PAGE, Rome Italy, 27th June 2024

Optimizing dosing strategies for post-kala-azar dermal leishmaniasis:
a geographical comparison of systemic and skin pharmacokinetics and pharmacodynamics of antileishmanial drugs

Wendy Chu [1,2], Fabiana Alves [3], Alwin Huitema [2,4,5], Thomas Dorlo [1,2]

UPPSALA UNIVERSITET

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENH(

DNDi
Best Science for the Most Neglected

1. Uppsala University, Uppsala, Sweden
2. Netherlands Cancer Institute, Amsterdam, the Netherlands
3. Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland
4. Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
5. University Medical Centre Utrecht, Utrecht, the Netherlands

Leishmaniasis

Leishmaniasis

- Neglected Tropical Disease
- Caused by *Leishmania* parasites
- Transmitted by infected female sandflies
- Affects the poorest populations of the world

> 1 million new cases / year
> 6000 death / year

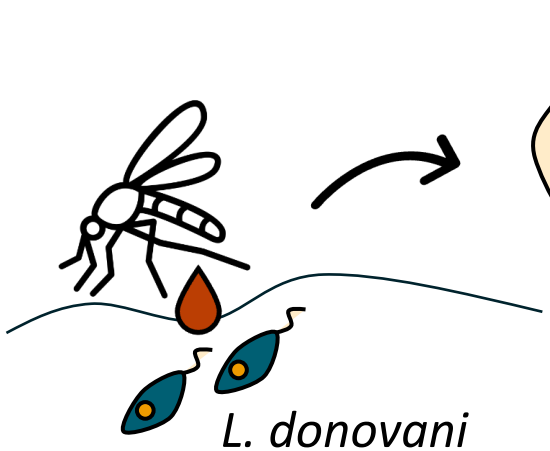
Post-kala-azar dermal leishmaniasis (PKDL)

- Skin complication of Visceral Leishmaniasis (VL, kala-azar)
- Caused by *Leishmania donovani*
- Geographical distribution:

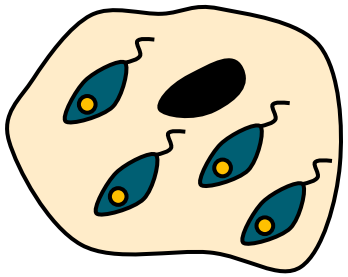
East Africa (Sudan)

South Asia (India, Bangladesh)

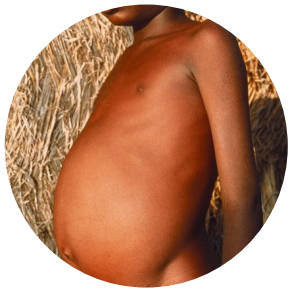
Post-kala-azar dermal leishmaniasis (PKDL)



L. donovani

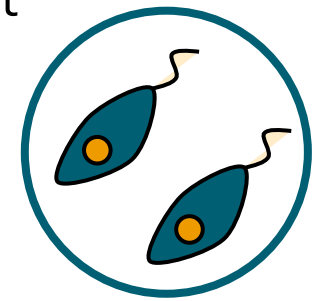


Macrophages

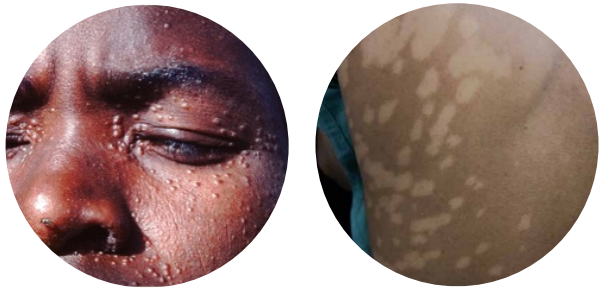


VL

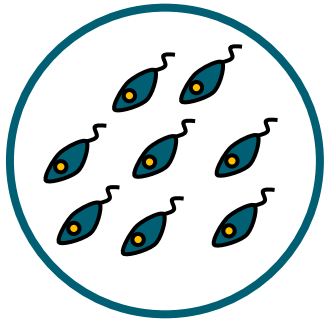
Successful treatment



Evading parasites hide in skin



PKDL skin lesions

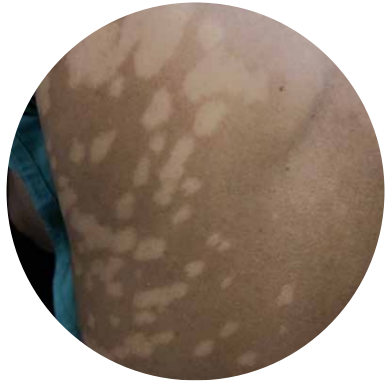


Parasite reservoir

PKDL in East Africa and South Asia

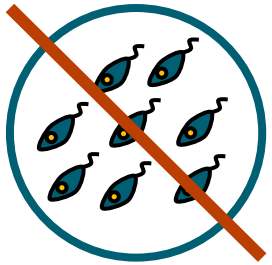
	East Africa	South Asia
Frequency	50-60%	5-10%
Interval	0-6 months	2-3 years
Immunobiology	Immune reactivation	Chronic inflammatory
Spontaneous cure	Yes	No
Age distribution	Children	Children/Young adults
Main lesion type	**Papular lesion**	**Macular lesion**

Small raised bumps



Flat discolored areas

Why it is important to treat PKDL?



Prevent disease (VL) transmission

Established transmission threshold: [1]

Skin parasite load < 416 parasites /µgDNA

Accelerate skin lesion healing

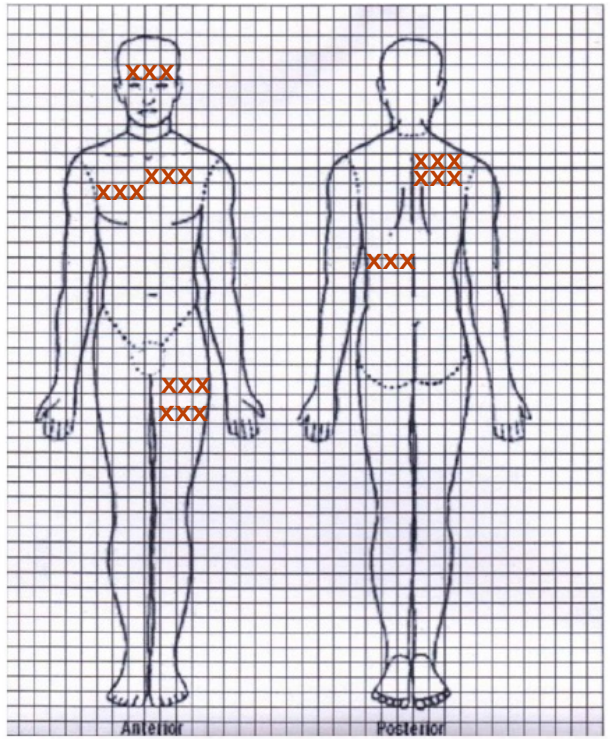
Quantitative efficacy endpoint:

$$\%lesions\ healed = \frac{Lesion\ size_{baseline} - Lesion\ size_{1-year}}{Lesion\ size_{baseline}}$$

1. Mondal et al., Clin Infect Dis, 2019

PKDL scoring system

- Semi-quantitative scoring system for lesion size assessment [2]
- Areas affected by skin lesions were plotted in squares
- Main lesion type (macular or papular) was defined



Example:

Visit	Lesion score	Lesion type
Screening	24	Papular
Day 30	12	Papular
Day 180	4	Papular
Day 365	0	No lesion

2. Mondal *et al, BMJ Open, 2016*

Clinical trials and shortened regimens

	East Africa	South Asia
Current Treatment	IM Sodium stibogluconate **2 months**	Oral Miltefosine **3 months**
Clinical Trial	Liposomal Amphotericin B **7**-day Paromomycin **14**-day + Miltefosine **28- or 42**-day	Liposomal Amphotericin B **15**-day + Miltefosine **21**-day
	 **95%** cure rate at 1-year [3] (quantitative endpoint)	 **30%** cure rate at 1-year [4] (quantitative endpoint)

3. Younis et al., PLoS Negl Trop Dis, 2023
4. Sundar et al., PLoS Negl Trop Dis, 2024 (accepted to be published)

Aims

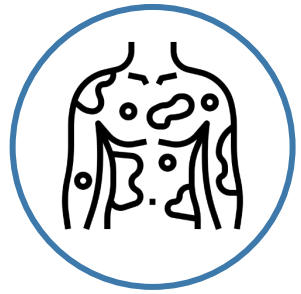
1

Geographical differences in?

Systemic PK

Skin target site PK

Parasite clearance



Lesion healing

2

Better treatment options for PKDL?

