

Swiss TPH Winter Symposium 2017

Helminth Infection – from Transmission to Control

Drug combinations against soil-transmitted helminths

Basel, 7 December 2017





Cure and egg reduction rates of recommended drugs (single dose) for soil-transmitted helminthiasis

Efficacy of Current Drugs Against Soil-Transmitted Helminth Infections Systematic Review and Meta-analysis

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Context More than a quarter of the human population is likely infected with soil-transmitted helminths (*Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*) in highly endemic areas. Preventive chemotherapy is the mainstay of control, but only 4 drugs

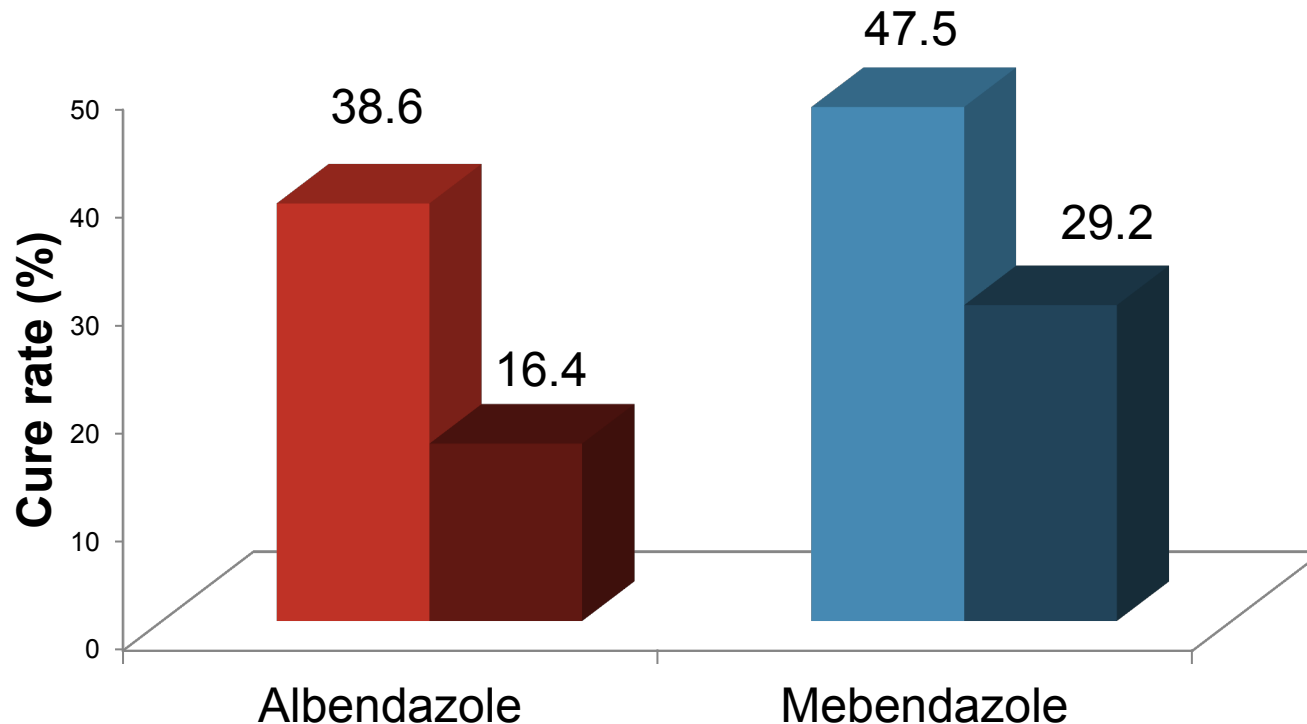


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Efficacy of recommended drugs against soil transmitted helminths: systematic review and network meta-analysis

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Cure rate *T. trichiura* 1995 versus 2015



Significantly reduced efficacy → Resistance development?

→ **Need for new anthelmintic treatments**

New/alternative drugs

- **Tribendimidine**
 - Broad spectrum of activity (nematodes and trematodes)
 - High activity against liver flukes
 - High activity against hookworm; else, similar to albendazole
 - FDA registration ongoing
- **Oxantel pamoate**
 - Excellent trichuricidal drug, no longer marketed
- **Ivermectin**
 - On the essential medicine list
 - Activity against filarial infections, *A. lumbricoides* and *S. stercoralis*
- **Moxidectin**
 - FDA registration ongoing for onchocerciasis
 - Activity against *S. stercoralis*

Drug combinations

- None of the recommended/alternative drugs covers all soil-transmitted helminth species with acceptable efficacy at a single dose
→ **broaden the spectrum of efficacy**
- Treating simultaneously with 2 drugs from different anthelmintic classes (e.g. benzimidazoles, macrocyclic lactones)
→ **slow development/ prevent drug resistance**
- Increased efficacy? Not known whether drug combinations exhibit
→ **synergistic effects**

