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RESEARCH ARTICLE

Life cycle assessment of a clinical malaria trial in Mali reveals large environmental impacts of electricity consumption and international travel

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Abstract

Climate change may be the single largest threat facing humanity and ecosystems, necessitating reductions in carbon emissions across all sectors, including healthcare and academia. With the aim of informing and supporting sustainable research practices, we performed a life cycle assessment of a clinical malaria trial conducted in Mali. The trial involved 80 malaria-infected participants in Ouélessébougou who were treated with antimalarials and monitored to determine clinical and transmission-blocking efficacy. Data on consumables, transportation, travel, and electricity use were collected in Mali and the Netherlands, where additional laboratory analyses and sample storage occurred. Data were analysed using the ReCiPe 2016 method for midpoint impact assessment. The trial involved 3 intercontinental shipments of materials and samples, 59,900 km of travel by research staff, and ~55 kg of plastic consumables. Trial conduct and reporting resulted in approximately 20.5 metric tons of CO_2-equivalent (CO_2e) emissions. Major carbon contributors were international travel (50%), electricity in Mali (28%), and air-transportation of materials (14%). Laboratory consumables, while contributing up to 20% of the trial's impact on land and water use, were less important sources of emissions (2% of CO_2e). The formation of fine particulate matter was another important contributor to human health damage, which was mainly attributed to electricity in Mali. Main contributors to ecosystem damage were carbon emissions, terrestrial acidification and ozone formation, with electricity in Mali and international travel as the two major contributors. With an eye on energy efficiency and sustainability, we observed no loss in stability of parasite genetic material (mRNA) in protective buffers when stored for 12 months at -20°C, compared to conventional -70°C. Switching to energy-efficient equipment settings could reduce electricity

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consumption of equipment by over 30%. Implementing solar panels could reduce overall CO_2e emissions substantially. Immediate CO_2e reductions can further be achieved through online conference attendance and alternative sample transportation; the latter would allow 10% CO_2e emission reduction. These results form a starting point for improving the environmental sustainability of clinical trials in Africa.

Author summary

Our study is the first to examine the environmental impact of a clinical trial conducted in Africa where we estimated carbon emissions and other environmental impacts. We found that the trial, which involved treating and monitoring malaria-infected participants, resulted in 20.5 tons of CO_2-equivalent emissions. The largest contributors were travel (50%) and electricity use in Mali (28%). Other important contributors to environmental damage were the formation of fine particulate matter, terrestrial acidification and ozone formation. For these impact factors, electricity use and international travel were also the two primary drivers. While laboratory consumables had a high impact on land and water use (up to 20%), their impact on the carbon footprint and other impact factors was minimal. In addition to measuring the trials environmental impact, we explored practical ways to reduce this impact, such as using energy-efficient equipment, storing samples at higher temperatures, and finding alternative ways to transport materials. Our work highlights the importance of making clinical research more sustainable and shows how similar studies can lower their environmental footprint. By reducing air travel and switching to renewable energy sources, future trials can significantly reduce their CO_2e emissions, fine particulate matter formation, terrestrial acidification and ozone formation. These findings offer guidance for researchers and organizations to adopt environmentally sustainable practices in their trials.

Introduction

Climate change is considered one of the largest – potentially the single largest – threat to humanity and global health [1,2]. Climate change affects many social and environmental determinants of health, including the availability of clean air, safe drinking water, sufficient food, and secure shelter. The health burden of climate change is disproportionally carried by poorer countries [3–5]. Whilst the African continent is responsible for less than 4% of global carbon emissions since the industrial revolution [6], its burden in terms of disability adjusted life years lost due to climate change is estimated to be over 100-fold larger than that of high-income countries [4]. One of the potential direct consequences of global warming on human health is the aggravation of human infectious diseases [7]. Health systems must adapt to the reality of climate change, but may also play a role in mitigation since they are relevant contributors to global warming and other ecological calamities. The healthcare sector is estimated to be responsible for 1-5% of the total ecological footprint of human activities, with considerable variation between countries [8]. The Dutch healthcare sector accounts for 7.3% of the nation's carbon footprint and contributes to a broad set of environmental impact categories beyond climate change [9]. Life cycle assessment (LCA) is a footprint analysis at product or service level that covers multiple impact categories. Trade-offs may occur between different impact categories. When considering environmental sustainability, global warming

receives most attention but other factors like fine particulate matter formation, acidification, ozone depletion, freshwater depletion, and land use are also major concerns for the earths ecosystems and, as a consequence, human health [10]. Here, we conducted an LCA of a clinical trial involving different antimalarial treatment regimens. Our work aimed to better understand the interplay between various environmental impact categories and make informed decisions that promote sustainable research practices.

Materials and methods

Overview clinical trial

During a phase 2 clinical trial investigating the efficacy of different antimalarial treatment regimens and their impact on malaria transmission to mosquitoes, a total of eighty participants underwent 28-days of follow-up [11]. Trial outcome measures encompassed safety, including clinical, hematological, and biochemical analyses, as well as microscopical and molecular quantification of *Plasmodium* parasites stages, and mosquito feeding assays. The study was conducted in Ouélessébougou, Mali, as part of an international collaboration between Malian, Dutch, and UK research institutes. During the conduct of the study in Mali, the ensuing analyses in the Netherlands, and the dissemination of study results at a conference in the United States, data on the use of consumables, electricity, transport, and travel were collected.