Drug-Parasite-Host response model




1. Systemic PK

Plasma
Miltefosine

Plasma
Liposomal AmB

Plasma
Paromomycin

2. Skin target site PK

Skin
Miltefosine

Skin
Liposomal AmB

Skin
Paromomycin

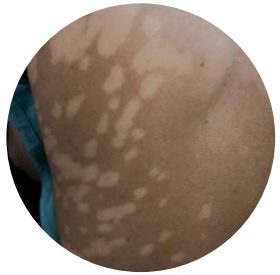
3. Parasite clearance

Skin
Parasite load

4. Lesion healing

Skin lesion
(macular/papular)

Demographics and disease manifestation

Demographics (median, [IQR])	East Africa (n=108) (NCT03399955)	South Asia (n=85) (CTRI/2017/04/008421)
Regimen (n patients)	LAmB 7-day + MF 28-day (n=54) PM 14-day + MF 42-day (n=54)	LAmB 15-day (n=30) LAmB 15-day + MF 21-day (n=55)
Country (n patients)	Sudan (n=108)	India (n=75), Bangladesh (n=10)
Age (years)	9 [7, 10]	24 [16, 38]
Weight (kg)	24 [19, 30]	47 [41, 55]
Main type of lesion	**Papular** 	**Macular** 

Part 1&2: Systemic & skin target site PK


1. Systemic PK | **2. Skin target site PK** | **3. Parasite clearance** | **4. Lesion healing**

1. Systemic PK	2. Skin target site PK	3. Parasite clearance	4. Lesion healing
Plasma Miltefosine	Skin Miltefosine	Skin Parasite load	Skin lesion (macular/papular)
Plasma Liposomal AmB	Skin Liposomal AmB		
Plasma Paromomycin	Skin Paromomycin		

