

Clinical Trial I

Case Studies

Nuno Sepúlveda, 28.03.2025

Calendar

- 1. March 28th - Today**
- 2. April 4th**
- 3. April 11th**
- 4. April 17th (Thursday)**
- 5. April 25th**

Course content

1. Basic concepts related to CTs
2. Designing CTs (Power)/Mendelian Randomisation/Survival Analysis
3. Reporting CTs (CONSORT guidelines)/Health Economics
4. Discussion on the controversial PACE trial
5. Project's Presentations/Course Summary

https://github.com/immune-stats/Clinical_Trials_2425

Evaluation

Presentation of a CT paper - 40%

+

Presentation project - 60%

Warm-up I

Any prospect of working in a pharmaceutical component?

What do you know about clinical trials?

Warm-up II

Beyond science?

Effects of remote, retroactive intercessory prayer on outcomes in patients with bloodstream infection: randomised controlled trial

Leonard Leibovici

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Leonard Leibovici professor
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BMJ 2001;323:1490-1

Abstract

Objective To determine whether remote, retroactive intercessory prayer, said for a group of patients with a bloodstream infection, has an effect on outcomes.

Design Double blind, parallel group, randomised controlled trial of a retroactive intervention.

Setting University hospital.

Subjects All 3393 adult patients whose bloodstream infection was detected at the hospital in 1990-6.

Intervention In July 2000 patients were randomised to a control group and an intervention group. A remote, retroactive intercessory prayer was said for the well being and full recovery of the intervention group.

Main outcome measures Mortality in hospital, length of stay in hospital, and duration of fever.

Results Mortality was 28.1% (475/1691) in the intervention group and 30.2% (514/1702) in the control group (P for difference = 0.4). Length of stay in hospital and duration of fever were significantly shorter in the intervention group than in the control group (P = 0.01 and P = 0.04, respectively).

Conclusions Remote, retroactive intercessory prayer said for a group is associated with a shorter stay in hospital and shorter duration of fever in patients with a bloodstream infection and should be considered for use in clinical practice.

Introduction

Two randomised controlled trials tested the effect of remote intercessory prayer (praying for persons unknown) on outcomes in patients admitted to an intensive coronary care unit.^{1,2} Both studies showed a beneficial effect. A recent systematic review of the efficacy of distant healing concluded that "approximately 57% (13 of 23) of the randomised, placebo-controlled trials of distant healing ... showed a positive treatment effect" and that "the evidence thus far warrants further study".³

The purpose of the present study was to extend these observations to patients with another severe disorder, bloodstream infection. As we cannot assume a priori that time is linear, as we perceive it,⁴ or that God is limited by a linear time, as we are,⁵ the intervention was carried out 4-10 years after the patients' infection and hospitalisation. The hypothesis was that remote, retroactive intercessory prayer reduces mortality and shortens the length of stay in hospital and duration of fever.

Methods

were included in the study. Bloodstream infection was defined as a positive blood culture (not resulting from contamination) in the presence of sepsis.

In July 2000 a random number generator (Proc Uniform, SAS, Cary, NC, USA) was used to randomise the patients into two groups. A coin was tossed to designate the intervention group. A list of the first names of the patients in the intervention group was given to a person who said a short prayer for the well being and full recovery of the group as a whole. There was no sham intervention.

Three primary outcomes were compared: the number of deaths in hospital, length of stay in hospital from the day of the first positive blood culture to discharge or death, and duration of fever. Patients were defined as having fever on a specific day if one of three temperature measurements taken on that day showed a temperature of $> 37.5^{\circ}\text{C}$.

The χ^2 test was used to test for the significance of the results shown in the tables. As most of the continuous variables did not have a normal distribution, the Wilcoxon rank sum test was used for comparisons.

Results

Of 3393 patients with a bloodstream infection, 1691 patients were randomised to the intervention group and 1702 to the control group. No patients were lost to



Clinical trials concern interventions for the benefit of patients

Drug or biologic
Behavioural
Surgical procedure
Device

Change of standard treatment (gold standard)

**UK's National Institute for Clinical Excellence
(NICE)**

Change of standard treatment/health care in National Health Systems

Medicine

Prevent

Diagnose

Treat

Medicine

Prevent

Diagnose

Treat

Develop

Improve

Repurpose

Clinical trial

Feasibility
Compliance
Safety

Medicine



Medicine



Pharmacological CTs

Finding new drug/treatment/therapy for a disease

Develop

Improve

Repurpose

New Treatment

New treatment

New Treatment

Existing treatment

Dose 1

Versus

Dose 2

Versus

Other doses

Versus

Versus

Versus

Placebo

Reference treatment

Placebo/Reference treatment

Less-Traditional Clinical trials (Public Health)

