Exploring the range of disease progression models for drug development

Steven E. Kern, Ph.D., Quantitative Sciences

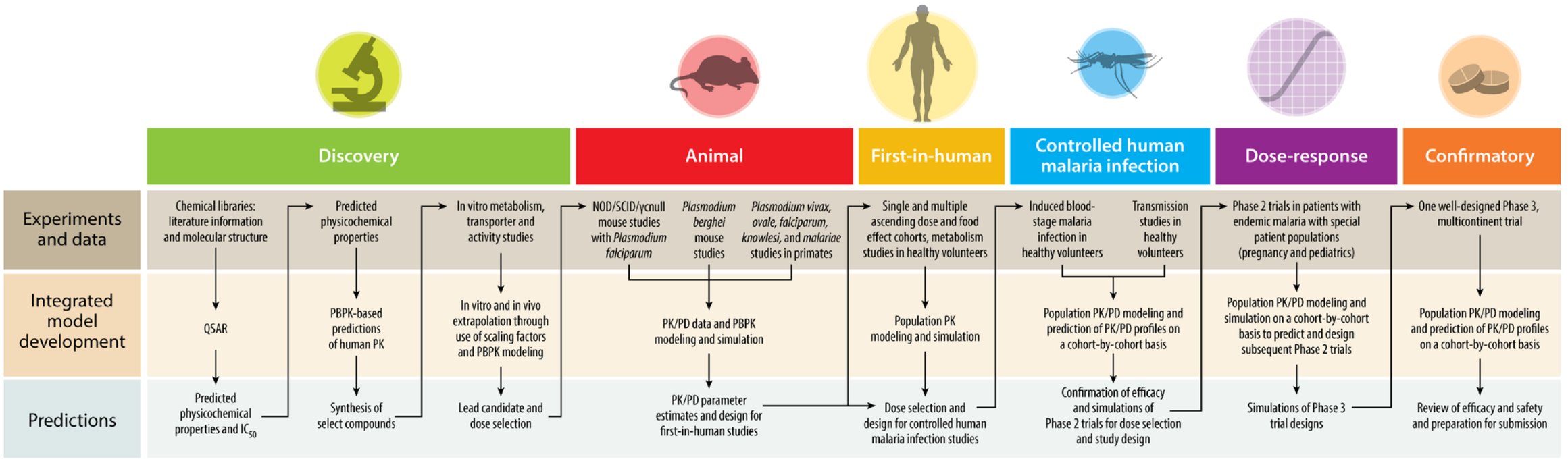
November 2021

BILL & MELINDA GATES foundation

A RANGE OF DISEASE PROGRESSION MODELS

- Quantitative models for disease progression
  - Population PK/PD models
  - Quantitative disease progression models linked to PD variables
- Disease/Organ on a Chip – microfluidic cellular tissue systems
  - Mimic temporal distribution of drug
  - Cellular organ compartments to assess permeability/activity/toxicity
- CHIM - Controlled Human Infection Models
  - Acute infectious diseases with suitable means of reversal
  - Robust intense sampling in fewer subjects to characterize dose/response
- Epidemiological Models of Disease Transmission/Progression
  - Integrating population solutions to assess larger scale progression
  - Assessment of Cost/Benefit or Cost Effectiveness for therapies

Models Support Decisions across the Drug Development Timeline



Andrews KA, et al. 2018.
Annu. Rev. Pharmacol. Toxicol. 58:567–82

Annual Review of Pharmacology and Toxicology

Model-Informed Drug Development for Malaria Therapeutics

Kayla Ann Andrews,[1,2] David Wesche,[3] James McCarthy,[4,5] Jörg J. Möhrle,[6] Joel Tarning,[7,8] Luann Phillips,[1] Steven Kern,[3] and Thaddeus Grasela[1]

