Bridges to Development

Ivermectin: an old drug with new tricks

Development and Roll out of Ivermectin, DEC, and albendazole (IDA) triple therapy for Lymphatic Filariasis

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Jan 30, 2020

Bridges to Development

Happy World NTD Day!!- The first!

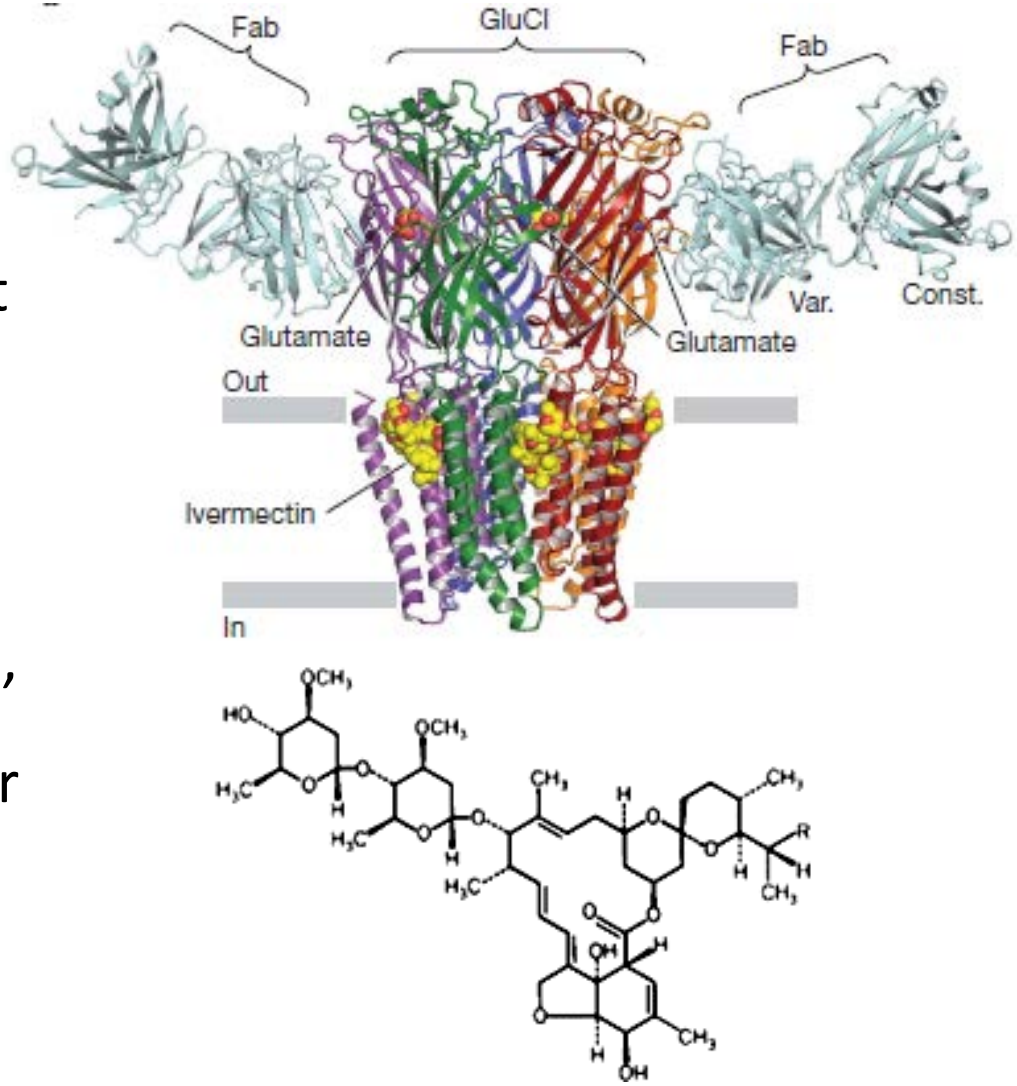
Join the team today!! https://worldntdday.org/

Overview

- Ivermectin
- Overview of the IDA accelerated Development and Introduction plan
  - LF
  - The finding
  - The engagement and planning
  - Progress
  - Outcomes
  - Plans
- What’s next
- Discussion

Ivermectin

- Macrocyclic lactone isolated from the *Streptomyces avermitilis*
- Mode of action – binds at subunit interfaces next to the glutamate-gated chloride (GluCl) ion channels, which distorts the channel from closed to open, hyperpolarizing the cell (Hibbs and Gouaux 2011)
- Leads to the paralysis of the nematode or ectoparasite musculature (Cully et al. 1994, 1996, Cane et al. 2000)
- Different class of insecticides than those used for ITNs or IRS



Ivermectin effects numerous human
Neglected Tropical Diseases

- Onchocerciasis – *Onchocerca volvulus*
- Lymphatic filariasis – *Wuchereria bancrofti, Brugia malayi,* and *Brugia timori*
- Ascariasis – *Ascaris lumbricoides*
- Trichuriasis – *Trichuris trichiura*
- Strongyloidiasis – *Strongyloides stercoralis*
  - Currently approved treatment in Thailand (200 µg/kg)
- Pediculosis – *Pediculus humanus humanus* and *P. h. capitus*
- Scabies – *Sarcoptes scabei*

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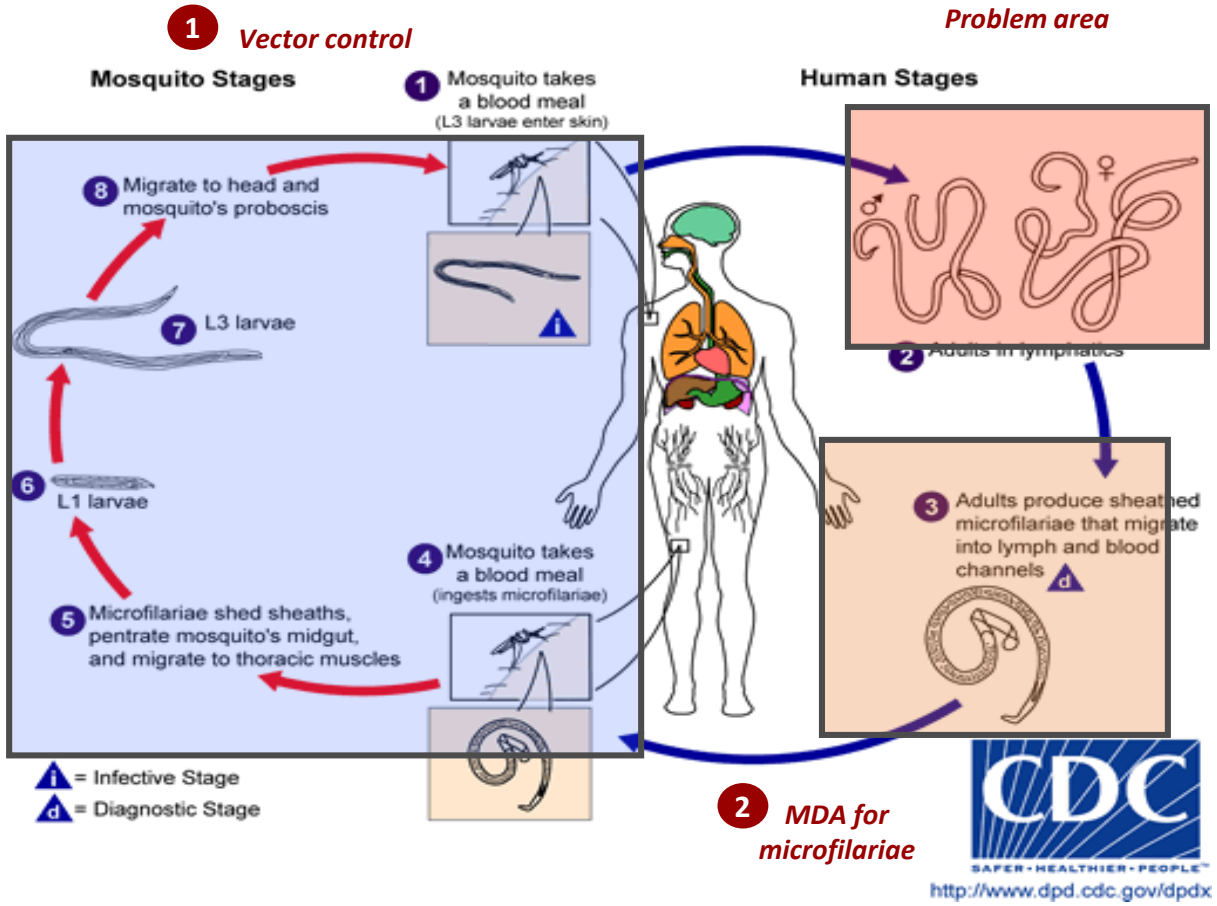
LF Background

- Filarial parasitic infection transmitted by the bite of a mosquito
- Elimination as a public health problem goal for 2020
- 1.5 Billion in need of treatment now decreasing to ~1 Billion
- Treatment is community wide MDA with ivermectin and albendazole or DEC and albendazole
- Only kills the larval stage (microfilaria) which requires 5 to 7 rounds of annual treatment with high coverage to break transmission.
- Looking for treatments that will kill the adult worm (macrofilaria)
- DOLF grant- had a study that looked at the combination of all three drugs co-administered- ivermectin, DEC, and albendazole at current dosages used in MDA

