

Increasing measles vaccination coverage with preventive small quantity lipid-based nutrient supplementation in children aged 6 to 23 months: NutriVax-Measles, a pediatric pragmatic superiority parallel cluster-randomized controlled trial in Yobe State, northern Nigeria

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

This is a clearly written and well-presented manuscript reporting the results of a cluster randomised trial of a strategy to integrate nutritional supplementation with immunisation aiming to improving uptake of vaccine uptake.

MAJOR COMMENTS

A key consideration is equipoise and an ethical concern.

The authors state that WHO guidance strongly recommends SQ-LNS in food-insecure contexts and it has also been included in recommendations to optimise health and growth. The trial setting is characterised by high prevalence of malnutrition in children. There are two concerns:

1) it is ethical to have a control arm that does not provide the supplementation when there is i) scientific evidence for ii) recommendation for iii) contextual need (high prevalence of malnutrition) in the control arm. I note that few households were using RUTF and RUSF

2) is the trial aiming to interrogate an integration strategy (i.e. vaccination with supplementation) or the use of SQ-LNS as an incentive. While they may at first appear to be the same, they are not. It would appear from the introduction that the aim is to investigate an integration strategy. The first would require comparison with the a strategy of providing both where there is no integration e.g. vaccination in a clinic and supplementation through other means e.g. community distribution. If it is about using SQ-LNS as an incentive, is there equipoise given the evidence and secondly is using supplementation (that has an evidence base and recommendation behind it) as an "incentive" in a food insecure setting ethical? 15% malnutrition is very high. Indeed, the authors mention that Nigeria is one of the places identified as one of the top 20 countries for scale-up of the supplementation. Therefore, having a control arm which does not include this supplement when there is a plan for scaling this appears to violate the principle of equipoise.

Was there an existing programme of distributing SQ-LNS prior to the trial taking place? this is relevant in the context of the concern listed above.

Consent: the authors mention that consent was obtained from individuals participating in the survey. What sort of consent if any was obtained from individuals who were given the SQ-LNS. By definition they would also be participants. What information were they given? were those individuals who came in for vaccination in the control arm during the intervention period given any information and specifically told that they were not receiving the supplementation. They obviously would not have the choice in the matter- how was consent handled beyond the participation in the survey.

Given that pentavalent is given at 14 weeks and distribution of supplementation was among those aged 6/12 and above,

how was there an expected impact on uptake of pentavalent3?

Can the authors justify the examination of vitamin A uptake as a secondary outcome?

What was the anticipated population of each cluster i.e. expected no of 12-23 year olds in each cluster? or overall population in each cluster. It would be helpful to understand what % constituted the sample of the cluster population and also what data was used to ascertain PPS selection of settlements.

What was the method used to select the settlements? using existing maps? how?

Could the authors explain the difference in % of households that had the father as a caregiver in the endline vs the baseline.

What were the survey participation rates?

I wonder whether the trial report should present the posthoc outcome in the intervention arm of those who received supplementation vs not. This is not a randomised sample. Overall, would suggest that the authors not present post hoc analyses in the trial paper. In grading evidence, one key aspect is randomisation and therefore would suggest that this not be included in the main trial paper.

Could the authors comment on the adequacy of the increase i.e. around 20% percentage points with respect to population level impact in achieving anticipated reduction in measles incidence. The trial shows does demonstrate important impact. However, high levels of herd immunity are required for reducing measles incidence impact and therefore this strategy would in itself not be sufficient. The Discussion needs to include more nuance about the multifactorial issue of vaccine uptake at individual, structural etc level, and what it is going to take to achieve immunisation rates- the barriers stated such as long waiting times, distance from facilities (particularly rural settings such as these) and maternal workload potentially both jeopardise the effectiveness of the strategy when considered for scale - even when delivered in a trial setting, the strategy on its own would be insufficient at population level. This issue merits further discussion.

MINOR COMMENTS

The authors mention that baseline data collectors were blinded to allocation but outcome assessors would not have been presumably because they would have asked about receipt of the supplementation. This makes it an open-label trial and this should be specifically stated.

the justification of the longitudinal cohort should be defined when mentioned in the methods. It doesnt appear until the penultimate sentence of the Discussion. Should this not have happened before the trial was undertaken before the trial?

Sentence on line 7 of the abstract is grammatically incorrect-needs a verb.

In Introduction,page 4, paragrpah 3, line 6, the no 4 needs to be removed.

Page 11, line 1, remove "odd ratio" and Line 2 should say Figure 2, not Figure 1.

Under Statistical analysis, the sentence in line 4 doesn't make sense..."settlement directly deserved"

Reviewer #2

(Remarks to the Author)

Statistical Review of "Increasing Measles Vaccination Coverage..."

Summary

This manuscript reports the results of a parallel-arm cluster-randomized trial evaluating the impact of nutritional assistance (SQ-LNS) administered with routine immunization programs on measles vaccination rates in Nigeria, as well as several secondary outcomes, mostly related to vaccination uptake. This is a useful study that provides information on what can improve the uptake of vaccination. The results are generally well-reported, with sensitivity analyses that provide consistent and robust results, although some important methodological detail of the study is missing. See below for specific comments to be addressed.

Major Comments

1. Abstract, ll. 50–53: the numbers reported here are cluster-conditional estimates and should be reported as such. The 20.1 pp figure should be more clearly described as a difference-in-differences type estimate.
2. Introduction: the first two paragraphs make it sound as if this paper will be about addressing nutrition, whereas the main outcome being assessed is vaccine uptake. This should be revised to clarify the goals for the reader as early as possible.
3. P. 5, ll. 134–138 and P. 24, ll. 607–619: Given the claims about malnutrition and the effectiveness of SQ-LNS, what is the ethical justification for withholding SQ-LNS from one arm of the trial? Is SQ-LNS distributed at PHCCs for other reasons? The intervention itself should be more clearly described as well: is it possible to obtain the SQ-LNS from the PHCC without getting the vaccine card and the first dose of vaccine?
4. P. 5, Fig. 1: the flow of participants (i.e., contacted, agreed to participate, full data collection/inclusion in analysis) should be documented in the diagram as well.
5. P. 6, ll. 144–153 and P. 24, ll. 621–630: What were the sampling frames used for this survey? What were the response

rates to invitations to participate at each stage of sampling? How was the survey implemented (i.e., in-person, telephone, electronic communication)?

6. P. 7, Tbl. 1: Are the clinical characteristics without a listed time frame for the visit to PHCC?

7. P. 11, l. 206: it is not clear what analysis the 20.1 pp increase is coming from; this should be clarified to some extent in the main text here.

8. P. 13, Table 3: The Footnotes are unclear. Are all the results here from the model explained in the footnote for DiD pp? If so, that should be in the main table caption rather than a footnote to a particular column. Then the distinction between the OR and DiD pp columns should be clarified.

9. P. 14, ll. 268–275: it should be noted explicitly that these are not randomized comparisons and, as far as I can tell, there are no attempts to adjust for confounders. The value of this analysis is also unclear given the limited information about why participants in the cluster arm would or would not receive SQ-LNS.

10. P. 16, ll. 300–301: this should explicitly state that these are compared to control/routine NPI.

11. P. 18, ll. 378–380: the claim about adherence being strengthened by open randomization is not well-supported here, especially with the limited discussion of why contamination may occur, or whether SQ-LNS was available at all at control sites.

12. P. 24, l. 627: the specific number of sampling units at each level should be described here. In addition, details should be given on the “systematic selection” of households, and on whether survey weights are required for the household sampling units.

13. P. 25, ll. 665–669: I have never seen a DID-type analysis with the baseline value itself as a fixed effects as well as the cluster as a random effect, and it makes the interpretation a bit less clear to me. Could a reference or justification for this approach be provided, or a more standard DID model used?

Minor Comments

1. P. 10, Tbl. 2: What does “vaccination card seen” mean?

2. P. 11, ll. 207–209: can you describe the latent vs. observed ICC distinction in the main text here? Also, ICC values are generally expressed as decimals, not percentages.

3. P. 11, l. 209: It would be helpful to report overall, within-, and between-cluster variance estimates as well to facilitate the planning of future studies. The distribution of cluster-specific baseline and endline outcome rates would be useful as well.

4. P. 13, Tbl. 3: The Footnotes should be for “Table 3” not “Table 2”.

5. P. 13, Tbl. 3: Re-formatting to put CIs and p-values on a single line for each row would be helpful for visual clarity.

6. P. 14, l. 254: should be MCV2, not MVC2

7. P. 17, ll. 335, 339: should be MCV1 and MCV2

8. P. 25, l. 661: should “deserved” be “served” here?

9. Pp. 39–41: These tables are never referenced, so it is a bit unclear to the reader what purpose they are serving. More detail in the sampling procedures would help, with explicit reference to these tables as indicating differences in the cluster-sampling results.

10. P. 42, Ex. Data Tbl. 6b: there is some odd formatting in this table. I also think this table and Ex. Data Tbl. 6a could be combined, using “Total” columns to indicate the information currently in 6a.

11. P. 45, Ex. Data Tbl. 9: If possible, please add overall or between- and within-cluster variances to these tables for better use in future study planning.

12. In general, many extended data tables do not have clear titles and may not be referred to anywhere in the text. Please refer to them in the text where appropriate to explain their inclusion, and ensure titles and notes are clear. Or, text in the supplement before each table explaining it could be included.

Reviewer #3

(Remarks to the Author)

Thank you for the opportunity to review the manuscript presenting the results of this large cluster randomised trial. The NutriVax-Measles trial utilised the distribution of nutritional supplements at health facilities to create an additional demand for vaccination services. In areas served by health facilities in the intervention group, children aged 6-23 months were eligible to receive micronutrients (a monthly supply / a supply for 3 months if living >10km away), when presenting at the health facilities. At health facilities, vaccination cards were inspected and missing vaccines provided. At a follow up survey after 12 months of intervention, vaccination coverage for first dose of measles vaccine is reported to have increased markedly: by an additional 20 percentage points relative to the control clusters corresponding to a doubling of the odds of being measles vaccinated.

The trial is important, and it has potential impact on future policies. The manuscript clearly presents the results and appropriate comparisons across arms. My main concern is the definition of the primary outcome.

The paper (and protocol) specifies that children without a vaccination card are considered unvaccinated. Yet, in the paper, vaccination card possession and vaccination card seen appear to have been equated. (Text: “Vaccination card possession, however, was higher in the control arm (384 children, 48%) than in the NutriVax arm (318 children, 40%).”; these numbers are in table 1 presented as “Vaccination card seen”).

If I interpret the analysis practice correctly and all children without an inspected card have been considered unvaccinated, I think there is a problem. The proportions presenting a vaccination card differs markedly between the trial arms, both for the baseline survey as presented in the text: “Vaccination card possession, however, was higher in the control arm (384 children, 48%) than in the NutriVax arm (318 children, 40%) and for the endline survey, where higher proportion is seen in the intervention arms, 552 (69%), than in the control arm, 474 (59%).

Indeed, the secondary result, MCV1 coverage based on card and recall, indicates that 33-42% (depending on timepoint and arm) of the children for whom no card was inspected, are reported to have received MCV1. I think the definition of the

measurement of the primary outcome should be clarified, and the validity of measurement of the primary outcome should be discussed. The 15pp increase in coverage when considering also recall, is by no means negligible, and I think this measure better describes the effect which should be anticipated. Therefore, I don't think your discussion of the outcome definition "Accordingly, while our primary outcome measure was vaccination verified by card, secondary outcomes relying on recall should be interpreted with caution." is adequate.

Minor comments:

Abstract: Typo – "diphtheria-pertussis-tetanus-containing"

I was surprised to see line "Coverage gains for age-appropriate and catch-up vaccines were even greater when comparing children who actually received SQ-LNS compared to those who did not in the NutriVax arm." – without having a baseline assessment, for recipients/non-recipients, conclusion on gains seem inappropriate. The coverage is higher, but that's not surprising for children in contact with the health centers.

Results: Inconsistent referencing to 'Supplementary Tables' or 'appendix 1 page 1'. Supplementary Table 6 before Table 3b. And the tables themselves are named "extended data tables"

Discussion: In the discussion you state "Limited overlap between MCV1 and MCV2 recipients has been documented in Nigeria and elsewhere, and receiving MCV1 before 12 months of age has been positively associated with MCV2 uptake (25)." – How can there be limited overlap between MCV1 and 2? As per definition MCV2 cannot be given without MCV1 – also, I don't think this is supported by ref 25.

Methods: Participation was voluntary – but what proportion of children presenting at the health facilities received supplements?

A description of how interviews on vaccination recall were conducted would be helpful. If the readers do not know that there are distinct anatomic locations for different vaccines, the recall does not seem reliable.

The formulation "binary variable of whether the settlement directly deserved by PHCC for immunization" at endline (post-hoc)" is unclear

Extended Data Table 1: You seem to have forgotten IPV2. I also think that it would be helpful to add (e.g. colour code) which vaccines were covered by the interview (finding the information in the appendix of the protocol was difficult) and which were secondary outcomes.

Extended Data Table 3a; You refer to the mother as "he"

Reviewer #4

(Remarks to the Author)

The authors report the results of a pragmatic cluster-randomized trial conducted in rural areas of Yobe State, Nigeria. The trial was designed to test whether distributing SQ-LNS in routine vaccination programming would lead to an increase in vaccination coverage. This is a relevant question, particularly given the low uptake of EPI and the pervasiveness of undernutrition in northern Nigeria. They found that provision of SQ-LNS (rations of either 30 or 90 sachets) via the EPI did lead to significantly higher vaccination coverage (OR 2.08, though the absolute endline MCV1 coverage in the intervention arm remained only 55%). For the reasons mentioned above, improving vaccination coverage and nutritional status are important in Nigeria and elsewhere, and this trial provides novel information about this question. The trial protocol has been published, and it is important to note that there are other secondary analyses and related studies that will be reported separately.

In terms of my specific comments to the authors and editors:

- The manuscript is far too long, and weighed down by excessively long tables, and would benefit from an overall rewrite with a goal of being more concise and precise. Even though there do not appear to be word/table limits, this at >1600 words, the discussion in particular should be more focused. I will make specific comments where possible, but in the absence of line numbering it is a bit difficult at times. Some of the tables are unreasonably long (Table 1 is 2.5 pages in 11-point font.) These should be reduced further, with non-essential information reported in appendices/supplemental tables.