Finding prophylactic interventions that could prevent disease

Develop

Intervention

Versus

No intervention

Improve

Pseudo-optimal intervention protocol

Versus

Feasible intervention protocol

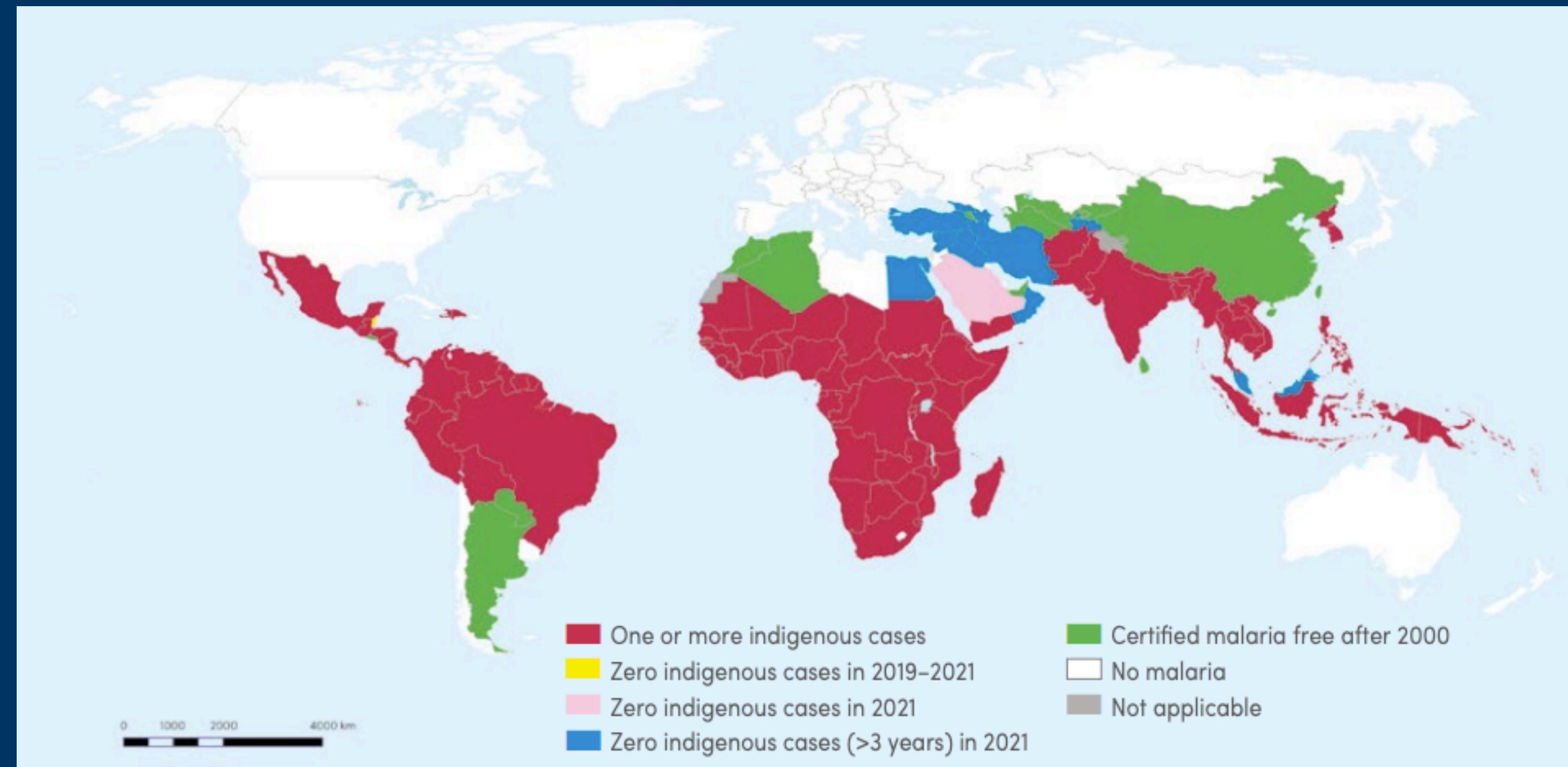
Repurpose

Existing treatment

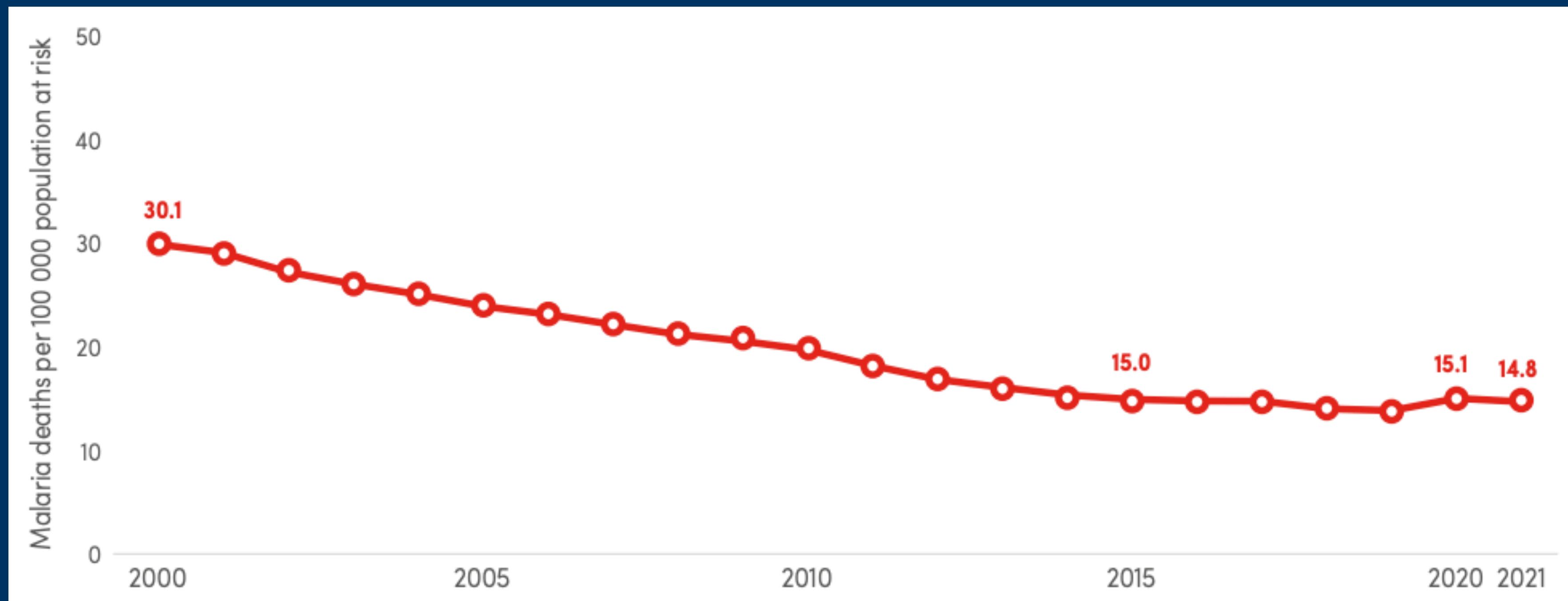
Versus

Placebo/No treatment

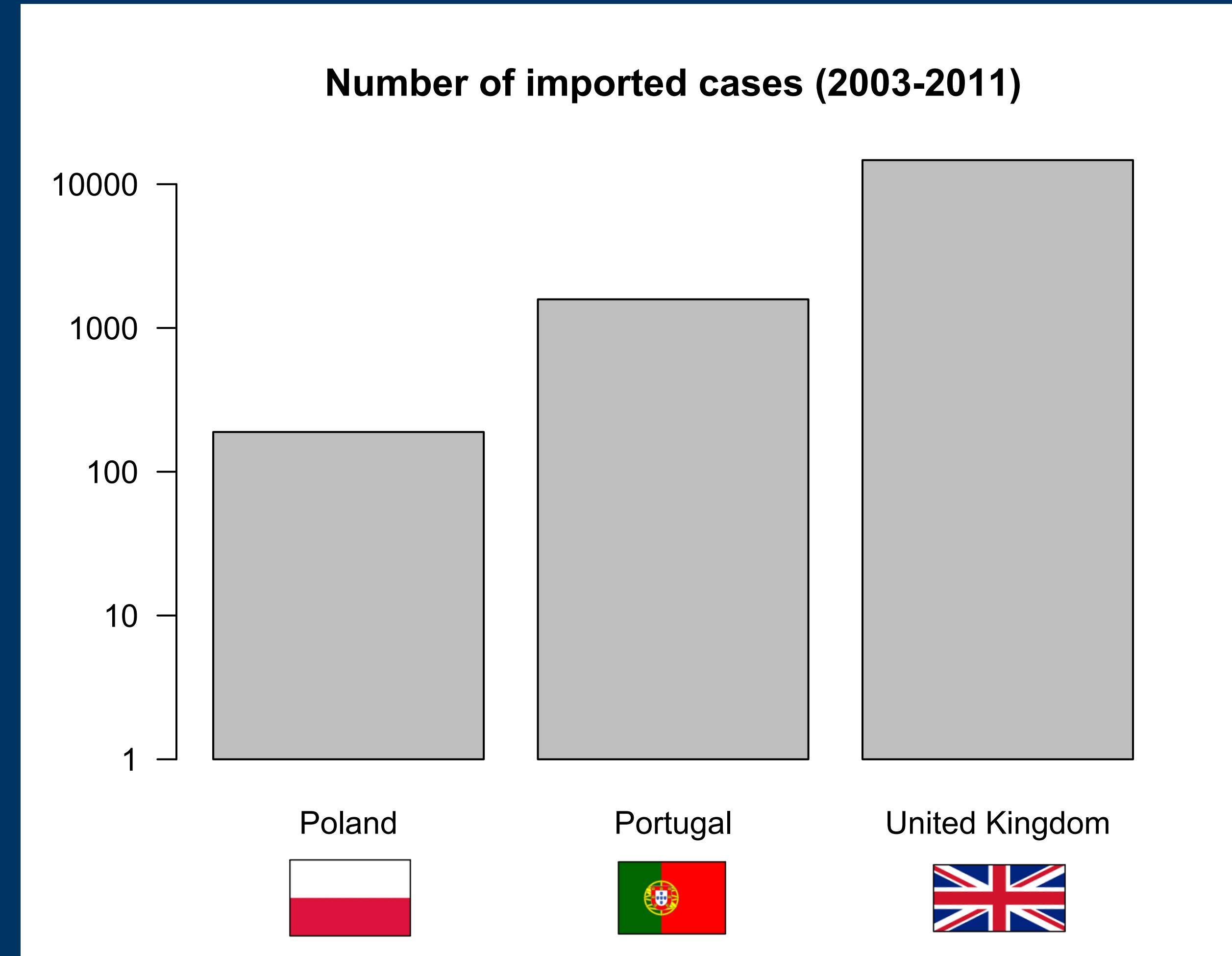
Malaria