MICROFLUIDIC PHYSIOLOGICAL SYSTEMS – DISEASE/ORGAN ON A CHIP

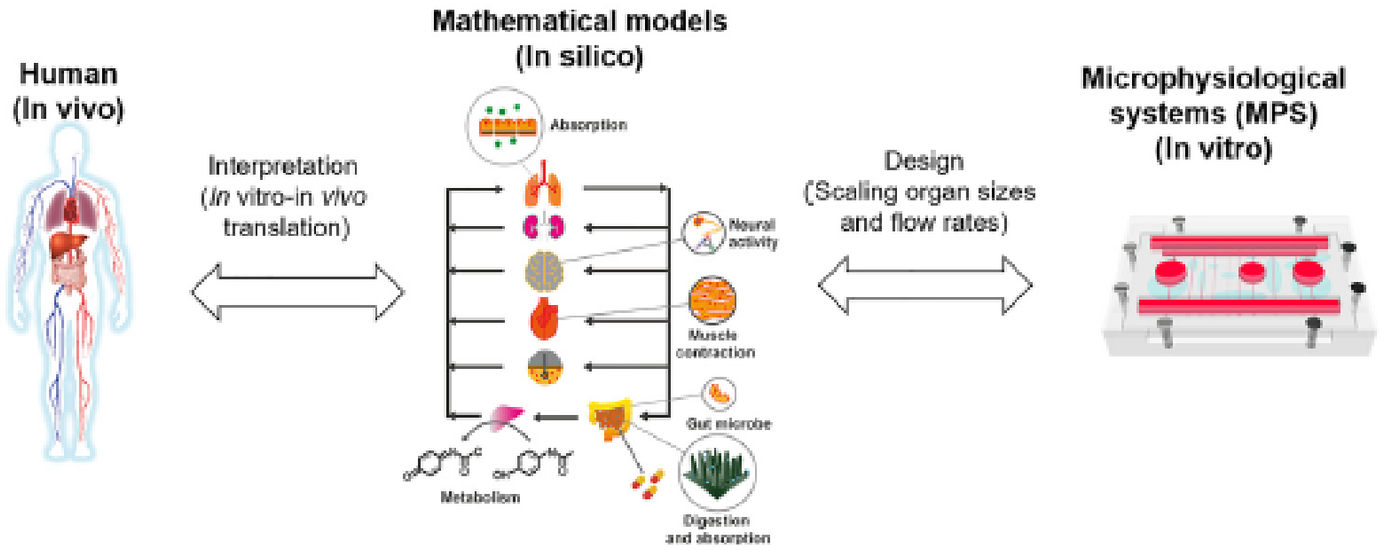
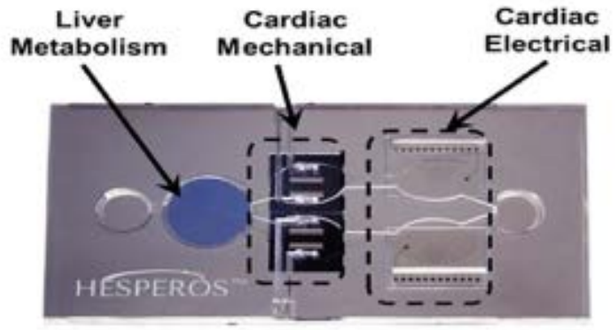


FIG. 1. Relationship between *in vivo* (human or animals), *in silico* (mathematical models), and *in vitro* (MPS) platforms.

APL Bioeng. **3**, 021501 (2019); doi: 10.1063/1.5097675

3, 021501-2

MICROPHYSIOLOGICAL SYSTEMS – DISEASE ON A CHIP



SCIENTIFIC REPORTS

OPEN

On the potential of *in vitro* organ-chip models to define temporal pharmacokinetic-pharmacodynamic relationships

Received: 13 March 2019
Accepted: 7 June 2019
Published online: 03 July 2019

Christopher W. McAleer[1], Amy Pointon[2], Christopher J. Long[1], Rocky L. Brighton[1], Benjamin D. Wilkin[1], L. Richard Bridges[1], Narasimham Narasimhan Sriram[1], Kristin Fabre[3], Robin McDougall[3], Victorine P. Muse[3], Jerome T. Mettetal[3], Abhishek Srivastava[2], Dominic Williams[2], Mark T. Schnepper[4], Jeff L. Roles[1], Michael L. Shuler[1], James J. Hickman[1,4] & Lorna Ewart[2]

SCIENTIFIC REPORTS
natureresearch

Check for updates

OPEN

Functional skeletal muscle model derived from SOD1-mutant ALS patient iPSCs recapitulates hallmarks of disease progression

Agnes Badu-Mensah[1,2], Xiufang Guo[1], Christopher W. McAleer[3], John W. Rumsey[3] & James J. Hickman[1,3]✉

