The environmental impact of a malaria clinical trial in Mali: Life cycle assessment reveals high emissions due to international travel and local electricity use and identifies opportunities for sustainable improvement

Short title: Life cycle assessment of a malaria clinical trial

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Abstract

Climate change may be the single largest threat facing humanity and ecosystems, necessitating decarbonization 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 trial conducted in Mali. The trial involved 80 malaria-infected participants in Ouélessébougou who were treated with antimalarials and followed for 28 days to determine their 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 plastics. Trial conduct and reporting resulted in 20.5 metric tonnes of CO_2-equivalent (CO_2e) emissions. Major contributors were international travel (50%), electricity in Mali (28%), and air-transportation (14%). Laboratory consumables, while contributing up to 22% of the trial's impact on land and water use, were less important sources of emissions (2% of CO_2e). Whereas the electricity mix in Mali, ~60% fossil-fuel-based, was disadvantageous for the carbon footprint, laboratory analyses in the Netherlands benefited from 100% wind energy, resulting in a minor overall contribution to emissions (<1%). 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. These results form a foundation for improving the environmental sustainability of clinical trials in Africa. Switching to energy-efficient equipment settings could reduce electricity consumption by over 30%. Implementing solar panels in the Mali laboratory would reduce CO_2e emissions by

28%. Immediate CO_2e reductions can be achieved through online conference attendance and alternative sample transportation, which would contribute an additional 10% CO_2e reduction.

Author summary: Our study is the first to examine the environmental impact of a clinical trial conducted in Africa. We measured how much activities like international travel, electricity use, and transporting materials contributed to carbon emissions. Our trial produced 20.5 metric tonnes of CO_2 emissions, with most of it coming from travel (50%) and electricity use in Mali (28%). We also 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 on air travel and switching to renewable energy sources, future trials can significantly reduce their emissions. These findings offer guidance for researchers and organizations to adopt greener practices in their work, which would influence environmental policies in future 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,(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) Vector-borne diseases, driven by environmental and climatic factors, are sensitive to climate change.(8) It remains unclear whether malaria burden will increase in response to rising temperatures.(9) The global malaria burden has declined in the last century despite a clear rise in mean temperatures.(10) At the same time, the geographical areas and number of months per year that conditions are favorable for malaria transmission are likely to increase in response to global warming(9, 10) and extreme weather events have been linked to increases in malaria burden. 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.(11) 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.(12) Life cycle assessment (LCA) is a footprint analysis on product or service level that typically

covers multiple impact categories, as trade-offs can occur between different impact categories. When considering environmental sustainability, global warming receives most attention but freshwater depletion and biodiversity loss are major concerns for the earths ecosystems and, as a consequence, human health.(13) Here, we conduct an LCA of a clinical trial of an anti-malarial intervention to better understand the interplay between various environmental impact categories and make informed decisions that promote sustainable research practices.

Results

Below, we provide a narrative of several of the key factors that influence the life cycle environment impact of the clinical trial. A comprehensive list of all (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 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. In total, 282 tablets of 20/120 mg artemether/lumefantrine (Coartem, Novartis), 138 tablets of 80/480 mg artemether/lumefantrine, 20 tablets of 30 mg primaquine (A-PQ 30; ACE Pharmaceuticals), 291 tablets of 500/50 mg sulfadoxine/pyrimethamine (Guilin Pharmaceutical), 361 tablets of 150 mg amodiaquine (Guilin Pharmaceutical), and 24 tablets of 100 mg tafenoquine (Arakoda, 60 Degrees Pharmaceuticals) were used during the trial. Given

the lack of data on the impact of the production of these antimalarials, we utilised available environmental impact data from vancomycin, an antibiotic, and tenofovir, an antiretroviral drug, as proxies. This resulted in a carbon footprint of 111 kg CO_2-equivalent (CO_2e) emissions for the study medication. 77 out of 80 participants completed the scheduled eight follow-up visits; three participants withdrew consent after the first follow-up visit. During sampling at screening, enrolment and follow-up visits, approximately 231 stainless steel lancets, 1607 needles, 1607 glass microscope slides, 4821 vacutainer tubes, and 3418 microtainer collection or storage tubes were used. All the materials were incinerated at 850 – 1000^{o}C after blood collection.

