The challenge of developing new treatments for onchocerciasis

SEMTSI

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OUTLINE

DNDi onchocerciasis program:

- Needs assessment
- TPP definition
- Identification of efficacy endpoints
- R&D onchocerciasis portfolio
- Challenge in clinical development
- Mathematical modeling to inform the clinical development (CDP)
- Need of new biomarkers

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DNDi onchocerciasis program

- Onchocerciasis remains a High Unmet Medical Need
- DNDi included onchocerciasis in the research portfolio with the aim to develop a

  "safe, efficacious, affordable and field-adapted macrofilaricidal drug for onchocerciasis as a treatment for individual case management and, after appropriate testing, as an alternative treatment in mass drug administration programs"
- Target product profile was developed with expert advice
- Several promising candidates are in the different stages of development

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Onchocerciasis
Remains a High Unmet Medical Need

- Only one drug, ivermectin, approved for onchocerciasis treatment (1987)
- Limitations of ivermectin
  - Microfilaricidal effect, some macrofilaricidal activity when repeated overtime.
  - Regular administration needed for at least 10 years (the reproductive life of the adult worm)
  - Limited use in regions with concomitant *Loa loa* infection

    Can induce neurologic Serious Adverse Events in subjects with high *Loa loa* microfilarial densities (>30,000 mf/mL)

  - Potential resistance to ivermectin

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TPP for onchocerciasis case management (2016 to be updated)

Variable	Acceptable	Ideal
Indication	For the treatment of : • Onchocerciasis patients due to the nematode parasite *Onchocerca volvulus*	For the treatment of: • Onchocerciasis patients due to the nematode parasite *Onchocerca volvulus* *And* • Other filariasis (Lymphatic filariasis due to the nematode parasites *Wuchereria bancrofti, Brugia malayi, Brugia timori* and Loiasis *due to Loa Loa*)
Product Description	Results in death of the adult onchocerciasis worms and of microfilaria. (macro and microfilaricide)	Results in death or of the adult onchocerciasis worms. (macrofilaricide)
Target population	All infected patients with the exception of pregnant women, children younger than 5 years.	All individuals who are at risk for onchocerciasis
Treatment regimen	• Oral dose, once or twice a day • Duration of treatment up to 14 days • One single intramuscular or subcutaneous injection or repeated after a week (2 injections) • One dose for adults and weight/age-adjusted or height-based dosing for children	• Oral dose, once a day, up to 3 • One dosage for all ages
Efficacy	70 – 80% macrofilaricidal effect (EP: Relative reduction of 50 – 60 % in the mean number of female alive worm per nodule/patient compared to the control group at 12 months)	95% of patients are cured by 12 months (cured =100% of worm are dead/moribund and below LLD mf/mg skin)
Safety	**Adverse events** Minor and manageable side effects • Monitoring for AE manageable at local healthcare post • Moderate impact on activities of daily living • No severe Mazzoti reaction • No adverse ocular reaction **Population for restricted use at registration** Pregnancy women Lactating woman (duration according to PK of the drug) **Precaution/Warnings** • Concomittant infections (eg.loaisis) • Acute illness (eg. Fever, bacterial infection) **Use in specific populations**: • Pre-treatment assessment and careful post-treatment follow-up should be available for patients with *Loa-loa* coinfection. • Exclusion of high *Loa loa* mf/mL co-infected patients	**Adverse events** • No monitoring for AE required • No impact on activities of daily living • No Mazzoti reaction • No adverse ocular reaction **Population for restricted use at registration** • None **Precaution/Warnings** None **Use in specific populations:** • Safe for use in patients co-infected with *L. loa* No monitoring needed. (no rapid microfilariae activity)
	Drug-drug interactions: Manageable for individual case treatment	Drug-drug interactions: • No clinically significant drug-drug interaction with commonly used anti-parasitic and anti-infective drugs • No evidence for clinically significant, adverse interactions with long-term/chronic use drugs (e.g., anti-tuberculosis drugs, anti-retrovirals, contraceptives) And • No evidence for clinically significant, adverse interactions with commonly administered MDA drugs (e.g.ivermectin, praziquantel, other benzimidazoles, azithromycin), and anti-malarial drugs.
Shelf Life	3 years in zone IVb	More than 3 years in zone IVb