Drug combination tiers

Expert meeting in Seattle (March 2016) identified priority combinations based on available evidence

Tier 1: albendazole + ivermectin

Tier 2: albendazole + oxantel (or oxantel/pyrantel)

Tier 3: tribendimidine and moxidectin combinations

Tier 4: novel treatments, e.g. emodepside plus partner drug

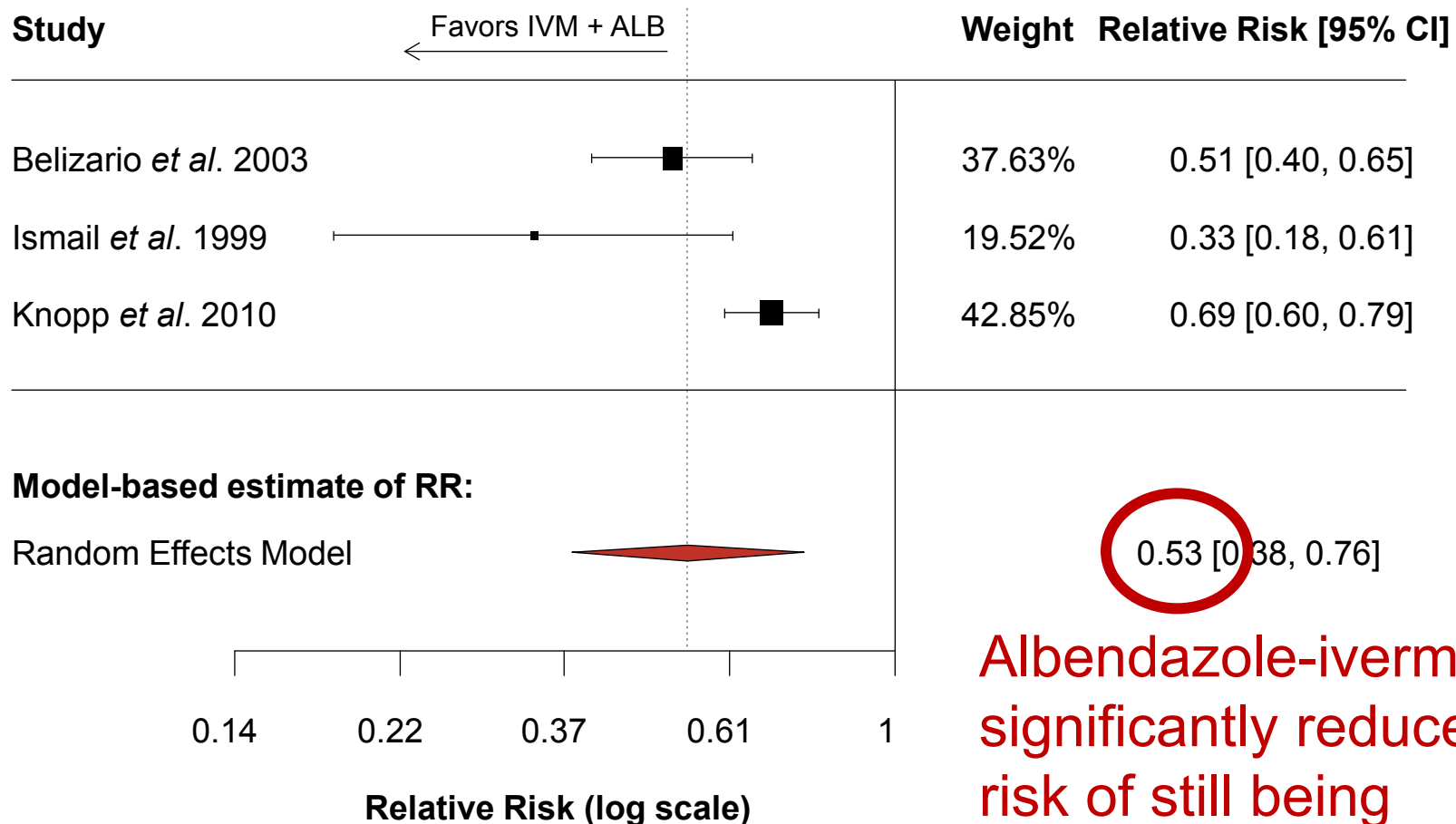
Tier 1: Albendazole-ivermectin



- BMGF grant (“Optimizing Drug Therapy against Soil-Transmitted Helminthiasis”) since 11/2016
- Combination included in Essential Medicine List for treatment of soil-transmitted helminthiasis early 2017
- Meta-analysis on efficacy and safety, analysis of individual patient data:
- 466 studies screened, 4 studies identified