Transportation of materials

Not all materials were sourced in Mali; two shipments and two parcels with 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.

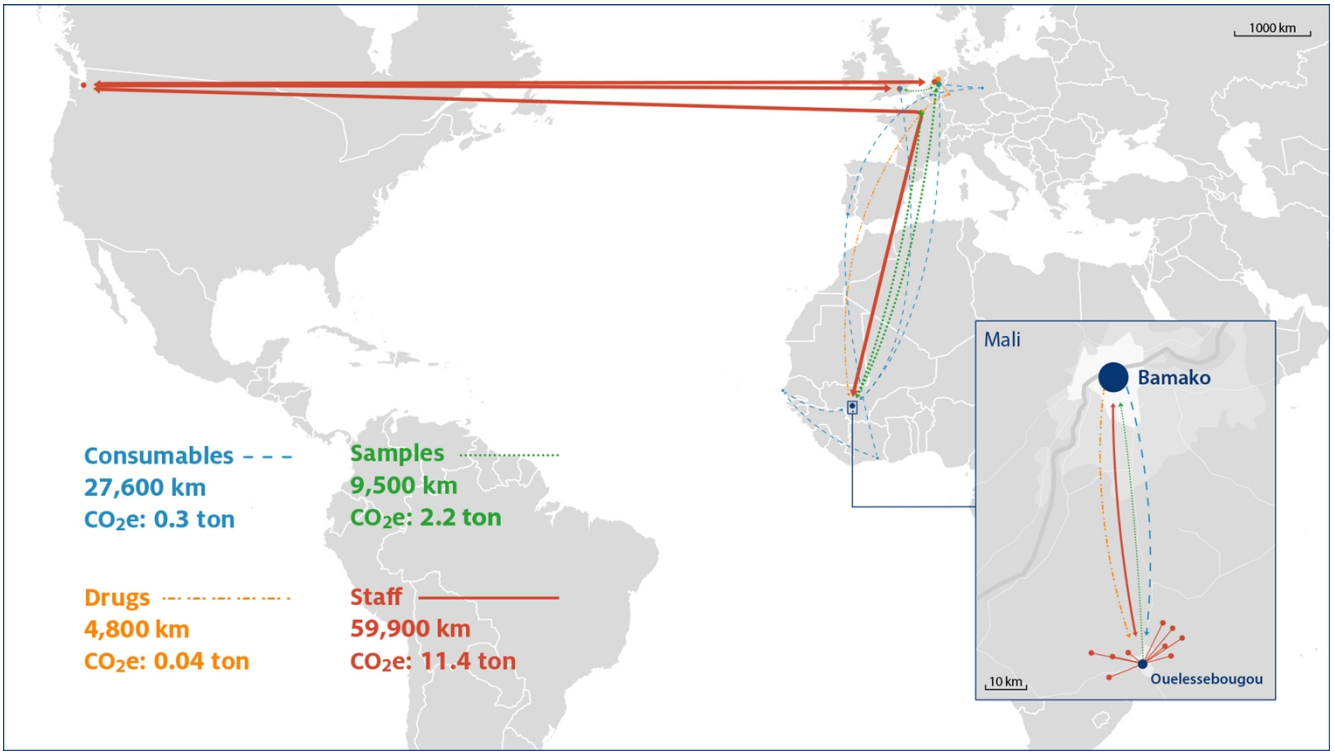

Figure 1. Travel and transport of consumables, samples, drugs, and staff. Distance is based on actual routes, emissions are based on the LCA outcomes and direct emissions (eg, CO_2), as well as emission of chemical species that alter radiatively active substances or trigger generation of aerosol particles. Conference travel of three staff members contributed to >56,000 km (~35,000 miles) in travel.

