Busting  trials

Florian Naudet, MD, PhD

You might need to read QR codes

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COIs

None in the past 5 years

Fundings

METRICS
ljaf laura and john arnold foundation
PROJET FINANCÉ PAR L'ANR - PROJECT FUNDED BY THE ANR
ANR
IUF institut universitaire de France
Fondation pour la Recherche Médicale
Région Bretagne
MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ
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Liberté Égalité Fraternité
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DISCLOSURE

I don’t claim that any of these studies is fraudulent.

But there is scientific evidence supporting the fact that those studies are « dead » studies, i.e. beyond repair.

Anaesthesia

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Original Article

False individual patientdataand zombie randomised controlled trialssubmittedto Anaesthesia

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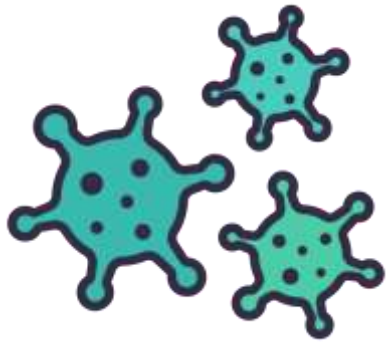
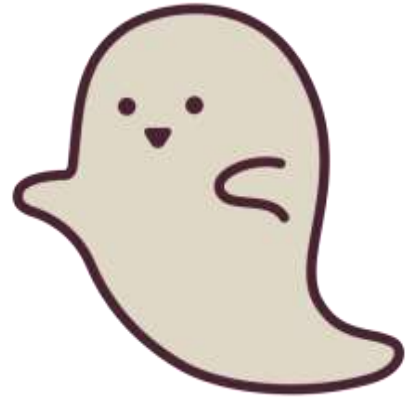
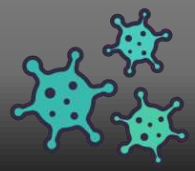
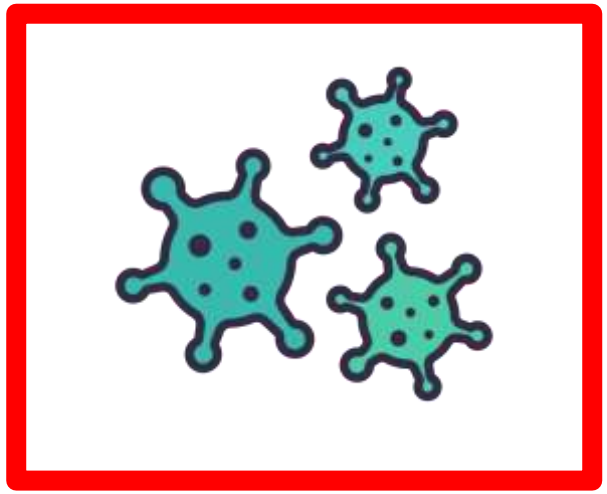
Summary

Concerned that studies contain false data, I analysed the baseline summary data of randomised controlled trials when they were submitted to Anaesthesia from February 2017 to March 2020. I categorised trials with false data as 'zombie' if I thought that the trial was fatally flawed. I analysed 526 submitted trials: 73 (14%) had false data and 43 (8%) I categorised zombie. Individual patient data increased detection of false data and categorisation of trials as zombie compared with trials without individual patient data: 67/153 (44%) false vs. 6/373 (2%) false; and 40/153 (26%) zombie vs. 3/373 (1%) zombie, respectively. The analysis of individual patient data was independently associated with false data (odds ratio (95% credible interval) 47 (17–144); p = 1.3 9 10^{-12}) and zombie trials (odds ratio (95% credible interval) 79 (19–384); p = 5.6 9 10^{-9}). Authors from five countries submitted the majority of trials: China 96 (18%); South Korea 87 (17%); India 44 (8%); Japan 35 (7%); and Egypt 32 (6%). I identified trials with false data and in turn categorised trials zombie for: 27/56 (48%) and 20/56 (36%) Chinese trials; 7/22 (32%) and 1/22 (5%) South Korean trials; 8/13 (62%) and 6/13 (46%) Indian trials; 2/11 (18%) and 2/11 (18%) Japanese trials; and 9/10 (90%) and 7/10 (70%) Egyptian trials, respectively. The review of individual patient data of submitted randomised controlled trials revealed false data in 44%. I think journals should assume that all submitted papers are potentially flawed and editors should review individual patient data before publishing randomised controlled trials.

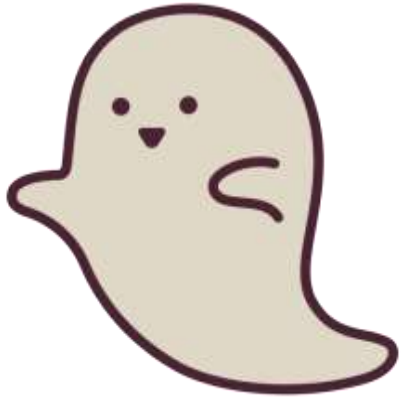


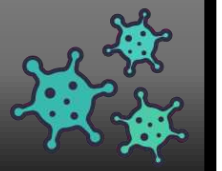






CHAPTER 1
DEADLY VIRUS





THE LANCET

Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia

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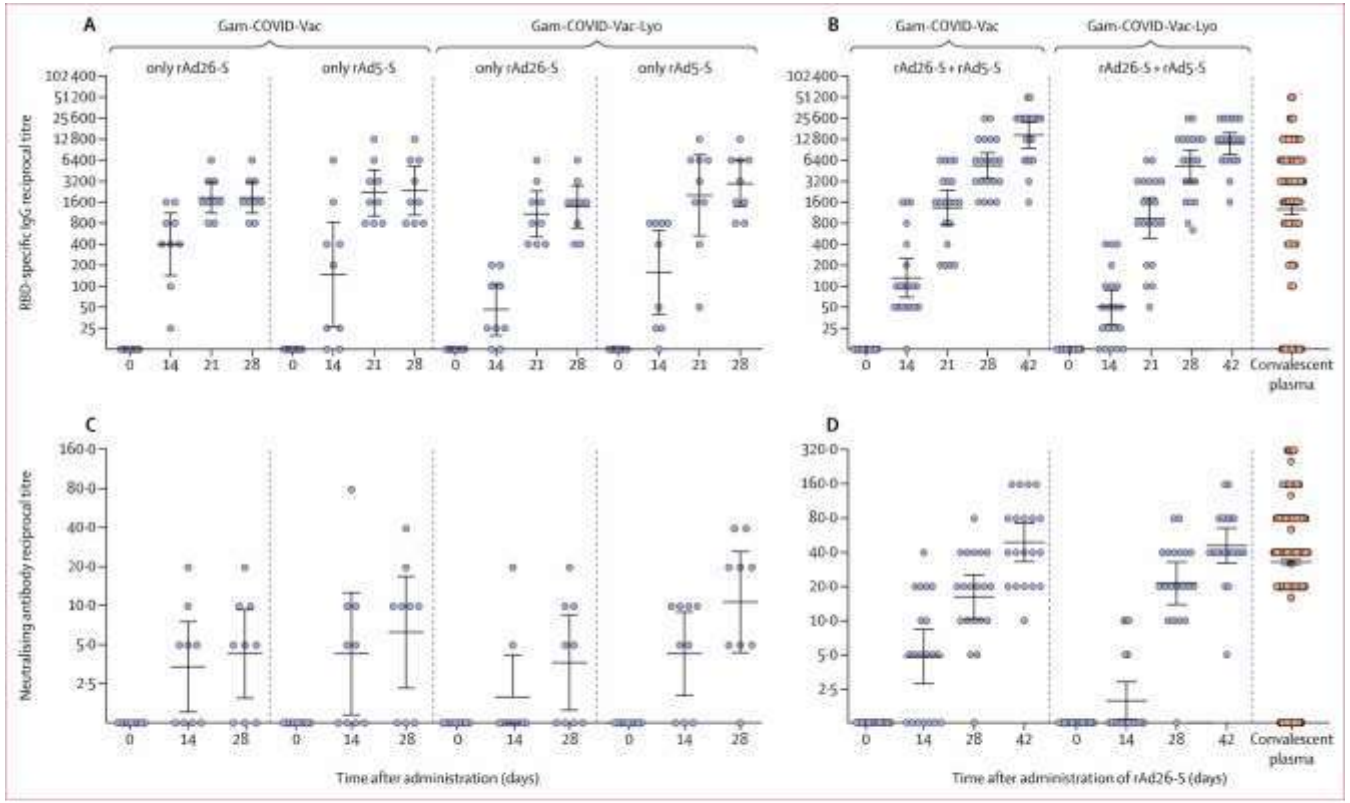

Figure 2: **Humoral immune response**

Data are geometric mean titres and 95% CIs. (A) RBD-specific antibodies on days 0, 14, 21, and 28, as measured by ELISA, in participants vaccinated with rAd26-S or rAd5-S only. (B) RBD-specific antibodies on days 0, 14, 21, 28, and 42, as measured by ELISA, in participants vaccinated with rAd26-S on day 0 and rAd5-S on day 21. (C) Neutralising antibodies on days 0, 14, and 28, as measured by neutralisation assay with 100 TCID50, in participants vaccinated with rAd26-S or rAd5-S only. (D) Neutralising antibodies on days 0, 14, 28, and 42, as measured by microneutralisation assay with 100 TCID50, in participants vaccinated with rAd26-S on day 0 and rAd5-S on day 21. RBD-specific IgGs and neutralising antibodies of in convalescent plasma are also shown in (B) and (D). Gam-COVID-Vac=frozen vaccine formulation. Gam-COVID-Vac-Lyo=lyophilised vaccine formulation. rAd26-S=recombinant adenovirus type 26 carrying the gene for SARS-CoV-2 full-length glycoprotein S. rAd5-S=recombinant adenovirus type 5 carrying the gene for SARS-CoV-2 full-length glycoprotein S. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. RBD=receptor-binding domain. TCID50=50% tissue culture infective dose.

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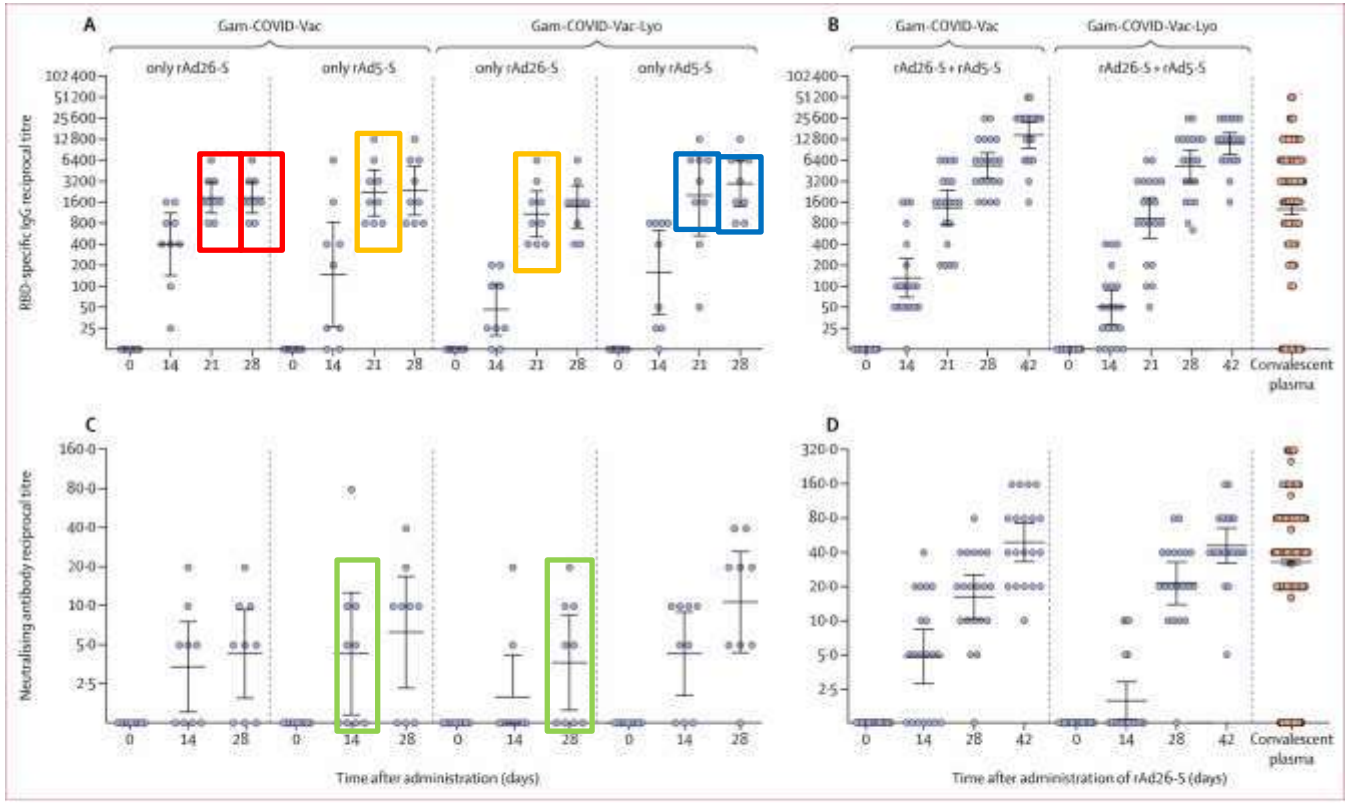

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Safety and efficacy of the Russian COVID-19 vaccine: more information needed

**Enrico Bucci, Konstantin Andreev, Anders Björkman, Raffaele Adolfo Calogero, Ernesto Carafoli, Piero Carninci, Paola Castagnoli, Andrea Cossarizza, Cristina Mussini, Philippe Guerin, Brian Lipworth, Gianluca Sbardella, Teresa Stocki, Loretta Tuosto, Christoffer van Tulleken, Antonella Viola*
enrico.bucci@resis-srl.com

We feel that a detailed answer and rendering the actual data available would considerably strengthen the significance of the study findings.

disproportionately higher numbers than have other groups in the United States. The panel determined that these groups are vulnerable chiefly for socio-economic reasons tied to systemic racism — for example, they have high-risk jobs and live in high-risk areas — and therefore addressed the request through this lens, without singling out the groups because of their identities.

"We really are trying to make sure that people of colour, who have been disproportionately impacted, will also have priority — but for the factors that put them at risk, not highlighting just their racial and ethnic make-up," says Helene Gayle, president and chief executive of the Chicago Community Trust in Illinois and a co-chair of the NASEM committee that drafted the proposal.

Faden says the recommendations acknowledge the current focus on racial injustice in the United States. "I was reading to see: does this report speak to the cultural moment in the United States, does it speak to racism and other forms of structural inequality? And it does," she says.

The WHO's strategic advisory group will continue to update its guidance, first to assign rankings to its priority groups, and then to include real data from vaccine trials, such as how effective a given vaccine is in older people. In the United States, the NASEM committee is due to issue a final plan in October. Ultimately, the CDC will consider these recommendations, among others, while developing its own vaccine-allocation plan for the country, expected later this year.

That will be the guidance that public-health departments, doctors and pharmacies throughout the United States should follow when handing out vaccines — assuming that one has been proved safe and people are willing to take it.

"We really are trying to make sure that people of colour will have priority."

Trump has been rooting for a vaccine to be ready by November, in time for the US presidential election — but a perception that the vaccine has been rushed could erode trust in it, says Sandra Crouse Quinn, a behavioural scientist at the Center for Health Equity at the University of Maryland in College Park. This could make vaccine-allocation plans less effective.

RESEARCHERS QUESTION RUSSIAN COVID VACCINE TRIAL RESULTS

Scientists flag trial findings that seem to be duplicated and call for access to the underlying data.

By Alison Abbott

A group of researchers have expressed concern about repetitive patterns of data in a paper describing early-phase clinical trials of Russia's coronavirus vaccine — the first jab worldwide to be approved for widespread use.

In an open letter to the study authors, who published the trial results[1] this month, the researchers highlight values that seem to be duplicated, and warn that the paper presents its results only as box plots, without providing a detailed breakdown of the data on which they are based. "While the research described in this study is potentially significant, the presentation of the data raises several concerns which require access to the original data to fully investigate", the letter says. It has been signed by almost 40 scientists (see go.nature.com/3kqvsqv).

The trials tested two slightly different viral-vector vaccines — which use genetically engineered adenoviruses to produce coronavirus proteins in the body — on 76 volunteers. The results indicated that the vaccine produced a strong immune response, and that side effects were limited to mild, short-term effects, such as irritation at injection sites or headaches, in a few people. In August, the Russian authorities approved the vaccine, called Sputnik V, for widespread use, and have said that it could be available to the general public within months. This fast-track approval caused consternation among researchers, who argued that the decision to roll out the vaccine before larger safety and efficacy trials had been completed was dangerously rushed.

Possible duplications

The open letter was posted on a blog run by molecular biologist Enrico Bucci, who heads a science-integrity company called Resis in Samone, Italy. Bucci says that he noticed irregularities in the paper soon after it was published (D. Y. Logunov *et al. Lancet* https://doi.org/gg96hq; 2020). For example, in one figure, in which the authors report their measurements of markers of a type of immune cell in the blood, many members of two groups of nine volunteers tested with different formulations of the vaccine seem to have the same levels. "The odds of this arising by coincidence are extremely small," Bucci says.

"To see such similar data patterns between unrelated measurements is really not likely," says Konstantin Andreev, who studies viral respiratory infections at Northwestern University at Evanston, Illinois. "These discrepancies are not minor." Andreev had been independently concerned about aspects of the clinical trial, and signed the open letter shortly after it was made public.

"We are not alleging scientific misconduct, but asking for clarification about how these apparently similar data points came about," says Bucci. "When we read reports that Russia had started to inject the vaccine into people outside clinical trials, we felt we had to speak out immediately." Late-phase clinical trials of the vaccine, which will involve tens of thousands of people, began on 26 August.

The paper's underlying data should be made available, says epidemiologist Michael Favorov, president of DiaPrep Systems, a diagnostics company in Atlanta, Georgia. "We have a lot of questionable data — in terms of its presentation," he says. "Maybe the data are good — we can't judge." He adds that the decision to publish the reports without the underlying data seems unusual. By contrast, when clinical studies involving a coronavirus vaccine that was developed by the pharmaceutical company AstraZeneca and the University of Oxford, UK, were published in the same journal, they were accompanied by a large amount of supplementary data that other researchers were able to scrutinize (P. M. Folegatti *et al. Lancet* **396**, 467–478; 2020).

