Azithromycin for childhood mortality: randomizing entire countries

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Azithromycin for childhood mortality: randomizing entire countries

TANA – Ethiopia

MORDOR – Niger, Tanzania, Malawi

CHAT – Burkina Faso

AVENIR – Niger

AVENIR II – Niger

Azithromycin for childhood mortality: randomizing entire countries

Cluster-randomized

Large Simple Trial

3 arms

Adaptive trial

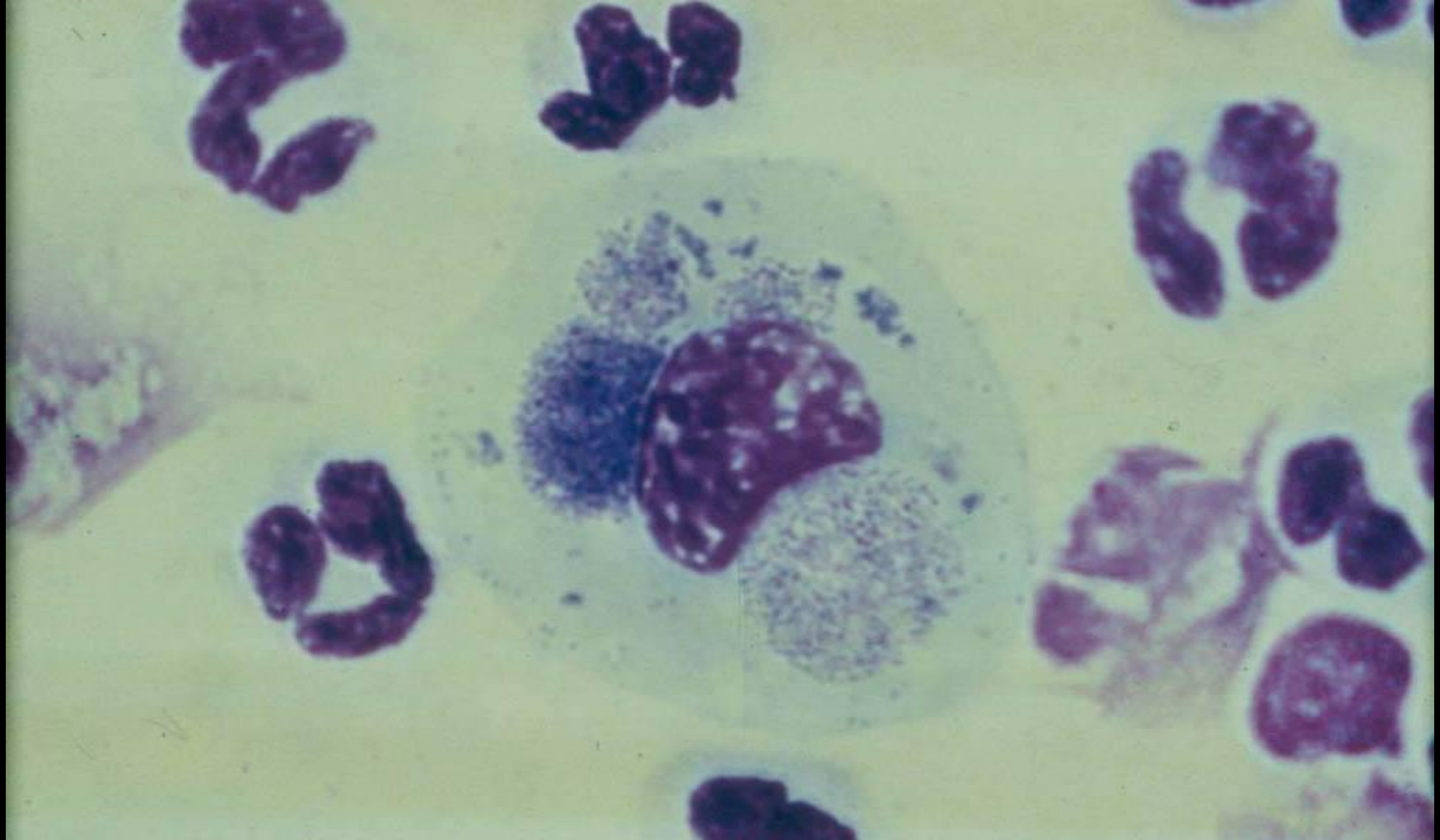
Platform trial

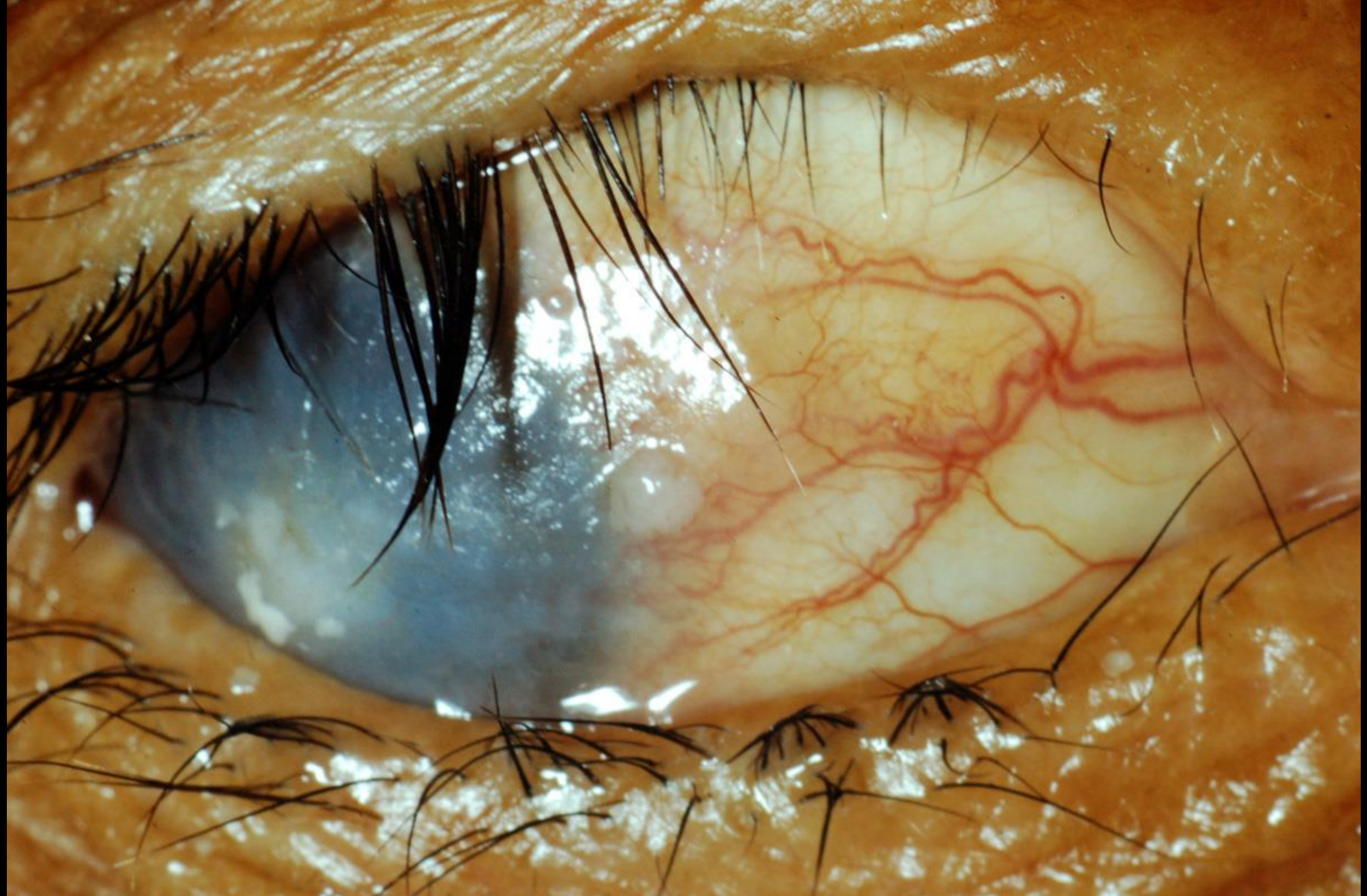
Azithromycin for childhood mortality: randomizing entire countries