Sample processing and laboratory analyses

Main laboratory procedures in Mali were blood biochemistry and hematology measurements, and mosquito feeding assays. In running the lab in Ouélessébougou, a total of 21,601 kWh of electricity was used. This figure was estimated by an equal allocation of exact electricity costs to three projects that were ongoing between 1st of October 2021 and 31st of December 2021; total electricity consumption of the field station was large with 6862 – 7763 kWh usage per month. Freezers, laboratory equipment, and air conditioners were important contributors to

the electricity consumption in Mali (Fig 2). Of note, the electricity mix in Mali was ~60% based on fossil fuels.(14) In the Netherlands, total nucleic acids were extracted from whole blood samples using an automated extractor (17 runs of 1.6 kWh) using a total of 2,040 plastic tips (0.8 kg of virgin polypropylene). For sustainability reasons, freezers with extracted and unextracted RNA are set to -70°C (instead of conventional -80°C) at Radboudumc. Following extraction, a single multiplex PCR was performed (7 runs of 0.55 kWh), using a total of 721 plastic tips. The electricity mix in the Netherlands was 100% renewable energy (i.e. >3 MW onshore wind turbines).

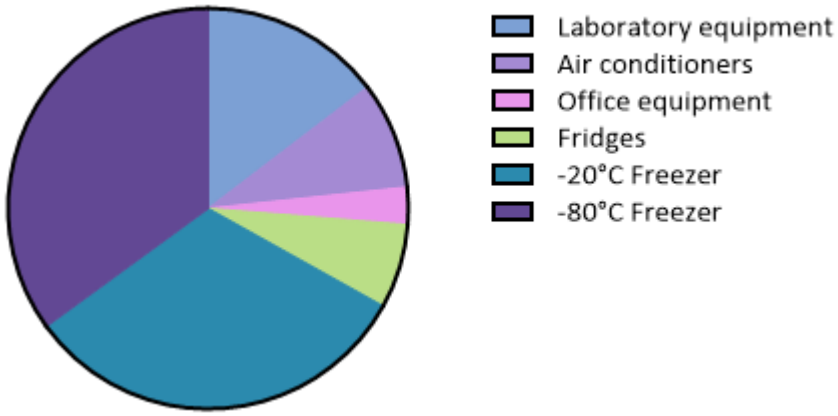

Figure 2. Sources of electricity consumption in Mali during the study period

Travel of people

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 over the course of the trial. In total, they covered over 3,300 km to conduct all the follow-up visits, which is roughly equivalent to the distance from the northern tip of Egypt to the southern border of Tanzania. During these journeys, approximately 334 litres of diesel were used, resulting in an estimated 1,150 kg of

CO_2e. This calculation includes not only the CO_2e emissions from diesel fuel consumption, but also takes into account the production of the vehicles and other indirect emissions associated with their use. 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, these team members travelled approximately 56,600 km and, in doing so, emitted an estimated 10,200 kg of CO_2e in total. Because of difficulties in obtaining a visa, a fourth person participated online and presented the main study results. Online conference participation is associated with approximately 0 to 5.87 kg of CO_2e per capita.(15)

Estimated impact of the study on global warming, water use and biodiversity

The aggregated findings of the LCA indicated approximately 20.5 metric tonnes of CO_2e emissions. Key contributors to these emissions were identified, with international travel emerging as the foremost factor, accounting for approximately 50% of the total emissions (Fig 3A). Electricity consumption in Mali constituted a significant proportion as well, contributing approximately 28% to the overall carbon footprint, followed by the air transportation of materials, which contributed approximately 14%. Laboratory consumables were considerable contributors to the ecological impact of the study in terms of land and water use impact (up to 22%) but only accounted for a relatively minor fraction (2%) of the total CO_2e emissions (Fig 3B-C).

