Solar-powered O_2 delivery for the treatment of children with hypoxaemia in Uganda: a stepped-wedge, cluster randomised controlled trial

Nicholas Conradi, Robert O Opoka, Qaasim Mian, Andrea L Conroy, Laura L Hermann, Olaro Charles, Jackson Amone, Juliet Nabwire, Bonita E Lee, Abdullah Saleh, Piush Mandhane, Sophie Namasopo, Michael T Hawkes

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Department of Pediatrics (N Conradi MBBS, Q Mian MD MPH, B E Lee MD, P Mandhane MD PhD, M T Hawkes MD PhD), **Department of Surgery** (O Charles MMed, J Amone MMed, A Saleh MD), **Department of Medical Microbiology and Immunology** (M T Hawkes), **and School of Public Health** (M T Hawkes), **University of Alberta, Edmonton, AB, Canada; Department of Paediatrics and Child Health, Mulago Hospital and Makerere University, Kampala, Uganda** (R O Opoka PhD); **Global Health Uganda, Kampala, Uganda** (R O Opoka, J Nabwire MPH); **Indiana University School of Medicine, Indianapolis, IN, USA** (A L Conroy PhD); **Kelowna General Hospital, Kelowna, BC, Canada** (L L Hermann MD PhD); **Ministry of Health, Kabale, Uganda; Kabale Regional Referral Hospital, Kabale, Uganda** (S Namasopo MMed); **Stollery Science Lab, Edmonton, AB, Canada** (M T Hawkes); **Women and Children's Health Research Institute, Edmonton, AB, Canada** (M T Hawkes)

Correspondence to: Dr Michael T Hawkes, Department of Pediatrics, University of Alberta, Edmonton, T6G1C9 AB, Canada **mthawkes@ualberta.ca**

Summary

Background Supplemental O_2 is not always available at health facilities in low-income and middle-income countries (LMICs). Solar-powered O_2 delivery can overcome gaps in O_2 access, generating O_2 independent of grid electricity. We hypothesized that installation of solar-powered O_2 systems on the paediatrics ward of rural Ugandan hospitals would lead to a reduction in mortality among hypoxaemic children.

Methods In this pragmatic, country-wide, stepped-wedge, cluster randomised controlled trial, solar-powered O_2 systems (ie, photovoltaic cells, battery bank, and O_2 concentrator) were sequentially installed at 20 rural health facilities in Uganda. Sites were selected for inclusion based on the following criteria: District Hospital or Health Centre IV with paediatric inpatient services; supplemental O_2 on the paediatric ward was not available or was unreliable; and adequate space to install solar panels, a battery bank, and electrical wiring. Allocation concealment was achieved for sites up to 2 weeks before installation, but the study was not masked overall. Children younger than 5 years admitted to hospital with hypoxaemia and respiratory signs were included. The primary outcome was mortality within 48 h of detection of hypoxaemia. The statistical analysis used a linear mixed effects logistic regression model accounting for cluster as random effect and calendar time as fixed effect. The trial is registered at ClinicalTrials.gov, NCT03851783.

Findings Between June 28, 2019, and Nov 30, 2021, 2409 children were enrolled across 20 hospitals and, after exclusions, 2405 children were analysed. 964 children were enrolled before site randomisation and 1441 children were enrolled after site randomisation (intention to treat). There were 104 deaths, 91 of which occurred within 48 h of detection of hypoxaemia. The 48 h mortality was 49 (5·1%) of 964 children before randomisation and 42 (2·9%) of 1440 (one individual did not have vital status documented at 48 h) after randomisation (adjusted odds ratio 0·50, 95% CI 0·27–0·91, p=0·023). Results were sensitive to alternative parameterisations of the secular trend. There was a relative risk reduction of 48·7% (95% CI 8·5–71·5), and a number needed to treat with solar-powered O_2 of 45 (95% CI 28–230) to save one life. Use of O_2 increased from 484 (50·2%) of 964 children before randomisation to 1424 (98·8%) of 1441 children after randomisation (p<0·0001). Adverse events were similar before and after randomisation and were not considered to be related to the intervention. The estimated cost-effectiveness was US$25 (6–505) per disability-adjusted life-year saved.

Interpretation This stepped-wedge, cluster randomised controlled trial shows the mortality benefit of improving O_2 access with solar-powered O_2. This study could serve as a model for scale-up of solar-powered O_2 as one solution to O_2 insecurity in LMICs.

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Introduction

Hypoxaemic illnesses are leading causes of child mortality worldwide. Of greatest concern, childhood pneumonia accounts for 740 000 deaths annually, mostly in low-income and middle-income countries (LMICs).[1] Supplemental O_2 therapy is a life-saving intervention and is listed in WHO's list of essential medicines.[2] A multi-hospital study conducted in Papua New Guinea showed a 35% reduction in child deaths from pneumonia following the implementation of improved O_2 delivery systems.[3] A recent meta-analysis demonstrated that O_2 systems-strengthening decreased childhood pneumonia mortality (odds ratio 0·52, 95% CI 0·39–0·70).[4]

In LMICs, O_2 is not always available in clinical settings due to cost or logistical challenges.[5] O_2 can be administered through compressed O_2 cylinders or O_2 concentrators.[6] O_2 cylinders require refilling in a centralised plant and transportation to clinical facilities, which can be complicated by high transport costs, weak supply management, and leakage of high-pressure tank contents.[6] O_2 concentrators provide onsite O_2 generation, but depend on a reliable and uninterrupted supply of electricity.[6,7]

Research in context

Evidence before this study

Hypoxaemic illnesses, including childhood pneumonia, are a leading cause of death worldwide. Supplemental O_2 is an essential therapy for pneumonia but is not always available in low-income and middle-income countries (LMICs). Previous studies have shown that solar energy can be used to concentrate O_2 from ambient air, providing a method of O_2 generation that is independent of grid electricity. A randomised non-inferiority trial compared solar-powered O_2 with cylinder O_2 among children with hypoxaemia and showed equivalent outcomes, including duration of hospitalisation and mortality. A cost-effectiveness analysis showed that solar-powered O_2 was cost-effective relative to a base case of no O_2, and cost-saving compared with fuel-powered generators. Other observational studies have shown the feasibility, utility, and acceptability of solar-powered O_2 in several LMICs, including in conflict zones.

