Regione Lombardia

UNIVERSITÀ DEGLI STUDI DI MILANO

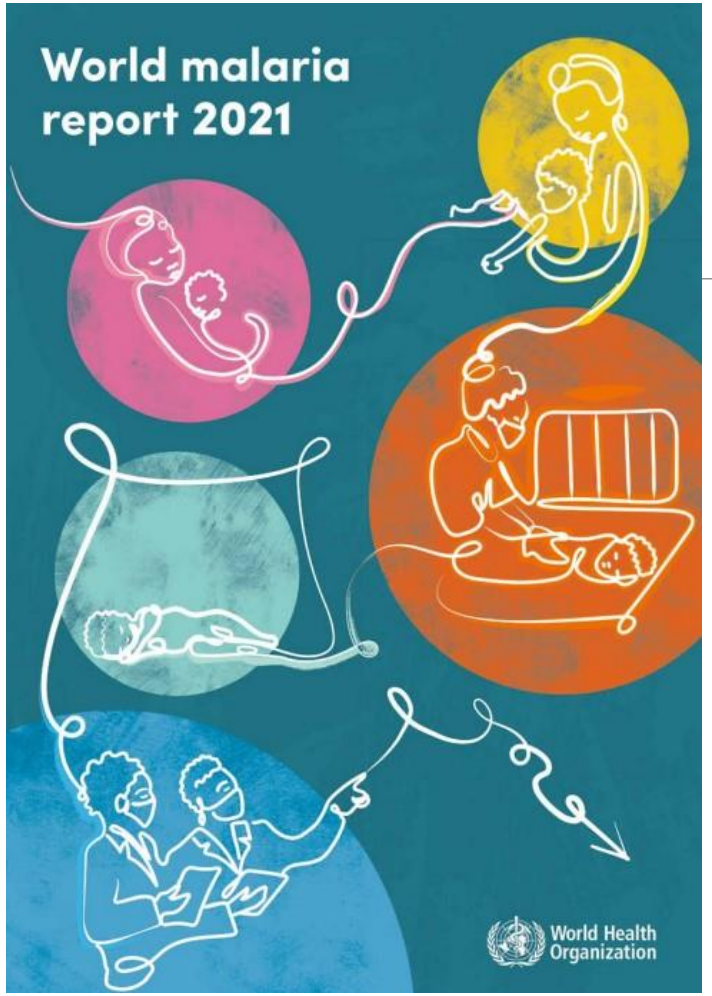
UNIVERSITÀ DEGLI STUDI DI BRESCIA

GIORNATE INFETTIVOLOGICHE "LUIGI SACCO" 2022

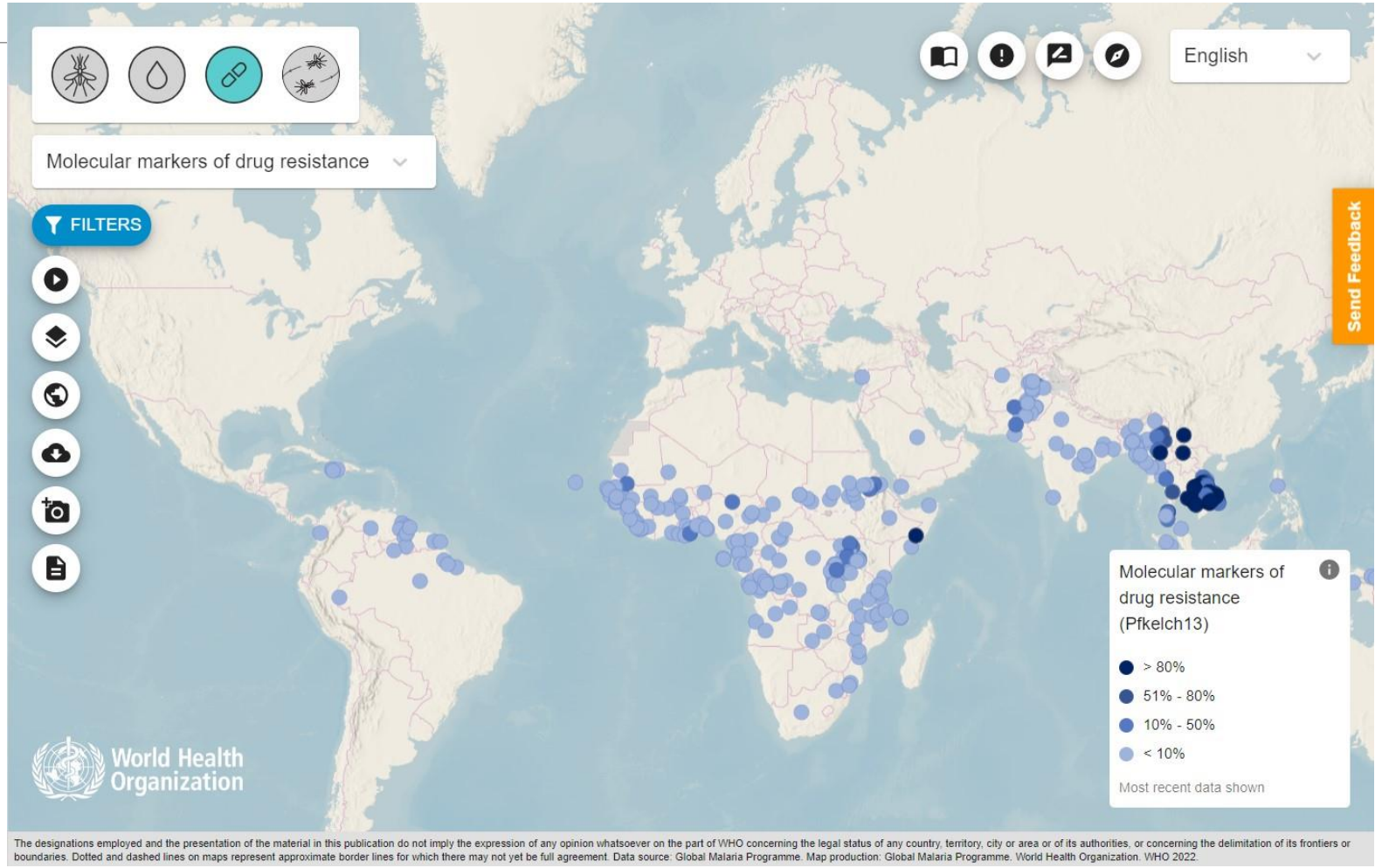
PATOLOGIE TROPICALI

Verena Crosato
Malattie Infettive e Tropicali
Università degli Studi di Brescia

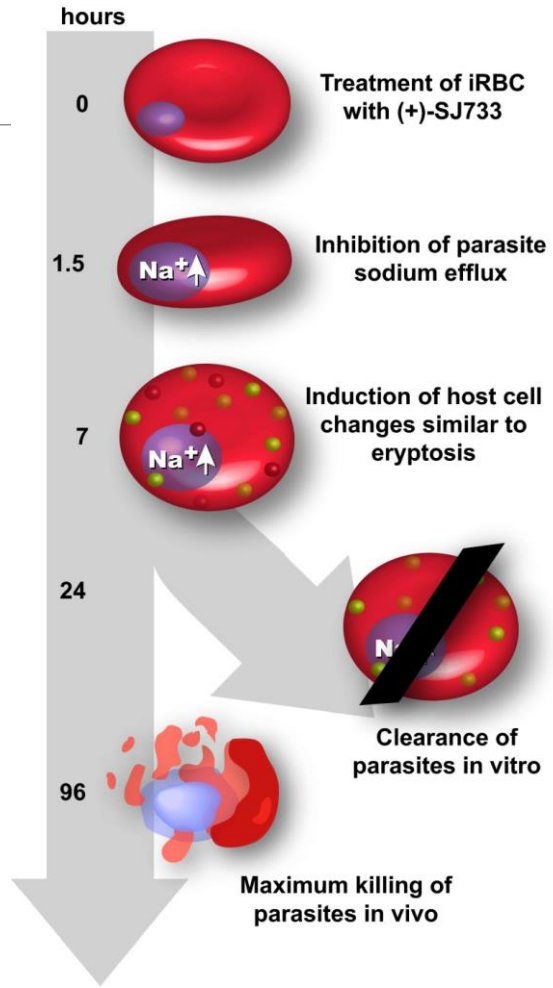
MILANO, 14-15 OTTOBRE 2022



2020 241 MILLION MALARIA CASES WORLDWIDE IN 85 MALARIA ENDEMIC COUNTRIES, MOSTLY IN SUBSAHARAN AFRICA WITH **627,000 DEATHS.**