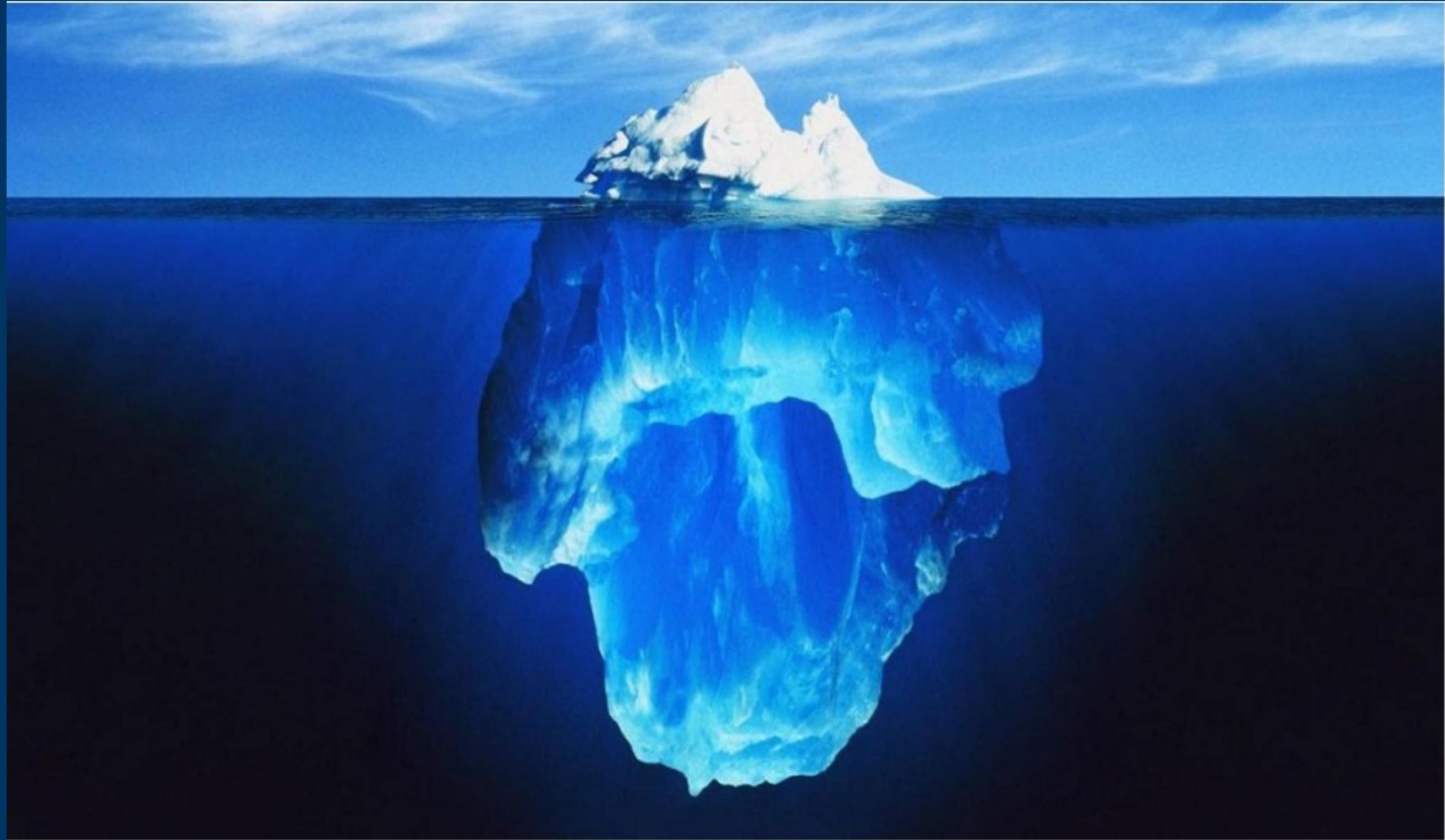
Malaria



Malaria near you



The real problem of malaria



Number of reported symptomatic cases

Number of unreported symptomatic cases

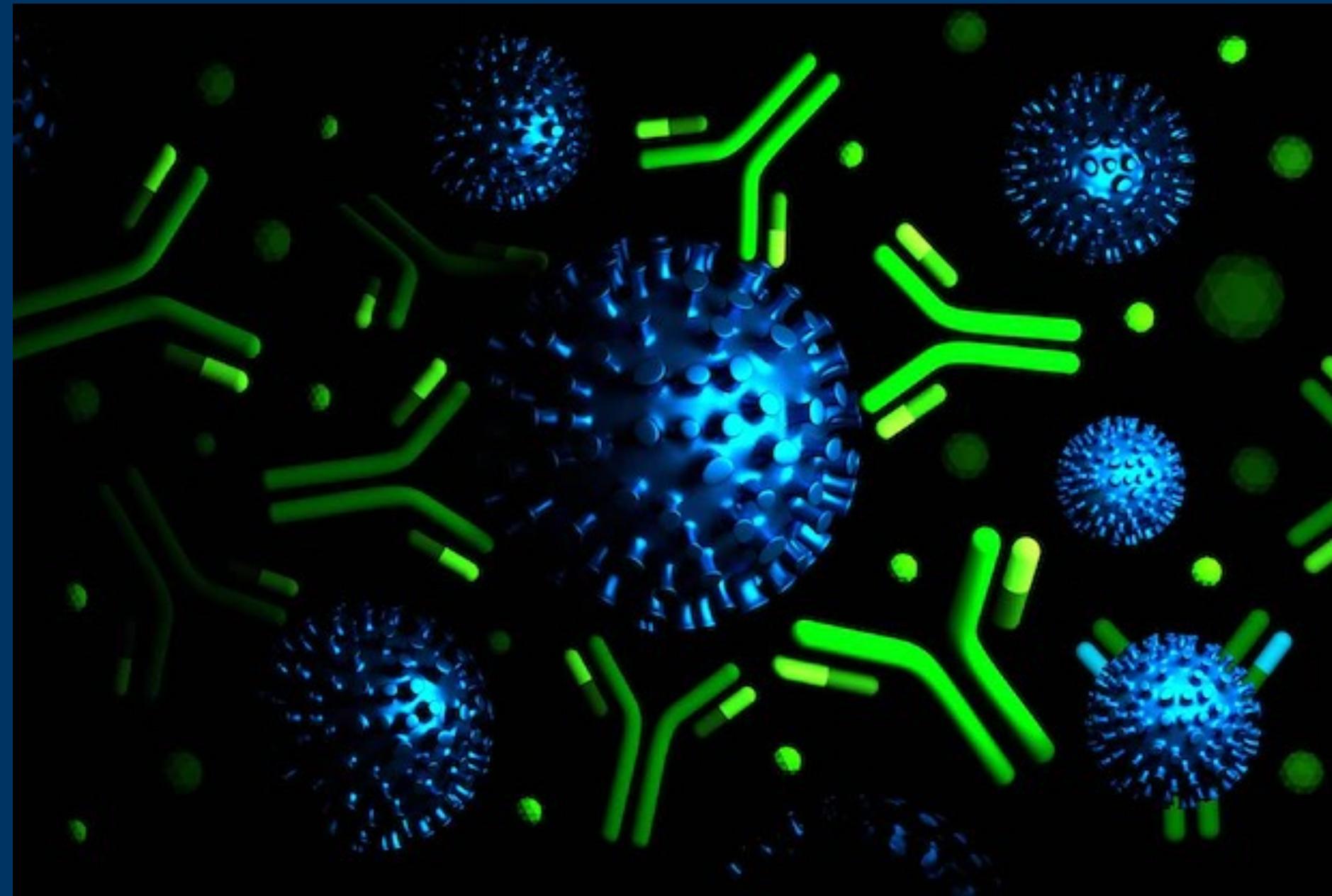
Number of asymptomatic cases

Number of exported cases

Number of imported symptomatic cases

Number of imported asymptomatic cases

Using Antibodies to Detect Exposure