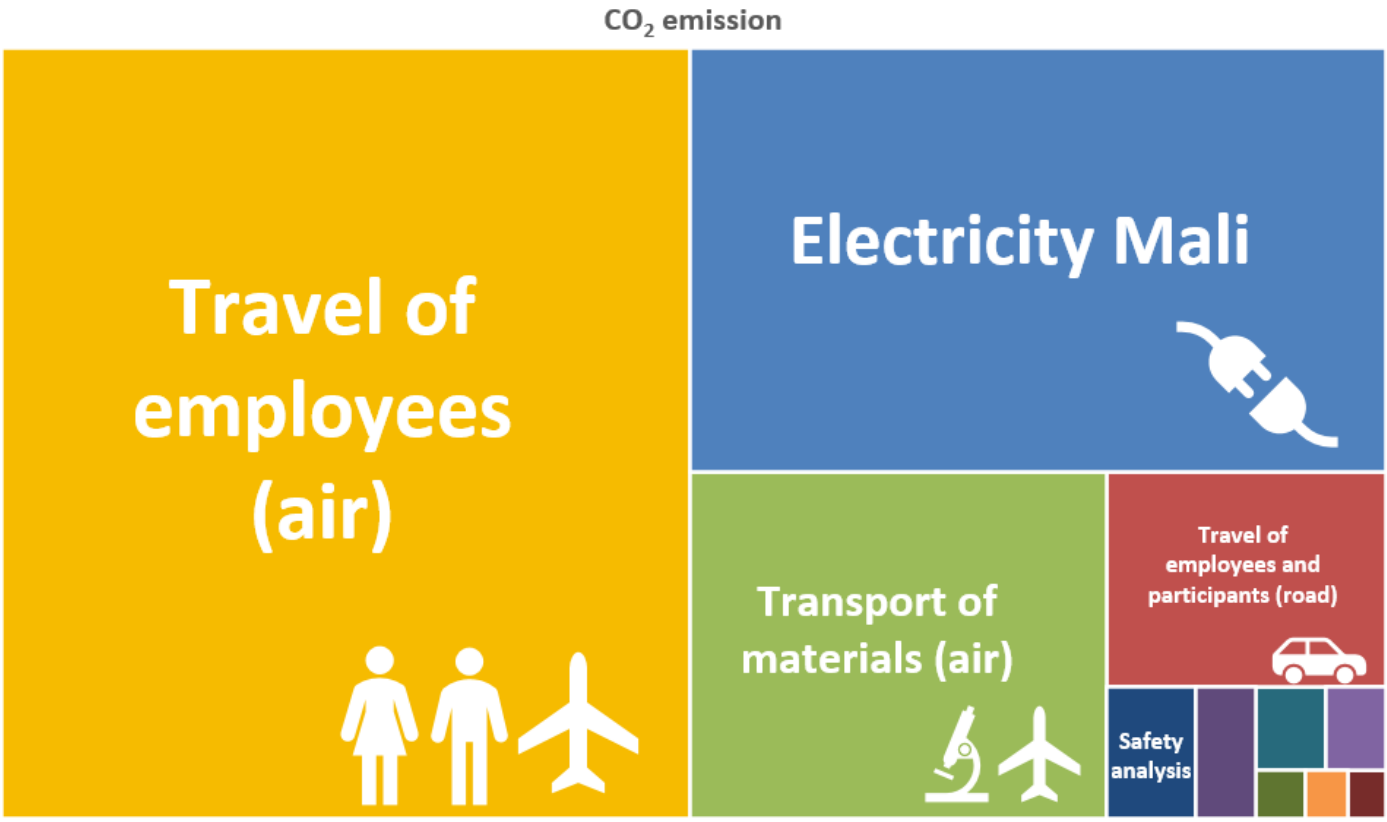

Figure 3A. Tree map of the distribution of CO_2e emission of the clinical trial. Each rectangle represents a different component of the trial, with the size of the rectangle proportional to the CO_2 emission. The colours indicate the different components of the trial: yellow for travel of employees via air (49.8%), blue for electricity in Mali (27.7%), green for transport of materials via air (13.5%), red for travel of employees and participants via 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%), green for mosquito infection analyses (0.2%), orange for electricity in the Netherlands (0.2%), and dark red for molecular analyses (0.2%).