Development Challenges - Different mechanisms of action need different endpoints

Drug effect on macrofilaria:

- Direct Macrofilaricidal: antiparasitic drugs (e.g. flubendazole, suramine)
- Indirect effect: Antiwolbachia drugs

Drug effect on microfilaria

- Mechanism of action with in situ death: e.g. DEC
- Not in situ death: e.g. ivermectin

Effect on the reproductive status of the adult worm:

- Temporary effect: Embriostatic (e.g ivermectin)
- Permanent effect: Embryotoxic. (e.g. anti-wolbacchia) BUT a clear definition is still needed

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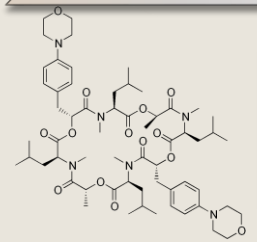
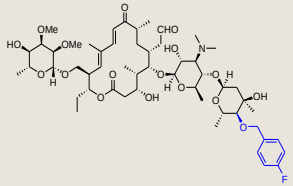
Filarial Disease Landscape 2017

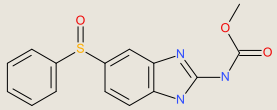
Pre Clinical	Translational / Phase 1	Phase 2 / POC



Emodepside
- SAD completed
- MAD to be started (Q4 2017)
- 1b in patients under preparation



Tylamac
- IND filing under preparation for phase I
-SAD to be started (Q4 2017)



Oxfendazole
- Preclinical studies for IND filing under preparation
- CMC development under preparation

Anacor/BMGF
AN15470

LSTM / EISAI

Celgene

Anti wolbachia *Macrofilaricidale* *Tubulin inhibitors*

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Development Challenges – Limitation of current endpoints to assess efficacy

Nodule examination: Macrofilaricidal effect is assessed by histological examinations of accessible the nodules

number of adult worms, viability, embryogenesis and spermiogenesis

- Invasive test
- Does not allow several time point assessments
- Up to 1/2 of nodules may be located in deep tissues

Skin biopsie (skin snip) to assess the presence of microfilaria (mf) in the skin counting number of mf/mg skin

- invasive test
- Inference the presence of fertile adult females
- low sensitivity in light infections
- doesn't differentiate infection vs. re-infection

Need to develop robust endpoints and biomarkers to measure macrofilaricidal effect

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Development Challenges - Registration of macrofilaricidal drugs

- No precedent of registration of macrofilaricidal drug
- No regulatory guidance on primary endpoint measures for registration
- No direct proof of macrofilaricidal efficacy
- Reinfection may have an impact on the reliability of longer-term endpoints

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Recomendations for clinical development

Based on the Onchocerciasis clinical and regulatory technical meeting on October 17th 2016

- Recommendation to use the **microfilaria density at 24 month** and demonstrate a sustained low level
  - as surrogate marker of clinical benefit
  - based on an effect on adult worms
- Nodulectomy at 6/12 month to assess the macrofilaricidal effect (and/or the potential embryotoxic effect) as Go / No go criteria for POC phase 2 to move to phase 3
- As we planned one **phase 3**, the **POC phase 2** should also measure microfilaria density **at 24 months**
- Long follow-up: 6 /12 months for go/no-go and 24 for confirmation

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Development Challenges – Safety evaluation

Drugs with direct effect on microfilaria can produce side effects due to inflammatory and immune reactions:

- Mazzotti reaction (observed with ivermectin and DEC)
- eye lesions (observed DEC)

Related to:

- Drug mechanism of action and the speed of microfilariae death
- Intensity of infection (microfilariae skin snip load)
- Could be due to autoimmune reaction (e.g. posterior segment eye lesions)

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Development Challenges –Safety evaluation loiasis co-infection

- Serious adverse events were observed with ivermectin and DEC in subjects infected patient with *Loa loa with high level of* microfilaremia

➢ Threshold for ivermectin treatment for loaisis patients is established at 20,000 mf/mL for test and not treat strategy, but unknown for new drugs (Need for ivermectin pretreatment?)