Study	IVM + ALB	ALB alone	IVM alone	Studied parasites
Belizario <i>et al.</i> , 2003	X	X	X	<i>T. trichiura</i> , <i>A. lumbricoides</i>
Speich <i>et al.</i> , 2015	X			<i>T. trichiura</i> , <i>A. lumbricoides</i> , hookworm
Knopp <i>et al.</i> , 2010	X	X		<i>T. trichiura</i> , <i>A. lumbricoides</i> , hookworm
Ismail <i>et al.</i> , 1999	X	X		<i>T. trichiura</i>

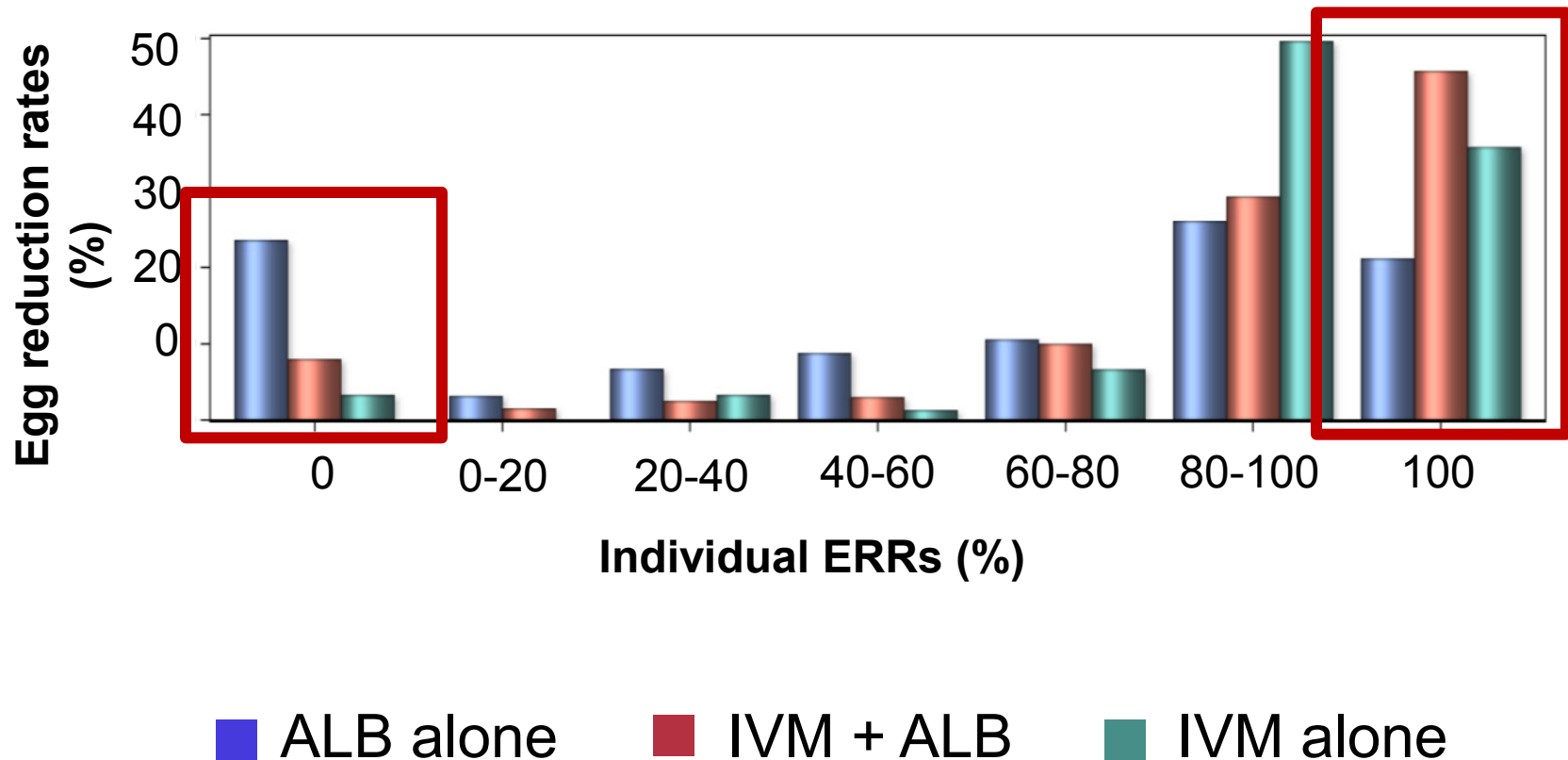
Albendazole-ivermectin versus albendazole *T. trichiura*