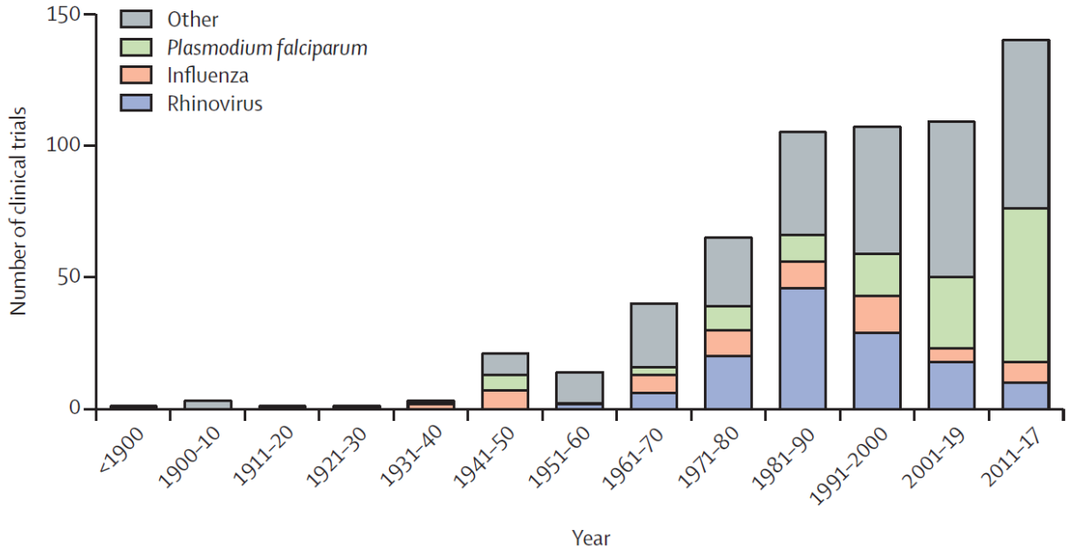
FULL PAPER

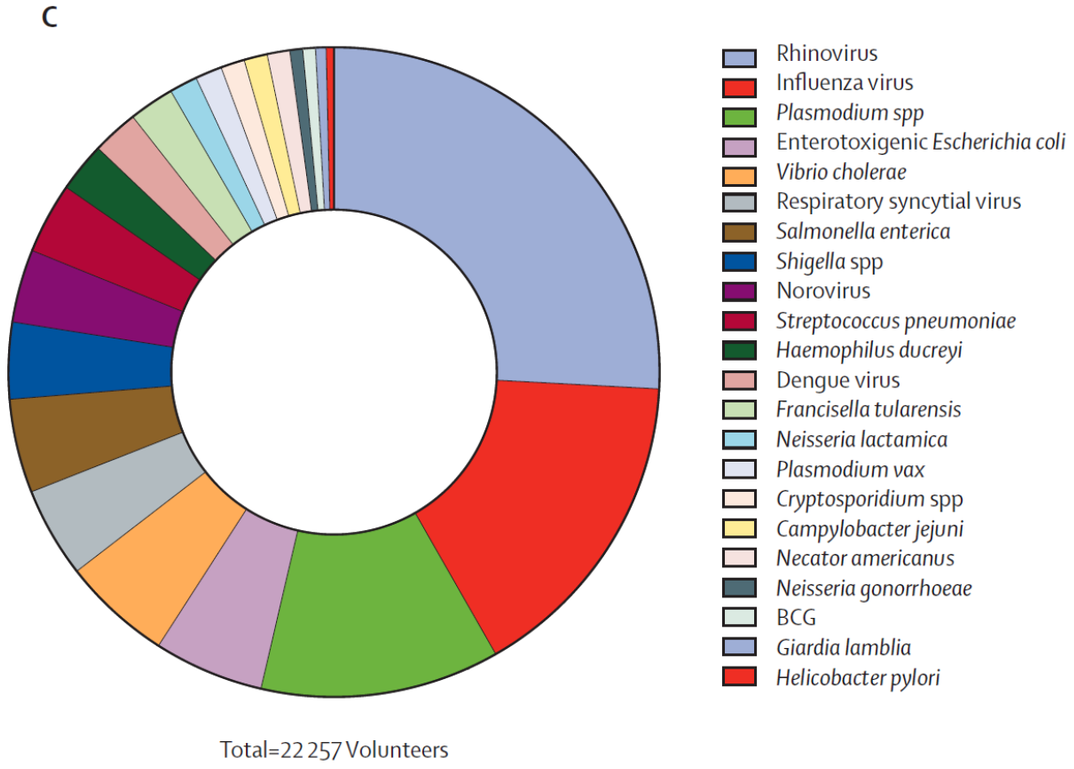
ADVANCED THERAPEUTICS
www.advtherap.com

A Human-Based Functional NMJ System for Personalized ALS Modeling and Drug Testing

*Xiufang Guo, Virginia Smith, Max Jackson, My Tran, Michael Thomas, Aakash Patel, Eric Lorusso, Siddharth Nimbalkar, Yunqing Cai, Christopher W. McAleer, Ying Wang, Christopher J. Long, and James J. Hickman**

CHIM – CONTROLLED HUMAN INFECTION MODELS





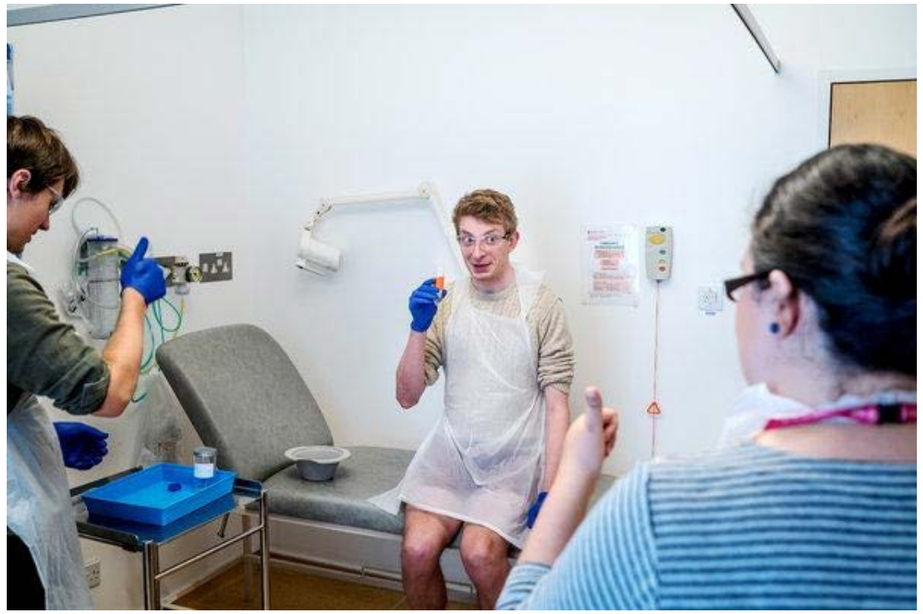
Total=22 257 Volunteers

Experimental infection of human volunteers

Meta Roestenberg, Marie-Astrid Hoogerwerf, Daniela M Ferreira, Benjamin Mordmüller, Maria Yazdanbakhsh