Added value of this study

This study was designed to examine the mortality benefit of solar-powered O_2. The study involved 2405 hypoxaemic children admitted to 20 hospitals across Uganda. The primary endpoint was mortality within 48 h of detection of hypoxaemia. After adjustment for calendar time and site in a linear mixed-effects logistic regression model, the relative risk of fatal outcome was reduced by 48·7% (95% CI 8·5–71·5). The estimated cost-effectiveness was US$25 per disability-adjusted life-year saved (6–505).

Implications of all the available evidence

Solar-powered O_2 delivery is life-saving and cost-effective. Implementation of solar-powered O_2 could address the gap in O_2 availability in LMICs. If solar-powered O_2 can be taken to scale across LMICs, it could contribute to improved global child survival.

However, grid power can be unreliable; in some LMIC settings, 26% of health facilities report no access to electricity and only 28% report reliable access.[8] Uganda has a high burden of paediatric pneumonia (16% of all child deaths in the country in 2015).[9] Many deaths occur in peripheral health facilities with unreliable electricity and an inadequate supply chain of O_2 cylinders (appendix pp 2–4).[10]

Solar-powered O_2 delivery is a novel strategy for improving access to medical O_2 in LMICs. We have previously described the design and implementation of solar-powered O_2 in Uganda,[11,12] the Democratic Republic of Congo,[13] and Somalia.[14] The system consists of photovoltaic cells (ie, solar panels) installed on the roof of a health facility, which collect solar energy that is stored in a bank of batteries and used to power an O_2 concentrator. Previous studies have demonstrated feasibility,[11] non-inferiority relative to cylinder O_2,[12] and cost-effectiveness of solar-powered O_2.[15] Another large-scale non-randomised[16] study showed a reduction in the incidence of pneumonia deaths after implementation of solar-powered O_2 systems at 38 centres in Papua New Guinea. Conversely, a study from Nigeria did not find a mortality benefit among children following the introduction of a multifaceted O_2 system that included solar power or petrol generators.[17] Another study[18] showed that improved O_2 systems were sustainable in the medium term and were highly cost-effective.

In this study, we present the results of a stepped-wedge, cluster randomised controlled trial assessing changes in mortality after the implementation of solar-powered O_2, among children younger than 5 years who were admitted to hospital with hypoxaemic illness.

Methods

Study design

In this stepped-wedge, cluster randomised controlled trial, we recruited children younger than five years of age admitted to hospital in Uganda. The rationale for using a stepped-wedge, cluster randomised trial design was as follows: individual random assignment to a group receiving no O_2 was considered unethical; all participating sites would have access to O_2 by the end of the trial; and step-wise implementation provided the necessary time for multiple installations at sites widely distributed across the country.

See Online for appendix

Sites were selected for inclusion based on the following criteria: District Hospital or Health Centre IV with paediatric inpatient services; supplemental O_2 on the paediatric ward was not available or was unreliable; and adequate space to install solar panels, a battery bank, and electrical wiring.[19] In consultation with the Ministry of Health, four to six sites were selected from each of Uganda's geographic regions (North, East, West, and Central), totalling 20 sites (appendix p 10).[19] Trial participants received free medical care at the participating government facilities as standard. The installed infrastructure (ie, solar panels and batteries) became the property of the hospital at the end of the trial.

The design of the trial has been previously published.[19] There were 20 clusters (ie, sites) and 21 steps in the trial: a 2-month period before solar-powered O_2 was installed at any site (from June 28, to Aug 31, 2019), monthly installations (Sept 1, 2019 to April 31, 2021), and a period of monitoring after solar-powered O_2 was installed at all sites, until the final sample size was reached (May 1, to Nov 30, 2021).

The study was reviewed and approved by the Makerere University School of Biomedical Sciences Research Ethics Committee (reference number SBSREC-644), Uganda National Science and Technology (reference number HS 2569), and the University of Alberta Health Research Ethics Board (reference number Pro00084784).

Participants

Children younger than 5 years were included in the trial if they had cough or difficulty breathing, had hypoxaemia (O_2 saturation <92%),[20] and required admission to hospital. Children were excluded if they had known cyanotic congenital heart disease or hypoxaemic ischaemic encephalopathy.

Written informed consent was obtained from the parent or guardian of all study participants.

Randomisation and masking

The sequence of equipment installation at each hospital was randomly generated using R (version 3.6.2) by ALC before the trial.[19] Randomisation was conducted in blocks of four, with each block including one site from each of the four geographic regions of the country. The order of the four regions within a block were random, and selection of a site within a region was randomly sampled without replacement. Site names were placed in sequentially numbered, sealed, opaque envelopes. Allocation was concealed until 2 weeks before scheduled installation, at which time the next envelope was opened to reveal the next site for implementation. The study was not masked.

Procedures

Children presenting to a participating site with cough or difficulty breathing were screened for hypoxaemia using pulse oximetry. The parent or guardian of an eligible child was approached for consent. If granted, the patient was provided with O_2 from a source at the facility, if available, in the period before site randomisation or from the solar-powered O_2 system after site randomisation. O_2 flowrate was titrated using standardised protocols, guided by pulse oximetry to administer the minimum flowrate required to maintain an O_2 saturation greater than 92%. The O_2 saturation and supplemental O_2 flowrate were recorded every 4 hours during the hospital stay while O_2 was administered, and every 8 hours if the patient was not on O_2 therapy. A standard procedure for weaning from O_2 was followed every morning to determine if supplemental O_2 could be safely reduced or discontinued.