If the drug has microfilaricidal effect the clinical development includes

- **1b studies** (Single Dose) to assess the *kinetic* of the decrease of microfilaria and the potential associated adverse reactions **in onchocerciasis**
- **1b studies** (Single Dose) to assess the *kinetic* of the decrease of microfilaria and the potential associated adverse reactions in **loasis**

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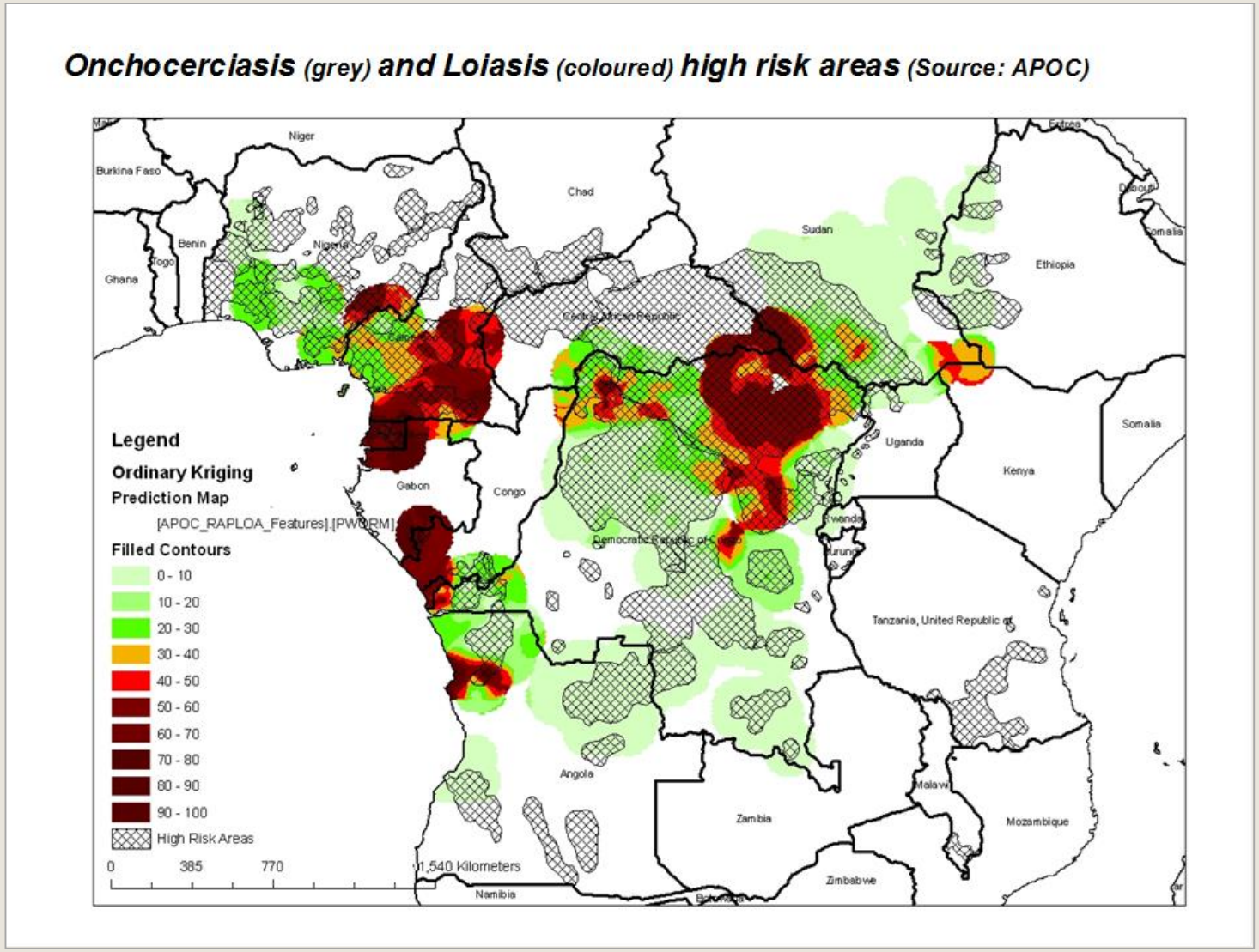
Loasis and onchocercaisis overlap