SJ733



PNAS PLUS

(+)-SJ733, a clinical candidate for malaria that acts through ATP4 to induce rapid host-mediated clearance of *Plasmodium*

María Belén Jiménez-Díaz[a], Daniel Ebert[b], Yandira Salinas[c], Anupam Pradhan[d], Adele M. Lehane[e], Marie-Eve Myrand-Lapierre[f], Kathleen G. O'Loughlin[g], David M. Shackleford[h], Mariana Justino de Almeida[i], Angela K. Carrillo[c], Julie A. Clark[c], Adelaide S. M. Dennis[e], Jonathon Diep[b], Xiaoyan Deng[f], Sandra Duffy[j], Aaron N. Endsley[g], Greg Fedewa[b], W. Armand Guiguemde[c], María G. Gómez[a], Gloria Holbrook[c], Jeremy Horst[b], Charles C. Kim[k], Jian Liu[l], Marcus C. S. Lee[i], Amy Matheny[c], María Santos Martínez[a], Gregory Miller[c], Ane Rodríguez-Alejandre[a], Laura Sanz[a], Martina Sigal[c], Natalie J. Spillman[e], Philip D. Stein[l], Zheng Wang[l], Fangyi Zhu[c], David Waterson[m], Spencer Knapp[l], Anang Shelat[c], Vicky M. Avery[j], David A. Fidock[i], Francisco-Javier Gamo[a], Susan A. Charman[h], Jon C. Mirsalis[g], Hongshen Ma[f], Santiago Ferrer[a], Kiaran Kirk[e], Iñigo Angulo-Barturen[a], Dennis E. Kyle[d], Joseph L. DeRisi[b], David M. Floyd[l], and R. Kiplin Guy[c,1]

Safety, tolerability, pharmacokinetics, and antimalarial efficacy of a novel *Plasmodium falciparum* ATP4 inhibitor SJ733: a first-in-human and induced blood-stage malaria phase 1a/b trial

Aditya H Gaur, James S McCarthy*, John C Panetta, Ronald H Dallas, John Woodford, Li Tang, Amber M Smith, Tracy B Stewart, Kristen C Branum, Burgess B Freeman III, Nehali D Patel, Elizabeth John, Stephan Chalon, Shelley Ost, Ryan N Heine, Julie L Richardson, Robbin Christensen, Patricia M Flynn, Yvonne Van Gessel, Branko Mitasev, Jörg J Möhrle, Fabian Gusovsky, Lidiya Bebrevska, R Kiplin Guy*

- Safe (AE mainly due to malarial activity)
- Well tolerated
- Favourable pharmacokinetic
- Good oral bioavailability
- Not influenced by food ingestion
- Rapid antiparasitic effect
- Exposure increase proportional to the dose through to the 600 mg dose, then saturable at higher doses

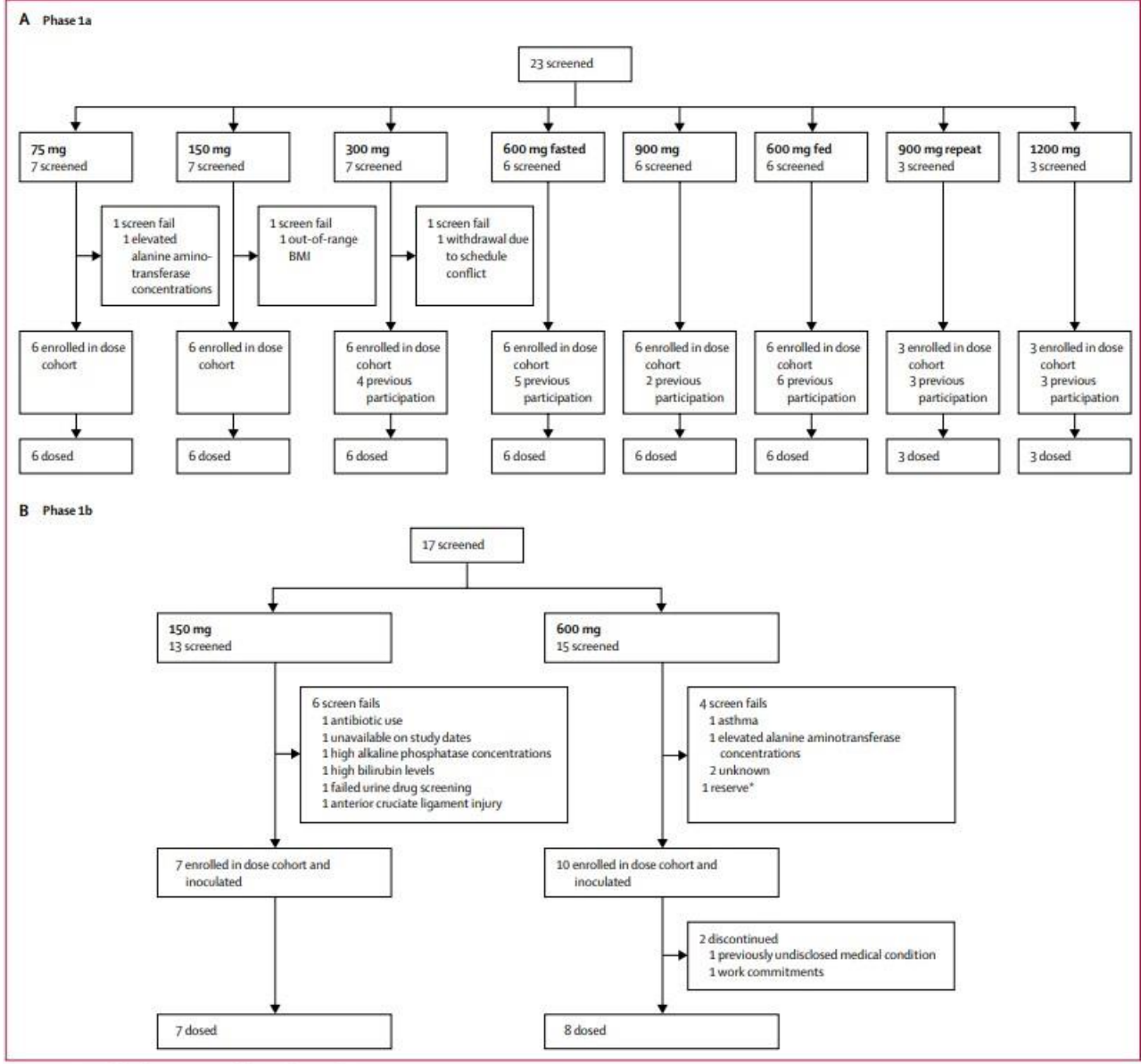


Figure 1: **Design of the phase 1a (A) and phase 1b (B) studies**
In phase 1a single ascending doses of SJ733 were tested in six fasted dose cohorts of 75, 150, 300, 600, 900 (repeated to confirm unexpected plateauing of study drug exposure compared with 600 mg dose cohort), and 1200 mg and one fed dose cohort of 600 mg. Enrolment in more than one non-consecutive dose cohort was allowed with at least 14 days required between doses. In phase 1b two doses of 150 and 600 mg were tested in fasted conditions. BMI=body-mass index. *Met inclusion criteria but was not required because the target cohort size had been met.

