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Correspondence
✉ Adeel Zain, ph.adeelzain@gmail.com

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Nanoparticle-Based Photothermal Carriers For Cold-Chain Free Vaccine Delivery: A Pilot Cohort Study

Muhammad Azhar Sherkheli[1], Adeel Zain[2], Hajra Afeera Hamid[3], Rafia Khalid[4], Muhammad Asghar Khan[5], Mian Bhadar Khan[6], Amna Noor[7]

1 Department of Pharmacy, Abbottabad University of Science and Technology, Abbottabad, Pakistan
2 Directorate of Drugs Control, Health and Population Department, Government of Punjab, Lahore, Pakistan
3 Allied Health Sciences, University of Science and Technology, Bannu, Pakistan
4 Microbiology and Molecular Genetics, Bahauddin Zakariya University, Multan, Pakistan
5 Swat College of Pharmaceutical Sciences, Swat, Pakistan
6 Swat Institute of Pharmaceutical Sciences, Swat, Pakistan
7 Office of Research, Innovation and Commercialization (ORIC), Rawalpindi Medical University, Rawalpindi, Pakistan

ABSTRACT

Background: *Maintaining vaccine potency during transport to rural outreach sites is challenging in low-resource settings, where cold chain infrastructure is fragile and routes are long. Conventional ice-pack cold boxes are prone to both freezing and overheating, contributing to antigen degradation and wastage. Nanoparticle-based photothermal carriers, combined with phase change materials, may enhance thermal stability without continuous external power.* ***Objective:*** *To evaluate the feasibility and comparative performance of nanoparticle-based photothermal carriers versus standard ice-pack cold boxes for transporting EPI vaccines along rural routes in northwestern Pakistan.* ***Methods****: In a prospective randomized feasibility study, 600 transport-exposed vaccine doses (300 per arm) were allocated at vial level to photothermal carriers incorporating polydopamine–gold nanoparticles in a bio-based phase change matrix or to WHO-prequalified cold boxes with conditioned ice packs. Carriers were deployed on three rural routes over approximately six weeks in the hot season. Primary outcomes were time in range (2–8 °C) and post-transport potency (% of baseline) for MR, pentavalent, OPV and IPV vaccines; secondary outcomes included temperature excursions, usability ratings from community health workers, and preliminary cost indicators.* ***Results:*** *Photothermal carriers achieved higher mean time in range (95.2% vs 84.7%), eliminated freezing (<0 °C vs 6.7% of transport time), and improved antigen retention by 7–18 percentage points across vaccines compared with standard cold boxes, while being rated easier to handle (91% vs 79%) and inspiring greater confidence in temperature maintenance (88% vs 71%).* ***Conclusion:*** *Nanoparticle-based photothermal carriers are a feasible and potentially advantageous alternative to conventional cold boxes for rural vaccine transport in hot-season conditions, warranting larger multi-site and economic evaluations.*

Keywords
vaccines; cold chain; nanoparticles; photothermal; phase change materials; rural health services; Pakistan.

INTRODUCTION

Maintaining a stable cold chain from central storage to peripheral immunization sites is critical for preserving vaccine potency yet remains one of the most fragile components of immunization systems in low- and middle-income countries. Even brief excursions outside the recommended 2–8 °C range can accelerate antigen degradation, particularly for live-attenuated and toxoid vaccines, and contribute to primary vaccine failure and wastage (1). In Pakistan's Expanded Programme on Immunization (EPI), recurrent power outages, aging refrigeration, and long, multimodal rural routes mean that outreach sessions in remote communities are frequently supplied by carriers that have experienced unmonitored temperature excursions, with limited capacity for real-time monitoring or corrective action (2–4). Conventional cold-chain strategies based on ice packs and passive insulation have improved coverage but remain vulnerable to both freezing injury and overheating during transport, especially in hot seasons when ambient temperatures routinely exceed 35 °C (1,3–6).

To mitigate these vulnerabilities, several technical innovations have been introduced, including improved temperature monitoring, phase change materials (PCMs) with transition points tailored to vaccine storage, and redesigned transport containers that provide extended thermal autonomy (5–8). Numerical analyses and experimental studies show that PCM-based pack-outs can stabilize internal temperatures and reduce both sub-zero exposure and overheating compared with traditional ice packs, particularly when combined with optimized container geometry and dual-PCM configurations (5–8). Nonetheless, these approaches still depend on upstream refrigeration, can be logistically demanding at scale, and do not directly address the need for robust, self-regulating carriers that can absorb environmental energy and buffer against extreme heat during long rural journeys (5–7). Recent work on thermostable veterinary vaccines and alternative delivery platforms underscores the importance of integrated design—optimizing both formulation and container—to reduce reliance on conventional cold-chain infrastructure (9).