Sampling and model development

Previously developed PK models

Plasma Miltefosine

Plasma Liposomal AmB

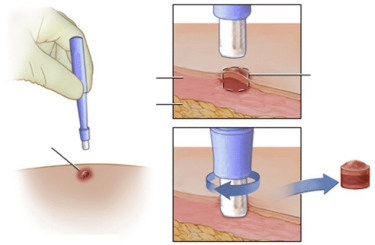
Plasma Paromomycin

$$\frac{dC_{skin}}{dt} = k_{p-s} \times (R_{s:p} \times C_{plasma} - C_{skin})$$

k_{p-s} : *Distribution rate to skin (h^{-1})*

$R_{s:p}$: *Skin to plasma ratio*

1 or 2 skin biopsies were taken around last dose

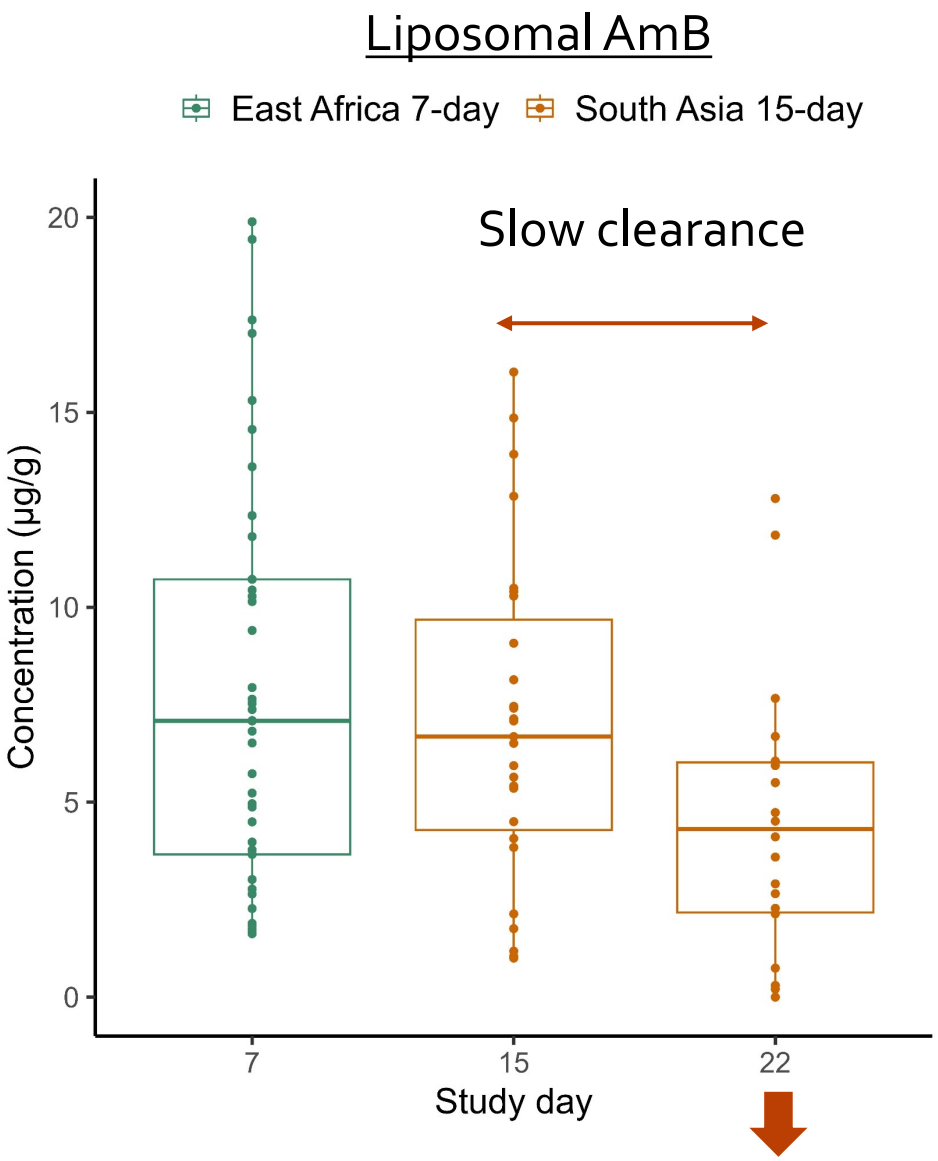


Skin Miltefosine

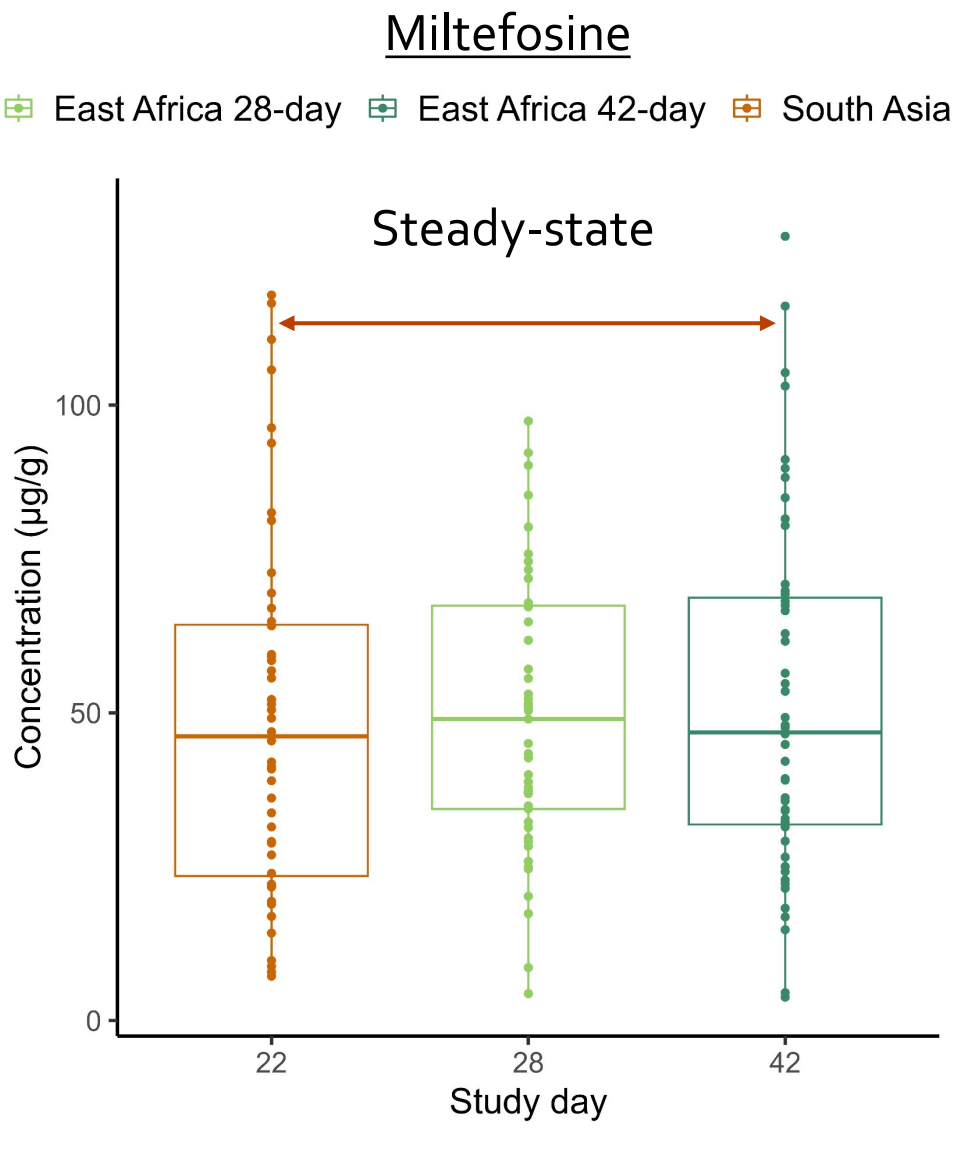
Skin Liposomal AmB

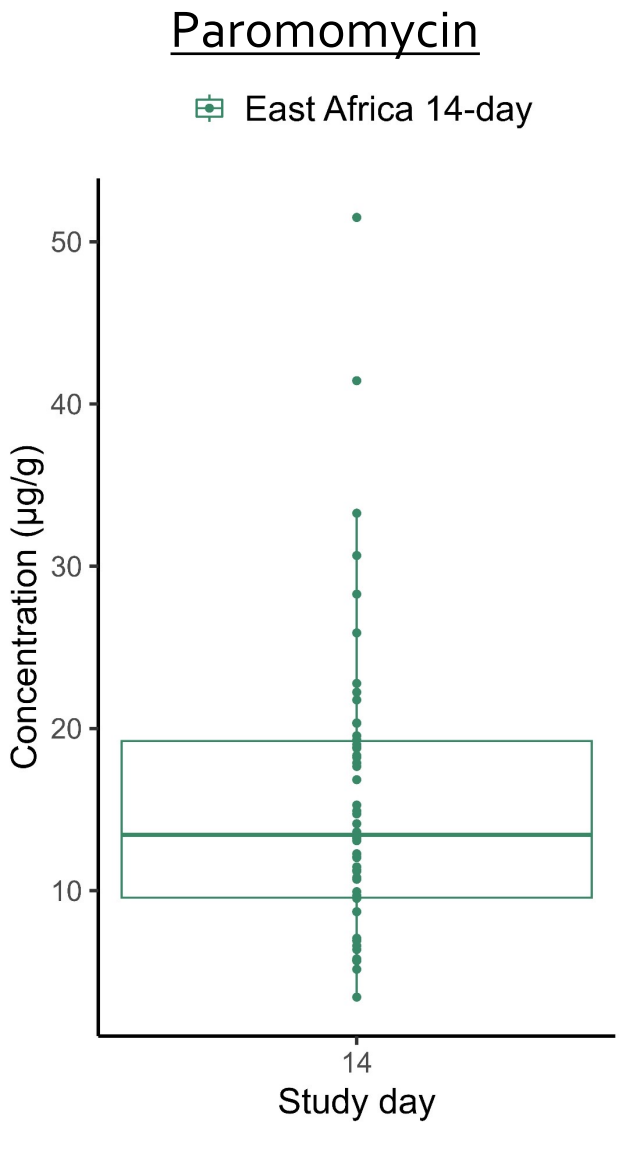
Skin Paromomycin

Observation: skin concentrations



A week after last dose



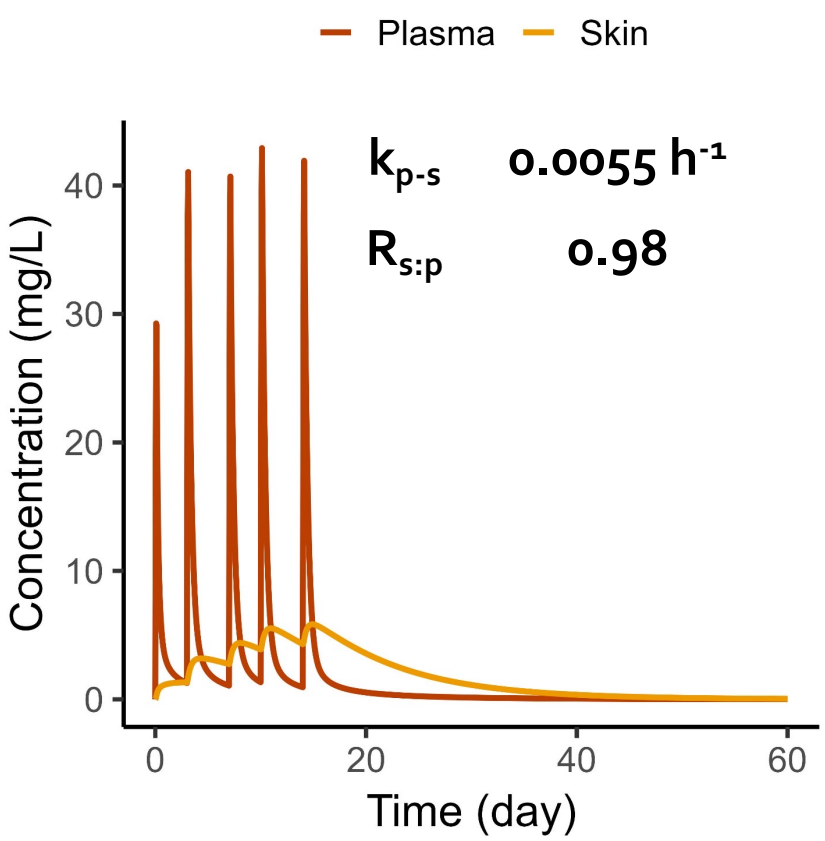


PK in plasma and skin target site

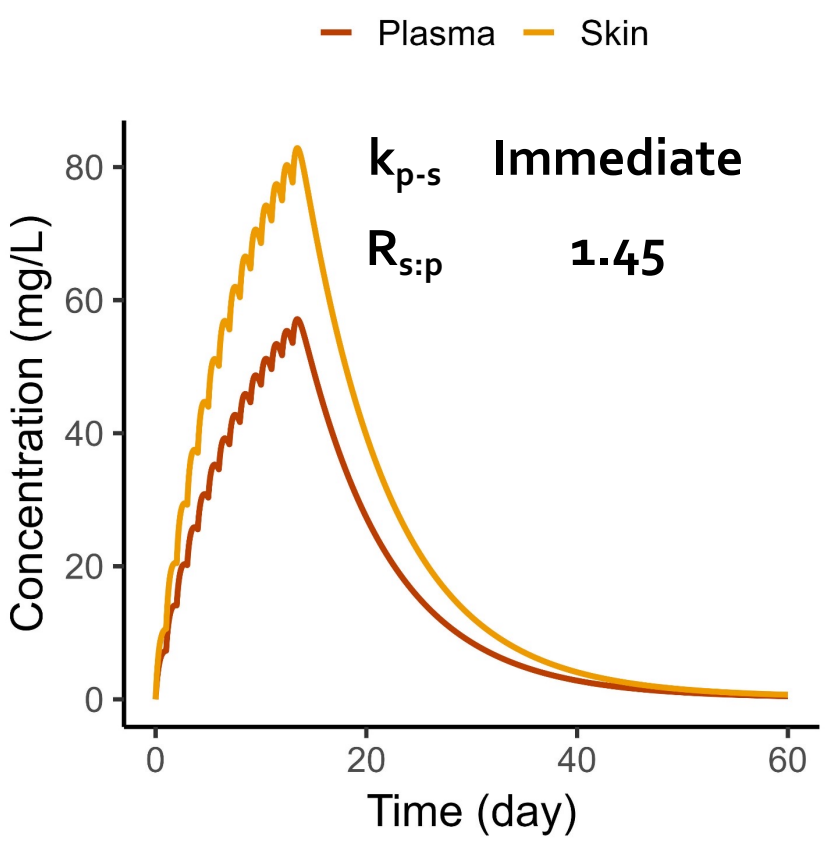
Distribution rate to skin ($k_{p\text{-}s}$)
Skin to plasma ratio ($R_{s:p}$)
Plasma
Skin