Trachoma

Mass distribution of azithromycin

Childhood mortality



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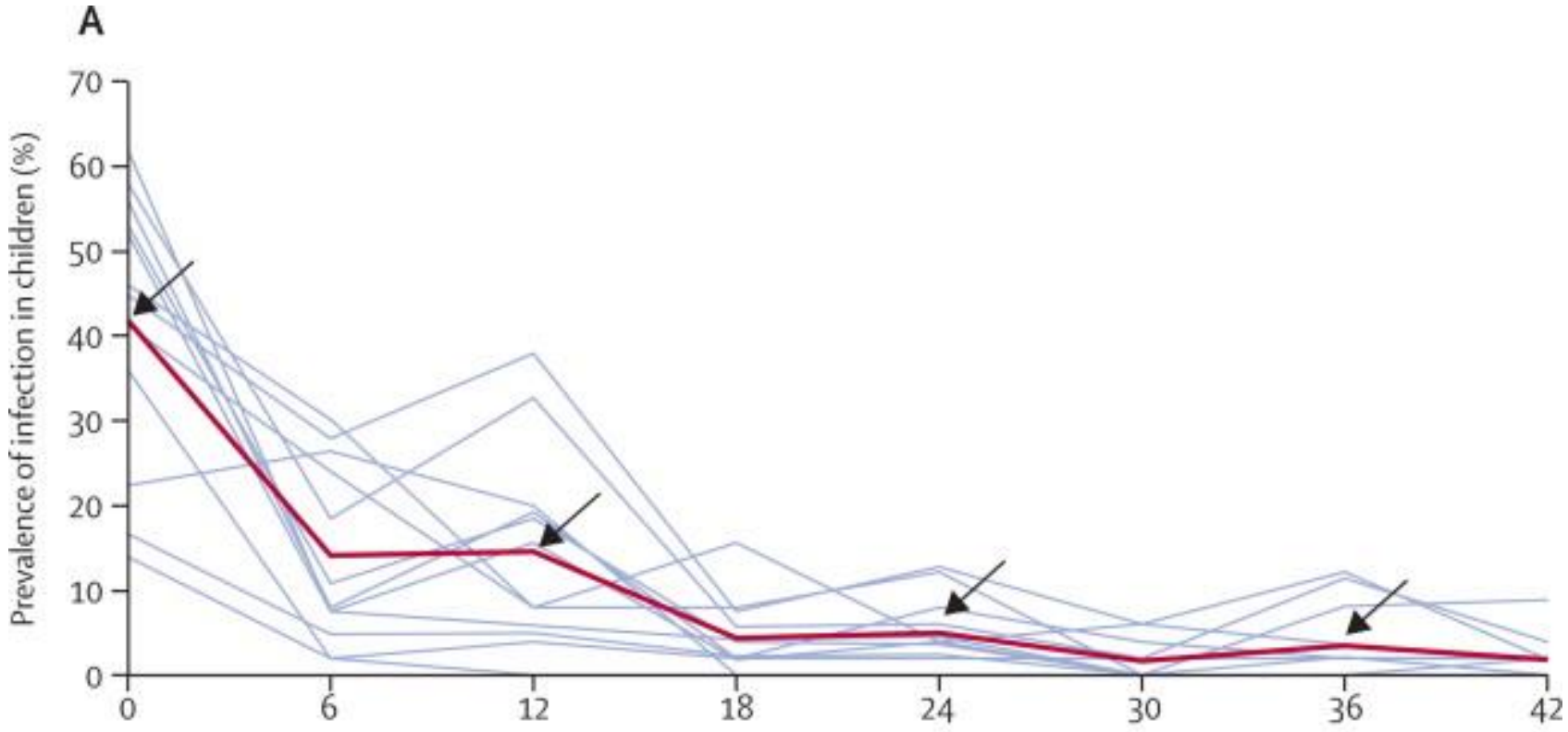
Mass azithromycin for trachoma



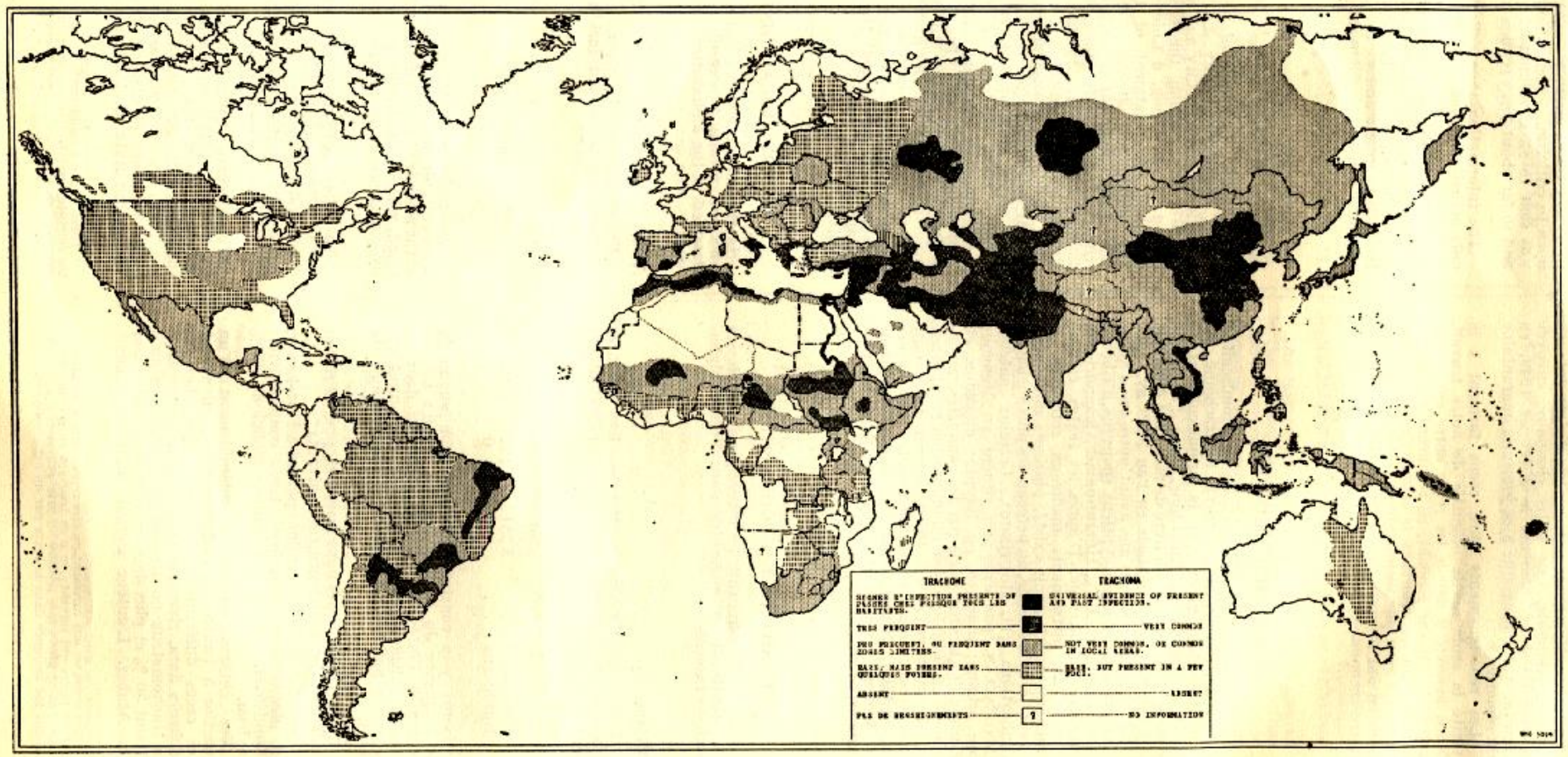
Gebre et al, *Lancet* 2012

DISTRIBUTION GÉOGRAPHIQUE (APPROXIMATIVE) DU TRACHOME

basée sur: estimations de divers auteurs, résultats récents d'enquêtes, données de cliniques ophtalmologiques ou enregistrement des cas.