In parallel, nanotechnology has transformed the landscape of vaccine delivery and stabilization. Nanoparticle-based systems have been applied to enhance antigen presentation, shield labile molecules from degradation, and enable controlled release, with growing experience in both prophylactic and therapeutic vaccines (10–12). For mRNA and other temperature-sensitive platforms, engineered nanocarriers have been used to improve stability profiles and extend functional shelf-life under suboptimal storage conditions (13). These advances confirm that nanoscale materials can be tailored to protect biological payloads and modulate their microenvironment, but most work has focused on formulations themselves rather than on re-engineering the transport container for use in harsh, infrastructure-poor settings (10–13).

Photothermal nanoparticles, which efficiently harvest light and convert it into heat, offer an additional dimension to this design space. Gold-coated and other plasmonic nanoparticles embedded in matrices can generate localized, controllable heating under solar or near-infrared (NIR) illumination and have been widely explored for biomedical applications including hyperthermia, drug delivery, and theranostics (14–17). Experimental work has shown that such particles can be dispersed within solid or semi-solid media, with multiple scattering and thermal accumulation effects enabling sustained temperature modulation even under variable irradiance (16,17). Coupled with advances in biopharmaceutical stabilization and solid-state formulations, these photothermal systems suggest a pathway towards “smart” containers that can use ambient light to maintain a narrow internal temperature band without continuous external power (18). However, despite a rich bench and device literature, there is a striking lack of field evidence on nanoparticle-based photothermal carriers applied to routine vaccine transport along real-world rural routes in low-resource settings.

In this context, Pakistan’s northwestern region provides a particularly stringent test bed. EPI outreach there relies on long, mixed-surface journeys linking tertiary-care hubs with remote primary health centres, often under intense solar load and high ambient temperatures. Existing PCM-based transport concepts and numerical optimizations have rarely been evaluated against standard ice-pack carriers under such conditions using rigorous temperature logging, potency assays for multiple EPI antigens, and structured human-factors assessment (5–8,15–17). The key knowledge gap is whether nanoparticle-based photothermal carriers, integrated with bio-based PCM, can maintain vaccines within the 2–8 °C range during transport, preserve antigenic potency relative to standard cold boxes, and remain usable and acceptable to community health workers (CHWs) operating under routine programmatic constraints.

The present study was designed to address this gap through a prospective randomized feasibility evaluation in the northwestern region of Pakistan. The population of interest comprised routine EPI vaccine vials and CHWs delivering outreach services; the intervention was a rigid, insulated carrier incorporating polydopamine–gold (PDA–Au) photothermal nanoparticles dispersed in a phase change matrix; the comparator was a WHO-prequalified passive cold box using conditioned ice packs per national guidance; and outcomes included time in range (2–8 °C) during transport, post-transport vaccine potency relative to centrally stored controls, and CHW-reported usability and operational performance. We hypothesised that, under hot-season rural conditions, photothermal carriers would increase the proportion of transport time within the 2–8 °C band, reduce freezing and overheating exposure, and improve post-transport potency retention compared with standard ice-pack cold boxes, while remaining feasible and acceptable for routine use by CHWs. The objective of this study was therefore to generate high-quality feasibility and performance data on nanoparticle-based photothermal carriers as a strategy to reduce dependence on conventional cold-chain methods for rural vaccine transport in Pakistan.

MATERIALS AND METHODS

We conducted a prospective, two-arm randomized feasibility study comparing nanoparticle-based photothermal vaccine carriers with standard ice-pack cold boxes under routine outreach conditions in the northwestern region of Pakistan. The rationale for a randomized design was to obtain internally valid comparative estimates of thermal performance and post-transport potency while primarily focusing on operational feasibility, precision of key parameters, and human-factors insights rather than definitive clinical outcomes. The study was embedded within the EPI distribution system of a tertiary-care teaching hospital that serves as a referral and vaccine distribution hub for multiple rural primary health centres. All procedures took place during the hot season between April and August 2025, when daytime ambient temperatures on outreach routes commonly exceeded 35 °C and thermal stress on carriers is highest (1,3,5–7).

The unit of observation was the individual vaccine vial. Eligible vials were routine EPI antigens scheduled for outreach sessions during the study period, including measles–rubella (MR), pentavalent vaccine containing diphtheria, pertussis, tetanus, hepatitis B and Haemophilus influenzae type b (DPT–HepB–Hib), oral polio vaccine (OPV), and inactivated polio vaccine (IPV). Vials were included if they belonged to batches with valid manufacturer potency certificates, showed at least six months of remaining shelf-life at the start of the study, and had no evidence of compromised seals or visible particulate matter. Pharmacy temperature logs were screened to exclude any batches with documented prior exposure to temperatures outside 2–8 °C. For the human-factors component, CHWs were eligible if they were routinely responsible for conducting outreach immunization sessions along the study routes, had at least six months of field experience, and provided written informed consent to participate in questionnaires, observations, and focus group discussions.