Participants provided written informed consent (≥18 years) or assent with written parental consent (for participants aged 10-17 years). Ethical approval for the clinical trial was granted by the Ethics Committee of the Faculty of Medicine, Pharmacy, and Dentistry of the University of Science, Techniques, and Technologies of Bamako (Bamako, Mali) (No2021/189/CE/USTTB), and the Research Ethics Committee of the London School of Hygiene and Tropical Medicine (London, United Kingdom) (LSHTM Ethics Ref: 26257).

Study medication

In preparation of the study, 1290 participants were screened for eligibility criteria in 9 villages near Ouélessébougou. Following enrolment into the clinical trial, 80 participants received the study medication with (combinations of) 20/120 mg or 80/480 mg artemether/lumefantrine tablets (Coartem, Novartis), 30 mg primaquine tablets (A-PQ 30; ACE Pharmaceuticals), 500/50 mg sulfadoxine/pyrimethamine tablets (Guilin Pharmaceutical), 150 mg amodiaquine tablets (Guilin Pharmaceutical), or 100 mg tafenoquine (Arakoda, 60 Degrees Pharmaceuticals) tablets. 77 out of 80 participants completed the scheduled eight follow-up visits; three participants withdrew consent after the first follow-up visit.

Materials and their transportation and disposal

In addition to locally sourced materials (including microtainers, slide boxes, lancets), two shipments and two parcels with additional consumables (including needles, tubes, pipet tips, gloves, pregnancy tests, labels, microscope slides) were shipped from the Netherlands and the UK to the study site (Fig 1). One of the parcels was routed through 6 different countries prior to delivery in Mali. Study medication that could not be sourced in Mali came from the Netherlands (Fig 1). In addition to this transportation to Mali, there was a single shipment of 34 standard 13 x 13 x 5 cm freezer boxes with study samples on dry ice after completion of the trial. For this shipment, 290 kg of dry ice was shipped from France to Mali and then on to the Netherlands to transport the study samples in frozen condition. All potentially infectious materials were incinerated at 850 – 1000°C.

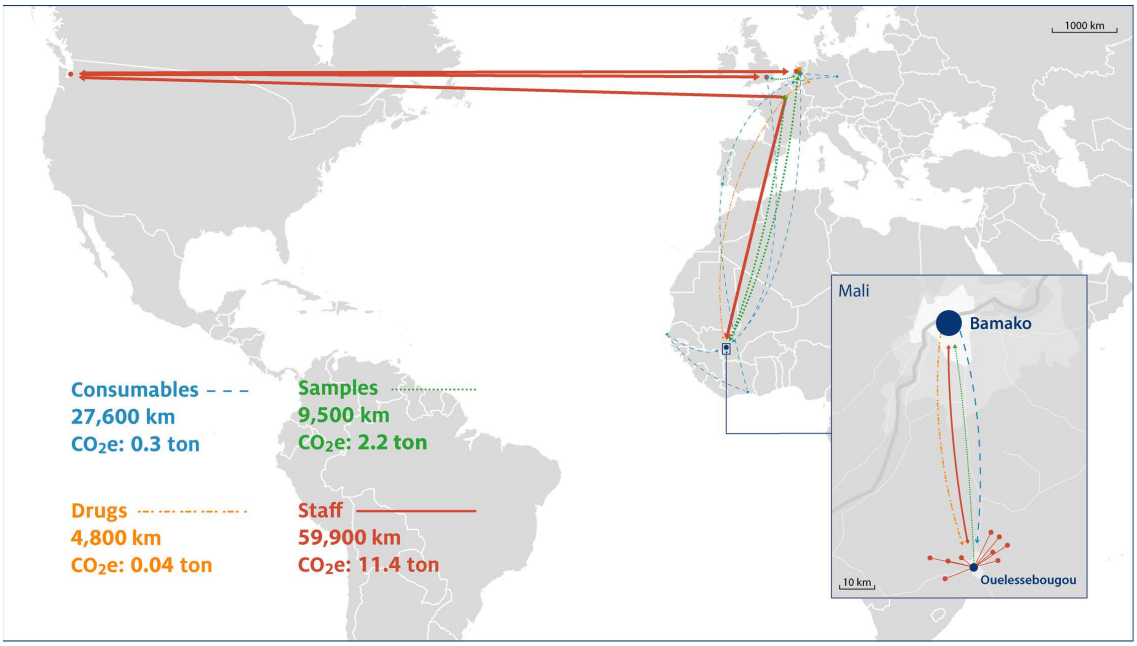

Fig 1. Travel and transport of consumables, samples, drugs, and staff. Distance is based on actual routes, emissions are based on the LCA outcomes and direct emissions (e.g., CO_2), as well as emission of chemical species that alter radiatively active substances or trigger generation of aerosol particles. Staff travel includes air travel and travel by road in Mali.

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Laboratory analyses

Stability of nucleic acids at higher storage conditions. To determine whether it is possible to avoid the use of energy-intensive ultra-low temperature freezers [12], we tested the stability of parasite messenger RNA, important for secondary outcomes of the trial, at different conditions. Freezers with extracted and unextracted RNA are set to -70°C (instead of conventional -80°C) at Radboudumc for sustainability reasons. Serial dilutions of the parasite stage that is of prime interest for the study (gametocytes, *Plasmodium falciparum* NF54 line) were cultured, diluted in whole-blood and preserved in RNAprotect Cell Reagent (Qiagen, Germany) to stabilize parasite mRNA for later gametocyte quantification. After mixing, samples were stored in either a -70°C or a -20°C freezer for 2 weeks, 3, 6, or 12 months after which total RNA was extracted using a MagNAPure automated extractor (Total Nucleic Acid Isolation Kit-High Performance; Roche Applied Science, Indianapolis, IN, USA). Gametocytes were detected by CCp4/PfMGET RT-qPCR [13]; CT-values that are indicative of mRNA abundance were presented for different storage conditions.