- In terms of trial design and methodology, the cluster-randomized design is appropriate, and there appears to have been minimal crossover between clusters (only a few children in control arms had SQ-LNS during surveys). Specific methodological/reporting concerns that I have include the following:

1. I think the paper would benefit from a more thorough description of the clusters - only total population is reported for the entire arms - what were the catchment areas of the different health centers, etc., number and size of villages per HC, etc.
2. For the surveys, it would also be helpful to understand how the sampling frames were made - PPS is used, but where did population data come from? Nigeria has not had a census for many years, and data is often unreliable. Did the investigators carry out a census in the study area prior to the trial? If not, incorrect assumptions about populations of villages may have led to bias.

3. I was surprised that there was not a description of permission-seeking for randomization of villages/HC by selected gatekeepers. The informed consent process for individual survey participants is described, but I would have expected the investigators to also seek some sort of formal permission from health and/or political leaders. (See various articles on ethical considerations of Cluster RCTs by Weijer.) Obviously involving the community in the randomization process is great, and it seems like there were real efforts at community engagement, but is that enough? I would appreciate a discussion of that.

- In terms of statistical analysis, the statistical analysis plan appears robust, but warrants review by a statistician specialised in the conduct of CRCTs, which I am not.

- In terms of the authors' conclusions and the inferences they have drawn:

1. At several points, including in the abstract, they refer to their intervention as "potentially cost-effective" or similar. Given that no cost data are presented, all such references should be removed from this manuscript.
2. There is no discussion of actual vaccination coverage, which is a major weakness of the discussion. The primary result showed an important impact of the intervention. But even in the intervention arm, MCV1 coverage among 12-23 month olds remained at 55%, well below thresholds for population immunity. I think this is a major limitation, and should temper some of the investigators' excitement over their results. Vaccination in northern Nigeria is very difficult, and marginal improvements are very welcome, but simply giving SQ-LNS is not going to solve the problem. It should also be noted that in the control arm, vaccination coverage increased by approximately 10% over the study period.
3. I find the 5th paragraph of the discussion confusing (begins with "Spatial heterogeneity"). I'm not sure how the spatial heterogeneity fits in with reasons for non-vaccination and vaccine acceptance. Likewise, I think that the claims that the intervention (giving SQ-LNS) led to increased faith in vaccination a little over the top, as well...I don't think that causation can be inferred.
4. In terms of generalizability, this is billed as a "pragmatic" trial, but there was still significant support provided by a well-funded international humanitarian organization. Managing stocks of vaccines and nutritional supplements often proves difficult for ministries of health - and similar results might not been seen in other settings with less support.

Overall, the manuscript is well-written, but far too long, and would benefit from substantial revision.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Reviewer #2

(Remarks to the Author)

I thank the authors for their revisions and attention to the comments of the reviewer. I think that this manuscript has been strengthened, especially in its clarity of reporting. I find the statistical analyses to be justified, appropriate, and properly reported, and have no additional recommendations.

Reviewer #4

(Remarks to the Author)

The authors have presented a heavily-revised version of their manuscript, which I have reviewed along with the comments of the other reviewers.

In general, the revised manuscript has been "toned down" and the conclusions/interpretations no longer go beyond the findings, which is an improvement.

The authors have responded adequately to my original concerns, though I still have some disagreements with them, particularly the documentation of community consent. The authors say permission was granted by health and LGA authorities, but still only discuss "community representatives" as "approving study procedures". There are two distinct issues here for me. First, how was this approval documented? I didn't see any information sheets, etc., that would allow for gatekeepers to have a standard set of information before giving their permission for inclusion of their LGA or village. Second, who were these "community representatives" and how were they chosen? On what basis did they speak for their "communities"? What was their legitimacy, and how might they have influenced (for good or for bad) participation of caregivers of children who were participating in the trial?

Likewise, I do think that the authors maintain the most optimistic interpretations possible of their results. I will not belabor this point - but I remain skeptical that the addition of SQ-LNS is "worth it" as a way to increase vaccination coverage - particularly when it's so low to begin with. The authors have at least addressed the low (in absolute terms) vaccination coverage, even post-intervention, which is the most important thing for this manuscript. I look forward to seeing their additional analyses, particularly those related to cost-effectiveness. Obviously vaccinating any unvaccinated child, or feeding any hungry child, is a good thing, but it will be interesting to see how this strategy works out as a matter of policy.

Finally, I read with interest the comments of the additional reviewer (or whatever the "comments received on April 1" were) and the responses of the authors. At times, I found the tone of both the reviewer in their comments and the authors in their response to be unfortunate. I think that some of the fundamental questions posed by the reviewer ("was this trial necessary?") are valid, even if posed in an unnecessarily confrontational way. Likewise, the authors, even if they felt attacked, showed little self-awareness in their responses. Beginning with their first sentence "We would like to respectfully

emphasize that as scientists from the North and the South, we do not find appropriate the way this reviewer is addressing his/her comments," they are skating on thin ice. As a white European global health researcher myself, I don't want to claim that I am in any way perfect in this regard, but I was gobsmacked to see the logo/slogan "Global Health in the Global South" on every page of the authors' rebuttal - for a trial that was conducted and largely run by Nigerian clinicians and researchers - but for which all 3 of the first and joint last authors are French. As the ancient Greeks said, "know thyself"...

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Reviewer #5

(Remarks to the Author)

April 20th, 2026

Response to Editor

I was asked to assess the revised manuscript specifically with respect to the appropriateness of the control arm, the standard of care provided to participants, and whether equipoise was adequately maintained. My assessment takes into account the authors' responses to prior reviewer comments and is based on the revised manuscript as currently presented. The trial is ethically defensible as designed and conducted, but the manuscript continues to under-articulate its ethical justification, particularly with respect to equipoise, in ways that require revision before publication.

1. Appropriateness of the control arm - The control arm is ethically appropriate. At the time of the trial, SQ-LNS had never been distributed in either study LGA, and there were no Ministry of Health plans for its distribution. The manuscript states clearly that "there had never been any SQ-LNS distribution program in either LGA nor were there any MoH plans to do so." Participants in the control arm were therefore not denied access to an intervention they would otherwise have received. All clusters received the full National Programme on Immunization (NPI) schedule, standard nutrition services including referral and treatment for acute malnutrition per national guidelines, and community sensitization activities on vaccination and infant and young child feeding. The control arm was not a placebo arm it represented genuine, fully operational standard care for this setting. This is an important ethical distinction. However, this argument is not made explicitly as an ethical principle anywhere in the manuscript. The non-availability of SQ-LNS in the study area is mentioned in passing across sections but is never articulated as the formal ethical rationale for the control arm design. The manuscript would benefit from a clearly stated non-deprivation statement, ideally in the Ethics subsection or early in the Methods, affirming that the control arm was not deprived of an accessible intervention and framing the study explicitly as a pragmatic implementation trial conducted under conditions of non-availability rather than a classical deprivation-based design.

2. Standard of care provided -The standard of care was preserved in both arms throughout the trial. I note that the revised manuscript has addressed a key concern from prior review: it now explicitly states in the Methods that SQ-LNS provision was not contingent on vaccination acceptance, and that caregivers could receive SQ-LNS even after declining vaccines. This is an important ethical safeguard against coercion and undue inducement, and its inclusion represents a meaningful improvement. What remains problematic is the continued use of the term "incentive" throughout the manuscript appearing in the abstract, introduction, and results without qualification. This creates an interpretive inconsistency with the Methods section and leaves the paper open to misreading, particularly in a vulnerable population. The authors should either (a) qualify each use of "incentive" by explicitly cross-referencing the non-conditionality described in the Methods, or (b) replace "incentive" in the abstract and introduction with more neutral language such as "co-delivered intervention" or "attendance facilitator," reserving "incentive" for the Discussion where the mechanism is being interpreted.

3. Whether equipoise was maintained -This remains the primary unaddressed ethical issue. The manuscript cites high-certainty WHO evidence for the benefits of SQ-LNS and notes that it is strongly recommended in food-insecure settings. It also documents a substantial burden of acute malnutrition among enrolled children. Yet the study randomizes access to SQ-LNS across clusters without explicitly reconciling this strong evidence base with the decision to "withhold" access from half of the clusters during the study period. The ethical justification that SQ-LNS was not part of the available preventive package in the study setting is sound, but it is only implied. For a study of this nature, implication is not sufficient; the argument needs to be made explicitly. The key distinction that needs to be articulated is that the trial was not designed to test whether SQ-LNS has nutritional benefit that question has been answered. Rather, it was designed to test whether delivering SQ-LNS through immunization platforms, in a specific operational and programmatic context, improves vaccination coverage at scale. This is a distinct question. Genuine uncertainty about this implementation question, combined with the non-availability of SQ-LNS in the setting, is what justifies randomization. This distinction is central to establishing equipoise and is currently missing from the manuscript. The authors should transfer the equipoise language from their rebuttal into the manuscript specifically a brief a dedicated paragraph in the Ethics subsection of the Methods or early in the Discussion that:

a) Acknowledges the strong evidence base for SQ-LNS and existing WHO recommendations
b) States that at the time of the trial, there was no evidence that SQ-LNS could improve vaccination coverage
c) Confirms that SQ-LNS was not available in the study setting at the time of the trial
d) Affirms that the trial did not withhold an accessible or a routinely provided intervention
e) Frames the study explicitly as a pragmatic implementation trial evaluating a policy-relevant delivery strategy under real-world conditions, situating it within an implementation ethics framework rather than a classical clinical equipoise framework. This will further affirm that the trial therefore did not withhold an accessible intervention and was conducted under conditions of clinical and programmatic equipoise.

4. Community engagement and stakeholder involvement - The rebuttal provides considerably more detail on community engagement than the manuscript presents, and this strength should be more fully reflected in the paper (can go into the supplementary and be cited in the main manuscript if word count limits present a constraint). The authors conducted formal meetings with State and LGA health authorities and community representatives before the trial, obtaining community-level

approval of the trial design, cluster allocation, and SQ-LNS distribution procedures. Randomisation was conducted transparently and publicly, with the active participation of community leaders a critical safeguard given that the absence of SQ-LNS in control clusters could otherwise have generated community tension or pressure. A national steering committee was in place throughout, comprising representatives from federal, state, and local Ministry of Health, international nutrition and immunization actors, and community leaders. Community leaders were kept informed of the trial's progress in real time and were the first to receive preliminary results. The Yobe State authorities' decision to allocate SQ-LNS budget in 2026 directly informed by those results exemplifies the kind of sustained stakeholder engagement and research-to-policy translation that is the hallmark of well-conducted pragmatic implementation trials. The Scientific Committee also included the lead researcher from analogous SQ-LNS cluster-randomised trials in Mali, who advised on methodology and ethical standards, an additional layer of external ethical scrutiny. I commend the multidisciplinary team for ensuring that local input was not a formality but a core and ongoing component of the trial. This depth of engagement substantially enhances the ethical legitimacy of the study and its potential for sustainable impact.

I recommend additional revision. The study addresses an important and underfunded area of child health, the design is scientifically sound, and the ethical safeguards are substantively in place. The issues identified by reviewers 1 and 5 are not fundamental design flaws but rather deficiencies in how the ethical rationale is articulated. With targeted revisions to the Ethics subsection, abstract, and relevant Methods language, the manuscript can meet the ethical and equipoise standards expected. The core argument that this was a pragmatic implementation trial conducted under conditions of genuine non-availability, with standard carefully preserved is defensible and simply needs to be stated explicitly and with appropriate rigor. I also note the substantial involvement of local stakeholders, including the Ministry of Health, in the planning and implementation of the study. This is a strong feature of pragmatic implementation trials of this nature. The authors should be commended for ensuring that local input was a core component of the study design and execution.

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2nd April, 2026

Dear Ming Yang and the *Nature Medecine* Editorial Board,

NMED-FT150449: Increasing measles vaccination coverage with preventive small quantity lipid-based nutrient supplementation in children aged 6 to 23 months: NutriVax-Measles, a pediatric pragmatic superiority parallel cluster-randomized controlled trial in Yobe State, northern Nigeria

We would like to thank you and the four reviewers for taking the time to consider our manuscript. Please find below our point-by-point response to the reviewers' comments. To maintain the full understanding of the document, we have kept the comments in black font, highlighted our responses in **blue font**, and provided the changes in the manuscript related to the comments in **red font**. Our page numbers refer to the clean manuscript.

The guidance on sex and gender has been respected and described in the Reporting Summary.

Reviewers' Comments:

Reviewer #1 (Remarks to the Author):

This is a clearly written and well-presented manuscript reporting the results of a cluster randomised trial of a strategy to integrate nutritional supplementation with immunisation aiming to improving uptake of vaccine uptake.

MAJOR COMMENTS

A key consideration is equipoise and an ethical concern.

The authors state that WHO guidance strongly recommends SQ-LNS in food-insecure contexts and it has also been included in recommendations to optimise health and growth. The trial setting is characterised by high prevalence of malnutrition in children. There are two concerns:

1) it is ethical to have a control arm that does not provide the supplementation when there is i) scientific evidence for ii) recommendation for iii) contextual need (high prevalence of malnutrition) in the control arm. I note that few households were using RUTF and RUSF.

Reply from the authors:

We thank the reviewer for raising this issue, as it is an important one. Broadly speaking, global and domestic financing for treating and preventing malnutrition remains woefully inadequate. While malnutrition poses the greatest risk to child survival, funding for treatment and prevention currently relies mainly on humanitarian aid, which is ad hoc, insufficient, and at the mercy of political shifts. Most other public health crises - HIV/AIDS, malaria, routine immunizations, family planning, etc. - have large, dedicated financing mechanisms, especially for therapeutic or preventive inputs like ARVs for HIV/AIDS, ACTs and bednets for malaria, vaccines for infectious diseases, or birth control for family planning. This is not the case for malnutrition. Even though SQ-LNS has strong scientific evidence and is recommended in some contexts of high needs like Northern Nigeria, this lack of international financing mechanisms and domestic investments has led to a very slow uptake of SQ-

LNS. This has changed dramatically in Nigeria since the study ended, as we describe below in response to your second question, but at the time of the study, there was little prospect of financing for SQ-LNS distributions in Nigeria.

