

NGDI.ubc.ca

Neglected Global Diseases Initiative



a place of mind

THE UNIVERSITY OF BRITISH COLUMBIA

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The Neglected Global Diseases Initiative at UBC

Developing Interventions for Developing Countries



a place of mind

THE UNIVERSITY OF BRITISH COLUMBIA

How can the Poorest of the Poor Share in University Discoveries?

- Need mechanisms for **encouraging** and **funding** expensive research and development for Neglected Diseases.
- Must **creatively protect** early discoveries.
- **Delivery!!!!**



Mission: Developing interventions for neglected global diseases and ensuring their delivery to those in need.

www.ngdi.ubc.ca



The NGDI brings together a variety of disciplines, including bench science, biotechnology, pharmaceutical, health, social sciences, business, social policy and law.

Researchers work collaboratively to develop ways to most effectively generate affordable, life-sustaining medicines that can be brought to scale, thus reaching those most in need.



What are neglected global diseases?

Hookworm

Leprosy

Elephantitis

Sleeping Sickness

Chagas

Dengue Fever

Leishmaniasis

Soil Transmitted Helminthes



one in seven people
worldwide
is affected by a
neglected tropical disease

HIV/AIDS

Malaria

Tuberculosis

Why are they neglected?

TOTAL R&D FUNDING BY DISEASE IN 2007

HIV/AIDS	MALARIA	TUBERCULOSIS	OTHER*
\$1,083,018,193	\$468,449,438	\$410,428,698	\$598,172,420
42.3%	18.3%	16%	23.4%



*OTHER

Disease	Amount (USD)	%
KINETOPLASTIDS	\$125,122,839	4.9
DIARRHOEAL DISEASES	\$113,889,118	4.4
DENGUE	\$82,013,895	3.2
HELMINTHS (WORMS & FLUKES)	\$51,591,838	2.0
BACTERIAL PNEUMONIA & MENINGITIS	\$32,517,311	1.3
TYPHOID & PARATYPHOID FEVER	\$9,117,212	0.4
LEPROSY	\$5,619,475	0.2
BURULI ULCER	\$2,412,950	0.1
TRACHOMA	\$1,679,711	0.1
RHEUMATIC FEVER	\$1,670,089	0.1
CORE FUNDING OF A MULTI-DISEASE R&D ORGANIZATION	\$110,921,673	4.3
PLATFORM TECHNOLOGIES	\$9,997,189	0.4
UNSPECIFIED DISEASE	\$51,619,120	2.0
Total R&D Funding	\$2,560,068,749	100.0

Why are they important?

Top 10 Causes of Death	Approximate Deaths
Ischaemic heart disease	7,029,300
Stroke and other cerebro-vascular disease	5,874,200
Chronic obstructive pulmonary disease	2,899,900
Lower Respiratory Infections	2,814,400
Trachea, bronchus, lung cancers	1,527,100
HIV/AIDS	1,465,400
Diarrhoeal Diseases	1,445,800
Road traffic accidents	1,328,500
Diabetes mellitus	1,281,300
Tuberculosis	1,196,000

Statistics from Global Burden of Disease, 2010

How has UBC responded to this?



UNIVERSITY-INDUSTRY
LIAISON OFFICE

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Neglected Global Diseases Initiative



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ACCESS



What is "GLOBAL ACCESS" to medicines?

1/3 OF ALL PEOPLE

IN THE DEVELOPING WORLD
DON'T HAVE AFFORDABLE ACCESS TO MEDICINES
THAT COULD SAVE THEIR LIVES.

INNOVATION



What are **NEGLECTED DISEASES**?

ILLNESSES that  **MAINLY AFFECT**  the **DEVELOPING WORLD**

RARELY addressed by researchers  because  **MOST OF THE PEOPLE** who suffer from them are

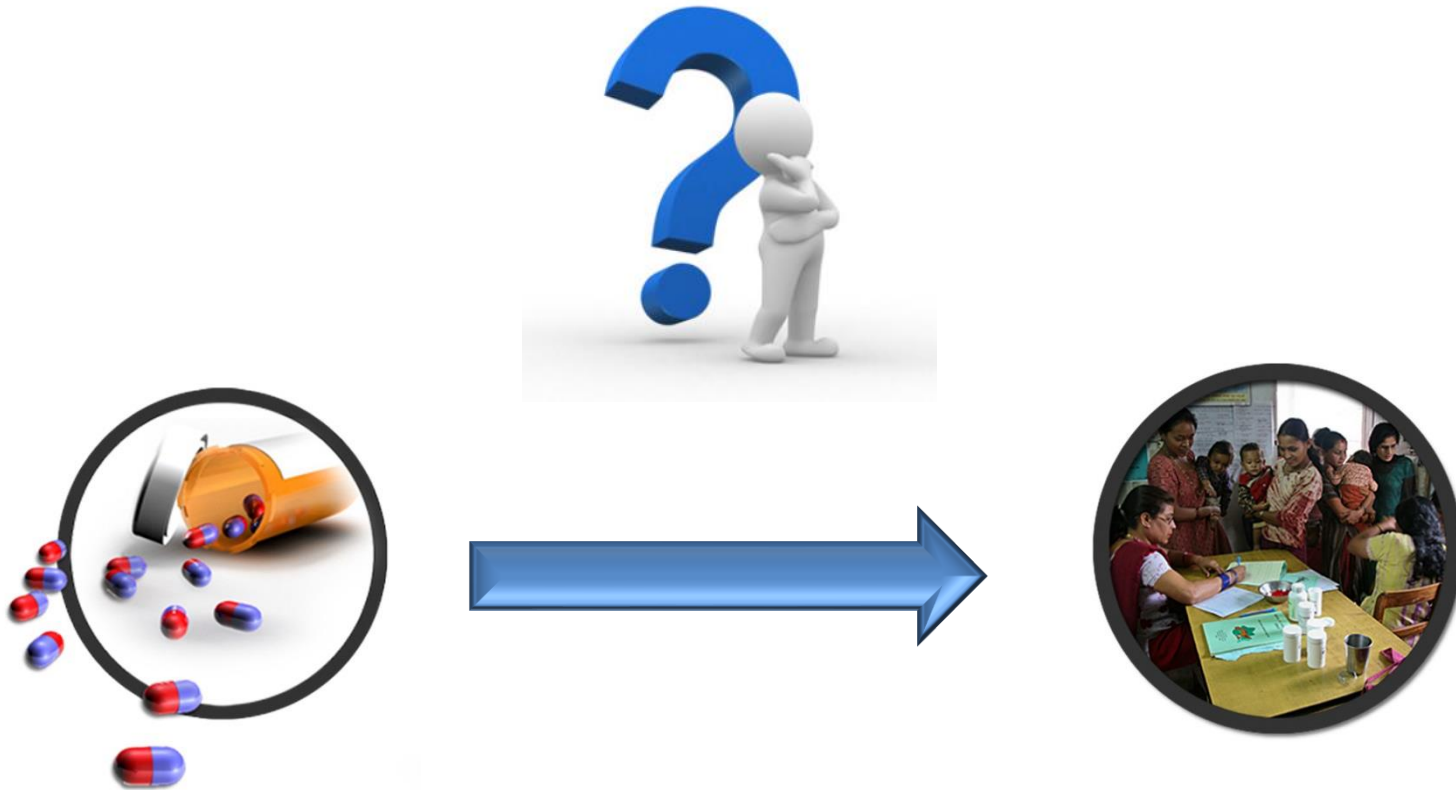
 **TOO POOR TO PAY**  **FOR NEW MEDICINES**

How did we do?