Figure 3B-C. Tree map of the impact categories 'Water consumption' and 'Land use' 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 travel of employees via air (17.9% and 18.0%), red for travel of employees and participants via road (10.3% and 9.6%), dark purple for

others (8.5% and 5.3%), green for transport of materials via air (7.0% and 11.4%), dark blue for the safety analysis (2.5% and 9.8%), 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%), dark red for molecular analyses (0.2% and 0.4%), and turquoise for medication (0.0% and 0.0%).

Sensitivity and uncertainty analysis

Sensitivity analyses assessing the influence of different database selections for electricity generation (energy mix of Mali vs. neighbouring countries Guinea and Niger) showed a variation in global warming from -10% to 7% (to a relative importance of electricity for the entire footprint of 18.35%). 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**). The 95% confidence interval for the global warming potential associated with the study was found to be between 16.1 and 22.0 metric tonnes CO_2 eq. Confidence intervals for other environmental impact categories are detailed in the **S1 appendix**.

Alternatives to reduce the ecological footprint of laboratory processes

Our RNA stability tests showed that materials stored for up to a year at -20°C and -70°C in protective buffers had comparable signal levels for quantification (Fig 4A). Whilst there were indications for increased CT-values after 6 months of storage, indicating lower mRNA concentrations, for the PfMGET target, this pattern was similar for both storage temperatures and not observed for the other target CCp4. In addition, we explored the Crēdo Cube™ as

alternative to dry ice for shipping frozen materials. We charged the Crēdo Cube™ elements for 24 hours in -20°C and -70°C and subsequently monitored temperature changes. The temperature log 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).