All patients received standard care for their underlying disease, including antibiotics for pneumonia, intravenous fluids, blood transfusion, and antipyretics. The study ensured availability of equipment and essential medications other than O_2 in the pre-randomisation period. Demographic and clinical data were collected using study-standardised case record forms, and patients were followed during their hospital admission with routine recording of vital signs.

A site champion at each participating facility (ie, a dedicated study nurse hired for the study), who was trained in study procedures, performed most study-related duties (eg, screening, obtaining consent, measuring pulse oximetry, administering O_2, providing clinical care, and collecting data). Local clinical nurses (ie, those employed at the facility by the Ministry of Health) assisted in identifying eligible patients, monitoring vital signs after the site champion went home (usual working hours were Monday to Saturday, 0800 h to 1700 h), and clinical care of the study patients. The study leadership (ROO, JN, SN, and MTH) and site champions worked closely with administrators, nursing staff, and biomedical technicians at each institution to integrate the clinical trial into the routine services offered on the paediatric ward. The site champion assisted with clinical duties for non-study patients, as time permitted. Local biomedical engineering technicians from the Regional Referral Hospital nearest to the study site participated in the planning and supervised the installation of the solar-powered O_2 systems, which ensured that they were familiar with the equipment and circuitry and promoted a teamwork approach to the solar-powered O_2 installation.

The solar-powered O_2 system consisted of solar panels, a charge controller, a bank of batteries, a direct current (known as DC) to alternating current (known as AC) inverter, and an O_2 concentrator.[11] There was one concentrator per site, for dedicated use on the paediatric ward. Components were purchased from and installed by Ugandan electrical engineers and technicians (Ultratec [U], Kampala, Uganda). Technical problems with the system that arose during the trial were also handled by Ultratec (U) (appendix pp 5–9).

There were no changes to the trial protocol after the trial commenced.

Outcomes

The primary endpoint was mortality within 48 h of hypoxaemia detection. This outcome was recorded based on direct observation or by telephone call if the patient was transferred to another facility before the 48 h completed.

Secondary endpoints included length of hospital stay among patients who did not die and were not transferred to another facility, overall mortality (before and after 48 h), costs of system installation and maintenance, and system failures (ie, when the installed solar-powered O_2 system did not deliver O_2 to an enrolled patient). Additional post-hoc secondary outcomes included access to O_2 treatment, patients requiring transfer to a higher level facility, discharge without disability, and cost-effectiveness of the intervention. The protocol specified the following secondary outcomes, which will be reported in subsequent publications: the duration of supplemental O_2 therapy; baseline and post-training nursing skills and skill retention at the end of the trial; ascertainment of microbial cause using dried blood spots, nasopharyngeal swabs, and plasma blood specimens; and measurement of diagnostic and prognostic host biomarkers of disease severity and outcome in paediatric pneumonia. Adverse events (related or unrelated to solar-powered O_2) were logged at each site and tabulated to compare rates before and after randomisation. Disease severity was assessed

using the Respiratory Index of Severity in Children (RISC).[21]

Statistical analysis

For 80% power and 95% confidence, 2400 children with hypoxaemia were required for inclusion to show a reduction in mortality after installation of solar-powered O_2. Using a computer simulation, we estimated monthly enrolment (modelled as a Poisson variable) and deaths (modelled as a Bernoulli trial) in a hypothetical clinical trial, as previously described.[19] Monthly random allocation of solar-powered O_2 to 20 sites was simulated, according to the stepped-wedge design. We assumed a mortality reduction of 35% after installation of solar-powered O_2.[3] Using the simulated trial data, we ran the planned statistical analysis, fitting a linear mixed effects (LME) logistic regression model. We repeated the simulation 5000 times and determined the proportion of trials that correctly detected a difference between patients receiving solar-powered O_2 and those not receiving solar-powered O_2 (ie, the statistical power). Using this simulation strategy, 20 sites enrolling a total of 2400 patients (average cluster size 120 patients) would provide more than 80% power to detect a 35% mortality benefit of solar-powered O_2 at an α level of 0·05.[19]

For the primary analysis, a LME logistic regression model was used to compare the 48 h mortality of patients admitted to a hospital with solar-powered O_2 (after randomisation) to patients admitted before randomisation. Patients were classified according to the date that hypoxaemia was detected (relative to the date randomly allocated for installation of solar-powered O_2 at their site) and whether they actually received solar-powered O_2. By using the randomisation date (rather than implementation date) to define the exposure (solar-powered O_2), an intention-to-treat analysis was used for the primary outcome. Alternative ways of classifying the exposure (ie, enrolment post-implementation and patients who actually received solar-powered O_2) was addressed in a sensitivity analysis. By using the randomisation date (rather than implementation date) to define the exposure (solar-powered O_2), an intention-to-treat analysis was used for the primary outcome. We addressed alternative ways of classifying the exposure (enrolment post-implementation and patients who actually received solar-powered O_2) in a sensitivity analysis. The model included terms to adjust for the secular trend (ie, fixed effect) and cluster (ie, random effect).[19,22] The secular trend was modelled using a three-level categorical variable (requiring two fixed effect parameters), corresponding to the calendar year (ie, patients enrolled from June 28 through Dec 31 2019; Jan 1, to Dec 31, 2020; or Jan 1, to Nov 30, 2021). The rationale for this parameterisation was: (1) parsimony of the statistical model and (2) natural division of calendar time. Alternative parameterisations for the secular effect were explored in a sensitivity analysis.