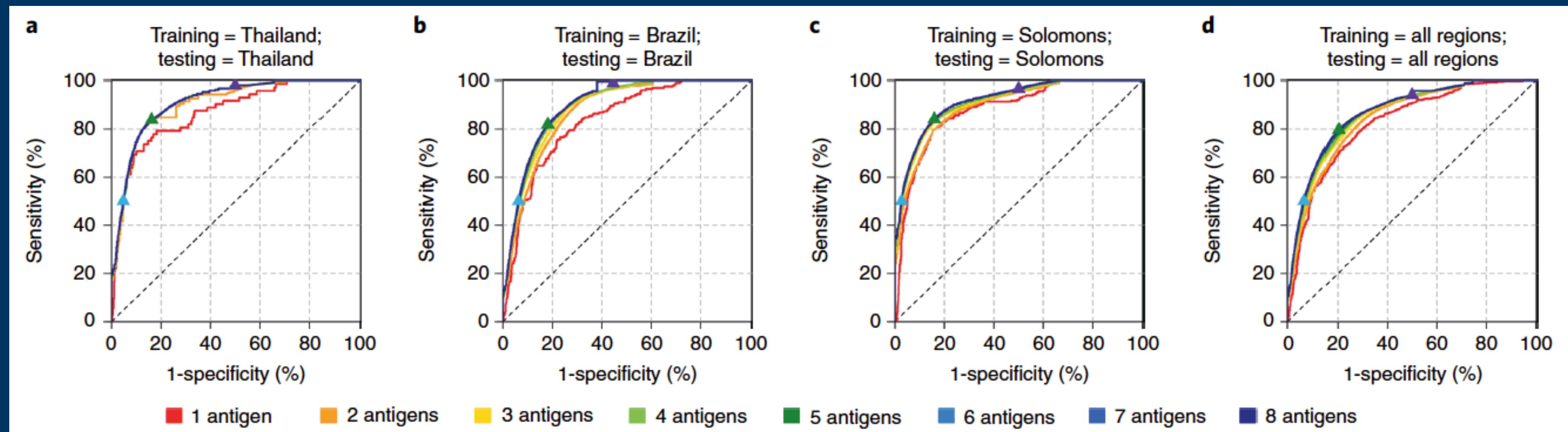
Data from three countries

Brazil
Thailand
Solomon Island

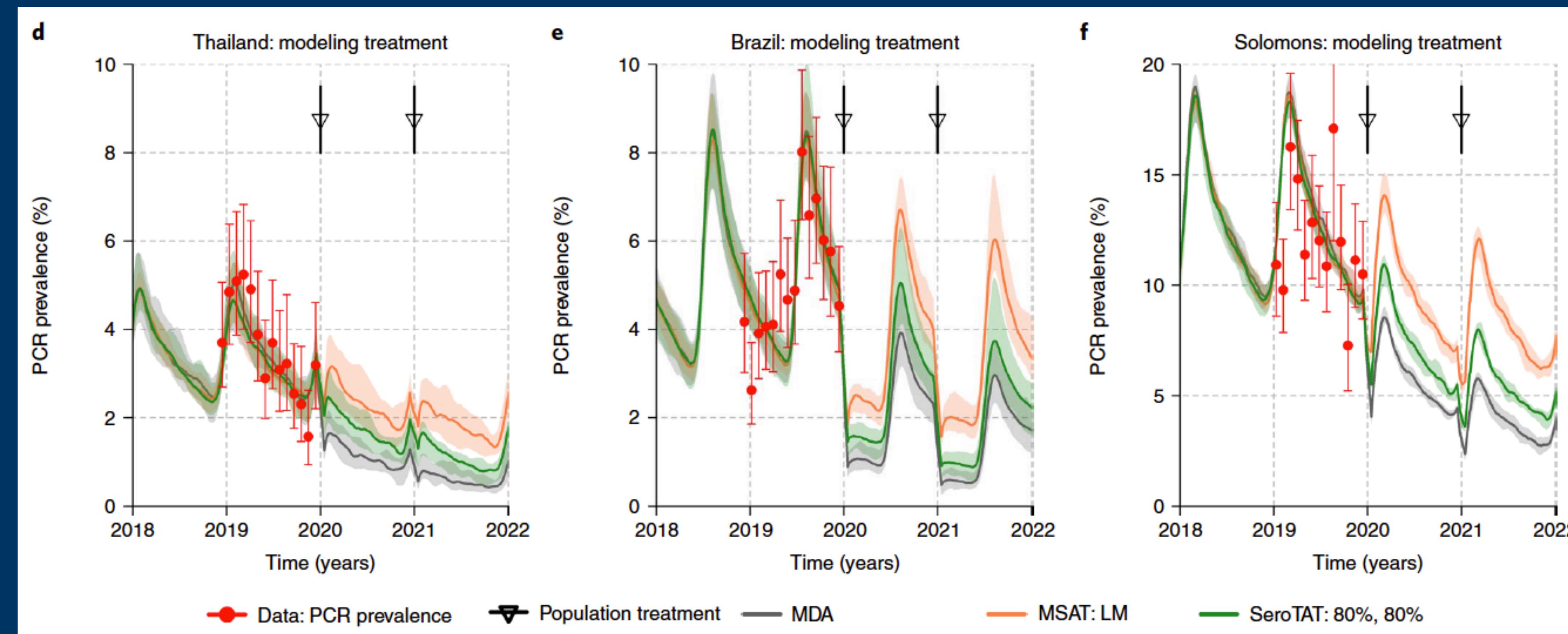
Screening of antimalarial antibodies

Prediction of exposure in the last 9 months

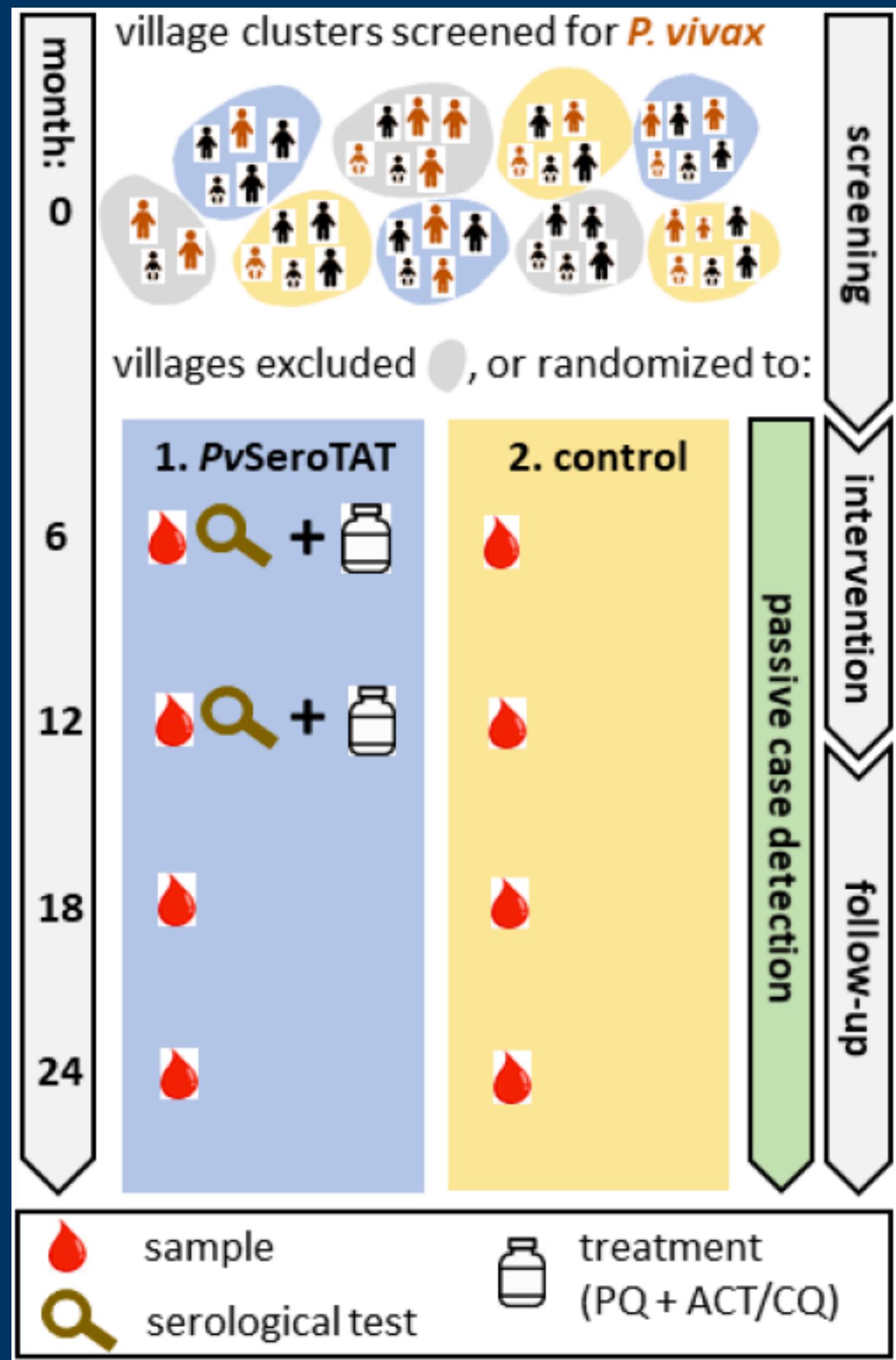
PvSTEM for malaria control



PvSTEM for malaria control



Future cluster randomised clinical trial



Box 2: Cluster Randomised Trial design summary.