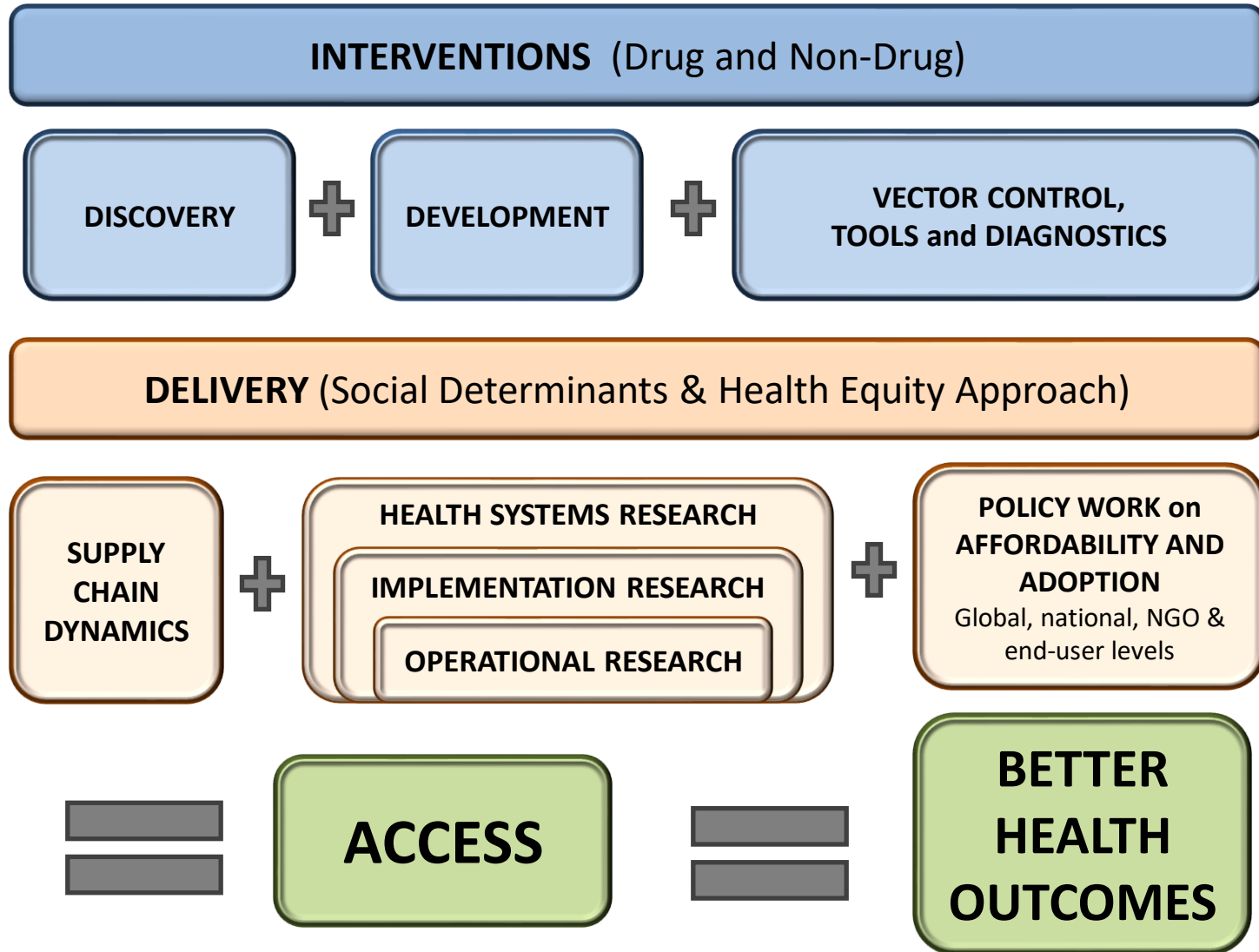


1. U. OF BRITISH COLUMBIA	A-
2. CASE WESTERN RESERVE	B+
3. JOHNS HOPKINS U.	B
4. U.C. IRVINE	B
5. HARVARD U.	B-
6. EMORY U.	B-
7. DUKE U.	C+
8. VANDERBILT U.	C+
8. U. OF PENNSYLVANIA	C+
10. U. OF MARYLAND BALTIMORE	C+

Developing interventions for neglected global diseases and ensuring their delivery to those in need.



NGDI Model of Collaboration



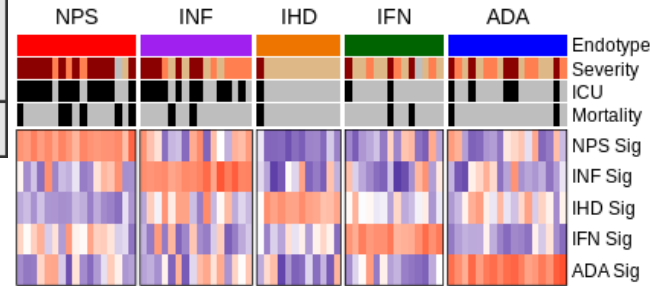
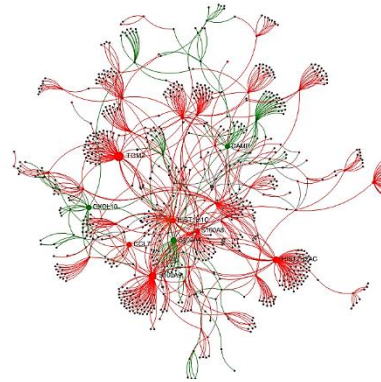
Addressing antibiotic failure



