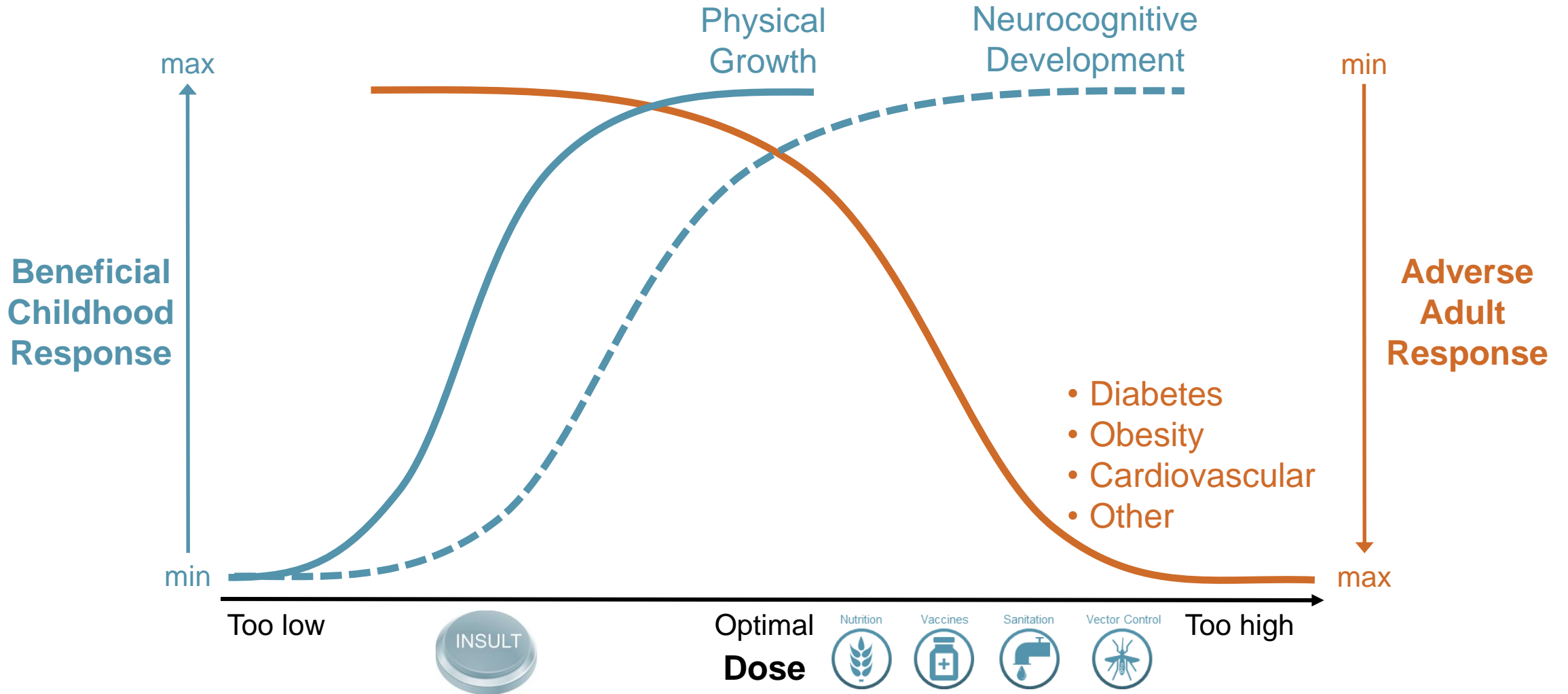
VECTOR
CONTROL



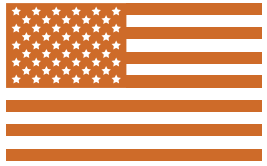
HEALTHY PREGNANCY,
BIRTH, GROWTH &
DEVELOPMENT



HBGD*ki* GOAL: COMBINE THE RIGHT INTERVENTIONS IN THE RIGHT DOSAGE TO GET THE RIGHT RESPONSE AND AVOID THE ADVERSE OUTCOMES