LF Transmission

Three intervention points to control disease



Source: CDC

Challenges

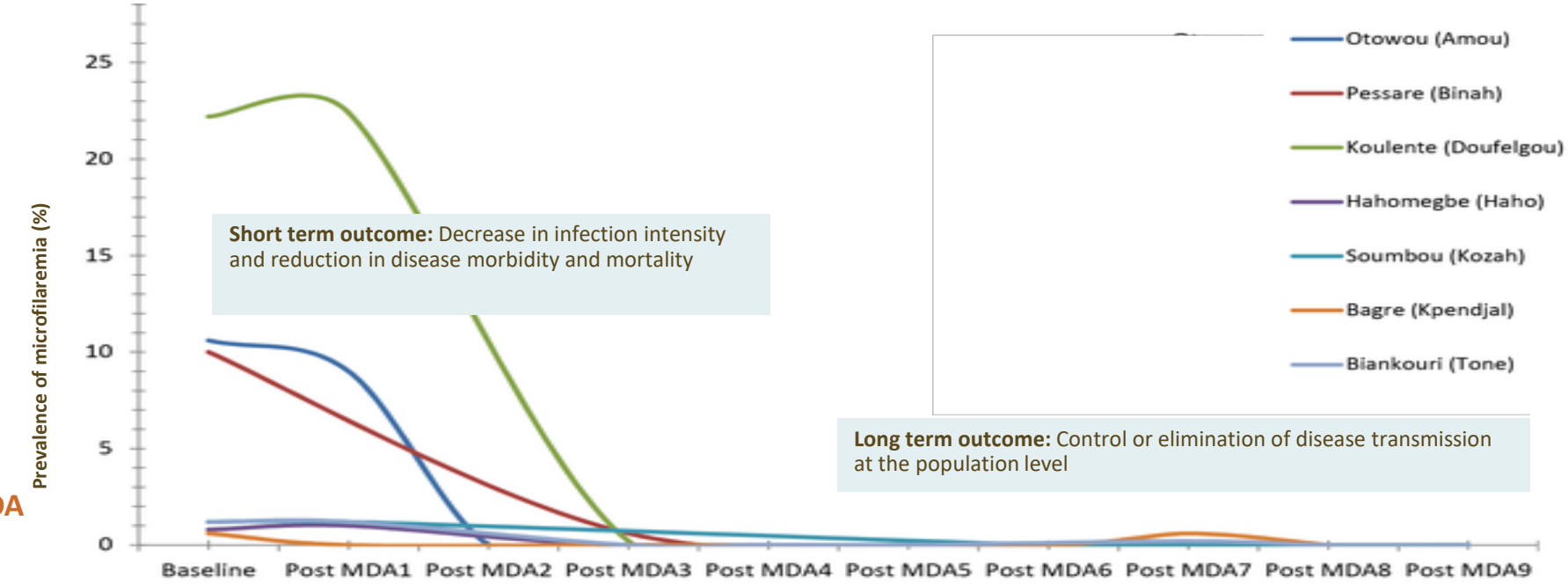
- **Reduce vector/parasite population**
  - » Vector control
  - » Large areas with transmission in remote sites, can be very focal
- **Prevent infection and disease**
  - » Very effective drug with no confirmed resistance but only works on microfilariae (mf) and not adult worms
  - » Humans are the only host so decrease in mf can stop transmission but adult worms persist and require repeated MDA (5-7 yrs)
  - » Adult worms live long time and produce millions of mf which continue to infect new people,
- **Prevent transmission**
  - » Treatment with IVM and albendazole kills mf and temporarily stops production of mf
  - » Vector control can help control programs especially where Loa is co-endemic

Community level treatment works to Interrupt transmission

Preventive chemotherapy (PC) through mass drug administration (MDA) using safe and low cost oral drugs

Example

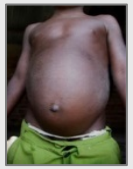
LF Microfilaremia in Togo following yearly MDAs



Short term outcome: Decrease in infection intensity and reduction in disease morbidity and mortality

Long term outcome: Control or elimination of disease transmission at the population level

Diseases treated through MDA include:

LF	Oncho	Schisto	STH	Trachoma
				
Ivermectin or diethylcarbamazine + albendazole	**Ivermectin**	**Praziquantel**	**Albendazole or mebendazole**	**Azithromycin**
Merck & Co, GSK, and EISAI	Merck & Co	Merck KGaA	GSK and J&J	Pfizer

What we do

The basis of the program is mass drug administration (MDA) at the community level

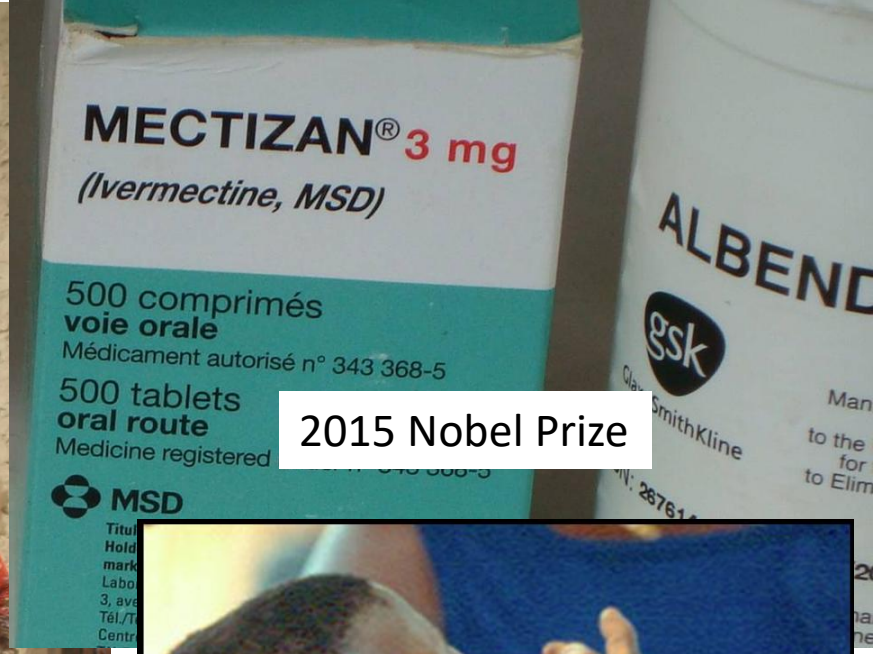
Community sensitized to the disease and the drugs to treat.

Census of the community

Community selects their drug distributor and plans the date to deliver the drugs.

Drugs delivered to the community

Dose pole to measure height and determine dose

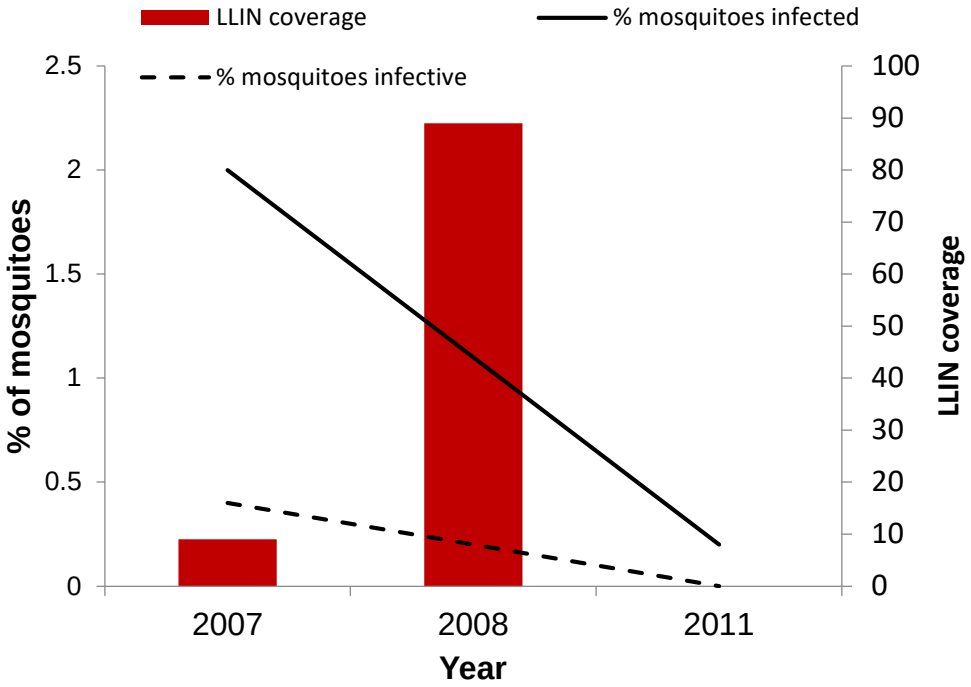


2015 Nobel Prize

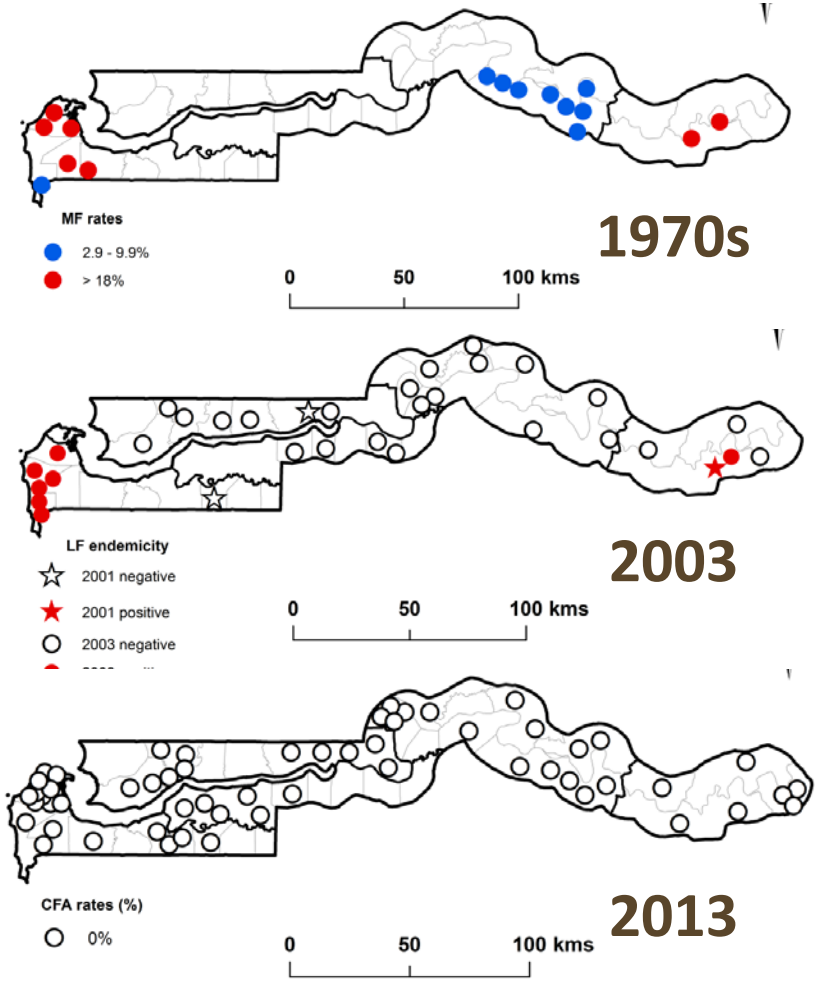
Vector control role in the elimination of LF

Synergy through integration with malaria control

Nigeria: First evidence on the role of Long Lasting Insecticidal Nets in interrupting LF transmission



The Gambia: Evidence at scale



The Mass Drug Administration strategy for LF and Oncho Transmission Elimination (once and for all!)