In fact, one aim of the study was to see if we could demonstrate additional benefits of SQ-LNS (i.e. increased vaccination coverage when distributed alongside routine immunizations in addition to the well established evidence on child growth) in order to give governments and international donors more reasons to invest in the intervention in contexts where there is a high burden of malnutrition and low vaccination coverage. After presenting preliminary results to the state ministry of health at the end of the study, Yobe State authorities actually agreed to dedicate some financing in their budget to purchasing SQ-LNS.

Other researchers have also used cluster randomization to investigate the impact of integrating SQ-LNS on acute malnutrition screening and relapse to acute malnutrition compared to the standard of care in those contexts:

Huybregts L, Le Port A, Becquey E, Zongrone A, Barba FM, Rawat R, Leroy JL, Ruel MT. Impact on child acute malnutrition of integrating small-quantity lipid-based nutrient supplements into community-level screening for acute malnutrition: A cluster-randomized controlled trial in Mali. *PLoS Med.* 2019 Aug 27;16(8):e1002892. doi: 10.1371/journal.pmed.1002892. PMID: 31454356; PMCID: PMC6711497.

Brander RL, Toure M, Becquey E, Ruel MT, Leroy JL, Huybregts L. Preventing Relapse From Wasting: The Role of Sociodemographic, Child Feeding, and Health Care Determinants and of Wasting Prevention Interventions in Burkina Faso and Mali. *J Nutr.* 2025 Jun 30:S0022-3166(25)00404-3. doi: 10.1016/j.tjnut.2025.06.019. Epub ahead of print. PMID: 40602719.

The lead researcher from those studies was part of a Scientific Committee whose experts advised our team on methodological questions and ensure NutriVax-Measles adhered to the highest ethical standards.

We also note in our reply to a comment from Reviewer 2 that SQ-LNS was not conditioned on receiving a vaccine. Rather all caregivers went to the vaccine circuit first to have the vaccine status of their child checked and updated as needed. In the event a caregiver refused a scheduled vaccine, the health care worker would discuss why with the caregiver and encourage him or her to see the benefits of the appropriate vaccination. If the caregiver still refused after this discussion, he or she would move on to the SQ-LNS station. That was specified in the Methods/Procedures paragraph.

Most importantly, though, we discussed this issue with State and LGA health authorities and community representatives in the design phase, and the protocol was granted ethical clearance in Nigeria by the Yobe State Ministry of Health's Ethics Committee and in France by the National Institute for Health and Medical Research (Inserm) Ethics Evaluation Committee. We made sure that randomization was done in a transparent fashion with full collaboration with State and LGA health authorities and community leaders. And we made sure to keep community leaders and state authorities informed of the study's progress, and ensured they were the first to know of the preliminary results. For these reasons we feel that we took sufficient care to ensure that the trial was conducted in an ethical fashion.

Finally, all children in both intervention and control clusters had access to routine National Programme on Immunization services and standard nutrition services. Importantly, children identified with acute malnutrition in either group were referred and treated according to national guidelines, explaining why some children were treated by RUTF for severe acute malnutrition and others supplemented with RUSF for moderate acute malnutrition. The control group therefore did not receive less than the standard of care available in the study setting at the time when the NutriVax-Measles trial was conducted.

2) is the trial aiming to interrogate an integration strategy (i.e. vaccination with supplementation) or the use of SQ-LNS as an incentive. While they may at first appear to be the same, they are not. It would appear from the introduction that the aim is to investigate an integration strategy. The first would require comparison with the a strategy of providing both where there is no integration e.g. vaccination in a clinic and supplementation through other means e.g. community distribution. If it is about using SQ-LNS as an incentive, is there equipoise given the evidence and secondly is using supplementation (that has an evidence base and recommendation behind it) as an "incentive" in a food insecure setting ethical? 15% malnutrition is very high. Indeed, the authors mention that Nigeria is one of the places identified as one of the top 20 countries for scale-up of the supplementation. Therefore, having a control arm which does not include this supplement when there is a plan for scaling this appears to violate the principle of equipoise.

Reply from the authors: We thank the authors for the opportunity to clarify the important matter of equipoise. Our objective was to test the use of SQ-LNS as an incentive. We use “integrated” as an adjective to describe how SQ-LNS distributions were opportunistically placed within the vaccine circuit at the PHCCs. We feel this is an appropriate descriptor, especially since there is an emerging area of global health that calls such delivery of both nutrition and immunisation services to children at key contact points “Integrated Nutrition and Immunisation” or “Immunisation-Nutrition-Integration” (INI). For examples, please see the report *Bridging the Gap: Integrated Nutrition and Immunisation* from the group Results and *A Literature Review and Proposed Learning Agenda on Immunisation-Nutrition-Integration* by authors from the Eleanor Crook Foundation (ECF) and Gavi, the vaccine alliance:

- https://results.org.uk/wp-content/uploads/2024/12/250107-Immunisation-Nutrition-Integration-Briefing-Paper_WEB.pdf
- <https://eleanorcrookfoundation.org/the-latest/resources/a-literature-review-on-immunization>

Based on the concerns you raised, however, and to avoid any confusion, we have now removed all mentions of “integration” or “integrated” from the abstract, and we greatly reduced the number of times we use either throughout the revised text. For example, in the **last paragraph of the Introduction (page 4)**, we changed the sentence:

*We conducted an open-label paediatric, pragmatic, superiority, two-arm, parallel, cluster-randomized, controlled trial with baseline measurements in northern Nigeria to evaluate whether **integrating** SQ-LNS distribution for children aged 6-23 months with the routine National Program of Immunization (NPI) - the NutriVax strategy - at primary health care centres (PHCCs) could serve as an incentive for caregivers to seek immunization services, thereby increasing vaccine uptake compared to routine NPI.*

To the following:

*We conducted an open-label paediatric, pragmatic, superiority, two-arm, parallel, cluster-randomized, controlled trial with baseline measurements in northern Nigeria to evaluate whether **distributing** SQ-LNS to children aged 6-23 months alongside the routine National Program of Immunization (NPI) - the NutriVax strategy - at primary health care centres (PHCCs) could serve as an incentive for caregivers to seek immunization services, thereby increasing vaccine uptake compared to routine NPI.*

As for the national plans to scale-up SQ-LNS distributions, the national government and World Bank financed a project Accelerating Nutrition Results in Nigeria (ANRiN) 2.0 that was deliberated and planned only after the NutriVax study was completed. We thus pleasantly learned, after the study concluded, that ANRiN 2.0 would include a sizable commitment to finance SQ-LNS. For this and for the other reasons we described in the first issue raised by this reviewer, we feel the NutriVax-Measles trial adhered to the principle of equipoise.

Was there an existing programme of distributing SQ-LNS prior to the trial taking place? this is relevant in the context of the concern listed above.

Reply from the authors:

It is important to again note that we had extensive discussions with the Ministry of Health at the state and local levels while conceiving the trial to have a clear picture whether there were or had been existing SQ-LNS distribution programs in Nigeria. There were no existing *large-scale* SQ-LNS distribution programmes in place in Nigeria prior to the trial nor were there any plans to begin such a program by the Ministry of Health or any other organization. To the best of our knowledge, only one SQ-LNS distribution program had been conducted in other LGAs of Yobe State in programs managed by the Mary Dinah Foundation and one other pilot in Gombe State run by UNICEF, but in both instances at a relatively small scale. After the trial ended, we shared preliminary results with Yobe State authorities, who decided to allocate funds for SQ-LNS procurement in their 2026 budget. We also shared preliminary results with the federal authorities managing ANRiN 2.0, and there is some consideration of applying NutriVax in some areas where SQ-LNS will be distributed.

To address this concern, we have added a clarification in the Introduction section (**page 4; end of fifth paragraph**) as follows: “SQ-LNS has also been included in recommendations for nutrition-specific interventions to optimize health and growth (3), **but is rarely routinely provided due to inadequate international and domestic financing.**”; in the Results section (end of page 4) within the description of the study sites: “**At the time of the study, there were no plans to run SQ-LNS distribution programs in either LGA,...**”.

Consent: the authors mention that consent was obtained from individuals participating in the survey. What sort of consent if any was obtained from individuals who were given the SQ-LNS. By definition they would also be participants. What information were they given? were those individuals who came in for vaccination in the control arm during the intervention period given any information and specifically told that they were not receiving the supplementation. They obviously would not have the choice in the matter- how was consent handled beyond the participation in the survey.

Reply from the authors:

We thank the reviewer for this important comment. Prior to trial implementation, we discussed largely with State and LGA health authorities, as well as community representatives about the study objectives, the trial design and procedures, and eligibility criteria for SQ-LNS supplementation. The evaluation of the NutriVax strategy compared to standard of care was deemed acceptable given its potential to address both undernutrition and immunization coverage and to foster the acceleration for

SQ-LNS funding and implementation. Community-level and MoH approval was obtained on trial design and procedures, along with ethical approval from the Yobe State Ethics Committee. As mentioned in the manuscript, community leaders were actively involved in the publicly conducted and transparent randomization process, which further supported acceptance of cluster allocation.

At individual level, in intervention clusters, caregivers were informed about SQ-LNS, including its purpose, eligibility criteria, and mode of distribution during community sensitization on IYCF and immunization sessions at health facilities and community level. Participation in SQ-LNS distribution was entirely voluntary, and caregivers could choose whether their child received the supplementation or not. Only aggregated and no individual-level data were collected as part of the SQ-LNS distribution activities.

In control clusters, information was explained, during community sensitization on IYCF and immunization sessions at health facilities and community level. Children attending health facilities in these clusters continued to receive routine care only. If caregivers asked for SQ-LNS supplementation of their children, they were informed that SQ-LNS would not be provided as part of the study in these zones.

Individual informed consent was obtained only for those who had been selected to participate in the household cross-sectional surveys conducted at home, either at baseline or endline.

For clarity, we have revised the section entitled “Ethical Approval and Inclusion Criteria” (**page 26-first and second paragraph**) as follows:

“Prior to trial implementation, the study objectives, trial design, cluster allocation, and SQ-LNS distribution procedures were reviewed and approved by State and LGA health authorities, as well as community representatives during formal meetings.”

“Community engagement was maintained throughout the study via regular meetings with local leaders and through the national steering committee, which included representatives from the federal, state, and local Ministry of Health, local and international nutrition and immunization actors, and community leaders. These activities ensured that community leaders and state authorities were fully committed to the trial’s design, outcomes and procedures and informed in real time of the trial’s progress.”

Given that pentavalent is given at 14 weeks and distribution of supplementation was among those aged 6/12 and above, how was there an expected impact on uptake of pentavalent3?

Reply from the authors:

Within the Nigerian National Programme on Immunization, catch-up vaccination for early childhood vaccines, including pentavalent doses, can be administered during any contact with health services for children who missed scheduled doses, including those older than 14 weeks, as specified in our original study protocol. An effect on pentavalent 3 coverage was plausible through improved contact with health services and catch-up vaccination for older infants who missed the scheduled doses. This is especially relevant in Nigeria as there is an ongoing outbreak of diphtheria.

The Procedures section (**page 22-first paragraph**) now reads: *“Catch-up doses for early childhood vaccines, including pentavalent doses, were provided for children older than 14 weeks according to Nigerian MoH policies.”*

Can the authors justify the examination of vitamin A uptake as a secondary outcome?

Reply from the authors:

Vitamin A supplementation is recorded on child health and vaccination cards in Nigeria and is commonly delivered alongside routine immunization and primary health care services, during the same contacts as immunization. Because our study collected data from vaccination cards, vitamin A supplementation was also systematically documented and therefore included as a secondary outcome, complemented by caregiver recall when card data were unavailable. Vitamin A uptake therefore served as an additional indicator of child health service utilization beyond vaccination alone.

We have revised the Method section (**page 24-end of first paragraph**), as follows: “.... *and vitamin A uptake, which is commonly delivered alongside routine immunization and recorded on the Nigerian vaccination card. Vitamin A uptake therefore served as an additional indicator of child health service utilization beyond vaccination alone.*”

What was the anticipated population of each cluster i.e. expected no of 12-23 year olds in each cluster? or overall population in each cluster. It would be helpful to understand what % constituted the sample of the cluster population and also what data was used to ascertain PPS selection of settlements.

What was the method used to select the settlements? using existing maps? how?

Reply from the authors:

The percentage of children aged 12–23 months included in the trial relative to the total population of children in this age group is now provided in **Table 1** and in the Results section **page 6** as follows:

“....*with an average cluster size of 80 participants at both time points (Fig. 1), representing approximately 12% of the overall population aged 12-23 months across all clusters (Table 1)*”.

Population data including the estimated number of children aged 12–23 months per settlement for each ward (cluster) within each Local Government Area were obtained from the Ministry of Health (Immunization Department of Yobe State, 2024). Method used to select settlements and households is now extensively detailed in the Method/participants sections of the revised manuscript as follows (**page 23-24**): “*Enrollment in each cross-sectional survey used a three-stage cluster sampling design, based on the estimated population of children aged 12–23 months per settlement (i.e. per random units) obtained from the 2024 Yobe State Ministry of Health immunization microplanning database. In stage one, 100 settlements out of 203 were randomly selected (50 per arm and 5 for each cluster) using the probability proportional to size sampling method. For each cluster, the cumulative estimated population of children aged 12-23 months per settlement was calculated, and the sampling interval was determined by dividing the total cumulative population by the number of settlements to be selected (n=5). The first sampling step was generated as a random number (using R software) between 1 and the sampling interval value. In stage two, households, defined as groups of individuals sharing food and livelihood under a recognized head of household, were sampled systematically following the Multiple Indicator Cluster Surveys (MICS) methodology and templates. Large settlements with >900 households were divided into four segments, and those with >480 households into two segments, with the support of community guides. Sampling intervals were calculated by dividing the estimated number of households to be visited by the number of households required to reach the target of eligible children (an anticipated non-response rate of 10.9% (21). A random starting point was selected in each segment, and households were visited sequentially according to the sampling interval until the required number of eligible children was reached. Stage three was applicable where households contained more than one eligible child aged 12–23 months, the oldest child being included under such circumstances.*”

Could the authors explain the difference in % of households that had the father as a caregiver in the endline vs the baseline.