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Mathematical modeling in onchocercaisis

- Modeling the burden of disease and the results of control programmes
  - Estimate and projected number of infected persons who could benefit from new drugs
- Modeling loaisis co-infection
  - Estimate and projected number of onchocerciasis patients co-infected with loaisis and at high risk of SAE with after ivermectin treatment

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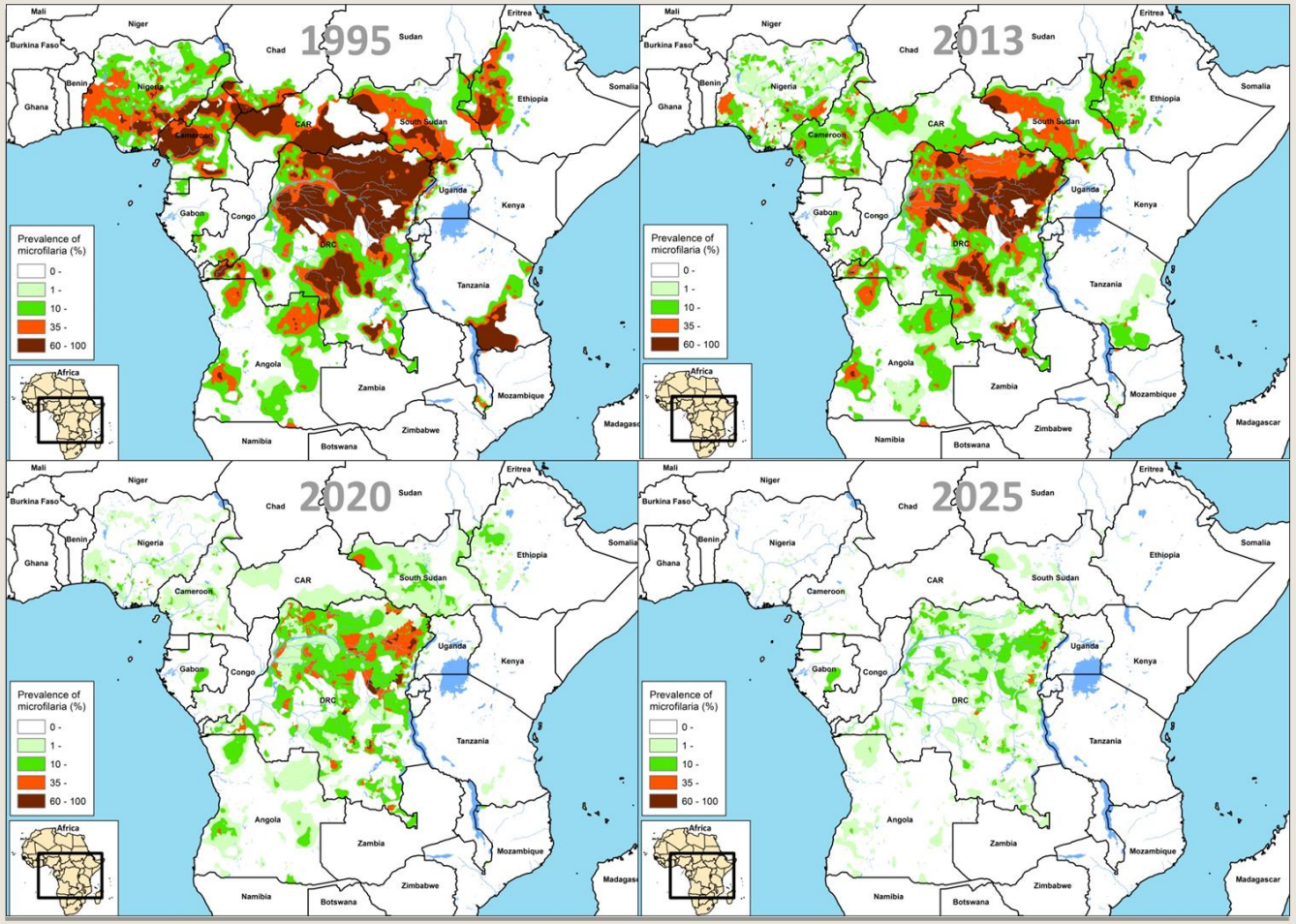
Towards Onchocerciasis Elimination in 2025?