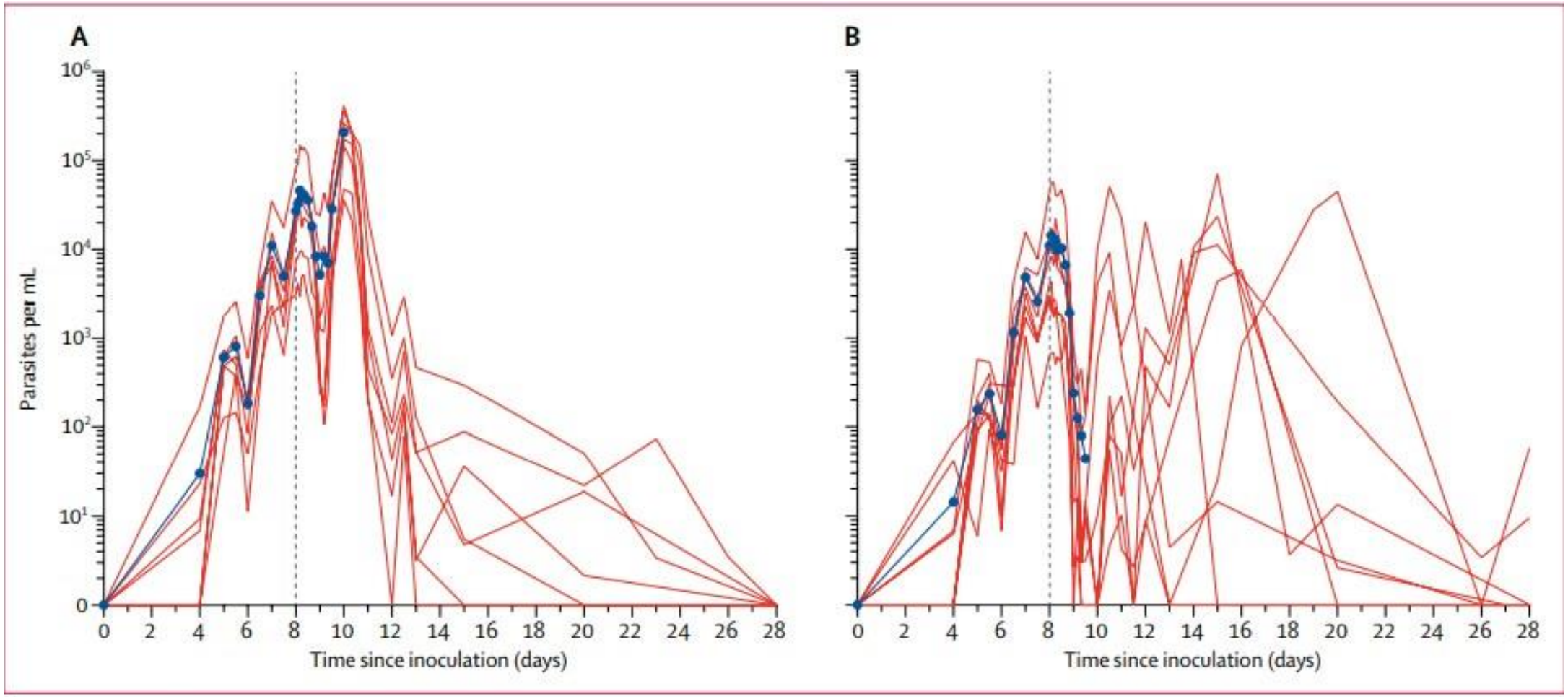


Figure 3: **Parasite clearance profiles in the phase 1b study**

Parasite clearance profiles for participants in the phase 1b 150 mg SJ733 dose cohort (A) and 600 mg SJ733 dose cohort (B). Participants were inoculated on day 0 and treated with 150 or 600 mg SJ733 on day 8 (vertical dashed line). Parasitaemia was measured by 18S ribosomal RNA quantitative PCR.[12] Red lines represent individual parasitaemia. Solid blue lines represent mean parasitaemia until earliest administration of artemether–lumefantrine in the dose cohort.

Drug exposure not maintained over the estimated MIC for a sufficient duration (> 96 h) to result in a single dose cure

Combining SJ733, an oral ATP4 inhibitor of *Plasmodium falciparum*, with the pharmacokinetic enhancer cobicistat: An innovative approach in antimalarial drug development

Aditya H. Gaur,[a,$,*] John C. Panetta,[a,$] Amber M. Smith,[b] Ronald H. Dallas,[a] Burgess B. FreemanIII[a] Tracy B. Stewart[a] Li Tang,[a] Elizabeth John,[c] Kristen C. Branum,[a] Nehali D. Patel,[a] Shelley Ost,[b] Ryan N. Heine,[a] Julie L. Richardson,[a] Jared T. Hammill,[d] Lidiya Bebrevska,[e] Fabian Gusovsky,[f] Noritsugu Maki,[f] Toshiharu Yanagi,[f] Patricia M. Flynn,[a] James S. McCarthy,[g] Stephan Chalon,[e,#] and R. Kiplin Guy[d,#]

eBioMedicine 2022;80: 104065
Published online 19 May 2022
https://doi.org/10.1016/j.ebiom.2022.104065

MATERIALS AND METHODS

Combining SJ733, an oral ATP4 inhibitor of *Plasmodium falciparum*, with the pharmacokinetic enhancer cobicistat: An innovative approach in antimalarial drug development