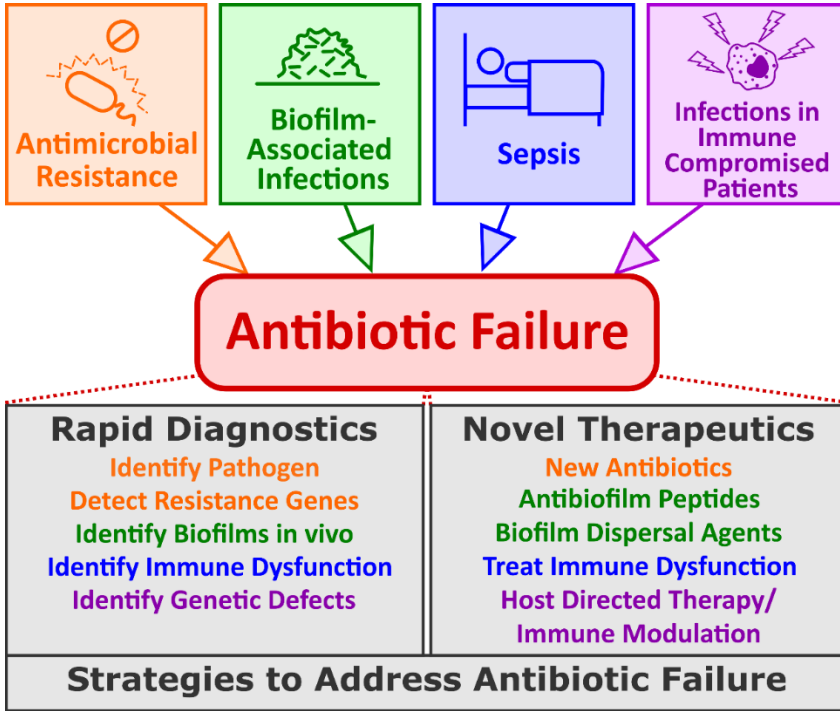
Bob Hancock

1. Sepsis (19.7% of all deaths 2017; 9M/yr Covid)

Defined **diagnostic CR** signature; **predicts severe sepsis** and organ failure in ER patients Accuracy 84-92% (all-cause & Covid sepsis - 750 patients)

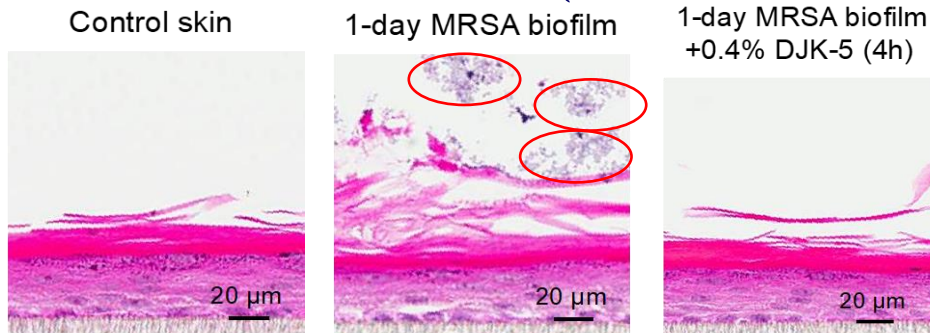


Separated ER patients into **endotypes** that define mechanisms & severity



Haney, EF, & REW Hancock. 2022 *Frontiers in Drug Discovery* 2:892975.

2. Biofilm infections (65% of infections; multidrug resistant).



Peptides work against biofilm infections of all ESKAPE (MDR) bacterial pathogens in human skin organoid models (left) and animal models; synergy with antibiotics

UBC mHealth Research

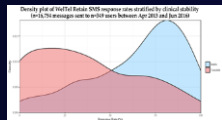


COVID-19 Pandemic
Rwanda National
Home-Based Care

>40,000 patients followed
18M SMS sent
NO deaths



AI, NLP
Predictive
Analytics



JEDI
Justice Equity
Diversity Inclusion



1. Inclusion



6. Response

5. Analysis

Digital Health Equity
Access • Ability • Language • Culture

WelTel Health

2. Evidence

First evidence that
SMS communication
could improve health
outcomes (HIV
treatment)



THE LANCET

The NEW ENGLAND
JOURNAL of MEDICINE



World Health
Organization

3. Expansion

- Additional use cases
- Chronic disease (NCD)
 - Mental Health & Addiction
 - Public Health