Temperature stability of a container for sample transport. Anticipating RNA stability at -20°C, we considered transportation of samples in a temperature controlled box (Crēdo Cube, Peli BioThermal, Torrance, United States) that allows maintaining temperature at or below this temperature. We tested temperature stability using a LIBERO CL V9.14 probe that was stored in the cube after its elements had been charged for 24 hours in a freezer set at -20°C or -70°C.

Life cycle assessment (LCA)

An LCA was conducted to estimate the environmental impact of the trial and identify areas where measures for reducing environmental impacts might be applied most effectively. The

LCA encompassed the entire life cycle of the product system including creation, use, and disposal of a product. This includes everything from extraction of raw materials to manufacturing, distribution, use, and finally the management of waste. It covers all stages of a product's life cycle, from its "cradle" to its "grave" [14]. The functional unit of this study is defined as the conduction of the entire clinical trial over a duration of three months in Mali followed by one additional month of analyses in the Netherlands. The inventory of material flows for the current study was categorized into eleven main groups: travel of employees via air, travel of employees and participants via road, transport of materials via air, transport of materials via road, electricity in Mali, electricity in the Netherlands, medication, safety analysis, mosquito infection analyses, molecular analyses, and others. The last four groups primarily consist of consumables. Due to the absence of life cycle inventory data on the production of the antimalarials used in this trial, data on CO_2e emissions from the production of other pharmaceuticals that are also produced on a large scale, namely vancomycin and tenofovir, were used instead [15]. We averaged the impacts of these two medications as estimated impact of the used malaria medication. For the packaging material, we modeled polyvinylchloride and aluminum blister packaging. For all other categories, we collected data on raw material extraction, product manufacturing, transportation, usage, and end-of-life stage. Data were gathered through a combination of direct observations by the study team, literature review, public databases (ecoinvent 3.9, Switzerland and healthcareLCA.com), and communication with manufacturers. Product consumption was based on the supplies purchased for the different study procedures and direct observations during study conduct (e.g., electricity consumption, transport of materials, and travel of participants and staff). Materials and their weight, quantity, and material composition were identified. A full list of measurements and assumptions are given in the S1 Appendix. Electricity usage at the research site in Mali was estimated by distributing the total electricity use of the field station (6862 – 7763 kWh usage per month) according to the number of studies being conducted during the study period (1st of October - 31st of December 2021). The electricity mix in Mali was assumed to be ~60% based on fossil fuels [16]. For electricity use in the Netherlands, we used a similar approach where electricity usage of the 7-floor research infrastructure in the month the analyses were performed (262.965 kWh usage for February 2022) was allocated to the project based on the size of the dedicated lab (20 m^2) relative to lab space in the entire building (3803 m^2). Radboudumc uses 100% renewable energy, supported by an institutional Guarantee of Origin for consumed electricity and the construction of an onshore windfarm by Radboudumc and Radboud University with ten >3MW wind turbines. To further gauge electricity use of equipment that was specifically used for the current study, we measured electricity use in kWh using the a plug-in electricity meter (Energie Meter Mini; EcoSavers, the Netherlands); also these data are provided in the S1 Appendix. For the current study, certain processes were considered non-contributory as they extended beyond the system's scope and expected to have a minimal contribution to the overall study impact. For example, the production of capital goods, such as routine lab equipment, and lab/hospital infrastructure were excluded from the system boundary (Fig 2).

Life cycle impact assessment and sensitivity analysis

The environmental impact scores in the Life Cycle Impact Assessment (LCIA) were computed using the ReCiPe 2016 method [17], which models the impact of (components of) products on environmental midpoints and endpoints. This method encompasses a total of 18 midpoint indicators/characterization factors that can be consolidated into three endpoint indicators: damage to human health, damage to ecosystems, and damage to resource availability. In the current study, the impact on global warming, land, and water usage was reported in detail.