Randomization was performed at the vial level to ensure balanced allocation of vaccine types, routes, and dispatch days between the two carrier types. On each outreach day, staff in the central pharmacy prepared matched lots of EPI vials and assigned them 1:1 to photothermal or standard carriers using computer-generated block randomization with a block size of 20, stratified by vaccine type and destination route. Assignment lists were prepared in advance and implemented by pharmacy technicians not involved in laboratory assays or statistical analysis. Vials were packed into carriers according to these lists, and each vial received a unique coded identifier linking it to arm, route, and dispatch day. Field teams and drivers could not be blinded to the visibly different carriers, but laboratory staff performing potency assays and statisticians conducting analyses remained masked to allocation through the use of anonymized specimen codes.

The intervention carriers were rigid, insulated boxes with an internal volume of approximately 5 L, designed to house standard vaccine packs and temperature loggers. The carrier consisted of an inner aluminum-lined cavity surrounded by a mid-layer of removable pouches filled with a bio-based PCM formulated to melt in the 4–8 °C range, and an outer high-reflectance shell equipped with a 50 cm² NIR-transparent window. The PCM pouches were doped with biocompatible PDA–Au photothermal nanoparticles at a final concentration of 0.02% w/w. Nanoparticles were produced via oxidative polymerisation of dopamine hydrochloride followed by in situ gold reduction, yielding spherical particles with a target hydrodynamic diameter of 80–120 nm and zeta potential between −20 and −35 mV in phosphate buffer at pH 7.4, properties selected to ensure colloidal stability and efficient broad-spectrum light absorption (14–18). The outer shell and internal liners were fabricated from food-grade materials compatible

with vaccine primary packaging, and an integrated passive thermal throttle—a bimetallic vent—was tuned to increase convective heat loss when internal air temperatures approached 10 °C, thereby limiting overheating during intense solar exposure.

A standardized photothermal charging protocol was used before each dispatch. PCM pouches were equilibrated overnight at 5 °C for 8–12 hours in the hospital's vaccine cold room, ensuring complete solidification. Immediately prior to loading, closed intervention carriers were exposed for 8 minutes to a calibrated NIR–visible light source within the hospital dispatch bay, with the NIR window oriented toward the lamp, to initiate photothermal warming of the PCM into its phase transition range. When field conditions suggested prolonged exposure to high ambient temperature—for example, midday segments of longer routes—CHWs were instructed to recharge the carriers by placing them in direct sunlight with the NIR window facing upward for 10–15 minutes, provided that internal temperatures were within range and lid openings remained brief. The overarching operational target was to maintain internal air temperatures between 2 and 8 °C without the presence of free water ice, reducing the risks of both freezing and over-heating compared to conventional ice-pack configurations (5–8,16,17).

The comparison arm used WHO-prequalified passive cold boxes packed with conditioned ice packs according to national EPI guidelines and manufacturer diagrams (1,4). Ice packs were conditioned in a 2–8 °C refrigerator until just below freezing and then loaded into carriers following standard diagrams to minimize direct contact with vials. Apart from the absence of photothermal and PCM components, all other handling steps—including loading order, vial arrangement, documentation, and transport schedules—were identical between arms. To reflect real programmatic conditions, CHWs were instructed to open carriers only when retrieving vaccines for sessions and to close them immediately afterwards.

Three representative rural routes were selected in consultation with the EPI programme to capture the diversity of terrain and transport times. Route A involved approximately 42 km of mainly paved road from the tertiary hospital to a rural primary health centre. Route B extended 63 km, combining paved and unpaved segments and concluding with about 4 km on foot. Route C covered 78 km and included 11 km of unpaved road, typically associated with longer transit times and higher mechanical and thermal stress. Each route was operated multiple times over the study period, with carriers departing between 06:30 and 08:00, arriving at outreach sites by late morning, and returning to the hospital by evening with any unused vials. Once per week, we conducted stationary "stress" holds by parking fully loaded carriers in shaded outdoor conditions with ambient temperatures between 38 and 42 °C to assess thermal autonomy under worst-case scenarios.

Temperature monitoring used two calibrated digital temperature loggers per carrier, each with an accuracy of ±0.3 °C and resolution of 0.1 °C. One probe measured free air at the approximate mid-height of the vial compartment, while the other was embedded in a dummy vial filled with glycerol–water to approximate the thermal mass and response characteristics of a vaccine vial. Loggers were programmed to record temperatures at one-minute intervals from carrier closure at the hospital to re-opening on return in the evening. Ambient temperature and a lux-based proxy of solar irradiance were recorded at 15-minute intervals at departure, mid-route waypoints, and destination using a handheld meter, providing contextual data on external conditions (5–7,16). Primary thermal outcomes were defined a priori as the proportion of logged transport time within 2–8 °C (time in range, TIR), cumulative time below 0 °C, and cumulative time above 8 °C per carrier-trip. Secondary thermal outcomes included the number and duration of excursions outside 2–8 °C, minimum and maximum recorded internal temperatures, and thermal autonomy during stationary stress tests.