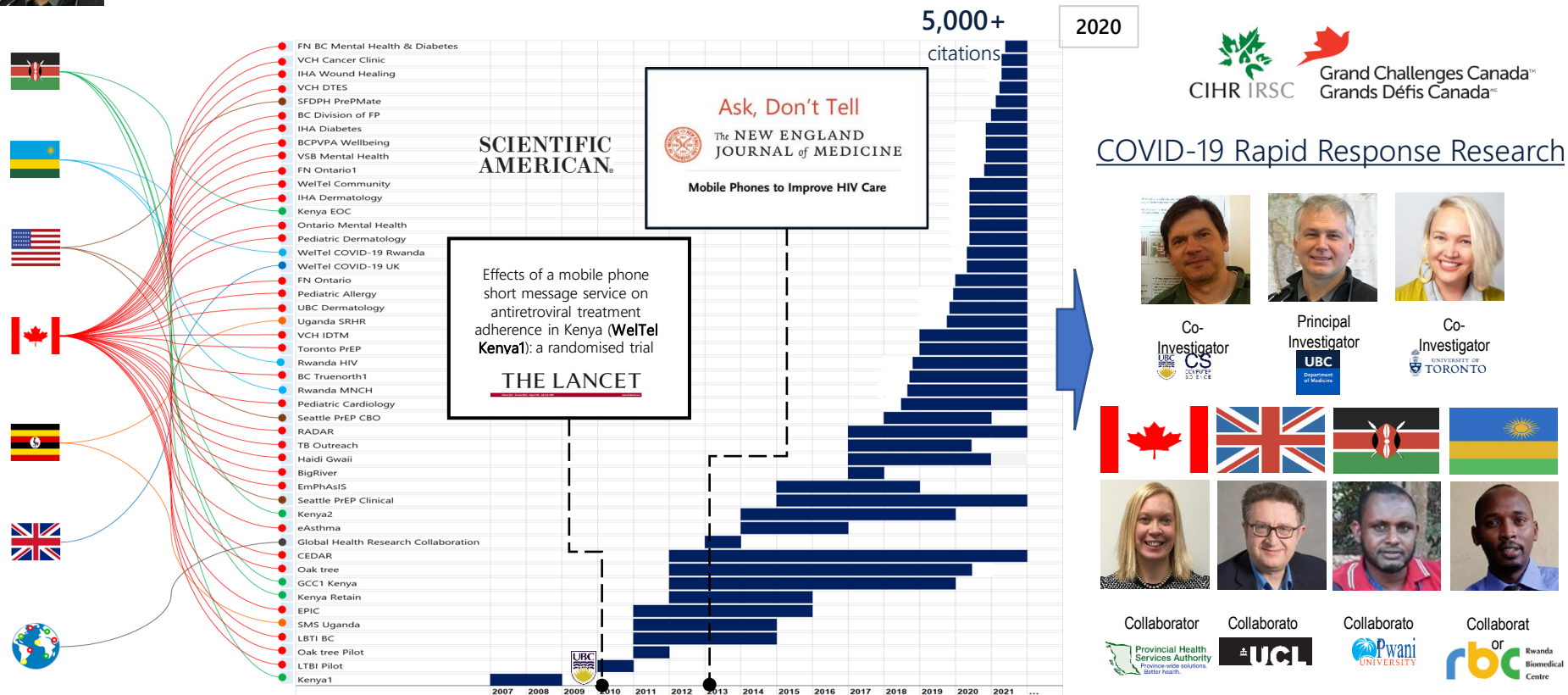


Dr. Richard Lester, MD, FRCPC





UBC Program of International mHealth Research



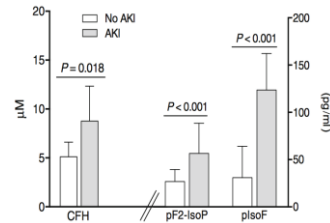
<http://www.scientificamerican.com/podcast/episode.cfm?id=text-message-outreach-improves-hiv-10-11-10>

UBC mHealth research in global settings

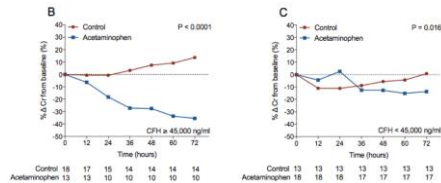
Addressing severe malaria renal dysfunction & adjunctive therapy

Dr. Katherine Plewes MD DPhil FRCPC

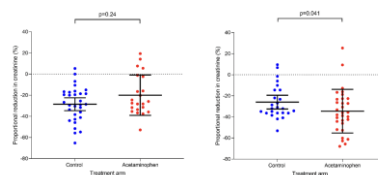
- Cell-free hemoglobin and oxidative stress markers correlate with renal dysfunction and are independent predictors of creatinine rise during admission and need for dialysis



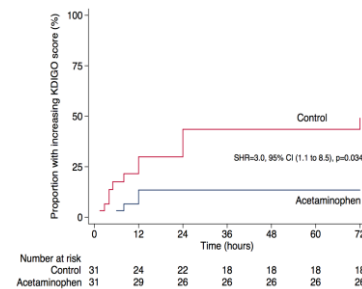
- Acetaminophen reduces creatinine in patients with elevated cell-free hemoglobin in falciparum and knowlesi malaria



Plewes K, *et al.* BMC ID 2017; 107:313-25.
 Boutaud *et al.* PNAS 2010; 107
 Plewes K, *et al.* CID 2018; 67 (7) 991-999.
 Cooper D, *et al.* CID 2022: ciac152



- Acetaminophen reduces risk of developing renal dysfunction in falciparum malaria



- PROTECTS:** Evaluating the renoprotective effect of acetaminophen in pediatric severe falciparum malaria: a randomized controlled trial



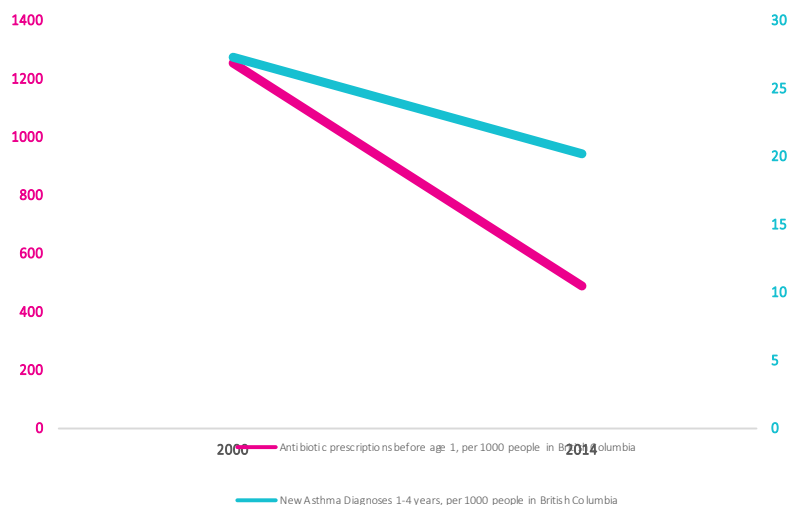
Preventing antibiotic harm | Asthma

338

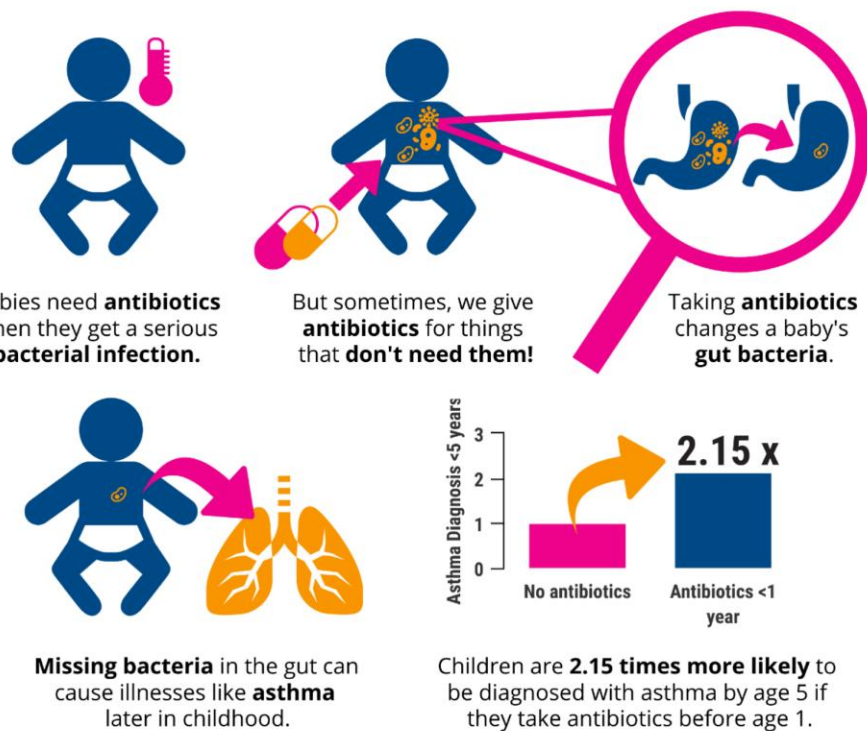
Preventing antibiotic harm | Asthma

There is growing evidence that reducing antibiotic use in infancy may significantly reduce childhood asthma.