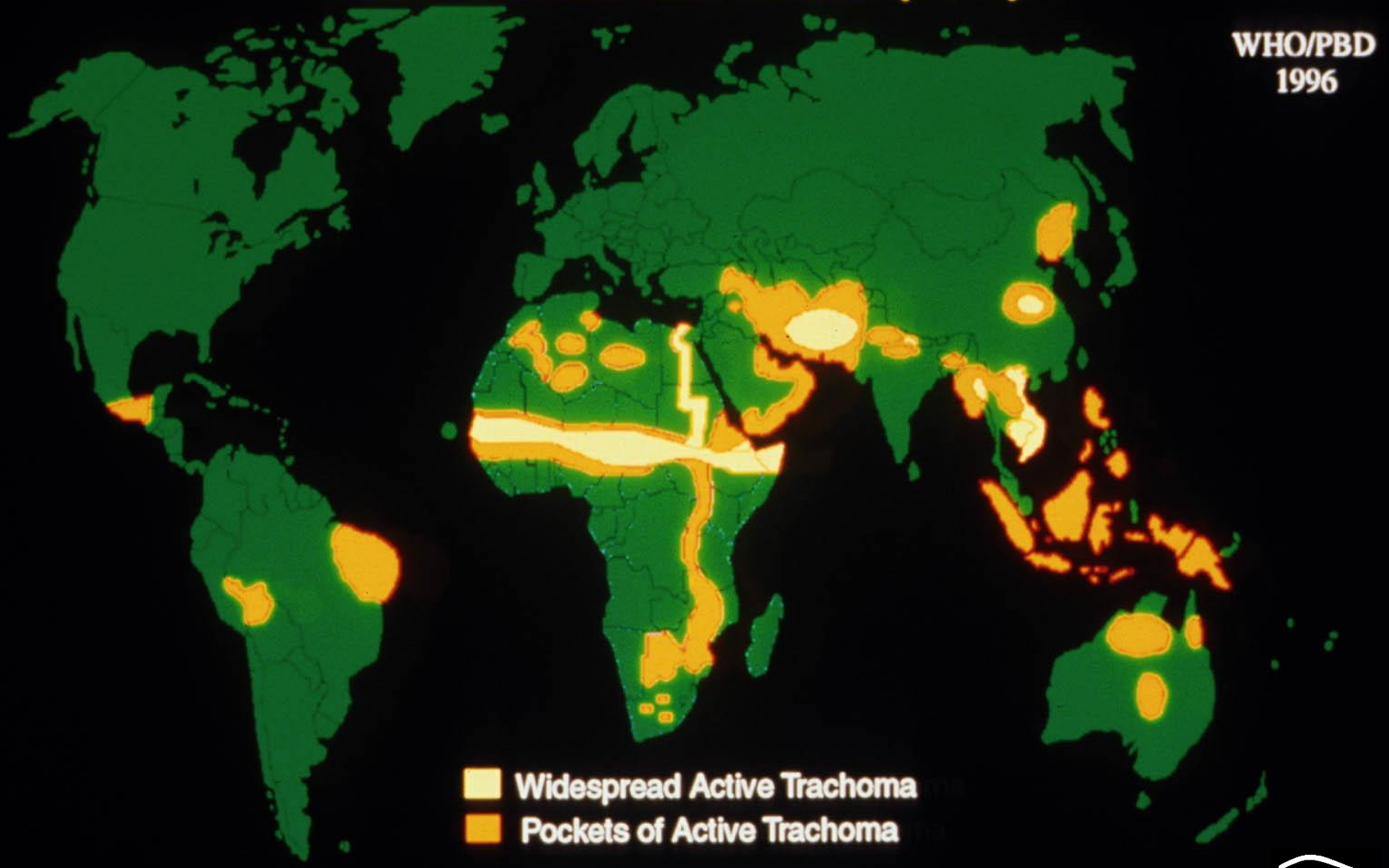
APPROXIMATE GEOGRAPHICAL DISTRIBUTION OF TRACHOMA

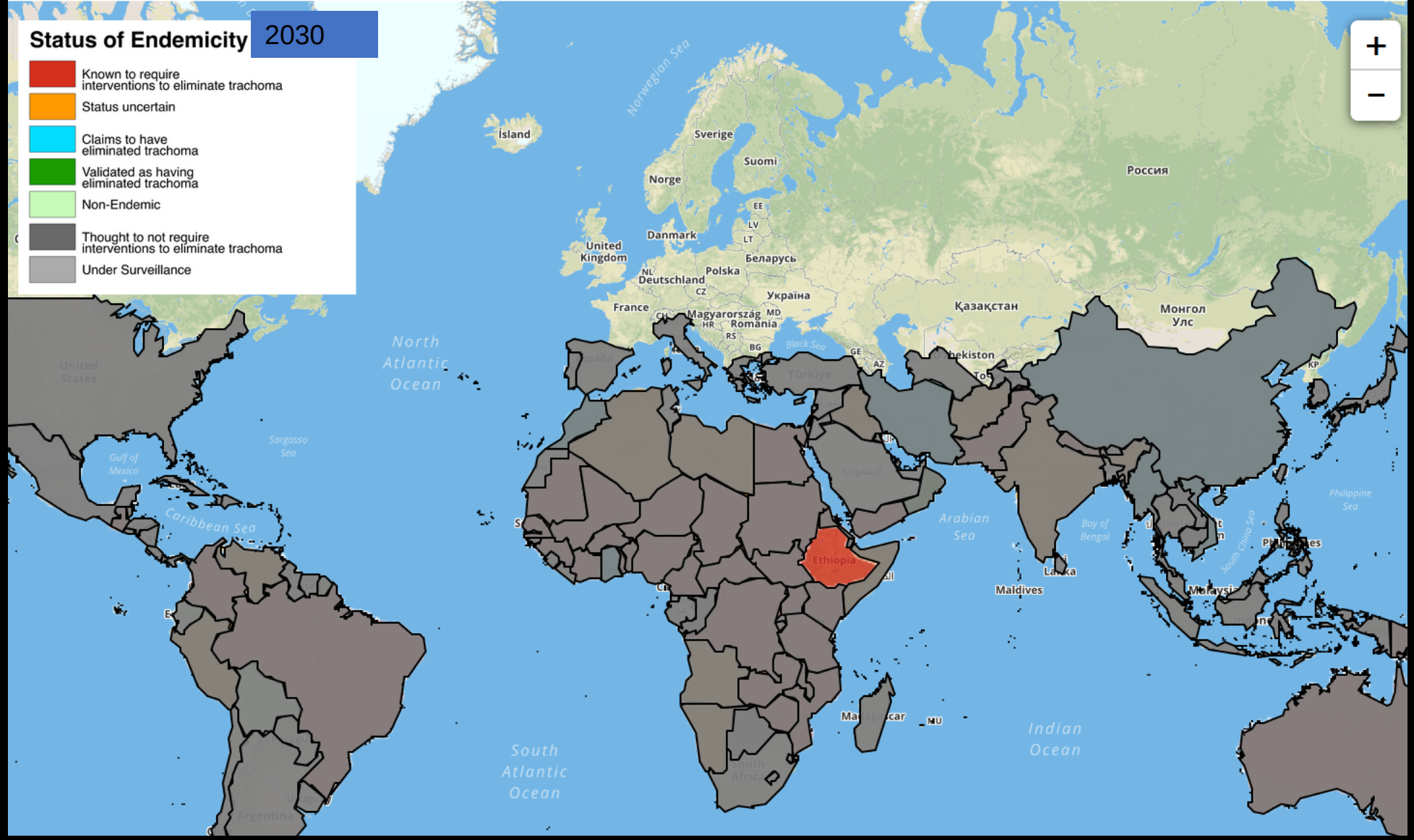
based on estimates by various authors, recent survey data, information from eye clinics or notification of cases.



TRACHOMA ACTIVE CASES (TF/TI)

WHO/PBD
1996




Status of Endemicity
2030
Known to require interventions to eliminate trachoma
Status uncertain
Claims to have eliminated trachoma
Validated as having eliminated trachoma
Non-Endemic
Thought to not require interventions to eliminate trachoma
Under Surveillance
Norwegian Sea
Ísland
Sverige
Suomi
Norge
Россия
Danmark
United Kingdom
Беларусь
Deutschland
Polska
Україна
France
Magyarország
Romania
Қазақстан
Монгол Улс
North Atlantic Ocean
United States
Türkiye
Sargasso Sea
Gulf of Mexico
Caribbean Sea
Ethiopia
Arabian Sea
Bay of Bengal
Philippine Sea
South China Sea
Maldives
Malaysia
Indian Ocean
South Atlantic Ocean
Argentina


Zithromax®
250 mg tablets
Azithromycin 250 mg
(as dihydrate)
comprimés à 250 mg
Azithromycine 250 mg
(sous forme de dihydrate)
30 Tablets/Comprimés
FOR TREATMENT OF TRACHOMA ONLY
DONATION

From: **Effect of Mass Distribution of Azithromycin for Trachoma Control on Overall Mortality in Ethiopian Children: A Randomized Trial**

JAMA. 2009;302(9):962-968. doi:10.1001/jama.2009.1266

Table 3. Estimated Mortality Rates in the 4 Groups

Treatment Group	Participant Mortality Rate per 1000 Person-Years (95% Conficence Interval) [No. of Deaths][a]		
	Age <1 y[b]	Age 1-9 y	Age >9 y
Annual	34.6 (20.9-57.2) [22]	3.2 (1.8-5.8) [12]	4.3 (3.1-6.0) [38]
Biannual	26.3 (17.0-40.8) [20]	4.9 (3.1-7.7) [19]	6.2 (4.5-8.8) [60]
Quarterly[c]	46.9 (29.5-74.7) [29]	4.7 (2.0-11.1) [14]	6.5 (5.0-8.6) [53]
Delayed[d]	42.9 (29.4-62.6) [27]	8.3 (5.3-13.1) [37]	6.1 (4.5-8.4) [62]

[a] Mortality rates were estimated by negative binomial regression. Mortality in 1- to 9-year-old participants was a prespecified outcome of the trial and was found to be significantly lower in the treated communities than in control communities.
[b] Children younger than 1 year were not treated with azithromycin in any study group.
[c] Treatment was only administered for participants aged 1 to 9 years.
[d] Denotes control group, untreated for the 1-year duration of this study, at which time mass administration of azithromycin was conducted.

Large Simple Trial

rare event
simple intervention
simple outcome

Yusuf, Stat Med 1984

Large Simple Trial

rare event
simple intervention
simple outcome
covariates unimportant

Yusuf, Stat Med 1984

MORDOR

Can biannual mass azithromycin distribution reduce mortality in 1-59 month old children?