- **Sites.** (i) Ethiopia; (ii) Madagascar.
- **Arms.** (i) Control; (ii) Intervention: *PvSeroTAT*.
- **Clusters screened per site.** 36
- **Clusters per arm per site.** 12
- **Total clusters.** (2 sites)*(2 arms)*(12 clusters) = 48
- **Participants per cluster.** 400 (200 – 600)
- **Samples per cluster.** 200
- **Target prevalence.** 3% (1% – 10%) *P. vivax* PCR prevalence.
- **Coefficient of variation.** $k = 0.4$ (0.3 – 0.5)
- **Intervention diagnostic test.** Serological test for recent *P. vivax* infection.
- **Intervention treatment.** Primaquine for 7 days at 1 mg/kg with G6PD testing. Directly observed.
- **Intervention rounds.** 2 rounds 6 months apart.
- **Expected effect size.** 60% (50 – 70%) reduction in *P. vivax* PCR prevalence.
- **Duration of follow-up.** 12 months.

Funding: 3.25 Million euros

Hot clinical trials in 2023

Table 1 | Clinical trials to watch in 2023

Treatment	Organization	Description	Phase	Lead indication
Exenatide	University College London	Neuroprotective effect of exenatide, used to treat type 2 diabetes, over a 2-year follow-up period	3	Parkinson's disease
Diet and exercise	Centros de Investigación en Red del Instituto de Salud Carlos III	Long-term effect of a weight-loss intervention based on a reduced-calorie Mediterranean diet, physical activity and behavioral support	3	Obesity and metabolic syndrome
Lecanemab	Eisai/Biogen	Monoclonal antibody to amyloid- β , for the treatment of mild cognitive impairment with Alzheimer's disease	3	Alzheimer's disease
mRNA-1273 and bivalent vaccine	South Africa Medical Research Council	Efficacy of vaccines against COVID-19 in people with HIV	3	COVID-19
Mirvetuximab soravtansine	Immunogen	ADC that targets tumors with high expression of folate receptor- α	3	Recurrent platinum-resistant ovarian cancer
Fexinidazole	Drugs for Neglected Diseases	Efficacy of the oral drug fexinidazole for <i>rhodesiense</i> sleeping sickness versus that of the existing drugs melarsoprol and suramine	2/3	Stage 2 <i>T. brucei rhodesiense</i> infection
CTX001	CRISPR Therapeutics and Vertex Pharmaceuticals	Autologous CRISPR-Cas9-modified CD34 $^+$ human hematopoietic stem and progenitor cells	1/2/3	Sickle-cell disease
GenPHSat	Charité-Universitätsmedizin Berlin	Base editing to repair a mutation in muscle stem cells, to rebuild muscle	1/2	Muscular dystrophy
Digoxin	ETH Zurich	Dissociation of CTC clusters	1	Metastatic breast cancer
PSA, kallikrein panel, MRI, and prostate biopsy	Tampere University	A new screening approach that reduces harm from PSA screening while maintaining mortality reduction	Population-based randomized trial	Prostate cancer
HPV DNA testing and liquid-based cytology	Australian Centre for the Prevention of Cervical Cancer	HPV testing versus Pap smears to detect early-stage cervical cancer	Population-based randomized trial	Cervical cancer

MRI, magnetic resonance imaging.

Hot clinical trials in 2024

Table 1 | Clinical trials to watch in 2024

Treatment	Organization	Description	Phase	Lead indication
Trastuzumab deruxtecan	AstraZeneca	Efficacy and safety of ADC in HER2-positive patients with and without brain metastases	3b/4	Breast cancer
R21/Matrix-M	University of Oxford and Serum Institute of India	Vaccine efficacy in children 5–36 months of age in four countries	3	Malaria
Ipilimumab and nivolumab	The Netherlands Cancer Institute	Neoadjuvant immunotherapy plus lymph-node dissection	3	Melanoma
VERVE-101	Verve Therapeutics	In vivo base editing of PCSK9	1b	Heterozygous familial hypercholesterolemia
VIR-1388	Vir Biotechnology	Safety, reactogenicity and immunogenicity of a CMV-based vaccine in adults	1	HIV
STEM-PD	Skåne University Hospital, Sweden	Intraputamenal transplantation of human embryonic stem cell derived dopaminergic cells	1	Parkinson's disease
qXR	Nottingham University Hospitals NHS Trust	Class IIa CE-certified deep learning algorithm to analyze chest X ray and computed tomography	Randomized trial	Lung cancer
RISKINDEX	Maastricht University Medical Center	Implementation of machine learning algorithm in the emergency room	Randomized trial	Emergency room admissions
New Orleans Intervention Model	University of Glasgow	Effectiveness and cost-effectiveness of a service for children 0–5 years of age in foster care	Randomized trial	Child mental health
CT scan	Erasmus Medical Center	Annual versus biennial CT scan screening of 26,000 people	Randomized trial	Lung cancer
THP-TA	Human Development Research Foundation, Pakistan	Technology-assisted version of Thinking Healthy Program delivered by peers	Randomized trial	Perinatal depression

Hot clinical trials in 2025

Table 1 | Clinical trials to watch in 2025

Treatment	Organization	Description	Phase	Indication
ION-717	Ionis Pharmaceuticals	Antisense oligonucleotide, to inhibit the production of prion protein	Phase 1/2	Prion disease
Dietary intervention	US National Institutes of Health	Participants receive one of three different diets for 2 weeks	Randomized trial	Nutrition
Cannabidiol	University of Oxford and Jazz Pharmaceuticals	CBD treatment in people at risk of psychosis	Randomized trial	Psychosis
BEAM-101	Beam Therapeutics	Safety and efficacy of autologous base-edited CD34 ⁺ HSCs and progenitor cells	Phase 1/2	Sickle-cell disease
Cool roofs	Heidelberg Institute of Global Health, Harvard T.H. Chan School of Public Health, Africa Health Research Institute and CRSN Burkina Faso	Health, environmental and economic outcomes in households in rural Burkina Faso with and without cool roofs	Randomized trial	Heat stress
Lutetium-177 vipivotide tetraxetan (Pluvicto)	Novartis	Radioligand targeted to PSMA-positive cancer cells	Phase 3	Minimally treated hormone-sensitive prostate cancer
Artificial intelligence chatbot	International Agency for Research on Cancer	Multi-language artificial intelligence chatbot decision aid for HPV testing	Randomized trial	Cervical cancer
mSELY	NYU Langone Health and University of Nairobi	Mobile health toolkit for adolescents and parents	Randomized trial	Mental health
Precision cancer screening	European Union	Polygenic risk score combined with other risk factors such as family history and breast density	Randomized trial	Breast cancer
Home gardening with nutrition and health counseling	KEMRI, CRSN Burkina Faso and Heidelberg Institute of Global Health	Height-for-age score of children in Kenya and Burkina Faso who received the intervention or not	Randomized trial	Malnutrition
GuessWhat	Stanford University	Educational game to recognize and understand emotion	Randomized trial	Autism

Clinical Trials and the Scientific method

Clinical Trials and the Scientific method



Phases of clinical trials (pharmacological)

Phase 0 - Discovery

Discovery motivated by a foundational study based on Basic Science

Phase I - Pilot study (optimal doses)

Small number of volunteers (n=20-100). Not randomised and prone to selective bias.

Phase II - Randomised clinical trials

Determination of clinical efficacy / Safety / Optimal dose with minimal adverse events
Larger number of volunteers and patients (n=50-300)
Use of Mendelian Randomisation if possible

Phases of clinical trials

Phase III - Pre-marketing

A - Evaluation in real clinical practice

Large scale study (n=300-3,000). Multicentric studies. Very expensive.
The use of Mendelian Randomisation if possible

B - Health Economic Evaluation

Cost-effectiveness analysis (weighting the costs with the clinical benefit)

Phase IV - Post-marketing (Evaluation of Adverse Events in Long-Term)

Post-marketing surveillance (side effects)

What are the scientific questions associated with each phase?