Both antibiotic prescribing in infancy and asthma in early childhood have gone down in British Columbia.



How can antibiotics lead to asthma?¹⁰



See Patrick et al. Lancet Respir Med. 2020 Nov;8(11):1094-1105.

Summary of policy instruments for prolonging effectiveness of existing antibiotics

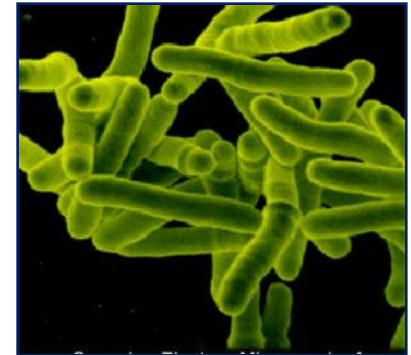
Eswaran and Gallini, "Can Competition and Patent Policies Avert the Antibiotic Crisis?", *Canadian Public Policy*, vol. 45, no. 1

- Facilitate competition, subject to:
 - Economic Breadth Requirement
 - Biological Breadth Requirement
 - "Safe harbor" on price/royalty/tax above which antitrust action would be triggered: internalize biological but not economic externality
- Set longer patent duration for narrow than broad patents to encourage firms to internalize both own- and cross-resistance.
- *If profits from patent sales do not provide adequate incentives for R&D, then:* supplement incentive with award that is independent of sales, e.g., Prizes, Cost-Sharing Agreements, Easing of FDA regulatory constraints.

Centre for TB Research at UBC

Overall objectives:

1. Improve our basic understanding of the physiology of *M. tuberculosis*, especially those processes that are critical to pathogenesis.
2. Establish a pipeline for the development of novel inhibitors.



Why now?

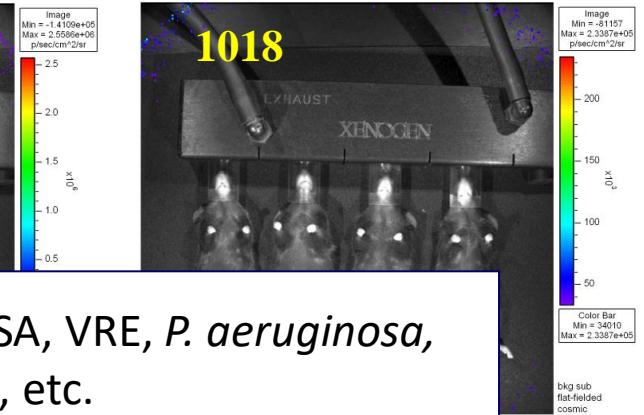
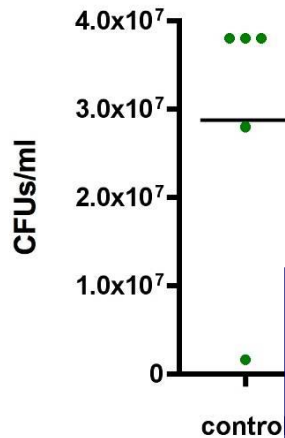
1. With the emergence of XDR strains, TB is a global threat
novel treatment strategies are urgently required
2. Researchers at UBC have recently discovered systems that contribute to *MTB*'s inherent resistance and unusual ability to persist in macrophages.

Undisputed leaders in Canada and internationally recognized

Centre for Microbial Diseases and Immunity Research

New immunomodulatory peptides show broad protection in mouse model infections

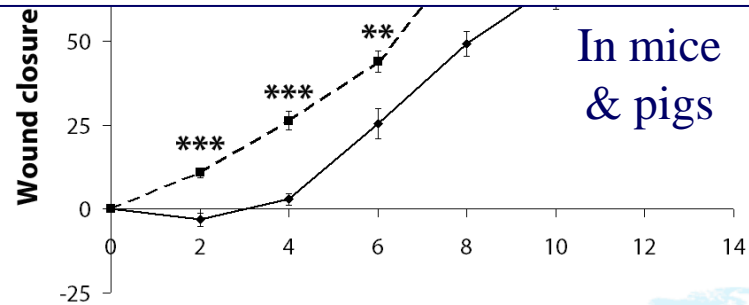
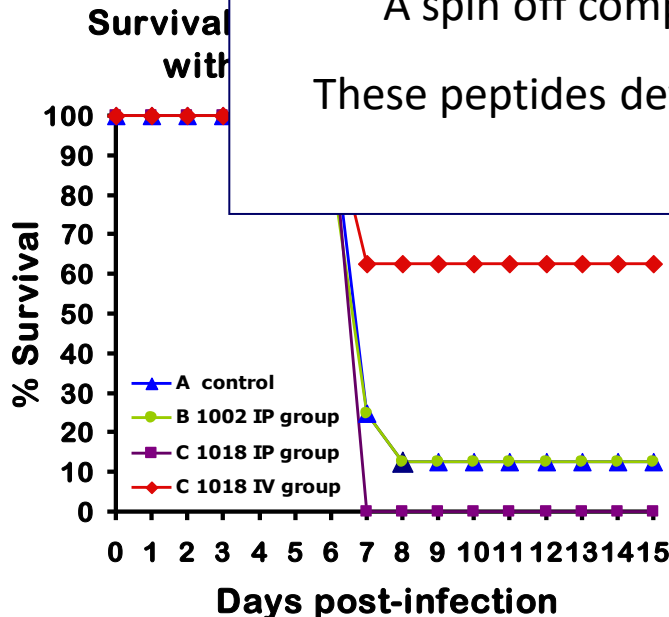
S.aureus in peritoneal lavages



Also protect vs. TB, *E. coli*, *Salmonella*, MRSA, VRE, *P. aeruginosa*, IBD Sterile inflammation, etc.

A spin off company has completed Phase I clinical trials.

These peptides developed independently for Grand Challenges Program.