Simulation in a typical African patient receiving a 14-day treatment

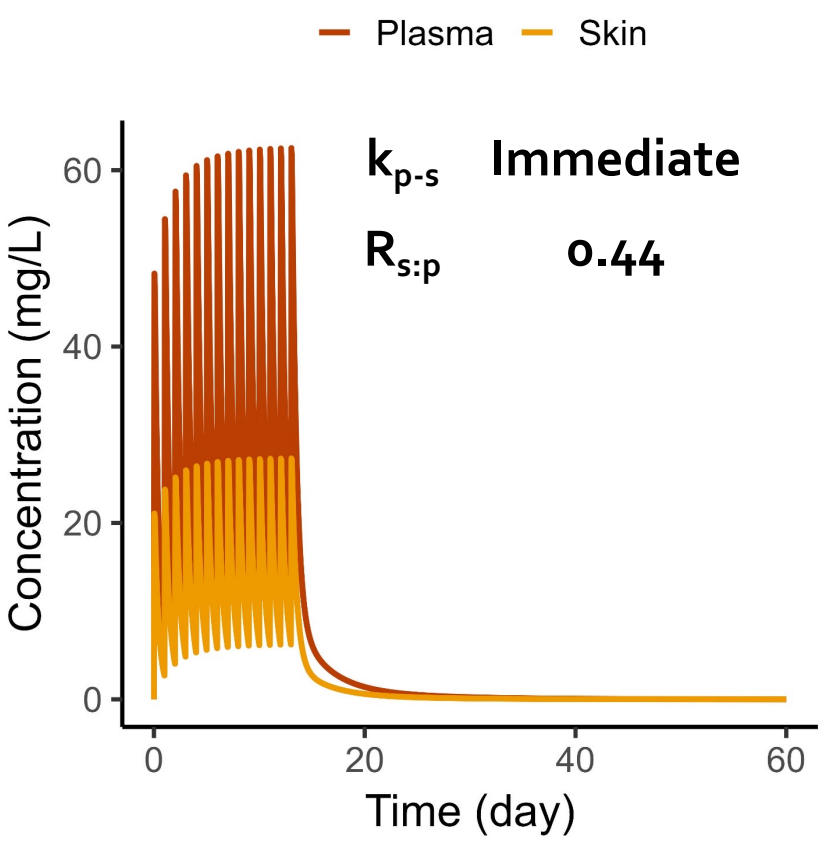
Liposomal AmB



Miltefosine

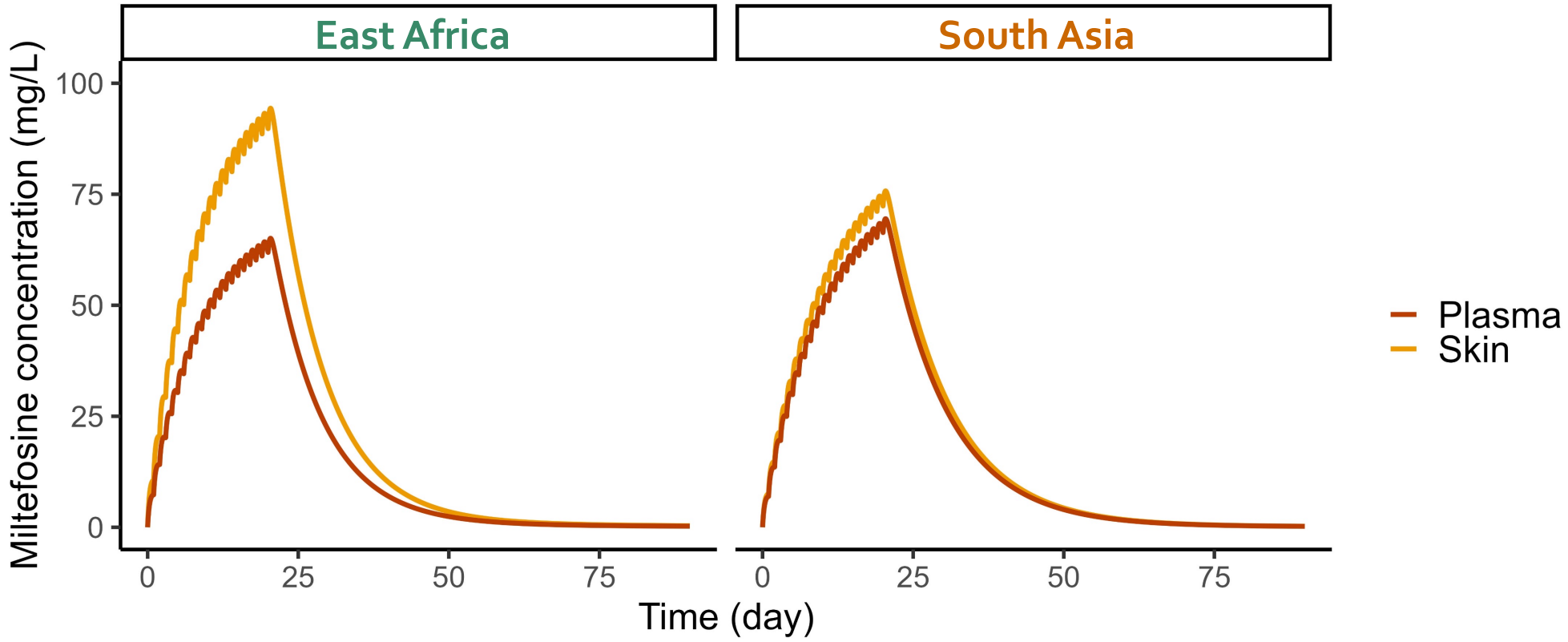


Paromomycin



Geographical differences in PK

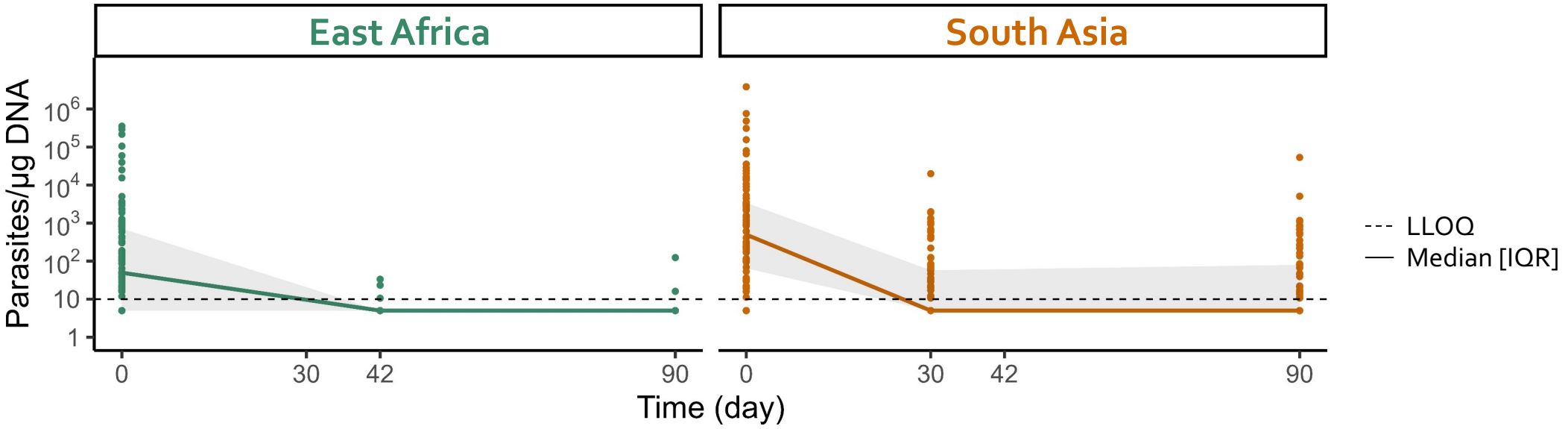
PK parameter	East Africa	South Asia	P-value
Miltefosine relative oral bioavailability (F)	0.85	1	<0.01
Miltefosine skin to plasma ratio ($R_{s:p}$)	1.45	1.09	<0.01

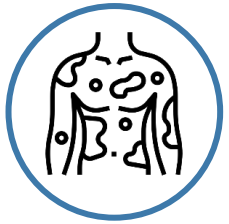


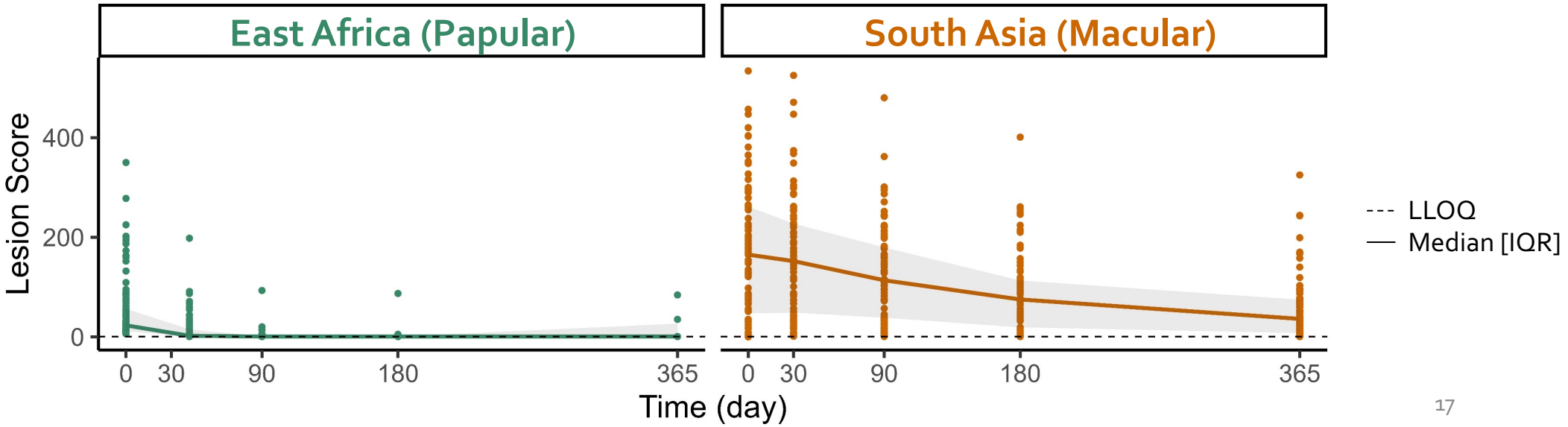
Part 3&4: Parasite load & skin lesion healing

1. Systemic PK	2. Skin target site PK	3. Parasite clearance	4. Lesion healing
Plasma Miltefosine	Skin Miltefosine	Skin Parasite load (qPCR)	Skin lesion (macular/papular)
Plasma Liposomal AmB	Skin Liposomal AmB		
Plasma Paromomycin	Skin Paromomycin		