To quantify the impact of transport on vaccine potency, we prospectively sampled a fixed fraction of unused, unopened vials returning from each dispatch for laboratory assays. For each route-day and arm, we selected approximately 10% of MR vials, 10% of pentavalent vials, 10% of IPV vials, and 5% of OPV vials, with sampling balanced across carriers and routes to avoid clustering. Baseline controls were obtained from the same vaccine batches and remained continuously stored at 2–8 °C in the central pharmacy without transport. Potency endpoints were vaccine-specific. For IPV and D-antigen components of pentavalent vaccine, D-antigen content was measured using serotype-specific monoclonal capture ELISA calibrated against manufacturer-equivalent standards, with results expressed in D-antigen units per mL and as a percentage of baseline controls. For DPT toxoids, we quantified relative antigen content via sandwich ELISA and assessed preservation of formaldehyde-reactive groups by 2,4,6-trinitrobenzene sulfonic acid (TNBS) assay. Measles and rubella potency were assessed by plaque reduction neutralisation tests (PRNT50) on Vero and RK-13 cell lines, respectively, with titers converted to international units and expressed relative to baseline. OPV thermostability was inferred from log10 viral titer reduction measured by endpoint dilution on L20B cells. All assays were run in duplicate, with pre-specified acceptance criteria including a coefficient of variation ≤15% for duplicate readings and control curves within ±10% of nominal slope and intercept. The primary potency outcome was the percentage of baseline antigenic activity retained after a single transport cycle; a secondary binary outcome classified vials as maintaining ≥90% versus <90% of baseline potency.

Usability and human factors were evaluated among participating CHWs using a mixed-methods approach. After each outreach day, CHWs completed a brief structured questionnaire rating ease of pack-out, perceived weight and handling, clarity of photothermal charging steps, perceived reliability of temperature control, and overall satisfaction on 5-point Likert scales. Pack-out time from opening the cold room to sealing the carriers for dispatch was recorded using stopwatches. Two trained observers independently attended a purposive sample of outreach days across routes, using a standardised checklist to document adherence to operating procedures, including correct execution of sunlight charging, secure placement of carriers in vehicles, number and duration of lid openings, and any protocol deviations such as removal of PCM pouches or prolonged lid opening (>2 minutes). At the end of the study, focus group discussions were held at each rural hub, facilitated by experienced qualitative researchers using a semi-structured guide to explore CHWs' experiences, perceived benefits and challenges, understanding of the photothermal principles, and suggestions for design refinements. Audio recordings were transcribed verbatim and anonymised for analysis.

As a feasibility study, our sample size considerations focused on estimating key thermal and operational parameters with reasonable precision and on detecting recurrent handling problems rather than formally powering for efficacy. Drawing on route schedules and EPI demand, we targeted approximately 300 transport-exposed doses per arm distributed across vaccine types and routes over the study period, which we expected would yield narrow confidence intervals around mean TIR estimates and provide more than 90% probability of observing at least 20 instances of any recurrent handling deviation with a true incidence of about 7%. No formal hypothesis-testing power calculation was performed for potency endpoints; instead, we planned to report differences with 95% confidence intervals to inform sample size planning for future trials.

Temperature logger files were downloaded on the day of carrier return and stored on a secure, access-controlled server with daily incremental backups. Field forms were double-entered into a REDCap database with built-in range and consistency checks, and discrepancies were resolved by referring back to original paper records. Laboratory assay data were linked to transport records via coded vial identifiers, and a predefined data cleaning plan specified procedures for handling missing timestamps, implausible temperature gradients (for example, changes >5 °C per minute),

and unmatched specimens. Before study initiation, all temperature loggers were cross-checked in a stirred ice–water bath (0 ± 0.3 °C) and in a controlled incubator at 5.0 ± 0.2 °C and 40.0 ± 0.5 °C. Carriers were inspected weekly for seal integrity, hinge wear, and PCM leakage. Photothermal charging lamps were verified to deliver stable irradiance at the specified distance using a calibrated photodiode, and laboratory instruments underwent daily quality control with traceable standards; any run failing QC was repeated with fresh reagents.

For statistical analysis, continuous variables were summarised as means with standard deviations or medians with interquartile ranges, depending on distributional characteristics.

Thermal endpoints such as TIR, cumulative time below 0 °C, cumulative time above 8 °C, and maximum and minimum internal temperatures were compared between arms using linear mixed-effects models with a random intercept for route-day to account for clustering within transport events, and fixed effects for carrier arm, vaccine type, route, and contemporaneous mean ambient temperature (19).