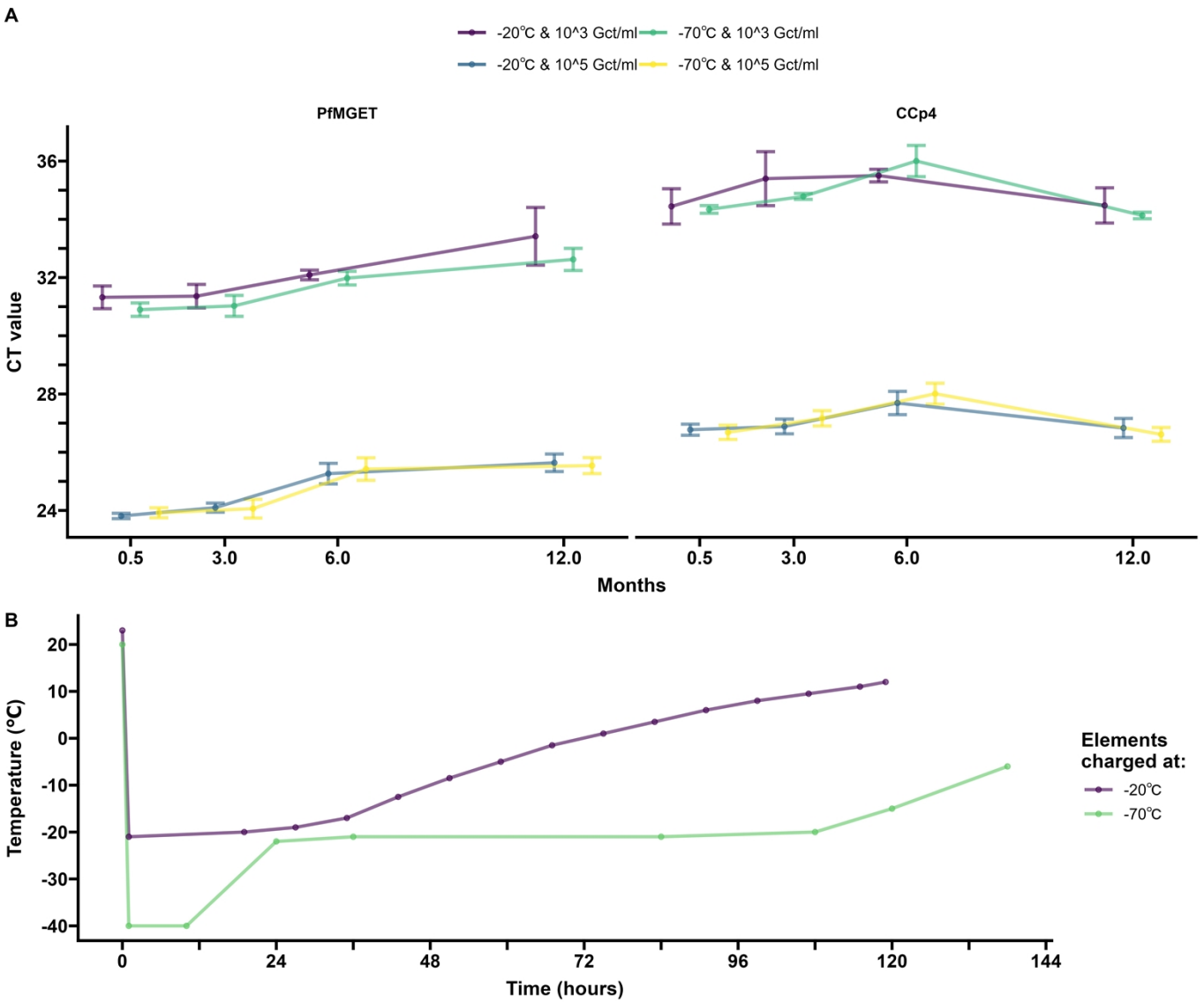

Figure 4. (A) RNA stability and (B) temperature stability of a temperature controlled box (Crēdo Cube™). (A) RNA stability was tested by quantifying gametocytes in *P. falciparum*-positive samples stored at -20°C and -70°C in protective buffers, based on the expression of the CCp4 (female gametocyte) 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 (Credo Cube) were charged at different temperatures (-20°C and -70°C), and the temperature in the box was monitored for several days.

Discussion

Our analysis estimates a carbon footprint of a clinical malaria trial and related activities of approximately 20.5 metric tonnes 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%). 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.(16) Our study identifies 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_2 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 tonnes 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).(17) Similarly, a retrospective LCA of three multicentre phase 3 trials in North America, South America, Europe, and Asia estimated total carbon footprints of 1,437 – 2,498 tonnes CO_2e per trial involving 668 – 4,744 participants and also identified travel and shipment of samples and materials as important drivers of this footprint.(18) Additionally, emissions were generated from the shipment and storage of samples for future use.(18) 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.(18)

We identified several other sources of emissions and material use that represent *low hanging fruit* for achieving reductions in future trials. First of all, we further showed that there is no difference in mRNA stability when stored in protective buffer between -20°C and -70°C for at least one year. This allows initial storage at -20^{o}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 temperature at 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. 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 requires attention. Additionally, sourcing plastics and reagents locally or regionally would be highly beneficial to reduce transport costs and emissions. Establishing industrial infrastructure for vaccines, drugs, and diagnostics is already being discussed and pushed, but this needs to run alongside the provision of the specialised consumables. Furthermore, working with companies to optimize multi-use and recyclable lab plastics is a fast developing field that can support the sustainability of trials.