Secondary outcomes and adverse events were compared between the groups before and after site randomisation using similar LME logistic regression models. Analyses stratified by O_2 source (none, facility O_2, or solar-powered O_2), disease severity, and site were done, comparing binary variables using the χ^2 test or Fisher's exact test for unmatched outcomes and the McNemar test for matched outcomes. Subgroup analyses using the same LME logistic regression model were done for: (1) children younger than 1 year of age and those aged 1 year and older; (2) female and male participants; (3) children with O_2 saturation less than 85% and of 85% or more; and (4) RISC less than 4 and of 4 or more. Sensitivity analyses were done as described in the appendix (pp 17–21). To calculate the intra-cluster correlation coefficient, we used the package performance (version 0.10.4).[23]

Data analysis was done using the package lme4 (version 1.1-33)[15] in the R statistical environment (version 3.6.2). Data visualisation used GraphPad Prism (version 6) and R.

Costs for equipment, transportation to the facility, and installation were tabulated for each site (appendix pp 44–45). Costs incurred by participant families were estimated via interview of the caregiver through a structured questionnaire (appendix pp 44–45). Additional costs (eg, maintenance and non-O_2 medical costs) were estimated based on literature review (appendix pp 44–45). For the cost-effectiveness analysis (ie, post-hoc secondary analysis), a list of health and non-health effects of the intervention that were considered and that were neglected is available in the appendix (appendix pp 39–41). For cost-effectiveness, we did an analysis from a limited-societal perspective, computing the incremental cost-effectiveness ratio (ICER) of solar-powered O_2 relative to the pre-solar-powered O_2 conditions, as observed in our trial. US$884 per disability-adjusted life-year (DALY), corresponding to the gross domestic product per capita of Uganda, was used as a threshold for cost-effectiveness (appendix pp 42–43).[15]

The trial is registered at ClinicalTrials.gov, NCT03851783.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 28, 2019, and Nov 30, 2021, 2409 individuals were enrolled into the study, with last patient contact on Dec 4, 2021. The trial ended when the pre-specified sample size was reached. Characteristics of the study sites are available in the appendix (p 10). Four patients who were enrolled in the study were excluded at the analysis stage because they did not meet inclusion criteria or met an exclusion criterion. One patient with a missing outcome was excluded from analyses.

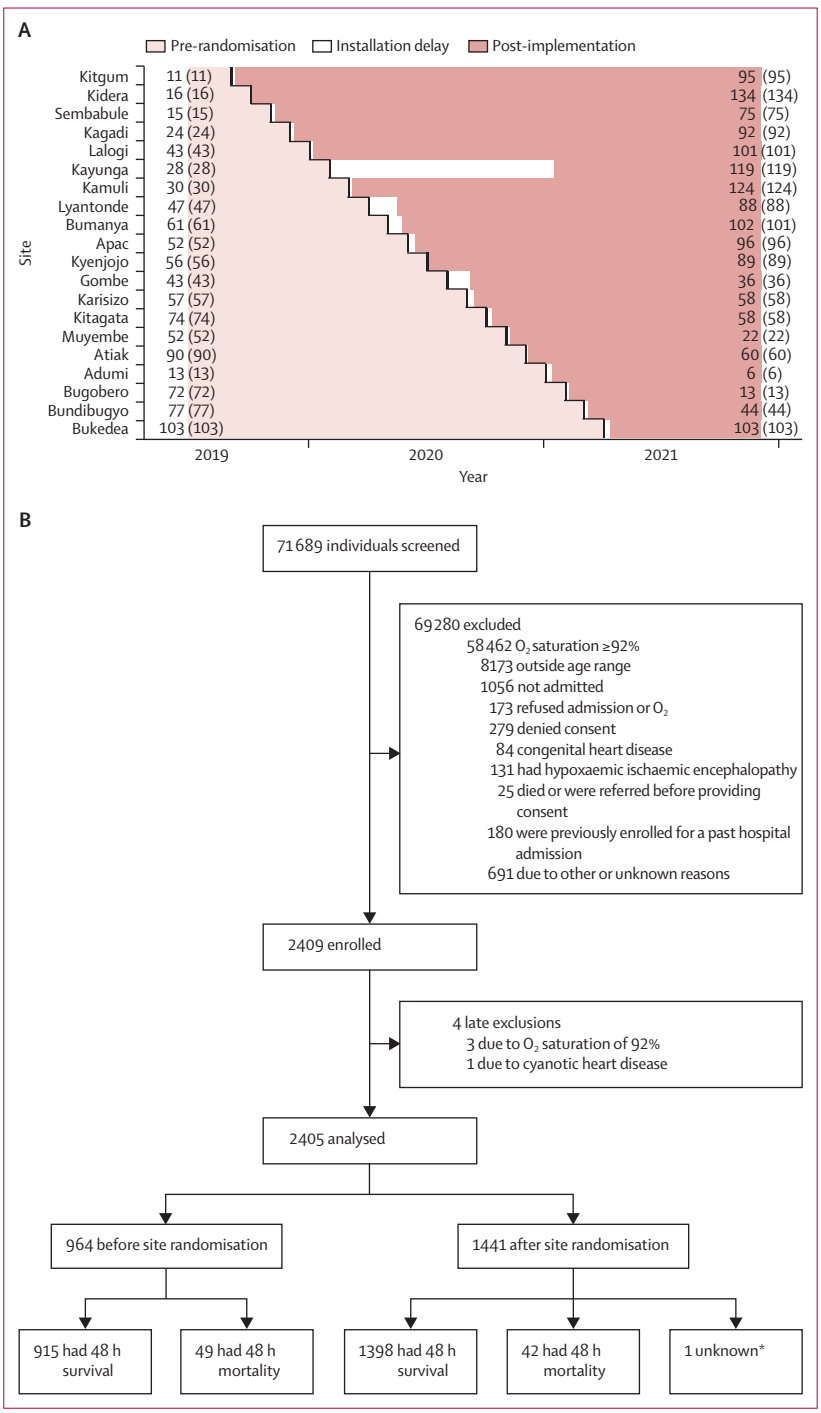

Figure 1: **Cluster randomised stepped-wedge study profile**
(A) Site randomisation. Installation occurred within 1 month of randomisation with three exceptions: (1) Kayunga Health Centre IV, delayed by 11 months due to ward renovations; (2) Lyantonde Health Centre IV, delayed by 6 weeks due to country-wide lockdown for SARS-CoV-2; and (3) Gombe Health Centre IV, delayed by 4 weeks due to repairs to the roof of the paediatric ward. In the primary (intention-to-treat) analysis, patients admitted in the period before randomisation were compared with those admitted after randomisation. Numbers on the left of the graph are the n of patients enrolled at each site in the pre-randomisation period (n of those who were included in the primary analysis). Numbers on the right of the graph are the n of patients at each site in the post-randomisation period (n of those who were included in the primary analysis). (B) Participant flow diagram. *The individual with an unknown 48 h outcome was excluded from the primary outcome and the secondary outcome of all deaths, but was included for all other secondary outcome analyses.