Source WHO

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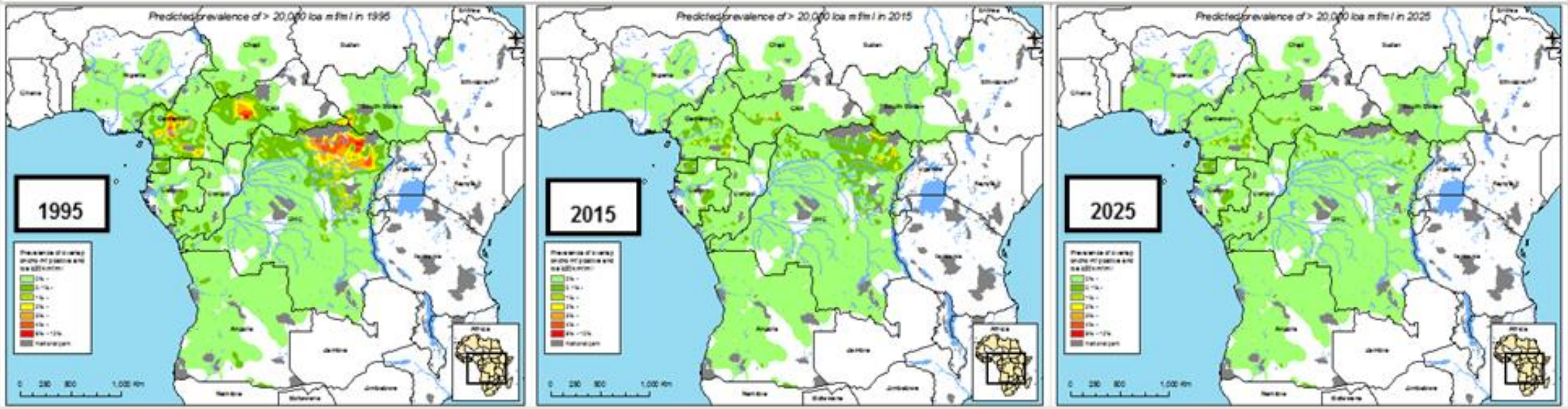
Projected number of people with onchocerciasis-loiasis co-infection in Africa, 1995-2025

Figure 1. Maps showing the prevalence of co-infection of onchocerciasis and very high-intensity *L. loa* infection (≥20,000/mL blood) for 1995, 2015, and 2025.



*Projected number of people with onchocerciasis-loiasis co-infection in Africa, 1995-2025 . Natalie V.S. Vinkeles Melchers[1], Afework H. Tekle[2], Luc E. Coffeng[1], Sébastien D.S. Pion[3], Honorat G.M. Zouré[2], Belén Pedrique[3], Michel Boussinesq[3],Samuel Wanji[5], Jan H.F. Remme[6], Wilma A. Poster ECTMIH 2017

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Overview of the projections for number of O. volvulus, L. loa and co-infected cases for 1995, 2015 and 2025*