Reducing some other sources of emissions will likely pose a greater challenge in efforts to minimize the trial's overall carbon footprint. 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 composition of the electricity mix in Mali, predominantly reliant on fossil fuels (~60%), had a major impact on emissions and is unlikely to change in the near future. The impacts of energy use in this location might in future be reduced by implementing solar panels in the Mali laboratory; during this trial this would have reduced CO_2e emissions by 28%. Long-term improvements in energy infrastructure are difficult to justify in trial specific budgeting, and we encourage funders to allow for budget to improve sustainability focused infrastructure. As well as infrastructural changes, trial procedures and laboratory practices can also be considered. The number of visits by trial

participants should be kept to a minimum. In certain trials, participants could self-sample at home, as recently demonstrated in Uganda.(19) Follow-up visits could be conducted via teleconference to minimize travel, or, as done in our study, by including a study population that lives within a short distance of the study center. Heavy use of laboratory consumables is often unavoidable in clinical trials. In our trial, consumables contributed considerably to the study's ecological impact in terms of land and water use impact (up to 22%) 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. Data on the environmental impact of specific medications are limited. The proxies used in this LCA, including packaging, contributed modestly to the trial's overall impact, accounting for approximately 0.5% of the total.

We conclude that the academic community has a role in exploring not just what we research but also how we research.(20) 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. Sustainable and low carbon research is relatively new territory, so the case needs to be made that this is important, necessary, possible, and stills delivers what we need.(20)

Materials and Methods

Overview clinical trial

During a phase 2 clinical trial investigating the effects of antimalarials on malaria transmission to mosquitoes, a total of eighty participants underwent 28-days of follow-up.(21) The trial outcome measures encompassed safety, including clinical, hematological and biochemical analyses, as well as 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 related to the primary and secondary study objectives, and the presentation of study results in the United States, data on the use of consumables, electricity and travel data were collected for the LCA.

Prior to screening and prior to enrolment in the clinical trial, participants provided written informed consent (≥18 years) or assent with written parental consent (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).

Life cycle assessment (LCA)

The primary objective of the LCA was to estimate the environmental impact of the trial and identify the areas where measures for reducing environmental impact might be applied most effectively. The LCA encompassed the entire life cycle of the product system. The product system refers to the entire

network of processes and activities involved in the 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".(22) 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, safety analysis, mosquito infection analyses, molecular analyses, medication, and others. The last five groups primarily consist of consumables. Due to the absence of data on the production of the antimalarials used in this trial, data on the production of other pharmaceuticals that are also produced on a large scale, namely vancomycin and tenofovir, were used instead.(23) To approximate the environmental impact of malaria medication with an unknown ecological footprint, we averaged the impacts of these two medications. In cases where a multifunctional process had relevance, we allocated the corresponding portion of the environmental impact from that process. This allocation was done based on size, mass, or time. For example, the environmental impact of the electricity usage at the research site was distributed according to the number of studies being conducted simultaneously during that time. 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**. To gauge the 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 5).