The Russian paper's lead author, Denis Logunov at the Gamaleya National Research Centre for Epidemiology and Microbiology in Moscow, did not respond to requests for comment from *Nature*'s news team. But he told the Russian news outlet Meduza that he did not intend to respond to the open letter. He denied that there were errors in the publication, and stated that measured antibody levels were "exactly as they were presented" in the figures. He added that he was in contact with *The Lancet* and "was ready to clarify any issues".

The Lancet declined to comment on its policy for providing data in support of clinical trials that it publishes, but said that it "has invited the authors of the Russian vaccine study to respond to the questions raised in the open letter by Enrico Bucci", and that it would continue to follow the situation closely.

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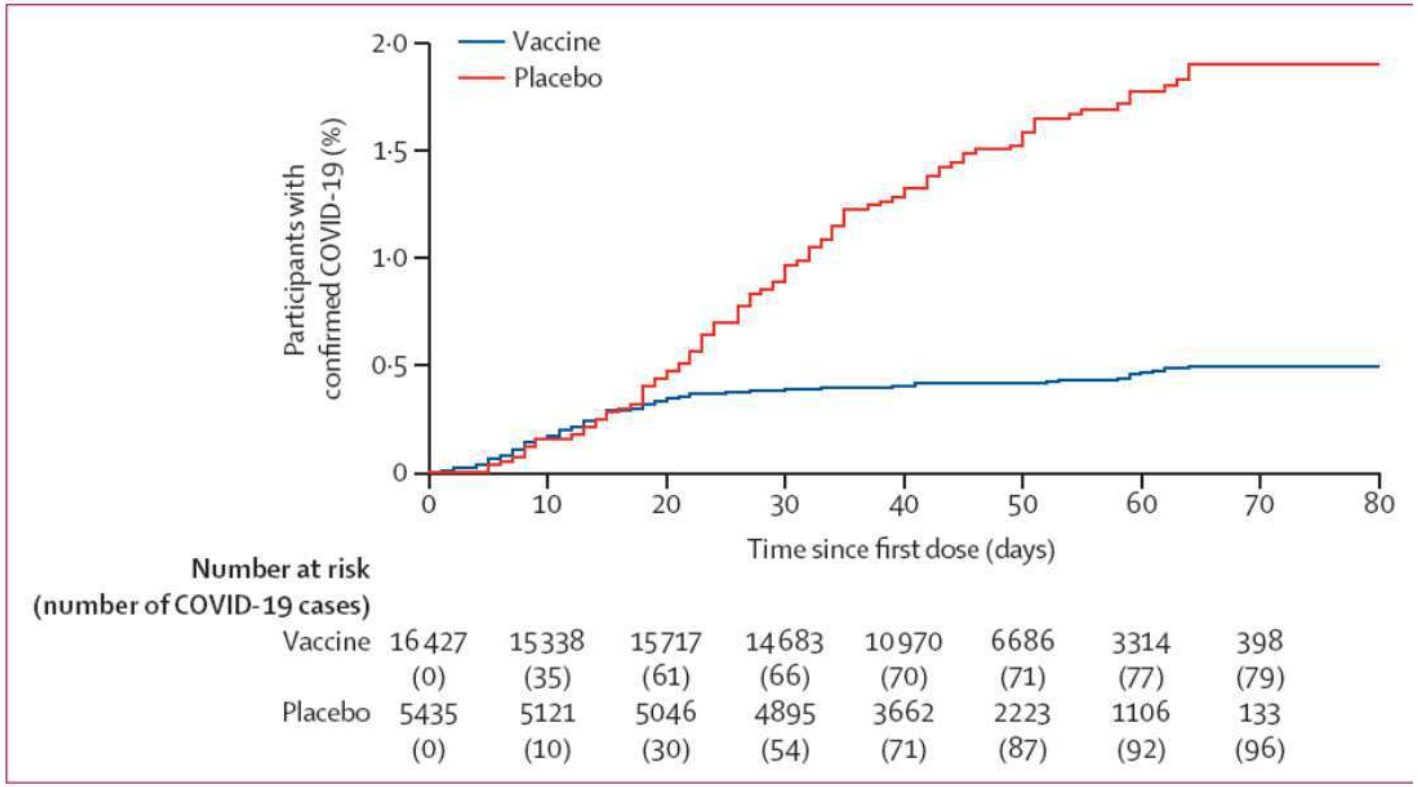

Number at risk (number of COVID-19 cases)

Vaccine	16427 (0)	15338 (35)	15717 (61)	14683 (66)	10970 (70)	6686 (71)	3314 (77)	398 (79)
Placebo	5435 (0)	5121 (10)	5046 (30)	4895 (54)	3662 (71)	2223 (87)	1106 (92)	133 (96)

Figure 2: Kaplan-Meier cumulative incidence curves for the first symptomatic, PCR-positive COVID-19 after dose 1, in participants who received at least one dose of vaccine or placebo

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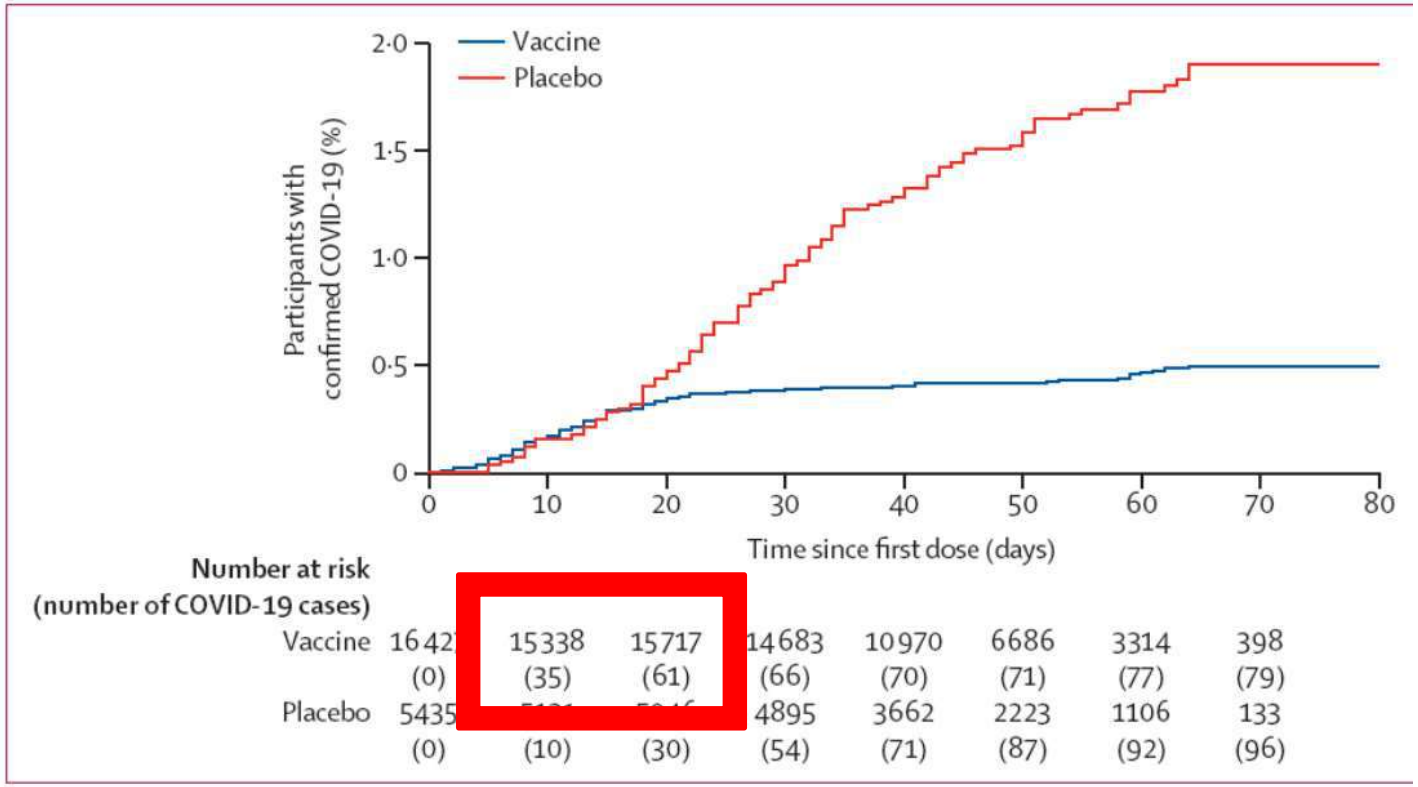

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	Total cases	Vaccine group	Placebo group	Vaccine efficacy (95% CI)	p value
First COVID-19 occurrence from 21 days after dose 1 (day of dose 2)*					
Overall	78	16/14 964 (0·1%)	62/4902 (1·3%)	91·6% (85·6–95·2)	<0·0001
Age group (years)					
18–30	5	1/1596 (0·1%)	4/521 (0·8%)	91·9% (51·2–99·3)	0·0146
31–40	17	4/3848 (0·1%)	13/1259 (1·0%)	90·0% (71·1–96·5)	<0·0001
41–50	19	4/4399 (0·1%)	15/1443 (1·0%)	91·3% (73·7–96·9)	<0·0001
51–60	27	5/3510 (0·1%)	22/1146 (1·9%)	92·7% (81·1–97·0)	<0·0001
>60	10	2/1611 (0·1%)	8/533 (1·5%)	91·8% (67·1–98·3)	0·0004
Sex					
Female	32	9/5821 (0·2%)	23/1887 (1·2%)	87·5% (73·4–94·2)	<0·0001
Male	46	7/9143 (0·1%)	39/3015 (1·3%)	94·2% (87·2–97·4)	<0·0001
Moderate or severe cases	20	0/14 964	20/4902 (0·4%)	100% (94·4–100·0)	<0·0001
First COVID-19 occurrence after dose 1†					
Any time after dose 1	175	79/16 427 (0·5%)	96/5435 (1·8%)	73·1% (63·7–80·1)	<0·0001
From 14 days after dose 1	109	30/14 999 (0·2%)	79/4950 (1·6%)	87·6% (81·1–91·8)	<0·0001
First COVID-19 occurrence after dose 2 (28 days after dose 1)*					
All	60	13/14 094 (0·1%)	47/4601 (1·0%)	91·1% (83·8–95·1)	<0·0001

Data are n/N (%), unless otherwise stated. *Includes those who received both doses. †Includes participants who received at least one dose.

Table 2: **Interim results on vaccine efficacy**

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31–40	17	4/3848 (0·1%)	13/1259 (1·0%)	90·0% (71·1–96·5)	<0·0001
41–50	19	4/4399 (0·1%)	15/1443 (1·0%)	91·3% (73·7–96·9)	<0·0001
51–60	27	5/3510 (0·1%)	22/1146 (1·9%)	92·7% (81·1–97·0)	<0·0001
>60	10	2/1611 (0·1%)	8/533 (1·5%)	91·8% (67·1–98·3)	0·0004
Female	32	9/5821 (0·2%)	23/1887 (1·2%)	87·5% (73·4–94·2)	<0·0001
Male	46	7/9143 (0·1%)	39/3015 (1·3%)	94·2% (87·2–97·4)	<0·0001
Moderate or severe cases	20	0/14 964	20/4902 (0·4%)	100% (94·4–100·0)	<0·0001
First COVID-19 occurrence after dose 1†					
Any time after dose 1	175	79/16 427 (0·5%)	96/5435 (1·8%)	73·1% (63·7–80·1)	<0·0001
From 14 days after dose 1	109	30/14 999 (0·2%)	79/4950 (1·6%)	87·6% (81·1–91·8)	<0·0001
First COVID-19 occurrence after dose 2 (28 days after dose 1)*					
All	60	13/14 094 (0·1%)	47/4601 (1·0%)	91·1% (83·8–95·1)	<0·0001

Data are n/N (%), unless otherwise stated. *Includes those who received both doses. †Includes participants who received at least one dose.

Table 2: **Interim results on vaccine efficacy**

Data discrepancies and substandard reporting of interim data of Sputnik V phase 3 trial

**Enrico M Bucci, Johannes Berkhof, André Gillibert, Gowri Gopalakrishna, Raffaele A Calogero, Lex M Bouter, Konstantin Andreev, Florian Naudet, Vasiliy Vlassov*

A very peculiar result of the major subgroup analysis of the primary outcome caught our attention. The vaccine efficacy was said to be high for all age groups. The reported percentages were 91·9% in the 18–30-year age group, 90·0% in the 31–40-year age group, 91·3% in the 41–50-year age group, 92·7% in the 51–60-year age group, and 91·8% in participants older than 60 years. We checked the homogeneity of vaccine efficacy across age groups (interaction tests): the p value of the Tarone-adjusted Breslow-Day test was 0·9963, and the p value of a non-asymptotic test was 0·9956,[6] indicating a very low probability of observing a homogeneity this good if the actual homogeneity is perfect.

THE LANCET

Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia

Denis Y Logunov, Inna V Dolzhikova*, Dmitry V Shcheblyakov, Amir I Tukhvatulin, Olga V Zubkova, Alina S Dzharullaeva, Anna V Kovyrshina, Nadezhda L Lubenets, Daria M Grousova, Alina S Erokhova, Andrei G Botikov, Fatima M Izhaeva, Olga Popova, Tatiana A Ozharovskaya, Ilias B Esmagambetov, Irina A Favorskaya, Denis I Zrelkin, Daria V Voronina, Dmitry N Shcherbinin, Alexander S Semikhin, Yana V Simakova, Elizaveta A Tokarskaya, Daria A Egorova, Maksim M Shmarov, Natalia A Nikitenko, Vladimir A Gushchin, Elena A Smolyarchuk, Sergey K Zyryanov, Sergei V Borisevich, Boris S Naroditsky, Alexander L Gintsburg, and the Gam-COVID-Vac Vaccine Trial Group†*

Source	Date	Rate of cases in vaccine group	Rate of cases in placebo group	Efficacy
Press release [9]	11/11/2020	4	16	92%
Press release [10]	11/24/2020	8/14,095	31/4,699	91,397%
Press release [11]	12/14/2020	16/17,032	62/5,682	91,391%
Lancet Article [1]	Database lock of 11/24/2020	16/14,964	62/4,902	91,546%

Table 1: efficacy of the vaccine in press releases and Lancet article [1]

THE LANCET

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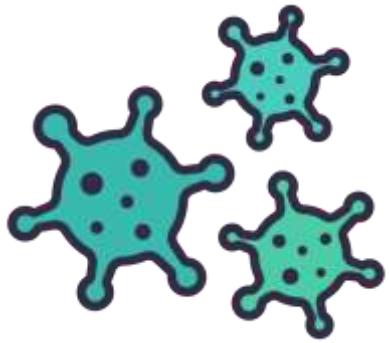
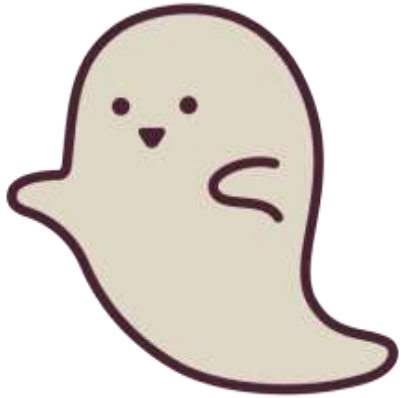
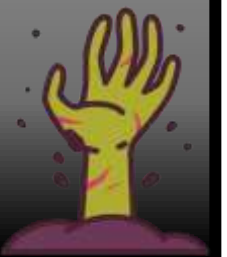


CHAPTER 2
BIRTH OF A ZOMBIE





RESEARCH ARTICLE Open Access

Transdiagnostic treatment of emotional disorders for women with multiple sclerosis: a randomized controlled trial

Nabi Nazari[1*], Akram Aligholipour[2] and Masoud Sadeghi[1]

BMC Women's Health

Abstract

Background: Multiple sclerosis (MS) is a chronic, unpredictable, neurodegenerative disease, significantly associated with psychological, behavioral, cognitive, and emotional consequences. MS is more common in females than males and frequently affects women during their reproductive years. Despite the frequent mental disorders, comorbidities, and emotional problems in People with MS (PwMS), these conditions are too often underdiagnosed and undertreated.

Objective: This study aimed to examine the efficacy of a group format of the Unified Protocol (UP) for the Transdiagnostic treatment of depression and anxiety disorders in females with MS.

Methods: In the present study, Sixty-four adult females diagnosed with MS were randomized to either the UP ($n = 32$) or treatment-as-usual conditions. The assessment protocol included semi-structured clinical interviews and self-reports evaluating diagnostic criteria, depression, anxiety and worry symptoms, emotional regulation, and affectivity.

Results: Repeated measure analysis of variance (ANOVA) revealed that the UP significantly improved depression scores [Cohen's $d = -2.11$, 95% CI (-2.72, -1.50)], anxiety scores [Cohen's $d = -3.34$, 95% CI (-4.01, -2.58)], positive and negative affect scale (PANAS)-positive affect scores [Cohen's $d = 1.46$, 95% CI (1.46, 2.01)], PANAS-negative affect scores [Coen's $d = -2.21$, 95% CI (-2.84, -1.60)], difficulties emotion regulation scale scores [Cohen's $d = 1.40$, 95% CI (-0.87, -0.03)], and Worry scale scores [Cohen's $d = -0.45$, 95% CI (-0.95, -0.04)] at the end of treatment relative to compared to the control condition. Also, treatment gains were maintained at the three-month follow-up ($p < 0.001$).

Conclusion: The findings provide the support that the UP could be an additional efficient psychological treatment for females with MS.

ISRCTN Number: ISRCTN95459505.

Keywords: Unified protocol, Emotion regulation, Comorbidity, Depression, Anxiety

Eligibility criteria

Inclusion criteria included: (a) fluent in Persian (b) at least 18 years of age, (c) a diagnosis of MS for three years or more, (d) received a diagnosis of depression or anxiety disorders (f) high score in difficulties emotion regulation scale (g) medical agreement or valid referral document for participation.