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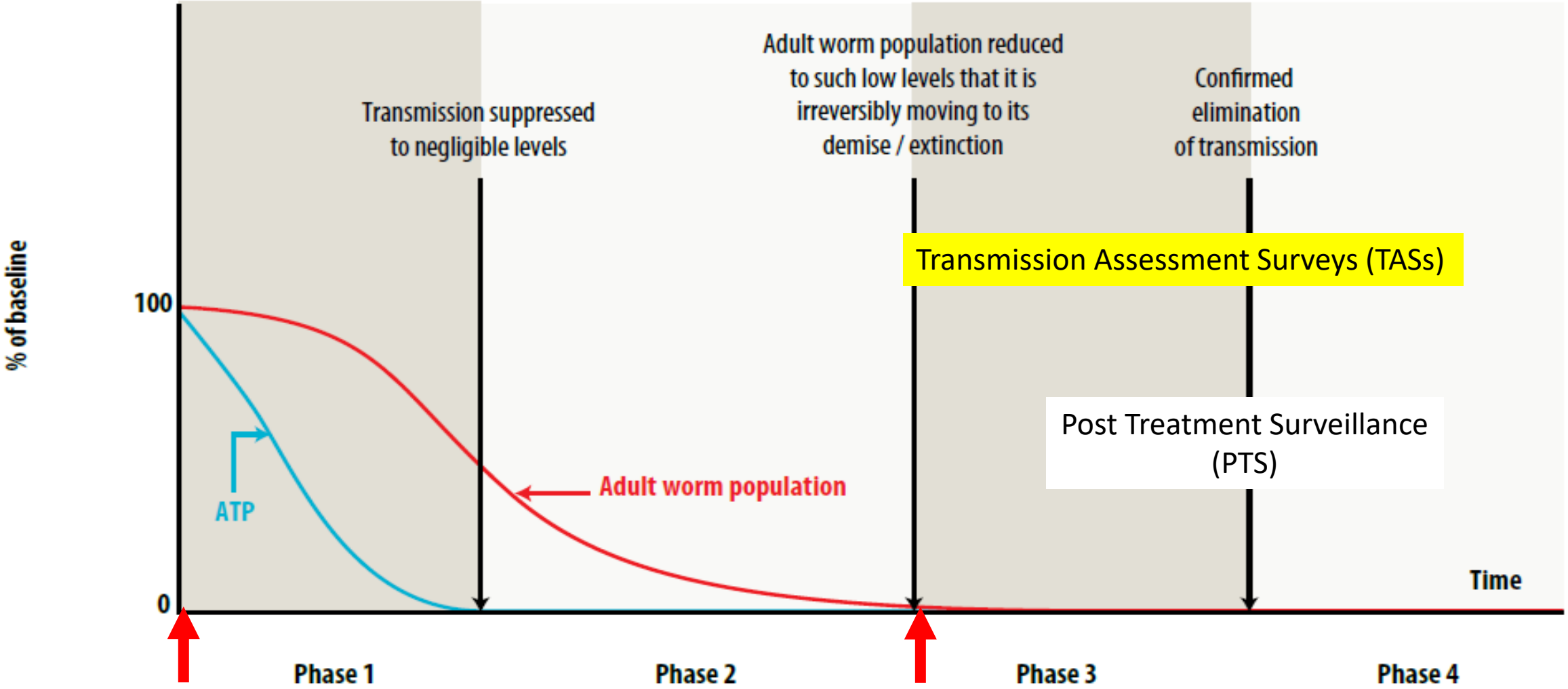


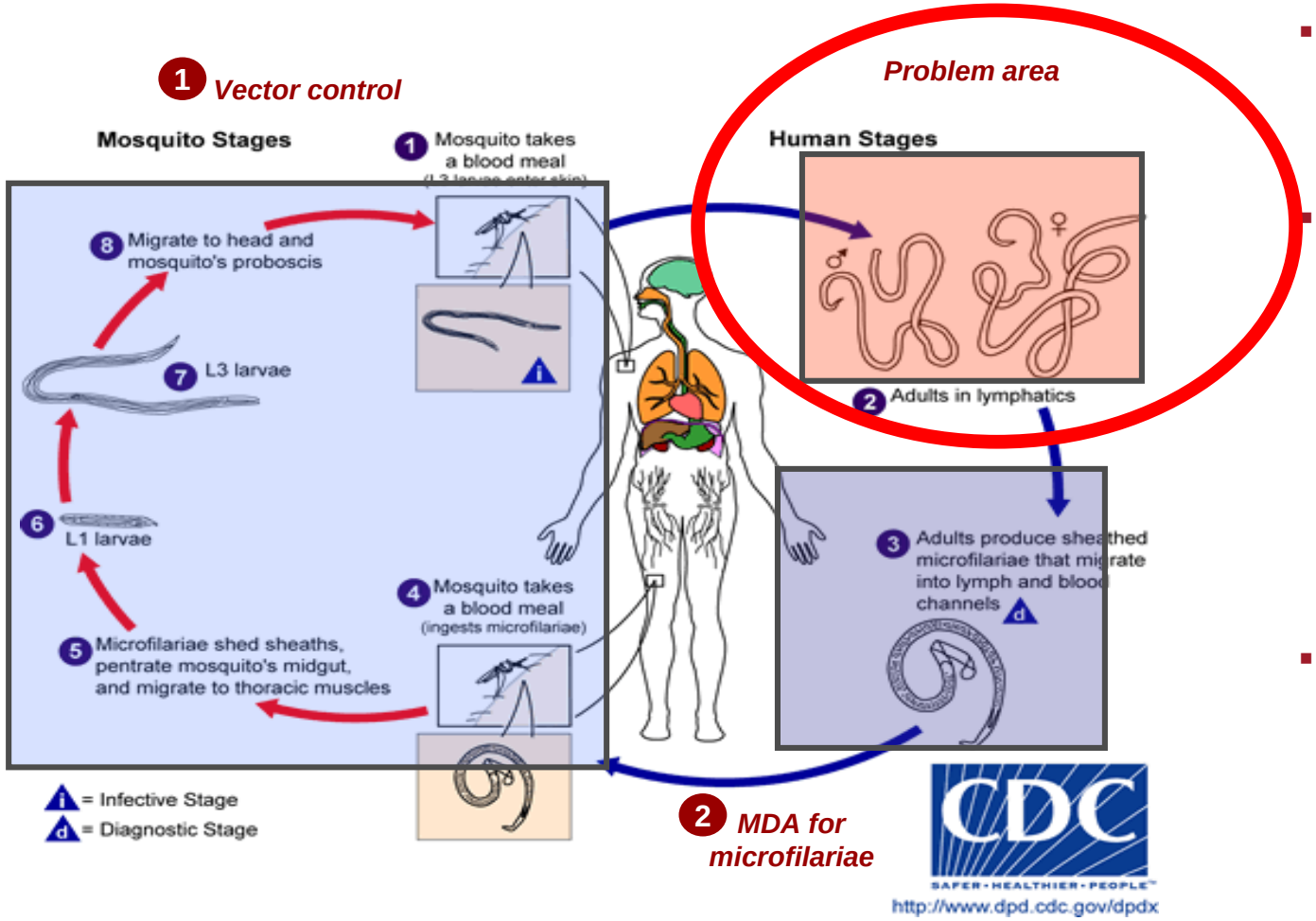
ATP=Infection in Vectors

Country Progress against LF: MDA status of countries 2019

MDA not started	MDA started but not at scale	MDA scaled to all endemic districts	Post-MDA Surveillance	Elimination as a Public Health Problem
Equatorial Guinea Gabon *New Caledonia*	Angola Central African Republic Chad Congo Democratic Republic Congo Guinea-Bissau Nigeria South Sudan Sudan *Madagascar* *Guyana* *Papua New Guinea*	Benin, Burkina Faso Côte d'Ivoire, Ethiopia, Ghana, Guinea, Liberia, Mali, Mozambique, Niger, Senegal, Sierra- Leone Tanzania, Uganda, *Comoros , Kenya, Eritrea* *Zambia, Zimbabwe* *Sao Tome & Principe* *Haiti* *India, Indonesia* *Myanmar* *Nepal* *Timor-Leste* *American Samoa* *French Polynesia, Tuvalu* *Fiji, FSM, Malaysia,* *Samoa, Philippines*	Cameroon Malawi *Brazil* *Dominican Republic* *Bangladesh* *Brunei Darussalam* *Lao PDR*	 *Egypt*, Yemen Togo *Maldives, Sri Lanka, Thailand* *Cambodia, Cook Islands* *Kiribati, Marshall Islands* *Niue, Tonga, Vanuatu* *Palau, Vietnam* *Wallis and Futuna*
0.8M in 3 (0)	233M in 12 (6.7M)	657M in 34 (461M)	0 in 7 (114M)	0 in 16 (16M)

Intervention points: Lymphatic Filariasis

Three intervention points to control disease



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Source: CDC

Can we use our existing drugs better?
Triple drug therapy for bancroftian filariasis

- Is single-dose triple drug therapy with DEC+ALB+IVM superior to the standard MDA regimen DEC+ALB?
- Does this triple drug therapy have an acceptable safety profile?

Study Design

Performed in a highly endemic area of Papua New Guinea (PNG) that has not received MDA.

Pilot study of triple-drug therapy to examine safety and drug interactions (pK).

N=24, 12 treated with DEC+ALB and 12 with DEC+ALB+IVM.

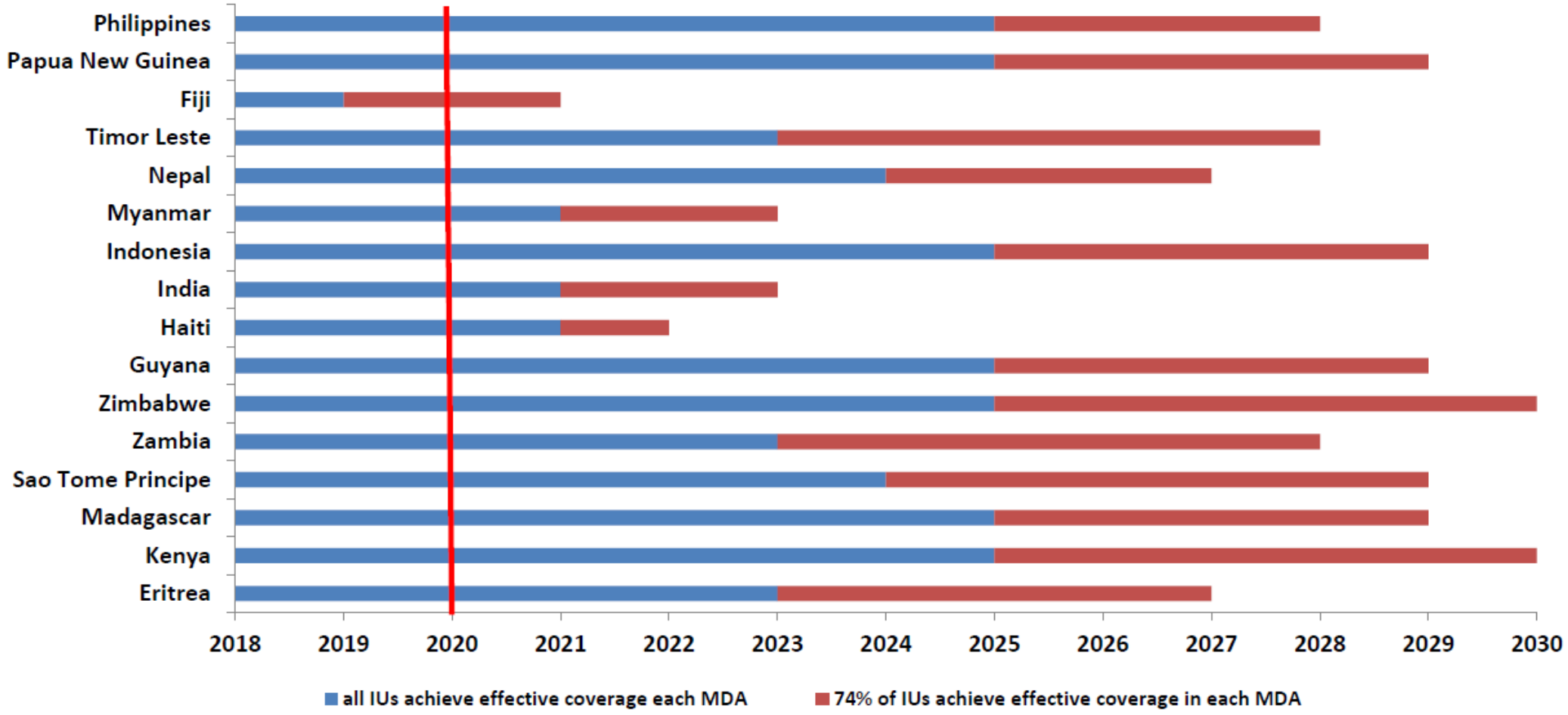
Mf (1 ml membrane filtration) levels at 0, 12 and 24 months post-treatment