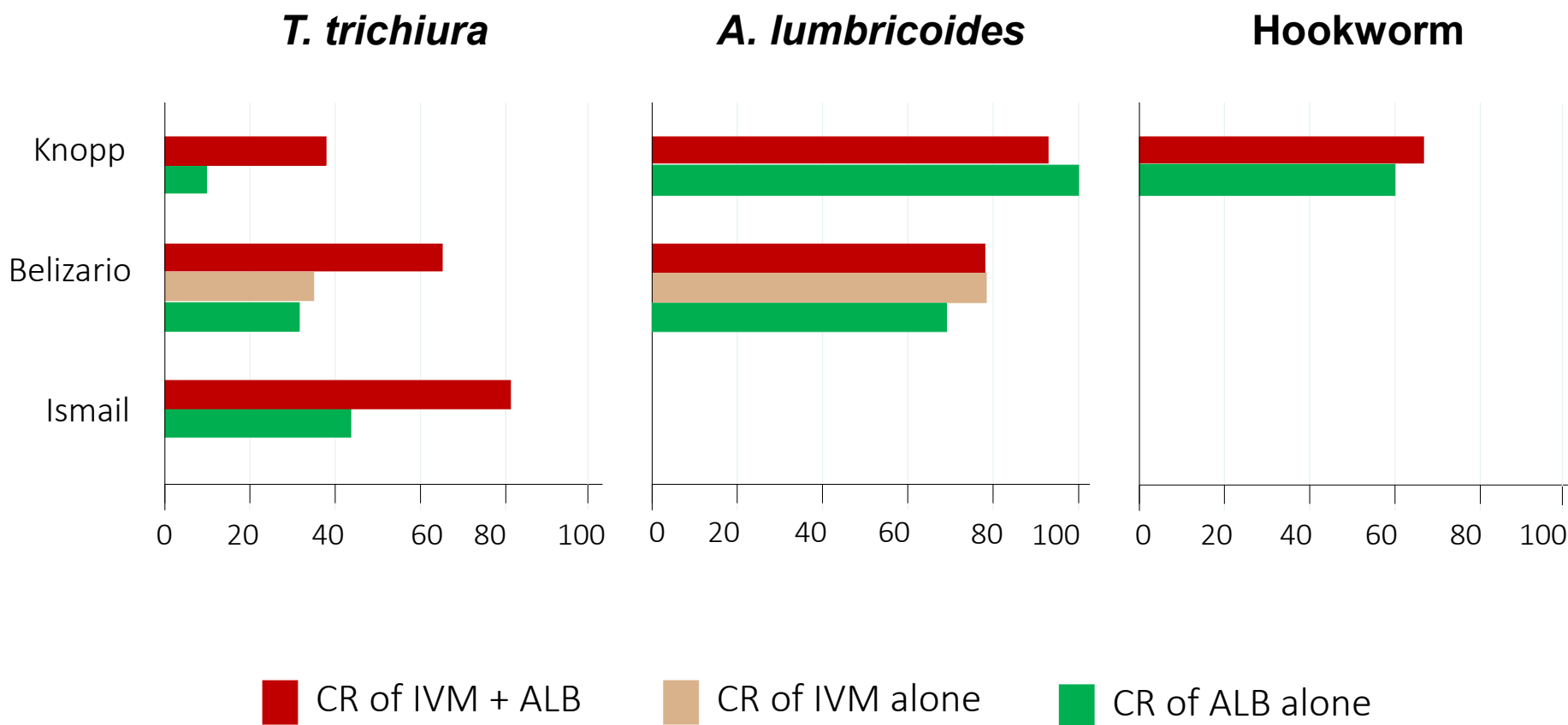
0.53 [0.38, 0.76]

Albendazole-ivermectin significantly reduces the risk of still being infected after treatment