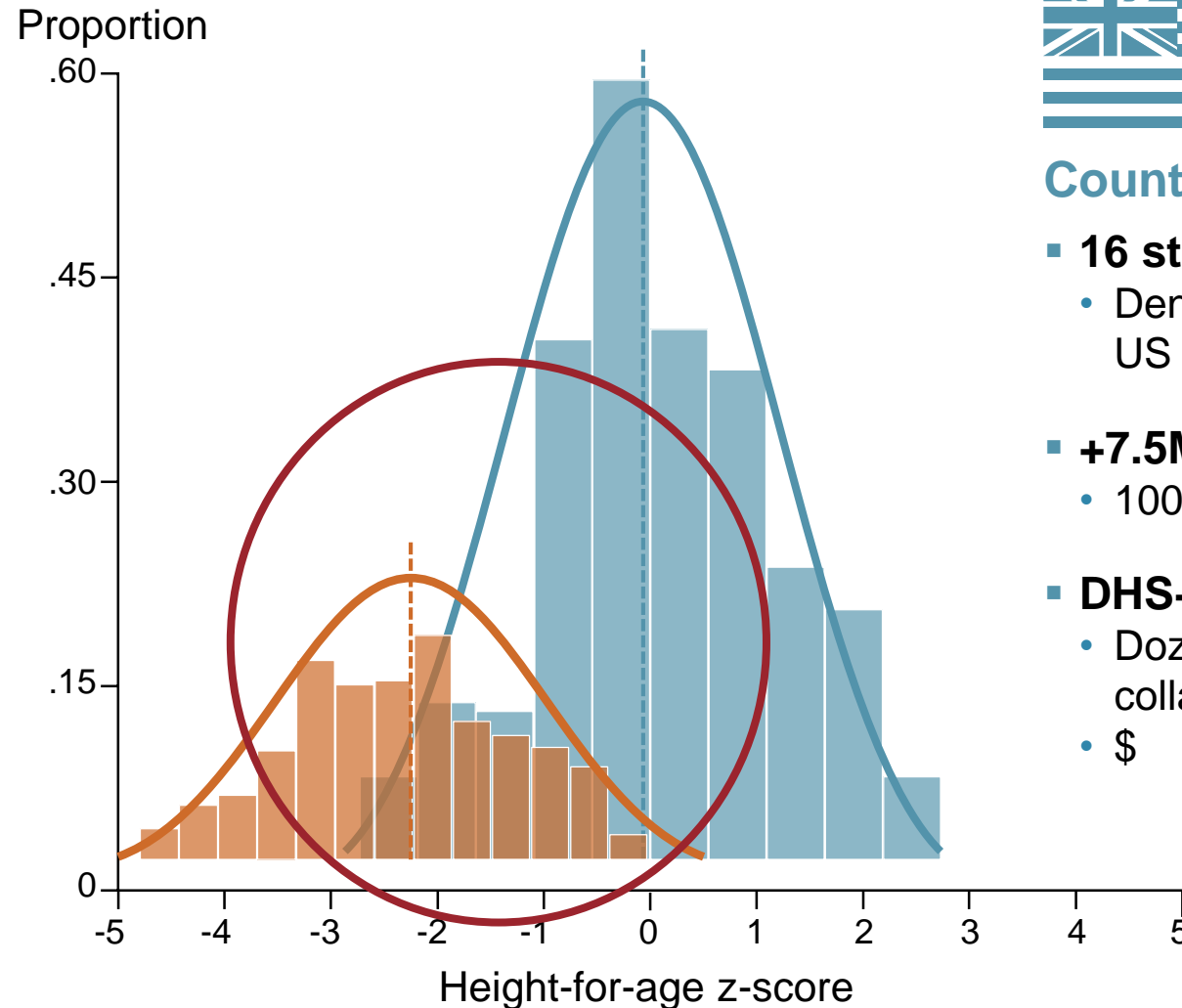


THE HBGD*ki* KNOWLEDGE BASE CONTAINS LMIC AND COUNTERFACTUAL HIC DATA AS NATURAL EXPERIMENTS



Reality: LMIC

- **53 studies:**
 - From most high stunting burden countries
- **~3.5M subjects data:**
 - 100s of covariates
- **DHS+:**
 - Dozens of prospective collaborations
 - \$\$\$