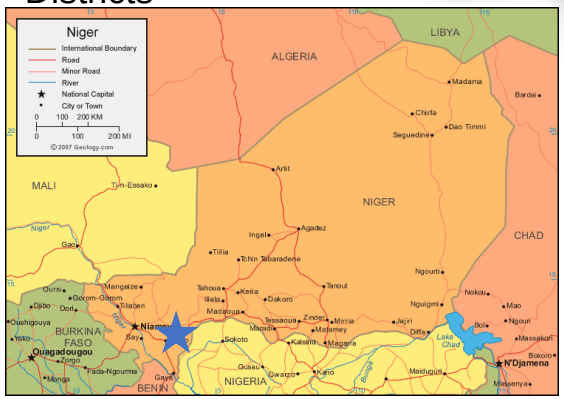
Primary outcome

All-cause mortality in 1-59 month olds

Presence on a census and absence on subsequent census due to death

Study sites

NIGER:
Loga and Boboye Districts



Malawi:
Mangochi District

TANZANIA:
Kilo istrict

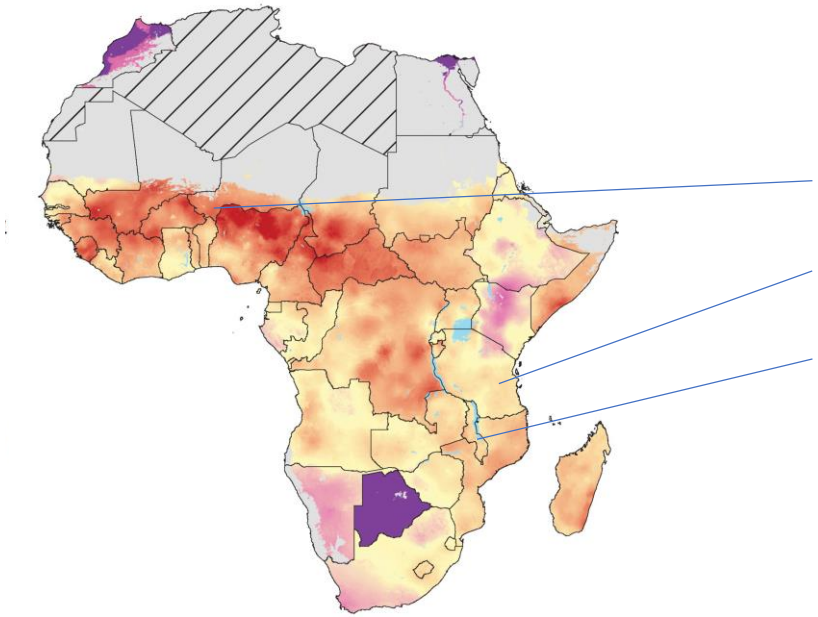
MORDOR

Mortality 1500 communities

Morbidity 90 communities

200-2000 people/community

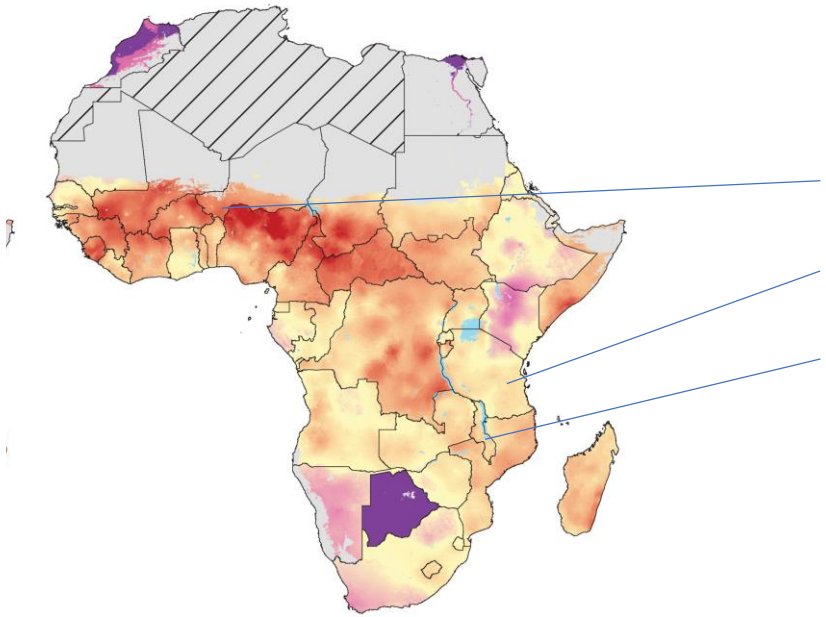
MORDOR I
Person-years monitored



- Niger: 145,597 py
- Tanzania: 66,146 py
- Malawi: 111,559 py

Golding et al, Lancet, 2017

MORDOR I
Mortality rate in placebo arm



- Niger: 27.5/1000 py
- Tanzania: 5.5/1000 py
- Malawi: 9.6/1000 py

Golding et al, Lancet, 2017

Census results

Category	All Countries		Malawi		Niger		Tanzania	
	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo
Census enrollments	**371592**	**358815**	**139150**	**141300**	**161257**	**143280**	**71185**	**74235**
Died	2404	2616	502	542	1727	1888	175	186
Moved	24415	23123	8351	7710	10084	8760	5980	6653
Unknown	18809	17587	11845	12160	6087	4508	877	919
Alive	325964	315489	118452	120888	143359	128124	64153	66477

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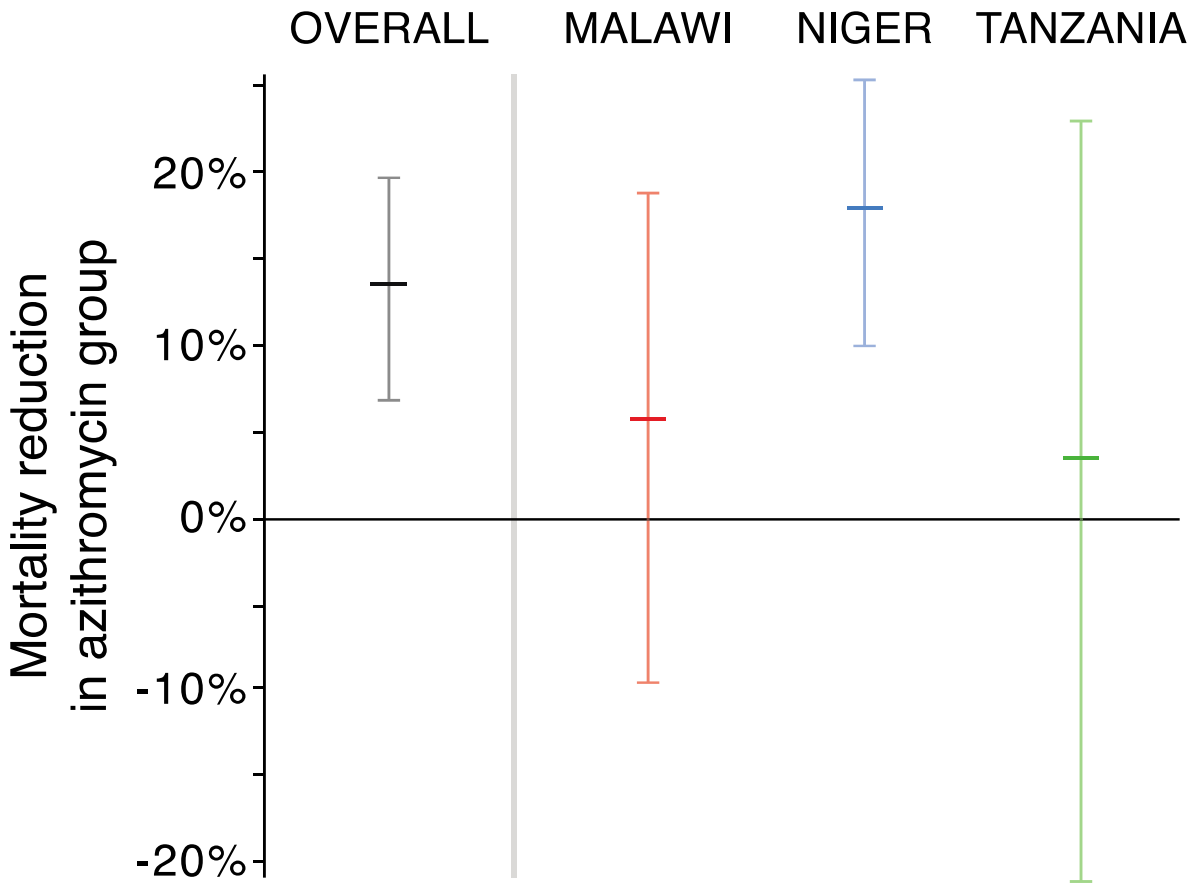
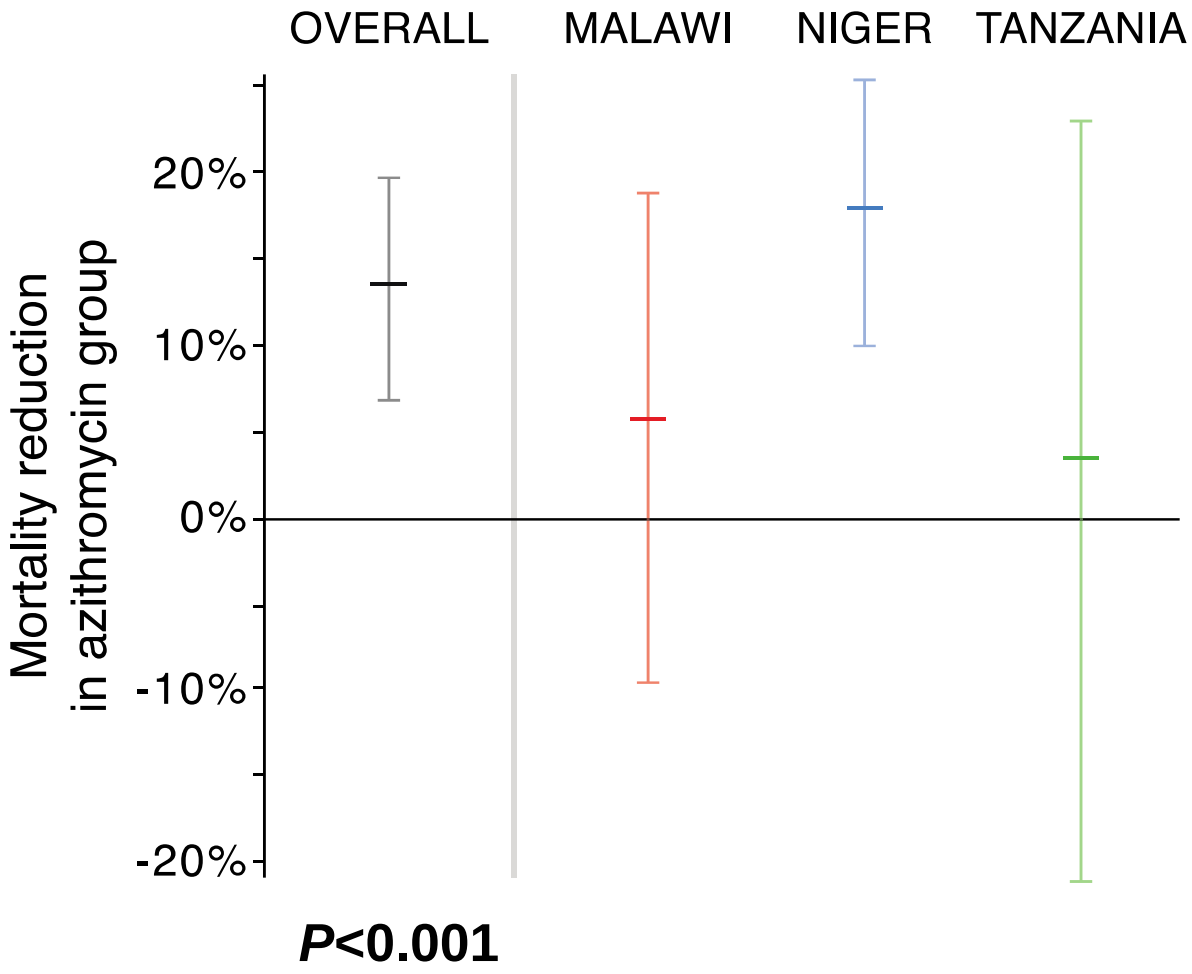
Moved ***P*=0.71**