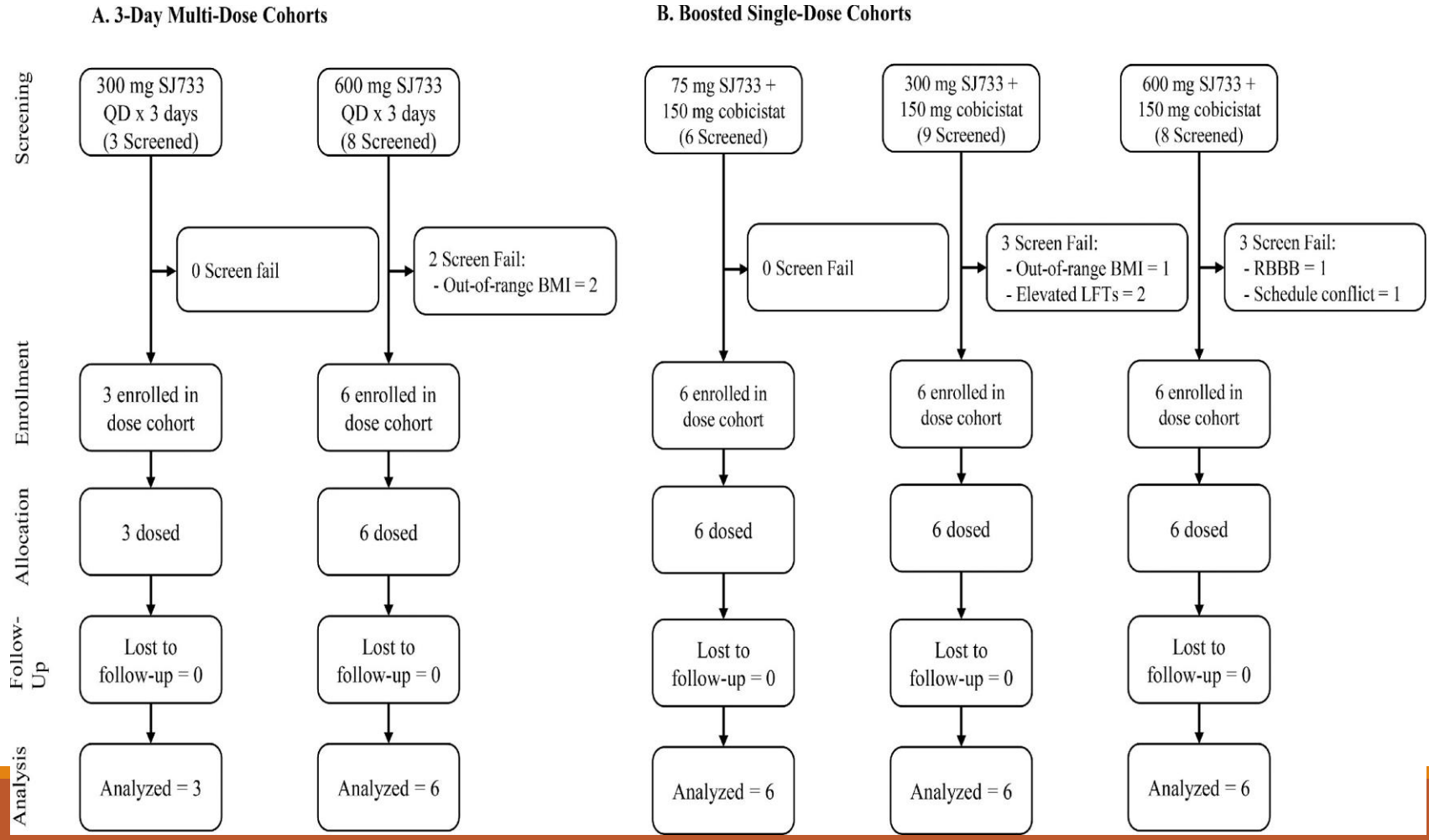
Aditya H. Gaur,[a,$,*] John C. Panetta,[a,$] Amber M. Smith,[b] Ronald H. Dallas,[a] Burgess B. FreemanIII[a] Tracy B. Stewart[a] Li Tang,[a] Elizabeth John,[c] Kristen C. Branum,[a] Nehali D. Patel,[a] Shelley Ost,[b] Ryan N. Heine,[a] Julie L. Richardson,[a] Jared T. Hammill,[d] Lidiya Bebrevska,[e] Fabian Gusovsky,[f] Noritsugu Maki,[f] Toshiharu Yanagi,[f] Patricia M. Flynn,[a] James S. McCarthy,[g] Stephan Chalon,[e,#] and R. Kiplin Guy[d,#]

Single-arm, unblinded Phase 1 study for the treatment of uncomplicated malaria

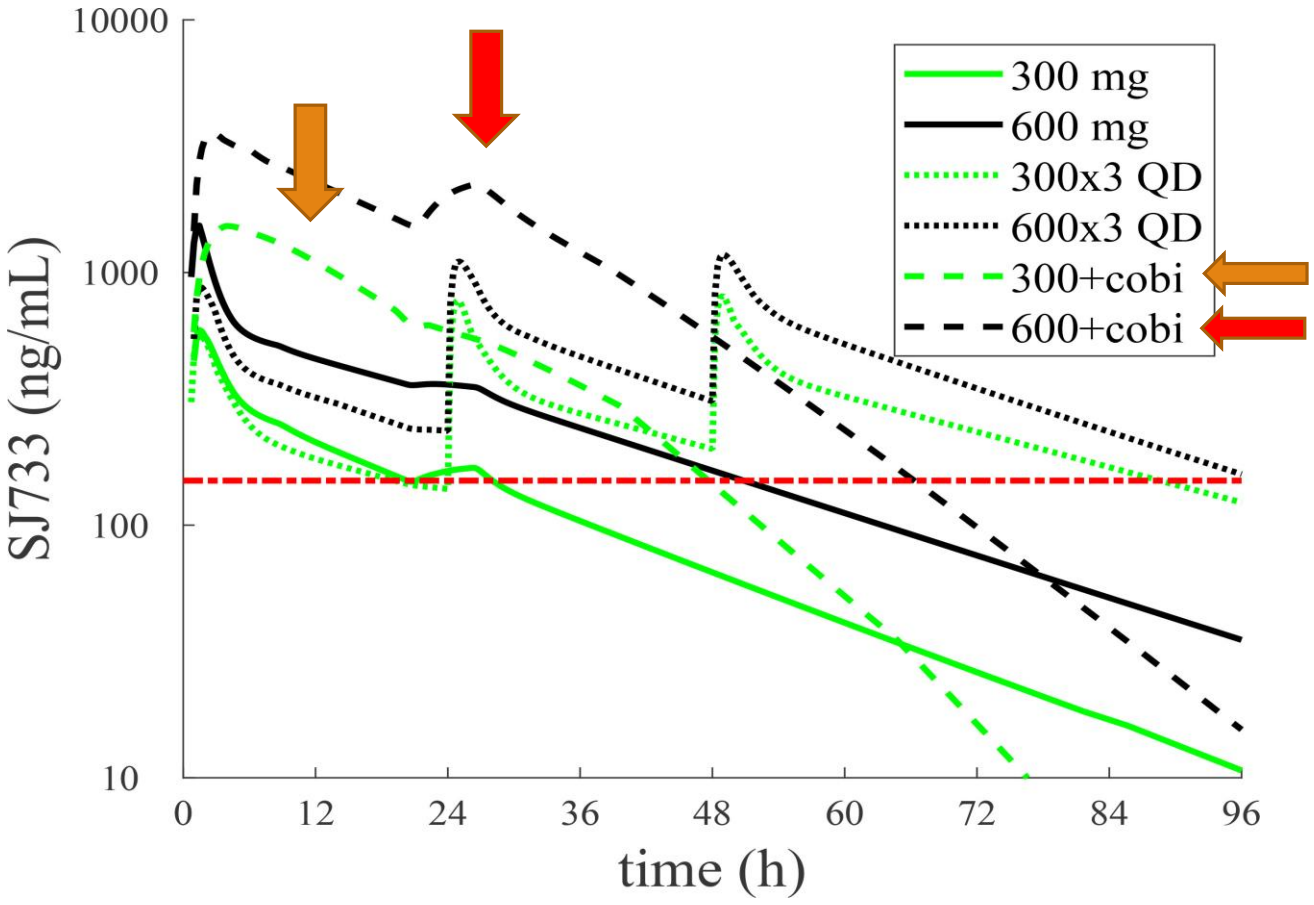
9 volunteers for MAD cohorts (3+6)
18 volunteers for boosted cohorts (6+6+6)