Egg reduction rates in *T. trichiura* patients



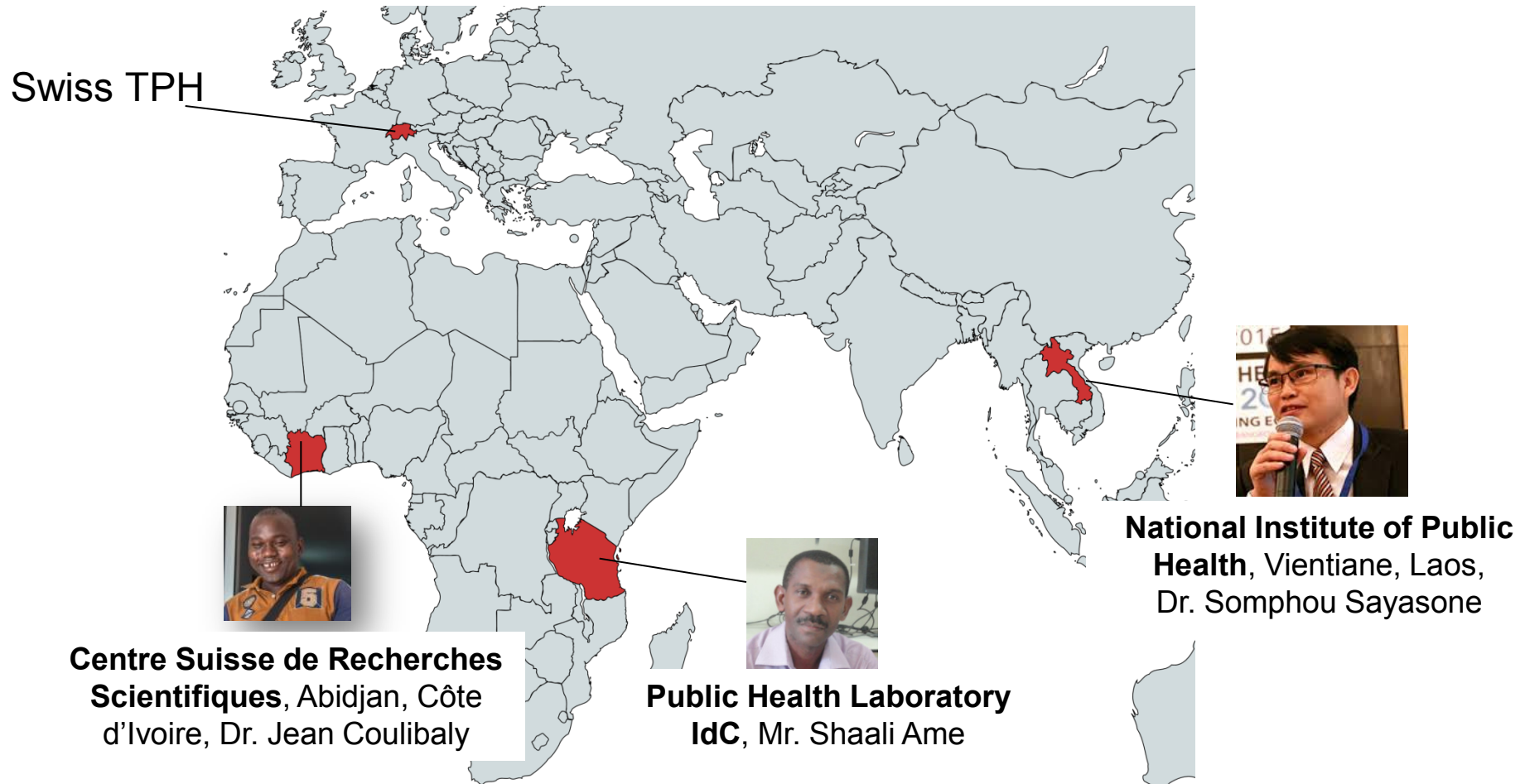
No greater benefit against hookworm and *A. lumbricoides*



Tier 1: Albendazole-ivermectin

- Multi-country/continent study planned:
- Evaluation of safety and efficacy of albendazole-ivermectin *versus* albendazole in Tanzania, Laos and Côte d'Ivoire
- Sample size: n=600 (300 per arm) per site
- One baseline and three follow-up assessments at day 21, day 180, and day 360
- Retreatment on day 180 of positive participants according to their trial allocation

Clinical studies





- Evaluation of 2 stool samples pre- and post-treatment (21 days) using the Kato-Katz method for the determination of cure and egg reduction rates

Clinical examination and treatment



Tier 2: Albendazole-oxantel pamoate

- Evidence from 4 studies (2012-2016)

	No.	Cure rates (95%CI)	Egg reduction rates (95%CI)
<i>A. lumbricoides</i>	312	95.5 (84.9-98.8)	98.9 (91.6-100.0)
Hookworm	395	66.1 (38.6-85.6)	85.7 (68.7-100.0)
<i>T. trichiura</i>	519	75.0 (44.8-91.7)	93.6 (79.3-100.0)