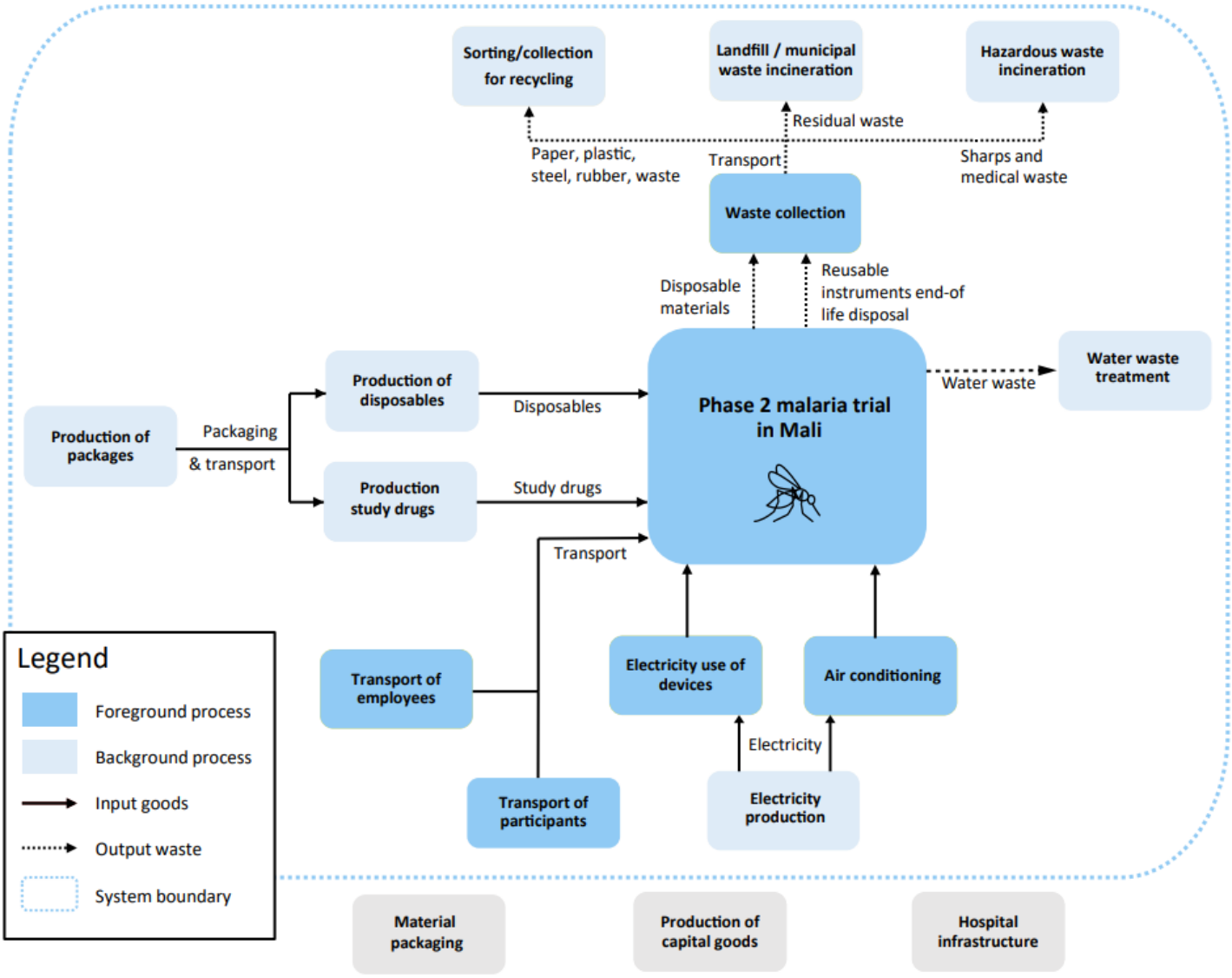

Figure 5. The system boundary

System boundary of what was included (within the blue dotted boundary) and excluded in this life cycle assessment.

The environmental impact scores in the Life Cycle Impact Assessment (LCIA) were computed using the ReCiPe 2016 method,(24) 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. 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 uses 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.(25) We conducted an uncertainty analysis using the pedigree matrix and the Monte Carlo algorithm. To confirm the reliability 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.(26)

Additional assessments

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,(27) we tested the stability of parasite messenger RNA at different conditions. Serial dilutions of the parasite stage that is of prime interest for the study (gametocytes, 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^{o}C or a -20^{o}C

freezer for 2 weeks, 3, 6, or 12 months after which total RNA was extracted using the MagNAPure automated extractor and gametocytes were determined by CCp4/PfMGET RT-qPCR.(28) CT-values that are indicative of mRNA abundance were compared between 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™) that allows maintaining temperature at or below this temperature for several days. 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.

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