Unknown ***P*=0.36**

Primary Outcome



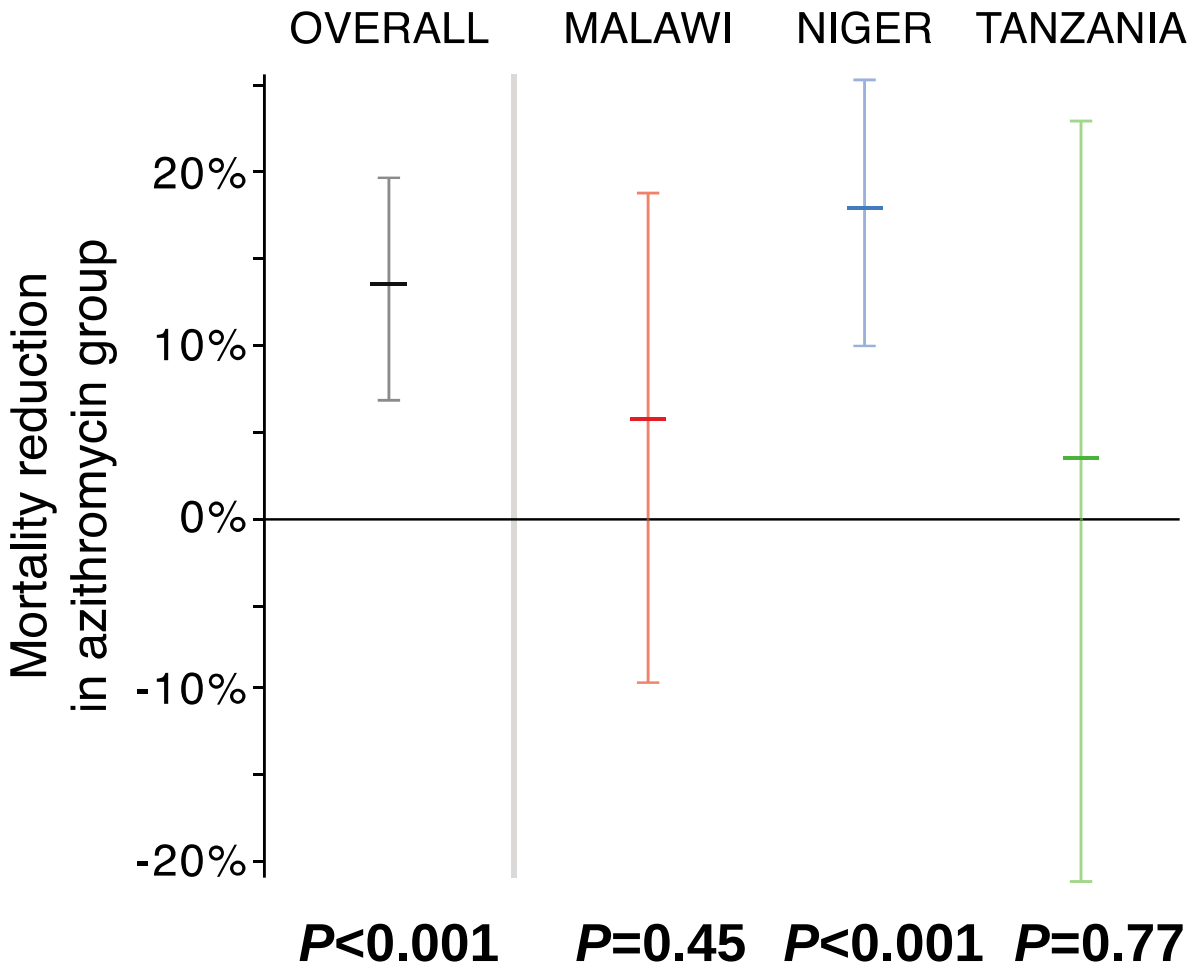
Primary Outcome



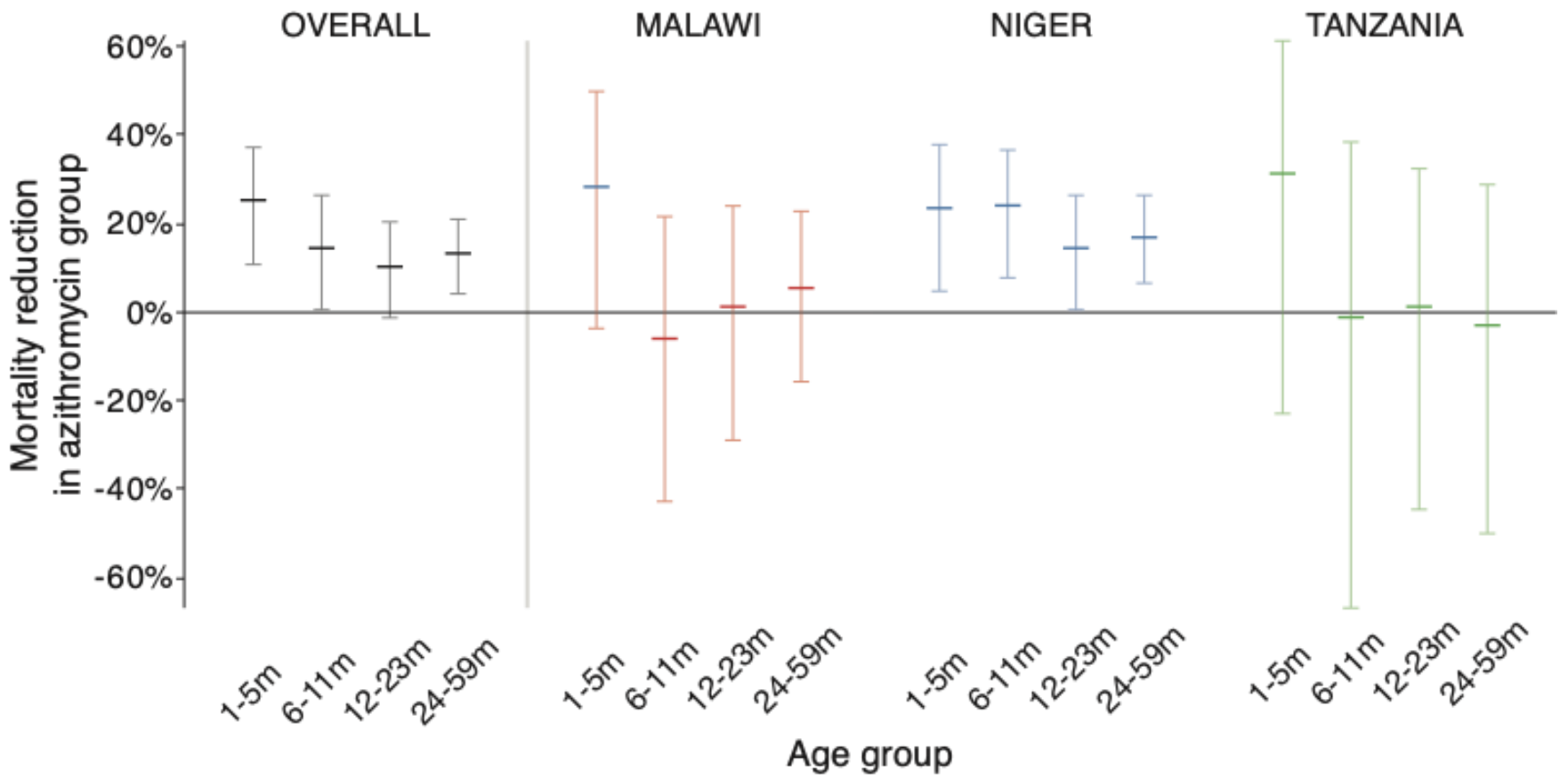
***P*<0.001**

MORDOR

Primary Outcome



MORDOR age-stratified results



Keenan et al, NEJM 2018.

WHO Guidelines

1. No universal implementation

2. Consideration in:

- High mortality sub-Saharan African settings
- Continued monitoring of mortality/AMR
- Other child survival programs (SMC)
- Children 1-11 months old

AVENIR DESIGN

Partners

- Funded by BMGF
- Azithromycin/placebo donated by Pfizer
- CRISP led by Ahmed Arzika
- PNSO, Niger MOH
- Proctor Foundation at UCSF

WHO (1-11m) vs MORDOR (1-59m)

- Rationale for 1-11m
  - Concern about AMR and desire to limit antibiotic distributions
  - Particularly high mortality rate in 1-11m, highest risk group
  - MORDOR results suggest stronger effect in youngest groups

- Rationale for 1-59m?
  - Existing evidence of efficacy is from treating 1-59m
  - Potential for herd effects of treating larger age group
  - Nearly 5 times as many 12-59m old vs 1-11m, all high mortality

Biannual Mass Azithromycin Distributions

- Replicate MORDOR in presence of SMC
  - Biannual azithromycin to 1-59 month-olds
  - Niger implemented SMC 2017-
    - Reported coverage >90%

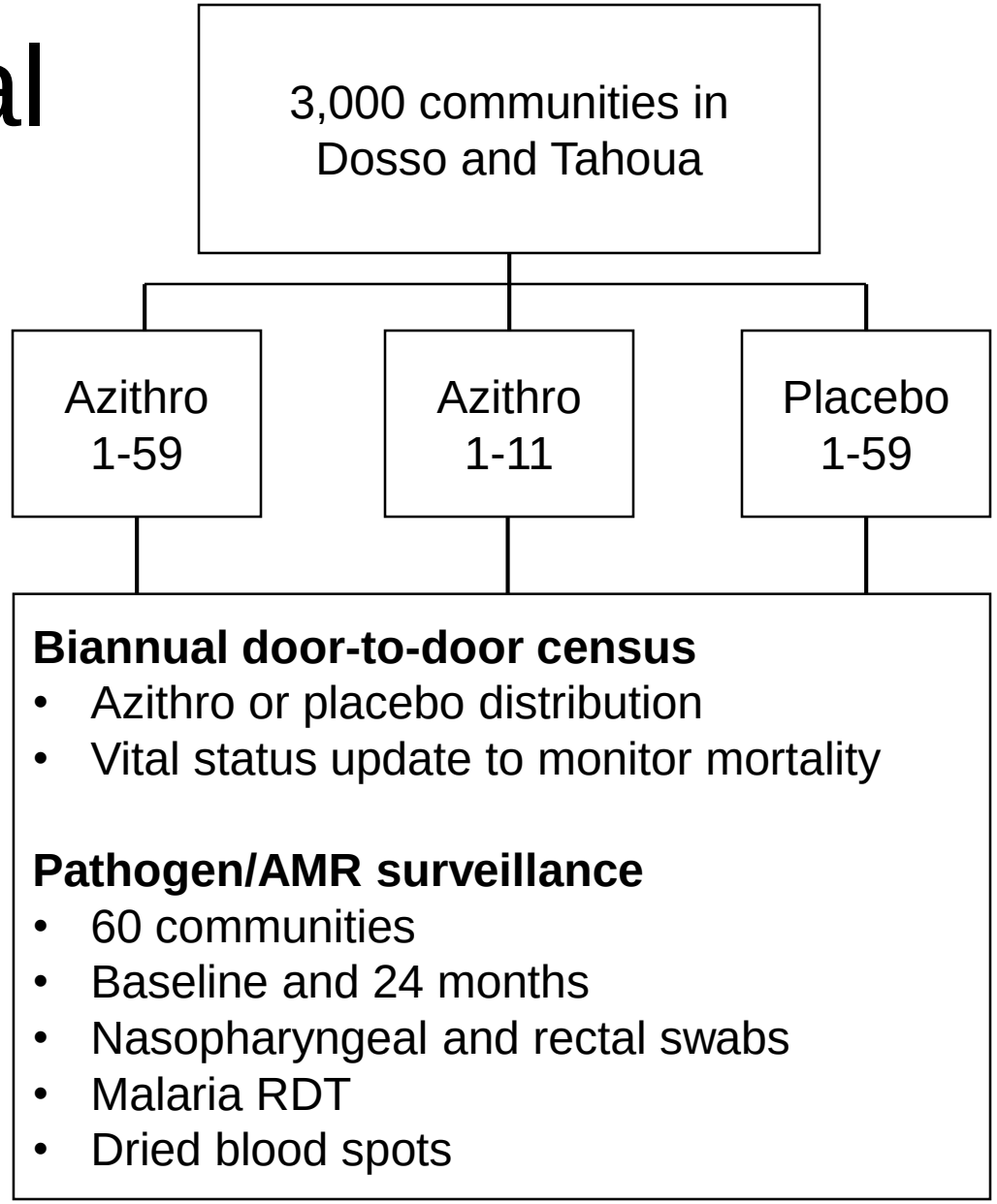
- Test WHO-guidelines
  - targeting 1-11 month-olds