In mice
& pigs

Grand Challenges
in Global Health

Prevention and Control of Dengue in Ecuador

Sustainable capacity-building and scaling-up challenges

Dr. Jerry Spiegel, SPPH / Liu Institute and Kendra Foster, ISGP PhD student

Funded by: IDRC  CRDI



Pilots an integrated community-based approach compared to reactive insecticide-based program

- comprehensive intervention effectiveness evaluation protocol
- information system for monitoring implementation & feasibility of transforming existing vector control programs





Clinical Care and Training

Infectious Diseases Specialist
Tropical Medicine Clinic, Vancouver General Hospital



Jan Hajek



Visiting Physician
Gulu Regional Referral Hospital, Uganda



Infectious Diseases Consultant
Doctors without Borders, TeleMedicine



Course Director
Tropical and Geographic Medicine Course, University of British Columbia

- ▢ Lobbying by strong UBC **UAEM chapter** and Grand Challenges funding led to consideration of new policy
- ▢ UBC **first Canadian university** to put forward a broad strategy to provide global access to appropriate technologies.
- ▢ Provide flexibility for tailored, technology-specific strategies.
- ▢ **Principles versus policy**; adopted by UBC in Fall 2007.

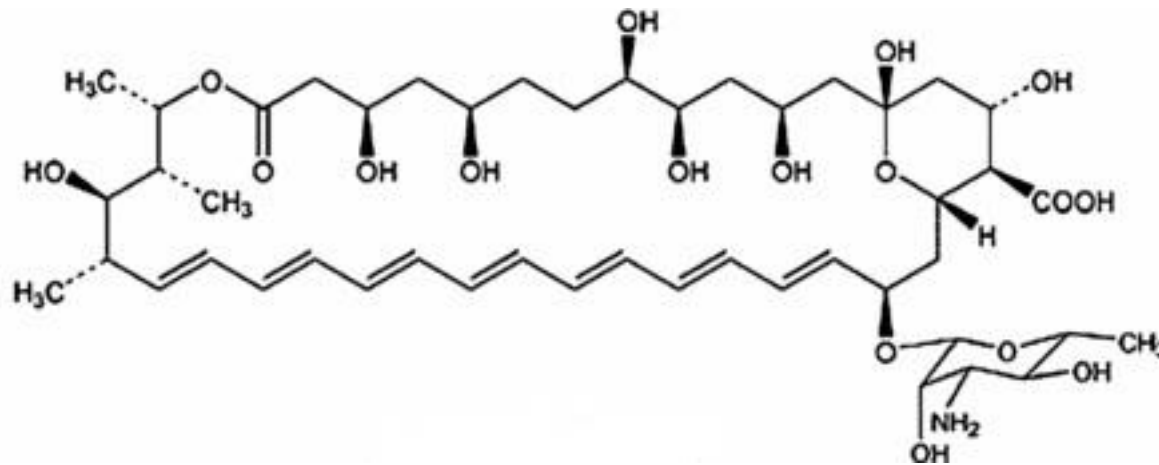


e.g. Reserved 4 of our patents with >50,000 immunomodulatory and antimicrobial peptides for the exclusive use of the Grand Challenges projects; One of these now optioned to a US company **with developing country rights reserved**

<http://www.uilo.ubc.ca/about/initiatives/global.html>



Amphotericin B

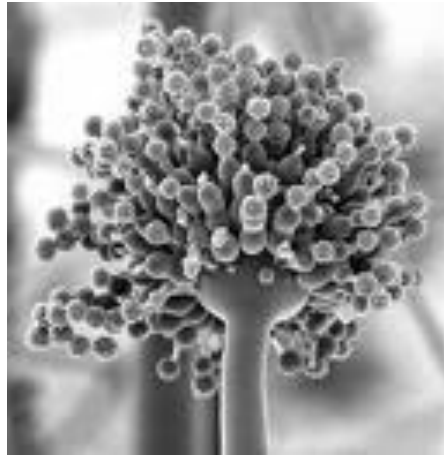
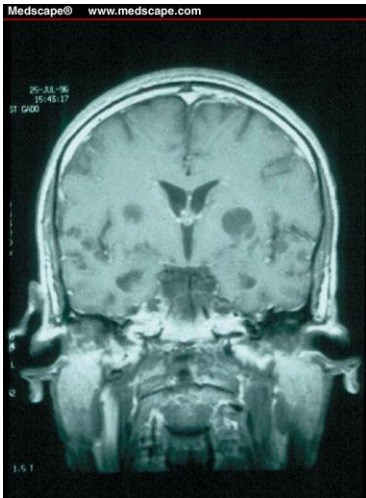


- AmB is a BCS Class IV drug
 - Low solubility and low permeability
 - Low oral bioavailability
 - Intravenous administration