Counterfactual: HIC

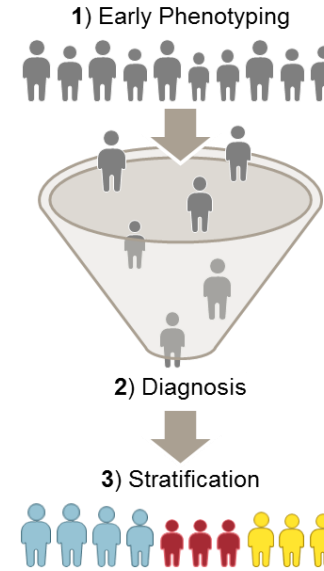
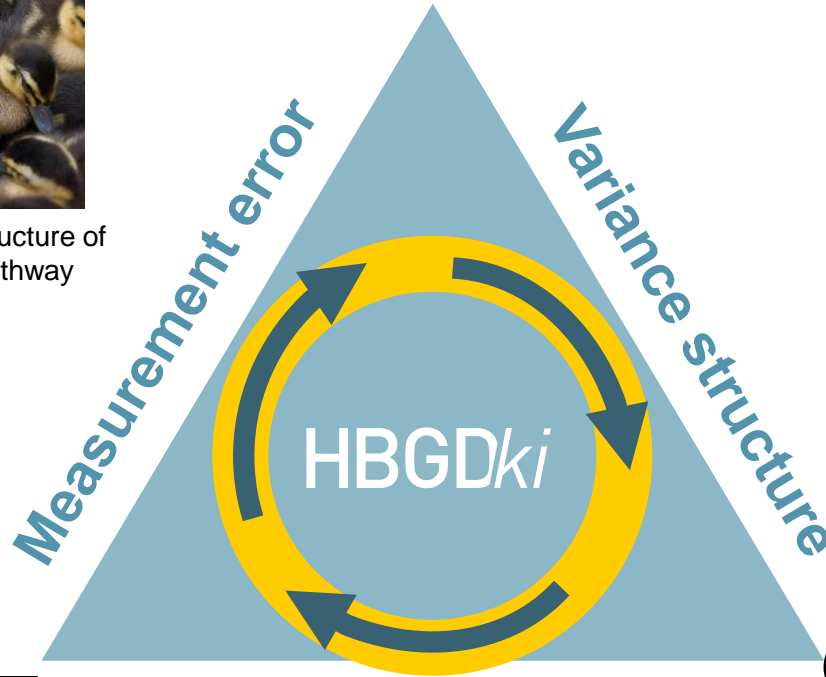
- **16 studies:**
 - Denmark, Netherlands, Singapore, US
- **+7.5M individual subject data:**
 - 1000s of covariates
- **DHS+:**
 - Dozens of prospective collaborations
 - \$

WHAT IS DIFFERENT ABOUT HBGDki?

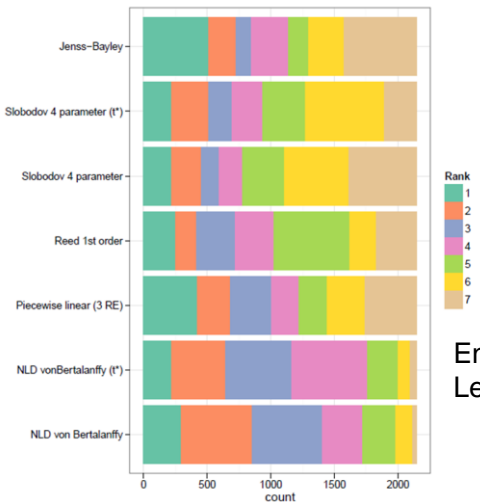


Leveraging accumulated data to estimate variance structure of multifactorial and highly nonlinear and time-varying pathway interactions

LEARN/EXECUTE



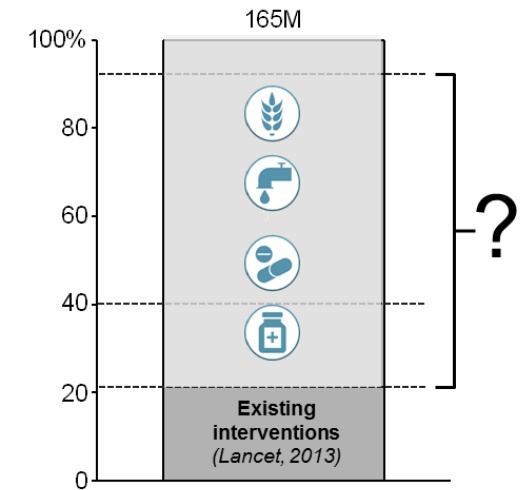
WASH Benefits SHINE



UPDATE

Ensemble Bayesian and Super Learner modeling platforms

**CONFIRM/
VALIDATE**



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