Reply from the authors:

Our initial wording was misleading. This variable actually corresponds to the question “Who accompanied the child at the time of the survey?”, which reflects the survey respondent rather than the primary caregiver. The lower proportion of fathers reported at endline (2%) compared with baseline (8%) likely reflects differences in respondent availability during survey visits, rather than a true change in caregiving patterns. As the surveys were conducted during daytime hours, respondent availability may have varied between survey periods due to seasonal, occupational, or contextual factors. For example, fathers may have been less available during the endline survey period due to work or other responsibilities outside from home, while mothers or other caregivers were more likely to be present and interviewed. Differences in timing of visits, household contact patterns, or fieldwork dynamics across the two survey rounds may also have contributed to this variation.

This finding should be interpreted as reflecting differences in survey respondents rather than caregiving roles. To improve clarity, we revised the variable label in **Table 1 (page 7)** and related supplementary tables from “Mother/Father as caregiver” to “*Mother/Father as survey respondent*”.

What were the survey participation rates?

Reply from the authors:

We are grateful to the reviewer for this important question that should have been specified in the original manuscript. Household refusals among those with at least one eligible child were minimal: n=5 at baseline and n=2 at endline, corresponding to participation rates of 99.7% at baseline and 99.9% at endline. These estimates were based on a standardized “Settlement Control Form” completed on paper by survey supervisors, which recorded households visited, eligible children, and participation.

We have added the total numbers of households with at least one child eligible who refused to participate **Table 1** and revised the Results section (**page 6**), as follows: “*Participation rates were >99.5% at both baseline and endline with very minimal household refusals (n=5 and n=2 at baseline and endline, respectively), ... (Table1)*”.

We have also emphasized this point in the discussion with the following new sentence **page 16/ paragraph on the strengths (last sentence)** : “*The very high (>99.5%) participation rates in both baseline and endline surveys is another strength that likely reflect the strong community engagement and mobilization in the NutriVax-Measles trial.*”

I wonder whether the trial report should present the posthoc outcome in the intervention arm of those who received supplementation vs not. This is not a randomised sample. Overall, would suggest that the authors not present post hoc analyses in the trial paper. In grading evidence, one key aspect is randomisation and therefore would suggest that this not be included in the main trial paper.

Reply from the authors: We have now explicitly indicated that this analysis is exploratory and non-randomized in the Results (**page 13**) and in the Methods/Statistical Analyses (**last sentence of the section-page 26**) sections, as follows: “*Outcomes stratified by SQ-LNS uptake in the NutriVax clusters were exploratory, non-randomised and presented post-hoc.*” Finally, to maintain focus on the

randomized comparisons and to avoid confusion in results interpretation, Table 4 is not a primary table anymore and has been moved to the supplementary/extended data section is now the **Extended data table 13 (page 51)**.

Could the authors comment on the adequacy of the increase i.e. around 20% percentage points with respect to population level impact in achieving anticipated reduction in measles incidence. The trial shows does demonstrate important impact. However, high levels of herd immunity are required for reducing measles incidence impact and therefore this strategy would in itself not be sufficient. The Discussion needs to include more nuance about the multifactorial issue of vaccine uptake at individual, structural etc level, and what it is going to take to achieve immunisation rates- the barriers stated such as long waiting times, distance from facilities (particularly rural settings such as these) and maternal workload potentially both jeopardise the effectiveness of the strategy when considered for scale - even when delivered in a trial setting, the strategy on its own would be insufficient at population level. This issue merits further discussion.

Reply from the authors:

We thank the reviewer for this comment that was shared by another reviewer, we fully agree. We have added the following paragraph in the Discussion section/ fourth paragraph (**page 14**) to address this more explicitly:

“While we report substantial gains in MCV1 coverage in the NutriVax arm, it is important to note that endline coverage by card (55.3%) or by card or recall (68.5%) was still well below the 95% immunization coverage needed to achieve herd immunity. Even though promising, solely associating SQ-LNS with routine immunizations in health centers would be insufficient to achieve the recommended vaccination coverage at population level in an environment as challenging as northern Nigeria. Decentralizing SQ-LNS distributions to lower level health posts, however, and not just PHCCs as in this trial), would likely further increase SQ-LNS uptake, and MCV1 coverage, as suggested by the exploratory, post hoc analysis (Extended Data Table 13). “

MINOR COMMENTS

The authors mention that baseline data collectors were blinded to allocation but outcome assessors would not have been presumably because they would have asked about receipt of the supplementation. This makes it an open-label trial and this should be specifically stated.

Reply from the authors: We are grateful to the reviewer for this important point. The trial was open-label indeed, and we have clarified this in the revised abstract, introduction (**page 4-last paragraph**) and methods/study design (**page 22-first sentence**) sections accordingly: *“We conducted an open-label, paediatric, pragmatic, superiority, ...”*

the justification of the longitudinal cohort should be defined when mentioned in the methods. It doesn't appear until the penultimate sentence of the Discussion. Should this not have happened before the trial was undertaken before the trial?

Reply from the authors: We have mentioned the other study components detailed in the separated methods section also in the main article Results (page 5) before the Discussion to improve clarity, as follows (**page 5-last paragraph**): *“We report here the results of the primary objectives of NutriVax-Measles trial. Findings from other study components answering to secondary objectives will be reported elsewhere and include vaccine and nutritional outcomes in a longitudinal survey of children*

aged 6-12 months at inclusion followed for one year; a qualitative assessment of acceptability of the NutriVax strategy; and cost-efficiency outcomes (39)”.

Sentence on line 7 of the abstract is grammatically incorrect-needs a verb.

Reply from the authors: We thank the reviewer for noting this error. The sentence has been corrected.

In Introduction, page 4, paragraph 3, line 6, the no 4 needs to be removed.

Reply from the authors: We thank the reviewer for noting this error. The correction has been done.

Page 11, line 1, remove "odd ratio" and Line 2 should say Figure 2, not Figure 1.

Reply from the authors: We thank the reviewer for carefully reviewing the manuscript. These errors have been corrected as requested: “odd ratio” has been removed and the figure citation has been corrected to Figure 2.

Under Statistical analysis, the sentence in line 4 doesn't make sense..."settlement directly deserved"

Reply from the authors: We thank the reviewer for pointing out this wording issue. The sentence has been corrected by adding the missing verb and rephrased for clarity. It now reads: “*the binary variable indicating whether the settlement **was** directly **served** by the PHCC for immunization at endline.*”

Reviewer #2 (Remarks to the Author):

Statistical Review of “Increasing Measles Vaccination Coverage...”

Summary

This manuscript reports the results of a parallel-arm cluster-randomized trial evaluating the impact of nutritional assistance (SQ-LNS) administered with routine immunization programs on measles vaccination rates in Nigeria, as well as several secondary outcomes, mostly related to vaccination uptake. This is a useful study that provides information on what can improve the uptake of vaccination. The results are generally well-reported, with sensitivity analyses that provide consistent and robust results, although some important methodological detail of the study is missing. See below for specific comments to be addressed.

Major Comments

1. Abstract, ll. 50–53: the numbers reported here are cluster-conditional estimates and should be reported as such. The 20.1 pp figure should be more clearly described as a difference-in-differences type estimate.

Reply from the authors:

We thank the reviewer for this comment and have revised the abstract accordingly: “*The **difference-in-differences, cluster-conditional analysis indicated** a 20.1 percentage-point (pp) increase in MCV1 coverage from baseline (95% CI 13.7–26.5 pp, $p < 0.0001$).*”

2. Introduction: the first two paragraphs make it sound as if this paper will be about addressing

nutrition, whereas the main outcome being assessed is vaccine uptake. This should be revised to clarify the goals for the reader as early as possible.

Reply from the authors:

As recommended, we have extensively revised the structure of the introduction to clarify from the beginning that the primary focus of the study was on vaccination uptake, particularly measles vaccination coverage. The text was revised to better balance the nutrition and immunization rationale while not giving the impression that the study primarily addressed nutrition outcomes (see **page 3-4**).

3. P. 5, ll. 134–138 and P. 24, ll. 607–619: Given the claims about malnutrition and the effectiveness of SQ-LNS, what is the ethical justification for withholding SQ-LNS from one arm of the trial? Is SQ-LNS distributed at PHCCs for other reasons? The intervention itself should be more clearly described as well: is it possible to obtain the SQ-LNS from the PHCC without getting the vaccine card and the first dose of vaccine?

Reply from the authors:

This important ethical consideration had already been raised by Reviewer 1, and we have clarified the ethical framework and standard of care provided in the control group during the trial in our response to that reviewer.

In brief, SQ-LNS was not part of the standard of care in Nigeria and was not routinely provided through the health system at the time the trial was designed and implemented.

To better address this concern, we have added a clarification in the revised Introduction section (**page 4- fifth paragraph**) as follows: “SQ-LNS has also been included in recommendations for nutrition-specific interventions to optimize health and growth (3), *but is rarely routinely provided due to inadequate international and domestic financing*. We also specified in the revised Results section (**page 4-first paragraph**) within the description of the study sites that: “*At the time of the study, there had never been any SQ-LNS distribution program in either LGA nor were there any MoH plans to do so,...*”.

There was also no prior evidence demonstrating that SQ-LNS could improve vaccination coverage. Therefore, the trial was conducted under conditions of clinical and programmatic equipoise. All children in both intervention and control clusters had access to routine National Programme on Immunization services and standard nutrition services. Importantly, children identified with acute malnutrition in either group were referred and treated according to national and WHO guidelines. The control group therefore did not receive less than the standard of care available in the study setting.

And yes, it was possible to obtain the SQ-LNS from the PHCC without getting the vaccine. SQ-LNS was not conditioned on receiving a vaccine, but rather all caregivers went to the vaccine circuit first to have the vaccine status of their child checked and updated as needed. In the event a caregiver refused a scheduled vaccine, the health care worker would discuss why with the caregiver and encourage him or her to see the benefits of the appropriate vaccination. If the caregiver still refused after this discussion, he or she would move on to the SQ-LNS station.

For the sake of clarity, the revised Methods/Procedures section (**page 22-end of last paragraph**) now reads: “*Participation was voluntary and SQ-LNS distribution was not conditional on vaccination, a caregiver could therefore still proceed to the SQ-LNS distribution station if he/she had declined a scheduled vaccine after discussion with the health-care worker.*”

4. P. 5, Fig. 1: the flow of participants (i.e., contacted, agreed to participate, full data collection/inclusion in analysis) should be documented in the diagram as well.

Reply from the authors: We are grateful to the reviewer for this important comment that was also raised by Reviewer 1, it should have been better explained in the original manuscript. Please see our response to Reviewer 1 on this matter.

We have added the total numbers of households with at least one child eligible who refused to participate table 1 and revised the Results section (**page 6-fourth sentence**), as follows: *"Participation rates were >99.5% at both baseline and endline with very minimal household refusals (n=5 and n=2 at baseline and at endline, respectively), ... (Table1)"*.

5. P. 6, ll. 144–153 and P. 24, ll. 621–630: What were the sampling frames used for this survey? What were the response rates to invitations to participate at each stage of sampling? How was the survey implemented (i.e., in-person, telephone, electronic communication)?

Reply from the authors: Sampling frames used were population data per settlement for each ward (cluster) within each Local Government Area obtained from the Ministry of Health (Immunization Department of Yobe State, 2024). These data, provided in an Excel file used for microplanning of immunization activities, listed the estimated number of children aged 12–23 months in each settlement. This is now mentioned **Table 1**, and accurately explained in the revised manuscript (**end of page 4 and 23-first paragraph**). Both baseline and endline surveys were population-based, household cross-sectional surveys conducted in-person at household level. The response rate is specified as follows (**page 6-first paragraph**): *"Participation rates were >99.5% at both baseline and endline very minimal household refusals (n=5 and n=2 at baseline and endline, respectively) and the sample represented approximately 12% at each survey of the total population of children aged 12–23 months across all clusters (Table 1)"*. Finally, wherever relevant, we have clarified throughout the revised abstract and manuscript that these surveys were household surveys.

6. P. 7, Tbl. 1: Are the clinical characteristics without a listed time frame for the visit to PHCC?

Reply from the authors: "Notion of fever" referred to fever within the 24 hours preceding the interview. For the other clinical conditions, interviewers assessed whether the child currently had the condition at the time of the household survey. This has now been clarified in the revised variable definitions and in the table footnotes (Table 1 and Extended Data Tables).

7. P. 11, l. 206: it is not clear what analysis the 20.1 pp increase is coming from; this should be clarified to some extent in the main text here.

Reply from the authors: We have clarified the manuscript as follows page 11: *"Overall, the difference-in-differences, cluster-conditional analysis indicated the NutriVax strategy increased card-verified MCV1 coverage by 20.1 pp (95% CI 13.7–26.5, $p < 0.0001$; Table 3) from baseline relative to the control arm."*

8. P. 13, **Table 3:** The Footnotes are unclear. Are all the results here from the model explained in the footnote for DiD pp? If so, that should be in the main table caption rather than a footnote to a particular column. Then the distinction between the OR and DiD pp columns should be clarified.

Reply from the authors:

All estimates in Table 3 are derived from the same difference-in-differences model, and this is now indicated in the main caption rather than a footnote. We have clarified the two effect measures: odds ratios (OR) quantify relative effects on the odds scale, while difference-in-differences (DiD pp) quantify absolute effects on the probability scale. These definitions are now provided directly below the revised table.

9. P. 14, ll. 268–275: it should be noted explicitly that these are not randomized comparisons and, as far as I can tell, there are no attempts to adjust for confounders. The value of this analysis is also unclear given the limited information about why participants in the cluster arm would or would not receive SQ-LNS.

Reply from the authors:

We have explicitly indicated this analysis was exploratory and not based on randomization in the revised Results (**page 13**): “*Post-hoc exploratory analysis of outcomes stratified by SQ-LNS uptake*”; and Methods/Statistical Analyses (**end of the last paragraph-page 26**) sections: “*Outcomes stratified by SQ-LNS uptake in the NutriVax clusters were exploratory, non-randomised and presented post-hoc*”.