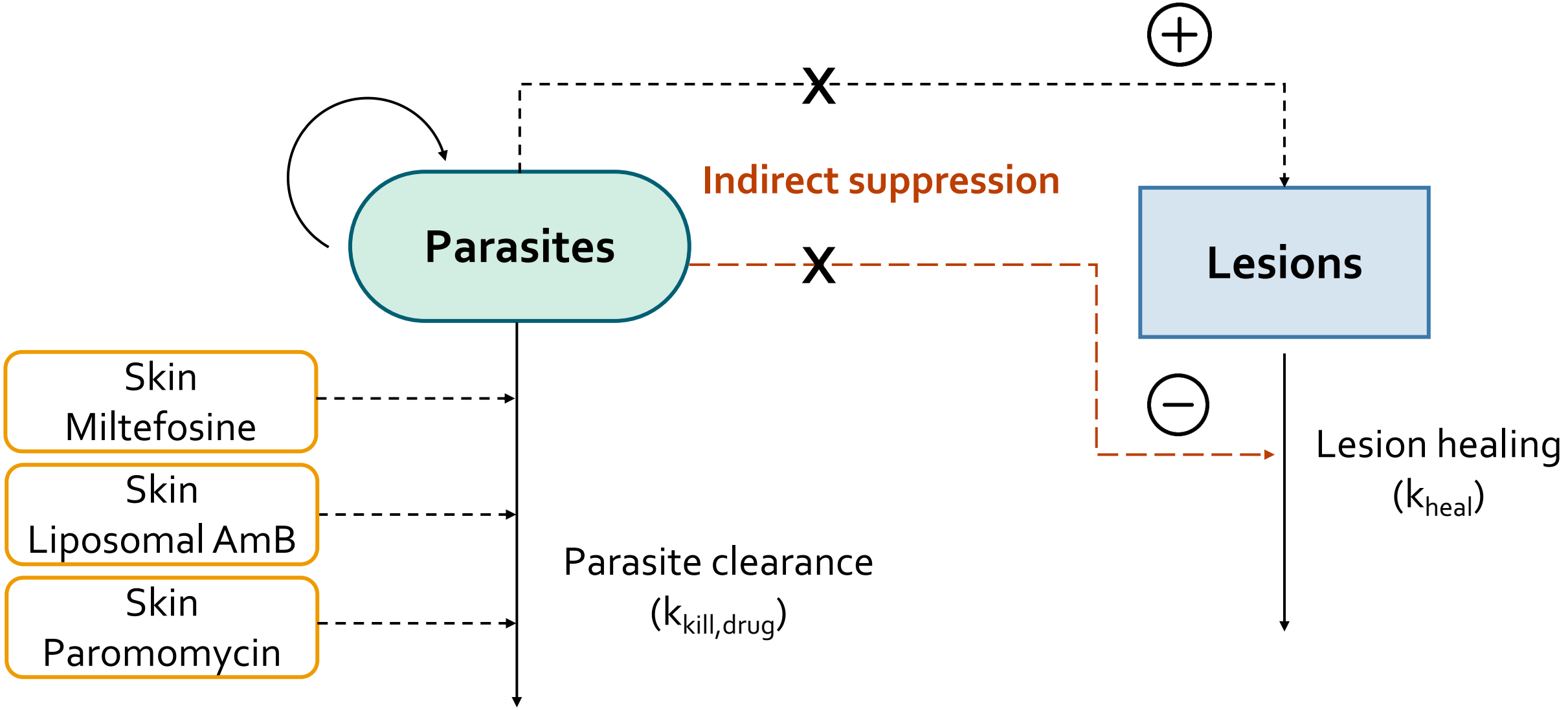
Observation: skin parasite load and lesion size





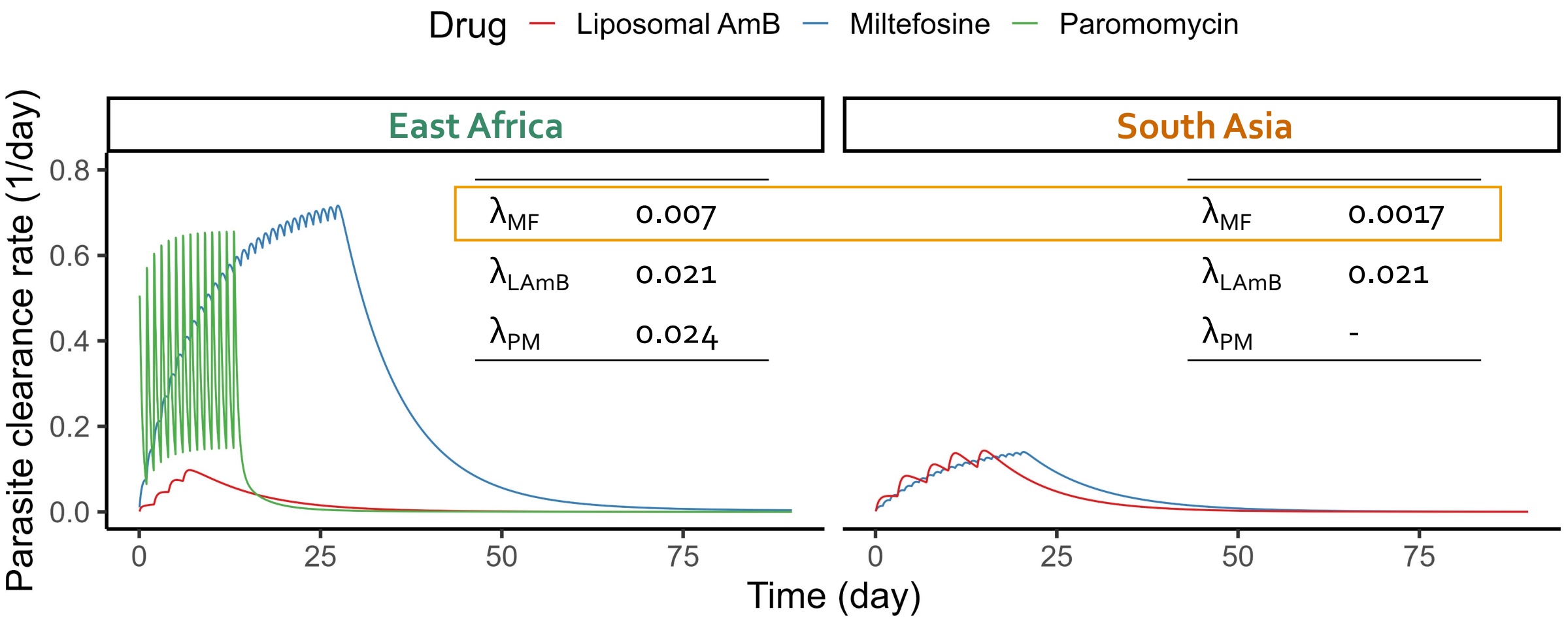


Drug-Parasite-Host response model



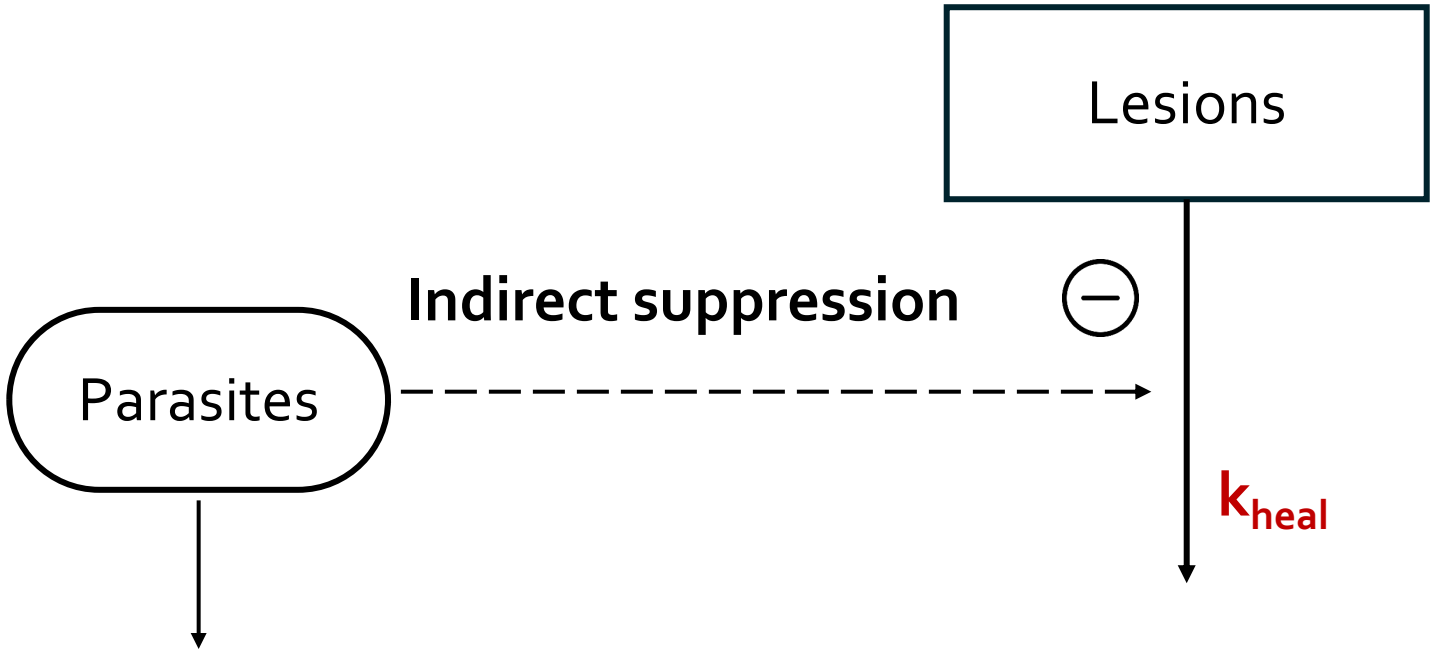
Geographical differences in parasite clearance

Parasite clearance ($kkill_{,drug}$) = $\lambda_{LAmB} * C_{skin,LAmB} + \lambda_{MF} * C_{skin,MF} + \lambda_{PM} * C_{skin,PM}$ (λ = L/mg*day)



East Africa		South Asia	
λ_{MF}	0.007	λ_{MF}	0.0017
λ_{LAmB}	0.021	λ_{LAmB}	0.021
λ_{PM}	0.024	λ_{PM}	-