In hospital active surveillance of adverse events for 48-72h post-treatment

Projection year all implementation Units pass TAS and stop MDA

- **Countries without co-endemic oncho or Loa**

DEC & ALB

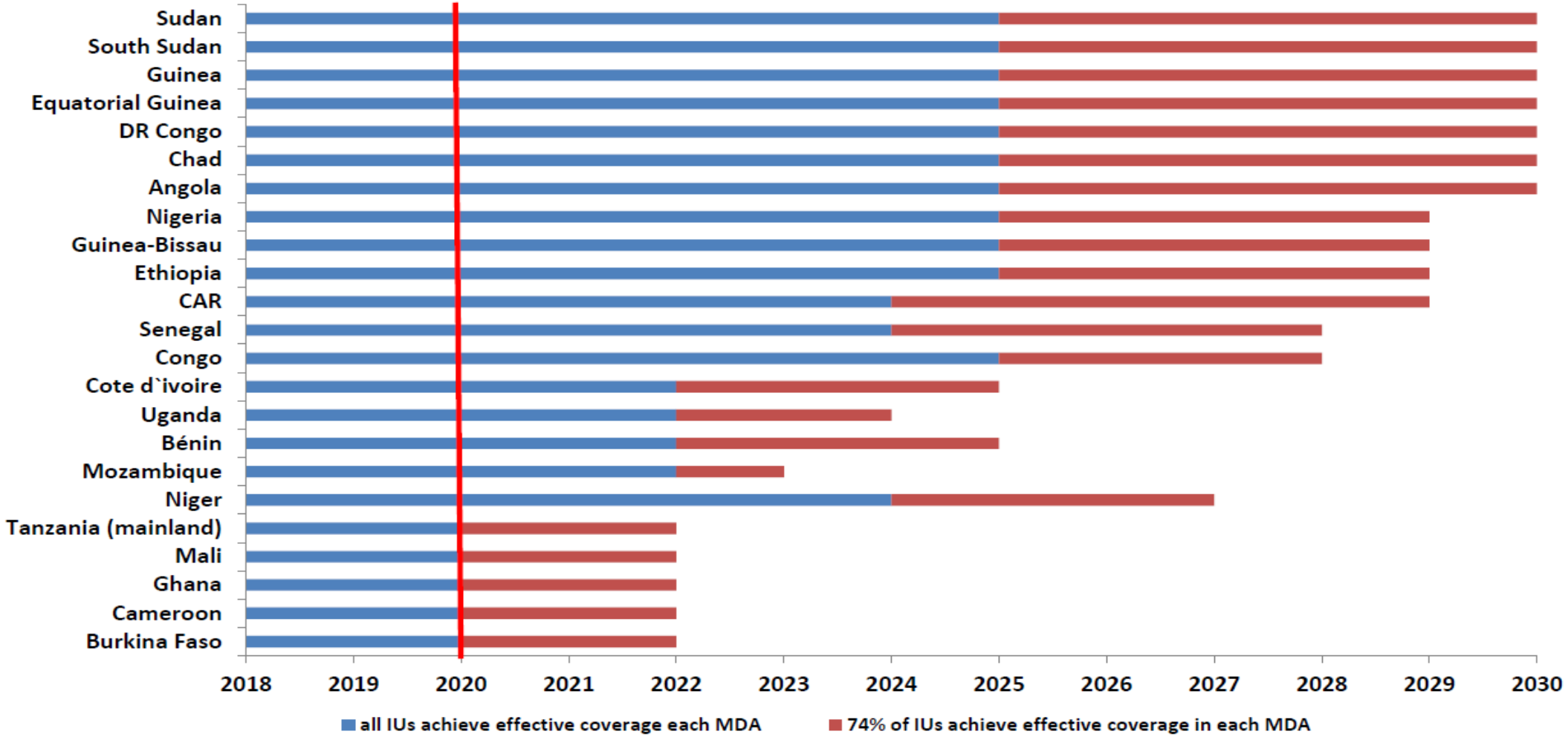


Source: WHO LF Program and NTD Modeling Consortium

Projection year all implementation Units pass TAS and stop MDA

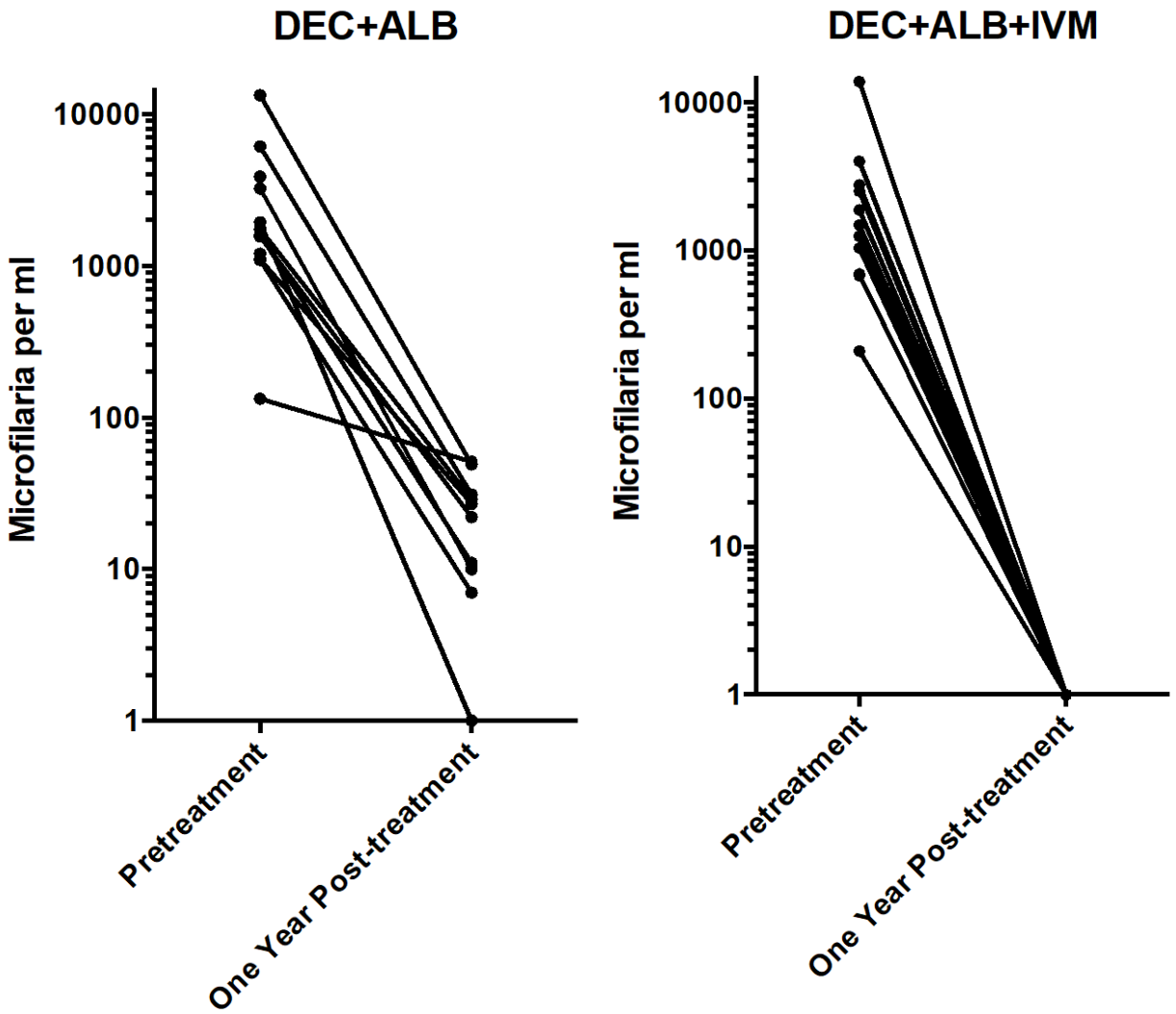
Countries with co-endemic oncho +/- Loa

IVM & ALB



Source: WHO LF Program and NTD Modeling Consortium

Is IVM+DEC+ALB superior to, as safe and acceptable as the current 2-drug regimen?



Findings were dramatic from the pilot study Reduction in Microfilaria and Antigen levels One Year Following Single Dose Treatment with ivermectin, DEC and albendazole (pK pilot study)