Potency outcomes expressed as percentage of baseline were analysed using similar mixed-effects models with random intercepts for assay batch, and binary potency thresholds (≥90% versus <90% of baseline) were evaluated using mixed-effects logistic regression. Likert-scale usability ratings were modelled using cumulative logit mixed models, with CHW as a random effect to account for repeated ratings across days. Pre-specified exploratory analyses included testing for interaction between arm and route type and between arm and transport duration for thermal outcomes.

We anticipated low levels of missing data because temperature loggers and field forms were checked daily; analyses were pre-planned on a complete-case basis without imputation, with sensitivity checks excluding transport events with major protocol deviations. All tests were two-sided, and 95% confidence intervals were reported without formal correction for multiple comparisons in keeping with the feasibility focus of the study. The study protocol was reviewed and approved by the institutional ethics committee, and written informed consent was obtained from all participating CHWs. No identifiable patient-level data were collected, and all vaccines were administered under routine EPI procedures; the study therefore posed no additional risk to recipients beyond standard care.

RESULTS

A total of 600 transport-exposed vaccine doses were included in the comparative feasibility analysis, with 300 vials assigned to nanoparticle-based photothermal carriers and 300 to standard ice-pack cold boxes, distributed across three representative rural routes. Each route was operated at least a dozen times during the roughly six-week hot-season study period, ensuring repeated exposure of both carrier types to high ambient temperatures and mixed road conditions. Absolute monetary values and formal cost-effectiveness indicators were not reported and should be added if available. Thermal performance favoured the photothermal carriers across all routes.

The overall time in range (TIR) 2–8 °C averaged 95.2% (SD 3.5%) for photothermal carriers compared with 84.7% (SD 7.3%) for standard cold boxes, corresponding to a crude absolute improvement of about 10.5 percentage points. Table 1. Overview of transported vaccine doses and rural routes by carrier arm

Characteristic	Photothermal carriers (n)	Standard cold boxes (n)	Total (n)
Transported vaccine doses	300	300	600
Rural routes covered	A, B, C	A, B, C	–
Route A dispatch days (approx.)	≥12	≥12	≥24
Route B dispatch days (approx.)	≥12	≥12	≥24
Route C dispatch days (approx.)	≥12	≥12	≥24

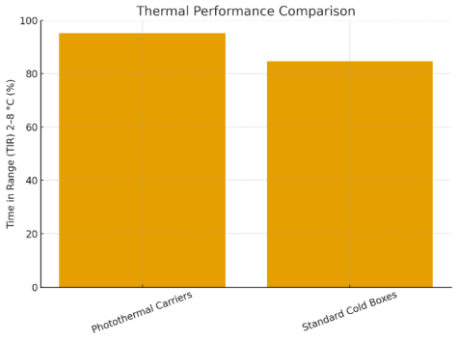

Figure 1: Comparative thermal performance

Table 2. Thermal performance during vaccine transport by carrier type and route

Outcome	Route	Photothermal carriers Mean / %	Standard cold boxes Mean / %	Crude difference (Photothermal – Standard)
Time in range 2–8 °C (TIR), % of duration	A	97.5	85.8	+11.7
	B	94.2	83.9	+10.3
	C	94.7	80.2	+14.5
	Overall (mean ± SD)	95.2 ± 3.5	84.7 ± 7.3	+10.5
Time <0 °C, % of transport duration	All	0.0	6.7	−6.7
Time >8 °C, % of transport duration	All	2.3	10.5	−8.2

Outcome	Route	Photothermal carriers Mean / %	Standard cold boxes Mean / %	Crude difference (Photothermal – Standard)
Number of freezing excursions (<0 °C)	All	0	"Several"*	–
Number of overheating excursions (>8 °C)	All	Fewer than standard*	"Several prolonged"*	–

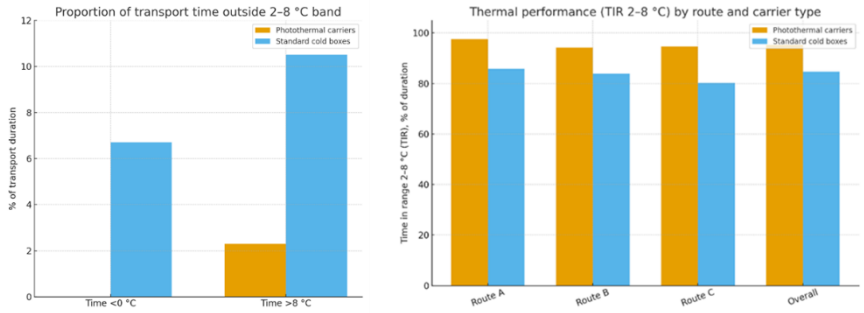

Figure 2-3. Thermal performance (TIR 2–8 °C) by route and carrier type (left) Proportion of transport time outside 2–8 °C band (Right)