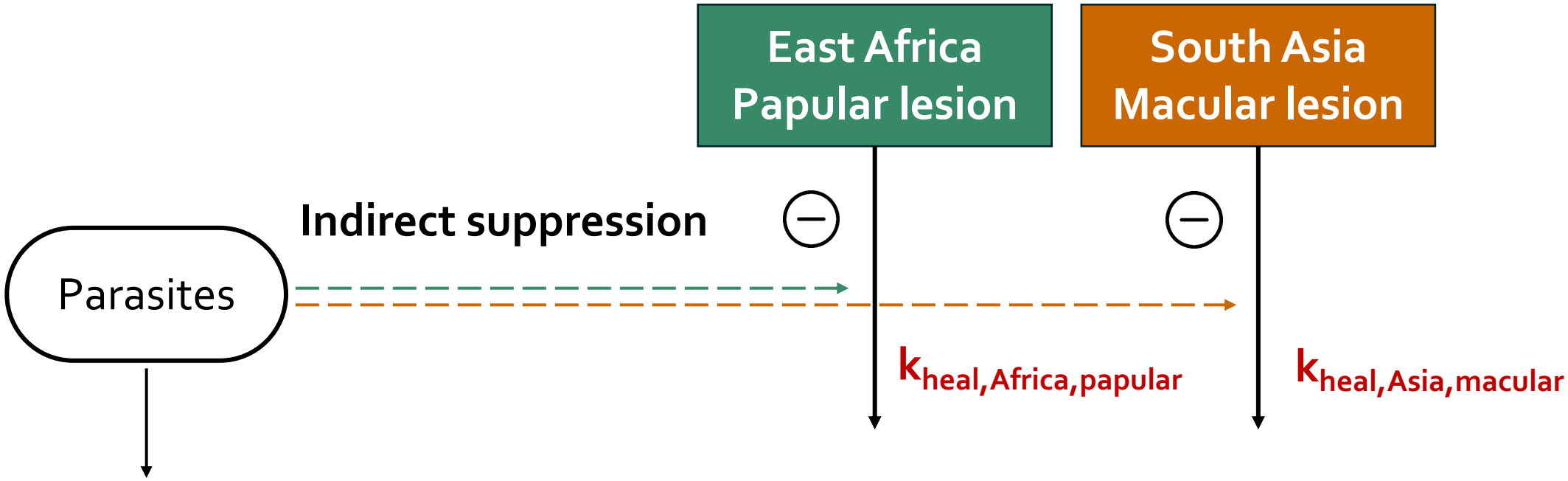
Suppression of lesion healing by parasites



$$k_{heal} * (1 - \frac{I_{max} \times Parasite^{\gamma}}{IP_{50}{}^{\gamma} + Parasite^{\gamma}})$$

I_{max}: Maximal inhibition of 1
IP50: Parasite load achieving 50% inhibition

Geographical differences in lesion healing



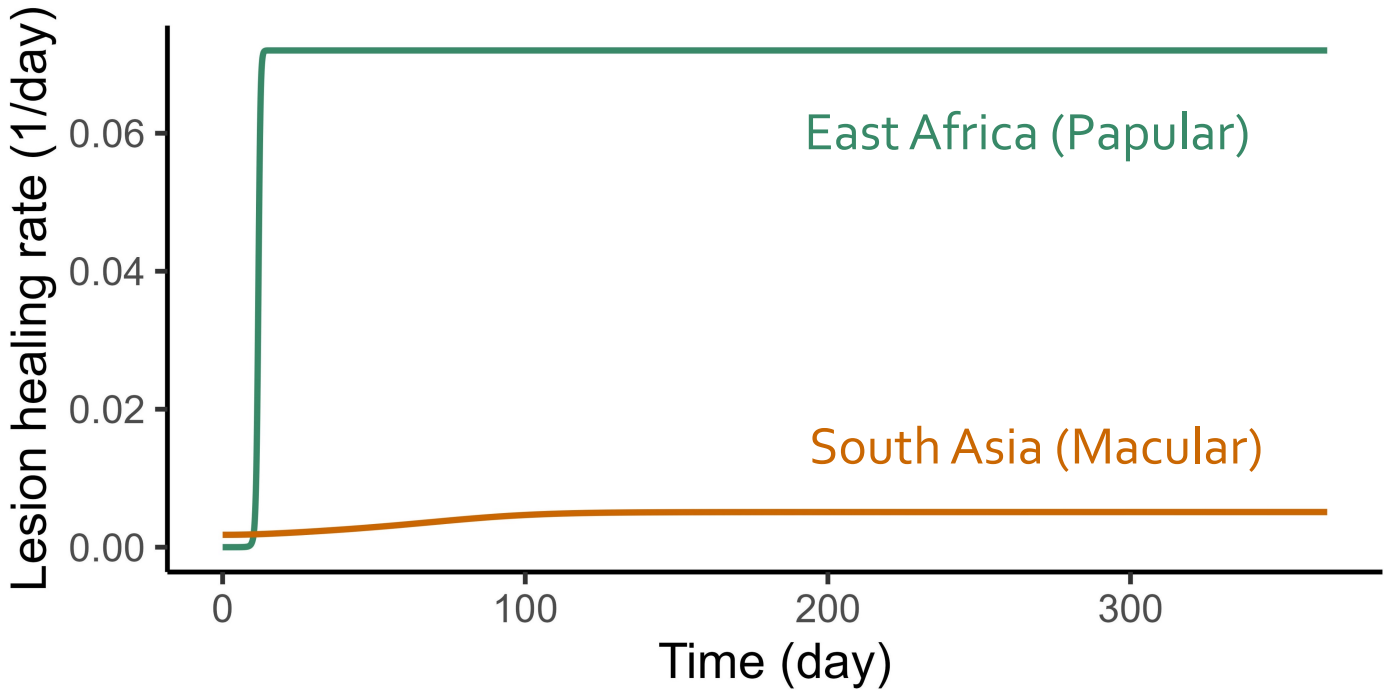
1 Rate of lesion healing differs

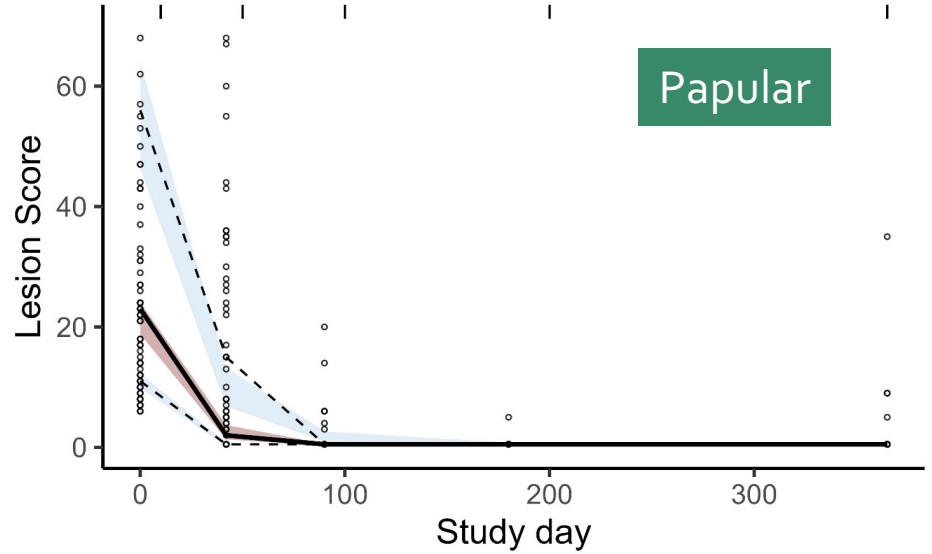
$$k_{heal} * (1 - \frac{I_{max} \times Parasite^{\gamma}}{IP_{50}{}^{\gamma} + Parasite^{\gamma}})$$

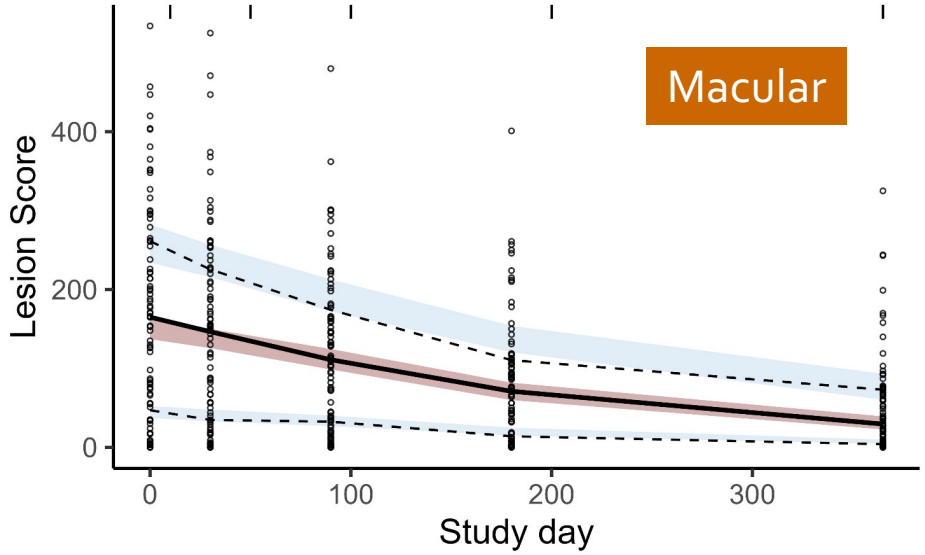
2 Suppression of lesion healing by parasites differs