* Published Nov 5, 2015 in Clinical Infectious Diseases

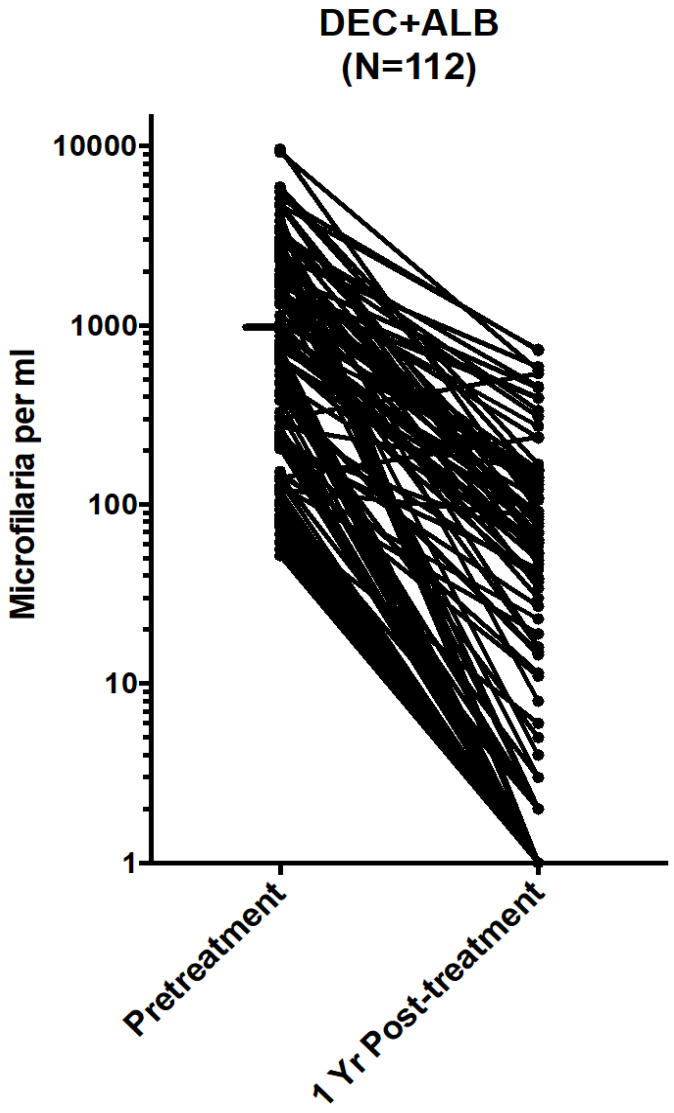
Bridges to Development

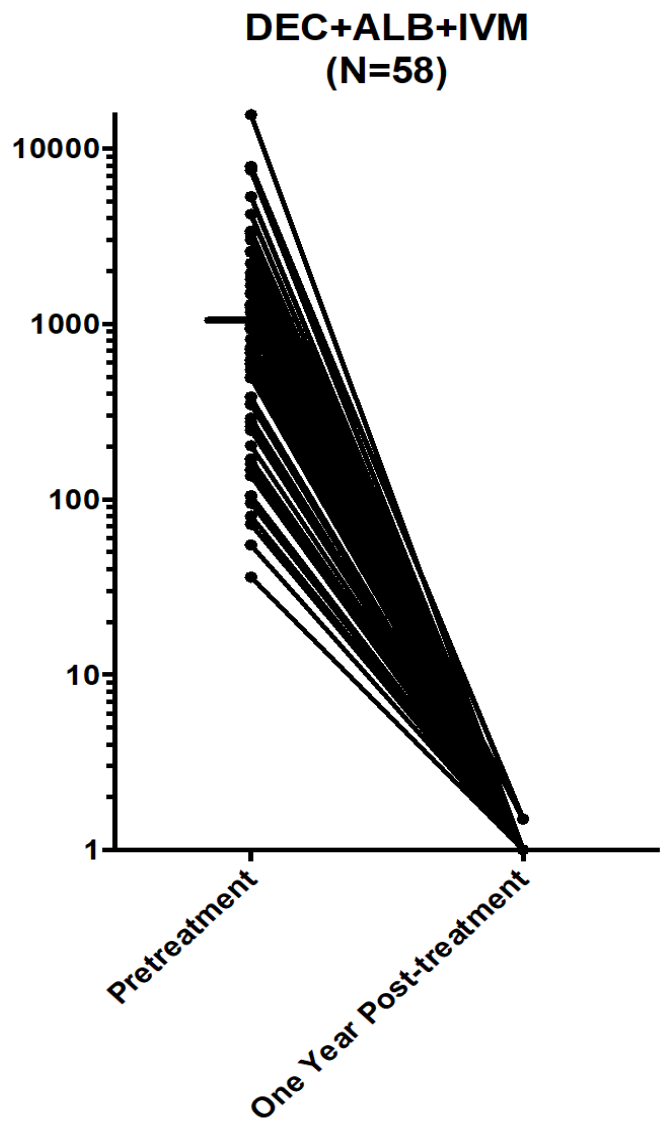
What happened next?

- A lot of excitement- we have a cure!

Dramatic starting place for IDA Triple Therapy for LF

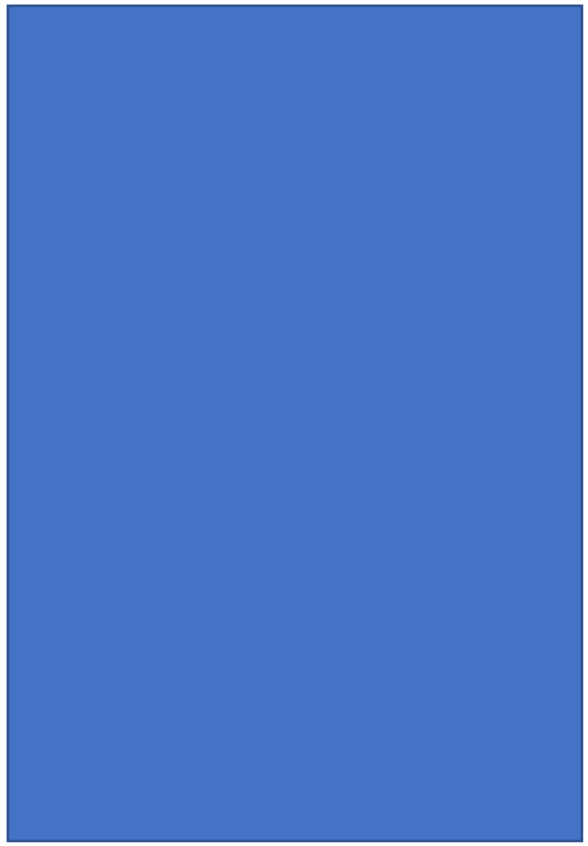
Single Dose Triple Drug Therapy: Almost Complete Elimination of Microfilariae One Year Post-treatment in Larger ONG Study





Quell the rumors

- One dose will not be enough
- Can’t go from 100 people to 800M! Need more data.
- All LF is not the same- need to understand Brugia



Bridges to Development

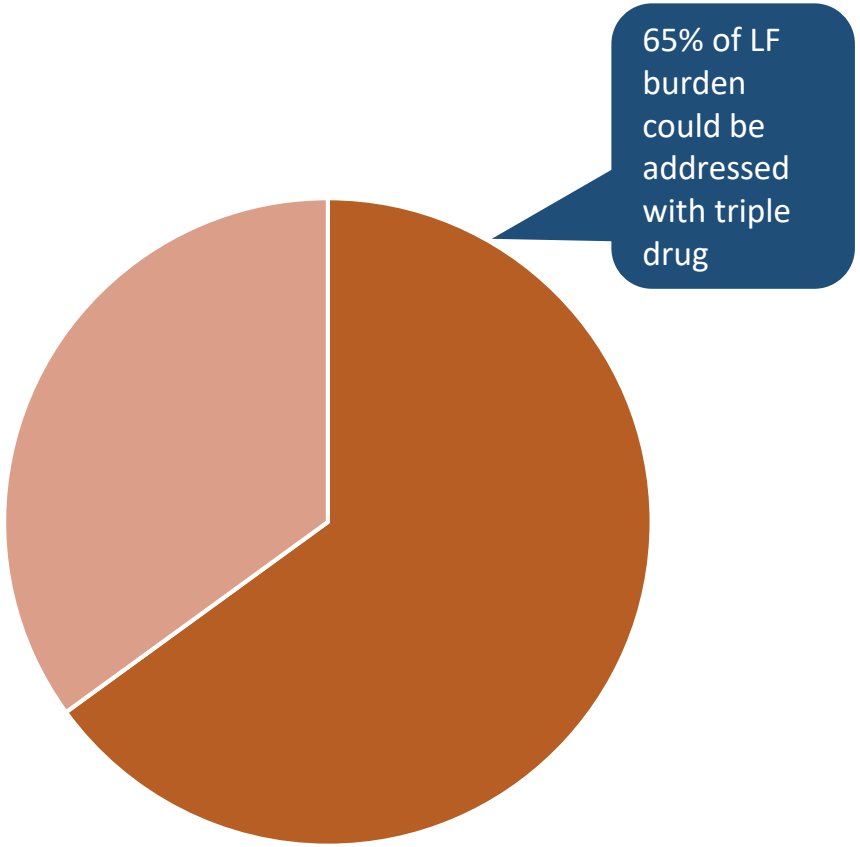
What happened next?

- A lot of excitement- we have a cure!
- Expert meeting with WHO to discuss how to safely move this from early clinical finding to policy
- Business as usual is complex and time consuming and expensive
- Think about how we can do business differently
- It took ~15 years for ivermectin to get from the clinical trial results to being in a program and getting out to communities
- We are trying to do it in under 2years!!!

New use of existing drugs for Lymphatic filariasis

- **Macrofilaricidal potential of triple therapy using existing drugs (IVM+DEC+ALB)**

- Funded as part of BMGF London Declaration commitment, ongoing study of a single treatment with ivermectin, DEC, and albendazole in heavily LF infected individuals in PNG
- Almost 100% clearance of microfilaria in all individuals in triple treatment arm
- Believe that the treatment kills or sterilizes the adult worm
- AEs more common but not more severe, no SAEs
- Could be a game changer in LF elimination and achieving targets



- Triple drug therapy could be used in up to 23 countries covering potentially ~800M people (particularly India and Indonesia)
- Accelerated development plan is under development to confirm safety and potential use in MDA setting
- Initial use would be limited to non-oncho and non-loa countries until further safety studies completed.

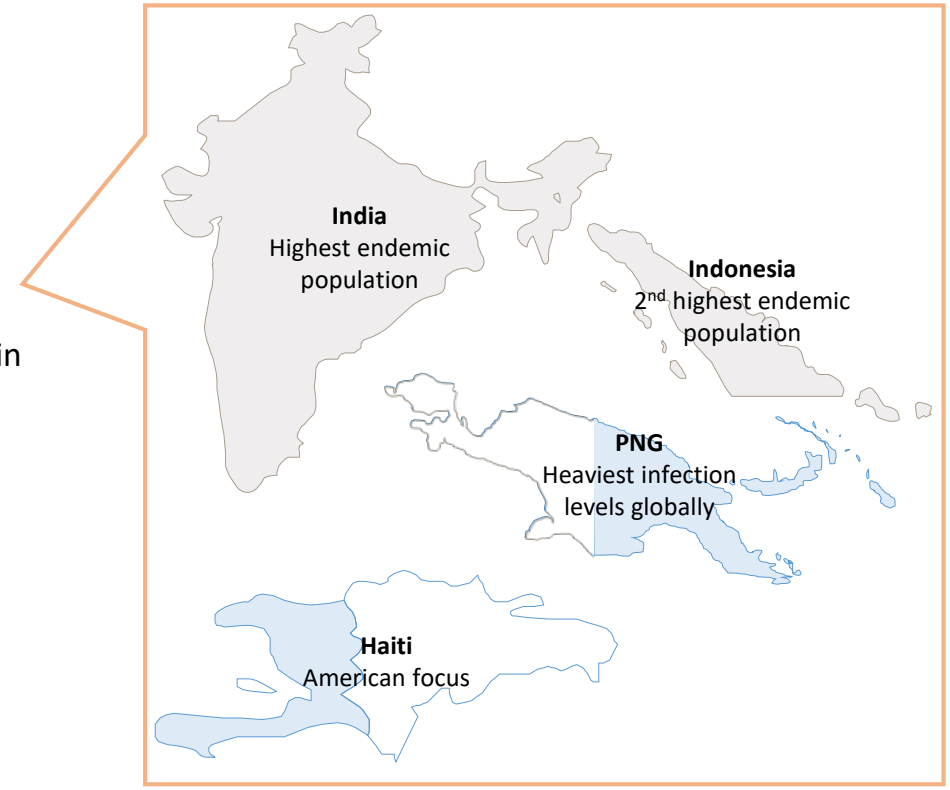
Priority considerations

- Safety is the primary concern going to scale.
- WHO is the primary policy and regulatory agency for recommendations
  - 10,000 patients in a safety database per the WHO guidelines review committee. Specific populations TBD but want a range
- We need the right diversity of relevant variables to allow uptake in countries with maximum potential for impact. Two main scenarios:
  - Low prevalence- previously treated mop up and quick wins for elimination
  - High prevalence- difficult delivery, high transmission, catch up for elimination
  - Between sites cover- High and low prevalence settings, parasite diversity, vector diversity, geographic diversity
- How can triple drug be utilized to achieve 2020 targets. What kind of scale up would be required? What data would be needed to support that decision?
  - For countries
    - WHO
    - Donors
    - Pharma