Bearing in mind that sociodemographic, household, and clinical characteristics were generally similar between groups, no adjustments for confounders were made. To maintain focus on the randomized comparisons and avoid misinterpretation, Table 4 has been moved to the supplementary/extended data section and is now **Extended Data table 13**. We have revised the Result section (**last paragraph-page 13**) as follows: “*Extended Data Table 13 presents an exploratory, non-randomized, post-hoc analysis comparing children who had ever received SQ-LNS with those who had not. MCV1 coverage was substantially higher among children who received SQ-LNS (73.3% vs 38.6%), with similar trends observed for MCV2, pentavalent 3, meningitis, and yellow fever vaccination. Likewise, the prevalence of zero-dose status by card or recall was lower among children who received SQ-LNS compared with those who did not: 7.3% versus 29.5%, respectively.*”

10. P. 16, ll. 300–301: this should explicitly state that these are compared to control/routine NPI.

Reply from the authors:

The text has been revised to explicitly indicate that these comparisons are made relative to the routine NPI group, as follows: “*The odds of receiving card-verified MCV1 were two times higher for children in the NutriVax arm compared to those in the control, translating into a 20-percentage point absolute increase in a low immunization coverage setting compared with routine NPI.*”

11. P. 18, ll. 378–380: the claim about adherence being strengthened by open randomization is not well-supported here, especially with the limited discussion of why contamination may occur, or whether SQ-LNS was available at all at control sites.

Reply from the authors: We thank the reviewer for this comment. We have clarified this point in the Discussion. In this sentence, we were referring to trial adherence in a context where the absence of SQ-LNS distribution in control clusters could have led to frustration or pressure at the community or PHCC level, potentially resulting in children from control clusters receiving SQ-LNS from intervention PHCCs. Extensive meetings were held with community leaders prior to trial implementation, and they were involved in the publicly conducted and transparent randomization.

This likely helped ensure community understanding and acceptance of the allocation and may have contributed to good adherence to the trial design and the low level of spillover observed (4%).

We have revised the manuscript to clarify this interpretation (**page 15-last sentence**), as follows:

“Furthermore, this may reflect the publicly conducted and transparent randomization, which may have fostered community trust and adherence to the trial allocation in a context where the absence of SQ-LNS distribution in control clusters could have otherwise led to tension within the community at PHCC level”.

12. P. 24, l. 627: the specific number of sampling units at each level should be described here. In addition, details should be given on the “systematic selection” of households, and on whether survey weights are required for the household sampling units.

Reply from the authors: We thank the reviewers for this comment that Reviewer 1 had also raised. We have added the total number of sampling units **Table 1**. In the Methods/Participants section, we have also provided more detailed information on the systematic selection of households: (**page 23-24**):

“Enrollment in each cross-sectional survey used a three-stage cluster sampling design, based on the estimated population of children aged 12–23 months per settlement (i.e. per random units) obtained from the 2024 Yobe State Ministry of Health immunization microplanning database. In stage one, 100 settlements out of 203 were randomly selected (50 per arm and 5 for each cluster) using the probability proportional to size sampling method. For each cluster, the cumulative estimated population of children aged 12–23 months per settlement was calculated, and the sampling interval was determined by dividing the total cumulative population by the number of settlements to be selected ($n=5$). The first sampling step was generated as a random number (using R software) between 1 and the sampling interval value. In stage two, households, defined as groups of individuals sharing food and livelihood under a recognized head of household, were sampled systematically following the Multiple Indicator Cluster Surveys (MICS) methodology and templates. Large settlements with >900 households were divided into four segments, and those with >480 households into two segments, with the support of community guides. Sampling intervals were calculated by dividing the estimated number of households to be visited by the number of households required to reach the target of eligible children (an anticipated non-response rate of 10.9% (21). A random starting point was selected in each segment, and households were visited sequentially according to the sampling interval until the required number of eligible children was reached. Stage three was applicable where households contained more than one eligible child aged 12–23 months, the oldest child being included under such circumstances.”

Survey weights for the household sampling units: in this cluster-randomized trial, survey weights were not applied to any analysis. The primary objective was to estimate a cluster-specific odds ratio, assessing the intervention’s effect within the randomized clusters. Cluster randomization balanced confounding factors, and conditional models (mixed-effects) accounted for within-cluster correlation, eliminating the need for weights. Secondary analyses, including those exploring marginal effects, also did not use weights, as they remained focused on the trial’s internal validity and cluster-level inference. For the sake of brevity, we have decided not to specify this in the revised manuscript. We would be pleased to revise it further should the editors deem it necessary.

13. P. 25, ll. 665–669: I have never seen a DID-type analysis with the baseline value itself as a fixed effect as well as the cluster as a random effect, and it makes the interpretation a bit less clear to me. Could a reference or justification for this approach be provided, or a more standard DID model used?

Reply from the authors:

We thank the reviewer for this comment regarding the inclusion of both cluster-level baseline coverage as fixed effect, and cluster as a random intercept in our DiD model. We can provide the following clarifications:

1. Rationale for including cluster-level baseline coverage as a fixed effect:

In a cluster trial with baseline measure, adjusting for baseline cluster-level coverage accounts for residual between-cluster differences at baseline, which can improve the precision of treatment effect estimates. This is particularly relevant in cluster trials where randomization may not fully balance baseline characteristics or if the number of clusters is limited [1,2].

2. Rationale for including a cluster random intercept:

A random intercept for cluster was specified to account for intra-cluster correlation (ICC) and unobserved heterogeneity between clusters [1,3].

3. No redundancy or collinearity:

The baseline fixed effect and the random intercept serve distinct purposes: the first adjusts for mean differences at baseline, while the latter accounts for unobserved cluster-level variability. We verified the absence of problematic collinearity (VIF for baseline = 1.048, VIF for interaction = 2.45; correlation = -0.116).

4. Sensitivity analysis for the primary outcome:

To address the reviewer's concern, we re-estimated the model for the primary outcome only (MCV1) without baseline adjustment. Results were nearly identical:

- Main model (with cluster-level baseline coverage as fixed effect) :

DiD pp=20.1 (95% CI 13.7 to 26.5) p-value<0.0001; OR = 2.39 (95% CI: 1.76–3.25)

- Standard model (without cluster-level baseline coverage as fixed effect):

DiD pp=20.2 (95% CI 13.2 to 26.9) p-value<0.0001; OR = 2.40 (95% CI: 1.77–3.26)

This confirms the robustness of our findings.

To conclude, we retained both the baseline cluster-level coverage adjustment and the cluster random intercept in the main model to maximize precision and validity. The sensitivity analysis demonstrates that our conclusions are not dependent on the inclusion of baseline cluster-level coverage adjustment.

For the sake of brevity, we have decided not to specify this in the revised manuscript. We would be pleased to revise it further however, should the editors deem it necessary.

[1] Campbell MK, Piaggio G, Elbourne DR, Altman DG, for the CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661–e5661. <https://doi.org/10.1136/bmj.e5661>.

[2] Angrist JD, Pischke J-S. Mostly harmless econometrics: An empiricist's companion. Princeton university press; 2009.

[3] Hayes RJ, Moulton LH. Cluster Randomised Trials. CRC Press; 2017.

Minor**Comments**

1. P. 10, Tbl. 2: What does “vaccination card seen” mean?

Reply from the authors: “Vaccination card seen” referred to children for whom a vaccination card was available at the time of the survey, allowing vaccination information to be verified directly from the card and accurately recorded. To improve clarity and consistency with standard terminology, we have renamed this variable as “Vaccine card retention” throughout the revised manuscript, tables, and figures.

2. P. 11, ll. 207–209: can you describe the latent vs. observed ICC distinction in the main text here? Also, ICC values are generally expressed as decimals, not percentages.

Reply from the authors:

We have revised the manuscript accordingly to clarify the distinction between latent-scale and observed-scale intracluster correlation coefficients (ICC) for binary outcomes. The latent ICC refers to the correlation on the underlying logistic scale from the mixed-effects model (assuming a within-cluster variance of $\pi^2/3$), whereas the observed ICC reflects clustering on the probability scale of the outcome. We have also expressed ICC values as decimals rather than percentages, in line with standard reporting practice.

3. P. 11, l. 209: It would be helpful to report overall, within-, and between-cluster variance estimates as well to facilitate the planning of future studies. The distribution of cluster-specific baseline and endline outcome rates would be useful as well.

Reply from the authors:

We thank the reviewer for this important suggestion aimed at facilitating planning of future studies. We now report the estimated between-cluster variance from the mixed-effects model (add in Extended Data table 9), as well as the empirical distribution of cluster-specific outcome rates at baseline and endline (mean, dispersion, and range) (add in text page 11 line 209). The within-cluster variance on the logistic scale is known and fixed at $\pi^2/3$, so only the between-cluster component varies.

We have revised the manuscript to clarify this point (**page 25-third paragraph**), as follows: *“To inform the design of future cluster-randomized studies, we report between-cluster variance estimates from the mixed-effects model (with the within-cluster variance fixed at $\pi^2/3$ on the logistic scale) and summarize empirical distributions of cluster-specific outcome rates at baseline and endline using the median (interquartile range) and range.”*

We added in the text **page 10-last paragraph** as follows: *The distribution of cluster-specific MCV1 coverage increased from a median of 26.2% at baseline (IQR 17.2%-33.9%; range 11.0%-57.5%) to 46.9% (IQR 36.2%-56.2%; range 23.8%-79.8%, based on **Extended Data table 6b**) at endline”.*

4. P. 13, Tbl. 3: The Footnotes should be for “Table 3” not “Table 2”.

Reply from the authors: we thank the reviewer for the careful review. The footnote has been corrected to refer to Table 3 instead of Table 2 as appropriate.

5. P. 13, Tbl. 3: Re-formatting to put CIs and p-values on a single line for each row would be helpful for visual clarity.

Reply from the authors: Table 3 is now reformatted in a landscape layout to improve clarity, with confidence intervals and p-values presented on a single line for each row.

6. P. 14, l. 254: should be MCV2, not MVC2

7. P. 17, ll. 335, 339: should be MCV1 and MCV2

8. P. 25, l. 661: should “deserved” be “served” here?

Reply from the authors: We thank the reviewer for the careful review; all these typo errors have been corrected accordingly.

9. Pp. 39–41: These tables are never referenced, so it is a bit unclear to the reader what purpose they are serving. More detail in the sampling procedures would help, with explicit reference to these tables as indicating differences in the cluster-sampling results.

Reply from the authors: We thank the reviewer for this comment. These Extended Data Tables 5 describe the distance (in kilometers) between settlements and primary health care centres and on the proportion of settlements directly served by PHCC for immunization, overall by study arm, by Local Government Area, and by ward at baseline and at endline. These variables reflect cluster-level variability in geographic access to immunization services and informed the second post-hoc sensitivity analysis of the primary outcome. To improve clarity, we have now added explicit references to these tables in the Methods section and clarified their purpose in relation to sensitivity analyses. For the sake of brevity, detailed descriptions of these variables were not included in the main Results section.

Page 25 - Statistical analysis section now reads: “*Sensitivity analyses excluded children aged 21–23 months (prespecified); were adjusted for LGA; and for settlement distance to PHCC (in kilometres) and the binary variable of whether the settlement directly was served by PHCC for immunization at endline (post-hoc), to account for cluster-level variability in geographic access to PHCCs (Extended Data table 5a to 5c).*”

10. P. 42, Ex. Data Tbl. 6b: there is some odd formatting in this table. I also think this table and Ex. Data Tbl. 6a could be combined, using “Total” columns to indicate the information currently in 6a.

Reply from the authors: We have addressed the formatting issues, combined both tables in one: **Extended Data table 6 (page 44)** and updated the reference on this table within the main text of Results (**page 8 - last sentence**). Moreover, to focus Extended Data Table 6a only on MCV1 coverage differences by arm and by clusters, we removed data on distance and PHCCs. These data were already detailed in Extended Data Table 5b-c.

11. P. 45, Ex. Data Tbl. 9: If possible, please add overall or between- and within-cluster variances to these tables for better use in future study planning.

Reply from the authors:

As indicated in our response to the third point from this reviewer, we now report the estimated between-cluster variance from the mixed-effects model (added in Extended Data table 9). The within-cluster variance on the logistic scale is known and fixed at $\pi^2/3$ (**add in comment in Extended Data**

table 9, page 46), so only the between-cluster component varies (add in Extended Data table 9, page 46). The total variance can be deduced from this.

12. In general, many extended data tables do not have clear titles and may not be referred to anywhere in the text. Please refer to them in the text where appropriate to explain their inclusion, and ensure titles and notes are clear. Or, text in the supplement before each table explaining it could be included.

Reply from the authors: We have verified that all Extended Data Tables are now properly referred to in the main text, and ensured that each table has a clear title.

Reviewer #3 (Remarks to the Author):

Thank you for the opportunity to review the manuscript presenting the results of this large cluster randomised trial. The NutriVax-Measles trial utilised the distribution of nutritional supplements at health facilities to create an additional demand for vaccination services. In areas served by health facilities in the intervention group, children aged 6-23 months were eligible to receive micronutrients (a monthly supply / a supply for 3 months if living >10km away), when presenting at the health facilities. At health facilities, vaccination cards were inspected and missing vaccines provided. At a follow up survey after 12 months of intervention, vaccination coverage for first dose of measles vaccine is reported to have increased markedly: by an additional 20 percentage points relative to the control clusters corresponding to a doubling of the odds of being measles vaccinated. The trial is important, and it has potential impact on future policies. The manuscript clearly presents the results and appropriate comparisons across arms. My main concern is the definition of the primary outcome.

The paper (and protocol) specifies that children without a vaccination card are considered unvaccinated. Yet, in the paper, vaccination card possession and vaccination card seen appear to have been equated. (Text: "Vaccination card possession, however, was higher in the control arm (384 children, 48%) than in the NutriVax arm (318 children, 40%)."; these numbers are in table 1 presented as "Vaccination card seen").

If I interpret the analysis practice correctly and all children without an inspected card have been considered unvaccinated, I think there is a problem. The proportions presenting a vaccination card differs markedly between the trial arms, both for the baseline survey as presented in the text: "Vaccination card possession, however, was higher in the control arm (384 children, 48%) than in the NutriVax arm (318 children, 40%) and for the endline survey, where higher proportion is seen in the intervention arms, 552 (69%), than in the control arm, 474 (59%).