Lancet Infect Dis **2018;**
18: e312–22

CHIM – CONTROLLED HUMAN INFECTION MODELS



From New York Times, Global Health Section Sept. 28, 2017

They Swallowed Live Typhoid Bacteria — On Purpose

"I was curious." That's how James M. Duggan, an Oxford University medical student, explains why he agreed to swallow a big dose of live typhoid bacteria.
"This may sound odd," he continued, "but as a medical student, it's quite interesting to go through the process of being very ill. It does help to create empathy for your patients."
Mr. Duggan, 33, was not on a self-destructive sympathy bender. Like more than 100 other residents of Oxford, England, he was taking part in a trial of a new typhoid vaccine.

Experimental infection of human volunteers

Meta Roestenberg, Marie-Astrid Hoogerwerf, Daniela M Ferreira, Benjamin Mordmüller, Maria Yazdanbakhsh

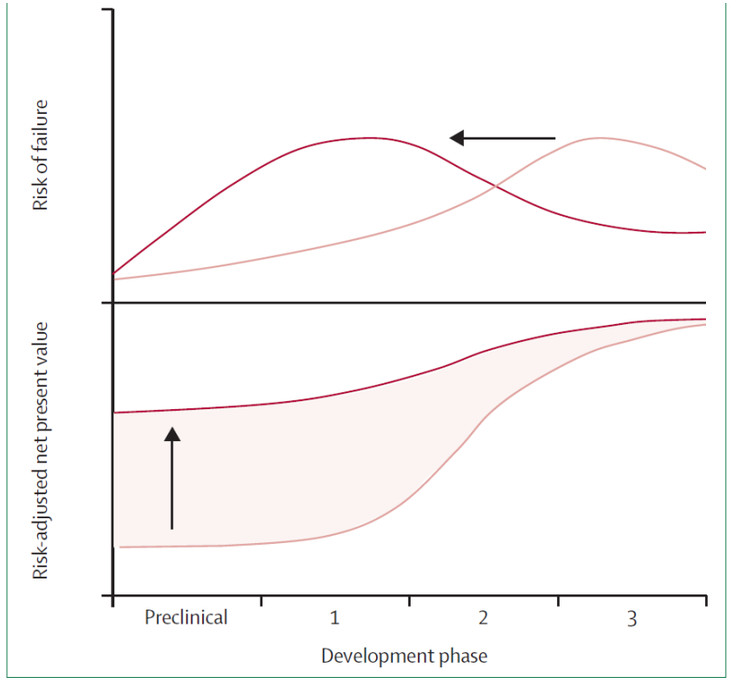


Figure 1: **Graphic representation of the risk of failure and the risk-adjusted net present value of a product before (light red) and after (dark red) introduction of a controlled human infection (CHI) model**