Solar-powered O_2 installation was completed within 1 month of the date randomly assigned a priori, with the exception of three sites, which delayed by 4 weeks, 6 weeks, and 11 months (figure 1A).

There were more patients admitted to study sites after randomisation of the site to solar-powered O_2 than before randomisation (figure 1B). Of note, the proportion of individuals who declined consent in the period before randomisation was 163 of 26 603 (0·61) compared with 116 of 44 247 (0·26) after randomisation (p<0·0001; appendix pp 12–15). Baseline characteristics of children in the periods before and after randomisation were similar (table 1). There were 144 participants (6·0%) younger than 2 months of age, and 31 (1·3%) younger than 1 month of age (appendix p 11). Due to delays in installation, 88 patients were included after randomisation but before equipment installation. After installation of solar-powered O_2, 128 (9·5%) of 1353 patients did not receive solar-powered O_2 treatment for the following reasons: the solar-powered concentrator was in use by another patient (n=49, 38·3%); urgent referral was necessary (n=43, 33·6%); another source of O_2 was used (n=16, 12·5%); system failure (n=15, 11·7%); or O_2 was not administered but the reason was not clearly documented (n=5, 3·9%).

Overall, there were 104 deaths among hypoxaemic children, including 91 that occurred within 48 h of detection of hypoxaemia. One patient (<0·1%) had unknown vital status at 48 h because the family left against medical advice and did not provide a contact telephone number and was excluded from the primary outcome (mortality at 48 h) and one of the secondary outcomes (overall mortality; appendix p 16). The 48 h mortality was 49 (5·1%) deaths of 964 participants in the group before randomisation group and 42 (2·9%) of 1440 in the group after randomisation. According to the pre-specified statistical plan, using an LME logistic regression model adjusting for time and site, the OR of fatal outcome was 0·50 (95% CI 0·27–0·91) in the group after randomisation compared with the group before randomisation (p=0·023). This finding represents an absolute risk reduction of 2·2% (95% CI 0·4–2·5), a relative risk reduction of 48·7% (8·5–71·5), and a number needed to treat with solar-powered O_2 of 45 (28–230) to save one life.

We verified the following assumptions of the logistic regression model: binary outcome variable, linear relationship between the fixed effects and the logit of the outcome, absence of influential observations, absence of multicollinearity, and large sample size. The intra-cluster correlation coefficient was 0·0068 and the time effect (ie, year-over-year change in mortality) had an adjusted OR of 1·19 (95% CI 0·80–1·79). On visual inspection, there was no obvious secular trend of improving outcome over time (appendix p 22). With respect to secondary trial endpoints, O_2 availability increased, total deaths (before and after 48 h) decreased, and transfers

to other facilities decreased in the period after randomisation (table 2). These secondary analyses were not adjusted for multiplicity of comparisons and should be considered exploratory outcomes. Compared with children who did not receive O_2, mortality was not significantly different in children treated with non-solar-powered O_2 from a cylinder or concentrator from the health facility (p=0·46; appendix p 26).

Subgroup analyses are shown in figure 2. Of note, patients with severe hypoxemiahypoxaemia (O_2 saturation <85%) and severe disease (RISC ≥4) had the greatest mortality reduction associated with solar-powered O_2 (figure 2).

There were 17 system failures affecting 11 sites and 23 patients (0·96%; appendix p 29). Eight (34·8%) patients received some O_2 before or after the system failed and 15 (65·2%) received no O_2 due to the system failure. System failures occurred when there was insufficient sunlight and grid electricity over several days, leading to depletion of the battery bank (accounting for eight [47·1%] failures), faults with the O_2 concentrator (six [35·3%] failures), and faults with the solar electrical circuit (three [17·7%] failures). Battery depletion occurred most frequently at the Lalogi site (appendix p 29). Three (13·0%) affected patients required referral to another facility and one (33·3%) of the referred patients subsequently died.

Adverse events were similar before and after randomisation (appendix p 28).

Sensitivity analyses were done to examine the effect of different model assumptions for the secular trend (table 3), different classification of exposure to solar-powered O_2, adjustment for clinical covariates, missing datum, protocol deviations, influential sites, alternative trial endpoint, randomisation stratified by region, and alternative statistical inference methods (appendix pp 21, 27). These analyses showed that the treatment effect was sensitive to the modelling assumptions about the secular trend (table 3). With an increasing number of parameters used to model the secular trend, the CI on the treatment effect became wider, although the point estimate did not change markedly. The treatment effect was not statistically significant in the model proposed by Hussey and Hughes.[22] A regression model that included the clinical covariates of age, sex, and RISC showed that the effect of solar-powered O_2 remained statistically significant. Additional analyses were explored, including a model with a cluster×period interaction term and a model with a duration×exposure interaction term (appendix pp 24-25).