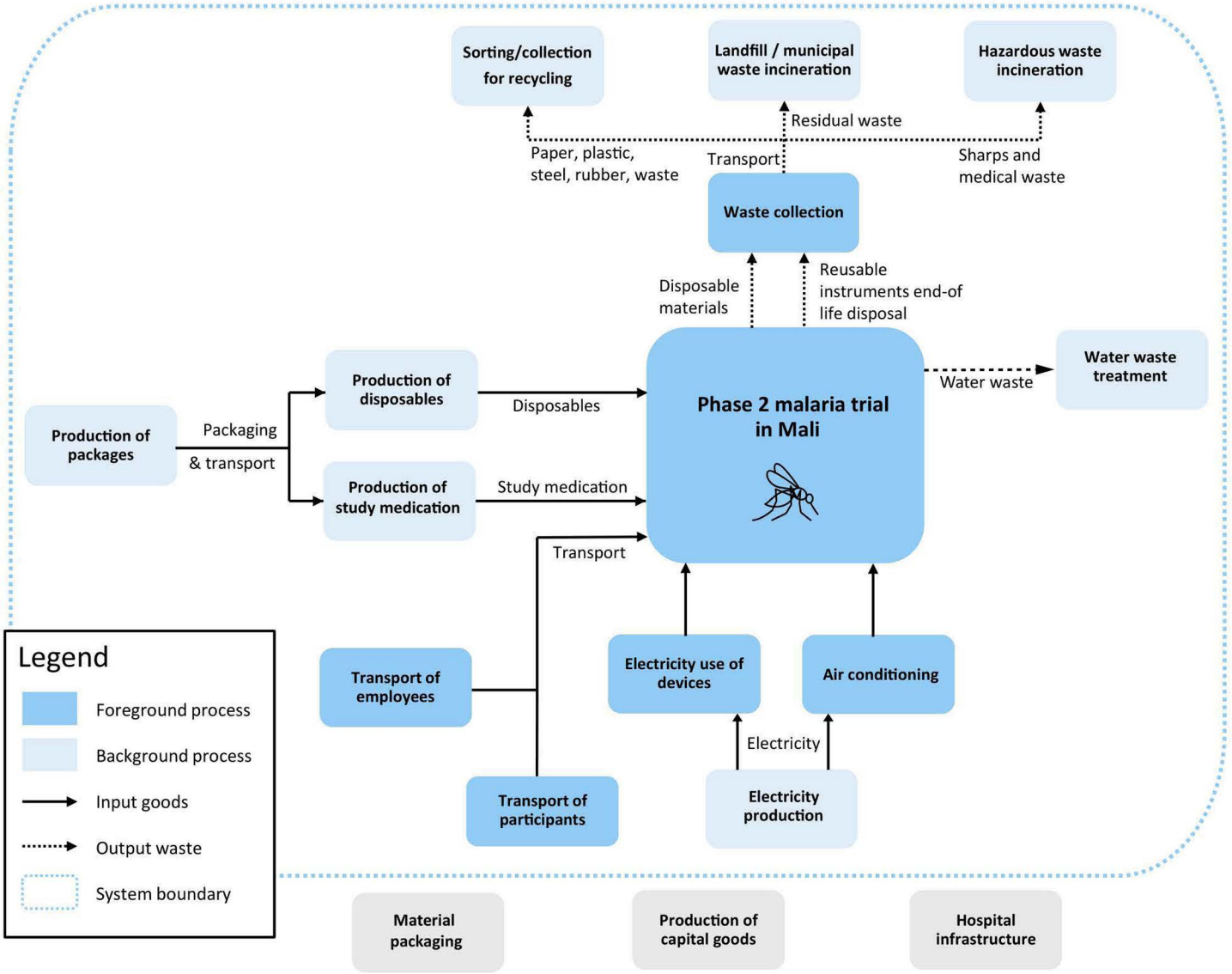

Fig 2. The system boundary. System boundary of what was included (within the blue dotted boundary) and excluded in the life cycle assessment.

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The data were modeled using Sima Pro 9 LCA software from PRé Consultants in Amersfoort, the Netherlands. To estimate the carbon emissions associated with air travel, we used established methodologies that use mean emission factors per km and per passenger of three independent sources and take into account direct emissions as well as indirect emissions resulting from chemical species that alter radiatively active substances and the generation of aerosol particles [18]. We conducted an uncertainty analysis using the pedigree matrix and the Monte Carlo algorithm with 1,000 runs. To confirm the robustness of the findings, we conducted a sensitivity analysis by examining the impact of various assumptions, database selections, and analytical methods on the identified key areas [19]. Within this sensitivity analysis, we focused on the comparison of different African energy mixes and the assumptions made for the impact calculations of medication. We also assumed an alternative method to estimate CO_2e emissions associated with air travel [17] (see S1 Appendix).

Results

Below, we provide a narrative of several key factors that influence the environmental impact of the clinical trial. A comprehensive list of (raw) material use, electricity consumption and travel/movement of goods for the study in Mali and associated activities in the Netherlands and the United Kingdom (UK) is presented in the S1 Appendix.

Consumables and electricity use

During sampling at screening, enrolment, and follow-up visits in Mali, 231 stainless steel lancets, 1607 needles, 1607 glass microscope slides, 4821 vacutainer tubes, and 3418 microtainer collection or storage tubes were used. Treatment involved 420 tablets artemether/lumefantrine, 20 tablets primaquine, 291 tablets sulfadoxine/pyrimethamine, 361 tablets amodiaquine, and 24 tablets tafenoquine.

In running the trial facilities in Ouélessébougou, a total of 7,200 kWh of electricity was used. Freezers, laboratory equipment, and air conditioners were important contributors to the electricity consumption in Mali (Fig 3). In the Netherlands, a total of 1,383 kWh of electricity was used. Laboratory activities included total nucleic acids extraction using an automated extractor (17 runs of 1.6 kWh) and a total of 2,040 plastic tips (0.8 kg of virgin polypropylene). Following extraction, a single multiplex PCR was performed (7 runs of 0.55 kWh), using a total of 721 plastic tips.

To explore more energy efficient study procedures, mRNA samples in whole blood were stored for up to one year at -20°C and -70°C in protective buffer. The two storage temperatures gave comparable signal levels for mRNA quantification (Fig 4A). Whilst there were indications for increased CT-values after 6 months of storage for one of the mRNA targets (PfMGET), indicating lower mRNA concentrations, this pattern was similar for both storage temperatures and not observed for the other mRNA target (CCp4). The temperature log in the temperature controlled box showed that when the elements were charged at -20°C, the temperature remained below -20°C for 20 hours; when elements were charged at -70°C for 24 hours, the temperature remained below -20°C for over 4 days (108 hours) (Fig 4B).