Lancet Infect Dis 2018;
18: e312–22

CHIM – CONTROLLED HUMAN INFECTION MODEL

The New York Times

OPINION

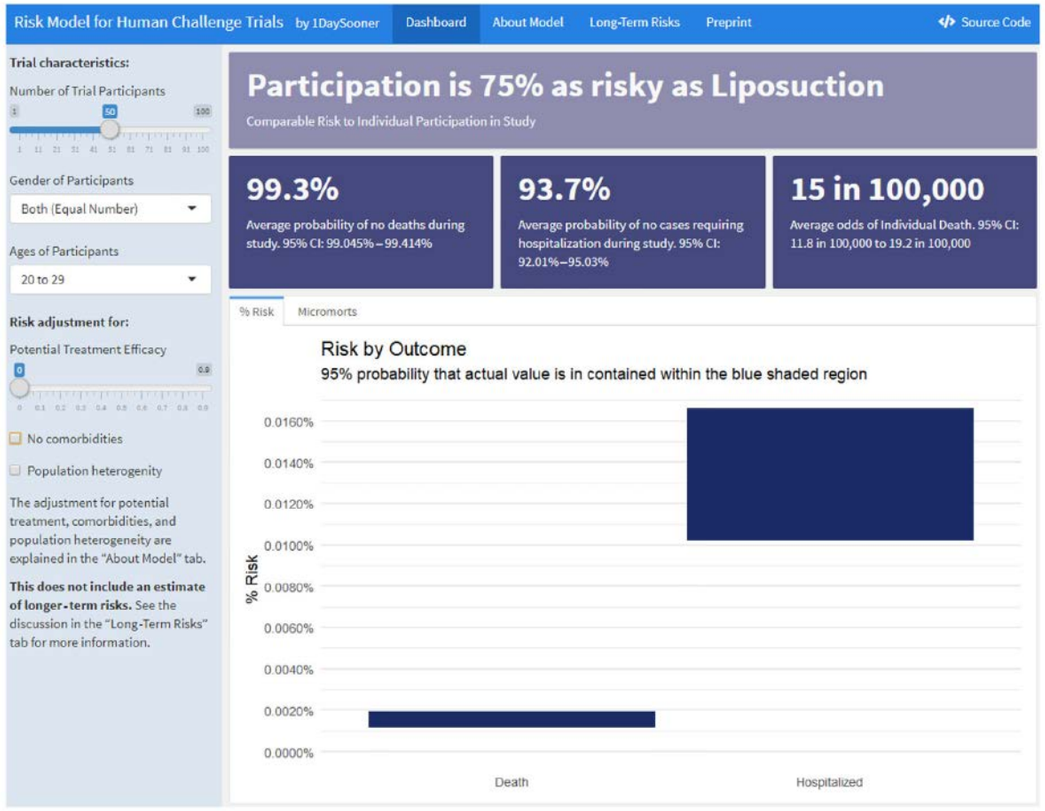
GUEST ESSAY

Britain Infected Volunteers With Covid. Why Won't the U.S.?

Oct. 14, 2021

Exploring Risks of Human Challenge Trials For COVID-19

David Manheim, Ph.D.,[1,2,*] Witold Więcek, Ph.D.,[1,3,†] Virginia Schmit, Ph.D.,[1] Josh Morrison,[1] and 1Day Sooner Research Team[1]



Risk Analysis, Vol. 41, No. 5, 2021

DOI: 10.1111/risa.13726

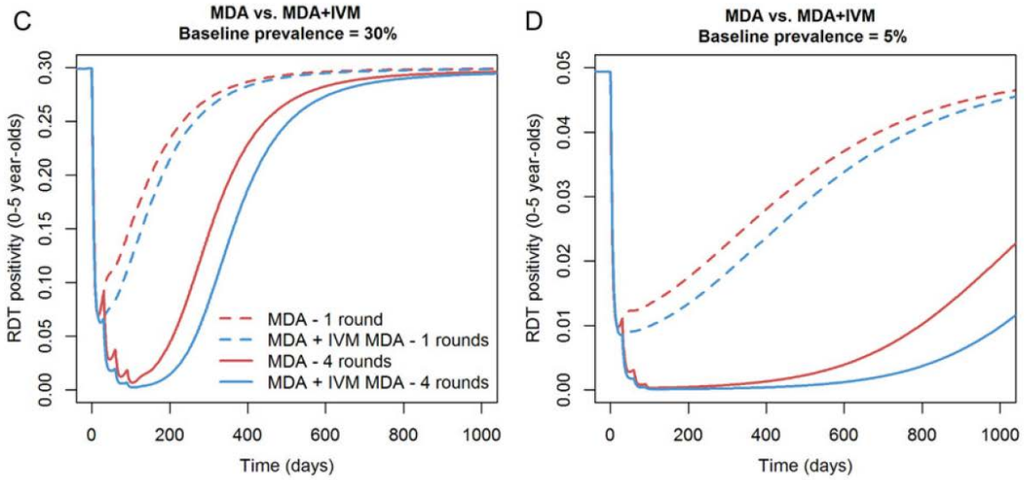
JOINING FORCES WITH EPIDEMIOLOGICAL MODELERS