Ethical Approval

Mandatory

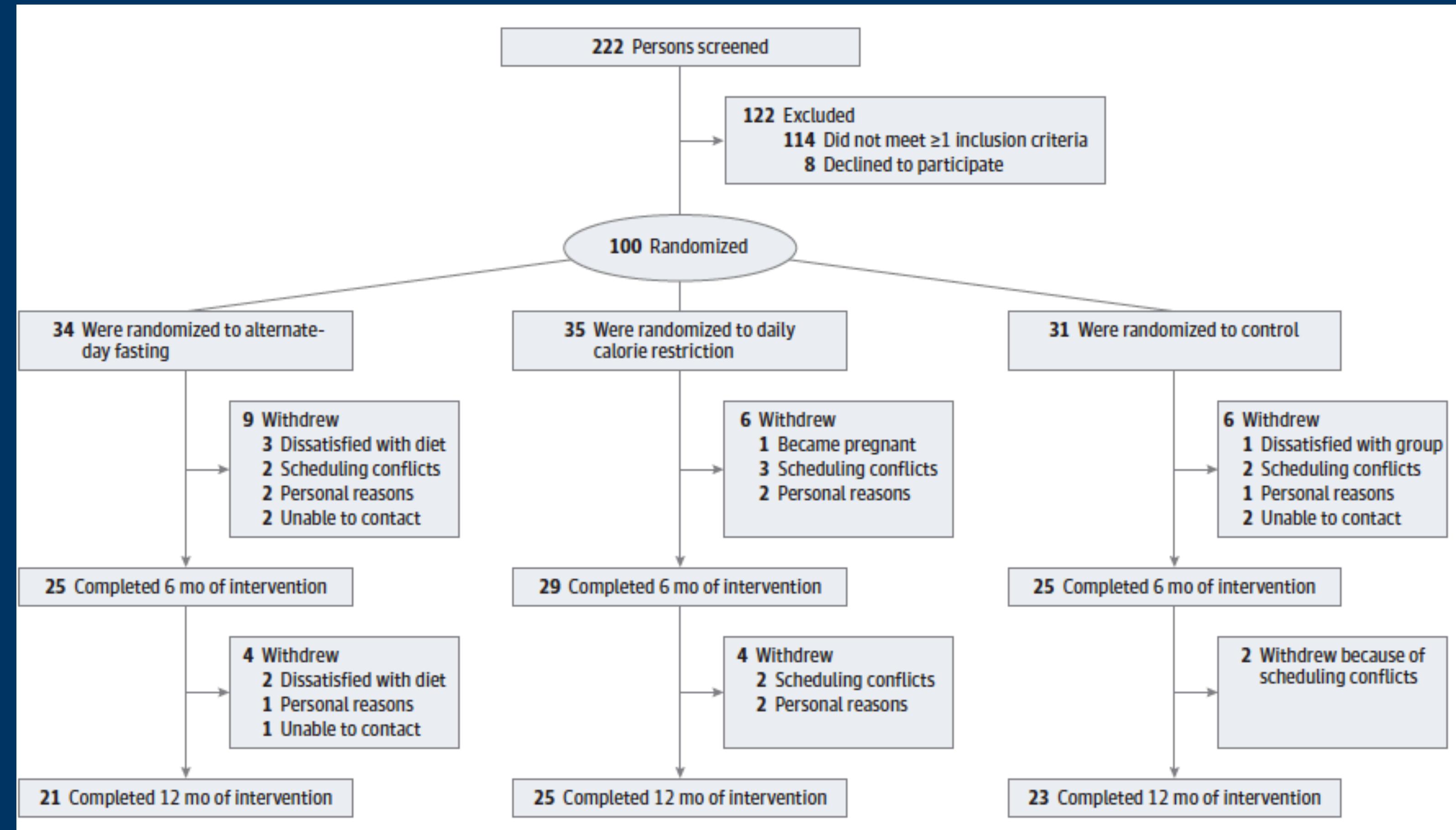
Written consent

What are the statistical consequences of written consent?

Effect of Alternate-Day Fasting on Weight Loss, Weight Maintenance, and Cardioprotection Among Metabolically Healthy Obese Adults

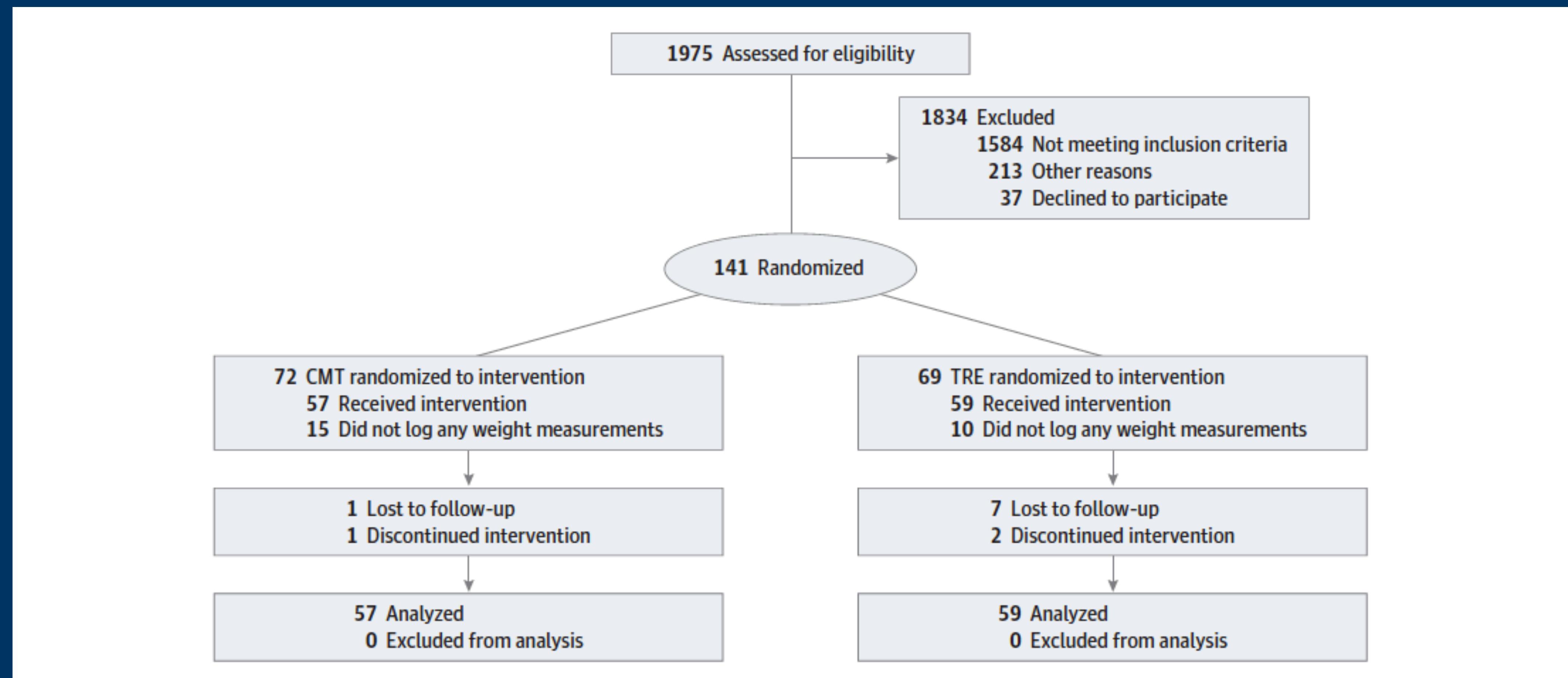
A Randomized Clinical Trial

John F. Trepanowski, PhD; Cynthia M. Kroeger, PhD; Adrienne Barnosky, MD; Monica C. Klempel, PhD; Surabhi Bhutani, PhD; Kristin K. Hoddy, PhD, RD; Kelsey Gabel, MS, RD; Sally Freels, PhD; Joseph Rigdon, PhD; Jennifer Rood, PhD; Eric Ravussin, PhD; Krista A. Varady, PhD



Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity The TREAT Randomized Clinical Trial

Dylan A. Lowe, PhD; Nancy Wu, MS; Linnea Rohdin-Bibby, BA; A. Holliston Moore, PhD; Nisa Kelly, MS; Yong En Liu, BS; Errol Philip, PhD; Eric Vittinghoff, PhD; Steven B. Heymsfield, MD; Jeffrey E. Ogin, MD; John A. Shepherd, PhD; Ethan J. Weiss, MD



What are the statistical consequences of written consent?