Travel-associated environmental impacts

During the conduct of the study, the Malian team utilized one Toyota Land Cruiser 105 and two Toyota Hilux pick-ups to travel to the 9 different villages where study participants

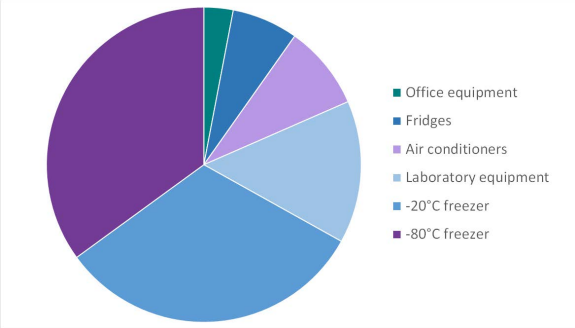

Fig 3. Sources of electricity consumption in Mali during the study period. Laboratory equipment included centrifuges, equipment for biochemistry and haematology, incubators and waterbaths but not freezers and fridges that are presented separately. Note that freezers in Mali were set at -80°C whilst in the Netherlands they were set at -70°C. Office equipment includes computers and printers.

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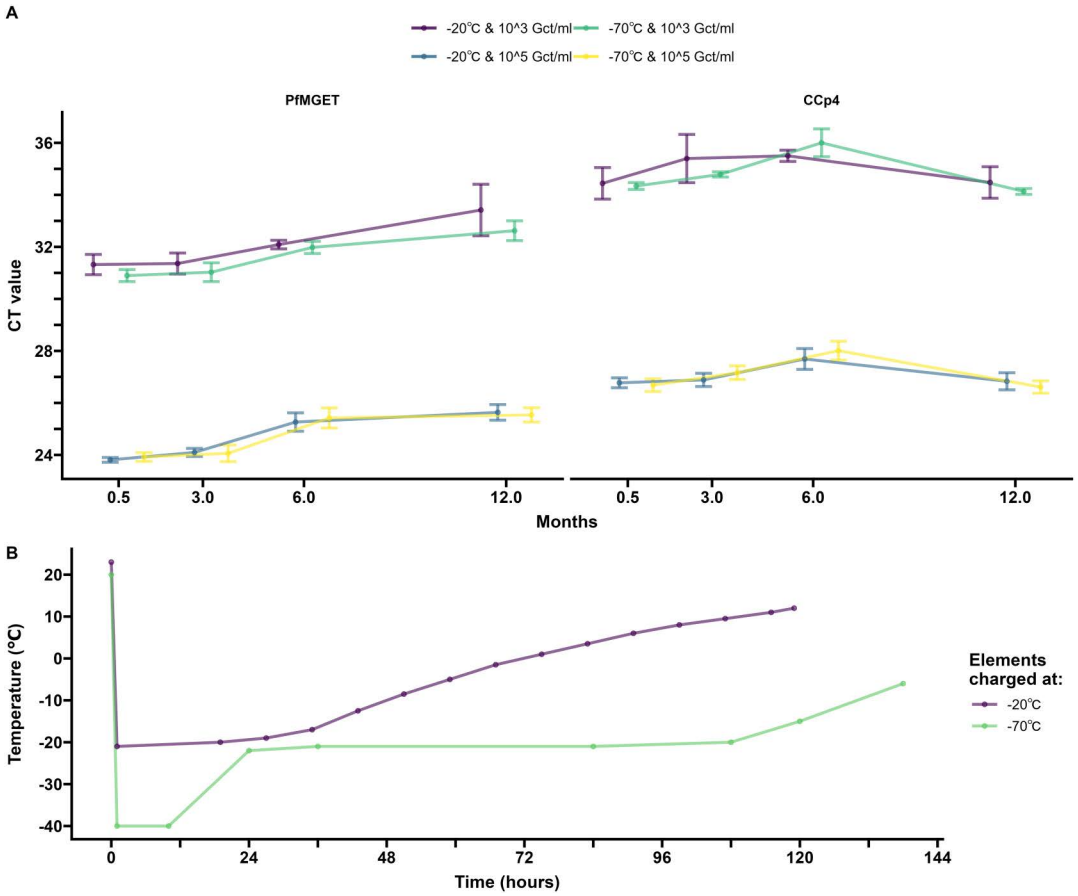

Fig 4. (A) RNA stability and (B) temperature stability of a temperature controlled box. (A) RNA stability was tested by quantifying gametocytes in *P. falciparum*-positive samples stored at -20°C and -70°C in protective buffers, based on the expression of the CCp4 (female gametocyte) and PfMGET (male gametocyte) genes using RT-qPCR. The average cycle threshold (CT) values for PfMGET and CCP4 transcripts at different temperatures are shown with error bars. (B) Elements of the temperature-controlled box were charged at different temperatures (-20°C and -70°C), and the temperature in the box was monitored for 5-6 days.

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resided. In total, they covered over 3,300 km to conduct follow-up visits. During these journeys, approximately 334 litres of diesel were used. Emissions associated with the use of vehicles were approximately 1,150 kg of CO_2e. After completion of primary data collection, three team members travelled to a conference in Seattle, the United States, to present study results to an international audience and discuss study progress with funders. For this conference, team members travelled approximately 56,600 km and, in doing so, emitted an estimated 10,200 kg of CO_2e emissions. Because of difficulties in obtaining a visa, a fourth person presented the main study results during online participation. This online participation was associated with approximately 0.33 kg of CO_2e emissions for the entire 4-day conference [20].