Indeed, the secondary result, MCV1 coverage based on card and recall, indicates that 33-42% (depending on timepoint and arm) of the children for whom no card was inspected, are reported to have received MCV1. I think the definition of the measurement of the primary outcome should be clarified, and the validity of measurement of the primary outcome should be discussed. The 15pp increase in coverage when considering also recall, is by no means negligible, and I think this measure better describes the effect which should be anticipated. Therefore, I don't think your discussion of the outcome definition "Accordingly, while our primary outcome measure was vaccination verified by card, secondary outcomes relying on recall should be interpreted with caution." is adequate.

Reply from the authors: We thank the reviewer for this important comment, which allows us to clarify the measurement of the primary outcome.

First, the variable previously labelled as “Vaccination card seen” in all tables and figures corresponded to “vaccination card possession” in the main text, which was confusing indeed. Second, while a child could possess a vaccination card, it was possible that the measles vaccine was not recorded or administered, which explains discrepancies between the proportion of children with a vaccination card and those with MCV1 verified by card. As specified in the Method/Statistical Analysis section, for the primary outcome, children without a vaccination card were considered unvaccinated. However, children with a card but without MCV1 recorded were also considered unvaccinated. This approach was applied consistently across all outcomes verified by card.

For secondary outcomes based on card or caretaker recall, caretaker recall was only used for children without a vaccination card. In these calculations, the numerator included children with vaccines recorded on the card plus children without a card whose caregiver reported vaccination.

For the sake of clarity, **all tables and figures have been updated to replace “Vaccination card seen” with “Vaccine card retention”** and we have provided more details at the start of the Methods/Statistical Analysis section (**page 25**) to clarify outcomes definition, as follows : for the primary outcome, *“Children without a vaccination cards were classified as unvaccinated, and children with a card but with no MCV1 recorded were also considered unvaccinated”*; and in the paragraph on secondary outcomes also **Page 25**: *“Secondary outcomes based on vaccination card or caretaker recall were calculated by including children with the vaccine recorded on the card, as well as children without a card whose caregiver reported that the vaccine had been received.”*

Minor comments:

Abstract: Typo – “diphtheria-pertussis-tetanus-containing”

I was surprised to see line “Coverage gains for age-appropriate and catch-up vaccines were even greater when comparing children who actually received SQ-LNS compared to those who did not in the NutriVax arm.” – without having a baseline assessment, for recipients/non-recipients, conclusion on gains seem inappropriate. The coverage is higher, but that’s not surprising for children in contact with the health centers.

Reply from the authors: The typo has been corrected to “diphtheria–tetanus–pertussis–containing.”

In the NutriVax arm, baseline coverage prior to SQ-LNS implementation was 25.0% (Table 2). At endline, 48% of children had ever received SQ-LNS and 52% had not. We conducted an exploratory, post-hoc analysis comparing outcomes by SQ-LNS uptake and observed differences in vaccination coverage. However, as this analysis was non-randomized and exploratory, it is not appropriate for inclusion in the abstract. To avoid misinterpretation, this post-hoc analysis (originally Table 4,) has been moved to the extended supplementary data (now **Extended Data table 13, page 51**), and the Results section (**last paragraph- page 13**) has been revised accordingly.

Results: Inconsistent referencing to ‘Supplementary Tables’ or ‘appendix 1 page 1’. Supplementary Table 6 before Table 3b. And the tables themselves are names “extended data tables”

Reply from the authors: We thank the reviewer for this observation. Inconsistent references to supplementary materials have been corrected throughout the main text, and all tables are now consistently referred to as “Extended Data Tables” in the text.

Discussion: In the discussion you state “Limited overlap between MCV1 and MCV2 recipients has been documented in Nigeria and elsewhere, and receiving MCV1 before 12 months of age has been

positively associated with MCV2 uptake (25).” – How can there be limited overlap between MCV1 and 2? As per definition MCV2 cannot be given without MCV1 – also, I don’t think this is supported by ref 25.

Reply from the authors: Indeed, by definition, MCV2 cannot be administered without prior MCV1. The intended point was to highlight that in some settings, coverage of MCV2 remains substantially lower than MCV1, leading to apparent gaps between children who receive the first versus the second dose. We have revised the sentence in the Discussion **page 14-fifth paragraph** to clarify this as follows: *“In Nigeria and elsewhere, substantial dropout between MCV1 and MCV2 has been documented in a pooled analysis of surveys (26).”*

Methods: Participation was voluntary – but what proportion of children presenting at the health facilities received supplements?

Reply from the authors: Unfortunately, we do not have data on the proportion of eligible children presenting at the facilities who actually received the supplements.

A description of how interviews on vaccination recall were conducted would be helpful. If the readers do not know that there are distinct anatomic locations for different vaccines, the recall does not seem reliable.

Reply from the authors: We have added further details on the recall procedures in the **Methods-Outcomes measures section in the second paragraph (page 24)** to clarify how we collected the data: *«Vaccination data were primarily obtained from vaccination cards, or caregiver recall when cards were unavailable (except for meningococcal vaccine) using standardized WHO questionnaires, which include prompts based on vaccine route of administration and anatomical injection site (e.g., BCG scar on the upper arm, pentavalent injections in the thigh, oral polio drops) (42).”*

The formulation “binary variable of whether the settlement directly deserved by PHCC for immunization” at endline (post-hoc)” is unclear

Reply from the authors: We thank the reviewer for pointing out this wording issue. The sentence has been corrected by adding the missing verb and rephrased for clarity. It now reads: *“the binary variable indicating whether the settlement **was** directly **served** by the PHCC for immunization at endline.”*

Extended Data Table 1: You seem to have forgotten IPV2. I also think that it would be helpful to add (e.g. colour code) which vaccines were covered by the interview (finding the information in the appendix of the protocol was difficult) and which were secondary outcomes.

Reply from the authors: We thank the reviewer for the careful review. IPV2 has now been added to Extended Data Table 1b. To improve clarity, we have also revised the Footnotes to **Extended Data table b1 table page 28** to indicate which vaccines corresponded to prespecified outcomes, as follows:

Pre-specified outcomes:

Primary outcome: *Measles coverage, defined as receipt of the first dose of measles-containing vaccine (MCV1)*

Secondary outcomes:

- **Timeliness of MCV1:** *Receipt of MCV1 within one month of the child’s 9-month birthday*
- **MCV2:** *Receipt of the second dose of measles-containing vaccine among children aged ≥ 15 months*
- **Other vaccines:** *Receipt of the third dose of pentavalent vaccine, meningitis vaccine, yellow fever vaccine*

- **Zero-dose:**
 - **WHO/Gavi definition:** Children who had not received any pentavalent vaccine
 - **Nigerian NPI definition:** Children with no BCG, no pentavalent-1, no PCV-1, no OPV-1, no MCV1, no yellow fever (confirmed by card or caregiver recall), and no IPV1 or meningitis vaccine (confirmed by card)
- **Fully vaccinated:** Children with BCG, pentavalent-3, PCV-3, OPV-3, at least one dose of measles vaccine, yellow fever (confirmed by card or caregiver recall), IPV-2, and meningitis vaccine (confirmed by card).

Extended Data Table 3a; You refer to the mother as “he”

[Reply from the authors:](#) We thank the reviewer for the careful review. This has been corrected.

Reviewer #4 (Remarks to the Author):

The authors report the results of a pragmatic cluster-randomized trial conducted in rural areas of Yobe State, Nigeria. The trial was designed to test whether distributing SQ-LNS in routine vaccination programming would lead to an increase in vaccination coverage. This is a relevant question, particularly given the low uptake of EPI and the pervasiveness of undernutrition in northern Nigeria. They found that provision of SQ-LNS (rations of either 30 or 90 sachets) via the EPI did lead to significantly higher vaccination coverage (OR 2.08, though the absolute endline MCV1 coverage in the intervention arm remained only 55%). For the reasons mentioned above, improving vaccination coverage and nutritional status are important in Nigeria and elsewhere, and this trial provides novel information about this question. The trial protocol has been published, and it is important to note that there are other secondary analyses and related studies that will be reported separately.

In terms of my specific comments to the authors and editors:

- The manuscript is far too long, and weighed down by excessively long tables, and would benefit from an overall rewrite with a goal of being more concise and precise. Even though there do not appear to be word/table limits, this At >1600 words, the discussion in particular should be more focused. I will make specific comments where possible, but in the absence of line numbering it is a bit difficult at times. Some of the tables are unreasonably long (Table 1 is 2.5 pages in 11-point font.) These should be reduced further, with non-essential information reported in appendices/supplemental tables.

[Reply from the authors:](#)

We have revised the manuscript to improve conciseness and clarity particularly in the Discussion, which has been more tightly focused on the main findings and their implications, within the journal's word limit (<4,000 words, excluding Methods). Table 1 has also been simplified and shortened. Detailed information on child morbidity and parental (mother and father) characteristics has been moved to **Extended Data table 3 (page 30) and is mentioned in the results page 6** to improve readability and maintain focus on essential results in the main text.

- In terms of trial design and methodology, the cluster-randomized design is appropriate, and there appears to have been minimal crossover between clusters (only a few children in control arms had SQ-LNS during surveys). Specific methodological/reporting concerns that I have include the following:

1. I think the paper would benefit from a more thorough description of the clusters - only total population is reported for the entire arms - what were the catchment areas of the different health centers, etc., number and size of villages per HC, etc.

Reply from the authors: Indeed, the description of clusters were insufficient and have reinforced to the addition of an Extended Data table 1a (page 5), that is now referenced in the results section.

2. For the surveys, it would also be helpful to understand how the sampling frames were made - PPS is used, but where did population data come from? Nigeria has not had a census for many years, and data is often unreliable. Did the investigators carry out a census in the study area prior to the trial? If not, incorrect assumptions about populations of villages may have led to bias.

Reply from the authors:

This important comment has already been addressed when answering to the other reviewers. The sampling frames were based on population data per settlement for each ward (cluster) within each Local Government Area, obtained from the Yobe State Ministry of Health, Immunization Department (updated 2024). These data included estimated numbers of children aged 12–23 months per settlement. This information has been clarified in the Results and Methods section (**end of page 4 and page 23**).

We acknowledge that in the absence of a recent national census in Nigeria, these estimates may be imperfect. However, in this cluster trial, per-cluster sample size was determined to ensure adequate power to detect the intervention effect rather than to reflect absolute population numbers. While inaccuracies in population estimates could influence cluster selection (via probability-proportional-to-size sampling), the internal validity of the primary estimand (cluster-specific OR) is maintained through randomization and analysis using mixed-effects models. Sensitivity analyses further ensure robustness against such biases, limiting their impact on inference.

For the sake of brevity, we have decided not to specify this in the revised manuscript. We would be pleased to revise it further however, should the editors deem it necessary.

3. I was surprised that there was not a description of permission-seeking for randomization of villages/HC by selected gatekeepers. The informed consent process for individual survey participants is described, but I would have expected the investigators to also seek some sort of formal permission from health and/or political leaders. (See various articles on ethical considerations of Cluster RCTs by Weijer.) Obviously involving the community in the randomization process is great, and it seems like there were real efforts at community engagement, but is that enough? I would appreciate a discussion of that.

Reply from the authors:

We are grateful for this comment, which allows us to provide more details in the Ethical section **page 26**:

“Prior to trial implementation, the study objectives, trial design, cluster allocation, and SQ-LNS distribution procedures were reviewed and approved by State and LGA health authorities, as well as community representatives during formal meetings

Community engagement was maintained throughout the study via regular meetings with local leaders and through the national steering committee, which included representatives from the Ministry of Health, local and international nutrition and immunization actors, and community leaders. These activities ensured that community leaders and state authorities were informed, supportive, and formally aware of the trial’s design, progress and outcomes.”

- In terms of statistical analysis, the statistical analysis plan appears robust, but warrants review by a statistician specialised in the conduct of CRCTs, which I am not.

Reply from the authors:

Reviewer 2 was a statistician and extensively reviewed our statistical methodology.

- In terms of the authors' conclusions and the inferences they have drawn:

1. At several points, including in the abstract, they refer to their intervention as "potentially cost-effective" or similar. Given that no cost data are presented, all such references should be removed from this manuscript.

Reply from the authors: We thank the reviewer for this comment. The reference to cost-effectiveness has been removed from the manuscript, as no cost data were presented here (but will be presented elsewhere).

2. There is no discussion of actual vaccination coverage, which is a major weakness of the discussion. The primary result showed an important impact of the intervention. But even in the intervention arm, MCV1 coverage among 12-23-month-old remained at 55%, well below thresholds for population immunity. I think this is a major limitation, and should temper some of the investigators' excitement over their results. Vaccination in northern Nigeria is very difficult, and marginal improvements are very welcome, but simply giving SQ-LNS is not going to solve the problem. It should also be noted that in the control arm, vaccination coverage increased by approximately 10% over the study period.

Reply from the authors: We thank the reviewer for this important comment. We have revised the Discussion to better reflect the absolute vaccination coverage levels observed in the study and to acknowledge that, although the intervention improved MCV1 coverage, coverage in the intervention arm remains insufficient to reach immunity herd. We now clearly state that SQ-LNS distribution through routine health services alone should be considered as a complementary strategy rather than a standalone solution. The discussion has been revised by adding a new paragraph, as follows page 14: *"We reported substantial the gains in MCV1 coverage in the NutriVax arm, but it is important to note that endline coverage by card (55.3%) or by card or recall (68.5%) were still well below the 95% immunization coverage needed to achieve herd immunity. Even though promising, solely associating SQ-LNS with routine immunizations at PHCCs would be insufficient to achieve this high vaccination coverage at population level in an environment as challenging as northern Nigeria. Decentralizing SQ-LNS distributions to lower level health posts, however, and not just PHCCs as in this trial), would likely further increase SQ-LNS uptake, and MCV1 coverage, as suggested by the exploratory, post hoc analysis (Extended Data Table 13).*

We have also more discussed the increase of MCV1 coverage in the control arm (page 15-second paragraph), as follows: *Community engagement interventions that foster trust and address concerns about vaccines have been shown to have modest but significant positive effects on immunization outcomes (34). In our study, fear of side effects decreased in both trial arms, likely reflecting ongoing community mobilization activities. This may have contributed to the increase in card-verified MCV1 coverage in the control arm and may also have contributed, in part, to increased vaccine uptake in the intervention arm."*

3. I find the 5th paragraph of the discussion confusing (begins with "Spatial heterogeneity"). I'm not sure how the spatial heterogeneity fits in with reasons for non-vaccination and vaccine acceptance. Likewise, I think that the claims that the intervention (giving SQ-LNS) led to increased faith in vaccination a little over the top, as well...I don't think that causation can be inferred.