- Monitor antimicrobial resistance

Mortality/Resistance Trial

- Cluster-randomized response-adaptive, large simple trial
  - Prior mortality informs allocation of new clusters

- Primary outcomes (2 years):
  - All-cause mortality
  - Antimicrobial resistance



Primary Mortality Outcomes

Mortality rate (deaths per 1,000 person-years at risk) after 2 years of distributions:

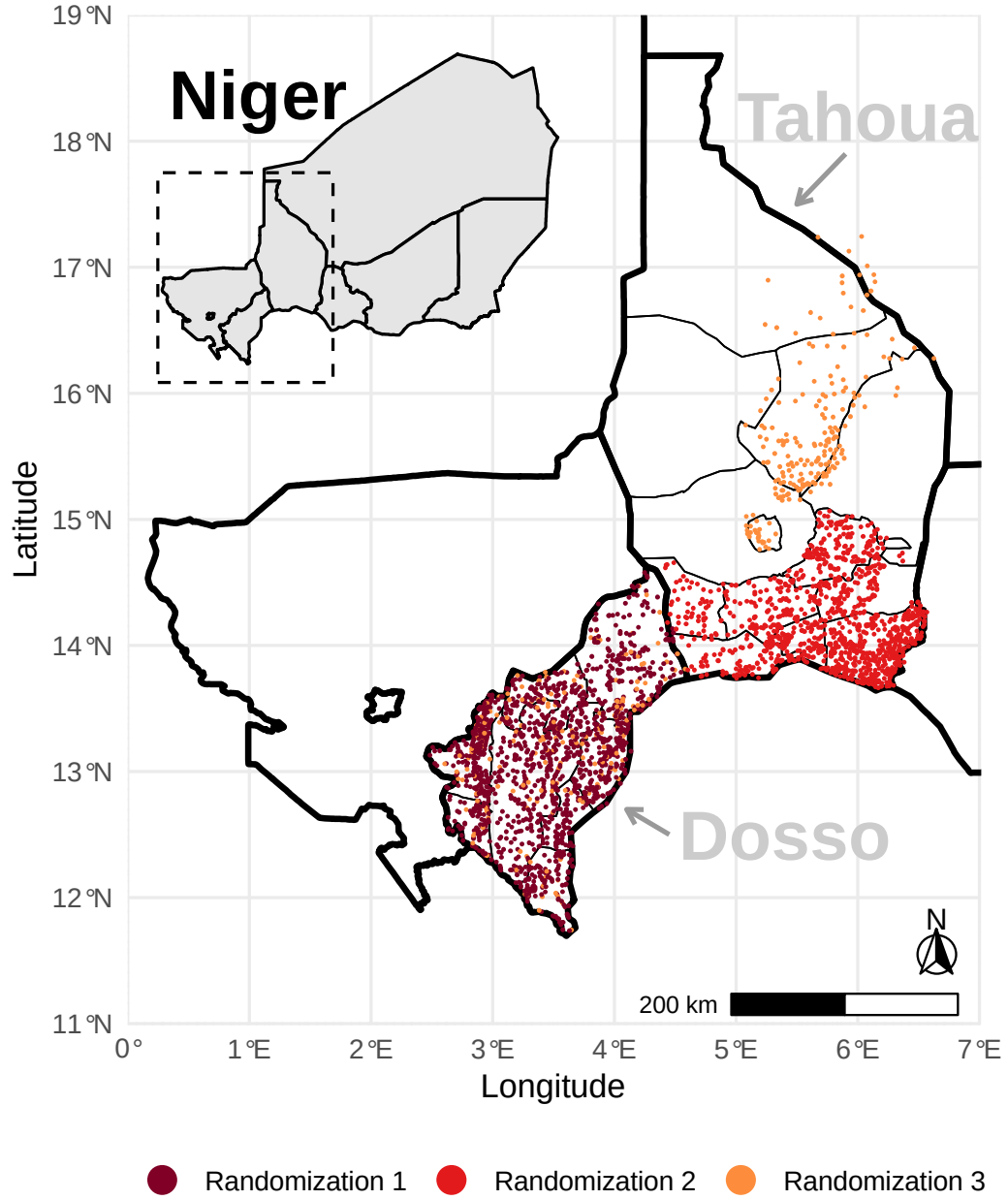
Outcome	Analysis Population (months)	Comparison
1	1-59	Azithro 1-59 vs placebo
2	1-11	Azithro 1-11 vs placebo
3	12-59	Azithro 1-59 vs azithro 1-11

RESULTS

Photos by Dominique Catton

AVENIR by the numbers

- **3,000 clusters** randomized
- **2,909 clusters** contributed to the analysis
  - 91 clusters excluded
    - 40 in red zone due to insecurity
    - 39 nonexistent
    - 7 refusals across all rounds
    - 2 did not find anyone in the community or community moved
    - 2 protocol deviation
    - 1 only had 1 household entered and did not contribute person time
- **382,586 children 1-59 months** contributed to the analysis
- **419,440 child-years** of observation
- **5,503 deaths**
- **4 days** between end of data collection and primary analysis unmasking


Niger
Tahoua
Dosso
19 °N
18 °N
17 °N
16 °N
15 °N
14 °N
13 °N
12 °N
11 °N
Latitude
0 °
1 °E
2 °E
3 °E
4 °E
5 °E
6 °E
7 °E
Longitude
N
200 km
Randomization 1
Randomization 2
Randomization 3

Hypothesis 1

Treatment: Azithromycin 1-59m vs Placebo

Outcome: 1-59m mortality

Treatment of children 1-59m reduced mortality by 14% (7% to 22%), P=0.0004

Group	Person-years	Deaths	Mortality rate per 1000	IRR (95% CI)	P-value
Placebo	138,148	1,923	13.9		
Azithro 1-59m	160,535	1,914	11.9	0.86 (0.78 to 0.93)	0.0004

Hypothesis 2

Treatment: Azithromycin 1-11m vs Placebo

Outcome: 1-11m mortality

Treatment of children 1-11m reduced mortality by 6%. Not Significant.

Group	Person-years	Deaths	Mortality rate per 1000	IRR (95% CI)	P-value
Placebo	21,958	524	23.9		
Azithro 1-11m	19,429	434	22.3	0.94 (0.81 to 1.08)	0.35

Hypothesis 3

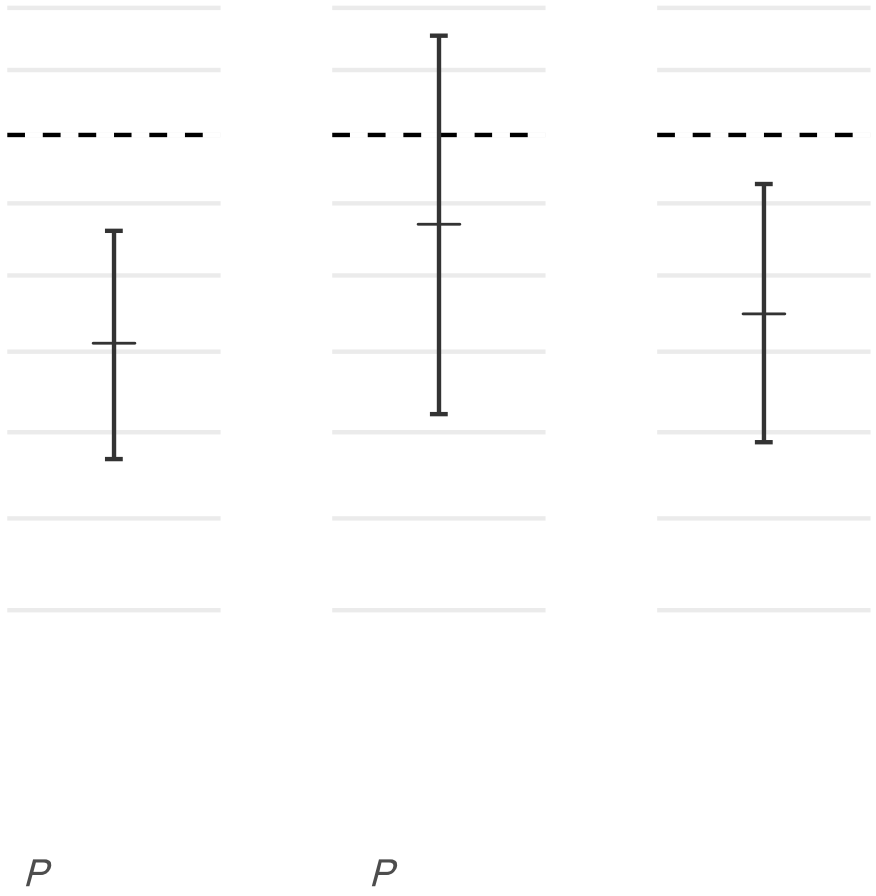
Treatment: Azithro 1-59m vs Azithro 1-11m + Placebo 12-59m