IDA Development plan and progress

Goal- maximize potential impact with safe scale up as appropriate to eliminate filariasis

- **Stage 1**: Focus on safety in non-oncho, non-Loa countries
- Plan*
  - Complete ongoing trials in PNG and Cote d'Ivoire and additional clinical studies focus on increasing the safety data for scale up in non-oncho, non-loa countries
  - Complete supportive clinical pharmacology study to increase the amount of safety data and supplement PK/PD data
  - Complete 10,000 person safety database to support a WHO guideline recommendation
  - Begin planning for further roll out and testing in oncho endemic settings and safety/efficacy in oncho
- Upcoming issues
  - Implications on timelines to elimination, cost of program, and drug supply (NTD modeling consortium), **will need WHO guidelines for stopping IDA treatment**
- Critical partners
  - WHO – for guidelines
  - Merck – for increased donation request
- **Stage 2**: Testing in oncho and Loa endemic countries, co-endemic communities, and co-endemic individuals



*Fiji added to risk mitigate the potential loss of one site and to evaluate impact on scabies

** Developed in close collaboration with WHO, donor partners, and MOH at national level*

IDA Triple Drug Study Site Summaries

Studies enrollment is powered to allow any single site to be delayed without delaying the 10,000 person data base for WHO recommendation

Country	Epidemiological setting	Study design	Unique factors
India	Low transmission, long term historical treatment, highest number of cases globally (~40%)	N= 6,000 12-month Two-arm study, open label	May be early adopter in high risk areas based on local data and not wait for formal WHO recommendation
Haiti	Low residual transmission, long term historical treatment	N= 3,000 12-month Two-arm study, open label	Will provide data for policy in the Americas, follow on transmission studies
Indonesia	Moderate to high transmission, Brugia transmission, second highest number of cases in region, not reaching all endemic areas	N= 3,000 12-month Two-arm study, open label	Will provide first safety and efficacy data in Brugia.
PNG	Highest infection rates globally with very difficult access issues, no real treatment given in the country	N= 3,000 12-month Two-arm study, open label	LF elimination success will likely depend on new strategy and treatment
Fiji	Low transmission, treated, isolated populations	N= 2000 12-month Single-arm study, open label	Will also look at scabies and stronyloides impact for use in cost benefit, community acceptability, and investment case, will provide data to support the end game in pacific island

Bridges to Development

Multicountry Safety Studies Were Completed

Country	Signed ICF	MDA Given	Male	Female	Two Drug	Three Drug
Haiti	6513	6016	2911	3602	3009	3007
India	9727	9271	4700	5027	4484	4787
Indonesia	4065	3938	1988	2077	1793	2145
PNG	4668	4579	2457	2211	2193	2386
Total	**24,973**	**23,804**	**12,057**	**12,916**	**11,479**	**12,325**

Report generated on 5May17

Cumulative Adverse events by treatment arm

Treatment	# treated	# (%) with AEs	Grade 1	Grade 2	Grade 3	SAE
Two drug-DA	10688	1138 (10.6)	1043 (9.8)	83 (0.8)	9 (0)	3 (0)
Triple drug-IDA	10525	1100 (10.5)	994 (9.4)	99 (0.9)	9 (0)	0

In cumulative global data no difference in adverse events between traditional and triple drug therapy

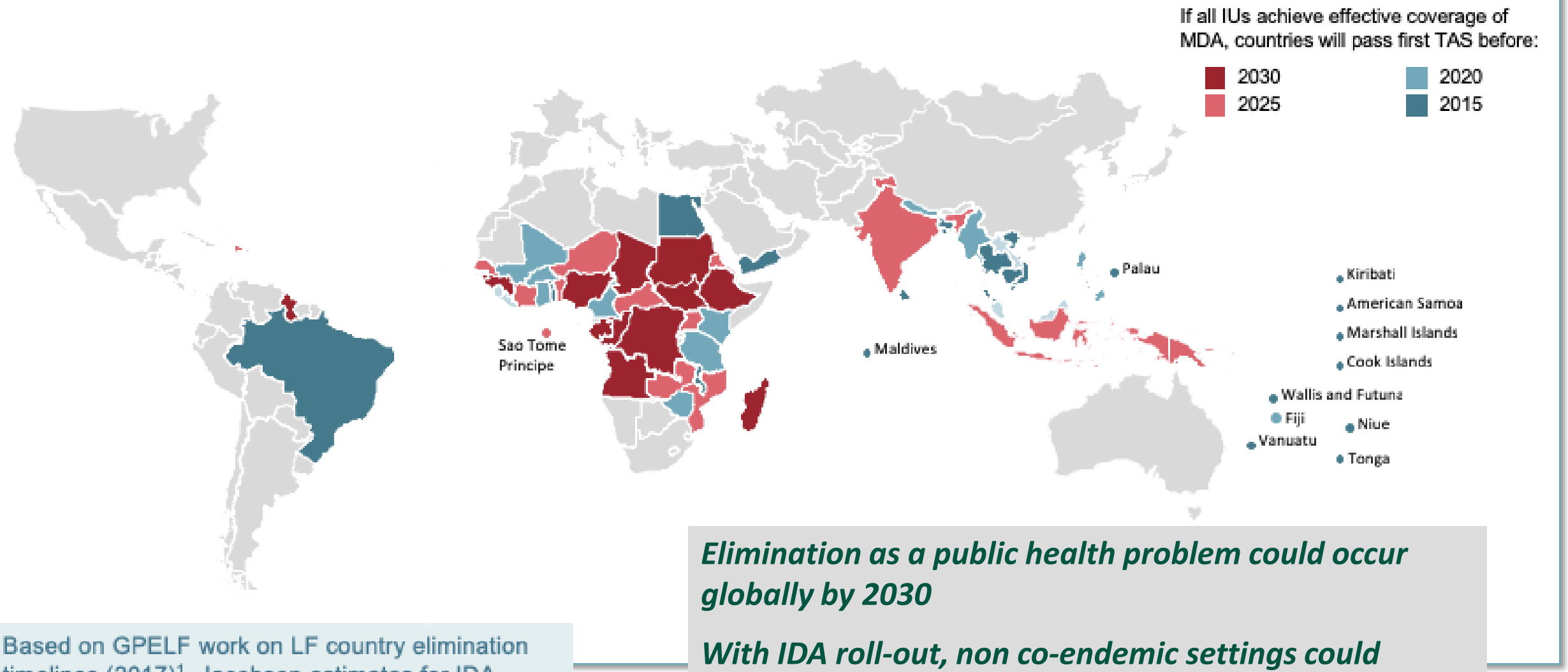
After the clinical trials: next steps to impact

- Complete WHO recommendation and guidelines process
  - Data submitted to WHO for independent analysis
  - Guidelines Review Expert committee, revised guidelines submitted
  - Guidelines committee decision and guidelines completed and posted
- Create full LF elimination plan including:
  - Program strengthening (enhanced MDA)
  - IDA introduction
  - 2X year albendazole with VC in LF and Loa co-endemic areas
  - MDA plus VC in targeted geographies
  - Answering strategic questions including how to determine if transmission has been blocked post IDA
- Coordinating with key partners on elimination planning
- Partnering with key donors in identified geographies (USAID, DFID, END Fund, WB)
- Working with pharma on forecasting and drug supply to support roll out

Information and data to support decision making

- Modeling- priority studies and data for key decision makers
- Policy- data to support impact and adoption
- Program support- where and how to introduce and monitor programs
- Drug supply- how much needed and when
- A shared integrated workplan to show interdependencies and timing of activities

IDA Triple Therapy can help accelerate LF elimination



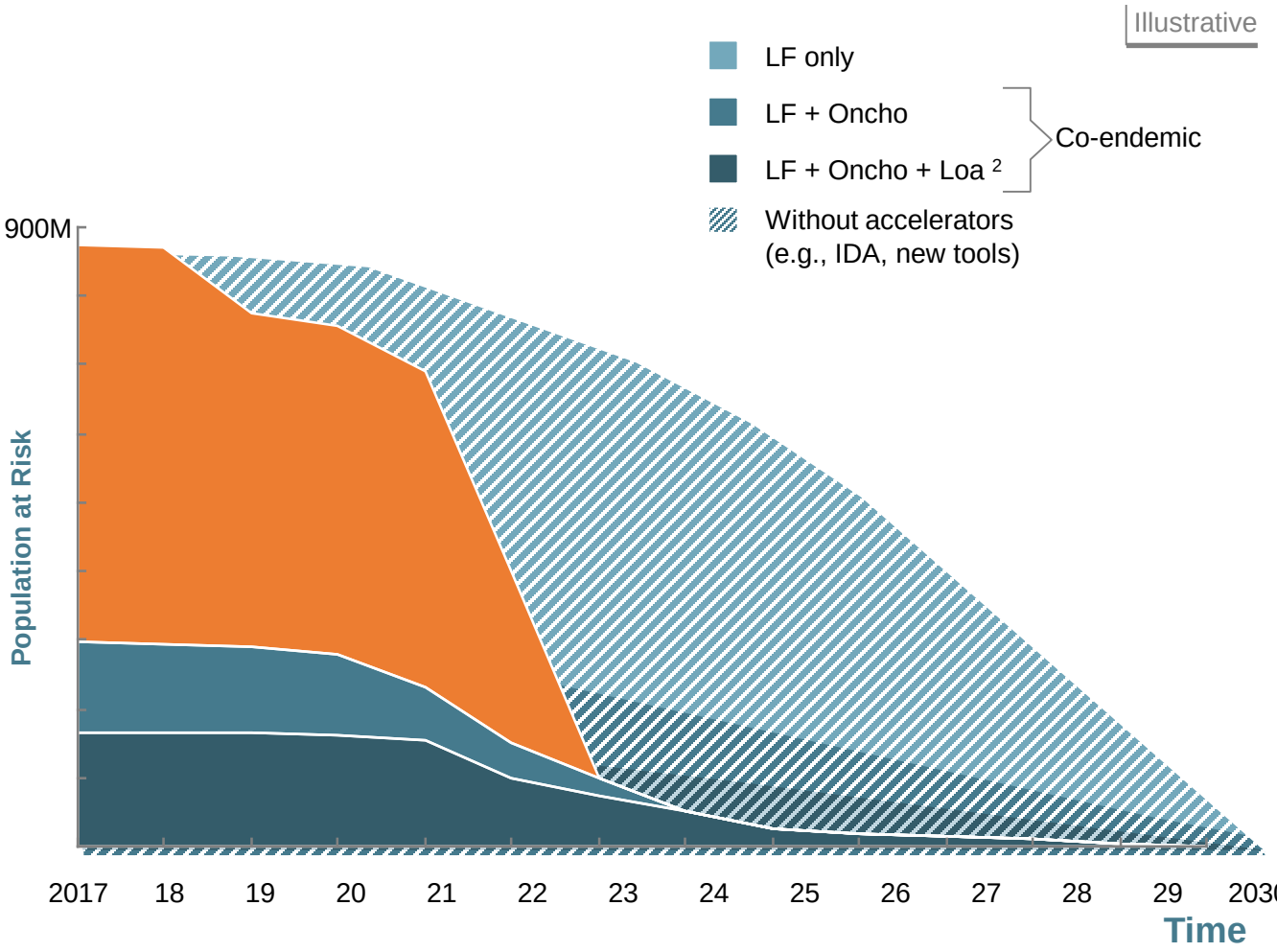
Based on GPELF work on LF country elimination timelines (2017)[1], Jacobson estimates for IDA

Elimination as a public health problem could occur globally by 2030

With IDA roll-out, non co-endemic settings could eliminate before 2025

LF elimination acceleration with strategies varied by setting

Baseline population[1]



Summary of strategy focus by setting

I

Non Co-endemic settings:
Improve delivery
In order to speed up elimination in non co-endemic settings (60% of the population at risk), focus on effectively launching IDA roll out and improving country level implementation and compliance.