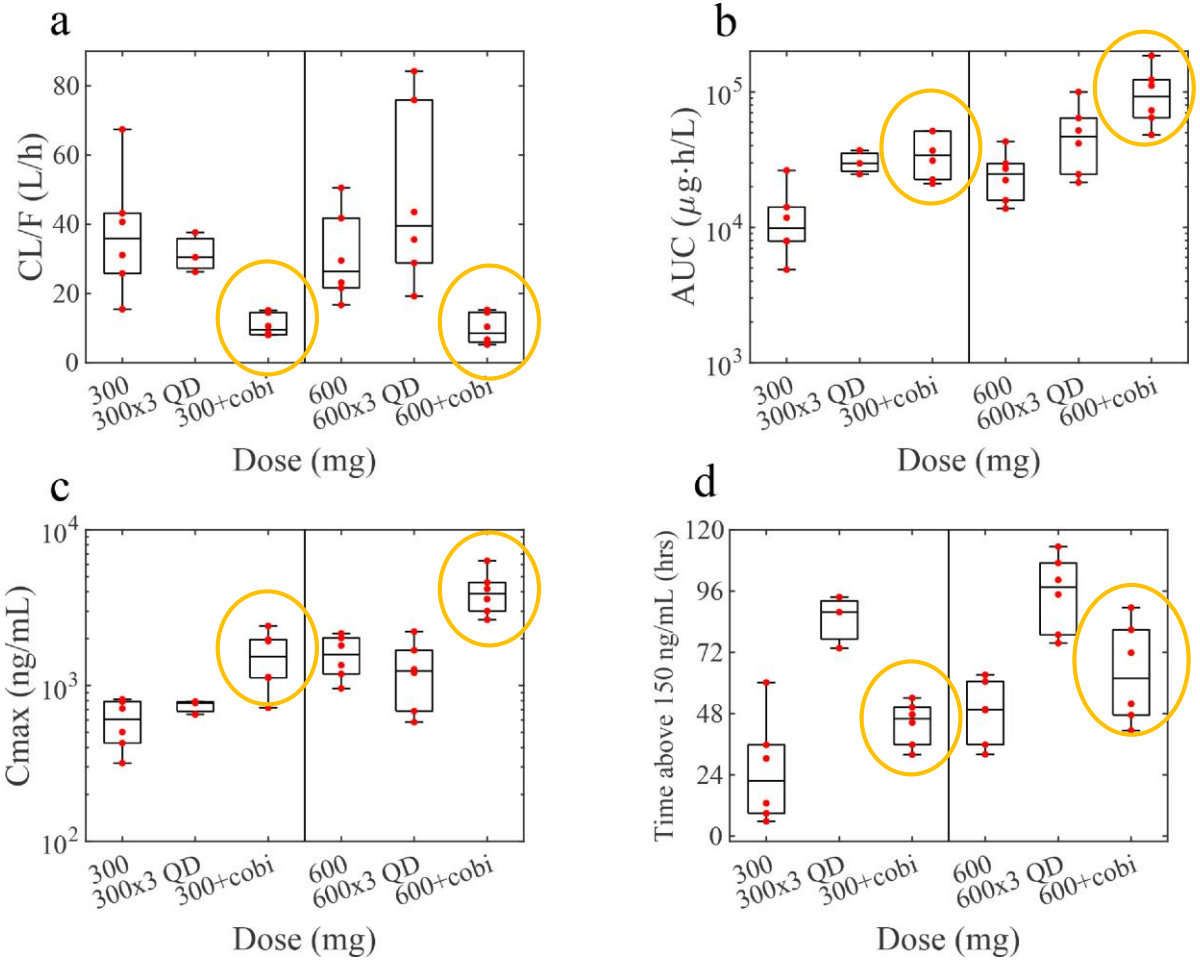
COBICISTAT: strong inhibitor of CYP3A4 with no antiretroviral activity

No SAEs
No QTc alterations



RESULTS





- Increase in SJ733 AUC, and Cmax and decrease of CL/F compared to SAD and MAD
- Increase in time above the MIC compared to SAD
- Reduction of inactive metabolite SJ506 blood levels by 78%

eBioMedicine 2022 80DOI: (10.1016/j.ebiom.2022.104065)

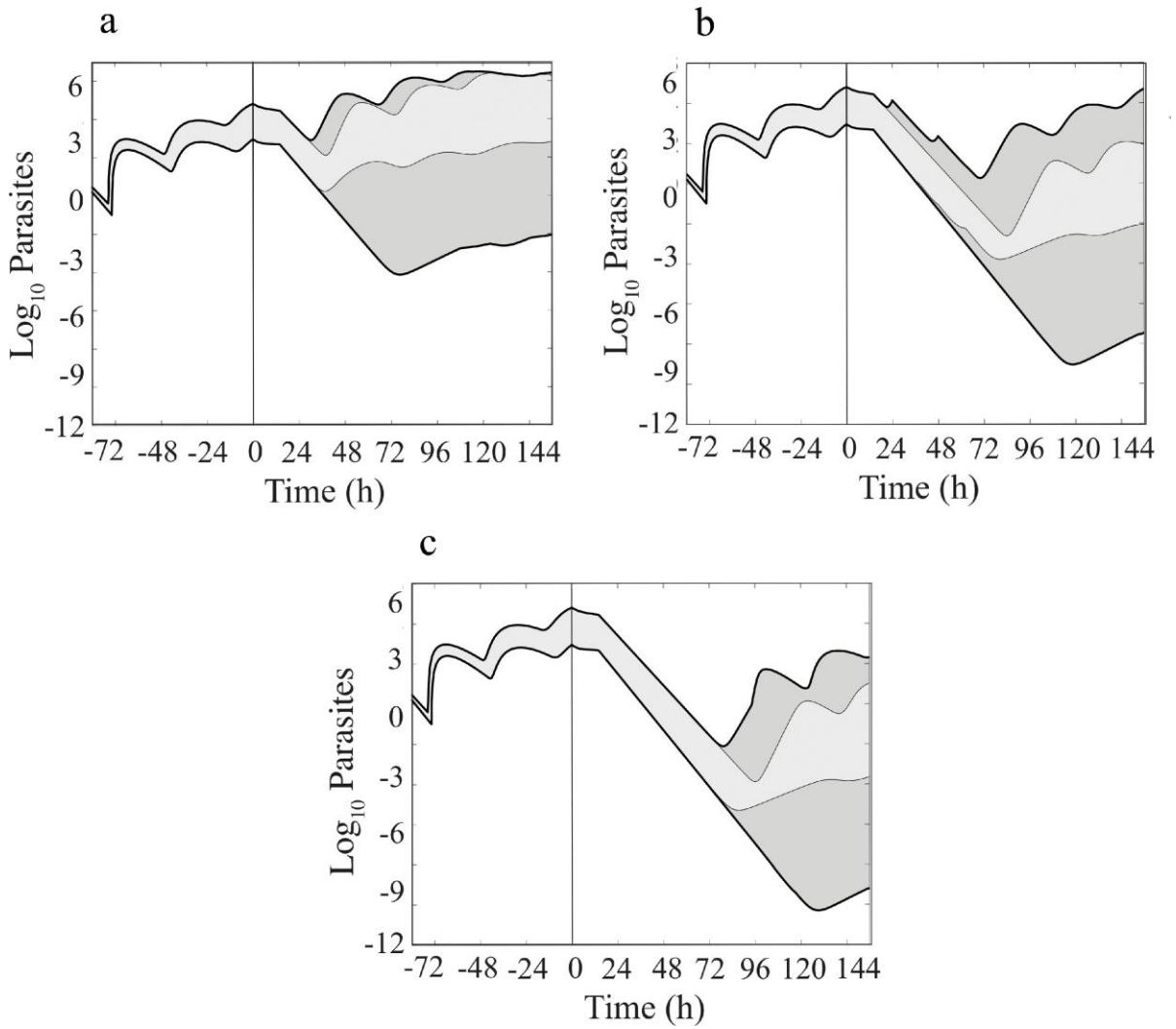


Figure 4. PK/PD simulations of the efficacy of SJ733 alone and SJ733 pharmacoboosted with cobicistat to cure malaria. (**a**) PK/PD model simulation of the effect of single-dose SJ733 (600 mg) alone (light gray) and that predicted for the same dose of SJ733 pharmacoboosted with cobicistat (dark gray). (**b-c**) The same simulations were used to assess multidose SJ733 (b: 300 mg daily for 3 days ± cobicistat and c: 600 mg daily for 3 days ± cobicistat).