Outcome: 12-59m mortality

Treatment of children 12-59m reduced mortality by 13% (4% to 21%)

Group	Person-years	Deaths	Mortality rate per 1000	IRR (95% CI)	P-value
Azithro 1-11m	101,327	1,232	12.2		
Azithro 1-59m	134,845	1,439	10.7	0.87 (0.79 to 0.96)	

Primary hypothesis summary



Pre-specified secondary mortality outcomes

- Mortality among 1-11m, comparison Azithro 1-59m vs Azithro 1-11m

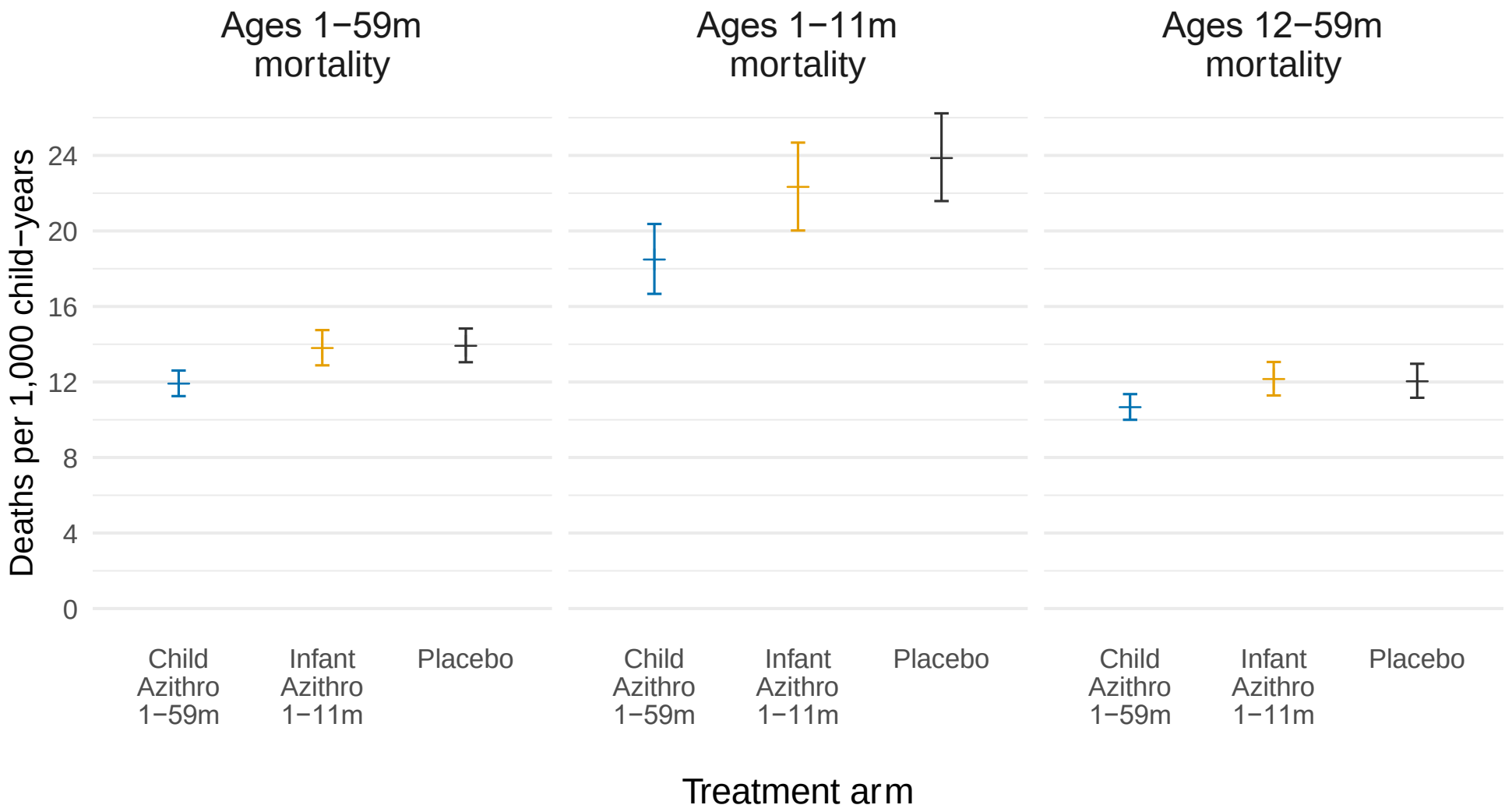
Hypothesis 3 (secondary)
Treatment: Azithro 1-59m vs Azithro 1-11m
Outcome: 1-11m mortality

Treatment of children 1-59m reduced mortality among 1-11m 17% (4% to 28%) compared to only treating 1-11m

Consistent with *indirect benefit* for 1-11m olds from treating the older age group.

Group	Person-years	Deaths	Mortality rate per 1000	IRR (95% CI)
Azithro 1-11m	19,429	434	22.3	
Azithro 1-59m	25,689	475	18.5	0.83 (0.72 to 0.96)

Mortality at all ages was lower among children in the 1-59m treatment arm



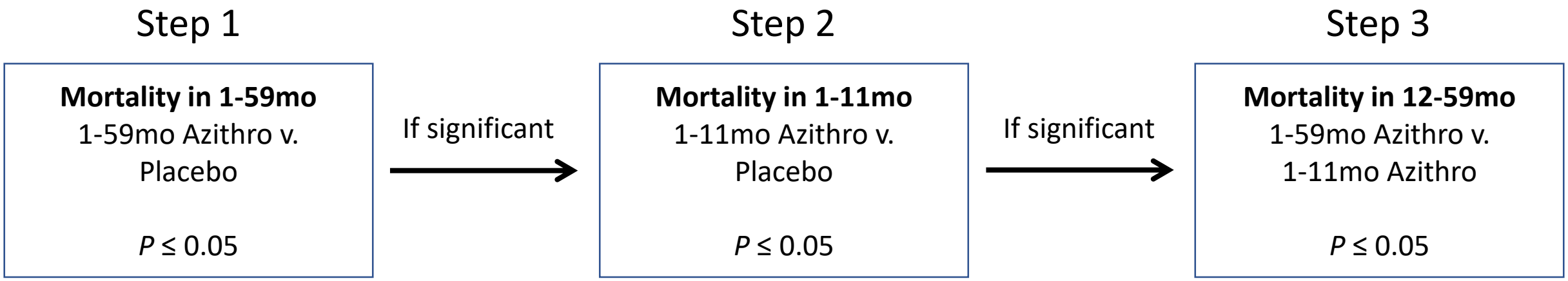
Antimicrobial resistance

- Distributions select for macrolide resistance
- Resistance decreases after distributions stopped
- Coselection for beta-lactam resistance?
- May plateau after 2-3 years of MDA

Biannual Mass Azithromycin Distributions

- Replicated MORDOR in presence of SMC
- Unable to prove efficacy of WHO-guidelines
  - Including 12-59 month olds benefits 1-11 month olds
- Antimicrobial resistance pending
- AVENIR II now randomizing entire country

Fixed-sequence, hierarchical testing approach for the 3 mortality primary outcomes:

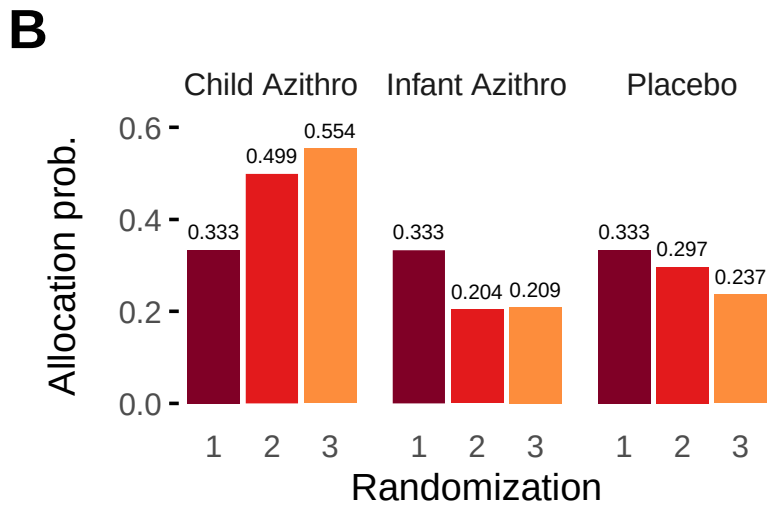


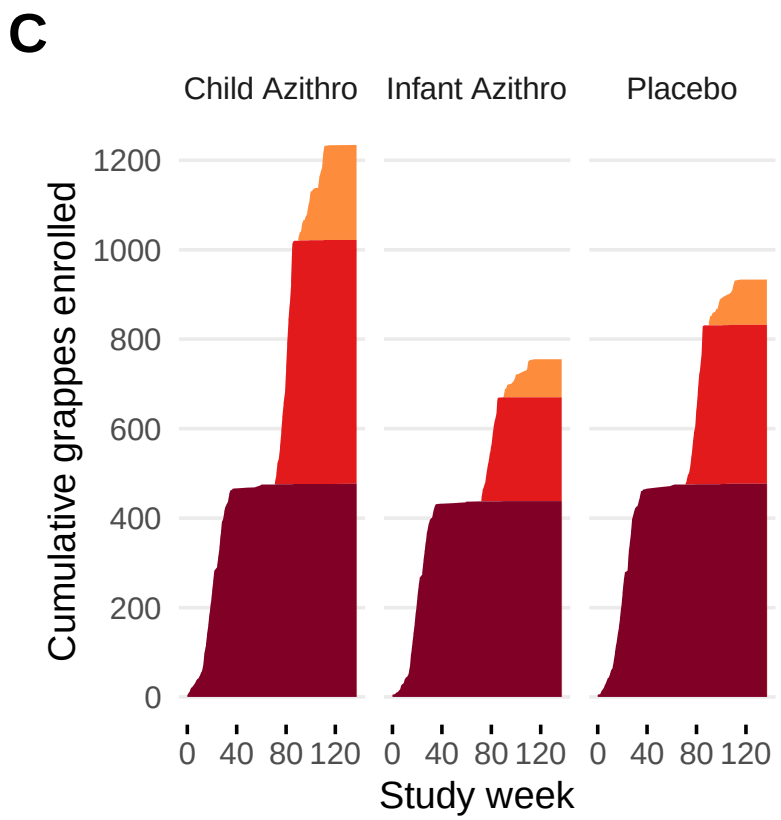
Adaptive Allocation Probabilities

- Trial successfully adapted toward the 1-59m treatment group
- Tempering algorithm avoided dramatic swings in allocation probabilities