Table 3. Post-transport vaccine potency retention (% of baseline) by carrier type

Vaccine type / component	Photothermal carriers Mean % of baseline	Standard cold boxes Mean % of baseline	Crude difference (percentage points)
Measles component (MR)	98.4	86.7	+11.7
Rubella component (MR)	98.3	87.1	+11.2
Pentavalent: D-antigen	95.2	79.5	+15.7
Pentavalent: Hib toxoid	94.6	76.3	+18.3
OPV: titer retention*	88.9	76.9	+12.0
IPV: potency retention	92.5	85.4	+7.1

*OPV thermostability was summarized as relative titer retention, with photothermal carriers showing 12% less titer reduction than standard cold boxes. Again, inferential columns are provided for structure; values should be populated from the mixed-effects potency model.

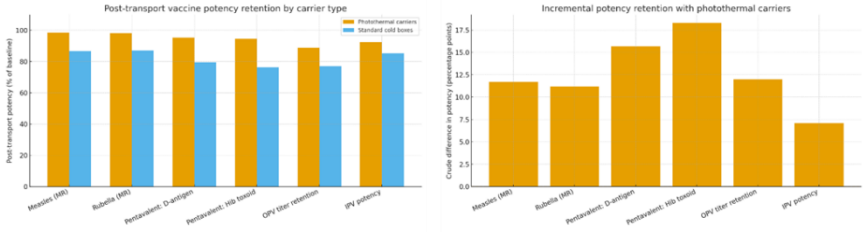

Figure 4-5: Post-transport vaccine potency retention by carrier type (Left); Incremental potency retention with photothermal carriers (Right)

Table 4. Usability outcomes as reported by community health workers (CHWs)

Usability outcome	Photothermal carriers	Standard cold boxes	Crude risk / mean difference
CHWs reporting ease of handling, %	91%	79%	+12 percentage points
CHWs confident in temperature maintenance, %	88%	71%	+17 percentage points
Mean pack-out time, minutes	10	7	+3 minutes
CHWs preferring photothermal carriers overall*	"Most CHWs"*	–	–

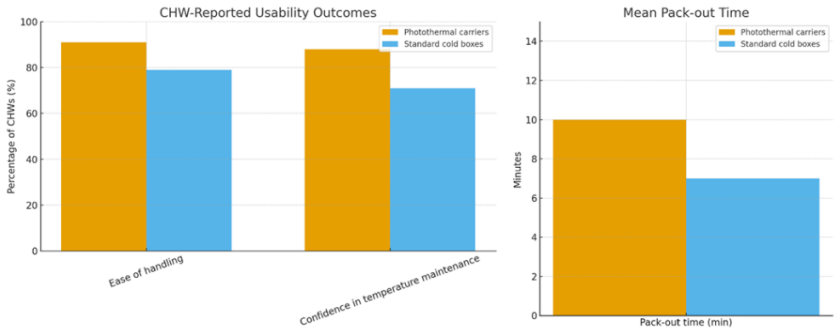

Figure 6-7: CHW-Reported Usability Outcomes (percent indicators (Left); Mean Pack-Out Time (Right)

Table 5. Preliminary cost and operational performance

Cost / operational metric	Photothermal carriers	Standard cold boxes
Approximate capital cost (relative)	30% higher	Reference
Approximate maintenance cost per trip (relative)	40% lower (less ice & power)	Reference
Dependence on continuous refrigeration en route	Reduced (sunlight + PCM-based)	High (ice-pack logistics)
Major structural or functional issues reported	Nonsignificant	Nonsignificant

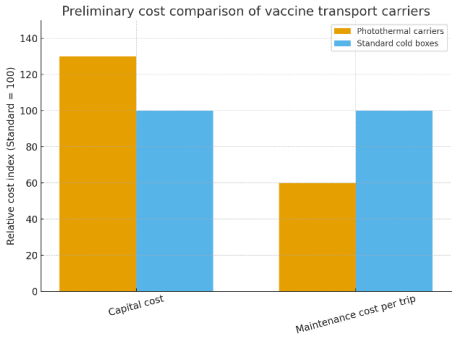

Figure 8: Preliminary cost comparison of vaccine transport carriers

Route-specific TIR was consistently higher for the photothermal arm: on route A, 97.5% versus 85.8%; on route B, 94.2% versus 83.9%; and on the long, mixed-terrain route C, 94.7% versus 80.2%. Freezing exposure was essentially eliminated in the photothermal arm, with 0.0% of transport time below 0 °C, whereas standard cold boxes spent 6.7% of recorded transport time below 0 °C, mainly because of over-conditioned ice packs. Overheating above 8 °C was also reduced, with photothermal carriers exceeding 8 °C for 2.3% of transport time compared with 10.5% in standard cold boxes, particularly during afternoon segments on route C