Consent to participate (placebo)



Decline to participate (nocebo)

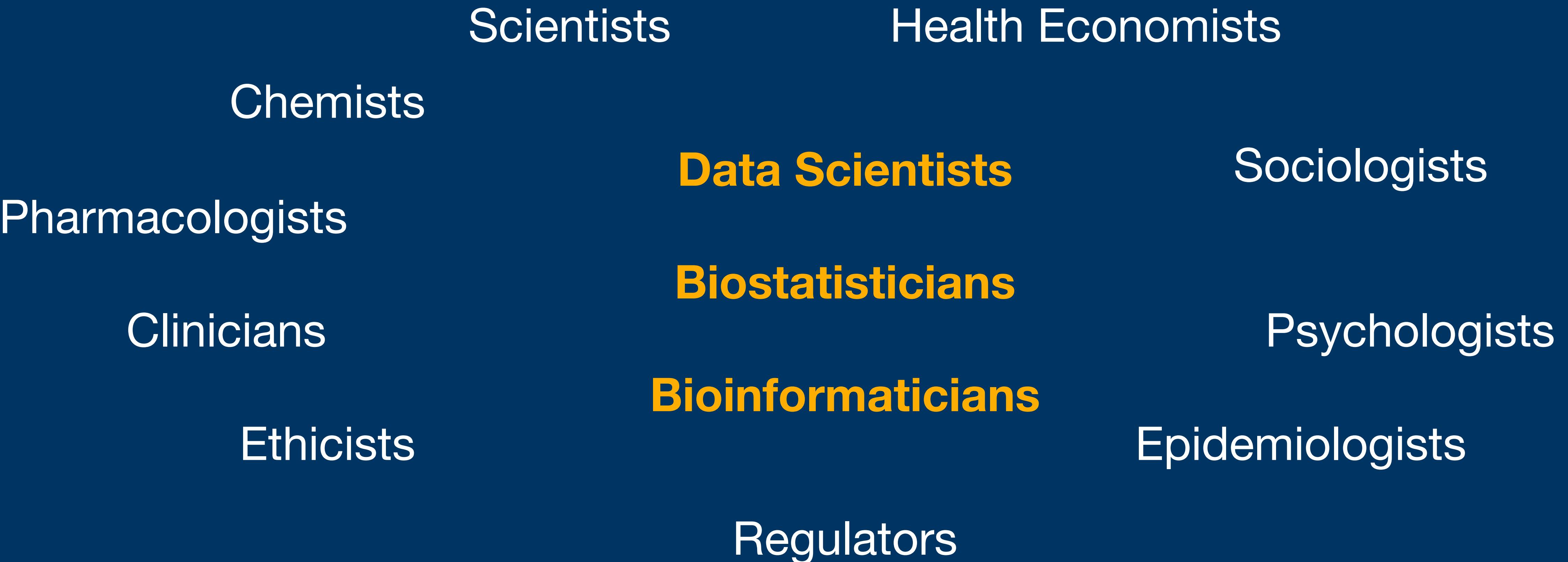


Data sharing versus Data protection

Data sharing versus Data protection

Multidisciplinary of CTs

For the benefit of Patients



The role of different stakeholders in each phases of CT

Phase 0 - Discovery

Basic Scientists/Pharmacologists/Biostatisticians/Data Scientists/Bioinformaticians

Phase I - Pilot study (optimal doses)

Clinicians/Pharmacologists/Biostatisticians/Data Scientists/Bioinformaticians

Phase II - Randomised clinical trials

Clinicians/Biostatisticians/Data Scientists/Bioinformaticians

The role of different stakeholders in each phases of CT

Phase III - Pre-marketing

A - Evaluation in real clinical practice

Clinicians/Epidemiologists/Biostatisticians/Data Scientists/Socialists/Psychologists

B - Health Economic Evaluation

Economists/Epidemiologists/Biostatisticians/Data Scientists



Submission of a Technical Report/Dossier



Approval by National Health Authorities (NICE, FDA, AOTMiT, InfarMed)

The role of different stakeholders in each phases of CT



Approval by National Health Authorities (NICE, FDA, InfarMed)

Phase IV - Post-marketing (Evaluation of Adverse Events in Long-Term)

Clinicians/Epidemiologists/Regulators



Clinical trial registration

Mandatory by the International Committee of Medical Journal Editors (ICMJE)

The declaration of Helsinki

Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject

Registration platforms

- ICTRP - International Clinical Trial Registration Platform (by WHO)
- ClinicalTrials.gov (US Government)
- EU Clinical Trials Register
- ISRCTN registry (BMC, part of Springer Nature)
- Others

Data from ClinicalTrial.gov

Study and Intervention type	# Registered Studies (%)	# Registered studies with posted results (%)
n	448 686	57 900
Interventional	346,021 (77.1%)	54,617 (94.3%)
Type of Intervention		
Drug/Biologic	180,674 (40.3%)	41,007 (70.8%)
Behavioural	119,676 (26.7%)	11,349 (19.6%)
Surgical procedure	35,889 (8.0%)	2,862 (4.9%)
Device	46,337 (10.3%)	7,992 (13.8%)
Observational	100,937 (22.5%)	3,283 (5.7%)
Expanded Access	887 (0.2%)	N/A

24 registration elements (ICTRP)

1. Primary registry and trial identifying number
2. Date of Registration in Primary Registration
3. Secondary Identifying Numbers
4. Sources of Monetary or Material Support
5. Primary Sponsor
6. Secondary Sponsor
7. Contact for Public Queries
8. Contact for Scientific Queries
9. Public Title
10. Scientific Title
11. Countries of Recruitment
12. Health Conditions/Problem Studied
13. Intervention(s)
14. Key Inclusion and Exclusion Criteria
15. Study type
16. Date of First Enrolment
17. Sample size
18. Recruitment Status
19. Primary Outcome
20. Key Secondary Outcomes
21. Ethics Review
22. Completion Date
23. Summary Results
24. Participant-level data sharing statement

Let's work with practical examples

Remdesvir trial for COVID-19

Rituximab trial for ME/CFS

Primaquine trial for Malaria

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial



Trials
Registration

Yeming Wang*, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*,
Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu,
Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang,
Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jakl, Frederick G Hayden, Peter W Harby, Bin Cao, Chen Wang

Summary

Background No specific antiviral drug has been proven effective for treatment of patients with severe coronavirus disease 2019 (COVID-19). Remdesivir (GS-5734), a nucleoside analogue prodrug, has inhibitory effects on pathogenic animal and human coronaviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro, and inhibits Middle East respiratory syndrome coronavirus, SARS-CoV-1, and SARS-CoV-2 replication in animal models.

Methods We did a randomised, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China. Eligible patients were adults (aged ≥ 18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, oxygen saturation of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. Primary analysis was done in the intention-to-treat (ITT) population and safety analysis was done in all patients who started their assigned treatment. This trial is registered with ClinicalTrials.gov, NCT04257656.

Findings Between Feb 6, 2020, and March 12, 2020, 237 patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo); one patient in the placebo group who withdrew after randomisation was not included in the ITT population. Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1·52 [0·95–2·43]). Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early.

Interpretation In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.

What did you learn from the summary?

Treatments

Remdesvir
Placebo

Study design

Randomized
Multicentric
Remdesvir vs Placebo (2:1)

Target population

Adults (>18 yo)
Confirmed
Oxygen saturation >

Sample size

158 Remdesvir
79 Placebo

Primary Endpoint

Time from randomisation to
decline of two points

Type of analysis

Intention-to-treat

**What statistical methods could be applied in
this trial?**

B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

A Randomized, Double-Blind, Placebo-Controlled Trial

Øystein Fluge, MD, PhD; Ingrid G. Rekeland, MD; Katarina Lien, MD; Hanne Thürmer, MD, PhD; Petter C. Borchgrevink, MD, PhD; Christoph Schäfer, MD; Kari Sørland, RN; Jörg Aßmus, PhD; Irini Ktoridou-Valen, MD; Ingrid Herder, MD; Merethe E. Gotaas, MD; Øivind Kvammen, MD; Katarzyna A. Baranowska, MD, PhD; Louis M.L.J. Bohnen, MD; Sissel S. Martinsen, RN; Ann E. Lonar, RN; Ann-Elise H. Solvang, RN; Arne E.S. Gya, RN; Ove Bruland, PhD; Kristin Risa, MSc; Kine Alme, MSc; Olav Dahl, MD, PhD; and Olav Mella, MD, PhD

Background: Previous phase 2 trials indicated benefit from B-lymphocyte depletion in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Objective: To evaluate the effect of the monoclonal anti-CD20 antibody rituximab versus placebo in patients with ME/CFS.