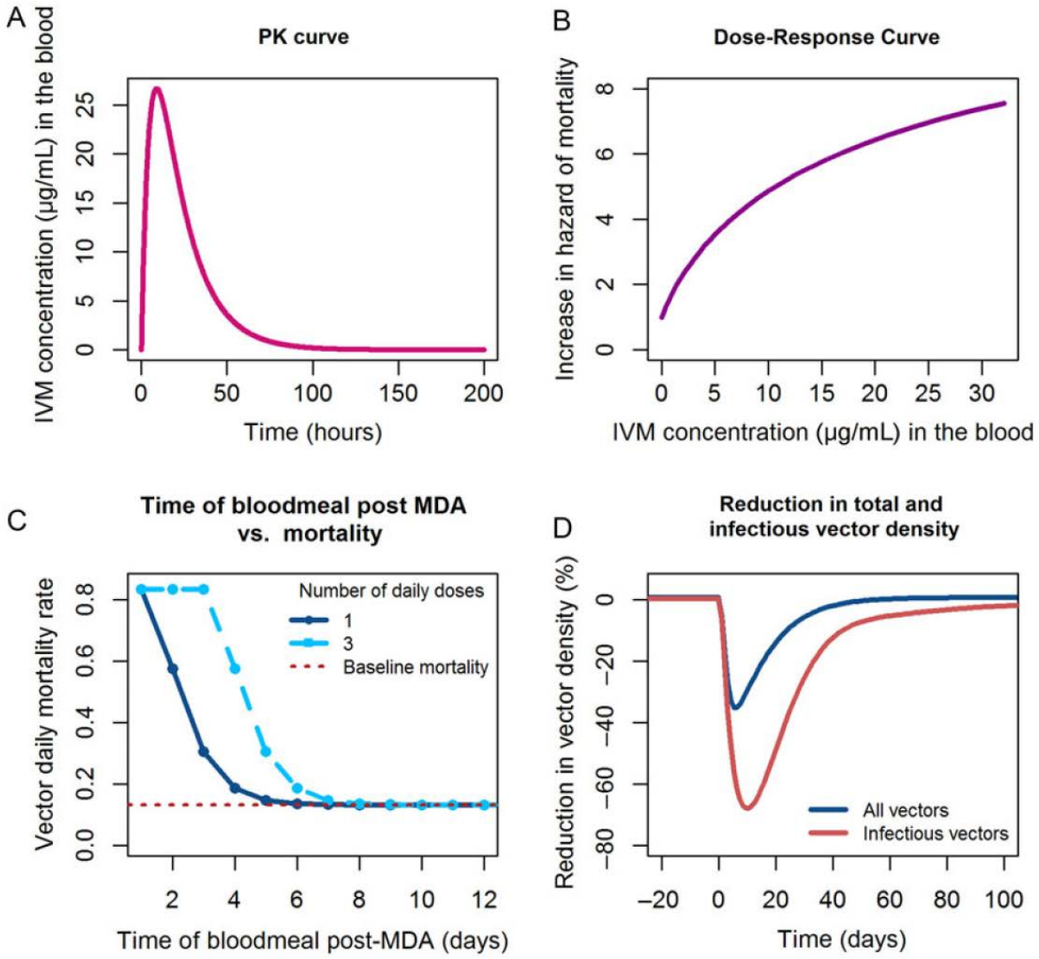
The Potential Impact of Adding Ivermectin to a Mass Treatment Intervention to Reduce Malaria Transmission: A Modelling Study

Hannah C. Slater,[1] Patrick G. T. Walker,[1] Teun Bousema,[2,3] Lucy C. Okell,[1] and Azra C. Ghani[1]

[1]MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London, Norfolk Place, United Kingdom; [2]Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Netherlands; and [3]Department of Immunology and Infection, London School of Hygiene and Tropical Medicine, United Kingdom

The Journal of Infectious Diseases® 2014;210:1972–80





Novel delivery systems with spatial epi modeling for analysis

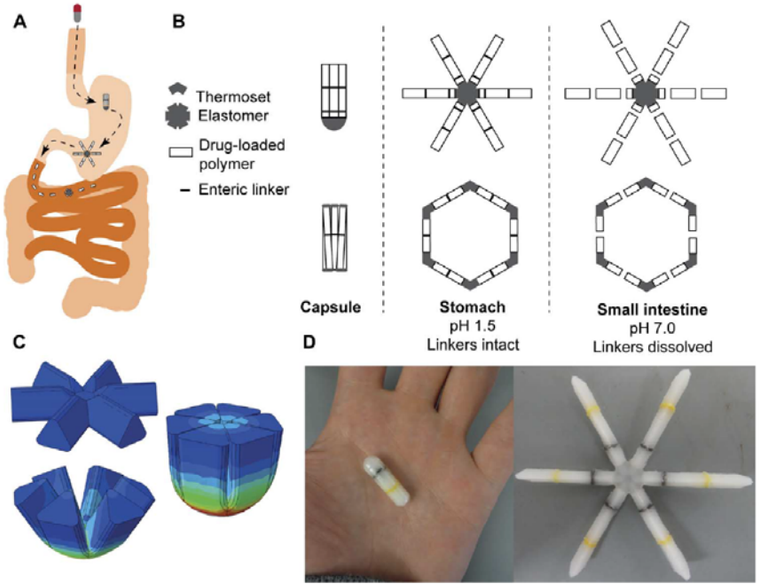
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