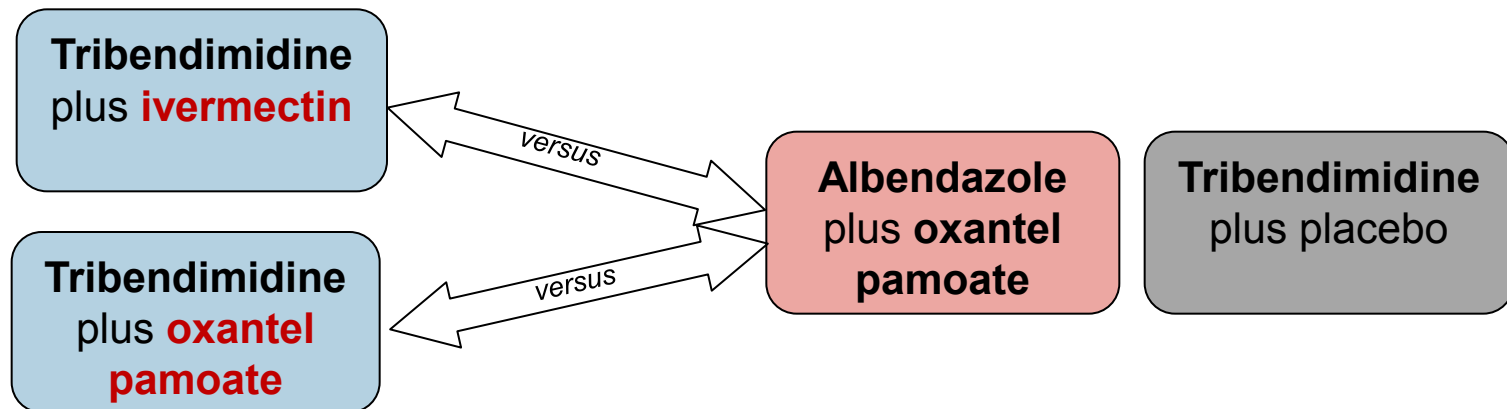
- Oxantel pamoate can be administered by weight independent dose (500 mg)



Tier 3: Tribendimidine combinations



Randomized trial on Pemba and in Côte d'Ivoire in 2016



Primary outcome: egg reduction rate against hookworm, assessed for non-inferiority (3% margin)

Secondary outcomes: safety, efficacy against *T. trichiura* and *A. lumbricoides*

Sample size: 640 adolescents aged 15-20 years (n=400 Pemba, 240 Côte d'Ivoire; 160 per treatment arm)

Results: Efficacy

Hookworm

TRB-IVER vs. ALB-OXP

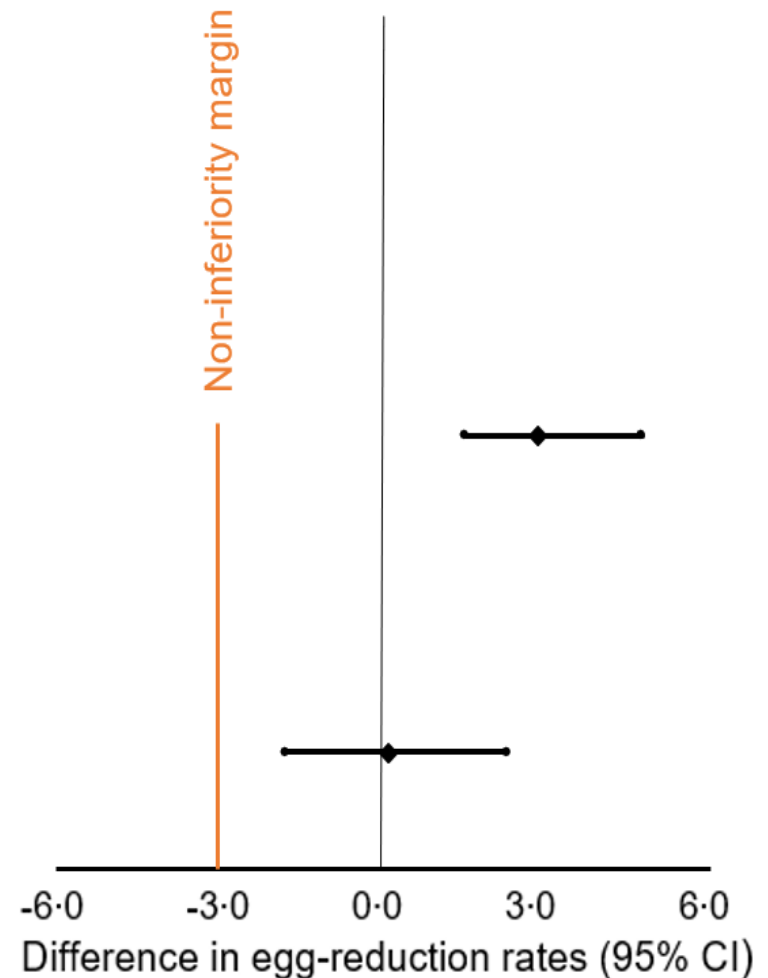
99.5% vs. 96.0%

Difference 3.52 (2.05 to 5.65)