Exclusion criteria included: (a) present or history diagnosis of schizophrenia, psychosis, or organic mental disorder, (b) other chronic physical illnesses (e.g., cancer, diabetes) (c) pregnancy or Breast-feeding, (d) risk or

Treatment results

Repeated measure ANOVA was conducted on HADS-D. The results showed a significant main effect for group, $F(1, 62) = 116.55$, $p < 0.001$, $\eta^2 p = 0.65$. Between groups analyses showed that the UP participants obtained statistically significant less HADS-D scores than TAU at post-treatment [$t(1,62) = 9.94$, $p < 0.001$, Cohen's $d = -2.11$ 95% CI (-2.72, -1.50)]. Also, there was a significant group × time interaction, $F(2, 124) = 64.63$, $p < 0.001$, $\eta^2 p = 0.51$.

Repeated measure ANOVA was conducted on HADS-A. The results showed a significant main effect for group, $F(1, 62) = 158.23$, $p < 0.001$, $\eta^2 p = 0.72$. Between groups analyses showed that the UP participants obtained statistically significant less HADS-A scores than TAU at post-treatment [$t(1,62) = 12.92$, $p < 0.001$, Cohen's $d = -3.34$, 95% CI (-4.01, -2.58)]. Also, there was a significant group × time interaction, $F(2, 124) = 63.27$, $p < 0.001$, $\eta^2 p = 0.50$.

Repeated measure ANOVA was conducted on DERS. The results showed a significant main effect for group, $F(1, 62) = 36.46$, $p < 0.001$, $\eta^2 p = 0.37$. Between groups analyses showed that the UP participants obtained statistically significant less DERS scores than TAU at post-treatment [$t(1,62) =$, $p < 0.001$, Cohen's $d =$95% CI (,)]. Also, there was a significant group × time interaction, $F(2, 124) = 22.02$, $p < 0.001$, $\eta^2 p = 0.26$.

Repeated measure ANOVA was conducted on PANAS-PA. The results showed a significant main effect for group, $F(1, 62) = 37.68$, $p < 0.001$, $\eta^2 p = 0.38$. Between groups analyses showed that the UP participants obtained statistically significant less PANAS-PA scores than TAU at post-treatment [$t(1,62) = 5.83$, $p < 0.001$, Cohen's $d = 1.46$, 95% CI (1.46, 2.01)]. Also, there was a significant group × time interaction, $F(2, 124) = 27.48$, $p < 0.001$, $\eta^2 p = 0.31$.

Repeated measure ANOVA was conducted on PANAS-NA. The results showed a significant main effect for group, $F(1, 62) = 156.25$, $p < 0.001$, $\eta^2 p = 0.59$. Between groups analyses showed that the UP participants obtained statistically significant less PANAS-NA scores than TAU at post-treatment [$t(1,62) =$, $p < 0.001$, Cohen's $d = -2.21$, 95% CI (-2.84, -1.60)]. Also, there was a significant group × time interaction, $F(2, 124) = 161.23$, $p < 0.001$, $\eta^2 p = 0.62$.

Repeated measure ANOVA was conducted on PSWQ. The results showed a significant main effect for group, $F(1, 62) = 24.90$, $p < 0.001$, $\eta^2 p = 0.29$, and a significant main time effect. Between groups analyses showed that the UP participants obtained statistically significant less PSWQ scores than TAU at post-treatment [$t(1,62) =$, $p < 0.001$, Cohen's $d = -0.45$, 95% CI (-0.95, -0.04)]. Also, there was a significant group × time interaction, $F(2, 124) = 19.24$, $p < 0.001$, $\eta^2 p = 0.24$ (Table 4).

The SCID-I–IV demonstrated 22 of 30 patients in the UP group (73.3%) no longer met diagnostic criteria for their principal diagnosis at the end of the study at Time 3. The SCID-I–IV demonstrated no worse condition for all participants at Time2 and Time 3.

Discussion

MS is associated with a broad array of emotional disorders, negative symptoms, social interference, and physical disability that compromise well-being [4]. This study aimed to examine the efficacy of a group format of the UP for the transdiagnostic treatment of emotional disorders and symptoms in adult MS women with emotion dysregulation. The results indicated the UP effectiveness on changes in depression and anxiety symptoms and improvement of the emotion regulation at post-treatment. Also, treatment gains were maintained at the three-month follow-up.

Our findings revealed significant changes in depression measure, in anxiety measure, and in worry at 3-month follow up in the UP group. The results are consistent with studies that indicate the UP is effective in improving emotional disorders. In anxiety disorders, worrying is a critical maladaptive cognitive process contributing to the

Peer Review Taxonomy

This journal is participating in a pilot of NISO/STM's Working Group on Peer Review Taxonomy, to identify and standardize definitions and terminology in peer review practices in order to make the peer review process for articles and journals more transparent. Further information on the pilot is available here.

The following summary describes the peer review process for this journal:

- **Identity transparency:** Single anonymized
- **Reviewer interacts with:** Editor
- **Review information published:** Review reports. Reviewer Identities reviewer opt in. Author/reviewer communication

We welcome your feedback on this Peer Review Taxonomy Pilot. Please can you take the time to complete this short survey.

BMC Women's Health

From: Transdiagnostic treatment of emotional disorders for women with multiple sclerosis: a randomized controlled trial

Original Submission		
2 Aug 2020	Submitted	Original manuscript
28 Aug 2020	Reviewed	Reviewer Report
8 Sep 2020	Reviewed	Reviewer Report
9 Sep 2020	Author responded	Author comments - Nabi Nazari
Resubmission - Version 2		
9 Sep 2020	Submitted	Manuscript version 2
28 Sep 2020	Reviewed	Reviewer Report
15 Oct 2020	Reviewed	Reviewer Report
Resubmission - Version 3		
	Submitted	Manuscript version 3
Publishing		
25 Oct 2020	Editorially accepted	
31 Oct 2020	Article published	10.1186/s12905-020-01109-z

BMC Women's Health

Reviewer's report

Title: Transdiagnostic Treatment of Emotional Disorders for women with Multiple Sclerosis: A Randomized Controlled Trial

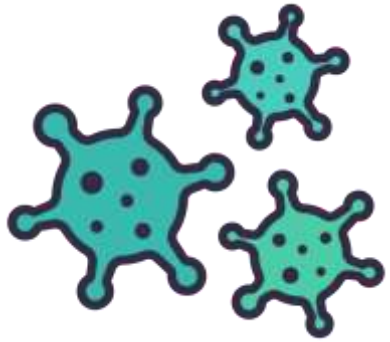
Version: 0 **Date:** 28 Aug 2020

Reviewer's report:

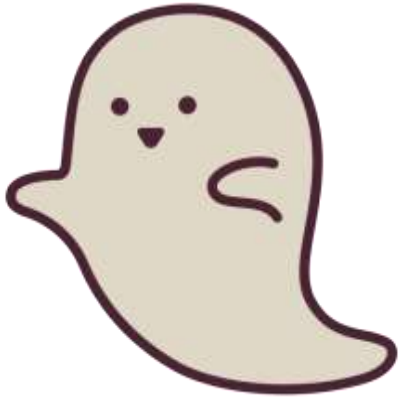
Its essentially a well written paper, I would recommend all the short forms have their expanded versions when you introduce them in the paper, please make these necessary correction.

Reviewer's comment: Page 6, Lines 52-54
Exclusion criteria included - (b) other chronic physical illnesses - I think that it is necessary to clarify which chronical diseases were excluded in the present study.
(g) moderate to high cognitive impairment or physical disabilities - which screening tool was used for cognitive impairment and how moderate to high cognitive impairment was defined?

Authors' response:
Thank you.
Item b was revised as following:
(b) Other chronic physical illnesses (e.g., cancer, diabetes).
Item (g) was deleted
In the present study; physical condition was examined by physician. However; we are agreed with your comment that item is not clear.



CHAPTER 3:
ZOMBIE MOVIE



MALARIA BUSINESS

French movie

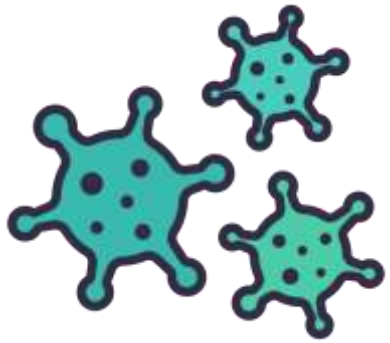
Showed at the French parliament

In presence of Cedric Villani (Fields medal 2010)

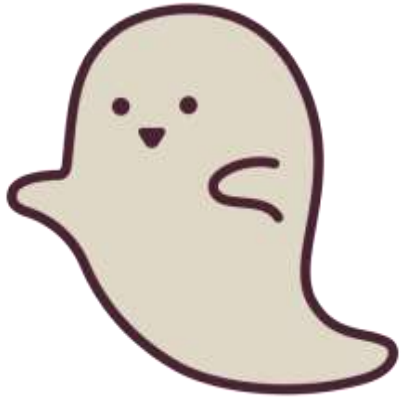
The movie

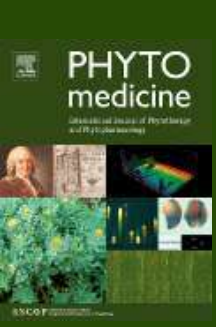
The meeting at the French parliament

nov 2018



CHAPTER 4:
ZOMBIE 1





Effect of *Artemisia annua* and *Artemisia afra* tea infusions on schistosomiasis in a large clinical trial

Jérôme Munyangi[a], Lucile Cornet-Vernet[b,*], Michel Idumbo[c], Chen Lu[d], Pierre Lutgen[e], Christian Perronne[f], Nadège Ngombe[g], Jacques Bianga[h], Bavon Mupenda[i], Paula Lalukala[j], Guy Mergeai[k], Dieudonné Mumba[l], Melissa Towler[m], Pamela Weathers[m]

Background and objective: Schistosomiasis (bilharzia), a serious neglected tropical disease affecting millions, has few cost-effective treatments, so two *Artemisia* wormwood species, *A. annua* and *A. afra,* were compared with the current standard praziquantel (PZQ) treatment in an 800 patient clinical trial, August-November of 2015.
Methods: The double blind, randomized, superiority clinical trial had three treatment arms: 400 for PZQ, 200 for *A. annua*, and 200 for *A. afra.* PZQ-treated patients followed manufacturer posology. *Artemisia*-treated patients received 1 l/d of dry leaf/twig tea infusions divided into 3 aliquots daily, for 7 days with 28-day follow-up.
Results: Of 800 enrolled patients having an average of >700 *Schistosoma mansoni* eggs per fecal sample, 780 completed the trial. Within 14 days of treatment, all *Artemisia*-treated patients had no detectable eggs in fecal smears, a result sustained 28 days post treatment. Eggs in fecal smears of PZQ-treated patients were undetectable after D21. More males than females who entered the trial had melena, but both genders responded equally well to treatment; by D28 melena disappeared in all patients. In all arms, eosinophil levels declined by about 27% from D0 to D28. From D0 to D28 hemoglobin increases were greater in PZQ and *A. afra*-treated patients than in *A. annua*-treated patients. Hematocrit increases were greater from D0 to D28 for patients treated with either PZQ or *A. annua* compared to those treated with *A. afra*. Gender comparison showed that *A. afra*–treated males had significantly greater hemoglobin and hematocrit increases by D28 than either PZQ or *A. annua*–treated males. In contrast, PZQ and *A. afra*-treated females had greater hemoglobin and hematocrit increases than *A. annua*-treated females. Both adults and pediatric patients treated with *A. annua* responded better compared to PZQ treatment.
Conclusion: Both *A. annua* and *A. afra* provided faster effective treatment of schistosomiasis and should be considered for implementation on a global scale.

Observed adverse effects	Number of subjects in the Artemisia arm	Frequency N/392 %	Number of subjects in the PZQ arm	Frequency N/390 =%
Abdominal discomfort	10	2.6	165	42.3
Abdominal pain	5	1.3	175	44.9
Anorexia	25	6.4	105	26.9
Arrhythmia	0	0	10	2.6
Asthenia	2	0.5	269	69.0
Cutaneous rash	0	0	22	5.6
Diarrhea	0	0	30	7.7
Dizziness	5	1.3	80	20.5
Drowsiness	0	0	20	5.1
Headaches	0	0	130	33.3
Itching	0	0	120	30.8
Myalgia	0	0	35	9.0
Nausea	25	6.4	200	51.3
Vomiting	7	1.8	15	3.8
400 Artemisia and 400 PZQ patients at trial inclusion.				

Table S1: Distribution among patients of adverse effects.

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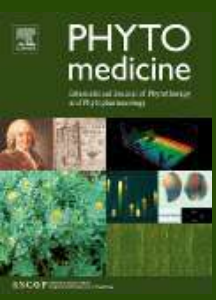
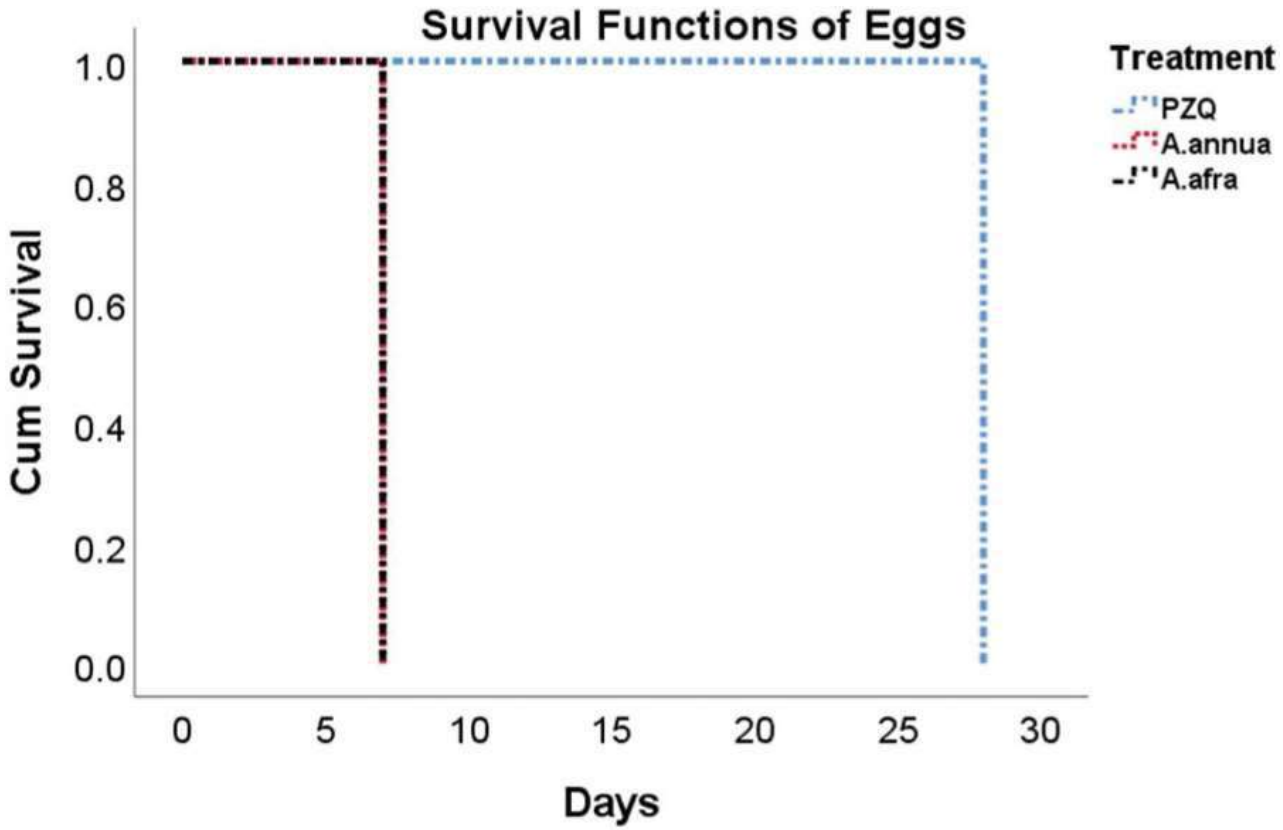


Effect of *Artemisia annua* and *Artemisia afra* tea infusions on schistosomiasis in a large clinical trial

Jérôme Munyangi[a], Lucile Cornet-Vernet[b,*], Michel Idumbo[c], Chen Lu[d], Pierre Lutgen[e], Christian Perronne[f], Nadège Ngombe[g], Jacques Bianga[h], Bavon Mupenda[i], Paula Lalukala[j], Guy Mergeai[k], Dieudonné Mumba[l], Melissa Towler[m], Pamela Weathers[m]



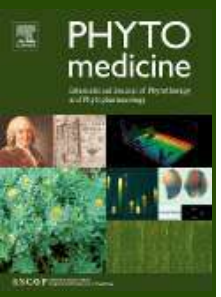
Log rank analysis of cumulative egg survival after treatment with *A. annua*, *A. afra*, or PZQ (praziquantel).

Comment on "Effect of Artemisia annua and Artemisia afra tea infusions on schistosomiasis in a large clinical trial"

Xavier Argemi[a,*], Yves Hansmann[a], Jean Gaudart[b], André Gillibert[c], Eric Caumes[d], Stéphane Jauréguiberry[e], Nicolas Meyer[f]

Third, there are a dozen of critical issues with the statistical methods.

> In addition, some data exhibit strange patterns. Table S1 contains many adverse effect frequencies that are multiples of five, with 17 multiples of five for 21 non-zero frequencies. According to a binomial distribution, the probability of 17 or more multiples of five for 21 frequencies occurring by chance is approximatively 3.4×10^{-9}.



Response to Argemi et al. 2019

Lucile Cornet-Vernet[a,*], **Jerome Munyangi**[b], **Lu Chen**[c], **Melissa Towler**[d], **Pamela Weathers**[d]

[a]Association More for Less-Maison de l'Artemisia, 20 Rue Pierre Demours, 75017 Paris, France

[b]Faculté de Médecine Université de University, Democratic Republic of the Congo

[c]Department of Mathematics, Worcester Polytechnic Institute, USA

[d]Department of Biology and Biotechnology, Worcester Polytechnic Institute, USA

We thank the authors for their in-depth analysis of our study and wish we had received many of their excellent comments prior to publication.

Regarding abnormal 5x values between *Artemisias* and PZQ data on adverse effects: first, we analyzed the data as received, second, results were similar to those for other *Artemisia* trials that were against malaria.