Demonstrated Efficacy



Cryptococcosis



Fungal infections



Aspergillosis



Candidiasis



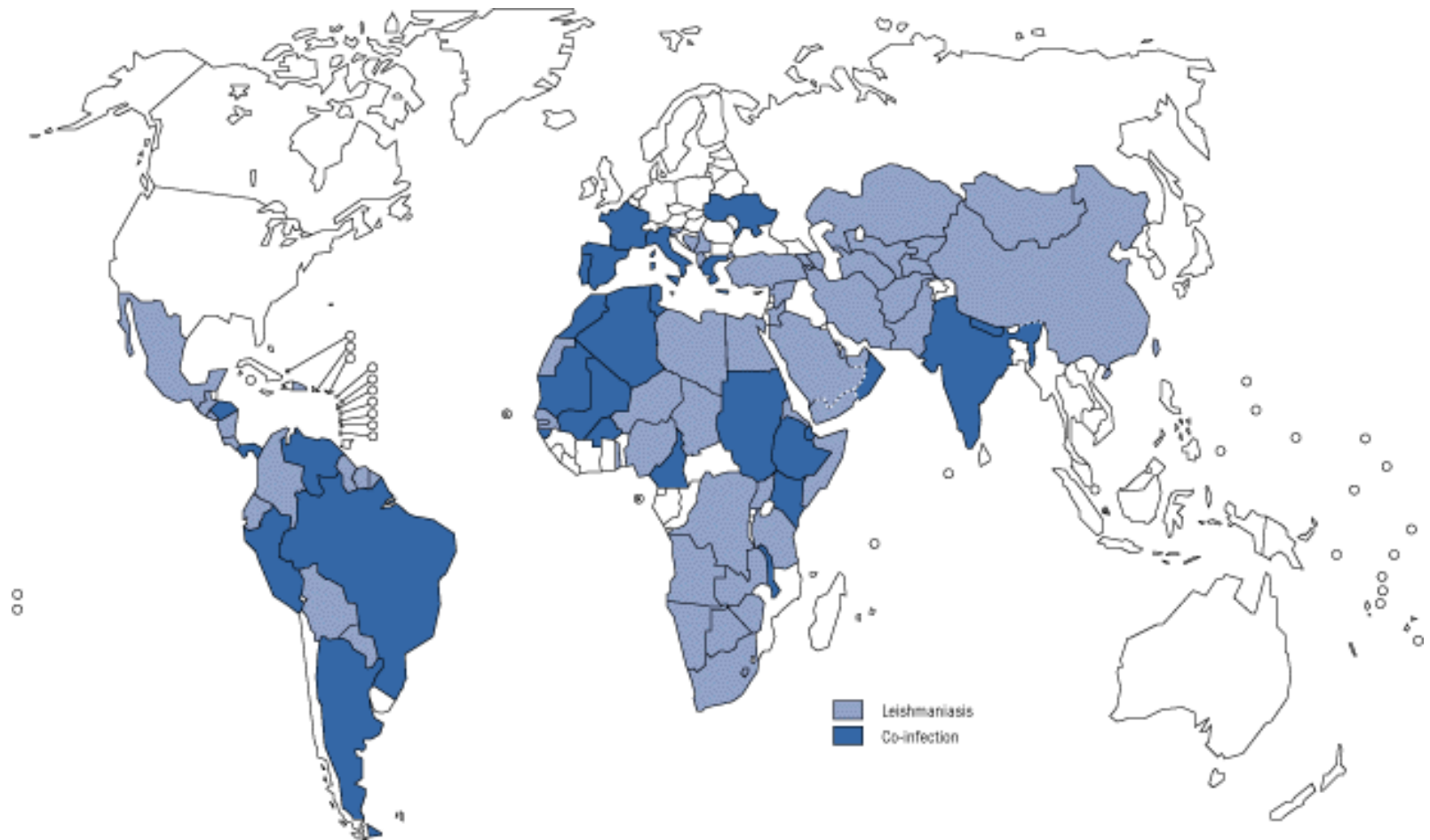
Leishmaniasis: Current Disease Status



Source: WHO/TDR/Marsden

- Spectrum of disease which affects approximately 12 million people in 88 countries
 - About 2 million new cases annually
 - 75% involve cutaneous leishmaniasis, with the remainder being visceral leishmaniasis (VL)
- Mortality rate for VL is close to 100% in the absence of treatment

“Real World” Efficacy



2 million new cases reported every year (WHO)

Visceral leishmaniasis causes ~59 000 deaths annually

Current Treatments of VL

	Liposomal amphotericin	Miltefosine	Paromomycin
Efficacy in VL	~99 %	~97%	~95%
Safety	Safe	G-I intolerance Potential foetotoxicity	Reversible ototoxicity 2% Painful injection
Administration	Intravenous infusion	Oral tablet. Contraception in child-bearing-age women	Intramuscular injection
Price for 35 kg Indian VL adult	~US \$140 –220	~US\$ 61 – 75	~US\$ 15

Wasan & Thornton 2009

Implications for Developing Countries



Parenteral administration results in:

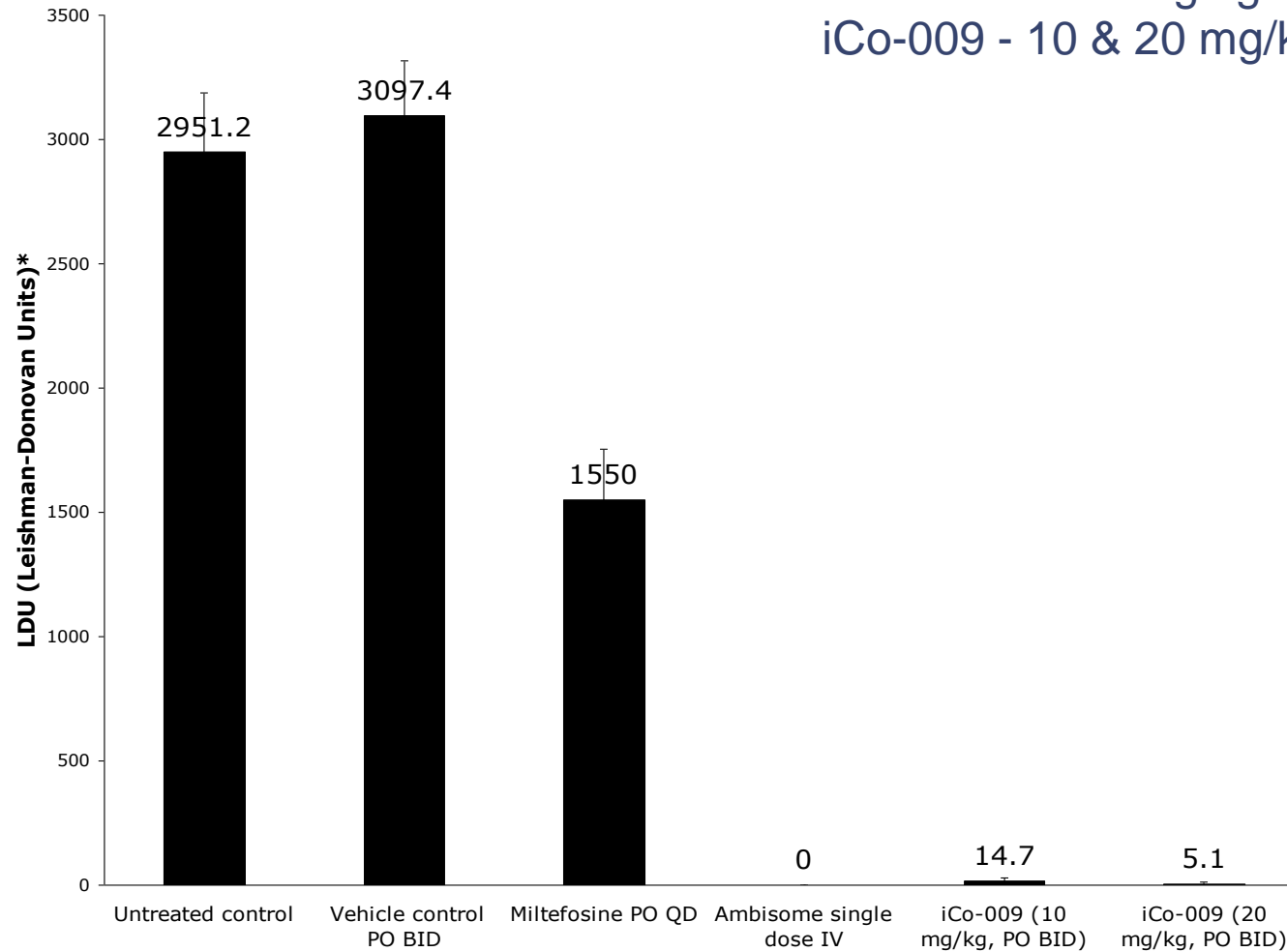
- Loss of income
- Increased cost of administration
- Increased risk of side effects
- Decreased availability of treatment