Geographical differences in lesion healing

Estimate [RSE%]	East Africa (Papular)	BSV	South Asia (Macular)	BSV
Healing half-life by k_{heal} (days)	**10** [15%]	73% [14%]	**120** [7%]	50% [14%]
IP_{50} (*p*/µgDNA)	3	-	63	-
Hill coefficient (Y)	6	-	1.6	-
Mean transit time (days)	-	-	30	249%

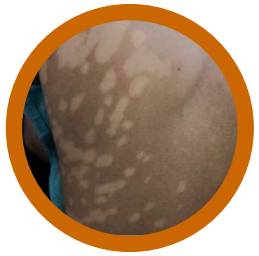




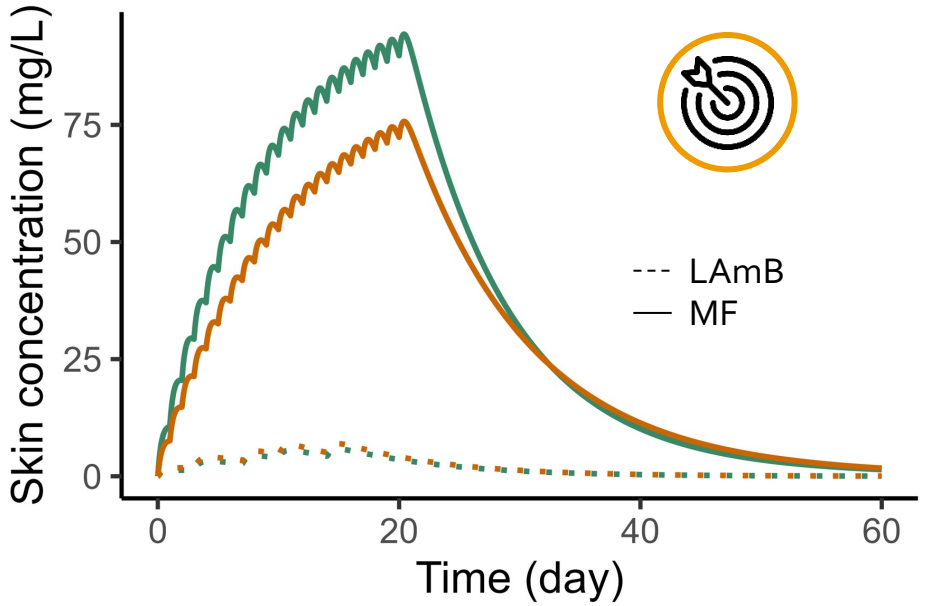


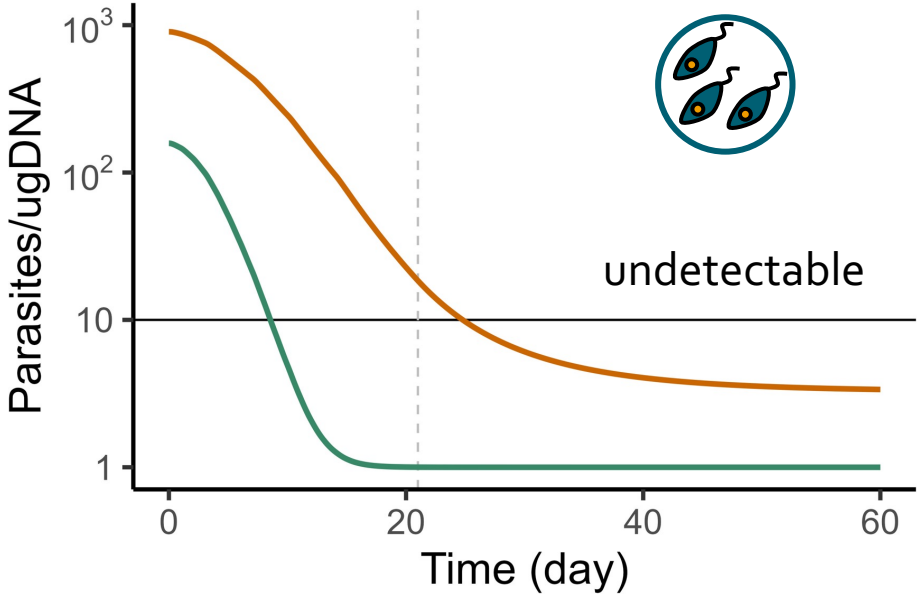
Liposomal AmB 15-day + Miltefosine 21-day in typical patients

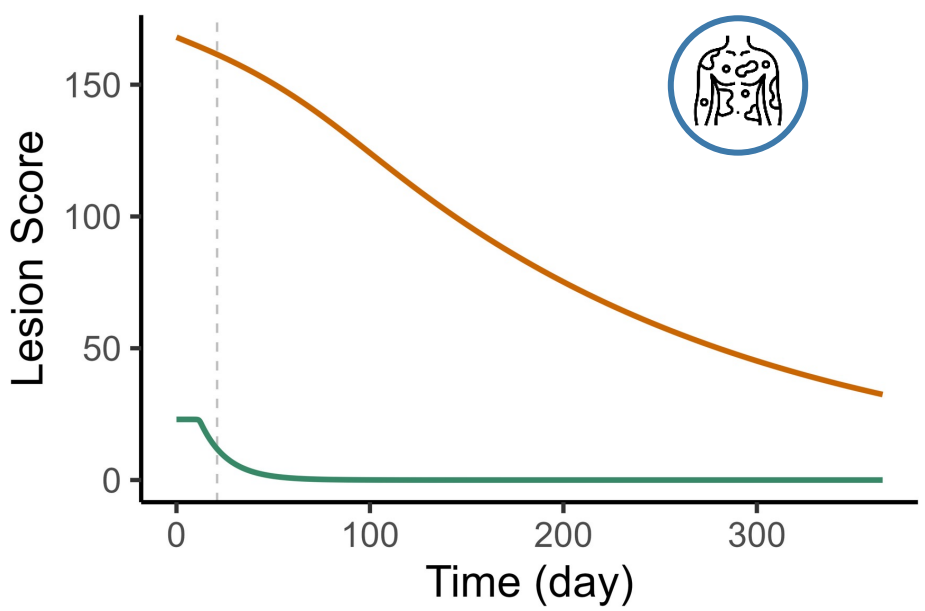
East Africa (Papular)

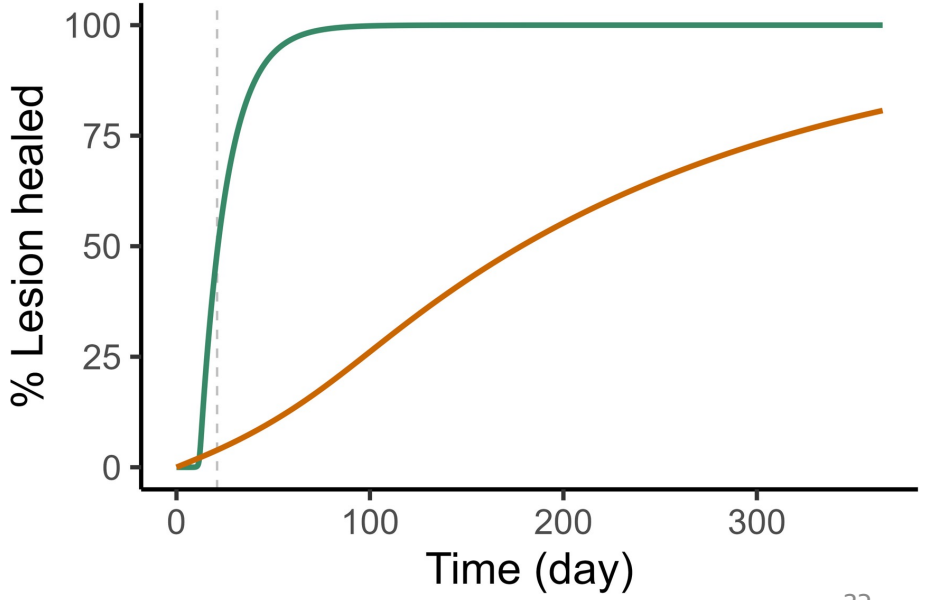


South Asia (Macular)