Response to Argemi et al. 2019

Lucile Cornet-Vernet[a,*], **Jerome Munyangi**[b], **Lu Chen**[c], **Melissa Towler**[d], **Pamela Weathers**[d]

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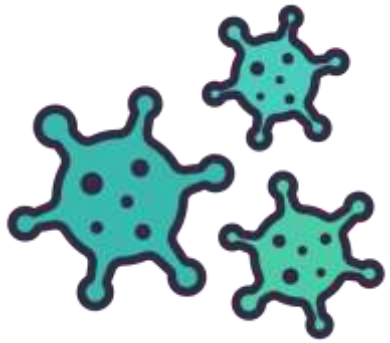
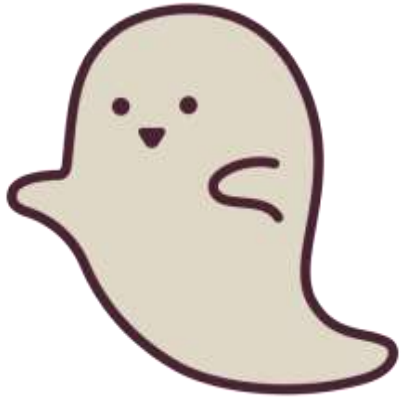
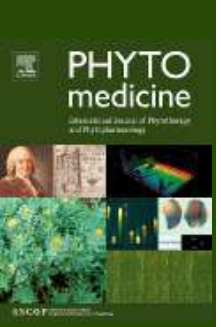


CHAPTER 5:
ZOMBIE 2





Artemisia annua and *Artemisia afra* tea infusions *vs.* artesunate-amodiaquine (ASAQ) in treating *Plasmodium falciparum* malaria in a large scale, double blind, randomized clinical trial

Jérôme Munyangi[a], Lucile Cornet-Vernet[b,*], Michel Idumbo[c], Chen Lu[d], Pierre Lutgen[e], Christian Perronne[f], Nadège Ngombe[g], Jacques Bianga[h], Bavon Mupenda[i], Paul Lalukala[j], Guy Mergeai[k], Dieudonné Mumba[l], Melissa Towler[m], Pamela Weathers[m]

ABSTRACT

Background and objective: Prior small-scale clinical trials showed that *Artemisia annua* and *Artemisia afra* infusions, decoctions, capsules, or tablets were low cost, easy to use, and efficient in curing malaria infections. In a larger-scale trial in Kalima district, Democratic Republic of Congo, we aimed to show *A. annua* and/or *A. afra* infusions were superior or at least equivalent to artesunate-amodiaquine (ASAQ) against malaria.

Methods: A double blind, randomized clinical trial with 957 malaria-infected patients had two treatment arms: 472 patients for ASAQ and 471 for *Artemisia* (248 *A. annua*, 223 *A. afra*) remained at end of the trial. ASAQ-treated patients were treated per manufacturer posology, and *Artemisia*-treated patients received 1 l/d of dry leaf/twig infusions for 7 d; both arms had 28 d follow-up. Parasitemia and gametocytes were measured microscopically with results statistically compared among arms for age and gender.

Results: Artemisinin content of *A. afra* was negligible, but therapeutic responses of patients were similar to *A. annua*-treated patients; trophozoites cleared after 24 h, but took up to 14 d to clear in ASAQ-treated patients. D28 cure rates defined as absence of parasitemia were for pediatrics 82, 91, and 50% for *A. afra, A. annua* and ASAQ; while for adults cure rates were 91, 100, and 30%, respectively. Fever clearance took 48 h for ASAQ, but 24 h for *Artemisia*. From D14-28 no *Artemisia*-treated patients had microscopically detectable gametocytes, while 10 ASAQ-treated patients remained gametocyte carriers at D28. More females than males were gametocyte carriers in the ASAQ arm but were unaffected in the *Artemisia* arms. Hemoglobin remained constant at 11 g/dl for *A. afra* after D1, while for *A. annua* and ASAQ it decreased to 9–9.5 g/dl. Only 5.0% of *Artemisia*-treated patients reported adverse effects, *vs.* 42.8% for ASAQ.

Conclusion: A. annua and *A. afra* infusions are polytherapies with better outcomes than ASAQ against malaria. In contrast to ASAQ, both *Artemisias* appeared to break the cycle of malaria by eliminating gametocytes. This study merits further investigation for possible inclusion of *Artemisia* tea infusions as an alternative for fighting and eradicating malaria.

PHYTO medicine

Table 4
Distribution among patients of adverse effects from treatment.

Observed adverse effects	Number of subjects in the *Artemisia* arms	Number of subjects in the ASAQ arm
Abdominal pain	0	25
Asthenia	0	30
Diarrhea	0	5
Drowsiness	0	3
Fatty cough	0	1
Hypoglycemia	0	20
Insomnia	0	10
Nausea	10	30
Pruritis	0	35
Vertigo	0	1
Vomiting	15	50
Total	25	210
% of total	5.0%	42.8%

Comment on "*A. annua* and *A. afra* infusions *vs.* Artesunate-amodiaquine (ASAQ) in treating *Plasmodium falciparum* malaria in a large scale, double blind, randomized clinical trial" Munyangi et al., 2019

Gillibert André[a,*], Jauréguiberry Stéphane[b], Hansmann Yves[c], Argemi Xavier[c], Landier Jordi[d], Caumes Eric[e], Gaudart Jean[f]

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RESPONSE to Gillibert et al. 2019

Lucile Cornet-Vernet[a]*, Jerome Munyangi[b], Lu Chen[c], Melissa Towler[d], Pamela Weathers[d]

[a]Association More for Less-Maison de l'Artemisia Paris, France; [b]Faculté de Médecine Université de Kolwezi, Congo DRC; [c]Department of Mathematics, Worcester Polytechnic Institute, USA; [d]Department of Biology and Biotechnology, Worcester Polytechnic Institute, USA.

Thank you to the authors for their in-depth analysis of our study.

Our response to the Argemi et al. 2018 critique is now published (Cornet-Vernet et al. 2019). The drug protocols were only different in that the control drugs, PZQ or ASAQ, were specific to their intended disease. The tea regimen was the same. The study approval date for this study was 2015; 2016 was a typographical error. Along with the data, the Approval Registration documentation also has been provided to the Gillibert team.

We reported our observed measurements. However, without more analysis (e.g. PCR) we cannot and should not speculate how or why. Dr. Munyangi had great difficulties implementing this *Artemisia* tea trial against malaria. Despite having received all appropriate approvals, several academics and ministers subsequently attempted to obstruct the trial. There were also attempts to sabotage his work by stealing his laptop. There were even efforts to poison him … he almost died. Nevertheless

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PHYTO
medicine

Suspicion of data fabrication on two Artemisia clinical trials

GILLIBERT André (MD) [a], MEYER Nicolas (MD, PhD) [b], HANSMANN Yves (MD, PhD) [c], NAUDET Florian (MD, PhD) [d], ARGEMI Xavier (MD, PhD) [c], CAUMES Eric (MD, PhD) [e], JAUREGUIBERRY Stéphane (MD, PhD) [e], LANDIER Jordi (MPH, PhD) [g], GAUDART Jean (MD, PhD) [f]

André Gillibert received legal threats from the sponsors' lawyers.

It was about copyrights of the database.

… he had to delete his submission…

… I won't show the database…

… but …

André Gillibert received legal threats from the sponsors' lawyers.

It was about copyrights of the database.

… he had to delete his submission…

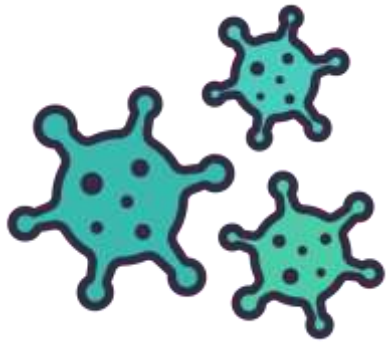
… I won't show the database…

… but …

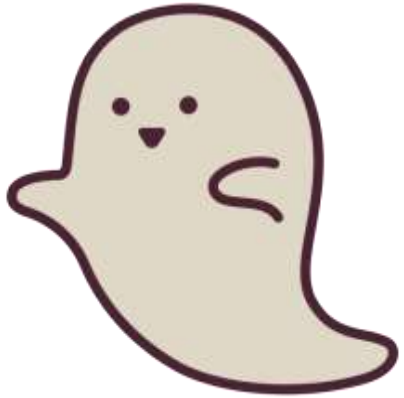
… wait for it …

MALARIA BUSINESS

The data base (not exactly the same)… at



CHAPTER 6:
ZOMBIE
DEAD



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Ivan Oransky

Retraction Watch
New York, USA

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Address for Whisteblower

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ars Agence Régionale de Santé Normandie

ansm Agence nationale de sécurité du médicament et des produits de santé

Address for Whisteblower

Thank you for your message!

Christian Perronne[f],

évaluation et qualité Hcéres

UVSQ université PARIS-SACLAY

université PARIS-SACLAY

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Does Science Self-Correct? What We've Learned at Retraction Watch

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Retraction Watch
New York, USA

A bitter aftertaste: Legal threats, alleged poisoning muddy the waters for a trial of a tea to treat malaria

Artemisia afra, via Wikimedia

august 2020

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Phytomedicine

journal homepage: www.elsevier.com/locate/phymed

Effect of *Artemisia annua* and *Artemisia afra* tea infusions on schistosomiasis in a large clinical trial

Jérôme Munyangi[a], Lucile Cornet-Vernet[b,*], Michel Idumbo[c], Chen Lu[d], Pierre Lutgen[e], Christian Perronne[f], Nadège Ngombe[g], Jacques Bianga[h], Bavon Mupenda[i], Paul Lalukala[j], Guy Mergeai[k], Dieudonné Mumba[l], Melissa Towler[m], Pamela Weathers[m]

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[b] Vice Présidente de La Maison de l'Artémisia (association Loi 1901), 20 rue Pierre Demours, 75017 Paris, France
[c] Centre de Santé de Lubile, Manitema, Democratic Republic of the Congo
[d] Department of Mathematics, Worcester Polytechnic Institute, USA
[e] Association IVER-BELIVER, Luxembourg
[f] Faculté de Médecine de Paris IDF Ouest, France
[g] Faculté de Pharmacie, Université de Kinshasa,Democratic Republic of the Congo
[h] Programme National Lutte Contre le Paludisme, Manitema, Democratic Republic of the Congo
[i] Ecole de Santé Publique Université de Kinshasa, Democratic Republic of the Congo
[j] Ministère Provincial de Santé Publique Manitema, Democratic Republic of the Congo
[k] Université de Liège, Belgium
[l] Faculté de Médecine Université de Kinshasa, Democratic Republic of the Congo
[m] Department of Biology and Biotechnology, Worcester Polytechnic Institute, USA

ARTICLE INFO

Keywords:
Artemisinin
Artemisia
Bilharzia
Tea infusion
Wormwood

ABSTRACT

Background: Schistosomiasis (bilharzia), a serious neglected tropical disease affecting millions, has few effective treatments. Two *Artemisia* wormwood species, *A. annua* and *A. afra*, were compared with the standard praziquantel (PZQ) treatment in an 800 patient clinical trial. August-November of 2015.

Methods: This randomized, superiority clinical trial had three treatment arms: 400 for PZQ, 200 for *A. annua*, 200 for *A. afra*. PZQ-treated patients followed manufacturer posology. Artemisia-treated patients received 5 g of dry leaf/twig tea infusion divided into 3 aliquots daily, for 7 days with 28-day follow-up.

Results: Of the enrolled patients having an average of >700 *Schistosoma mansoni* eggs per fecal sample, 780 completed the trial. Within 14 days of treatment, all Artemisia-treated patients had no detectable eggs in fecal exams, a result sustained 28 days post treatment. Eggs in fecal smears of PZQ-treated patients were undetectable by D21. More males than females who entered the trial had melena, but both genders responded equally well to treatment; by D28 melena disappeared in all patients. In all arms, eosinophil levels declined by about 27% from D0 to D28. From D0 to D28 hemoglobin increases were greater in PZQ and *A. afra*-treated patients than in *A. annua*-treated patients. Hematocrit increases were greater from D0 to D28 for patients treated with either PZQ or *A. annua* compared to those treated with *A. afra*. Gender comparison showed that *A. afra*-treated males had significantly greater hemoglobin and hematocrit increases by D28 than either PZQ or *A. annua*-treated males. In contrast, PZQ and *A. afra*-treated females had greater hemoglobin and hematocrit increases than *A. annua*-treated females. Both adults and pediatric patients treated with *A. annua* responded better compared to PZQ treatment.

Conclusion: Both *A. annua* and *A. afra* provided faster effective treatment of schistosomiasis and should be considered for implementation on a global scale.

Abbreviations: AM, artemether; ASAQ, artesunate amodiaquine; ART, artemisinin; AS, artesunate; PZQ, praziquantel
* Corresponding author.
E-mail address: lcv@maison-artemisia.org (L. Cornet-Vernet).

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Phytomedicine 57 (2019) 49–56

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Artemisia annua and *Artemisia afra* tea infusions *vs.* artesunate-amodiaquine (ASAQ) in treating *Plasmodium falciparum* malaria in a large scale, double blind, randomized clinical trial

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[m] Department of Biology and Biotechnology, Worcester Polytechnic Institute, USA

ARTICLE INFO

Keywords:
ACT
ASAQ
Artemisinin
Malaria
Clinical trial
Tea infusion

ABSTRACT

Background and objective: Two small-scale clinical trials showed that *Artemisia annua* and *Artemisia afra* infusions were low cost, easy to use, and efficient in curing malaria infections. In a large scale district, Democratic Republic of Congo, we aimed to show *A. annua* and/or *A. afra* infusion to be superior or at least equivalent to artesunate amodiaquine (ASAQ) against malaria.

Methods: This double blind, randomized clinical trial with 957 malaria-infected patients had two treatment arms: 472 patients for ASAQ and 471 for *Artemisia* (248 *A. annua*, 223 *A. afra*) remained at end of the trial. ASAQ-treated patients were treated per manufacturer posology, and *Artemisia*-treated patients received 5 l/d of dry leaf/twig infusions for 7 d; both arms had 28 d follow-up. Parasitemia and gametocytes were measured microscopically with results statistically compared among arms for age and gender.

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Conclusion: *A. annua* and *A. afra* infusions are polytherapies with better outcomes than ASAQ against malaria. In contrast to ASAQ, both *Artemisia* appeared to break the cycle of malaria by eliminating gametocytes. This study merits further investigation for possible inclusion of *Artemisia* tea infusions as an alternative for fighting and eradicating malaria.

Abbreviations: ACT, artemisinin combination therapy; ASAQ, artesunate-amodiaquine; DLA, dried leaf Artemisia; I.v., intravenous; PNLP, programme national de Lutte contre le Paludisme
* Corresponding author.
E-mail address: lcv@maison-artemisia.org (L. Cornet-Vernet).

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0944-7113/

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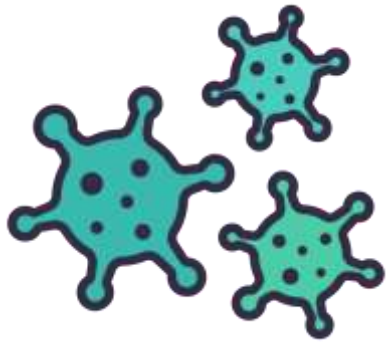
ROYAL SOCIETY OF CHEMISTRY

Artemisinin as a therapeutic *vs.* its more complex *Artemisia* source material

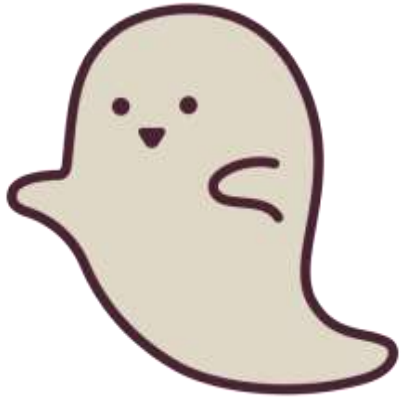
Pamela J. Weathers

a result similar to a human trial using tea infusions of *A. annua* and *A. afra* in several hundred malaria patients.[65] When compared to the standard malaria treatment recommended by WHO for that region of Africa, neither ALT nor AST were significantly altered post-treatment with *A. afra* or *A. annua*.[65] Together these human trials demonstrated the safety of both *A. afra* and *A. annua*.

Natural Product Reports



CHAPTER 7: CLONE WARS




Clinical
Medicine
Research


LOW LEVEL LASER THERAPY
TO HELP WITH
AUTISM?
ALIGN
INTEGRATED MEDICAL CLINIC

Effects of Low-Level Laser Therapy in Autism Spectrum Disorder

Gerry Leisman, Calixto Machado, Yanin Machado, and Mauricio Chinchilla-Acosta

Contacts and Locations

This section provides the contact details for those conducting the study, and information on where this study is being conducted.

Israel

Nazareth, Israel, 16470
Institute for Brain and Rehabilitation Sciences

Region of Enrollment

Measure Type: Number | Unit of measure: participants

Number Analyzed	21 participants	19 participants	40 participants
Cuba	21	19	40

Effects of Low-Level Laser Therapy in Autism Spectrum Disorder

Gerry Leisman, Calixto Machado, Yanin Machado, and Mauricio Chinchilla-Acosta

1. Mean Change From Baseline to Study Endpoint in the Aberrant Behavior Checklist (ABC) Irritability & Agitation Subscale Score.