Data Overview

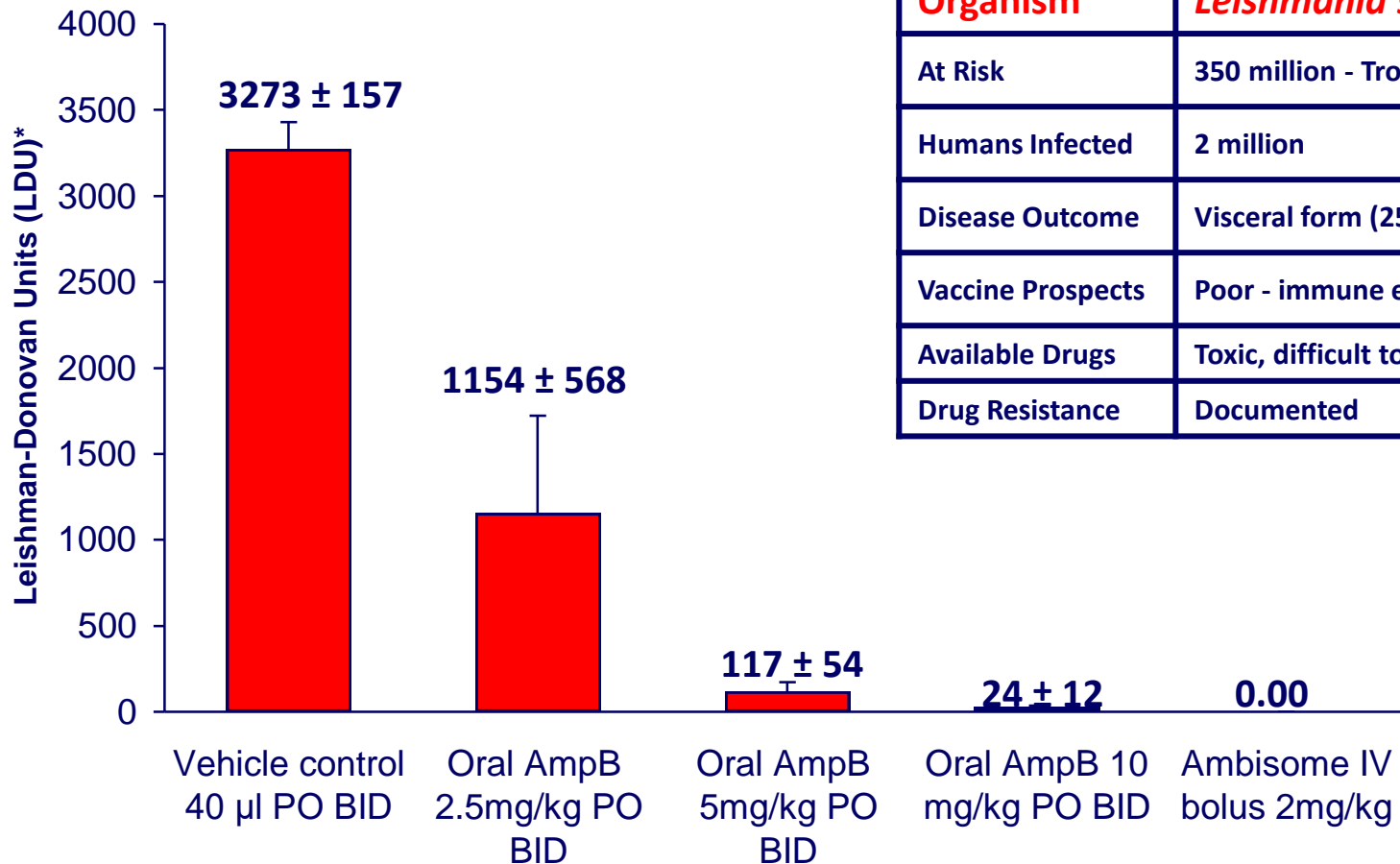
Visceral Leishmania (VL)

- Mice were infected i.v. with 1×10^7 *Leishmania donovani*
- Treatment begins on Day 7 post infection
- Oral Amp B administered bid for 5 consecutive days
- Mice were sacrificed Day 14 post infection
- Livers were then weighed and impression smears prepared
- The number of *Leishmania* amastigotes per liver cell nuclei was determined microscopically
- studies performed in independent laboratory
 - part of the Consortium for Parasitic Drug Development, a Gates Foundation funded organization

Miltefosine - 3mg/kg PO, qd x 5 d
Ambisome - 2 mg/kg iv, once
iCo-009 - 10 & 20 mg/kg PO, bid x 5 d



A new oral amphotericin B formulation (iCo 009) works well vs. visceral Leishmaniasis in animals



Organism	<i>Leishmania spp.</i>
At Risk	350 million - Tropics and Subtropics
Humans Infected	2 million
Disease Outcome	Visceral form (25% above) fatal
Vaccine Prospects	Poor - immune evasion
Available Drugs	Toxic, difficult to deliver
Drug Resistance	Documented

Oral Amphotericin B Formulation Technology

- Proprietary blend of mono- and di-glycerides (FDA GRAS approved)
- Solubilized AmpB Formulations
- Nanosuspensions/dispersions
- Affordable lipid excipients
- Ease of formulation scale-up
- Formulation Stability over 120 days
- Drug Stability at 43°C over 120 days



Advantages of Oral Amphotericin B Formulation


- Affordable
- Easy to store
- Easy to administer
- Lack of kidney toxicity
- Lack of Infusion-related side effects (i.e. fever, chills etc.)
- Lack of liver and GI toxicity



Advantages of Oral Amphotericin B Formulation

- Treating patients with drug-resistant strains (decrease hospitalization and eliminate IV AmpB Therapy)
- First available Oral **Fungicidal** Agent (only Fungistatic Agents, Diflucan® from Pfizer)
- Orphan Drug Designation FDA (2010)
- US Patent Issuances 2013 & 2014
- Positive Human Phase 1a/1b Safety Results

What else can you do?

	<p>Jennifer Choi Ph.D. Student, Dept. of Biochemistry and Molecular Biology Member of the NGDI-UBC Working Group Email: jenniferkchoi@gmail.com</p>
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BECOME A MEMBER OF THE NGDI

Membership is the impetus behind this grass roots initiative. The level of commitment you are able to pursue at this time will define how we communicate with each other.

Ben Warren, *"I believe that in a global community we have a responsibility to one another no matter what part of the world we come from."*

WHO

» M

» St

» Bt



September, 2013
NGDI-UBC Newsletter

Advocate, Educate, Participate

Collaborate outside your discipline to expand
your research

Initiate your own neglected disease research