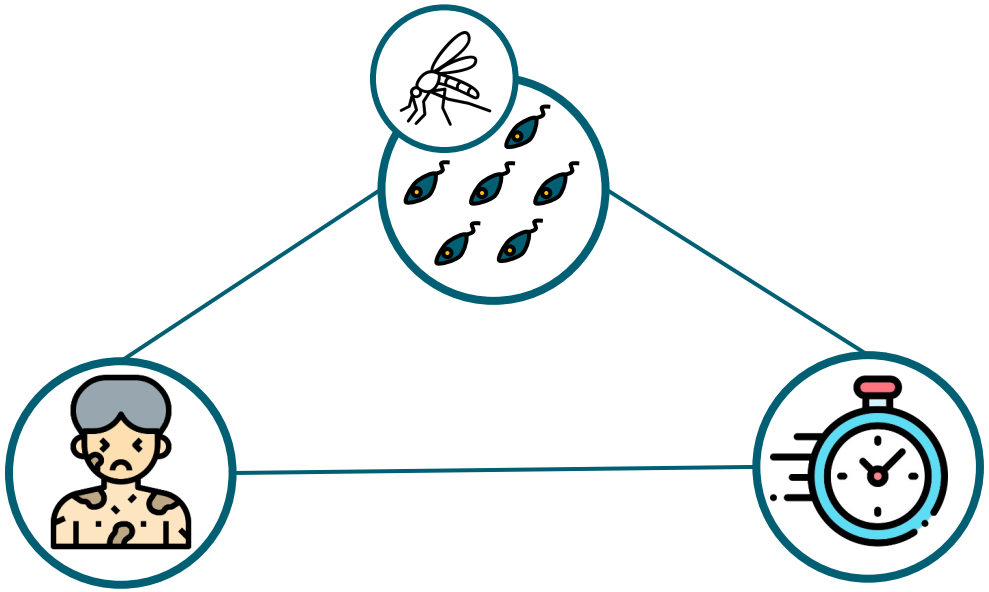






Improve treatment of PKDL

1 Ensure parasite load below established transmission threshold [1]



2 Accelerate lesion healing

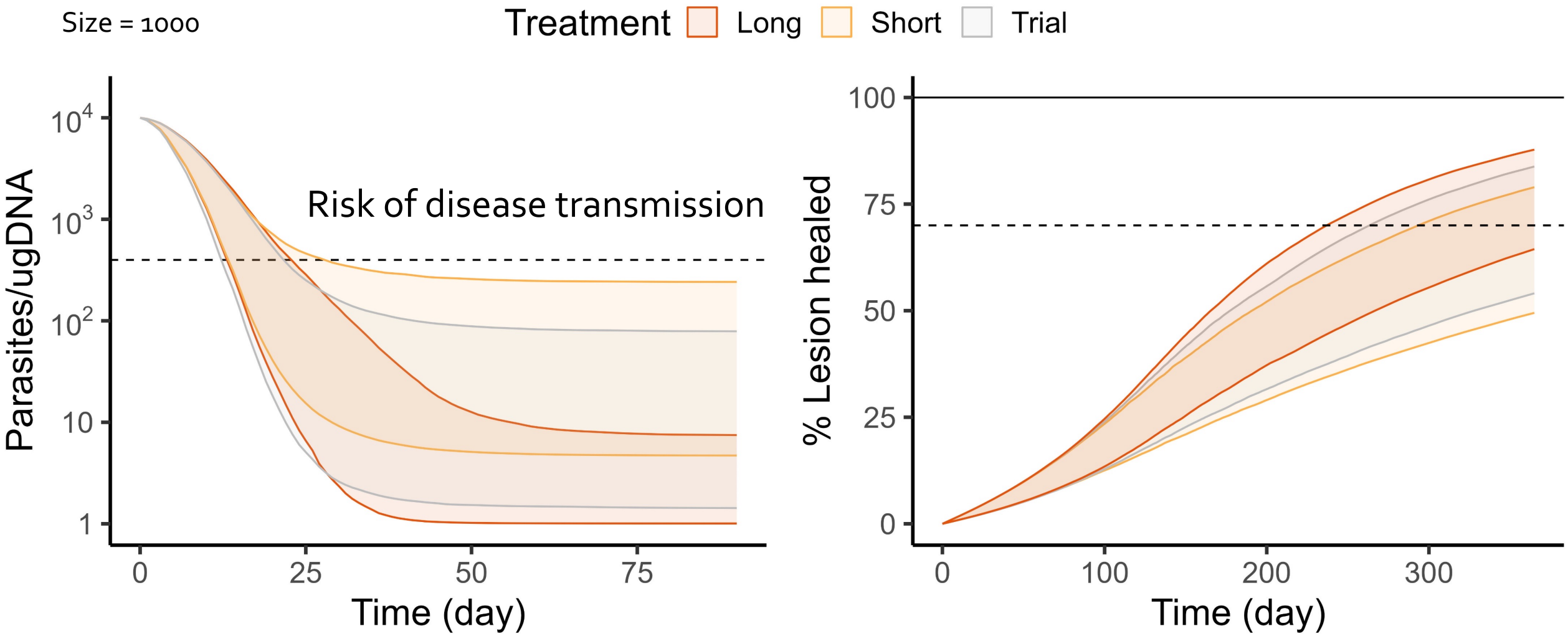
3 Shorten treatment duration

1. Mondal et al., Clin Infect Dis, 2019

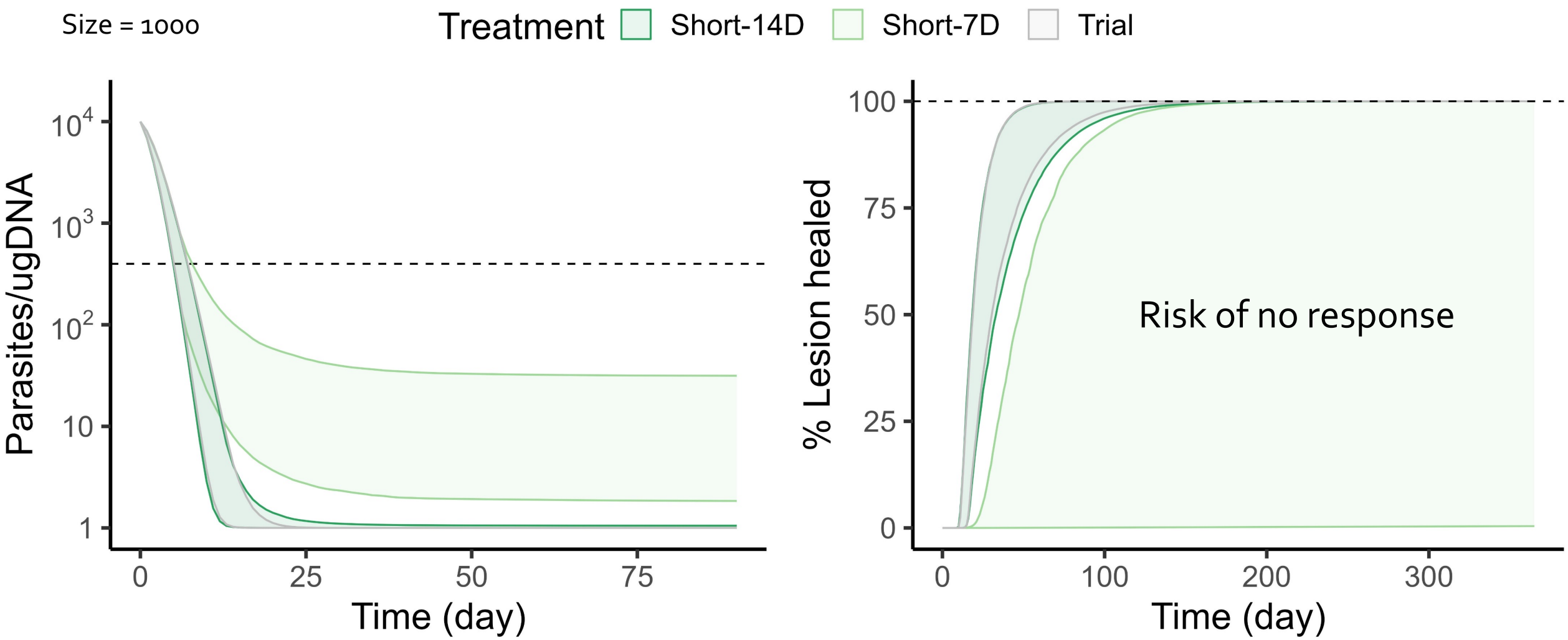
Simulations of severe PKDL cases

	South Asia (Macular)	East Africa (Papular)
Trial regimens	LAmB 15-day MF 21-day	PM 14-day MF 42-day
Simulated regimen 1	LAmB 15-day MF 42-day	PM 14-day MF 14-day
Simulated regimen 2	LAmB 15-day MF 14-day	PM 7-day MF 7-day

Simulation of a severe macular case in South Asia :



Simulation of a severe papular case in East Africa:



Conclusion

Summary of geographical differences

Plasma miltefosine exposure	South Asia	>	East Africa
Skin miltefosine exposure	East Africa	>	South Asia
Miltefosine-induced parasite clearance	East Africa	>	South Asia
Lesion healing rate (half-life)	Papular (10 days)	>>>	Macular (120 days)

Potential treatment optimization

Trial regimens were adequate for preventing disease transmission

→ Shorten treatment in East Africa to 14 days

Correlation between parasite load and lesion healing:

East Africa: PK → Parasite → Lesion

South Asia: PK → Parasite ? Lesion

→ Parasite load as a potential marker for efficacy endpoint in South Asia

Acknowledgement

- **Patients involved in the clinical studies, their families and communities**
- **Principal Investigators, co-investigators, nurses, laboratory personnel, and staff at**
  - Professor El-Hassan Centre for Tropical Medicine, Doka, Sudan
  - University of Khartoum, Khartoum, Sudan
    - Brima Younis, Ahmed Musa
  - Kala-azar Medical Research Center (KAMRC), Muzaffarpur, India
  - Banaras Hindu University, Varanasi, India
    - Shyam Sundar, Om Prakash Singh
  - Rajendra Medical Research Institute of Medical Sciences (RMRIMS), Patna, India
    - Krishna Pandey, Pradeep Das
  - International Centre for Diarrhoeal Disease Research (icddr,b), Bangladesh
    - Dinesh Mondal
- **Instituto de Salud Carlos III, Madrid, Spain**
  - Eugenia Carrillo, Ana Torres
- **Netherlands Cancer Institute, Amsterdam, the Netherlands**
  - Ignace Roseboom, Wietse Schouten
- **Pharmacometrics group, Uppsala University, Uppsala, Sweden**
- **Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland**

UPPSALA UNIVERSITET

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

DNDi
Best Science for the Most Neglected

THANKS FOR LISTENING