We did a post-hoc cost-effectiveness analysis of solar-powered O_2, using trial data to inform model inputs (appendix pp 42–52). The solar-powered O_2 system cost at each health facility was $12 800 (appendix p 48). The ICER from a limited-societal perspective was $25 per DALY saved (95% CI 6–505) and $1490 per life saved (334–27 100). At a threshold of $884 per DALY saved,[15] solar-powered O_2 was cost-effective from a limited societal perspective in more than 98% of simulations in a probabilistic multiway sensitivity analysis (appendix pp 42–43). The Consolidated Health Economic Evaluation Reporting Standards 2022 checklist for the cost-effectiveness analysis is available in the appendix (pp 49–52).

	Before randomisation (n=964)	After randomisation (n=1441)
Demographics		
Sex		
Female	413 (42·8%)	648 (45·0%)
Male	551 (57·2%)	793 (55·0%)
Age (years)	1·0 (0·5–2·0)	1·1 (0·5–2·3)
Clinical features at enrolment		
Tactile fever	821 (85·2%)	1269 (88·1%)
Cough	869 (90·2%)	1345 (93·3%)
Difficulty breathing	848 (88·0%)	1337 (92·8%)
Convulsions	186 (19·3%)	241 (16·7%)
Altered consciousness	246 (25·5%)	390 (27·1%)
Vomiting	300 (31·1%)	377 (26·2%)
Unable to feed or drink	545 (56·5%)	842 (58·4%)
WHO danger signs*	809 (83·9%)	1163 (80·7%)
Physical exam		
Severely underweight†	91 (9·4%)	145 (10·1%)
O_2 saturation (%)	85 (78–88)	85 (80–88)
Tachypnea‡	533 (53·3%)	826 (57·3%)
Tachycardia‡	328 (34·0%)	506 (35·1%)
Temperature (°C)	37·9 (37·0–38·5)	37·6 (36·8–38·1)
Level of consciousness		
Alert	617 (64·0%)	994 (69·0%)
Voice	110 (11·4%)	147 (10·2%)
Pain	163 (16·9%)	223 (15·5%)
Unresponsive	71 (7·4%)	76 (5·3%)
Deep breathing	372 (38·6%)	623 (43·2%)
Chest indrawing	782 (81·1%)	1221 (84·7%)
Grunting	591 (61·3%)	783 (54·3%)
Stridor	286 (29·7%)	424 (29·4%)
Cyanosis	248 (25·7%)	298 (20·7%)
Disease severity (RISC)	3 (2–4)	3 (2–4)
Diagnosis		
Pneumonia	822 (85·3%)	1297 (90·0%)
Malaria	467 (48·4%)	724 (50·2%)
Asthma	17 (1·8%)	12 (0·8%)
Foreign body aspiration	14 (1·5%)	22 (1·5%)
Meningitis	15 (1·6%)	12 (0·8%)
HIV co-infection	10 (1·0%)	19 (1·3%)

Data are n (%) or median (IQR). RISC=Respiratory Index of Severity in Children. *WHO danger signs include convulsions, altered consciousness, vomiting, stridor, and being unable to feed or drink. †Weight-for-age below –3SD.[24] ‡Vital sign >99 percentile for age.[25]

Table 1: **Characteristics at admission of 2405 children admitted to hospital with hypoxaemia**

Discussion

This stepped-wedge, cluster randomised controlled trial showed that implementation of solar-powered O_2 was associated with a 48·7% (95% CI 8·5–71·5) relative

	Children admitted before site randomisation (n=964)	Children admitted after site randomisation (n=1441)	Adjusted OR (95% CI)	Estimated difference (95% CI)	p value
Primary outcome					
48 h mortality	49 (5·1%)	42 (2·9%)	0·50 (0·27 to 0·91)	..	0·023
Secondary outcomes					
Access to O_2 treatment*	484 (50·2%)	1424 (98·8%)	180 (60 to 560)	..	<0·0001
Transferred to another facility*	217 (22·5%)	150 (10·4%)	0·60 (0·39 to 0·93)	..	0·024
Discharged without disability*	685 (71·0%)	1230 (85·4%)	2·0 (1·4 to 2·9)	..	0·0004
Length of hospital stay (days)†	2·9 (2·0 to 3·9)	3·1 (2·2 to 4·1)	..	0·19 (–0·02 to 0·40)	0·073
Overall mortality	55 (5·7%)	49 (3·4%)	0·47 (0·26 to 0·85)	..	0·011

Data are n (%) or median (IQR) unless otherwise specified. Adjusted OR represents odds of outcome among children enrolled before randomisation compared with children enrolled after randomisation (intention-to-treat analysis), estimated using a linear mixed effects model adjusting for calendar time (fixed effect) and site (random effect). Confidence intervals and p values for the five secondary outcomes were not corrected for multiple comparisons and these results should be considered exploratory. 48h mortality was defined as death within 48 h of detection of hypoxaemia. OR=odds ratio. *These post-hoc endpoints were not specified in the protocol. †Excludes those transferred out of the study health facilities and those who died.

***Table 2*: Outcomes among hypoxaemic children enrolled before and after site randomisation to solar-powered O_2**

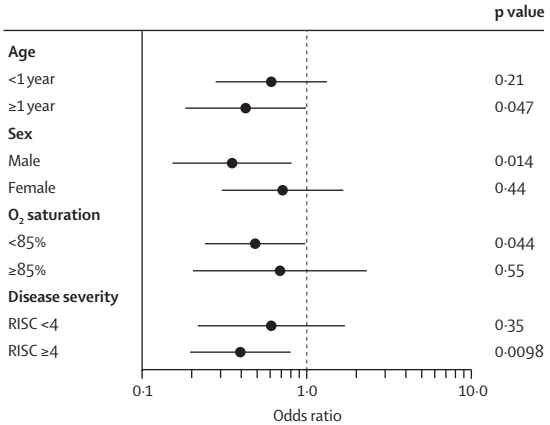

***Figure 2*: Subgroup analyses of the period after randomisation period compared with before randomisation**

The odds of 48 h mortality in the period after randomisation, relative to before randomisation, was assessed in four subgroups based on: (1) age; (2) sex; (3) O_2 saturation; and (4) disease severity, quantified using RISC. Of note, hypoxaemia <85% and RISC ≥4 were subgroups in which solar powered O_2 exposure appeared to have the greatest benefit in reducing mortality. p values were not corrected for multiple comparisons and these results should be considered exploratory. RISC=Respiratory Index of Severity in Children.