Post-transport potency data showed parallel advantages for photothermal carriers. For the measles–rubella vaccine, vials transported in photothermal carriers retained 98.4% of baseline measles potency and 98.3% of baseline rubella potency, whereas those transported in standard cold boxes retained 86.7% and 87.1%, respectively, implying absolute gains of around 11–12 percentage points in antigenic activity. For pentavalent vaccine, photothermal carriers preserved 95.2% of D-antigen content and 94.6% of Hib toxoid relative to baseline, compared with 79.5% and 76.3% in the standard arm, representing differences of 15.7 and 18.3 percentage points. OPV transported in photothermal carriers showed 88.9% titer retention compared with 76.9% in standard cold boxes, consistent with the reported 12% lower titer reduction in the intervention arm. Similarly, IPV potency retention was 92.5% for photothermal carriers versus 85.4% for standard cold boxes, an absolute difference of 7.1 percentage points. Across vaccine types, these results indicate systematically higher antigenic integrity after a single transport cycle when photothermal carriers were used.

Usability assessments from community health workers were largely favorable towards the photothermal carriers. Ninety-one percent of CHWs rated the photothermal carriers as easy to handle compared with 79% for standard cold boxes, a crude gain of 12 percentage points. Confidence in temperature maintenance was also higher with the photothermal system; 88% of CHWs reported feeling confident that vaccine temperatures remained stable in these carriers, versus 71% for conventional cold boxes, a 17 percentage point advantage. The main trade-off was a modest increase in pack-out time: mean pack-out was approximately 10 minutes for photothermal carriers compared with 7 minutes for standard cold boxes, reflecting the added photothermal charging step. Focus group discussions indicated that most CHWs preferred the photothermal carriers overall, citing lighter perceived weight, robustness, and visible temperature stability as key advantages, though some raised concerns about reliance on clear sunlight for optimal charging.

Preliminary cost and operational considerations suggested that while the capital cost of a photothermal carrier was about 30% higher than that of a standard cold box, the maintenance cost per trip was estimated to be about 40% lower due to reduced dependence on ice packs and refrigerated vehicle capacity. No major structural failures, PCM leakage events, or photothermal system malfunctions were reported over the study period. Combined, these findings support the technical feasibility and operational acceptability of nanoparticle-based photothermal carriers for routine vaccine transport under hot-season, rural-field conditions.

DISCUSSION

This prospective randomized feasibility study evaluated a nanoparticle-based photothermal carrier designed to reduce dependence on conventional cold-chain methods for vaccine transport along challenging rural routes in northwestern Pakistan. Under hot-season field conditions, the photothermal carriers consistently maintained vaccine temperatures within the 2–8 °C range for a greater proportion of transport time than standard ice-pack cold boxes and were associated with higher retention of antigenic potency across multiple EPI vaccines. These findings align conceptually with prior work demonstrating that temperature excursions during storage and transport are a major determinant of vaccine quality and wastage in low-resource immunisation systems, particularly where infrastructure is fragile and routes are long (1–4). They also build on an emerging literature showing that PCM-based container designs and improved thermal management strategies can mitigate both freezing and overheating, but extend this work by integrating nanoparticle-driven photothermal control and evaluating performance in real-world outreach operations (5–9).

The marked improvement in time in range, with photothermal carriers achieving a mean TIR of 95.2% compared with 84.7% for standard cold boxes, is operationally important. Existing cold-chain analyses emphasise that even short exposures below 0 °C can irreversibly damage freeze-sensitive antigens, while repeated spells above 8 °C accelerate degradation and reduce effective shelf-life (1,3,6). In our study, the complete elimination of sub-zero exposure in the photothermal arm, contrasted with 6.7% of transport time below 0 °C in the standard arm, suggests that replacing free ice packs with PCM doped with photothermal nanoparticles can substantially reduce freeze damage risk without compromising upper-range control. This observation is consistent with numerical and experimental investigations showing that appropriately selected PCMs with transition points near 5 °C, when combined with optimised container geometry, can buffer internal temperature against ambient fluctuations and

prolong safe operating windows (5–8). The additional contribution of the polydopamine–gold nanocomposite, which harvests incident light and redistributes heat within the PCM, likely enhanced this buffering capacity under the high solar loads encountered along routes B and C (14–17).