Clinically meaningful parasite clearance with

- 600 mg for 3 days
- 300 mg plus cobicistat for 2 days

Ideal parasite clearance with 600 mg+ cobicistat for 2 days

eBioMedicine 2022 80DOI: (10.1016/j.ebiom.2022.104065)

DISCUSSION

Novel ATP4 inhibitor with rapid antimalarial activity (clears peripheral blood of trophozoites and schizonts in 12 hours)

Efficacy requires SJ733 to remain above 150 ng/mL for at least 4 days, or by achieving maximal exposure for at least 3 days

Ideal killing with SJ733 600 mg + cobicistat
-> shortest regimen for malaria

- Less pharmacological interactions
- Less adverse events
- Increased compliance

No concerns about HIV resistance with cobicistat: also suited for high HIV incidence populations

LIMITS

Not studied in pregnant women and childred (cobicistat not indicated in children)

Small study groups

Ethnicity mainly caucasian is not representative of most affected populations

Single dose treatment not yet feasible

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Strongy Detect: Preliminary Validation of a Prototype Recombinant Ss-NIE/Ss-IR Based ELISA to Detect *Strongyloides stercoralis* Infection

William J. Sears*, Thomas B. Nutman

Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, United States of America

* william.sears@nih.gov

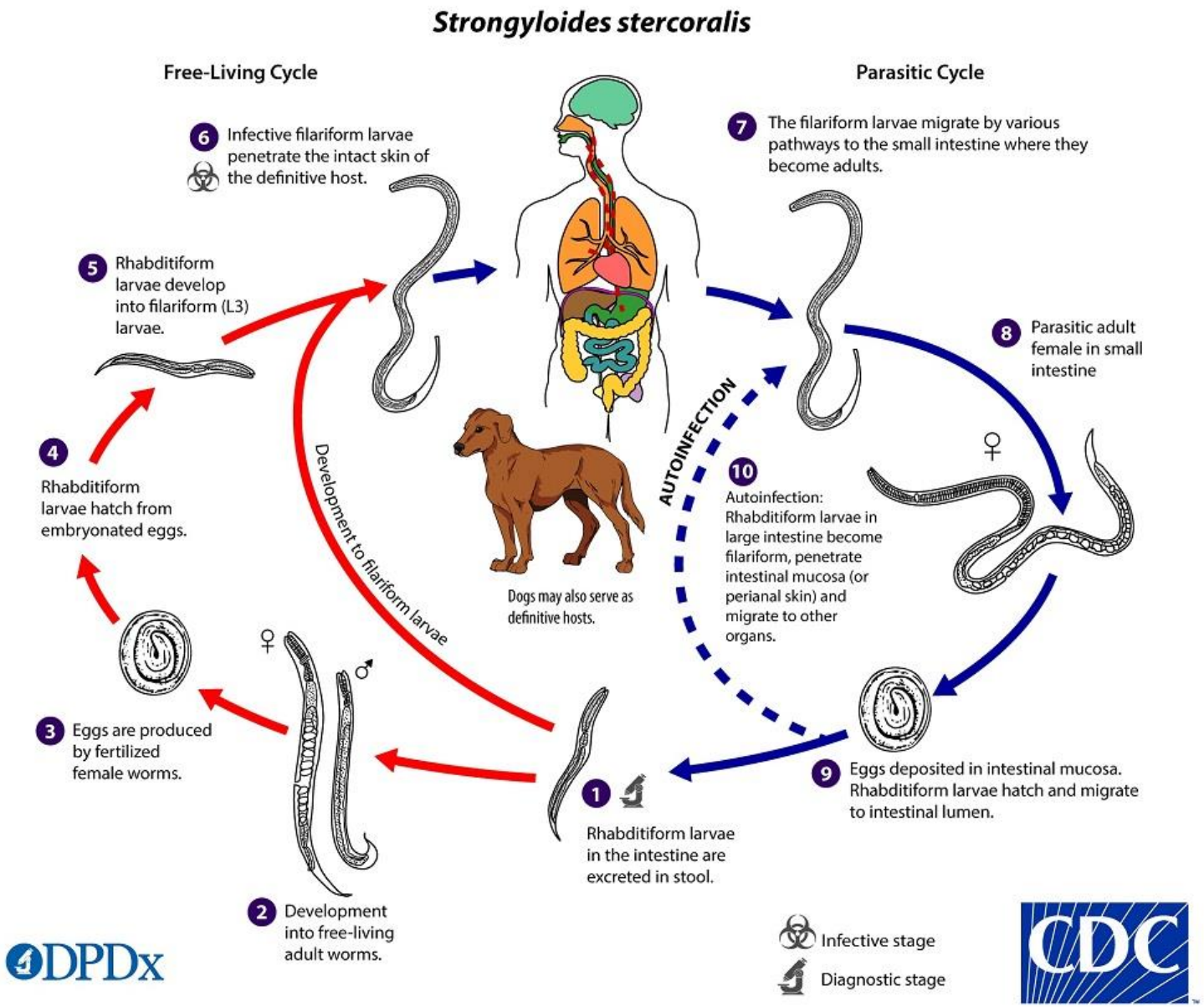
Citation: Sears WJ, Nutman TB (2022) Strongy Detect: Preliminary Validation of a Prototype Recombinant Ss-NIE/Ss-IR Based ELISA to Detect *Strongyloides stercoralis* Infection. PLoS Negl Trop Dis 16(1): e0010126. https://doi.org/10.1371/journal.pntd.0010126

Editor: Alessandra Morassutti, University of Passo Fundo: Universidade de Passo Fundo, BRAZIL