Estimated impact of the trial on global warming, fine particulate matter formation, terrestrial acidification, ozone formation, water use, and land use

Total carbon emissions, as estimated by LCA, were approximately 20.5 metric tons of CO_2e. International travel accounted for approximately 50% of this total (Fig 5A); other important

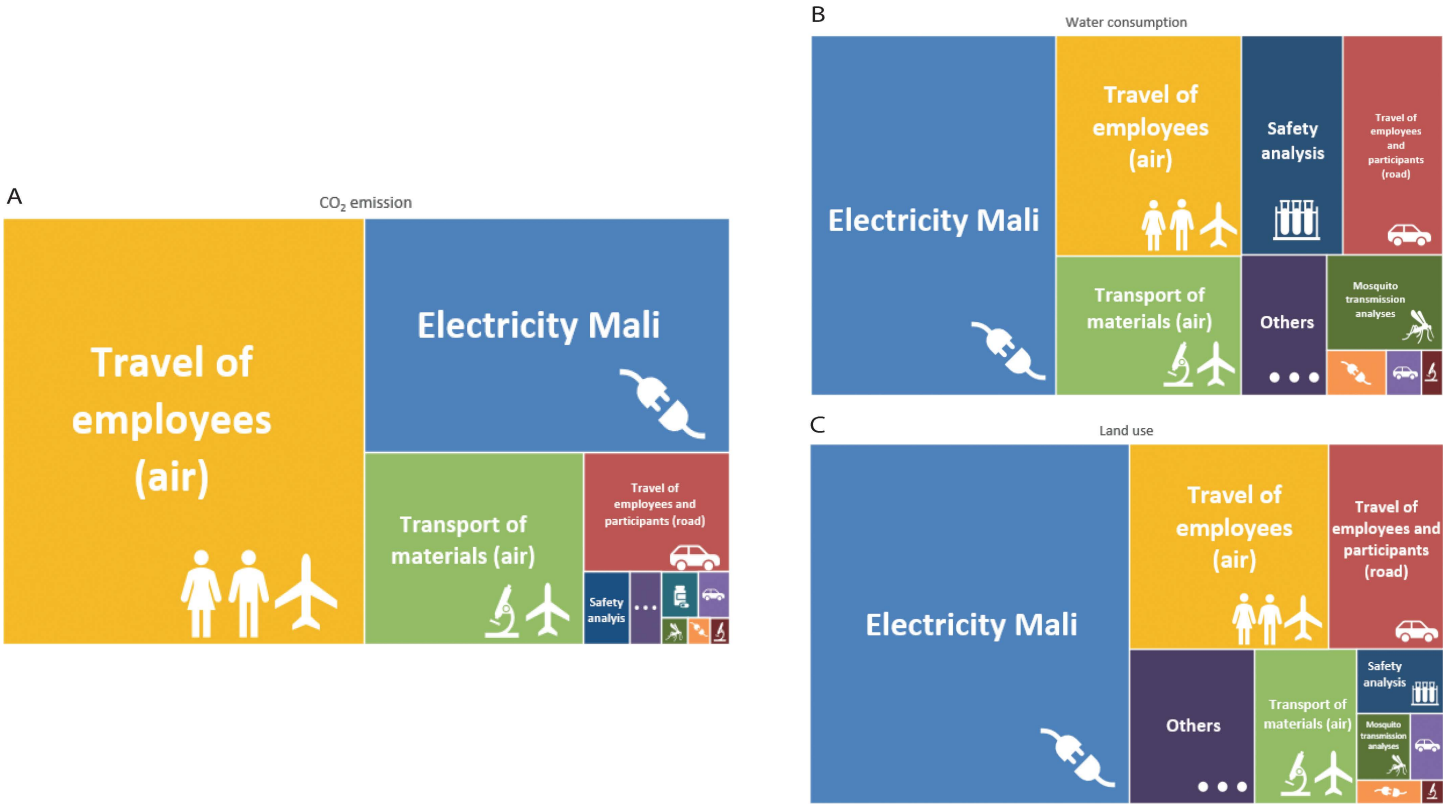

Fig 5. A. Tree map of the distribution of CO2e emission of the clinical trial. Each rectangle represents a different component of the trial, with the size of the rectangle proportional to the CO_2e emission. The colours indicate the different components of the trial: yellow for air travel of employees (49.8%), blue for electricity in Mali (27.7%), light green for transport of materials via air (13.5%), red for travel of employees and participants by road (5.6%), dark blue for the safety analysis (1.1%), dark purple for others (0.7%), turquoise for medication (0.5%), light purple for transport of materials via road (0.5%), dark green for mosquito infection analyses (0.2%), orange for electricity in the Netherlands (0.2%), and maroon red for molecular analyses (0.2%). **Fig 5B-C. Tree map of the impact categories 'Land use' and 'Water consumption' of the clinical trial.** The colours indicate the different components of the trial: blue for electricity in Mali (50.5% and 38.7% in land use and water consumption, respectively), yellow for air travel of employees (17.9% and 18.0%), red for travel of employees and participants by road (10.3% and 9.6%), dark purple for others (8.5% and 5.3%), light green for transport of materials via air (7.0% and 11.4%), dark blue for the safety analysis (2.5% and 9.8%), dark green for mosquito infection analyses (1.6% and 4.9%), light purple for transport of materials via road (0.9% and 0.7%), orange for electricity in the Netherlands (0.7% and 1.2%), maroon red for molecular analyses (0.2% and 0.4%), and turquoise for medication (0.0% and 0.0%).

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contributors were electricity consumption in Mali (28%) and air transportation of materials (14%). Laboratory consumables were considerable contributors to the ecological impact of the study in terms of land and water use impact (up to 20%) but only accounted for 2% of the total CO_2e emissions (Fig 5B-C).