Reply from the authors: We thank the reviewer for this comment that gave us the opportunity to rephrase this paragraph in line with the variability of cluster-specific MCV1 coverage results from **Extended Data table 6 (page 44)**, and the reasons given by the respondents for explaining why their

children were not being fully vaccinated. This reasons were presented by arm (Table 1) and by LGA (**Extended Data table 3a, page 31**). We have ensured that the revised text is more accurate and avoids overinterpretation (**page 15-second paragraph**): *“Cluster-specific variability of MVC1 coverage was observed both at baseline and at endline, reflecting the context-specific barriers faced by caregivers in accessing immunization services, more broadly in sub-Saharan Africa (30). In our trial, like in other studies (8), maternal workload was a persistent barrier to vaccine coverage across arms and time points, but most importantly in Karasuwa LGA. Other previously identified barriers like long distances to facilities, inconvenient vaccination times, long waiting times, fear of side effects and faith in immunization also varied among LGAs, highlighting the importance of understanding local factors when trying to facilitate access to essential health care interventions (31–33).”*

4. In terms of generalizability, this is billed as a "pragmatic" trial, but there was still significant support provided by a well-funded international humanitarian organization. Managing stocks of vaccines and nutritional supplements often proves difficult for ministries of health - and similar results might not been seen in other settings with less support.

Reply from the authors: We thank the reviewer for this important point. We have added a last sentence in the paragraph on the Limitations (**page 16**), as follows: *“Finally, the intervention was delivered pragmatically at points of care with minimal additional human resources. However, ALIMA provided some support to the MoH to ensure continuous availability of SQ-LNS and help prevent vaccines stockouts. Therefore, the results may not be fully generalizable to settings with less continuous supply of SQ-LNS or vaccines.*

“

Overall, the manuscript is well-written, but far too long, and would benefit from substantial revision.

Reply from the authors: The manuscript was within the <4,000 words limit recommended by Nature Medicine and it is still the case after revision. We thank all 4 reviewers for their insightful comments that clearly helped improving the manuscript.

Reply to the additional comments received on April 1, 2026:

We would like to respectfully emphasize that as scientists from the North and the South, we do not find appropriate the way this reviewer is addressing his/her comments. These strong and unnuanced comments are not in line with those more balanced from the four previous reviewers. This reviewer does not cite any scientific references to support his claims, which are therefore unreferenced personal opinions. We did our best to address these sometimes difficult to follow comments.

Please find attached with my comments as comment bubbles on the manuscript's pdf. You will see my overall impression. It is an unnecessary trial, and in my view, largely useless one too, while I agree with you that it was operationally well conducted, if one can say such a trial that betrays such little attention to context and complexity was well conducted. I'm struck by how much the "intervention" itself was so poorly thought through and specified (is it an incentive or is it a nutritional supplementation) as this has strong bearing on the meaning of the work, how one interprets it and makes sense of its value.

Reply from the authors: Arguing without further justification that the trial was “unnecessary” and “useless” and the intervention “poorly thought” is an attack on our scientific integrity and that of our funders (GAVI, Eleanor Crook Foundation, ANRS-MIE) and our Scientific Advisory Board: Katherin

Dewey (University of California, USA), Indi Trehan (University of Washington, USA), Lieven Huybregts (International Food Policy Research Institute - IFPRI, USA), Saskia de Pee (World Food Program - WFP, Italy) and Alison Connor (IDinsight, Kenya). It is also an attack on the professionalism of the two Ethical Review Boards in Nigeria and France who assessed the trial on various dimensions including appropriateness and usefulness. Finally, it is an attack on the African researchers and clinicians involved in the trial who have been treating and preventing illnesses in children in the field for 20 years, knowing better than anyone the realities of that field, and therefore have no desire to spend several years investigating a pointless question. To say that money and energy are being spent on “useless” research is a very serious accusation, because it amounts to saying that our research was unethical.

For a further description of the intervention itself that this reviewer (and this reviewer only) declared as “poorly specified”, we invite the reviewer to carefully read the Method section of the article (surprisingly, this reviewer did not comment on that section at all).

Per the wording of the intervention itself, we acknowledge having wrongfully used the word “integration” in some instances of the previous version of the manuscript and invite the reviewer to read our answer to the second major comment of Reviewer 1.

This research was co-built by African & European scientists and humanitarian aid workers from the NGO ALIMA. The unique field expertise from ALIMA allowed us to implement this randomized trial in a particularly complex setting in Northern Nigeria where under-five mortality is one of the highest in the world but totally overlooked by clinical research. An analysis of trials registered on the International Clinical Trial Registry Platform between 2000 and 2023 found that only 10% included children; of those that were explicitly paediatric trials, only 9% were conducted in low-income and middle-income countries (Berkley JA. Lancet Glob Health. 2025;13:e732–39). Our successfully conducted trial on an innovative child global health intervention - that showed very positive results - originally contributed to fill in that gap and to ensure that no child should be excluded from clinical research.

With regards to the specific humanitarian context, ALIMA has been supporting Nigeria's MoH for the outpatient and inpatient treatment of malnutrition in northern Nigeria since 2016. In 2025, ALIMA teams supported the outpatient treatment of 65,000 children for malnutrition, including 12,500 who required hospitalized care in Katsina, Borno, and Yobe states. This long-term presence and collaborative work with the MoH was instrumental in being able to identify two senior academic medical professionals from Yobe State as co PIs. Dr. Baba Goni Waru and Dr. Nuru Suleiman Muhammad. They provided invaluable insights in the design stage to make sure the trial was sensitive to context-specific factors; that all notices, informed consent forms, and sensitization materials were in line with Nigeria's standard of care and in appropriate language for the population where the study was being conducted. During the trial, they helped ensure there was good protocol adherence, that the trial was conducted in an ethical fashion, and that state, local and federal stakeholders were regularly updated on the study's progress. After the trial, they helped us present the preliminary results in multiple events with community leaders, LGA, state and federal health authorities.

As we described in our answer to Reviewer 1, global and domestic financing for treating and preventing malnutrition remains woefully inadequate. While malnutrition poses the greatest risk to child survival, funding for treatment and prevention currently relies mainly on humanitarian aid, which is *ad hoc*, insufficient, and at the mercy of political shifts. Most other public health crises - HIV/AIDS, malaria, routine immunizations, family planning, etc. - have large, dedicated financing mechanisms, especially for therapeutic or preventive inputs like ARVs for HIV/AIDS, ACTs and bednets for malaria, vaccines for infectious diseases, or birth control for family planning. This is not the case for malnutrition. So even though SQ-LNS has strong scientific evidence and is recommended in some contexts of high needs like Northern Nigeria, this lack of international financing mechanisms

and domestic investments has led to a very slow uptake of SQ-LNS. This has changed dramatically in Nigeria since the study ended, as we described in our response to Reviewer 1's second question, but at the time of the study, there was little prospect of financing for SQ-LNS distributions in Nigeria.

As we also said in our reply to Reviewer 1, one aim of the study was to see if we could demonstrate even further additional benefits of SQ-LNS (i.e. increased vaccination coverage when distributed alongside routine immunizations in addition to the well-established evidence on child growth) in order to give governments and international donors more reasons to invest in the intervention in contexts where there is a high burden of malnutrition and low vaccination coverage.

And because we were aware of the food security situation in Yobe state, we explicitly stated in the protocol of the study and in the text of the manuscript that receiving SQ-LNS was not conditioned on receiving a scheduled vaccine. If a caretaker refused a vaccine even after a discussion with a health care professional to address parental concerns, any eligible child could still receive their SQ-LNS ration

I'm also struck by how much the trial appears to skirt around any serious engagement with the obstacles to routine immunisation uptake in Yobe state, Nigeria and what a package of interventions designed to address them, with those obstacles as the focus, may really look like, conceived by attending to context and complexity. I'm left wondering whose question, whose knowledge/learning need this trial was designed to address.

Reply from the authors: Obstacles to routine immunization are well known, in Nigeria especially. We specifically cite several Nigerian studies and a systematic review of Nigerian studies on this very theme, many of which oriented us before, during, and after the trial. However, a recent review of previous experimental studies reported little or no effect of health education, SMS reminders, or financial incentives on vaccine coverage; but the only study included in the review that used a food-based incentive did show a significant increase in coverage. Our intervention consists in breaking the boundaries and creating synergies between two vertical programs by distributing SQ-LNS for children aged 6-23 months alongside with the routine National Program of Immunization. The simplicity of the intervention seems to be an issue for the reviewer. However, our data show that a simple intervention has the potential to address a complex issue.

Our knowledge/learning message is that the NutriVax strategy consisting in distributing SQ-LNS alongside routine immunization in northern Nigeria substantially improved measles vaccination coverage in a population of children 12-23 months, as well as coverage for other routine vaccines, while dramatically reducing the percentage of zero-dose children and the percentage of children who were simultaneously zero-dose and acutely malnourished. NutriVax is therefore a very promising Immunization-Nutrition-Integration strategy, and should be urgently considered for scale-up in contexts facing the dual burden of high malnutrition prevalence and low vaccination coverage.

After the trial ended, we shared the results presented in this article with Yobe State authorities, who fully understood the knowledge/learning message brought by the NutriVax-Measles trial and decided to allocate funds for SQ-LNS procurement in their 2026 budget. Nigerian federal authorities are now also considering applying the NutriVax strategy. Our results are therefore meaningful to Nigerian health authorities.

Please find below our answers to the 29 bubbles comments in the manuscript's PDF.

Comment #1 - Abstract

It appears, and this is borne out in the rest of the paper, that this was really the (active mechanism in the) intervention. Not nutrition supplementation.

Reply from the authors: We do not understand what the reviewer is referring to here. Can you please clarify.

Comment #2 - Introduction

These are recommendations with incredible logical validity; claims one can make even without "high-certainty evidence". In other words, giving children who are hungry food is good for their health and growth.

Reply from the authors: There seems to be a misinterpretation of the wording consistently used in WHO guidelines since 2012. Per the *WHO handbook for guideline development (Second edition, 2014)*, to improve the guideline development process and facilitate the explicit, systematic and transparent formulation of recommendations from evidence, WHO adopted GRADE (Grading of Recommendations Assessment, Development and Evaluation) as the method for assessing the quality of a body of evidence and for determining the direction and strength of the resulting recommendations. The certainty or level of confidence in an effect estimate depends on several factors, namely risk of bias, imprecision, indirectness, inconsistency and publication bias. GRADE rates certainty as high, moderate, low and very low based on a combination of these factors.

We were then just reporting a WHO recommendation on a preventive formulation of nutritional supplements in children living in high food insecure contexts, with its level of confidence (high-certainty evidence) as recommended.

We agree that "giving children who are hungry food is good for their health and growth", but the reviewer might be surprised at how many international and domestic actors feel otherwise, and focus on education rather than food access.

Comments #3 & 4 - Introduction

But this is inevitable, to be expected, even necessary. The evidence cannot not be mixed. The context in which those interventions are being implemented varies so widely that the problem will be if the evidence were NOT mixed!

It will be unwise to take any of these claims (that is, evidence) as given. There are many reasons, independent of the "intervention" why there may be little or no effect. There are also many reasons to do with the "intervention" (dosage, tailoring to context, comprehensiveness, etc) why there may be little or no effect. So, the findings of a Cochrane review on interventions so complex, inserted into contexts so varied, are simply unreliable.

Reply from the authors: The reviewer seems to question the purpose of Cochrane Systematic Reviews without offering an alternative solution on how to report previous work on interventions to improve vaccine coverage. But we are assuming that the suggestion was to emphasize that these interventions and their effects are context-dependent.

We have modified the sentence as follows: "*Evidence on interventions to improve childhood vaccine coverage in low- and middle-income countries is mixed and context-dependent*".

Comments #5 - Introduction

This is not true. This is at least as old as the 1970s and 1980s "selective" and "comprehensive" versions of Primary Health Care.

Reply from the authors: WHO and UNICEF have first included in 2005 the concept of integrating the delivery of other maternal health and child-survival interventions with immunization services as one of four key strategic areas of the 2006–2015 Global Immunization and Vision Strategy framework.

We have therefore re-worded the sentence as follows: *“Integrated delivery of essential nutrition interventions and routine immunization services has been a key strategic area in global child health for two decades, but a scoping review found that, to date, the only approach implemented at scale has been vitamin A supplementation delivered alongside routine vaccines.”*

Comments #6 - Introduction

This is the key point here; that "routine immunization" is there for SQ-LNS to be integrated into.

Reply from the authors: We had already reworded this sentence to address one of Reviewer 1 issues.

The sentence now reads: *“Delivering small quantity lipid-based nutrient supplements (SQ-LNS) supplementation integrated with routine immunization meets these criteria...”*

Comments #7 - Introduction

Not present here is the basic requirement for an incentive to work: the extent to which one may expect that there is a perception that what is to be given is considered valuable.

In this case, it appears that this is a function of how "low-income" the people being incentivised are in this particular setting. Put crudely, how hungry are parents and children for this incentive?

This is an important consideration in thinking about the point and purpose of this trial. For whom can it work? Where can it work? How long can it work in a particular place? What are the potential negative consequences?

Reply from the authors: We have already justified throughout the manuscript the particularity of the context of Northern Nigeria cumulating the worst child nutrition and immunization outcomes.