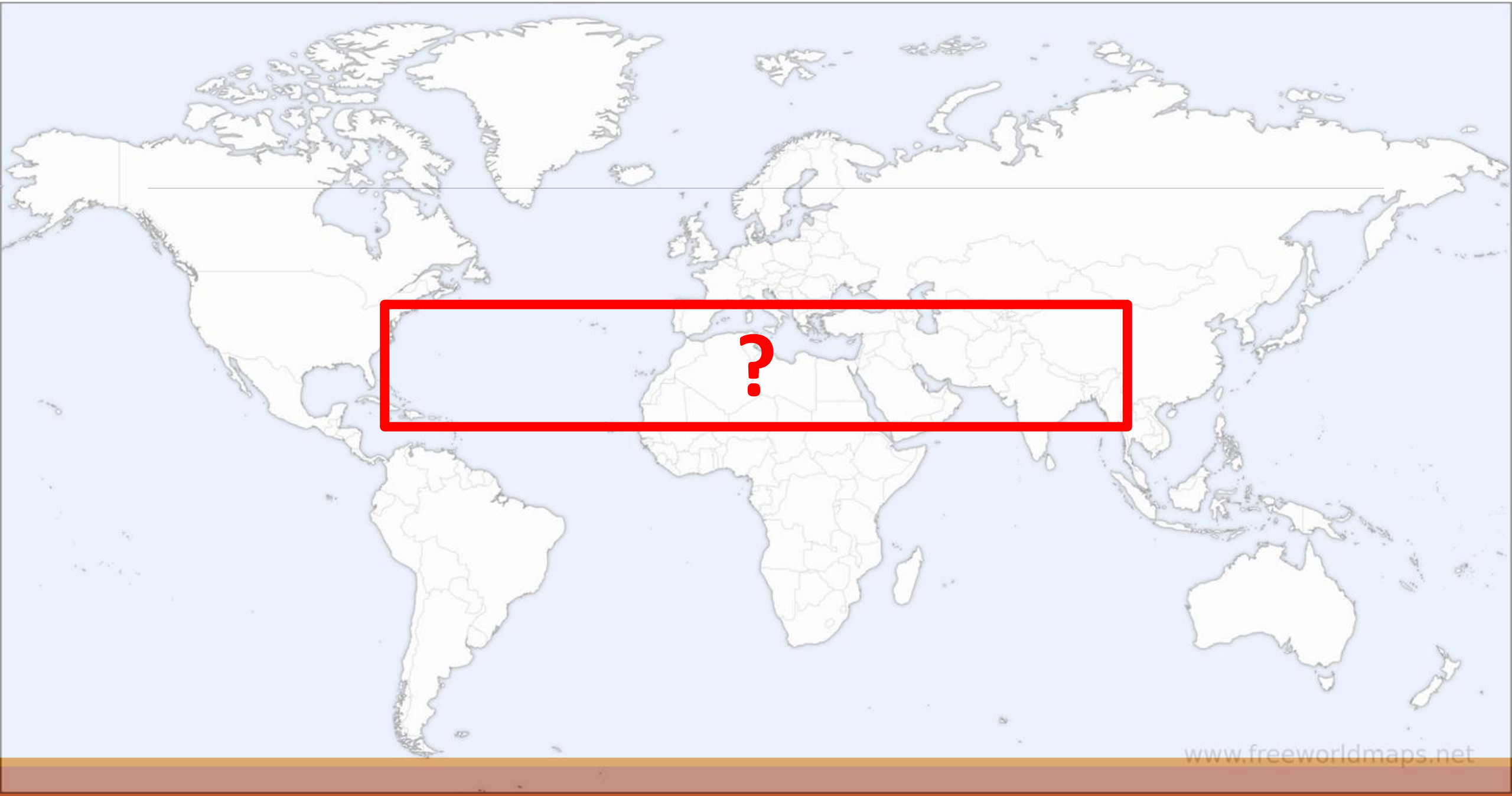
Received: August 19, 2021

Accepted: December 22, 2021

Published: January 25, 2022



Buonfrate D, Bisanzio D, Giorli G, Odermatt P, Fürst T, Greenaway C, French M, Reithinger R, Gobbi F, Montresor A, Bisoffi Z. The Global Prevalence of *Strongyloides stercoralis* Infection. Pathogens. 2020 Jun 13;9(6):468. doi: 10.3390/pathogens9060468. PMID: 32545787; PMCID: PMC7349647.


?
www.freeworldmaps.net

DIAGNOSIS OF *S. stercoralis* INFECTION

- **HIGH SPECIFICITY**
- **HIGH SENSITIVITY**
- **HIGH POSITIVE AND NEGATIVE PREDICTIVE VALUE**
- **NO CROSS REACTIONS**
- **GOOD DETERMINATION OF CURE AFTER TREATMENT**

DIAGNOSIS OF *S. stercoralis* INFECTION

- **Direct stool microscopy**: larvae examination in stool samples. Routine diagnostic exam, lacks sensitivity

- **Agar culture plate followed by microscopy**: increases sensitivity but is inconvenient and time consuming

- **Nucleic acid amplification tests and multiplex PCR**: intermittent release of larvae affects sensitivity; expensive; not applicable in low income countries

- **Serology (ELISA, Western Blot, luciferase immunoprecipitation system):** detection of antibodies against S. stercoralis. Risk of cross reactivity with other helmints (filaria, ascaris, schistosoma)

30 January 2022
WORLD NTD DAY
NEGLECTED TROPICAL DISEASES

1. Crude antigen-based immunoassays
2. Recombinant Ss-NIE antigen
3. Recombinant Ss-IR antigens

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

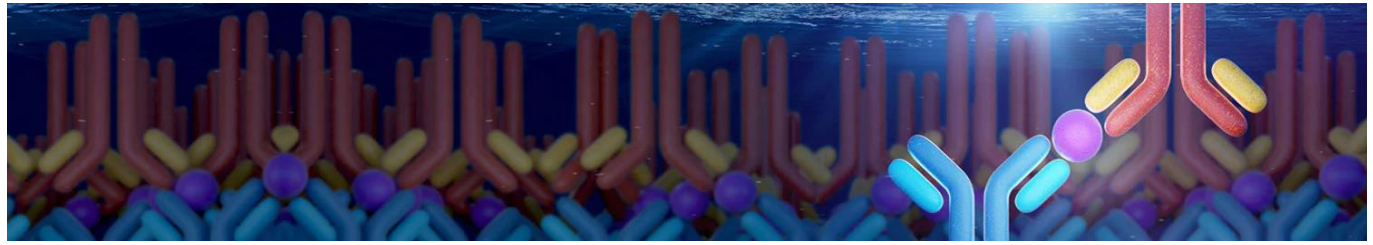
Strongy Detect: Preliminary Validation of a Prototype Recombinant Ss-NIE/Ss-IR Based ELISA to Detect *Strongyloides stercoralis* Infection

William J. Sears*, Thomas B. Nutman

Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, United States of America

* william.sears@nih.gov

IgG and/or IgG4 of combined recombinant Ss-NIE + Ss-IR



3 groups of patients:

- Ss positive patients with documented larvae in the stool (n=74)
- Healthy donors without epidemiologic risk of Ss infection (n = 47)
- Ss negative patients infected by other helmints (n = 29): *W. bancrofti* (n = 1), *Schistosoma* spp (n = 1), *T. trichiura* (n = 1), *T. canis* (n = 1), *O. volvulus* (n = 1), *L. loa* (n = 22), *O. volvulus/L. loa* coinfection (n = 2)

IgG and IgG4 capture assays for Ss negative patients and for Ss positive patients pre and post treatment with ivermectin or thiabendazole

RESULTS

Table 1. The sensitivity and specificity of the optimal cutoffs for signal-to-noise (S/N) and optical density (OD) was calculated for the IgG and IgG4 assays. (SN = Signal/Noise Ratio, OD = Optical Density).

	Sensitivity (%)	Specificity (%)	Cutoff
SNIgG	98.6	98.7	6.7
SNIgG4	95.9	100	1.8
ODIgG	98.6	98.7	0.24
ODIgG4	95.9	100	0.07