Another midpoint significantly contributing to human health damage was fine particulate matter formation with 21 kg PM2.5eq (Fig 6). Electricity in Mali (49%) and international travel (31%) were also the main contributors within this impact category. When investigating the impact on ecosystem damage, next to global warming, also terrestrial acidification (64 kg SO_2 eq) and ozone formation (75 kg NO_x eq) were major contributors, again mostly attributed to electricity in Mali (34 kg of SO_2 eq and 19 kg of NO_x eq) and international travel (19 kg of SO_2 eq and 39 kg of NO_x eq). Other impact factors, like water use (35,000 litre) and land use (286 m^2a crop eq) had a relatively small contribution to the overall environmental damage. The category contributing most to these impact factors was the use of laboratory consumables, mainly the production of disposables and soap.

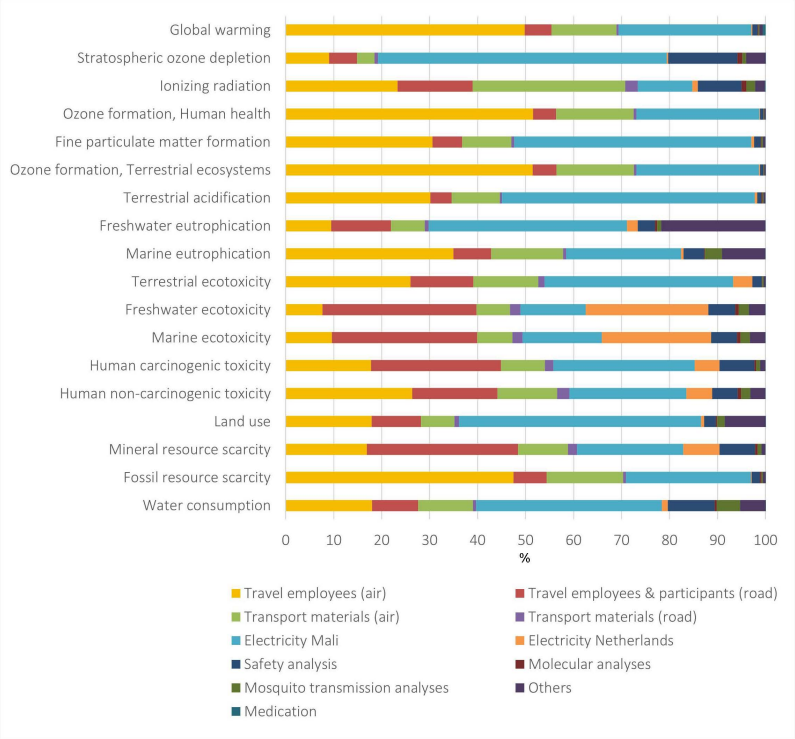

Fig 6. The contribution of each category of the trial to 18 midpoint environmental impact categories. For each category the total impact is set to 100% and the relative contribution of different activities and products is indicated in the same colour scheme that was used for Fig 5.

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Sensitivity and uncertainty analysis

To assess robustness of findings, we performed a sensitivity analysis where we assumed a different energy mix for electricity generation (the energy mix of Mali vs. neighbouring countries Guinea and Niger); this resulted in a variation in global warming from -12% to 11%. In the case of the energy mix of Niger, the total CO_2e emission increased from 20.5 to 22.8 metric tons, whereas the emission decreased to 18.0 metric tons if the energy mix of Guinea was used. However, these variations did not reveal different hotspots than the original analyses. Similarly, testing assumptions for medication did not significantly change the identified hotspots or results (see S1 Appendix). Depending on the choice of proxy for the medication calculation, the relative impact of medication varied between 0.1% and 1% of the total CO_2e emissions. Utilising the established ReCiPe 2016 method with ecoinvent 3.9 as background data source to calculate the CO_2e contribution from international air travel in the sensitivity analysis resulted in a lower estimate (7.9 metric tons) compared to the more conservative approach (10.2 metric tons), which also included indirect sources of CO_2e emissions, such as radiatively active substances and substances that trigger generation of aerosol particles. Despite the differences in calculations, the top two contributors to the trial's carbon footprint—electricity consumption in Mali and air travel—remain the same, regardless of the approach used. The 95% confidence interval for the global warming potential associated with the study was found to be between 16.1 and 22.0 metric tons CO_2e. Confidence intervals for other environmental impact categories are detailed in the S1 Appendix.

Discussion

Here, we present one of the first life cycle assessments of a clinical trial, examining the trial's ecological impact beyond its carbon footprint alone. Our analysis estimates the environmental impact of the clinical malaria trial and related activities to be approximately 20.5 metric tons of CO_2e. The main sources of CO_2e emissions were international travel (50%), electricity usage in Mali (28%), and air-transportation of materials (14%). Besides the carbon footprint, fine particulate matter formation, terrestrial acidification and ozone formation had a substantial overall impact on the environment (more than 90% of the total impact on human health and ecosystem damage). Notably, the major contributing categories to the latter impact factors did not differ from the categories contributing to the carbon footprint. Goods travelled a total of 41,900 km while study personnel travelled 3,300 km to and from study sites and 56,600 km to a conference. We estimate that the study used a total of 55 kg of plastics and 5 kg of glass across participating centres.