Type: Primary | Time Frame: Baseline and 4 weeks (Study Endpoint)

Description	Primary outcome measure in this study is defined as the mean change from baseline to 4 weeks of intervention (study endpoint), in the Aberrant Behavior Checklist (ABC) Irritability Subscale score. The ABC Irritability Subscale contains 15 items relating to aggression, self-injury, tantrums, agitation and unstable mood in individuals with developmental disorders. Each item is rated from 0 (not at all a problem) to 3 (the problem is severe in degree). The individual scores are summed for a total score from 0 to 45, with higher scores indicating greater severity. A negative (-) change indicates a decrease in symptom severity and is positive for improvement. A positive (+) change indicates an increase in symptom severity and is negative for improvement. Study success is established as the detection of a minimum mean difference of -8.5 points between test and placebo groups in the change in ABC Irritability Subscale score.	
Time Frame	Baseline and 4 weeks (Study Endpoint)	
Analysis Population Description	[Not Specified]	
Arm/Group Title	Erchonia HLS Laser	Placebo Laser
Arm/Group Description	The Erchonia HLS Laser is administered 8 times across 4 weeks for 5 minutes each time to the skull at the base of the brain and temporal areas.... + Show more	The Placebo Laser is administered 8 times across 4 weeks for 5 minutes each time to the skull at the base of the brain and temporal areas.... + Show more
Overall Number of Participants Analyzed	21	19
Mean (Standard Deviation) | Unit of Measure: score on a scale	-14.81 (6.40)	0.37 (1.38)

Effects of Low-Level Laser Therapy in Autism Spectrum Disorder

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Effects of Low-Level Laser Therapy in Autism Spectrum Disorder

Gerry Leisman, Calixto Machado, Yanin Machado, and Mauricio Chinchilla-Acosta

Table 7 ABC global and subscale scores by the procedure group

	Test[a] (n = 21)	Placebo (n = 19)
	Mean ± SD	Mean ± SD
Global score	30.5 ± 6.7	29.6 ± 6.8
Irritability and agitation	23.1 ± 9.3	24.7 ± 5.1
Lethargy and social withdrawal	13.7 ± 4.1	12.3 ± 5.6
Stereotypic behavior	32.8 ± 7.8	36.9 ± 7.9
Hyperactivity and noncompliance	7.2 ± 3.1	6.4 ± 4.0
Inappropriate speech	107.3 ± 20.3	104.7 ± 28.7

[a]Test group was the active treatment group

Table 11 ABC irritability subscale score from baseline to endpoint by the procedure group

	Test[a] (n = 21)	Placebo (n = 19)
ABC irritability subscale score	Mean ± SD	Mean ± SD
Baseline	30.5 ± 6.7	29.6 ± 6.8
Endpoint	15.7 ± 9.9	29.9 ± 6.6
Change	**−14.8 ± 6.4**	**0.3 ± 1.4**

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Effects of Low-Level Laser Therapy in Autism Spectrum Disorder

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Baseline	30.5 ± 6.7	29.6 ± 6.8
Endpoint	15.7 ± 9.9	29.9 ± 6.6
Change	**−14.8 ± 6.4**	**0.3 ± 1.4**

[a]Test group was the active treatment group

Effects of Low-Level Laser Therapy in Autism Spectrum Disorder

Gerry Leisman, Calixto Machado, Yanin Machado, and Mauricio Chinchilla-Acosta

Table 15 ABC global and subscale scores from baseline to endpoint by the procedure group

		Test[a] (n = 21)	Placebo (n = 19)
		Mean ± SD	Mean ± SD
Global score	Baseline	107.3 ± 20.3	104.7 ± 28.7
	Endpoint	63.8 ± 30.5	105.4 ± 28.4
	Change	−43.5 ± 19.1	0.7 ± 2.6
Lethargy and social withdrawal	Baseline	23.1 ± 9.3	24.7 ± 5.1
	Endpoint	13.8 ± 8.8	24.7 ± 5.1
	Change	−9.3 ± 5.8	0.1 ± 0.2
Stereotypic behavior	Baseline	13.7 ± 4.1	12.3 ± 5.6
	Endpoint	8.2 ± 5.1	12.3 ± 5.6
	Change	−5.5 ± 4.0	0.0 ± 0.0
Hyperactivity and noncompliance	Baseline	32.8 ± 7.8	36.9 ± 7.9
	Endpoint	21.1 ± 9.5	37.3 ± 7.4
	Change	−11.7 ± 7.5	0.4 ± 1.1
Inappropriate speech	Baseline	7.2 ± 3.1	6.4 ± 4.0
	Endpoint	4.9 ± 2.4	6.4 ± 3.9
	Change	−2.3 ± 2.3	0.0 ± 0.3

[a]Test group was the active treatment group

Effects of Low-Level Laser Therapy in Autism Spectrum Disorder

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Hyperactivity and noncompliance	Baseline	32.8 ± 7.8	36.9 ± 7.9
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	Change	−11.7 ± 7.5	0.4 ± 1.1
Inappropriate speech	Baseline	7.2 ± 3.1	6.4 ± 4.0
	Endpoint	4.9 ± 2.4	6.4 ± 3.9
	Change	−2.3 ± 2.3	0.0 ± 0.3

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EFFECTS OF LOW LEVEL-LASER THERAPY IN AUTISM SPECTRUM DISORDER

Data File

Gerry Leisman, Calixto Machado, Yanin Machado, Mauricio Chinchilla-Acosta

Subject ID	Group	Baseline	Week 2	Week 4	Week 8
CM002	Test	21	14	6	4
CM003	Test	31	22	13	9
CM005	Test	22	16	10	5
CM007	Test	25	17	7	1
CM010	Test	30	19	9	6
CM011	Test	30	25	16	14
CM014	Test	39	39	39	37
CM015	Test	29	23	17	5
CM018	Test	37	26	12	8
CM019	Test	30	21	14	14
CM022	Test	24	21	18	15
CM024	Test	32	21	13	11
CM027	Test	35	26	7	1
CM028	Test	24	18	1	1
CM029	Test	44	37	34	31
CM034	Test	27	21	15	11

EFFECTS OF LOW LEVEL-LASER THERAPY IN AUTISM SPECTRUM DISORDER

Data File

Gerry Leisman, Calixto Machado, Yanin Machado, Mauricio Chinchilla-Acosta

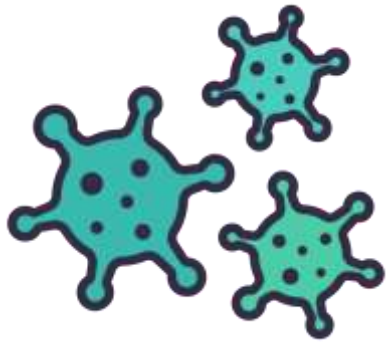
Subject ID	Group	Baseline	Week 2	Week 4	Week 8
CM001	Placebo	21	21	21	21
CM004	Placebo	21	21	27	27
CM006	Placebo	20	20	20	20
CM008	Placebo	33	33	33	33
CM009	Placebo	28	28	28	28
CM012	Placebo	35	35	35	35
CM013	Placebo	22	22	22	22
CM016	Placebo	23	23	23	23
CM017	Placebo	32	32	32	32
CM020	Placebo	41	47	41	41
CM021	Placebo	32	32	32	32
CM023	Placebo	30	30	30	30
CM025	Placebo	35	35	35	35
CM026	Placebo	34	34	34	34
CM030	Placebo	24	24	24	24
CM031	Placebo	25	25	25	25
CM032	Placebo	32	32	32	32
CM033	Placebo	44	44	44	44

EFFECTS OF LOW LEVEL-LASER THERAPY IN AUTISM SPECTRUM DISORDER

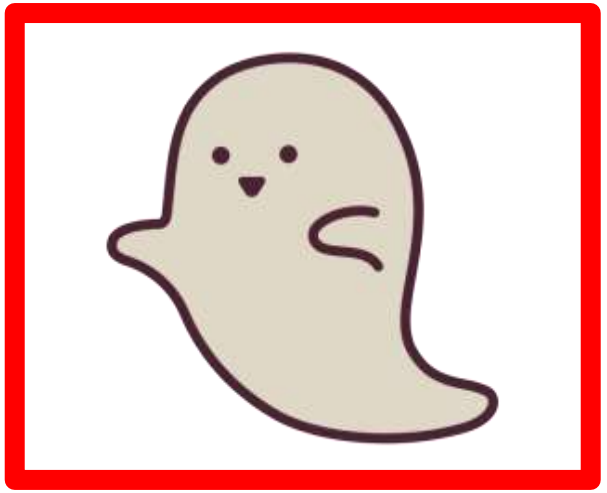
Data File

Gerry Leisman, Calixto Machado, Yanin Machado, Mauricio Chinchilla-Acosta

Subject ID	Group	Baseline	Week 2	Week 4	Week 8
CM001	Placebo	21	21	21	21
CM004	Placebo	21	21	27	27
CM006	Placebo	20	20	20	20
CM008	Placebo	33	33	33	33
CM009	Placebo	28	28	28	28
CM012	Placebo	35	35	35	35
CM013	Placebo	22	22	22	22
CM016	Placebo	23	23	23	23
CM017	Placebo	32	32	32	32
CM020	Placebo	41	47	41	41
CM021	Placebo	32	32	32	32
CM023	Placebo	30	30	30	30
CM025	Placebo	35	35	35	35
CM026	Placebo	34	34	34	34
CM030	Placebo	24	24	24	24
CM031	Placebo	25	25	25	25
CM032	Placebo	32	32	32	32
CM033	Placebo	44	44	44	44



CHAPTER 8:
GHOST STUDIES



PROCEEDINGS
OF THE ROYAL SOCIETY B
BIOLOGICAL SCIENCES

Left-right asymmetry of the Maxwell spot centroids in adults without and with dyslexia

Albert Le Floch[1,2,3] and Guy Ropars[1,3]

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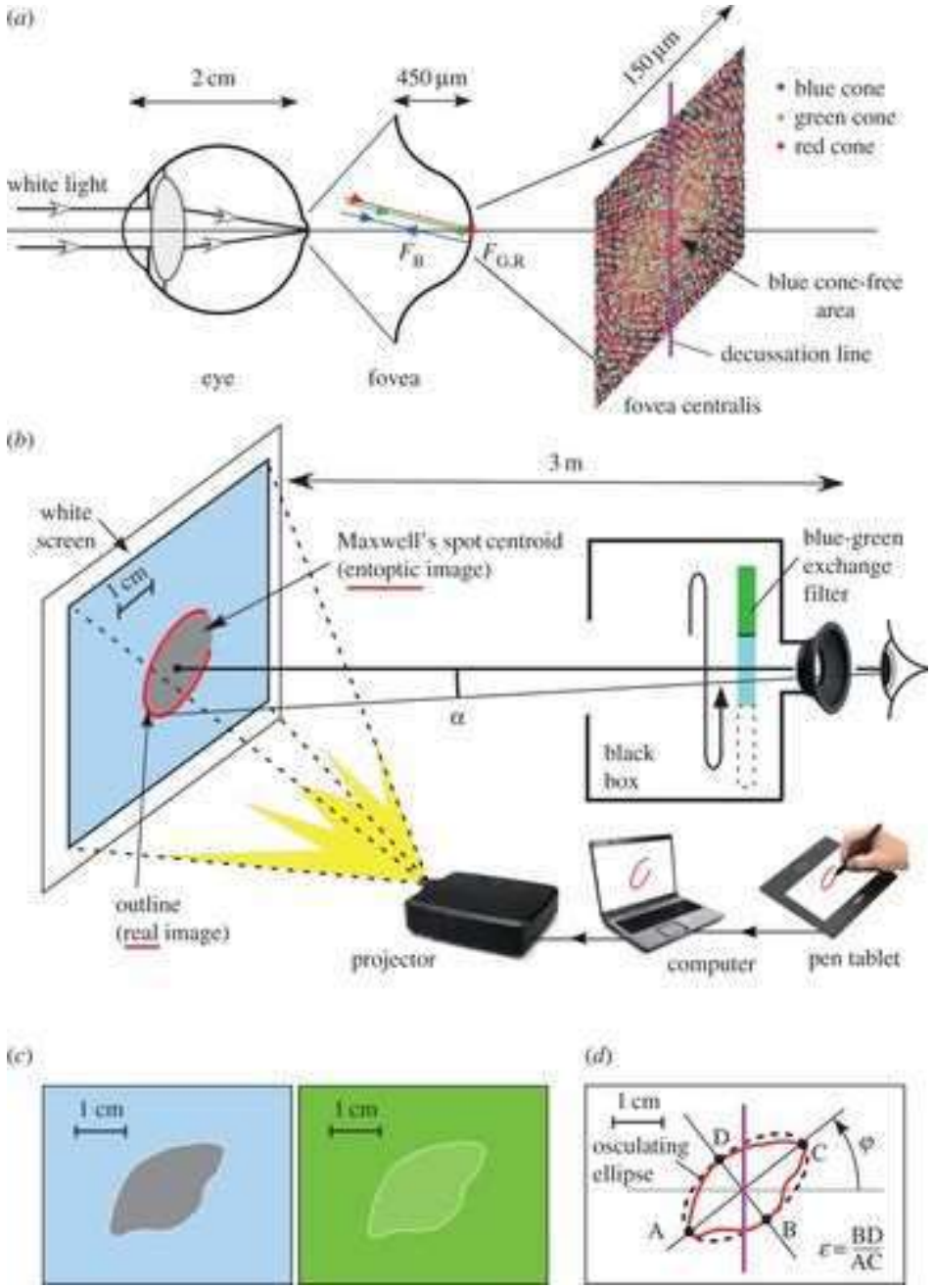

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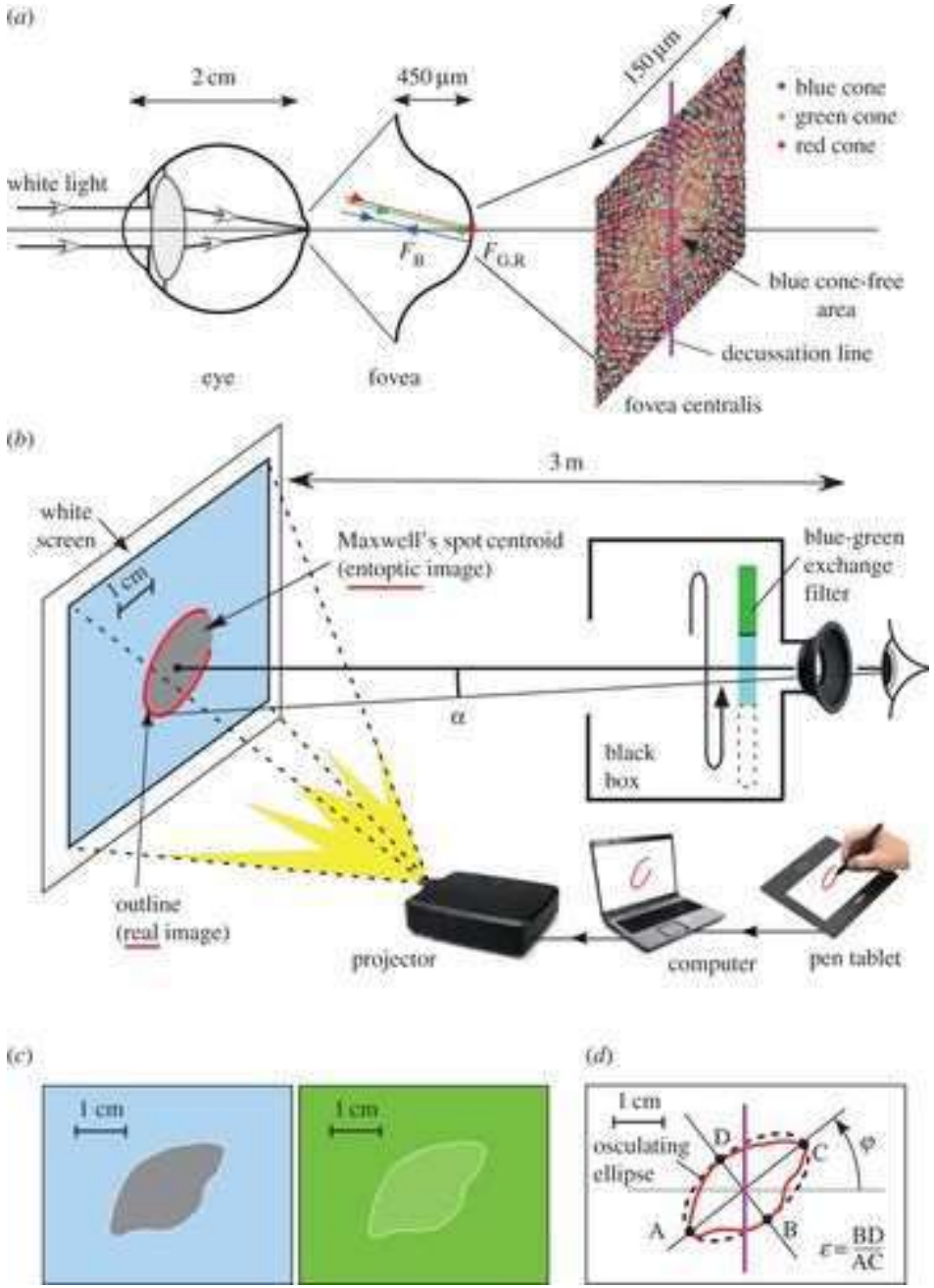
SCAN ME



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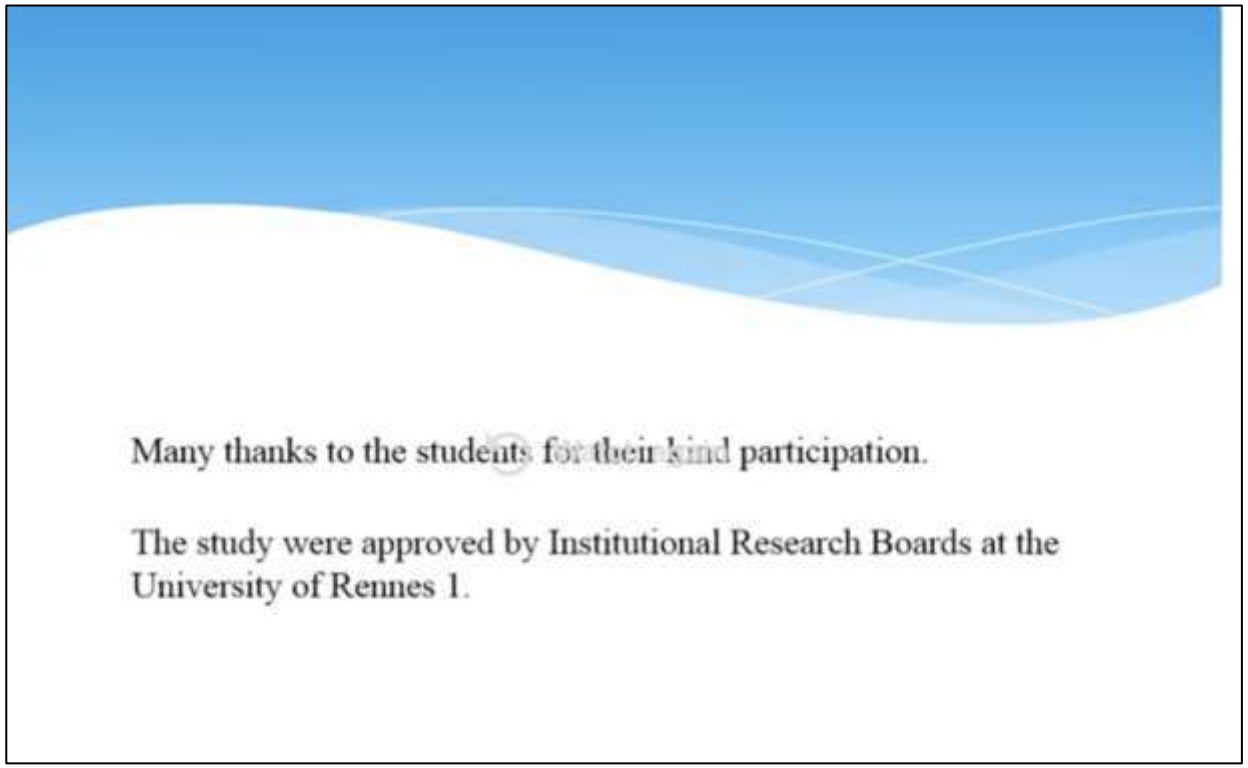