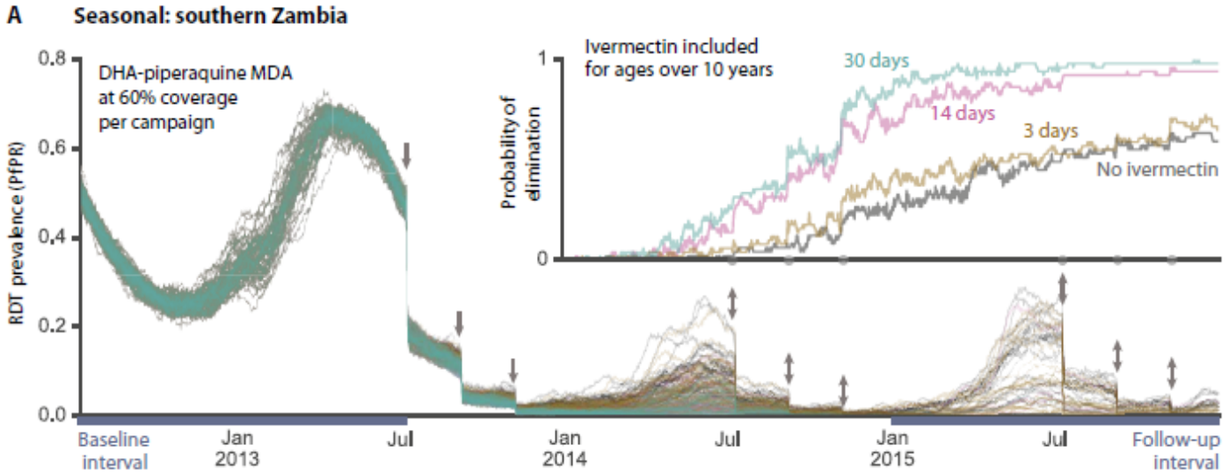
DRUG DELIVERY

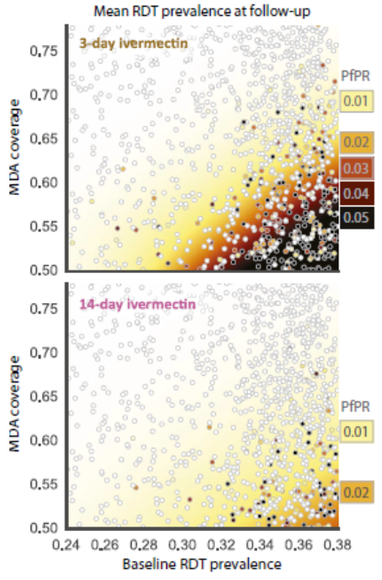
Oral, ultra–long-lasting drug delivery: Application toward malaria elimination goals

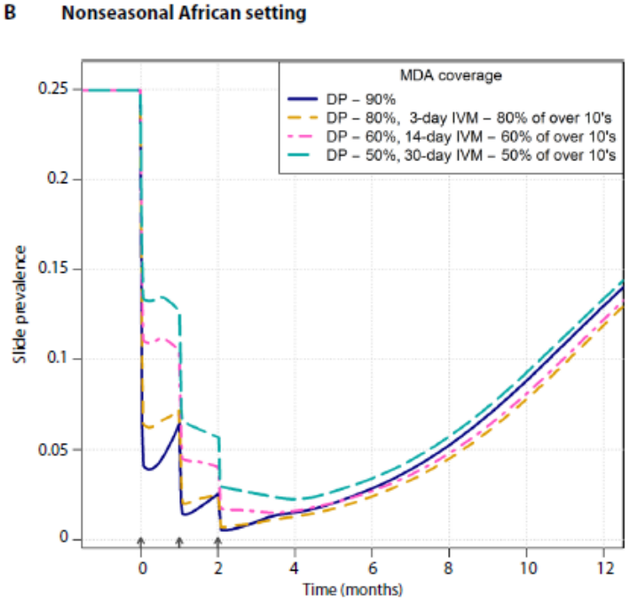
Andrew M. Bellinger,[1,2,3]* Mousa Jafari,[1]* Tyler M. Grant,[1,3]* Shiyi Zhang,[1]*† Hannah C. Slater,[4] Edward A. Wenger,[5] Stacy Mo,[1] Young-Ah Lucy Lee,[1] Hormoz Mazdiyasni,[1] Lawrence Kogan,[1] Ross Barman,[1] Cody Cleveland,[1,6] Lucas Booth,[1] Taylor Bensel,[1] Daniel Minahan,[1] Haley M. Hurowitz,[1] Tammy Tai,[1] Johanna Daily,[7] Boris Nikolic,[8] Lowell Wood,[5] Philip A. Eckhoff,[5] Robert Langer,[1,9,10]‡ Giovanni Traverso[1,6,11]‡