https://doi.org/10.1371/journal.pntd.0010126.t001

HIGH DEGREE OF SEPARATION BETWEEN TRUE POSITIVES AND NEGATIVES

NO FALSE POSITIVES IN SERA FROM PATIENTS INFECTED WITH HELMINTS OTHER THAN Ss

S/N equal to OD in specificity and sensitivity in both assays

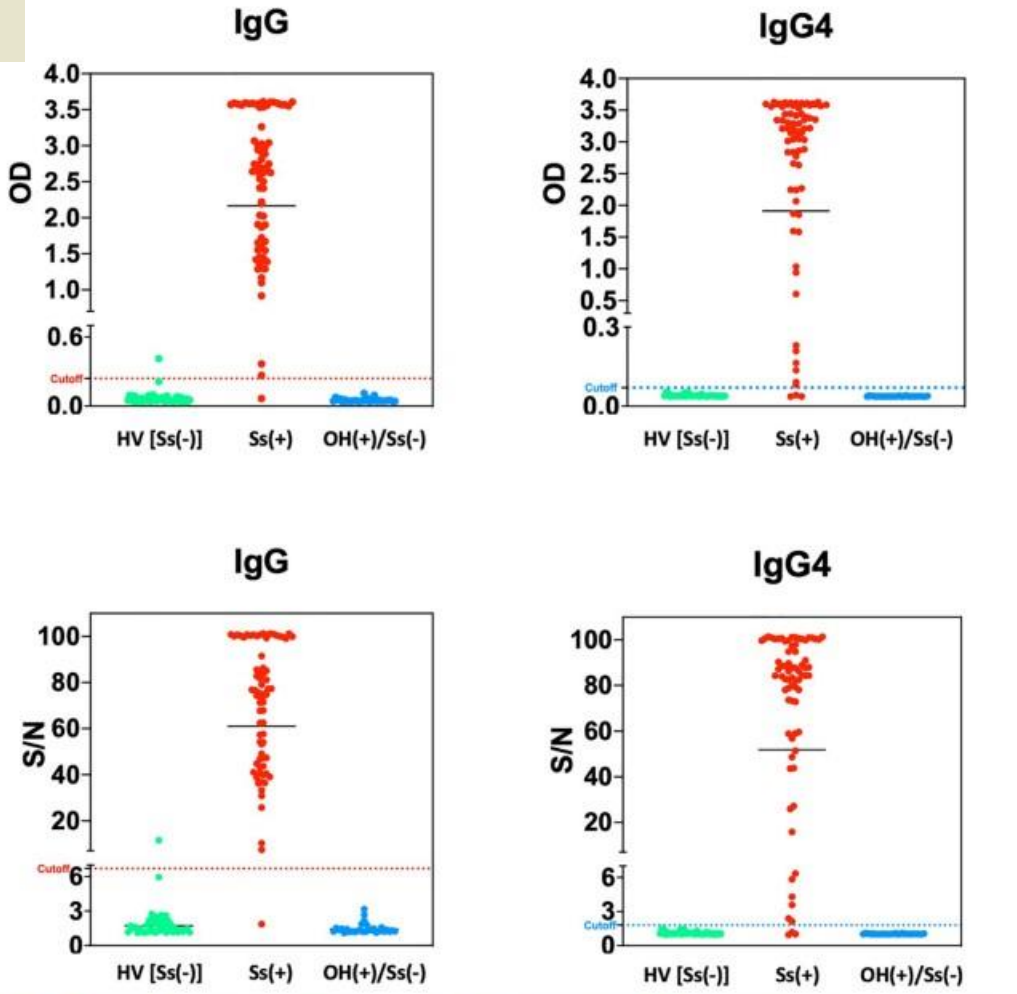


Fig 1. A comparison between the performance of the IgG and IgG4 based ELISA assays using raw optical density (OD) measurements and signal-to-noise ratio (S/N) when applied to sera from healthy controls, *Strongyloides stercoralis* (Ss) infected (documented larvae in stool), and those with helminth infections other than Ss. The dashed line represents the cutoff of the respective tests calculated from the cumulative data. The data points above the dotted line are considered positive and those below are considered negative. (HV = Healthy Volunteers; SS+ = Ss larvae in stool; OH = patients infected with helminths other than Ss).

https://doi.org/10.1371/journal.pntd.0010126.g001

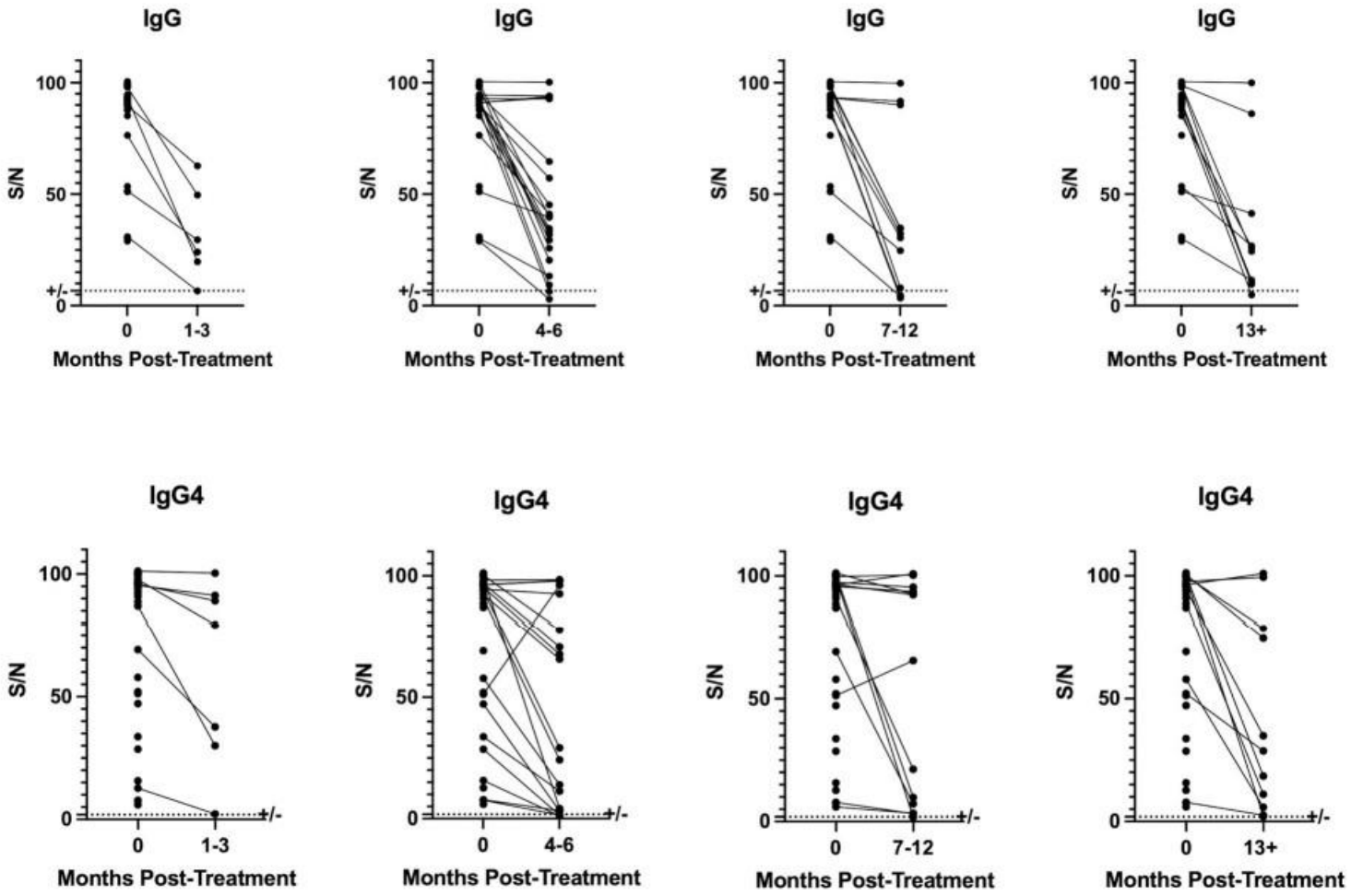


Fig 3. The values of IgG and IgG4 serum based ELISA assays before treatment was compared to post-treatment serum ELISA values obtained at 1–3 months, 4–6 months, 7–12 months or greater than a year post-treatment. The dotted line represents the calculated cutoffs for the respective assays.

https://doi.org/10.1371/journal.pntd.0010126.g003

Statistically significant decline in most patients' antibody levels ($p < 0{,}001$)

BUT

Few patients' levels declined to below the the positive cut off at any timepoint of follow-up

DISCUSSION

First diagnostic tool to incorporate Ss-NIE and Ss-IR: holds promise to bridge recombinant technology with clinical labs possessing ELISA machines

High improvement in differential diagnostics with other helmintiasis

Improved specificity and positive predictive value will help clinical diagnosis and give finer estimates of the global burden of disease, especially in areas with a wide range of helmintiasis

LIMITS

Not able to determine cure after treatment

Will need further studies for improvement

GRAZIE PER L'ATTENZIONE!

Verena Crosato
Malattie Infettive e Tropicali
Università degli Studi di Brescia