Numbers x1,000

	1995	2015	2025
Population size living in *Loa*-mapped areas	81,400	134,900	169,400
Population size in *Loa*-onchocerciasis co-endemic areas	59,800	98,500	123,600
Population size in Loa-onchocerciasis co-endemic areas where MDA cannot be applied	8,185	13,542	16,965
No. of people with *Loa* mf (% of population size in *Loa*-mapped areas)	3,800 (4.7%)	5,200 (3.8%)	6,300 (3.7%)
No. of people with *O. volvulus* mf (% of population size in co-endemic areas)	18,400 (30.7%)	10,900 (11.0%)	3,200 (2.6%)
No. of people with *Loa* mf (% of population size in co-endemic areas)	2,800 (4.6%)	3,500 (3.6%)	4,200 (3.4%)
No. of onchocerciasis- *Loa* co-infected cases with ≥20,000 *Loa* mf/mL (% among all *O. volvulus* cases)	107.0 (0.6%)	44.1 (0.4%)	24.6 (0.6%)
Idem, in areas where MDA cannot be applied (% among total co-infected cases with very high *Loa* mf intensity)	11.7 (10.9%)	18.8 (42.5%)	23.0 (93.5%)

*Projected number of people with onchocerciasis-loiasis co-infection in Africa, 1995-2025 . Natalie V.S. Vinkeles Melchers[1], Afework H. Tekle[2], Luc E. Coffeng[1], Sébastien D.S. Pion[3], Honorat G.M. Zouré[2], Belén Pedrique[3], Michel Boussinesq[3],Samuel Wanji[5], Jan H.F. Remme[6], Wilma A.
Poster ECTMIH 2017

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Mathematical modelling of novel macrofilaricidal drugs for river blindness:

Given the current endpoint limitations, the use of clinical trial simulators that project patient outcomes can be helpful when designing clinical trials, predicting efficacy endpoints over time when applying different assumptions on efficacy and ongoing transmission.

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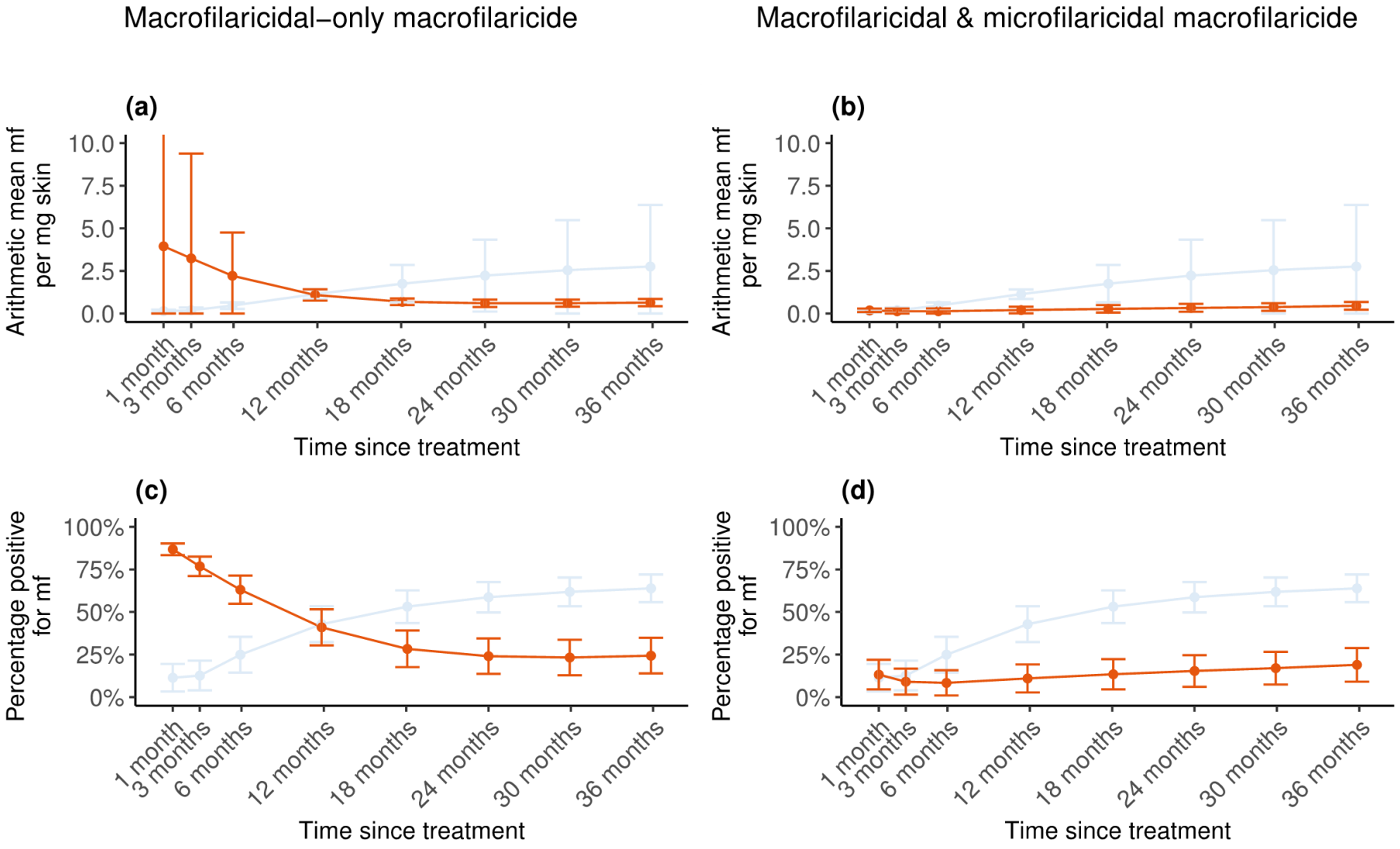
Parasitological response dynamics of two 50-participant cohorts treated with either ivermectin or a hypothetical macrofilaricide