Bellinger *et al.*, *Sci. Transl. Med.* **8**, 365ra157 (2016) 16 November 2016









Optimizing interventions: What to do where

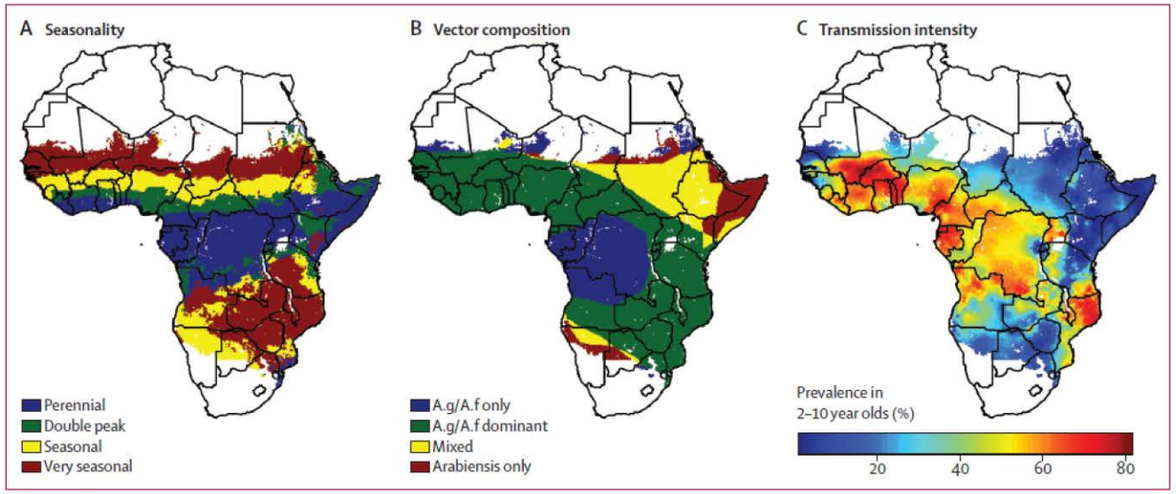


Figure 1: **Defining transmission settings across Africa**
(A) Distribution of the four seasonality templates based on rainfall patterns. (B) Vector species distribution for three key species groupings, based on presence and absence data.[35] A.g=*Anopheles gambiae* sensu stricto. A.f=*Anopheles funestus*. Arabiensis=*Anopheles arabiensis*. Mixed=all three species. (C) Estimates of malaria prevalence (blood film positivity) in children aged 2–10 years in 2000, back-calculated from estimates made for 2010,[6] using country-based estimates of scale-up for long-lasting insecticide-treated nets.

Estimating the most efficient allocation of interventions to achieve reductions in *Plasmodium falciparum* malaria burden and transmission in Africa: a modelling study

Patrick G T Walker, Jamie T Griffin, Neil M Ferguson, Azra C Ghani

Lancet Glob Health 2016; 4: e474–84

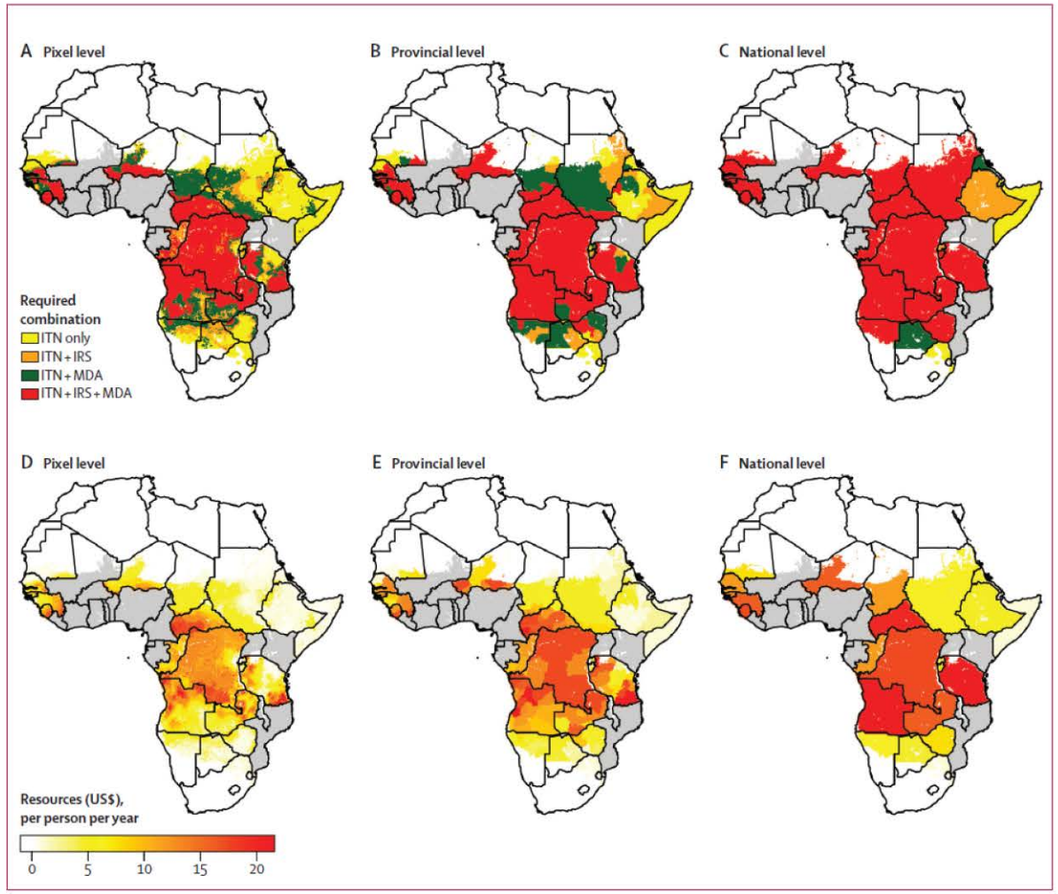


Figure 4: **Optimum combinations of interventions and minimum resources needed to achieve pre-elimination status across Africa**
IRS=indoor residual spraying. ITN=insecticide-treated nets. MDA=mass drug administration. Upper maps show packages when policies are optimised at (A) pixel, (B) provincial, and (C) national levels. Lower maps show the resources needed to implement these packages at (D) pixel, (E) provincial, and (F) national levels.

SUMMARY

Disease progression model landscape extending beyond mathematics

Exploiting Novel and Existing Tools to assess candidate viability

Combining forces with other modeling communities to understand impact

Spatial Epi modelers need our partnership, Impact starts at Regulatory Approval

Regulatory Authorities are expanding the use of Disease Progression Models

Unprecedented opportunity to improve the science of ALL drug development