reduction in 48 h mortality, among Ugandan children admitted to hospital with hypoxaemic illness (table 2). Solar-powered O_2 was not associated with adverse effects above the baseline rate and was cost-effective. Together, these results suggest that solar-powered O_2 is a promising strategy that could be taken to scale to reduce childhood deaths from hypoxaemic illness in LMICs. This study builds on evidence showing reduced mortality with implementation of solar-powered O_2 delivery systems in Papua New Guinea[16] and the cost-effectiveness of improved O_2 systems.[4]

The 20 hospitals and health centres in our study are probably representative of rural and semi-urban paediatric inpatient facilities in LMICs. The sites spanned all geographic regions of Uganda, admitted children with pneumonia and hypoxaemia, did not have easy access to an O_2 cylinder-filling plant, and had intermittent grid electricity. Only 50% of hypoxaemic children in our study had access to O_2 before randomisation (table 2), consistent with previous studies which have highlighted O_2 insecurity in hospitals across sub-Saharan Africa.[5,26] The mortality was not significantly different in children treated with O_2 from a cylinder or concentrator from the health facility in the pre-randomisation period compared with children who did not receive O_2, suggesting that the quality of this O_2 might have been poor. Particulars of the Ugandan context that facilitated the success of our project included the collaboration of the Ministry of Health and 20 public health sector facilities, freely available clinical services for patients from rural and low-income households, and the abundance of solar energy at the equator. The study was done during the COVID-19 pandemic, showing the feasibility of implementing solar-powered O_2 under challenging conditions (ie, a country-wide transportation lockdown). Further discussion of the effect of the COVID-19 pandemic on the trial is available in the appendix (p 53).

Our primary analysis examined the 48 h mortality before and after randomisation, which represents an intention-to-treat analysis and follows the cluster-randomised design. Sensitivity analyses suggested that our findings were robust to alternative ways of classifying exposure to solar-powered O_2, adjustment for clinical covariates, and randomisation stratified by region. Alternative models with cluster-by-period and duration-by-treatment interaction terms also showed that the treatment effect remained significant. We continued enrolment until the pre-specified sample size was reached, rather than stopping the trial after the last solar-powered O_2 system

was installed. This choice resulted in a longer final step in the study (figure 1A) and a larger number of patients enrolled after randomisation. A sensitivity analysis on the subgroup of patients that would have been enrolled, had the trial been stopped after the last installation, showed similar results, which suggests that the decision to extend the trial to meet the pre-specified sample size did not affect the main findings of the study.

System failures occurred but affected less than 1% of study participants. Increased battery capacity would reduce system failures due to battery depletion but would increase the capital cost. Faults in the O_2 concentrator and circuitry also occurred, emphasising the need for ongoing equipment monitoring, maintenance, and repair.

Even after solar-powered O_2 was installed, 9·5% of patients did not receive solar-powered O_2 treatment; for 38·3% of those patients, this occurred when the number of patients admitted with hypoxaemia exceeded the number of available ports on the solar-powered O_2 concentrator. Increased capacity of the solar-powered O_2 system (eg, multiple concentrators) would reduce this occurrence but would increase capital costs. Urgent transfer to another facility was another common reason (33·6%) that available solar-powered O_2 was not used for hypoxaemic children. Improving O_2 availability does not fill all gaps in patient care at rural health facilities; a more comprehensive package of health service interventions would be needed to further reduce the need for referrals. Nonetheless, transfers decreased from 22·5% to 10·4% after installation of solar-powered O_2 (table 2).

Capacity building for the rational use of O_2 (ie, universal use of pulse oximetry, systematic titration of O_2 flowrate, and standardised weaning protocols) was implemented at the beginning of the trial and was in place for all children before and after randomisation. In a study in Nigeria, pulse oximetry improved O_2 practices before a full O_2 system was implemented and was associated with lower mortality among children with pneumonia.[17] The mortality reduction observed in our trial could not have been identified without training and O_2 protocols. Nonetheless, the stepped-wedge, cluster randomised design might allow separate measurement of the effects of capacity building and the solar-powered O_2 systems themselves. The asynchronous implementation of capacity building at the beginning of the trial and subsequent introduction of solar-powered O_2 equipment in a stepped manner suggests that the observed change in mortality was attributable to the solar-powered O_2 systems.

The capital costs of the solar-powered O_2 system was $12 800 for each health facility. Despite the life-saving benefit of solar-powered O_2, this capital cost might represent a barrier for resource-limited hospitals. From a limited societal perspective, the median ICER was estimated at $25 per DALY saved and $1490 per life saved. This was below the threshold for cost-effectiveness in 98% of simulations in a multiway sensitivity analysis. The ICER was higher than a previous estimate,[15] which can be explained by lower use of the solar-powered O_2 system (median 544 patients in our study *vs* 870 in the previous study) and lower baseline mortality in our study (6·0% in our study *vs* 8·9% in the previous study).[15] Solar-powered O_2 systems have the lowest ICER in facilities with low baseline O_2 availability, unreliable grid electricity, and high volume of hypoxaemic patients.[15] Solar-powered O_2 systems could be feasibly introduced at rural or remote health facilities in LMICs by local groups. Equipment (ie, photovoltaic cells, associated circuitry, and O_2 concentrators) and technical expertise for installation are now widely available in LMICs. Transportation of equipment and personnel (ie, an electrician) to the site might be challenging, but not impossible, for some remote or conflict-affected locations. We have successfully implemented solar-powered O_2 systems with philanthropic funding in challenging settings (ie, conflict zones) in the Democratic Republic of the Congo[13] and Somalia.[14]