Clinical trials are associated with considerable CO_2e emissions, notably through energy use at research premises, transportation, and (air) travel [21]. Our study identifies that international travel and electricity consumption in Mali collectively accounted for 78% of the trial's carbon footprint. Assessments of the ecological impact of clinical (research) activities on the African continent are very sparse and drivers of this impact may differ from other settings. In our study, we observed a large CO_2e contribution of international air travel. Of note, this study was conducted in a period when COVID-19 related travel restrictions were imposed and there was no international travel during the preparation and conduct of the clinical trial. Whilst the nature of the collaboration, being intercontinental, may have increased travel and shipment kilometers, the importance of transport as driver of emissions appears a consistent finding across LCA studies on clinical trials. For example, an LCA of a phase 1 clinical trial in Belgium involving 28 participants generated 17.65 tons of CO_2e, with the movement of participants and staff accounting for the majority of emissions (51%), followed by trial site utilities (16% of overall emissions) [22]. A phase 2 international trial in the UK, Spain, and Australia, testing an investigational medicinal product with 48 participants, reported a carbon footprint of 72 tons CO_2e, with the majority of emissions coming from the clinical trials unit and staff travel [23]. However, main contributors do differ between trials. For instance, a phase 3 trial conducted in the UK with 1,962 patients for a non-investigational medicinal product, generated 89 tons CO_2e, largely due to the intramural assessments required for participants [23]. A retrospective assessment of the total carbon footprints of three multicentre phase 3 trials in North America, South America, Europe, and Asia estimated a total of 1,437 – 2,498 tons CO_2e per trial involving 668 – 4,744 participants and identified travel and shipment of samples and materials as important drivers of this footprint [24]. Additionally, there were considerable emissions attributed to the shipment and storage of samples for future use [24]. This means that also the 'hotspots' for adjustments to reduce the environmental impact can differ between studies.

Long-term storage of materials was not included in our analysis and is likely to have minimal impact considering the use of renewable energy in the country where the samples are stored. Storage does, however, allow for simple improvements in electricity consumption and freezer purchases [24]. We identified several other sources of emissions and material use that offer opportunities for emission reductions. First of all, we demonstrated similar stability of samples when stored at -20°C as compared to -70°C for at least one year. This allows initial storage at -20°C and a more environmentally conscious method for transporting study samples (i.e., temperature controlled boxes compared to using air-transported dry ice). We confirmed that these temperature controlled boxes indeed maintain appropriate freezing conditions. Another easily effected change would be to reduce the amount of (air-)travel involved in trial

conduct and dissemination. Large CO_2e reductions can clearly be achieved by limiting the number of team members attending international conferences in person and instead encouraging virtual conference attendance for some team members. Furthermore, maintaining the shift in academic expertise from north to south would also lessen the need for air travel. Whilst we consider in-person meetings important to sustain collaborations and offer career development opportunities, the frequency of intercontinental flights offers opportunities for emission reduction. Our sensitivity analysis demonstrates that the assumptions underlying the estimated CO_2e emissions of travel are relevant. Logically, calculations that include indirect sources of emissions due to the emission of chemical species that alter radiatively active substances or trigger generation of aerosol particles [18,25], increase the estimated impact of air travel. However, even with the conservative ReCiPe 2016 method, air travel is a major source of CO_2e emissions. In addition to reducing air travel, sourcing plastics and reagents locally or regionally would be highly beneficial to reduce transport costs and emissions.

Several other sources of emission will likely pose a greater challenge. The importance of the local energy generation mix was demonstrated by the negligible (<1%) contribution of analyses and storage in the Netherlands that benefited from renewable energy. The stronger reliance on fossil fuels for electricity generation in Mali, had a major impact on emissions and is unlikely to change in the near future. Implementing solar panels in the Mali laboratory could have reduced CO_2e emissions by 28%.

In our trial, consumables contributed considerably to the study's ecological impact in terms of land and water use impact (up to 20%), but represented only a relatively minor fraction (2%) of the total CO_2e emissions. This underscores the complex interplay between components within the trial's life cycle and their respective contributions to environmental impact.

Whilst the assessment of environmental impacts other than carbon emissions is a relevant strength of our study, our study also has several limitations. Several environmental impacts will be setting and study dependent; our study in Africa with an international research team plausibly resulted in a larger contribution of air travel. Our study was also modest in size and short in duration; the period of data collection and laboratory analyses may be considerably longer for other phase II studies. We also made assumptions on the impacts of study medication based on the CO_2e emissions of other medications that are produced at similarly large scale. However, we were limited to including only the CO_2e emissions of the study medication, leaving out the other 17 factors, which represents a knowledge gap. Whilst our assumptions are unlikely to have affected the relative impact of different sources, it will have affected generalizability. Lastly, while we provide an assessment of the environmental impact of this specific trial, it is important to weigh this impact against the knowledge and health benefits that well-designed studies, which address relevant knowledge gaps, bring.

Our analysis also indicates that dissemination activities, particularly international travel for conferences, were a major contributor to the trial's overall environmental footprint. This highlights the need to consider the environmental implications of dissemination in future studies, particularly in relation to air travel. Approaches such as encouraging virtual conference participation and decentralizing academic expertise to reduce the necessity for travel could help reduce these impacts.

We conclude that the academic community has a role in exploring not just what we research but also how we research [26]. Global health research faces the complex task of addressing climate-driven health and health system challenges while at the same time reducing its own ecological impact. The healthcare industry can utilize research, data, and quantitative analysis tools to make informed environmental decisions for practice, as we demonstrate here at the scale of a single clinical trial. It is important to adopt sustainable and low carbon research practices that still deliver the scientific advances that society needs [26].

Supporting information

S1 Appendix. Tab 1. Consumables, Tab 2. Electricity, Tab 3. Energy consumption Mali, Tab 4. Travel, Tab 5. Shipments, Tab 6. Tree maps, Tab 7. Sensitivity analysis, Tab 8. Uncertainty analysis, Tab 9. SimaPro Output, Tab 10. Endpoints, Tab 11. Fig impact categories, Tab 12. RNA stability PfMGET, Tab 13. RNA stability CCp4, Tab 14. Temperature controlled box.
(XLSX)

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