Ivermectin-treated control participants

Macrofilaricidal-treated test participants (e = 90%)

Source: Walker M et al Poster ASMTH 2017 in preparation

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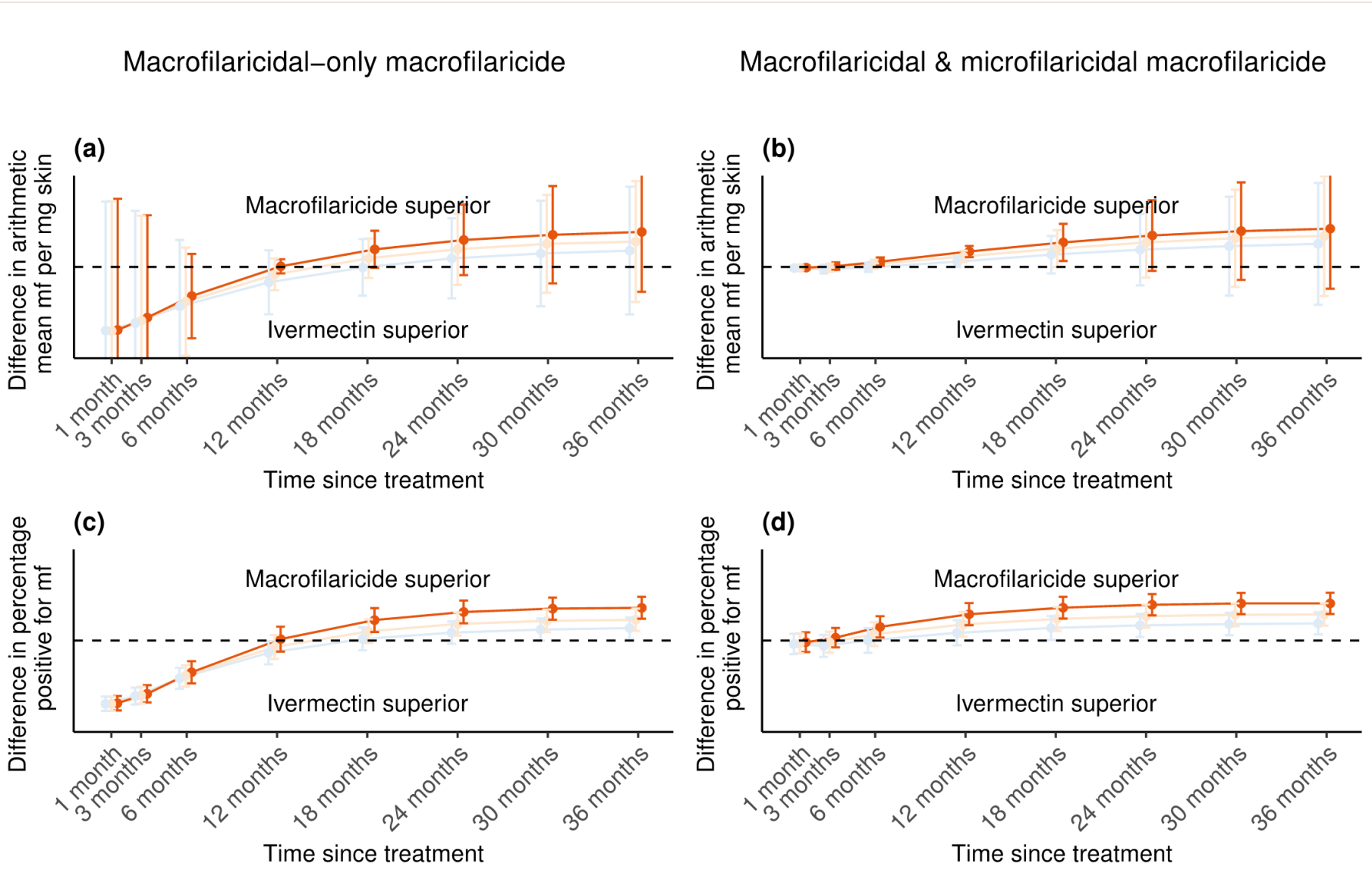
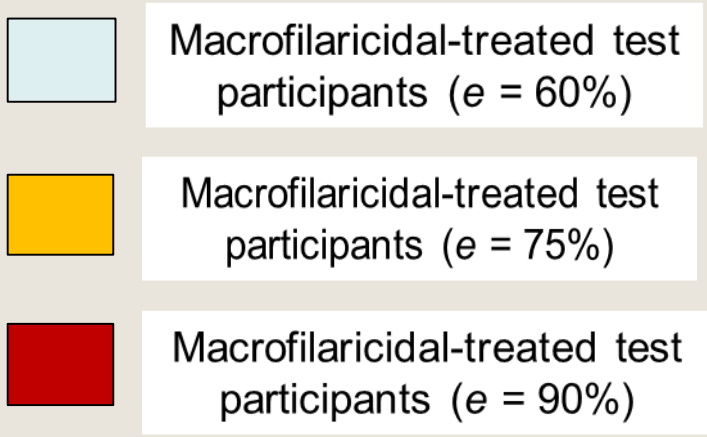
Difference in parasitological outcome measures between two 50-participant cohorts treated with either ivermectin or a hypothetical macrofilaricide





Source: Walker M et al Poster ASMTH 2017 in preparation

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Mathematical modelling: Principal conclusions

1. Opportune follow up times for demonstrating superiority of a macrofilaricide (over ivermectin) depend on macrofilaricidal efficacy & concomitant microfilaricidal activity

   ≥18 months for a macrofilaricidal only macrofilaricide with ≥ 75% efficacy

   ≥ 12 months for a macrofilaricide with microfilaricidal activity with ≥ 75% efficacy

2. Taking 4 vs. 2 skin snips provides negligibly lower required sample sizes but will make it more likely that the required sample size is achieved (i.e. detecting enough infected people in a low transmission setting)

3. Inclusion criterion of > 5 mf per mg skin ***inflates*** required sample sizes compared to > 0 mf per mg because of increased variability in mf measurements repeated on more heavily infected participants

4. Percentage positive for mf yields lower required sample sizes than arithmetic mean mf per mg ***in this transmission setting*** (but this is unlikely to be true across all settings)

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Need of new biomarkers

In addition to the need for better treatments, there is a parallel, urgent need for better diagnostic methods to assess the impact of treatment on viability of adult *Onchocerca volvulus* worms.

Current field of research

- Imaging techniques
- Biomarkers in blood / urine
- Microfilaria finger print
- Quick diagnostic test for loaisis

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