TRB-OXP vs. ALB-OXP

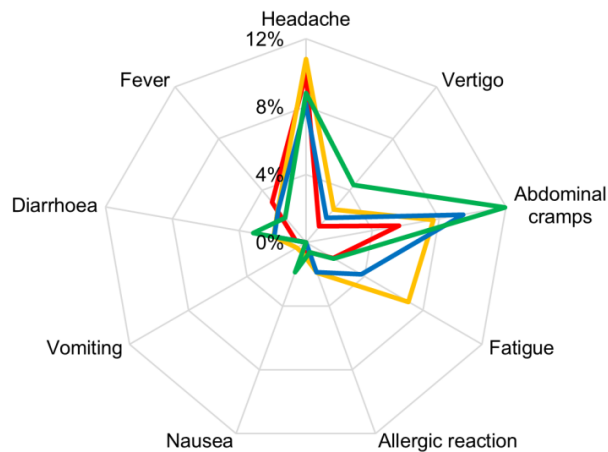
96.5% vs. 96.0%

Difference 0.48 (-1.61 to 2.88)

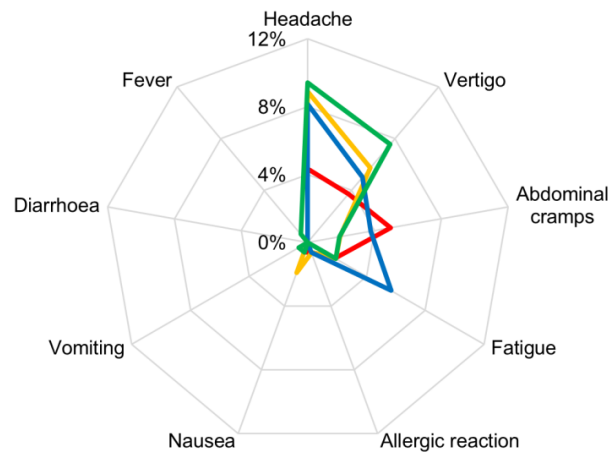


Results: Adverse events

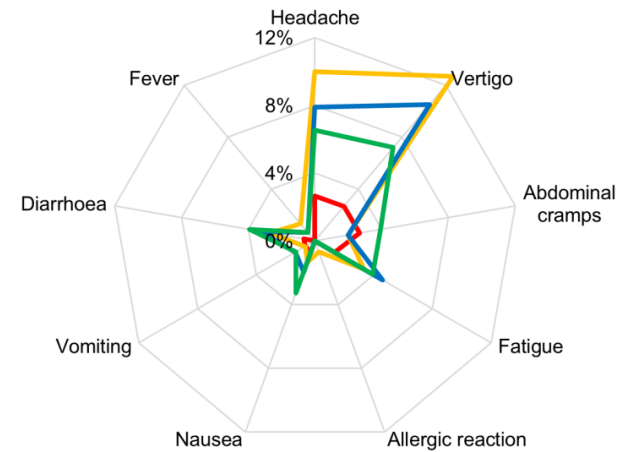
Pre-treatment



3 hours post-treatment



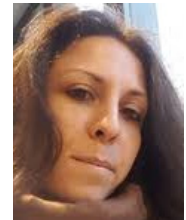
24 hours post-treatment



— Tribendimidine
 — Tribendimidine plus ivermectin
 — Tribendimidine plus oxantel pamoate
 — Albendazole plus oxantel pamoate

Efficacy and safety of tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel pamoate, and albendazole plus oxantel pamoate against hookworm and concomitant soil-transmitted helminth infections in Tanzania and Côte d'Ivoire: a randomised, controlled, single-blinded, non-inferiority trial