II

Co-endemic settings + hard to reach settings:
Enhance tools
To reach the end game by 2030 in co-endemic settings, additional research is likely needed to improve approaches to diagnostics, treatment, and vector control. Improved delivery complements these tools.

III

All Settings:
Effectively Mobilize
None of the goals are achievable without stronger governance, increased funding and supply, and WHO supporting guidelines.

1Includes full population at risk per country and does not account for coverage levels; Includes LF + Loa which is estimated at 2M

Source: DFEAT population at risk estimates (co-endemic); PCT data portal population requiring treatment (LF Only); Julie Jacobson estimates for IDA roll out dates and years saved by non co-endemic country; Team analysis

Engaging decision makers early

- Keeping the Promise: Ending the NTDs on time in WHO SEA Region- Regional Ministerial meeting,
- Jakarta 25-27th April
- Recommendation to start introduction!

Keeping the Promise: Ending NTD's on time in the SEA Region
Regional ministerial meeting, Jakarta, Indonesia
25-27 April 2017

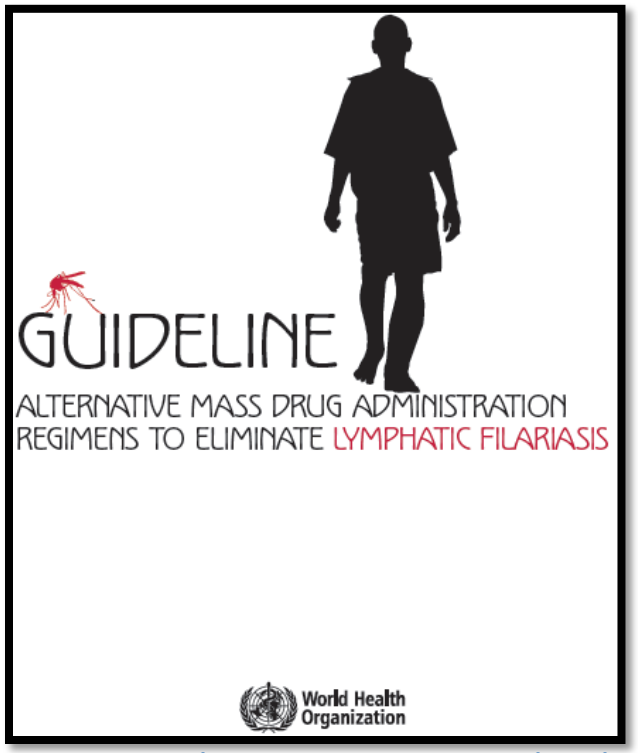
Recommendations

1. Learning from Leprosy experience, political commitment and adequate financial and other resources need to be sustained at national and sub-national levels even after the target of elimination of NTDs as a public health problem is achieved.
2. Data from the region has demonstrated superior safety and efficacy on Mass Drug Administration (MDA) with co-administration of Ivermectin, DEC and Albendazole (IDA) for elimination of Lymphatic filariasis (LF). To accelerate LF elimination and to achieve 2020 targets the region should begin targeted pilots to support sub-sequent phased scale up introduction of IDA that includes social mobilization, Directly Observed Treatment (DOT) to achieve 80% coverage or higher, management of adverse events (AEs) and address remaining operational questions. Member States request donors, technical and pharma partners continue to support the countries in this roll out.
3. Recommends WHO and Member States to work together with academia and partners to

New WHO guideline for LF MDA
(in countries currently using *DEC + ALB*)

Bridges to Development

- WHO recommends annual IVER + DEC + ALB (**IDA**) :
  a) for IUs with fewer than 4 effective rounds and…
  b) for IUs not passing pre-TAS or TAS and…
  c) for communities where post-MDA or post-validation surveillance suggests local transmission



http://www.who.int/lymphatic_filariasis/resources/9789241550161/en/

World Health Organization

IDA is warranted in…

Countries where *DEC + ALB* is being used

	< 4 effective rounds	Failed impact assessments	Post-MDA / Validation Surveillance response
AFRO	Kenya, Eritrea, Madagascar Sao Tome & Principe Zambia, Zimbabwe	Comoros	
AMRO	Guyana	Haiti	
EMRO			Egypt
SEARO	Indonesia Timor Leste	India Indonesia, Myanmar, Nepal	
WPRO	PNG, New Caledonia, FSM	American Samoa, Samoa, Fiji, Tuvalu, French Polynesia Malaysia, Philippines	

Status of IDA implementation 2019

Assessing need for IDA	Considering IDA	Planning IDA	Started IDA	Nation-wide IDA
Comoros	Nepal	Eritrea	Kenya	Sao Tome & Principe
Zambia	Myanmar	Madagascar	Guyana	Timor Leste
Zimbabwe	New Caledonia	Haiti	Egypt	American Samoa
French Polynesia	Philippines	Indonesia	India	Samoa
Federated States of Micronesia		Tuvalu	Fiji	
			Malaysia	
			Papua New Guinea	
5	3	5	7	4

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Preliminary results of IDA MDA 2018-2019

	IUs targeted	Population	Coverage (treated / population)
Kenya	3	286,640	>80%
American Samoa	National	52,936	>65%*
Samoa	National	195,979	>80%
PNG	2	278,162	>65%**
India	5 (4 completed)	10.74 million	>70%
Timor Leste	National	1.28 million	>75%
Egypt	2 villages	28,800	>85%
Sao Tome	National	206,423	>70%

*independent coverage evaluation, **implementation interrupted due to polio outbreak

World Health Organization

Introduction

- Got a WHO recommendation and had 5 countries introduce in one year!
- However to do that
- Had Increased drug donation commitment form Merck with a defined process of how to get the drug requests approved through the MEC
- Had countries ready for introduction
- Had donors interested in supporting introduction
- Had operational research questions for introduction defined and resources ready for measuring impact and learning from the early introduction
- Had WHO HQ and regions set to share guidelines and provide technical support in implementing

Now what

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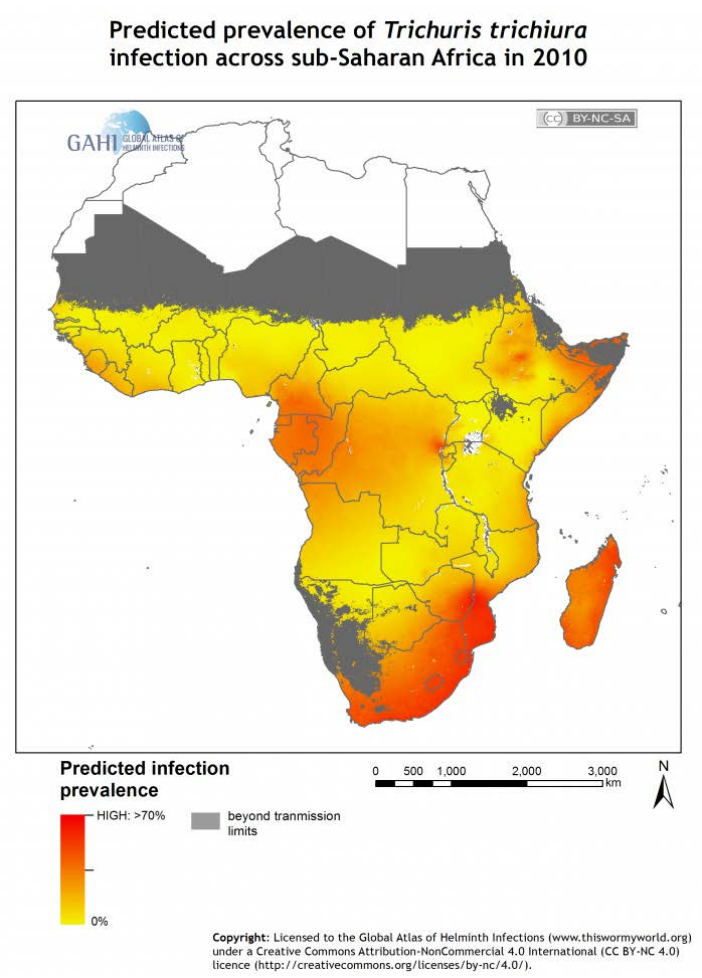
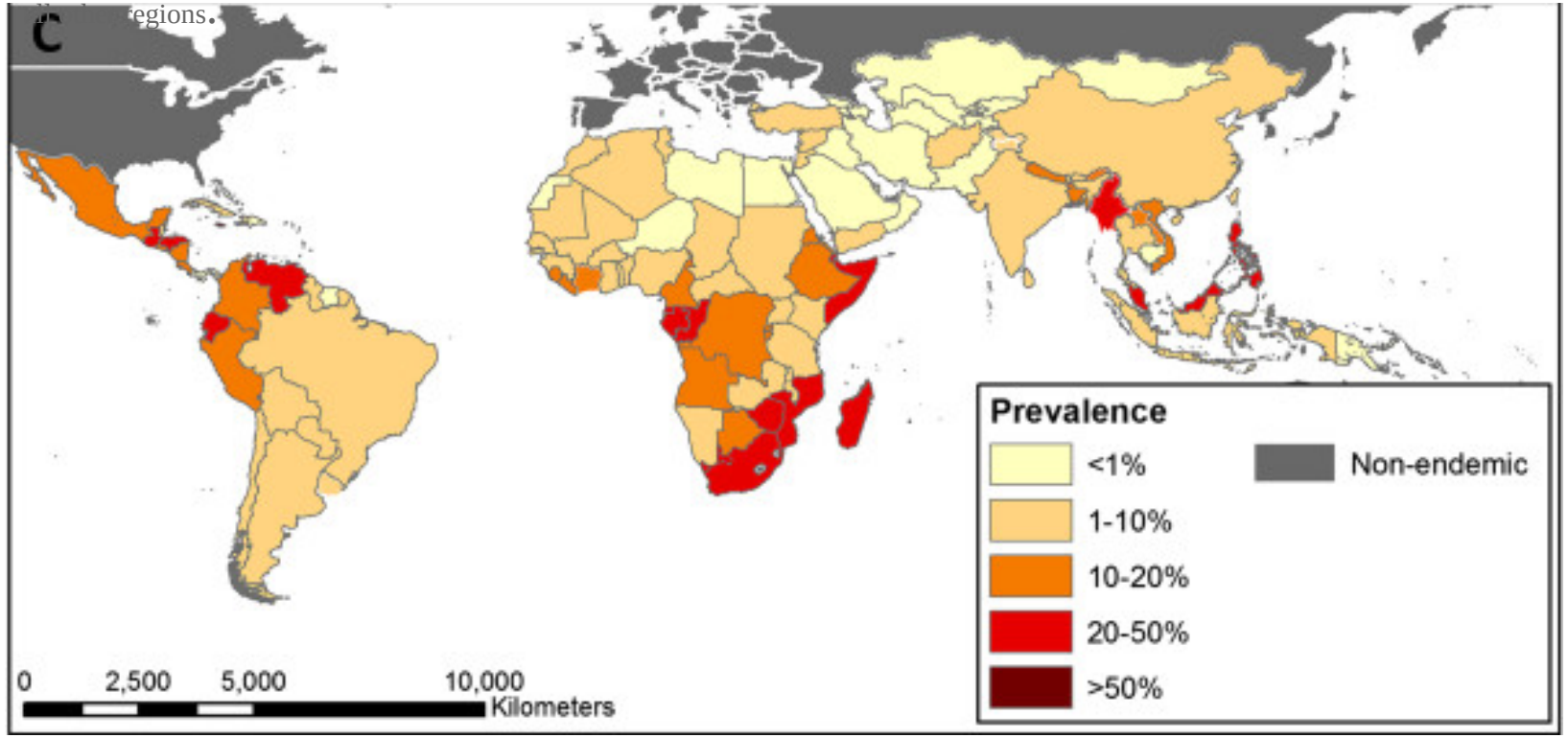
- Scabies – *Sarcoptes scabei*