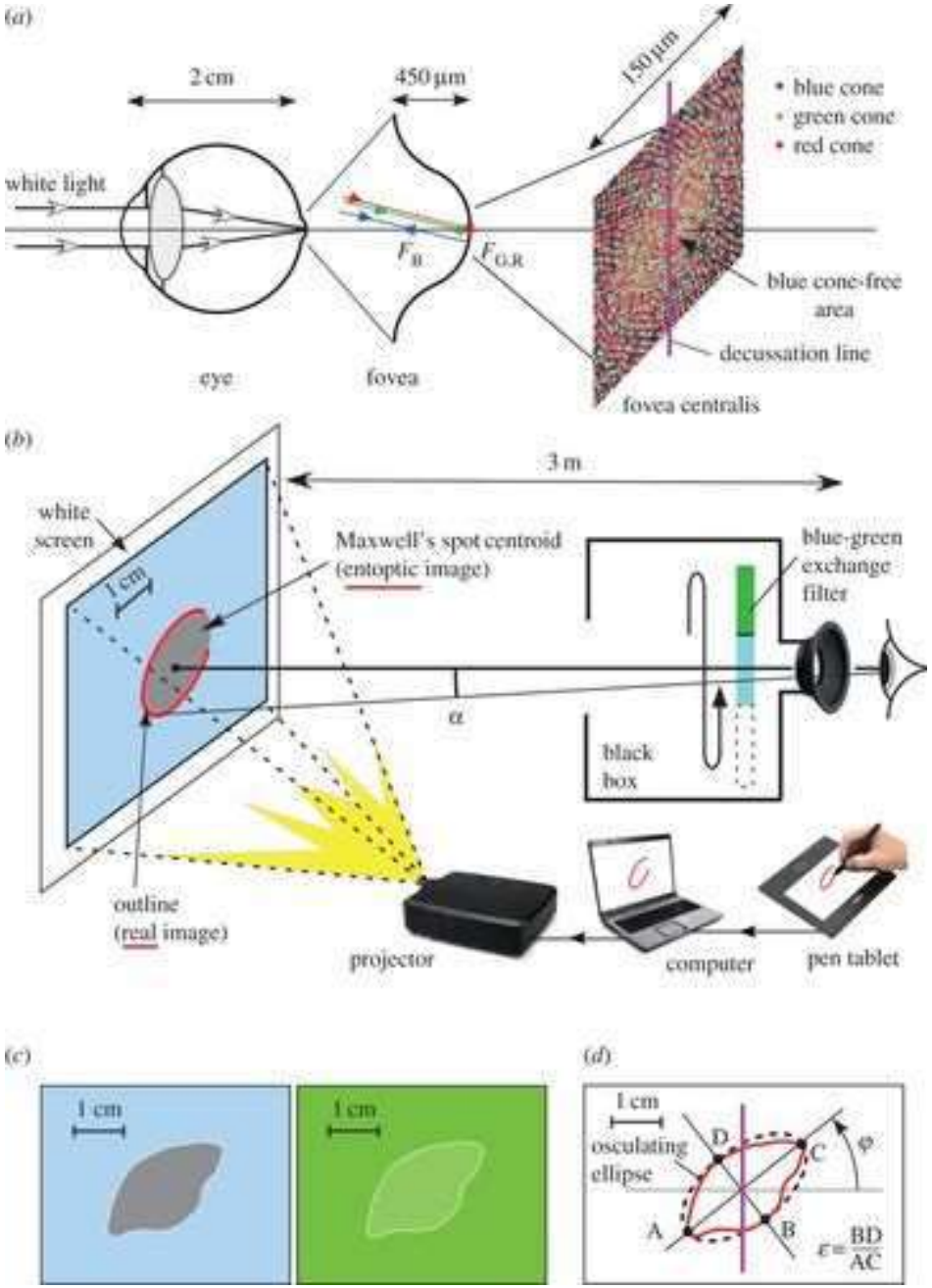

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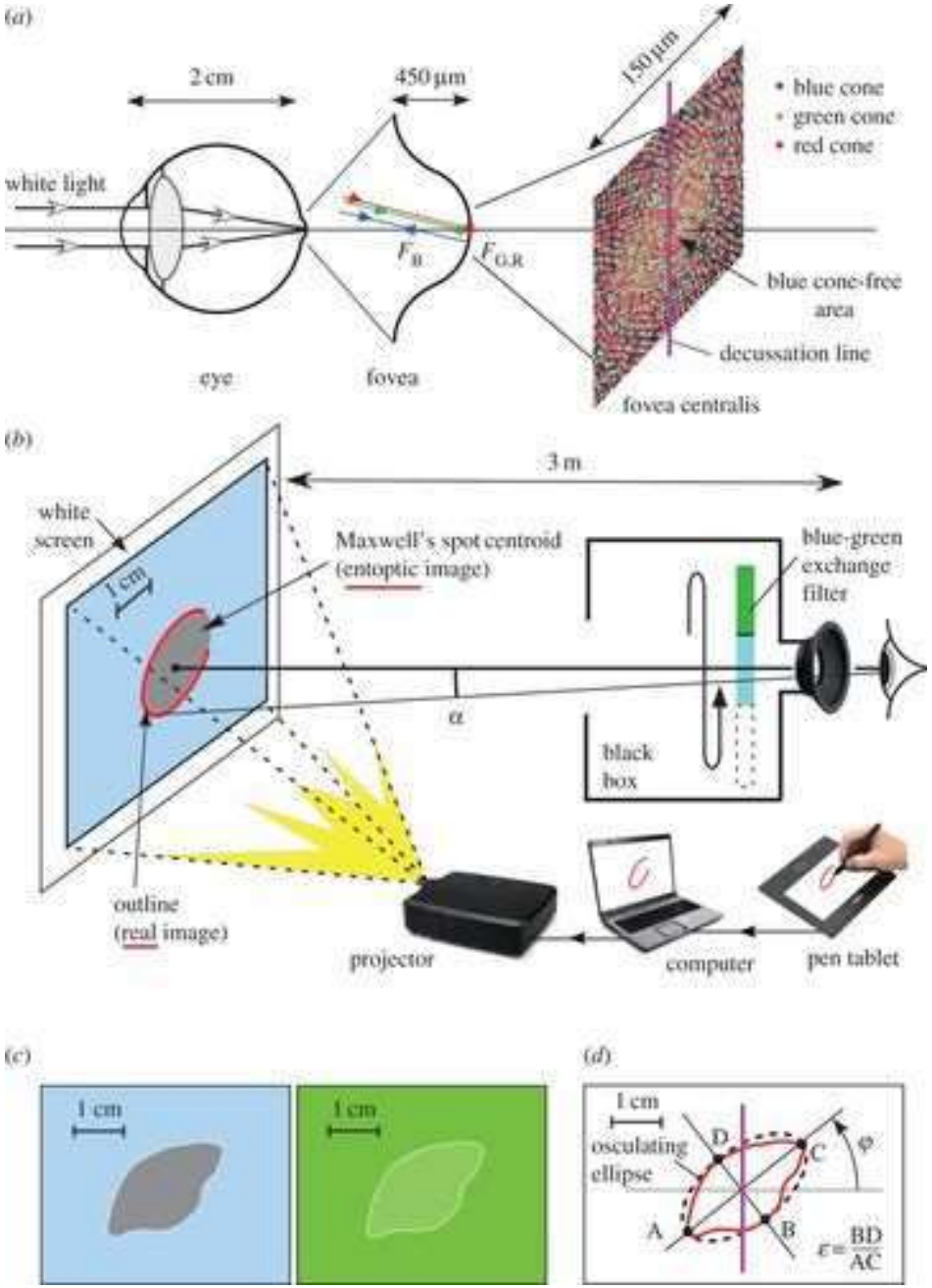

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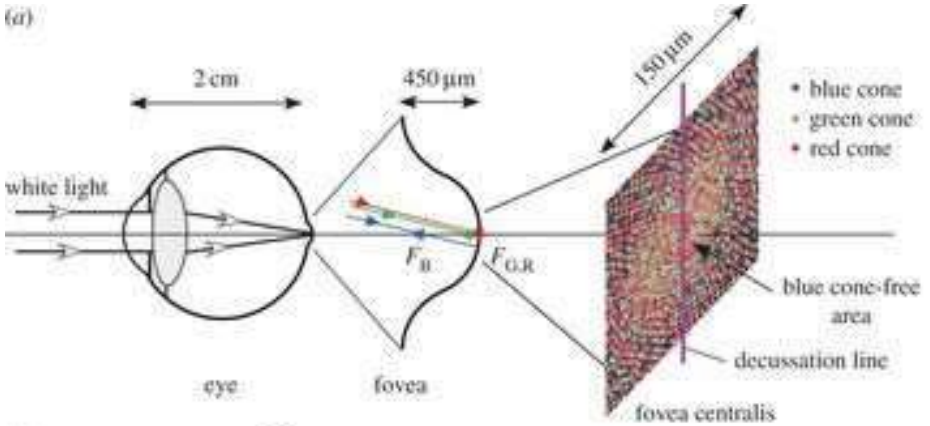

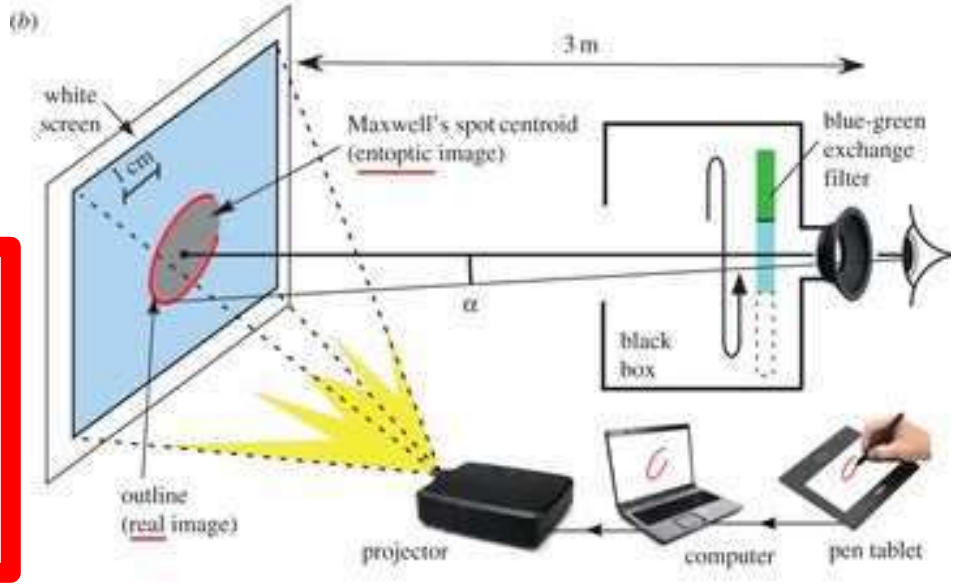

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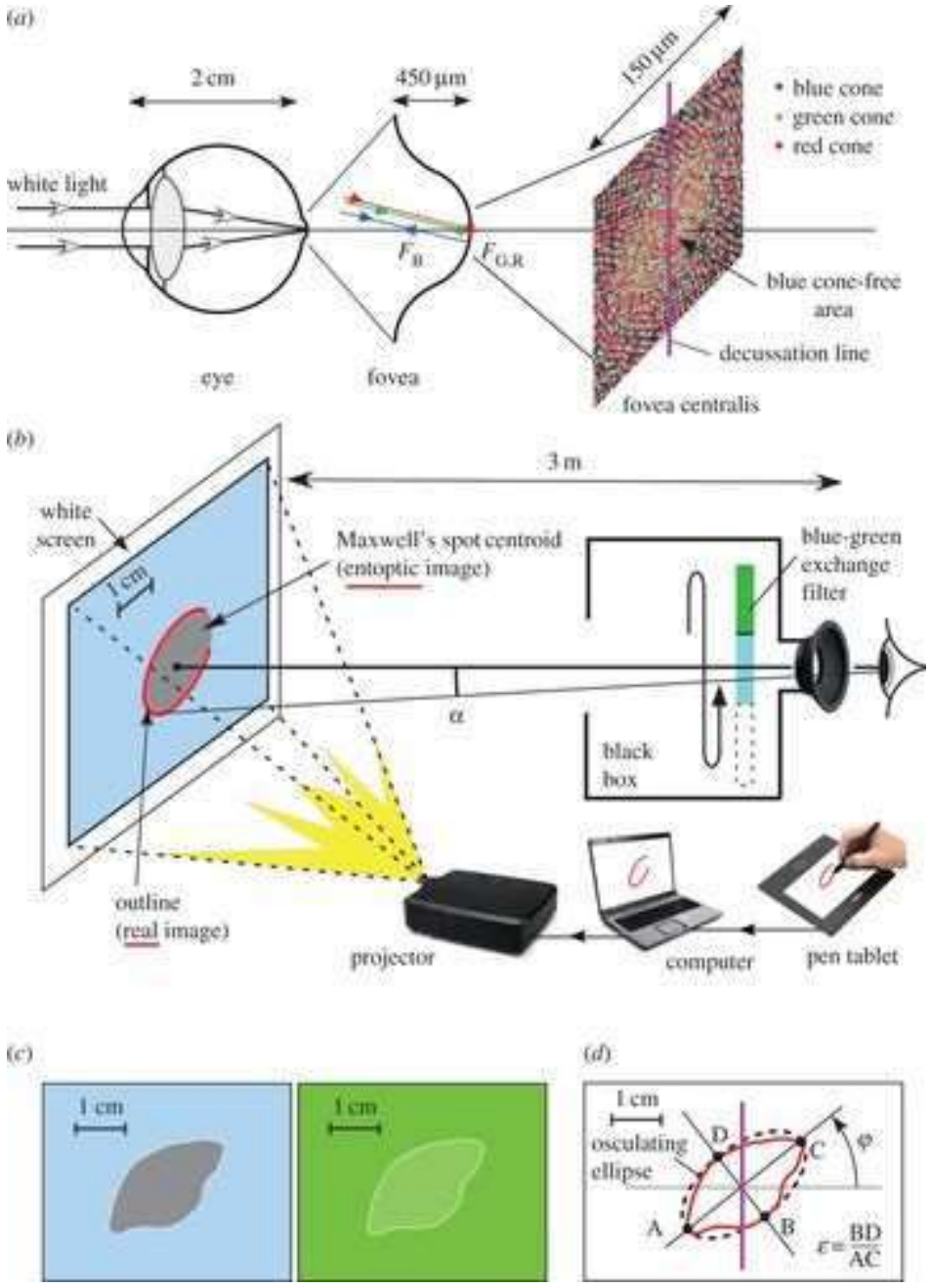

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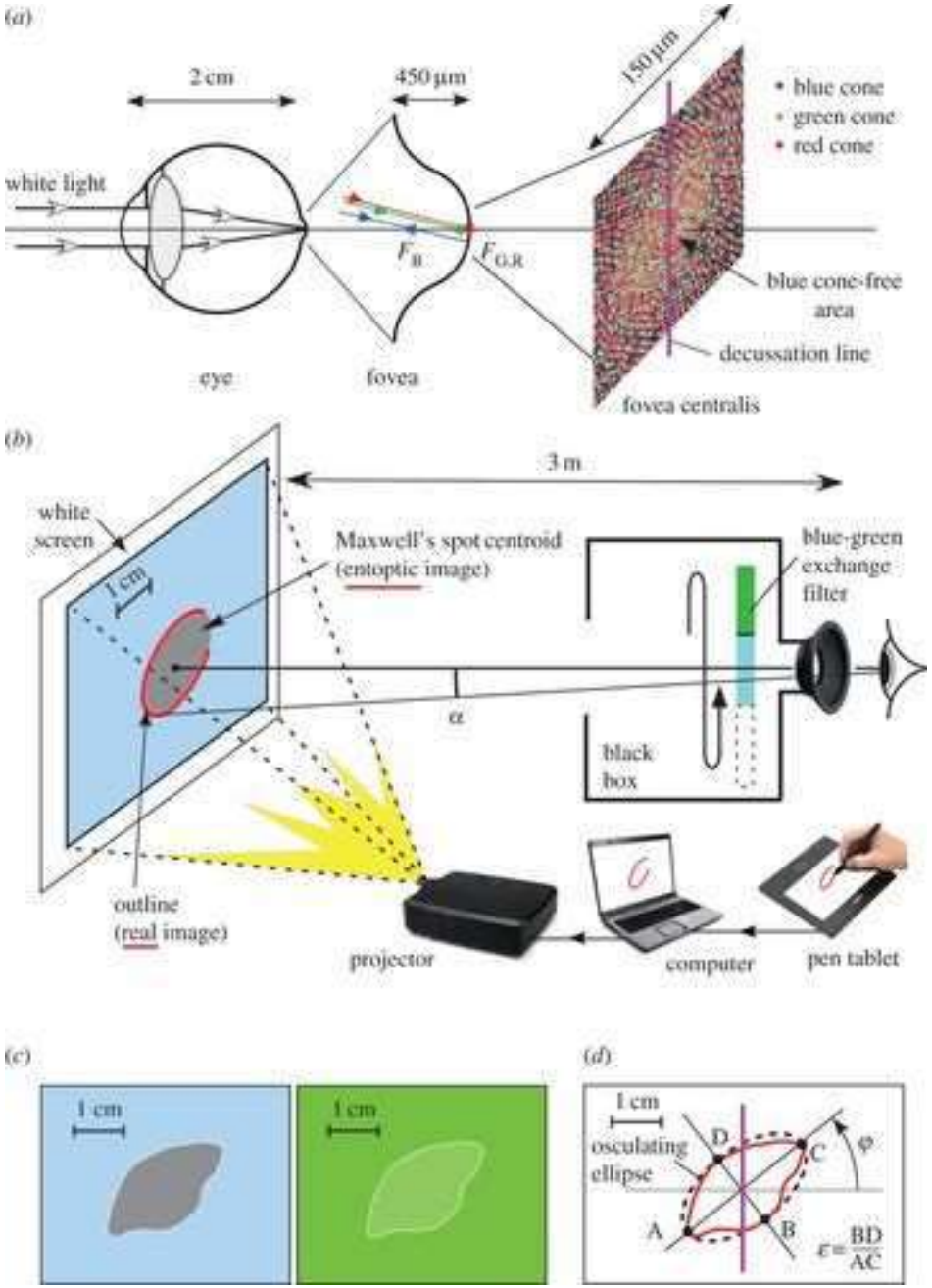