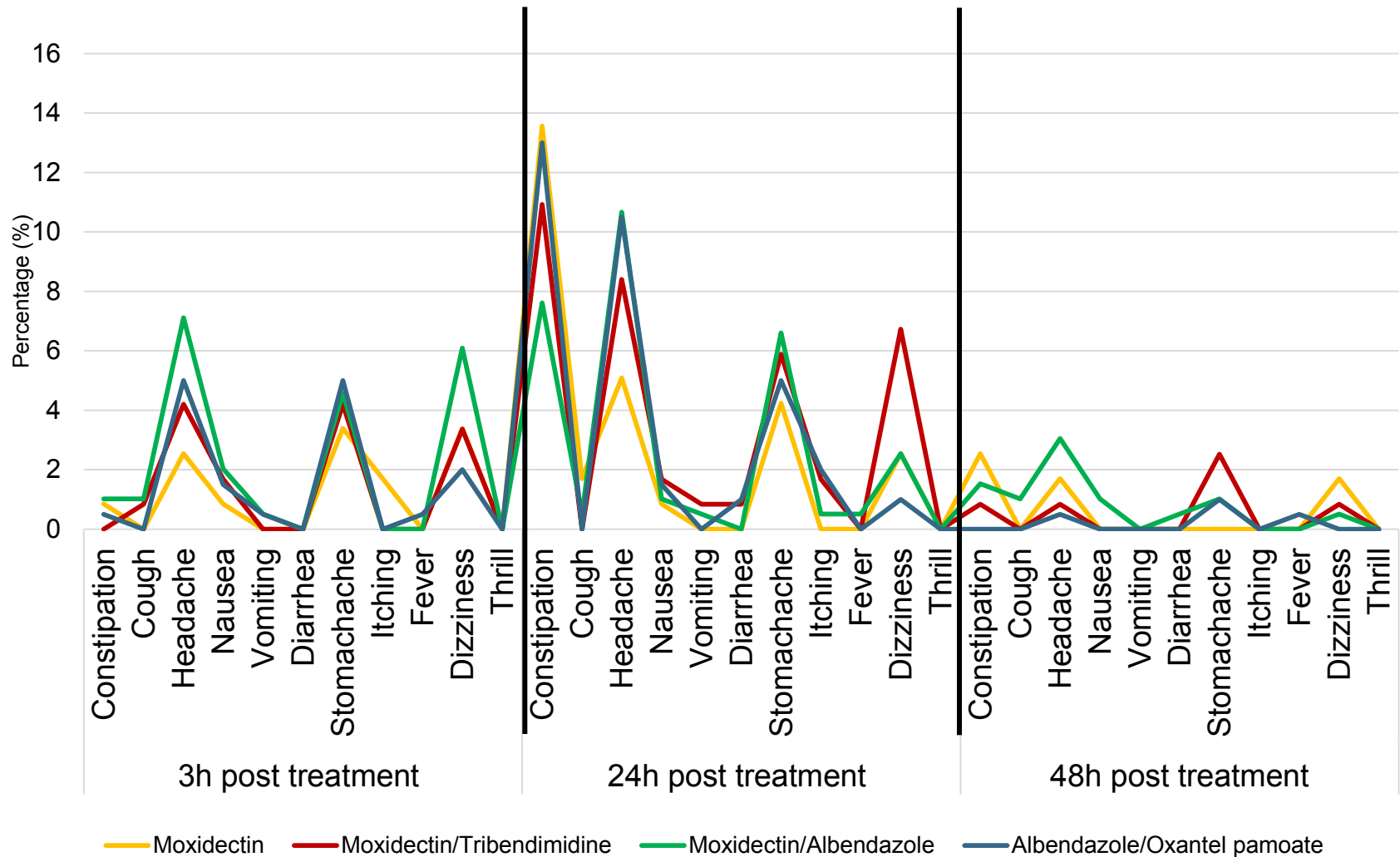
Tier 3: Moxidectin combinations

- Randomized controlled trial on Pemba, Tanzania in 2017

Albendazole (400 mg)	Oxantel pamoate (25 mg/kg)
Moxidectin (8 mg)	Placebo
Moxidectin (8 mg)	Albendazole (400 mg)
Moxidectin (8 mg)	Tribendimidine (400 mg)

- Moxidectin-albendazole not inferior to albendazole-oxantel (egg reduction rate against *T. trichiura*)
- Moxidectin-albendazole *versus* moxidectin
- Moxidectin-albendazole *versus* moxidectin-tribendimidine
- Sample size: 640 adolescents aged 15-20 years

Results: Adverse events



Tier 4: Novel drugs--emodepside

- Veterinary anthelmintic used in dogs and cats
- Development by DNDi for the treatment of onchocerciasis ongoing
- Hookworm and whipworm *in vitro* and *in vivo* models at Swiss TPH
- High activity against *T. muris* in vivo: ED₅₀ of 2.25 mg/kg
- High activity against *N. americanus* in vivo: ED₅₀ of 1.4 mg/kg
- *A. ceylanicum* evaluation ongoing



A. ceylanicum L3



T. muris L1

Conclusion

- Drug combinations are the way forward for the treatment of soil-transmitted helminthiases
- Generated a large body of evidence on the efficacy of different drug combinations
- Oxantel pamoate combinations reveal highest efficacy against *T. trichiura* infections followed by ivermectin or moxidectin combinations
- Tribendimidine has high efficacy against hookworm, particular in combination with ivermectin and moxidectin (synergism?)
- Triple dose therapy pyrantel-oxantel pamoate-albendazole significant higher activity than co-administrations with 2 drugs
- Availability of drugs need to be secured
- Emodepside might be a promising alternative anthelmintic drug alone or in combination

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