Supplemental O_2 is generally a safe therapeutic, although toxicities are recognised. In a systematic review and meta-analysis,[27] among critically ill adults, liberal O_2 use with O_2 saturations above a range of 94% to 96% was associated with increased mortality. Among neonates, resuscitation with 100% O_2 might be associated with increased mortality.[28] We compared the frequency of recorded unsolicited adverse events in before and after randomisation and found no statistically significant differences. Systematic monitoring for specific toxicities in future studies would help to define the risks associated with supplemental O_2 therapy in children in LMICs. If

	Number of fixed effect parameters	Secular trend (p value)	Treatment effect adjusted OR (95% CI)	Treatment effect (p value)
Single parameter, calendar year*	1	0·39	0·47 (0·25–0·88)	0·018
Calendar year†	2	0·13	0·50 (0·27–0·91)	0·023
Categorical variable, 4 levels‡	3	0·054	0·52 (0·30–0·91)	0·025
Categorical variable, 5 levels‡	4	0·10	0·54 (0·30–0·99)	0·049
Categorical variable, 6 levels‡	5	0·13	0·52 (0·28–0·97)	0·040
Categorical variable, 7 levels‡	6	0·089	0·51 (0·28–0·94)	0·031
Categorical variable, 8 levels‡	7	0·080	0·57 (0·30–1·06)	0·078
Categorical variable, 9 levels‡	8	0·076	0·60 (0·32–1·14)	0·13
Categorical variable, 21 levels corresponding to steps§	20	0·14	0·60 (0·32–1·16)	0·13
Single parameter, linear, continuous¶	1	0·48	0·68 (0·35–1·34)	0·26

p values were derived from a likelihood ratio test. For secular trend, the test compared the full model with all parameters for secular trend to a reduced model without parameters for secular trend. For treatment effect, the test compared the full model to a reduced model without a predictor for treatment effect. OR=odds ratio. *Year-over-year OR between subsequent calendar years was constrained to a single fitted parameter. †Primary analysis, included for comparison with other models. ‡The cutoffs used to define bins for the categorical variable were chosen to align with steps in the trial, with roughly equal numbers of patients in each bin. §Model proposed by Hussey and Hughes,[22] the large number of dummy variables required might result in an overfitted model. ¶Time since study initiation was modelled as a continuous variable (one parameter).

Table 3: **Effect of assumptions for modeling secular trend (calendar time) on treatment effect (linear mixed-effects logistic regression model)**

the use of O_2 in clinical settings increases with increased availability, use of a pulse oximeter to guide therapy and careful following of protocols to titrate the flowrate according to need will be important.

Our study has several methodological limitations. Individual randomisation is not ethical for O_2 therapy; therefore, we relied on cluster randomisation with statistical adjustment for the random effect of the cluster in an LME model. Stepped-wedge implementation was also more feasible than a parallel arm design because the intervention involved infrastructure modifications.[22] In a sensitivity analysis (table 3), the treatment effect was not significant in the model proposed by Hussey and Hughes,[22] nor in the model with time included as a continuous variable, counted from the beginning of the trial. The confounding effects of calendar time are well recognised in stepped-wedge, cluster randomised trials and a variety of methods of statistical adjustment for calendar time have been used in the published literature.[29] We chose a parsimonious model using two parameters to model the secular trend; more complex parameterisations (ie, more than six parameters) resulted in wider CIs on the estimate of treatment effect (table 3). A larger study is needed to definitively exclude possible confounding effects of calendar time. Findings were also sensitive to exclusion of data from one influential site, which had the largest effect size. The study was not masked; however, the allocation (order of installation) was randomised and concealed (sequential sealed opaque envelopes) until 2 weeks before installation. Furthermore, the primary outcome of mortality was objective and unlikely to be affected by an absence of masking. Delays in installation meant that some patients in the group after randomisation did not receive solar-powered O_2. However, we did sensitivity analyses to account for the delays in installation and for patients who did not receive solar-powered O_2 after implementation.

Few previous studies have reported on the use of solar energy for O_2 generation.[11,12] Solar power can bridge the outages in grid electricity in LMICs.[11,26] Relative to fuel powered backup generators, solar energy can reduce operating costs,[15] pollution, and carbon footprint. Solar-powered O_2 is easy to use and has advantages over cylinder O_2, reducing transportation costs and circumventing the need for careful stock management. Given the magnitude of paediatric pneumonia deaths (740 000 per year worldwide), solar-powered O_2 delivery has the potential for global impact if taken to scale across Africa and Asia, where most pneumonia deaths occur.[1]

Our results suggest that solar-powered O_2 is a lifesaving and cost-effective intervention for the treatment of children with hypoxaemia in low-resource hospitals, with the limitation that our findings were sensitive to the parameterisation of secular trend in the statistical model. Solar-powered O_2 addresses a crucial gap in access to O_2 across LMICs and has the potential to reduce preventable childhood pneumonia deaths.

Contributors

ALC devised the idea of solar-powered O_2 delivery. SN, ALC, ROO, and MTH designed the study. ROO and MTH obtained ethical approval for the trial. MTH obtained funding and did the data collection. MTH and NC did the data analysis and wrote the paper. BEL, AS, PM, ROO, and MTH, SN, QM, and LLH supervised the study. OC and JA guided site selection and acted as a liaison with the Ministry of Health of Uganda. NC, SN, QM, ALC, LLH, OC, AJ, BEL, AS, PM, and ROO critically reviewed the manuscript. NC and MTH accessed and verified the data. All authors had full access to the data in the study and had final responsibility to submit the manuscript for publication.

Declaration of interests

MH, ROO, SN, and ALC are listed as inventors on a provisional patent for solar-powered O_2 delivery, owned by the Governors of the University of Alberta (New International [PCT] Patent Application Serial number PCT/CA2018/051151). All other authors declare no competing interests.

Data sharing

Data will be made available upon reasonable request to the corresponding author.

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