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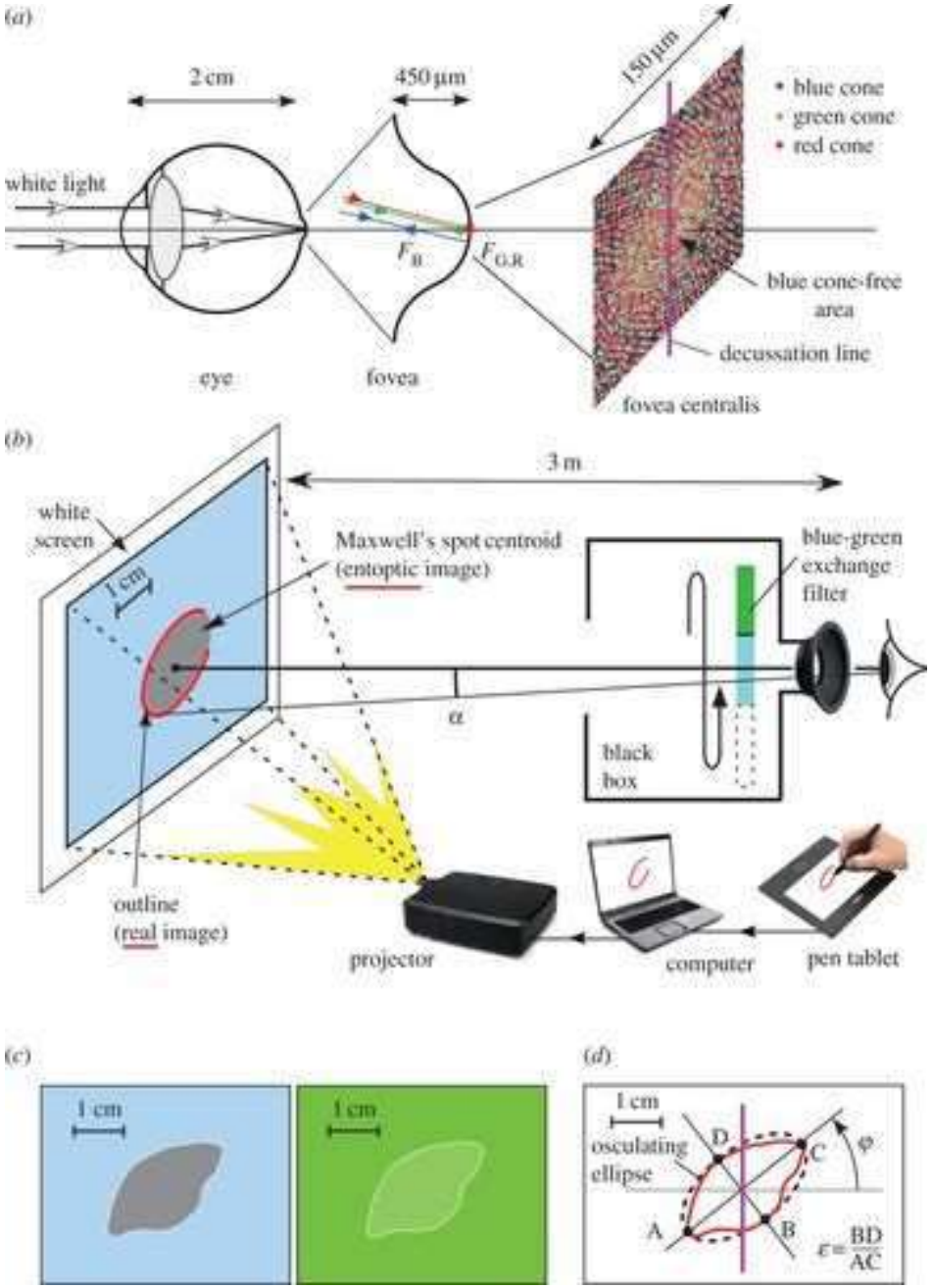

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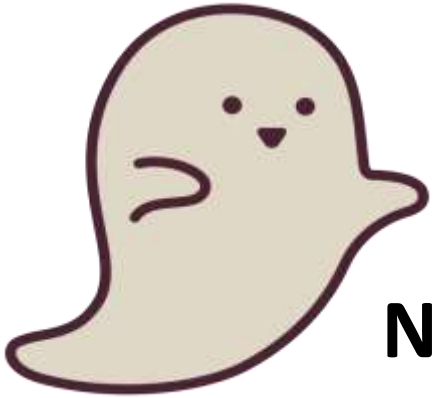

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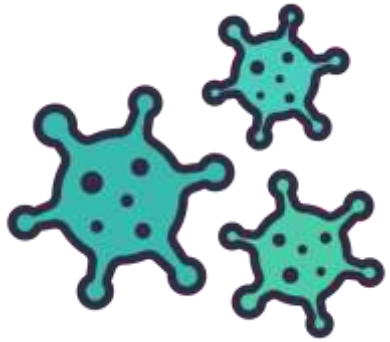
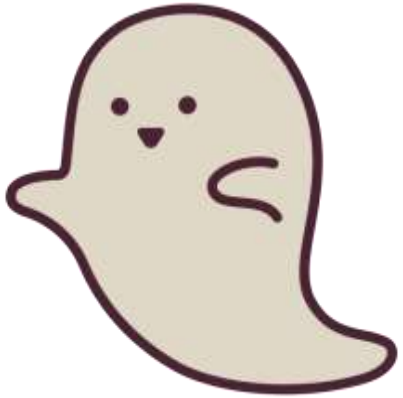
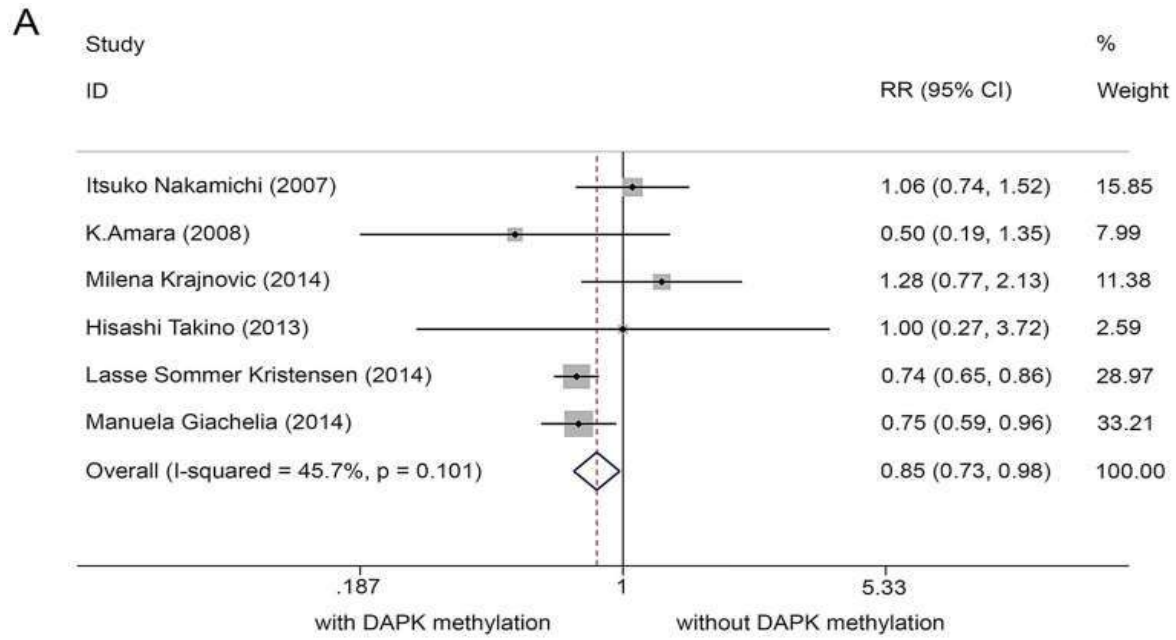


CHAPTER 9:
HOUSE OF THE DEAD





RESEARCH ARTICLE

Prognostic significance of DAPK promoter methylation in lymphoma: A meta-analysis

Hong Wang[1], Lin-Yu Zhou[2], Ze-Bing Guan[1], Wen-Bin Zeng[1], Lan-Lan Zhou[1], Ya-Nan Liu[1], Xue-Yi Pan[1]*

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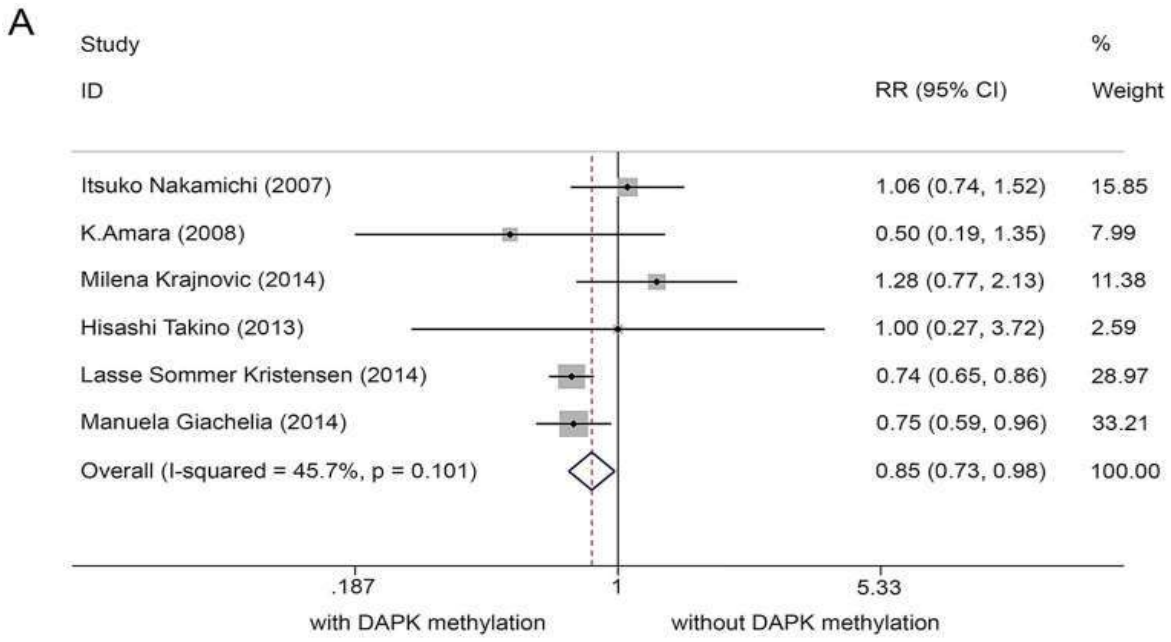
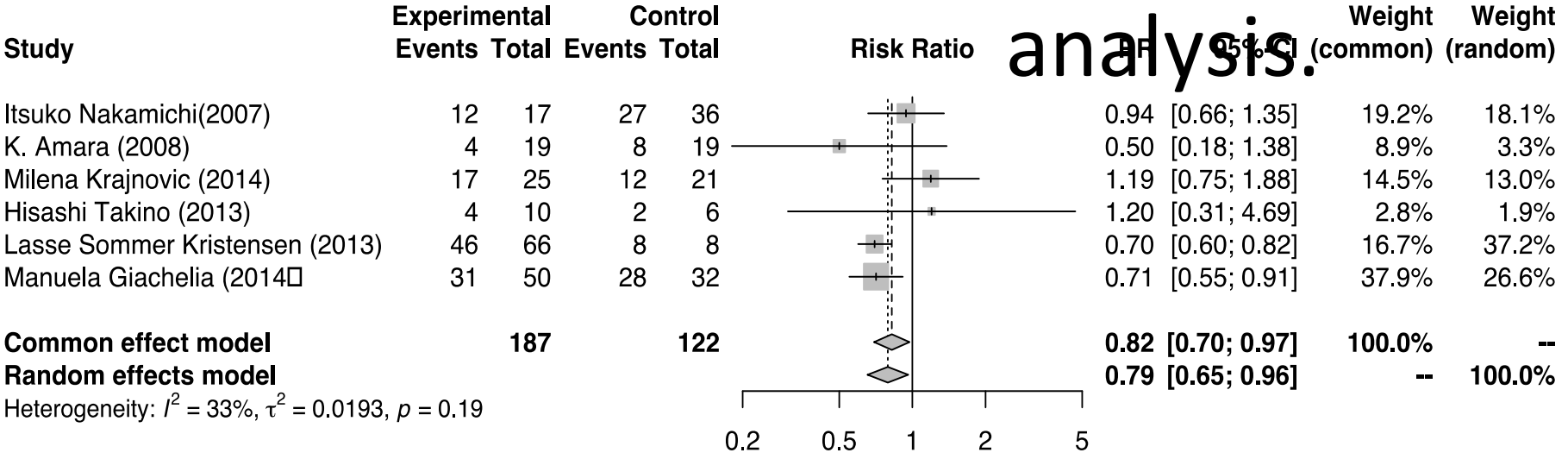
362 patients included Versus 309 in the re-analysis.





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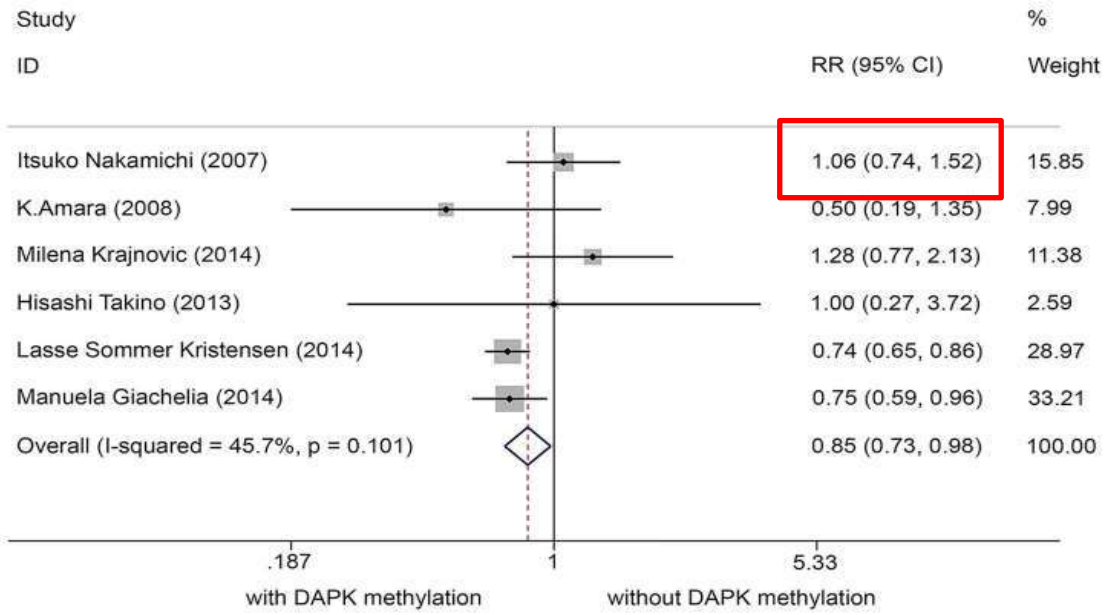

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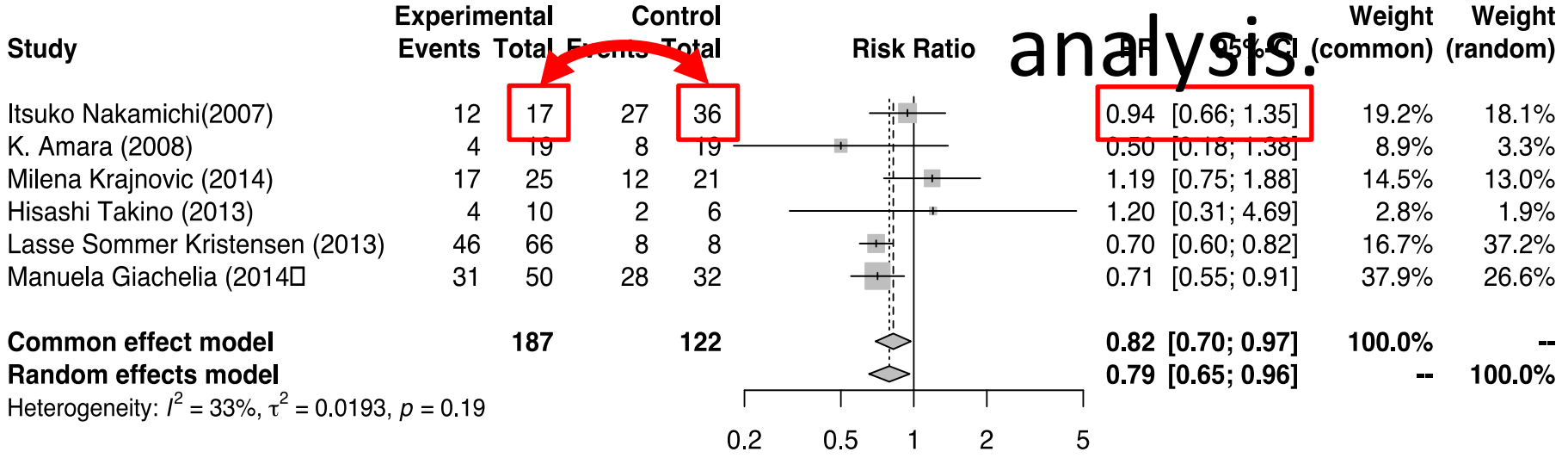