Trichuris



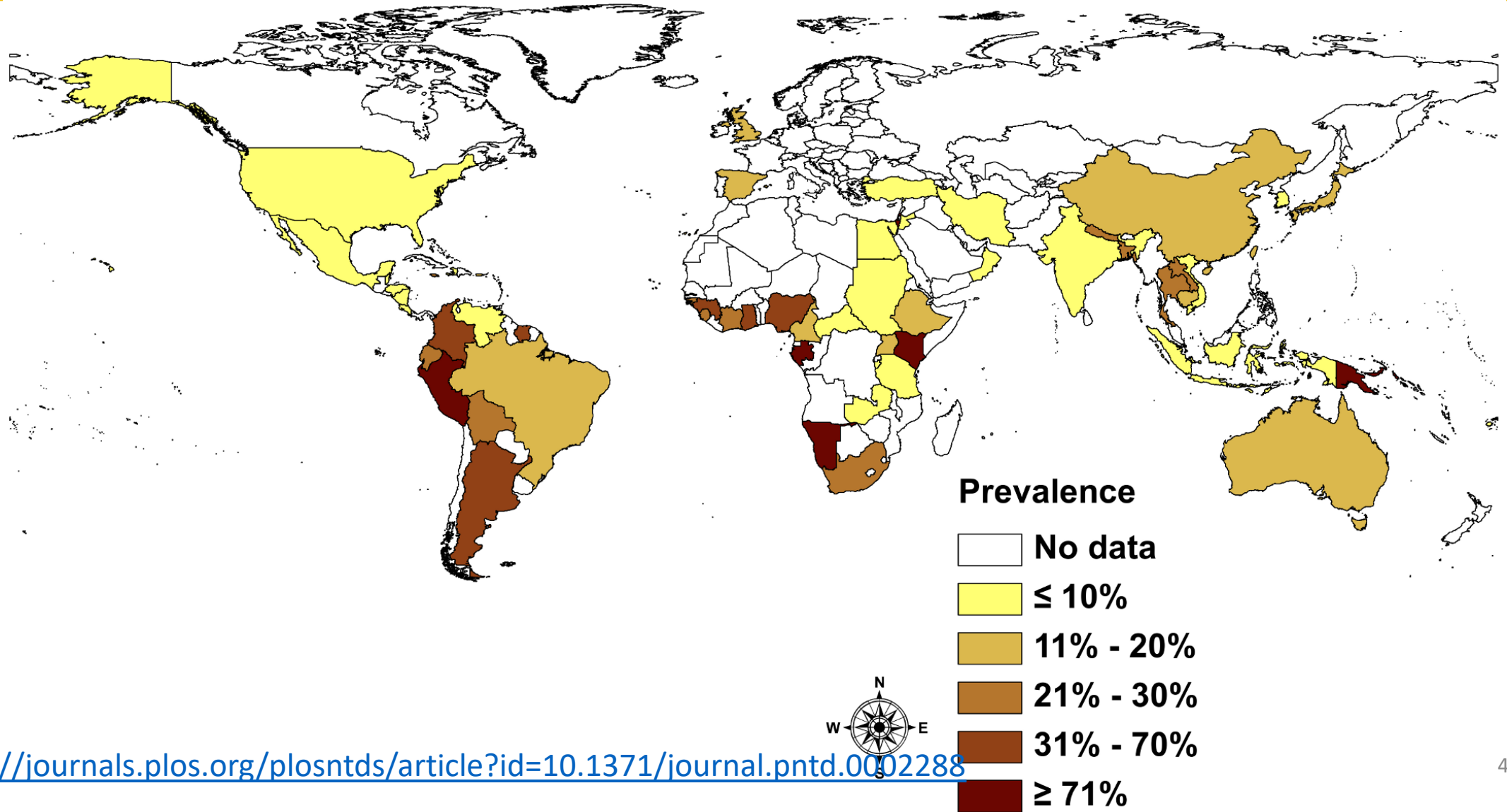
LASER – London School of Hygiene & Tropical Medicine
http://www.thiswormyworld.org/maps/predicted-prevalence-of-trichuris-trichiura-infection-in-sub-saharan-africa-in-2010

Distribution of *Trichuris trichiura* infection prevalence in 2010; based on geostatistical models for sub-Saharan Africa and available empirical information for [illegible]egions.



Pullan, 2014
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3905661/

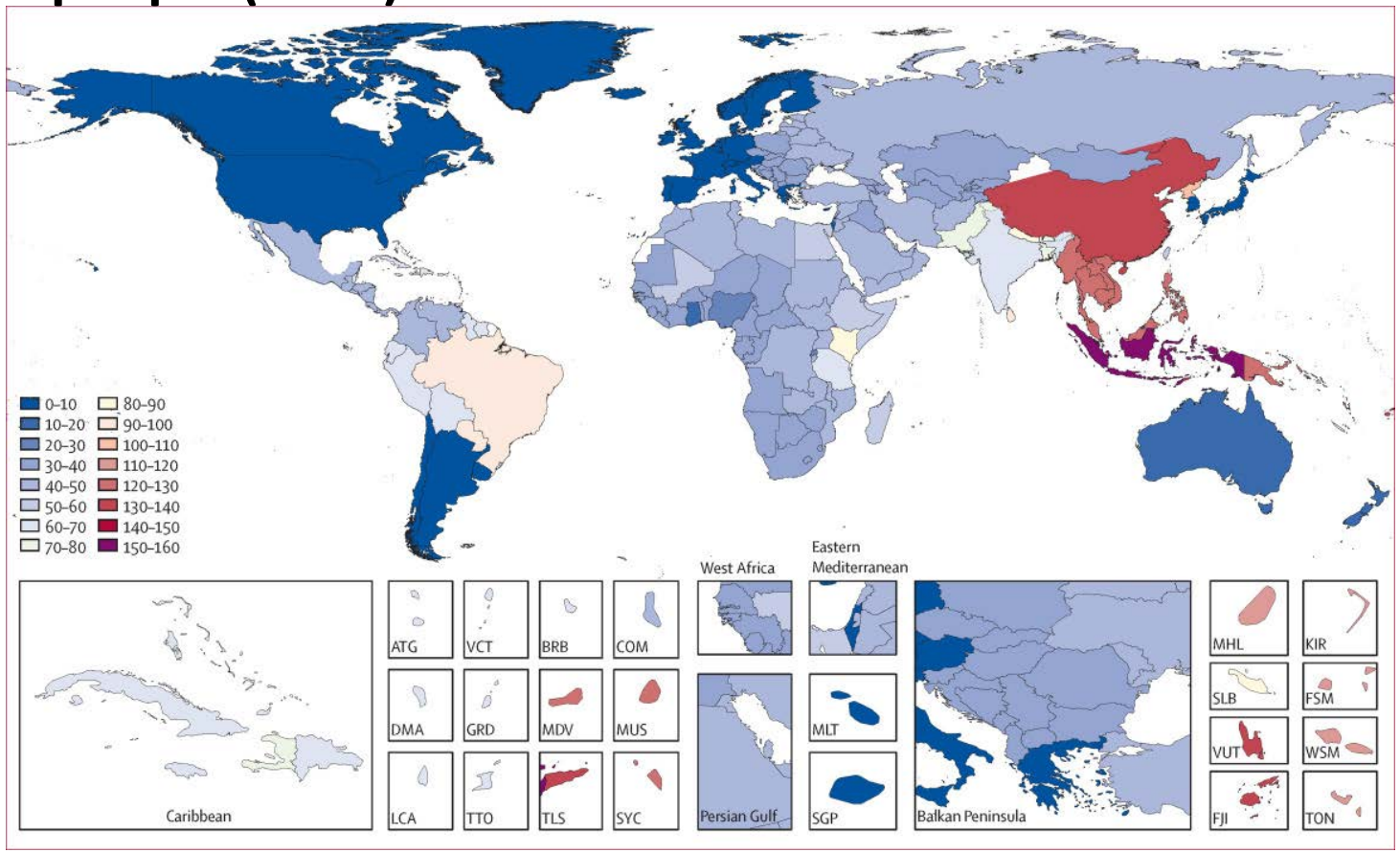
Strongyloidiasis from Community Based Studies, 2013



https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002288

Scabies

World map of scabies age-standardised disability-adjusted life-years per 100 000 people (2015)



Karimkhani, 2017
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30483-8/fulltext

Bridges to Development

The possibilities for ivermectin are many

- New WHO NTD 2030 Roadmap with new target
- Work in malaria with ivermectin as endectocide
- Kigali Malaria and NTD Summit June
- Way forward will require coordination and partnership especially across NTDs and malaria.

Bridges to Development

Happy World NTD Day!!- Where will we go from here??

- Looking forward to discussing with you the future as we create it together
- It will take many minds and a lot of creativity
- Strong partnership and commitment
- Willingness to look beyond specialty and break the silos and borders that separate us in service of a healthier world for all.

Join the team today!! https://worldntdday.org/