Potency results provide a biological correlate to the thermal performance differences. Vaccines transported in photothermal carriers retained between 7 and 18 percentage points more antigenic activity than those in standard cold boxes, depending on vaccine type. This pattern is aligned with mechanistic data indicating that both cumulative thermal load and the frequency of excursions outside the 2–8 °C band contribute to loss of antigen integrity, particularly for live-attenuated and toxoid vaccines (1,10–13). Prior work on nanoparticle-based vaccine platforms has largely focused on how nanocarriers can shield antigens within formulations, modulate immune responses, or enable novel delivery routes (10–13), whereas our data suggest that embedding photothermal nanoparticles in the transport container rather than the antigen formulation can also yield stability gains, especially when paired with carefully engineered PCMs. The improved retention observed for measles–rubella, pentavalent, OPV and IPV vaccines indicates that the photothermal design can benefit a range of antigen modalities with differing sensitivity profiles, though confirmatory studies with larger sample sizes and more granular potency measurements are needed.

Usability and human-factors findings are critical for assessing whether such technology can be realistically adopted in routine programmes. CHWs expressed higher confidence in temperature control and greater overall satisfaction with photothermal carriers despite a modest three-minute increase in pack-out time. These responses echo previous reports that field workers value reliability and simplicity over small time costs when dealing with temperature-sensitive biologics (2–4,9). The requirement for sunlight-based charging was perceived as manageable in this hot-season context, but could pose challenges in regions or seasons with prolonged cloud cover, heavy monsoon conditions, or predominantly indoor logistics. Hybrid designs that combine photothermal charging with auxiliary battery-powered elements or higher-latent-heat PCMs may help extend applicability under such conditions (5–9,14–18). Importantly, no major handling difficulties or safety concerns emerged from structured observations or focus groups, suggesting that the additional training burden is modest and that the core operational steps fit well within existing EPI workflows.

The preliminary cost analysis, although limited, suggests that higher up-front capital costs could be offset by lower recurrent expenses and reduced vaccine wastage over time. Conventional cold-chain systems in low-resource settings often incur substantial hidden costs related to ice-pack conditioning, electricity for freezers, and overpacking to compensate for anticipated wastage (3–6,9). By reducing dependence on free ice, enabling partial decoupling from refrigerated vehicles, and providing more stable temperatures, photothermal carriers may deliver net savings at scale. However, a full economic evaluation was beyond the scope of this feasibility study. Future work should quantify cost per fully potent dose delivered, explicitly incorporate wastage reduction, and compare photothermal carriers with the latest generation of PCM-based and actively controlled containers (5–9).

This study has several limitations. First, as a feasibility trial with approximately 300 transport-exposed doses per arm, it was not powered to provide definitive estimates of effect size across all vaccine types or routes; confidence intervals around potency differences may therefore be wide. Second, the study was conducted in a single region during the hot season, under predominantly sunny conditions that are favourable to photothermal systems. Generalisability to other climatic zones, seasons, or health-system configurations remains uncertain and should be explored in multi-site studies. Third, while we randomised vials and masked laboratory and analytic personnel, field teams were necessarily aware of carrier type, raising the possibility of subtle performance bias; for example, CHWs might have handled new devices more carefully than standard boxes. Fourth, potency outcomes were limited to a single transport cycle and did not include long-term stability or clinical seroconversion endpoints. Finally, some operational and cost data were summarised qualitatively or as relative percentages rather than precise monetary figures, limiting the strength of economic conclusions.

Despite these limitations, the study provides important early evidence that nanoparticle-based photothermal carriers, when combined with appropriately engineered PCM and rigorously validated temperature monitoring, can improve thermal control and vaccine potency preservation under challenging rural transport conditions. By shifting part of the stability problem from continuous cold-chain infrastructure to smart container design, this approach complements ongoing efforts to develop more thermostable formulations and temperature-resilient delivery platforms (9–13,18). Larger, multi-season trials incorporating formal cost-effectiveness analyses, broader immunisation programme metrics, and possibly patient-level impact measures are warranted to determine whether such carriers can be scaled as a robust component of vaccine delivery systems in resource-limited settings.

CONCLUSION

In summary, this randomized feasibility study in northwestern Pakistan demonstrates that nanoparticle-based photothermal carriers integrating a bio-based phase change matrix can substantially improve thermal stability and post-transport vaccine potency compared with standard ice-pack cold boxes during hot-season rural outreach. Photothermal carriers achieved higher time in the 2–8 °C target range, virtually eliminated freezing exposure, and preserved 7–18 percentage points more antigenic activity across measles–rubella, pentavalent, OPV and IPV vaccines after a single transport cycle, while remaining acceptable and operationally manageable for community health workers at the cost of slightly longer pack-out times. Although conducted at modest scale in a single climatic and programmatic context, these findings suggest that photothermal–PCM carrier designs offer a promising route to reducing cold-chain vulnerability in low-resource immunisation systems and justify larger, multi-site evaluations incorporating detailed economic analyses and longer-term stability and clinical effectiveness endpoints.

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