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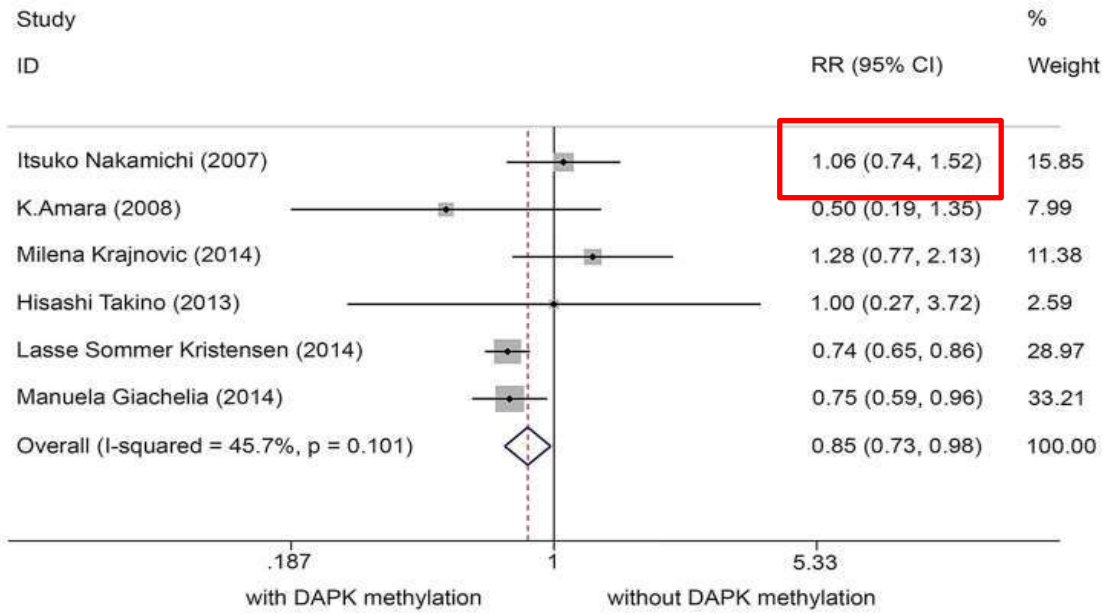

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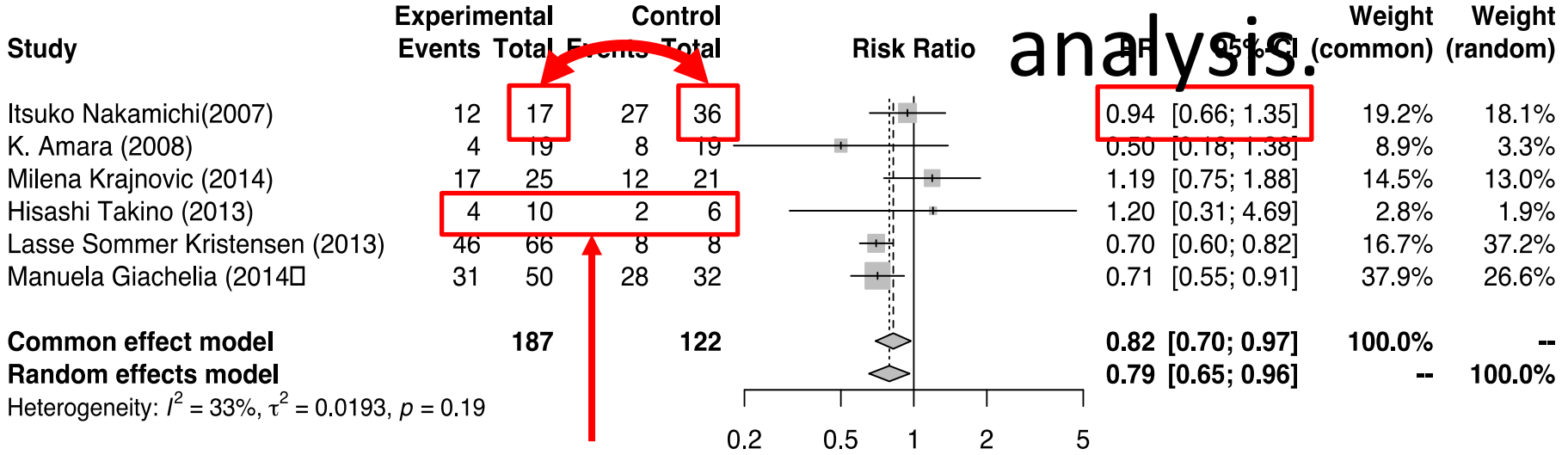

Only 6 patients with a 5 year follow up in the paper.

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

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Abstract

We aimed to characterize the clinical significance of epigenetic loss of death-associated protein kinase (DAPK) gene function through promoter methylation in the development and prognosis of lymphoma. PubMed, Web of Science and ProQuest databases were searched for relevant studies. Twelve studies involving 709 patients with lymphoma were identified. The prognostic value of DAPK methylation was expressed as risk ratio (RR) and its corresponding 95% confidence interval (CI), while the associations between DAPK methylation and the clinical characteristics of patients with lymphoma were expressed as odd ratios (ORs) and their corresponding 95% CIs. Meta-analysis showed that the 5-year survival rate was significantly lower in lymphoma patients with hypermethylated DAPK (RR = 0.85, 95% CI (0.73, 0.98), P = 0.025). Sensitivity analysis demonstrated consistent result. However, no associations were found between DAPK methylation and clinicopathological features of lymphoma, in relation to gender (OR = 1.07, 95% CI (0.72, 1.59), P = 0.751), age (OR = 1.01, 95% CI (0.66, 1.55), P = 0.974), international prognostic index (OR = 1.20, 95% CI (0.63, 2.27), P = 0.575), B symptoms (OR = 0.76, 95% CI (0.38, 1.51), P = 0.452), serum lactate dehydrogenase (OR = 1.13, 95% CI (0.62, 2.05), P = 0.683), and BCL-2 expression (OR = 1.55, 95% CI (0.91, 2.66), P = 0.106). Lymphoma patients with hypermethylated DAPK are at risk for poorer 5-year survival rate. DAPK methylation may serve as a negative prognostic biomarker among lymphoma patients, although it may not be associated with the progression of lymphoma.

Introduction

Lymphoma accounts for about 3.6% of all cancer-related deaths in the developed countries [1]. It is a highly heterogeneous hematological malignancy that arises from the lymphatic system. Lymphoma patients exhibit wide range of responses to treatments and clinical outcomes [2–4]. At present, the international prognostic index (IPI) based on clinical parameters is widely applied to predict clinical outcomes. However, the variability observed in the patients' outcome with similar clinical presentations undermines its prognostic value. However, the

RETRACTION

Retraction: Prognostic significance of DAPK promoter methylation in lymphoma: A meta-analysis

The *PLOS ONE* Editors

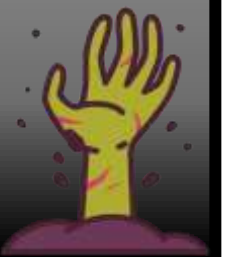
After this article was published, similarities were noted between this article and submissions by other research groups which call into question the validity and provenance of the reported results. In addition, during editorial follow-up, a number of data extraction and analysis errors were found and confirmed by the first author, meaning it is not clear the conclusions are supported.

In light of these issues, *PLOS ONE* cannot stand by the reliability of the reported research, and the *PLOS ONE* Editors retract this article [1].

HW agreed with the retraction. LYZ, ZBG, WBZ, LLZ, YNL, and XYP either did not respond or could not be reached.

Reference

1. Wang H, Zhou L- Y, Guan Z- B, Zeng W- B, Zhou L- L, Liu Y- N, et al. (2019) Prognostic significance of DAPK promoter methylation in lymphoma: A meta-analysis. PLoS ONE 14(1): e0210943. https://doi.org/10.1371/journal.pone.0210943 PMID: 30682070



WP4: ETHICAL OVERSIGHT AND EPISTEMOLOGICAL ASPECTS

ETHICAL OVERSIGHT

. To oversee the project with an external committee
. To explore the overlap/hierarchy researchers make about integrity and ethics

WP1: ZOMBIE TRIALS

. To build a cohort of Zombies trials
. To implement the INSPECT-SR tool
. To explore impact on meta-analyses
. To develop teaching materials

WP2: NEPOTISTIC EDITORS

. To conduct a massive survey of nepotistic editors
. To describe features of studies by nepotistic editors
. To describe features of RCTs by nepotistic editors
. To develop teaching materials

WP3: FINANCIAL COIs

. To describe undisclosed COIs
. To explore factors associated with undisclosed COIs
. To develop a prototype helping to disclose COIs

QUALITATIVE RESEARCH

With authors
With co-autors
With institutions

With editors
With authors
With co-authors

With authors

Figure 1: RestoRe research program

nature medicine

Implementing clinical trial data sharing requires training a new generation of biomedical researchers

Ulrich Mansmann, Clara Locher, Fabian Prasser, Tracey Weissgerber, Ulrich Sax, Martin Posch, Evelyne Decullier, Ioana A. Cristea, Thomas P. A. Debray, Leonhard Held, David Moher, John P. A. Ioannidis, Joseph S. Ross, Christian Ohmann & Florian Naudet

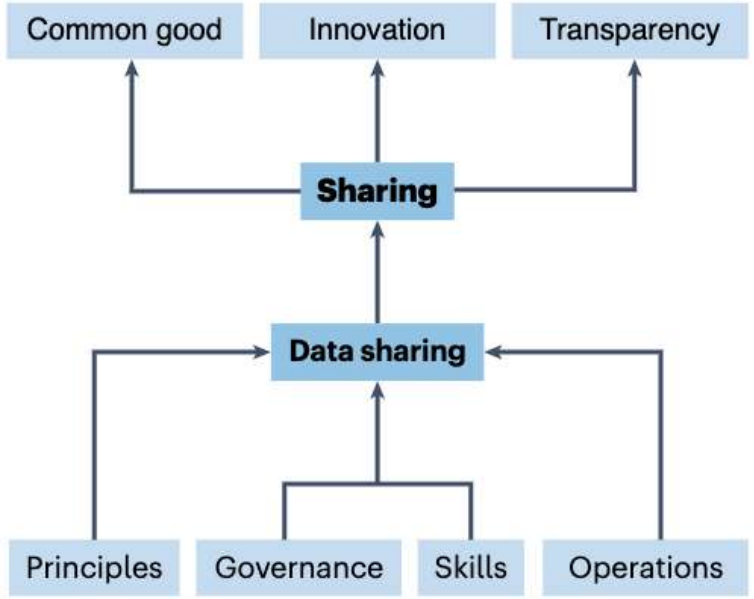
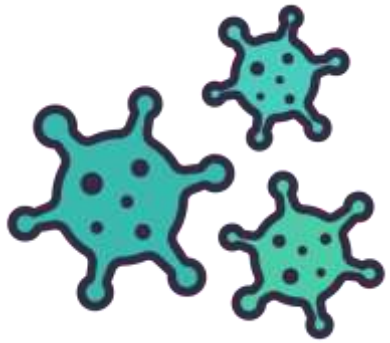


Fig. 1 | Elements of data sharing. Data sharing is built on principles, governance structures, skills and operation infrastructure. It shapes scientific openness, transparency and reproducibility as virtues of a scientific community that demonstrates good practice and supports change.

Data sharing enhances the value of medical research and builds trust in clinical trials, but more biomedical researchers need to be trained in these approaches, which include meta-research, data science and ethical, legal and social issues.

SCAN ME



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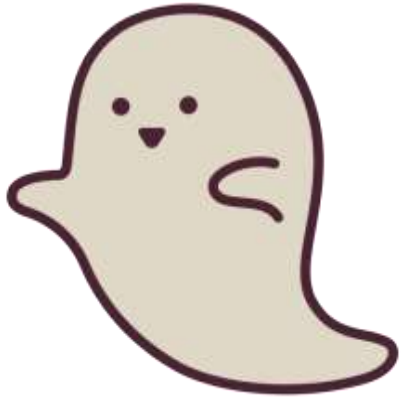
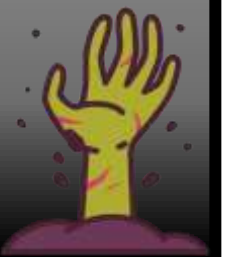
Victoruler @flaticon

The ZOMBIEBUSTERS featuring André Gillibert, Dorothy Bishop





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Rapid Response:

Concerns with the Sputnik V vaccine data

Dear Editor

In a commissioned commentary, Chris Baraniuk reviews the "knowns and unknowns" about Russian vaccines against Covid-19, with a specific focus on Sputnik V [1]. While the commentary correctly emphasizes the inconsistencies identified in the phase 1/2 trial results published in the Lancet [2], it mainly discusses the more recently published phase 3 trial results [3].

Our previous concerns regarding the phase 1/2 trial included problematic data patterns with an excess homogeneity of vaccine efficacy across different time points [4]. The authors responded that the unusual data pattern was "a coincidence" due to the small sample size of their study and the discrete distributions of their outcomes [5].

Following such a reasoning, inconsistencies should not be expected in the subsequent larger phase 3 trial. However, we noticed an unexpected homogeneity of vaccine efficacy, this time between age groups. This analysis is central in the Lancet paper at issue because of the disproportionate disease burden in older people. Of course, implausible results can still be observed by chance. However, we have also identified a similar feature, i.e. an excessive homogeneity of the reported vaccine efficacy in the values reported in earlier interim analyses and the published article.

On 11 November 2020, a first press release announced a 92 % efficacy [6]. From this press release we can compute that there were four Covid cases in the vaccine group and 16 in the placebo group. On 24 November 2020, a second press release announced a 91% efficacy with 8/14,095 cases in the vaccine group and 31/4,699 in the placebo group [7]. On 14 December 2020 a third press release announced again a 91% efficacy with 16/17,032 cases in the vaccine group and 62/5,682 in the placebo group [8]. Much to

06 April 2021
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A previous publication presenting the phase 1/2 results[2] contained problematic data, as detected by several experts.[3,4] We have made multiple independent requests for access to the raw data set, which were never answered by the corresponding author. Despite publicly denying some problems, formal corrections were made to the article, thus addressing some concerns.[5]

Notwithstanding the previous issues and lack of transparency, the publication of interim results from the

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ESSAY

Covid-19: Sputnik vaccine rockets, thanks to Lancet boost

Journals risk being used in place of regulators when they publish studies of novel vaccines that have not yet been authorised by a major regulator. **Chris van Tulleken** argues that peer review is inadequate to decide the risk-benefit ratio of new drugs

Christoffer van Tulleken *honorary associate professor*

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We have a serious concern regarding the availability of the data from which the investigators draw their conclusions. The investigators state that data will not be shared before the trial is completed, and then only by approval of stakeholders, including a so-called security department. Data sharing is one of the cornerstones of research integrity; it should not be conditional and should follow the FAIR principles.

The second concern pertains to the trial protocol, as already described in an open letter by the Russian Society for Evidence-Based Medicine.[3] The Sputnik V investigators mention that three interim analyses were added to the study on Nov 5, 2020,[1] but this change was not recorded on ClinicalTrials.gov (NCT04530396). Unfortunately, the full study protocol has not been made publicly available, so the rationale behind this change or the type I error rate adjustment, if any, is not known. According to the ClinicalTrials.gov record NCT04530396, the primary outcome was changed on Sept 17, 2020. Initially, the primary outcome was to be assessed after the first dose, but the evaluation was postponed to after the second dose. The presented primary result (efficacy of 91·6%) is dependent on this change, but the reasons for the change have not been made public. Moreover, the latest ClinicalTrials.gov record (Jan 22, 2021) defines the primary outcome inconsistently: "Primary Outcome Measures: percentage of trial subjects…after the first dose…based on the percentage…after the second dose".

Besides these protocol amendments, the definition of the primary outcome is unclear in the Article,[1] where it says that when COVID-19 was suspected, participants were assessed with "COVID-19 diagnostic protocols, including PCR testing". Here, we lack some crucial information, such as the clinical parameters determining suspected COVID-19, what diagnostic protocols were used, when the PCR testing was done, what specific method was used, or how many amplification cycles were used. The way cases of suspected COVID-19 were defined could have led to bias in PCR testing used to assess the number of confirmed COVID-19 cases, which is crucial for the efficacy determination.

A final point of concern about the study protocol relates to the enrolment and randomisation of patients. According to the trial profile in figure 1 of the Article,[1] 35 963 individuals were screened and 21 977 individuals were randomised. The ClinicalTrials.gov record for NCT04530396 (Jan 20, 2021) mentions that 33 758 patients were enrolled. We would expect that this last figure should be equal to either the number of participants screened or randomised. Moreover, there is no information about what caused the exclusion of 13 986 participants, as per the trial profile.

The third concern relates to the data reported and numerical results. We found the following data inconsistencies: (1) in figure 2 of the Article,[1] data for the vaccinated group on day 20 refer to more individuals than at day 10, as if there was either information missing for 100 participants at day 10, or participants were enrolled after day 10 (figure 2 was formally corrected on Feb 20, 2021, but the correction statement did not state the reasons leading to such correction); and (2) in table S1 of the appendix,[1] the number of participants reported for the different vaccinated age cohorts do not add up to the reported total (n=338 *vs* n=342). With such inconsistencies, we question the accuracy of the reported data.

A very peculiar result of the major subgroup analysis of the primary outcome caught our attention. The vaccine efficacy was said to be high for all age groups. The reported percentages were 91·9% in the 18–30-year age group, 90·0% in the 31–40-year age group, 91·3% in the 41–50-year age group, 92·7% in the 51–60-year age group, and 91·8% in participants older than 60 years. We checked the homogeneity of vaccine efficacy across age groups (interaction tests): the p value of the Tarone-adjusted Breslow-Day test was 0·9963, and the p value of a non-asymptotic test was 0·9956,[6] indicating a very low probability of observing a homogeneity this good if the actual homogeneity is perfect. By applying 18 other homogeneity tests (six in table 1, seven in table S6, six in table 2 of the Article[1]), we could not find other major abnormality in the overall distribution of p values (appendix).

We also found some highly coincidental results reported in table S3 of the appendix. In particular, two upper confidence limit values for two different distributions (placebo group at baseline for unstimulated and

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Authors' reply

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Numerical inconsistencies were simple typing errors that were formally corrected.

The homogeneity of the values only confirms the fact that, as described in the Article, the effectiveness of the vaccine does not differ between age groups. In this case, the main parameter by which one can judge the difference in effectiveness is the confidence interval, the differences in which are quite significant due to the different sample sizes and the number of COVID-19 cases at the time of analysis.