Design: Randomized, placebo-controlled, double-blind, multi-center trial. (ClinicalTrials.gov: NCT02229942)

Setting: 4 university hospitals and 1 general hospital in Norway.

Patients: 151 patients aged 18 to 65 years who had ME/CFS according to Canadian consensus criteria and had had the disease for 2 to 15 years.

Intervention: Treatment induction with 2 infusions of rituximab, 500 mg/m² of body surface area, 2 weeks apart, followed by 4 maintenance infusions with a fixed dose of 500 mg at 3, 6, 9, and 12 months ($n = 77$), or placebo ($n = 74$).

Measurements: Primary outcomes were overall response rate (fatigue score ≥ 4.5 for ≥ 8 consecutive weeks) and repeated measurements of fatigue score over 24 months. Secondary outcomes included repeated measurements of self-reported function over 24 months, components of the Short Form-36 Health Survey and Fatigue Severity Scale over 24 months, and changes from baseline to

18 months in these measures and physical activity level. Between-group differences in outcome measures over time were assessed by general linear models for repeated measures.

Results: Overall response rates were 35.1% in the placebo group and 26.0% in the rituximab group (difference, 9.2 percentage points [95% CI, -5.5 to 23.3 percentage points]; $P = 0.22$). The treatment groups did not differ in fatigue score over 24 months (difference in average score, 0.02 [CI, -0.27 to 0.31]; $P = 0.80$) or any of the secondary end points. Twenty patients (26.0%) in the rituximab group and 14 (18.9%) in the placebo group had serious adverse events.

Limitation: Self-reported primary outcome measures and possible recall bias.

Conclusion: B-cell depletion using several infusions of rituximab over 12 months was not associated with clinical improvement in patients with ME/CFS.

Primary Funding Source: The Norwegian Research Council, Norwegian Regional Health Trusts, Kavli Trust, MEandYou Foundation, and Norwegian ME Association.

Ann Intern Med. 2019;170:585-593. doi:10.7326/M18-1451

Annals.org

For author affiliations, see end of text.

This article was published at Annals.org on 2 April 2019.

What did you learn from the summary?

Treatments

Rituximab
Placebo

Sample size

77 Rituximab
74 Placebo

Study design

Randomized
Multicentric
Double-Blind
Placebo vs Control

Primary Endpoint

Overall response rate

Target population

Adults (18-65) with ME/CFS
with duration of 2-15 years

Type of analysis

No stated.

**What statistical methods could be applied in
this trial?**



Single dose primaquine for clearance of *Plasmodium falciparum* gametocytes in children with uncomplicated malaria in Uganda: a randomised, controlled, double-blind, dose-ranging trial



Alice C Eziefula, Teun Bousema, Shunmay Yeung, Moses Kamya, Asiphias Owaraganise, Grace Gabagaya, John Bradley, Lynn Grignard, Kjerstin H W Lanke, Humphrey Wanzira, Arthur Mpimbaza, Samuel Nsobya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley

Summary

Background Primaquine is the only available drug that clears mature *Plasmodium falciparum* gametocytes in infected human hosts, thereby preventing transmission of malaria to mosquitoes. However, concerns about dose-dependent haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiencies have limited its use. We assessed the dose-response association of single-dose primaquine for gametocyte clearance and for safety in *P falciparum* malaria.

Methods We undertook this randomised, double-blind, placebo-controlled trial with four parallel groups in Jinja district, eastern Uganda. We randomly allocated Ugandan children aged 1–10 years with uncomplicated falciparum malaria and normal G6PD enzyme function to receive artemether-lumefantrine, combined with either placebo or with 0·1 mg/kg, 0·4 mg/kg, or 0·75 mg/kg (WHO reference dose) primaquine base. Randomisation was done with computer-generated four-digit treatment assignment codes allocated to random dose groups in block sizes of 16. Study staff who provided care or assessed outcomes and the participants remained masked to the intervention group after assignment. The primary efficacy endpoint was the non-inferiority of the mean duration of gametocyte carriage in the test doses compared with the reference group of 0·75 mg primaquine per kg, with a non-inferiority margin of 2·5 days. The primary safety endpoint was the superiority of the arithmetic mean maximum decrease in haemoglobin concentration from enrolment to day 28 of follow-up in the primaquine treatment groups compared with placebo, with use of significance testing of pairwise comparisons with a cutoff of $p=0\cdot05$. The trial is registered with ClinicalTrials.gov, number NCT01365598.

Findings We randomly allocated 468 participants to receive artemether-lumefantrine combined with placebo (119 children) or with 0·1 mg/kg (116), 0·4 mg/kg (116), or 0·75 mg/kg (117) primaquine base. The mean duration of gametocyte carriage was 6·6 days (95% CI 5·3–7·8) in the 0·75 mg/kg reference group, 6·3 days (5·1–7·5) in the 0·4 mg/kg primaquine group ($p=0\cdot74$), 8·0 days (6·6–9·4) in the 0·1 mg/kg primaquine group ($p=0\cdot14$), and 12·4 days (9·9–15·0) in the placebo group ($p<0\cdot0001$). No children showed evidence of treatment-related haemolysis, and the mean maximum decrease in haemoglobin concentration was not associated with the dose of primaquine received—it did not differ significantly compared with placebo (10·7 g/L, SD 11·1) in the 0·1 mg/kg (11·4 g/L, 9·4; $p=0\cdot61$), 0·4 mg/kg (11·3 g/L, 10·0; $p=0\cdot67$), or 0·75 mg/kg (12·7 g/L, 8·2; $p=0\cdot11$) primaquine groups.

Interpretation We conclude that 0·4 mg/kg primaquine has similar gametocytocidal efficacy to the reference 0·75 mg/kg primaquine dose, but a dose of 0·1 mg/kg was inconclusive for non-inferiority. Our findings call for the prioritisation of further trials into the efficacy and safety of doses of primaquine between 0·1 mg/kg and 0·4 mg/kg (including the dose of 0·25 mg/kg recently recommended by WHO), in view of the potential for widespread use of the drug to block malaria transmission.

What did you learn from the summary?

Treatments

Primaquine
3 doses
Placebo

Study design

Randomized, double blind,
dose range

Target population

Children with
uncomplicated malaria
and G6PD normal function

Sample size

n=119, Placebo,
n=116, 0.1mg/kg
n=116 0.4mg/kg
n=117, 0.75mg/kg

Primary Endpoint

Efficacy endpoint
Safety endpoint

Type of analysis

Not clear

**What statistical methods could be applied in
this trial?**

Let's go practical!

RESEARCH ARTICLE

B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment

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Abstract

Background

Myalgic Encephalopathy/Chronic Fatigue Syndrome (ME/CFS) is a disease of unknown etiology. We previously reported a pilot case series followed by a small, randomized, placebo-controlled phase II study, suggesting that B-cell depletion using the monoclonal anti-CD20 antibody rituximab can yield clinical benefit in ME/CFS.

Methods

In this single-center, open-label, one-armed phase II study (NCT01156909), 29 patients were included for treatment with rituximab (500 mg/m^2) two infusions two weeks apart, followed by maintenance rituximab infusions after 3, 6, 10 and 15 months, and with follow-up for 36 months.

Findings

Major or moderate responses, predefined as lasting improvements in self-reported *Fatigue* score, were detected in 18 out of 29 patients (intention to treat). Clinically significant responses were seen in 18 out of 28 patients (64%) receiving rituximab maintenance treatment. For these 18 patients, the mean response durations within the 156 weeks study period were 105 weeks in 14 major responders, and 69 weeks in four moderate responders. At end of follow-up (36 months), 11 out of 18 responding patients were still in ongoing clinical remission. For major responders, the mean lag time from first rituximab infusion until start of clinical response was 23 weeks (range 8–66). Among the nine patients from the placebo group in the previous randomized study with no significant improvement during 12

Let's analyse some data

Estimate the probability of treatment response

What are the factors affecting the probability of treatment response?

Results

n=29

Men/women= 20 women ; 9 men; 2.2:1 women:men

Age (mean/median; range) = 40.3 yo / 42.2 yo (21-59yo)

Disease duration (mean/median; range) = 8.9 y / 8 y (1-20 y)

Infection trigger
Yes/No/Possible

Infection

Treatment Response
11/29 (0.38; 38%): 95% CI = (0.20;0.58) Binom.test (0.21; 0.58) Prop.test