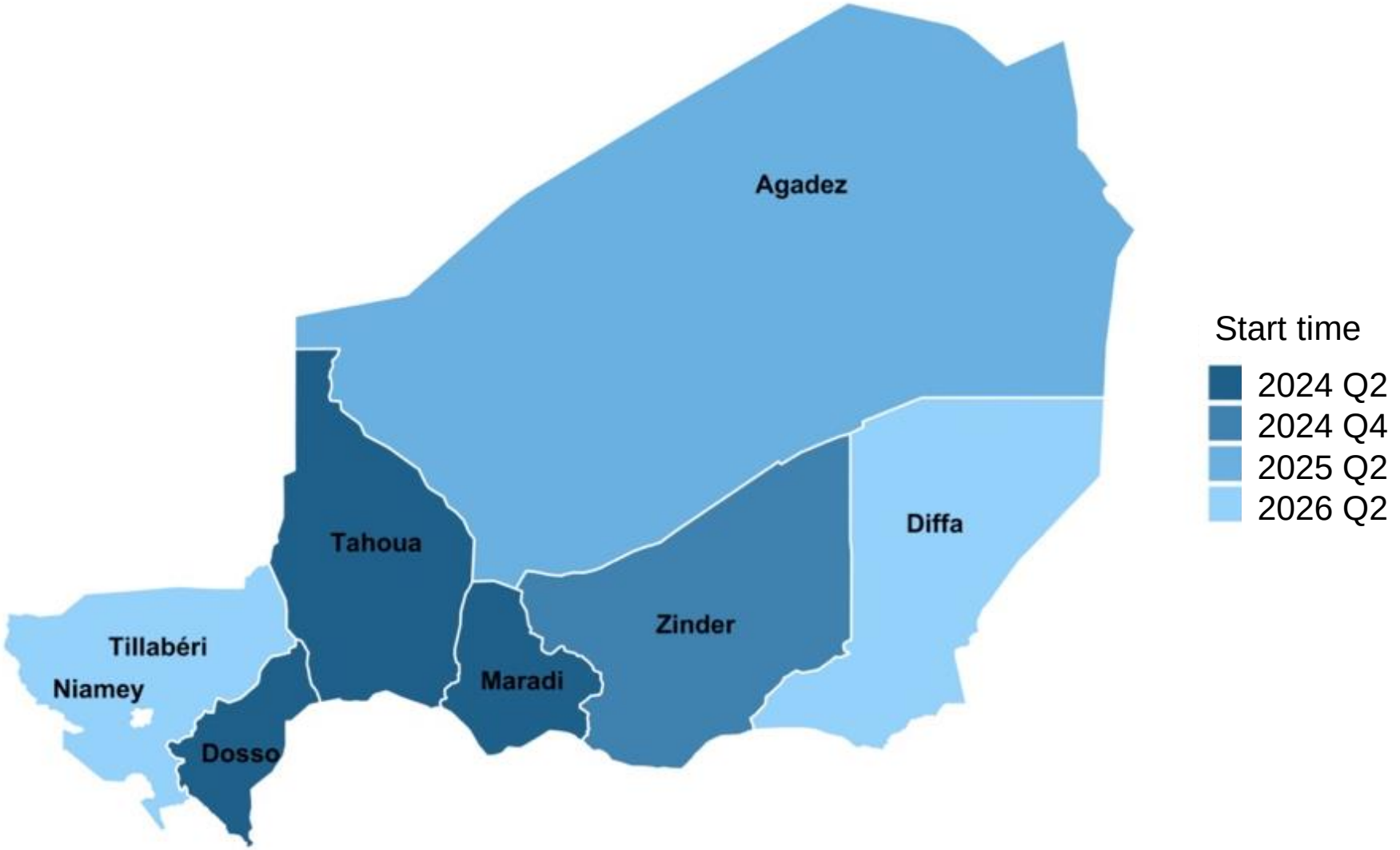
Treatment	**Initial Randomization**	**1st Adaptation at 12 months**	**2nd Adaptation at 18 months**
Azithro 1-59 months	0.333	0.499	0.554
Azithro 1-11 months	0.333	0.204	0.209
Placebo	0.333	0.297	0.237

Adaptive algorithm favored 1-59m arm without dramatic swings in allocation





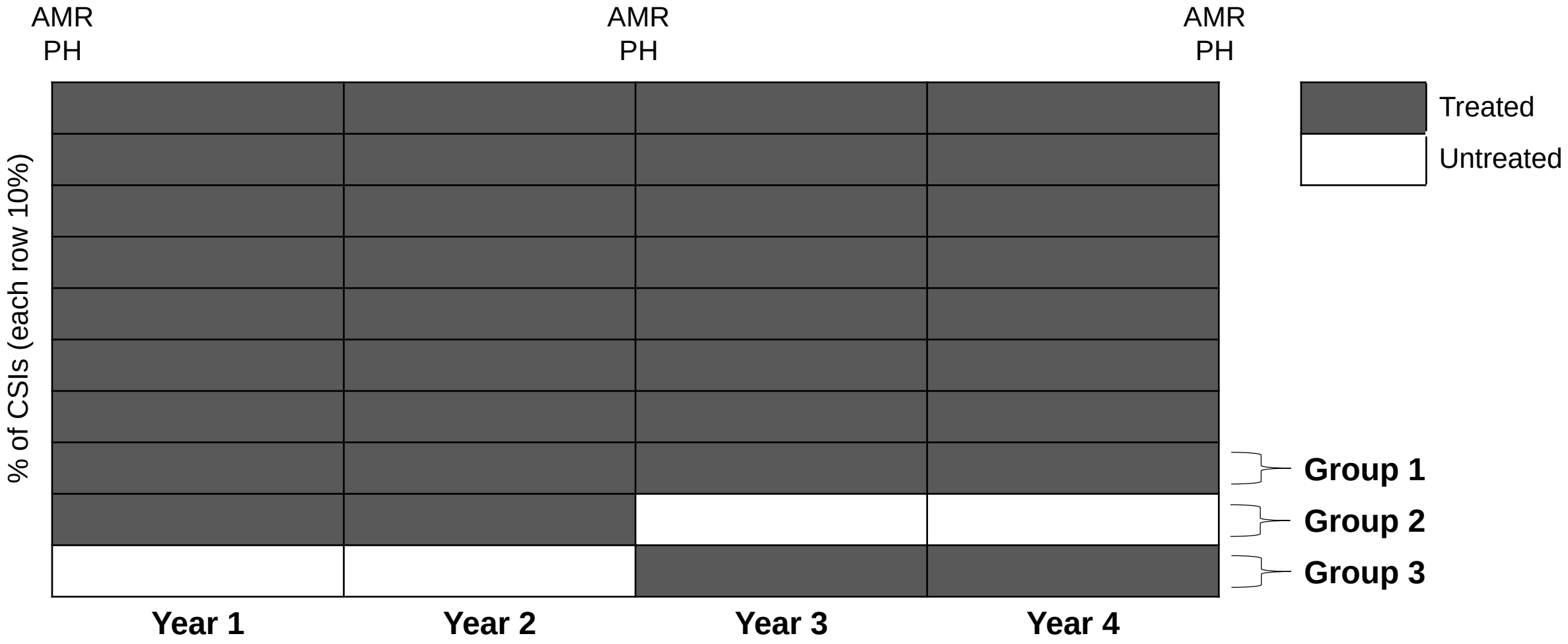
AVENIR II: Niger Expansion Plan



Expansion Details

Region	Start Time	Districts	CSIs	MDAs[1]	Total Children 1-59m[2]	Doses Delivered Overall[3]	Deaths Averted during Program Expansion
Dosso	2024 Q2	8	192	7	431,461	2,416,182	2,939
Tahoua	2024 Q2	13	267	7	670,002	3,752,011	4,563
Maradi	2024 Q2	9	216	7	665,826	3,728,626	4,535
Zinder	2024 Q4	11	219	6	731,986	3,513,533	4,273
Agadez	2025 Q2	7	92	5	67,298	269,192	327
Tillabéri	2026 Q2	13	270	3	585,215	1,404,516	1,708
Diffa	2026 Q2	6	72	3	129,642	311,141	378
Total		**67**	**1328**	**38**	**3,281,430**	**15,395,200**	**18,724**

[1]Assuming twice yearly MDA
[2]Population estimates including rural and peri-urban communities, produced by the Institute for Disease Modeling (IDM)
[3]Using IDM population estimates and assuming 80% coverage



Trial	Outcomes	Time point	Comparison
Selection	AMR	Year 2	Group 2 vs Group 3
Stopping	AMR	Year 4	Group 1 vs Group 2
Saturation	AMR	Year 4	Group 1 vs Group 3

AVENIR II Study Design Overview

- Design
  - Cluster-randomized adaptive platform trial
  - Unit of randomization: CSI (Centre de Santé Intégré)
- Intervention
  - Biannual oral azithromycin distribution vs delayed (10% of CSIs)
  - Door to door distribution by community health workers
  - Children 1-59 months old
- Monitoring
  - Mortality and AMR monitored at baseline, Y2, Y4 (20% of CSIs)
  - Safety and program outcomes monitored continuously