We have added this sentence in the introduction to emphasize the expected value of SQ-LNS in the Nigeria context: *“Beyond nutritional benefits, free provision of SQ-LNS at primary health care facilities at the end of the vaccine circuit may encourage caregiver attendance, thus creating additional opportunities for vaccination and help overcome previously identified barriers such as distance, distrust, and vaccine hesitancy.”*

As already described in the manuscript, NutriVax-Measles embedded other populations and data collection methods of which results will be presented elsewhere. It includes an implementation science sub-study consisting of two qualitative acceptability and feasibility surveys including parents/legal guardian of children aged 6–23 months, community representatives, community health workers, and health care providers: one after 3–4 months of the intervention implementation and one during the last 2 months of the study. This sub-study will help understanding the questions raised by the reviewer but these questions were not the primary outcomes of the NutriVax-Measles trial that are reported in this manuscript.

Comments #8 & 9 - Results

This appears to be the only thing done in this intervention that may be interpreted as reflecting a response to context.

How is the intervention calibrated to this context? I note the point about giving three-month packs to caregivers living further away, but what else?

Reply from the authors: Indeed, we adapted monthly SQ-LNS rations to three-month rations when families lived >10km from the health facility based on feedback from families as well as the interim qualitative assessment. Other parts of the intervention that were calibrated to this context included the sensitization materials developed with our two national Co PIs. For example, we learned from

colleagues at Mary Dinah who ran small pilot distributions in a different part that SQ-LNS were commonly referred to as “child fertilizer” because it helped children grow. We used this moniker but made sure to note that it wasn't real fertilizer. Another example that also arose from our interim qualitative assessment was the importance of sensitivating fathers as to the importance of vaccinations. So we added men's groups - equally in the control and intervention arms- to the vaccine sensitization activities with Nigeria's standard messaging. Additional adaptations to the context will be discussed in our manuscript analyzing the results from the qualitative component of the study.

Comments #10 & 11 - Table 1

How is the intervention calibrated to this context? I note the point about giving three-month packs to caregivers living further away, but what else?

As above, shouldn't this be where you design your intervention from? It appears you decided the solution before investigating the problem!

Reply from the authors: Immunization barriers are well known and documented in Nigeria and our results are in line with what was documented, as discussed in the manuscript already. Most of these barriers required community mobilization awareness, this is why continuous sensitization on vaccination within communities and at PHCCs was implemented in both control and intervention arms. And our hypothesis was that providing free SQ-LNS at health facilities could further help overcome barriers such as distance and vaccine hesitancy by increasing caregiver attendance and, consequently, opportunities for vaccination.

Continuous sensitization on vaccination within communities and at PHCCs showed less fear of side effects at endline and higher faith in immunization in both arms. SQ-LNS in addition to this sensitization more than doubled the odds of receiving MCV1.

Of course, all barriers cannot be addressed through sensitization and SQ-LNS distribution. Barriers such as maternal workload, poor roads or lack of transportation would need further decentralization of immunization services and SQ-LNS distributions, as suggested in the discussion.

Comment #12 - Table 2

I can't help wondering how much more effective your efforts might be if you started by paying careful attention to context, including local, situated knowledge about what works or might work here given prior efforts.

I also can't help wondering how stable one might expect this outcome pattern to be over time.

I also can't help wondering how the authors are theorising or explaining the improvement in the control arm.

Reply from the authors: The national co-investigators of the NutriVax-Measles trial from Yobe State and the NGO ALIMIA have been working in the area for 20+ and 5 years, respectively. More than anyone, they are familiar with the contextual realities and the programs implemented and already evaluated in the trial area, in addition to an extensive knowledge reported in the literature on this region. As stated in the response to reviewers 1 and 2, health actors at all levels of the health system, as well as civil society through its community representatives, were involved from the trial's inception and endorsed the study's objectives, design, and the evaluated intervention, deeming it relevant and appropriate to the context. The revised version of the article better highlights this strong involvement of local actors throughout the project cycle.

How stable one might expect this outcome pattern to be over time is a different question than the one addressed in this article. Our trial showed how efficient the intervention could be in a pragmatic clinical trial setting, and this intervention now needs to be implemented at scale to check the stability of the outcome. We are showing a consistent and strong OR of 2.11 (95% CI 1.25-3.59) and a 20% (95%CI 13.7 to 26.5) increase in card-verified MCV1 coverage and these results received the highest consideration and attention by national (see our previous answers) and international stakeholders such as GAVI. Given these substantial gains in MCV1 and other infant vaccine coverage in routine EPI, immediate action for funding SQ-LNS has taken place at the Yobe state level.

Concerning the improvement in MCV1 coverage between baseline and endline observed in the control arm, this was already addressed in the discussion: we hypothesized the improvement may be due to continuous sensitization with messages around the importance of vaccines within Nigerian communities, those being made available in both intervention and control clusters.

Comment #13 - Results page 11

We shouldn't need a trial to tell us this; certainly, not yet another trial. I wonder whose doubt, whose knowledge, or learning need this study was designed to address.

There are clearly questions in the location where this study was conducted begging for answers. This question (does providing nutritional supplement as incentive to come to health facilities) is not one of those.

Reply from the authors: This comment is difficult to understand precisely because no study had previously evaluated a strategy such as distributing SQ-LNS alongside routine immunization services at PHCCs. Therefore, this is not just another study but, to the best of our knowledge, the first one of its kind.

Furthermore, the 2-fold increase in MCV1 coverage shown in our trial is much more significant compared to all other interventions evaluating measles vaccination strategies in routine EPI programs and reported in the recent meta-analysis that was mentioned in the discussion (Yitbarek K. BMJ Glob Health. 2025;10(2):e016647).

Comment #14 - Discussion page 15 (313-316)

This is such an unnecessary study. The mechanism of action (incentives) is well researched, there is no need to do this trial to, once again, confirm it, or to confirm it specifically for "immunisation". There are many reasons (some mentioned above) as to why there are far more important questions begging for answers in the location where this study was conducted.

Reply from the authors: The study by Banerjee in India and published in the BMJ is the only randomized trial with NutriVax-Measles having specifically evaluated the impact on vaccine coverage of implementing preventive nutritional interventions within routine immunization services. Given the importance of both nutrition and immunization interventions in these Indian and Nigerian contexts of high malnutrition and low vaccination coverage, and the particularly high impact we demonstrate with NutriVax-Measles, we strongly disagree with the reviewer's personal opinion.

Comment #15 - Discussion page 15 (318)

Of course! What you need to be stating, and working through carefully are the context-specific explanations for the variations!

Reply from the authors: It is quite disturbing because the reviewer seems to be repeating the same strong opinion without any sound scientific argument to support his/her say. We have already addressed this comment in our previous answers to this reviewer.

Comment #16 - Discussion page 15 (320)

Again, unnecessary quest. The answers were clear without the question being asked.

[Reply from the authors:](#) We do not understand what the reviewer is referring to here. Please clarify.

Comment #17 - Discussion page 15 (324-327)

It is important to recognise that incentives can vary in their effects over time (attenuated for various reasons), including by becoming the norm (which, paradoxically, should be the goal here).

Also, for an intervention that is as prone to rumours as vaccination, incentives or a singular focus can have a counter/negative effect by triggering rumours, as it did in Nigeria a couple of decades ago.

[Reply from the authors:](#) Indeed, and that is why combining community outreach activities with community engagement is essential. This is well demonstrated in the evaluation of the intervention's acceptability, for which another manuscript is being prepared. The results of the qualitative survey will help to further contextualize the quantitative findings presented here. Notably, the implication of husbands in the sensitization sessions has been shown to help overcome some barriers related to lack of faith on immunization or for giving authorization to mothers to accompany children to vaccination sessions.

Comment #18 - Discussion page 17 (339-340)

Yet, you largely assumed away, ignored "the complex and context-specific barriers"; conducted this study as if they were not there.

[Reply from the authors:](#) This is a repetition of a previous comment, and we feel we have already addressed this comment in our previous answers to this reviewer.

Comment #19 - Discussion page 17 (344-345)

I wonder how else you are theorising the improvements in the control arm.

[Reply from the authors:](#) The contribution on vaccine coverage of community sensitization in both arms is better hypothesized in a paragraph in the revised discussion section, on remaining barriers. However, the data presented in this paper do not allow for bringing more insights than this hypothesis. The results of the qualitative survey however may help in understanding the quantitative findings presented here.

Comments #20 & 21 - Discussion page 17 (350, 361)

But what you did here is not just "SQ0LNS supplementation". What you did is also incentivise; perhaps the incentive is the real intervention here and not the supplementation.

Incentivising parents to attend routine immunisation or PHC facility visits? This seems to me to be the real intervention here.

[Reply from the authors:](#) These are again a repetition of the same comment we had already addressed in our previous answers to this reviewer.

Comment #22 - Discussion page 17 (364-365)

You have to remember that once SQ0LNS becomes the norm, the effect you are seeing here may go away or significantly diminish.

[Reply from the authors:](#) We do not understand what the reviewer was meaning here. Please reformulate.

Comment #23 - Discussion page 18 (371-372)

I won't be so sure, as I've indicated above. I don't think your study is able to tell us this, in large part because the approach you took is not sensitive to context and to the "particular circumstances of time and place" involved in immunisation uptake. But also, it seems you are not clear about what this trial was really testing. You are conflating, it seems, nutrition supplementation with incentives to use PHC facilities or attend routine immunisation visits.

Reply from the authors: This is once again a repetition of the previous comment we feel we have already addressed in our previous answers to this reviewer.

Comment #24 - Discussion page 18 (374)

I don't think your results change any policy. As you noted already. Nigeria was going to do the roll out (as supplementation), the logical validity of the strategy (as incentive) is without doubt.

Reply from the authors: We already explained in our previous answers how our results are actually already changing policy in Nigeria. GAVI was one of the two primary funders of the NutriVax-Measles trial, and they of course wanted from us sound scientific evidence so that it could inform actual policy change. We delivered much better results than anticipated, and we are now logically expecting policy change.

Comment #25 - Discussion page 18 (380-382)

But you must know that this is an artificially engineered context that in fact reduces that external validity (to elsewhere in Nigeria, and across time in Nigeria) of your trial.

Reply from the authors: Our results are replicable to contexts where MoH is supported by local and international NGOs, which is the case in many parts of Nigeria if not most sub-Saharan Africa. But the ANRiN 2.0 plan for SQ-LNS distributions for nutritional outcomes (which we described in an earlier response to another reviewer), will be a Nigeria-led process for the largest SQ-LNS program globally to date.

We are not sure what the reviewer means exactly with artificial contexts, but we invite him/her to carefully read the Method section of the manuscript where we emphasize in practical and precise terms how the intervention was delivered, nothing was artificial.

Comment #26 - Discussion page 18 (390)

This is NOT a limitation. You are trying to serve one country, primarily. It is a strength that others may be able to learn from what you did.

Reply from the authors: It was our goal indeed and we thank the reviewer for acknowledging that, but showing the same positive results in several countries would have clearly been an added value.

Comment #27 - Discussion page 18 (390)

The big error of this trial (as is the case with most such trials) is to put "generalizability" ahead of being meaningful in a place and over time in that place.

Reply from the authors: The reviewer has already expressed this when arguing our trial was "unnecessary" and "useless" and the intervention "poorly thought". We have already addressed this comment.

Comment #28 - Discussion page 18 (403)

I will rewrite the sentence thus: "Incentivising the use of routine immunisation (with SQ-LNS distribution) in northern Nigeria substantially improved measles... over a time period of X months.

Reply from the authors: We have already reworded that sentence as follows: “Distributing SQ-LNS alongside routine immunization in northern Nigeria substantially improved measles vaccination coverage...”

Comment #29 - Conclusion page 19 (406-407)

It is not clear to me that this was the mechanism of action for this intervention. It seems what happened here was potentially further reinforcing a vertical intervention by offering an incentive for its uptake.

Reply from the authors: We strongly believe that our revised manuscript is very much improved and we warmly thank all reviewers for that. We are hoping this reviewer now has a better understanding of what we did, why it was important to do it, and how important the results from the NutriVax-Measles trial are to address the dramatic mortality of children in contexts like Northern Nigeria.

Your sincerely,

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Responses to Editors and Reviewers

Manuscript NMED-A150449B: Increasing measles vaccination coverage with preventive small quantity lipid-based nutrient supplementation in children aged 6 to 23 months: NutriVax-Measles, a pediatric pragmatic superiority parallel cluster-randomized controlled trial in Yobe State, northern Nigeria

10th June, 2026

Dear Dr Ming Yang and the Nature Medicine Editorial Board,

We would like to sincerely thank you and the four reviewers for the careful evaluation of our revised manuscript and for the constructive comments provided throughout the review process. We greatly appreciate the time and expertise devoted to assessing our work.

Please find below our point-by-point responses to all comments. To facilitate review and preserve the context of each exchange, reviewer and editor comments are presented in black, [our responses in blue](#), and [the corresponding changes made to the revised manuscript in red](#). All page numbers cited in our responses refer to the final revised manuscript without tracked changes.

We believe that the revisions made in response to the reviewers' and editors' comments have substantially strengthened the manuscript. We are grateful for the opportunity to revise our work and hope that the revised version will now be suitable for publication in Nature Medicine.

The editorial team have a number of substantial concerns regarding the manuscript, which will need to be addressed in addition to the peer reviewers' concerns:

Editors' comment 1- The framing of the trial suggests that food supplementation was linked to vaccination activities as an incentive, raising the question of whether receiving SQ LNS was contingent on being vaccinated. Although your response indicates that SQ LNS was provided regardless of vaccination uptake, the manuscript itself does not make this sufficiently clear. Please clarify whether vaccination was required to access SQ LNS, and confirm that denial of supplementation did not occur on the basis of vaccine refusal in the manuscript.

Reply from the authors:

We thank the editorial team for highlighting this important point. We agree that the manuscript did not sufficiently clarify that receiving SQ-LNS was not conditional on receiving vaccination. We have removed the term "incentive" in reference to SQ-LNS from most of the manuscript, reserving it for the Discussion in line with Reviewer 5's Comment 2. Furthermore, we also revised both the main text and the Methods/Procedures section to state explicitly that participation in the SQ-LNS program was voluntary, that receipt of SQ-LNS was not conditional on receiving any scheduled vaccine, and that supplementation was not denied to eligible children on the basis of vaccine refusal.

Change made in the manuscript:

We added the following sentence on page 5:

["Participation in the SQ-LNS programme was voluntary, and caregivers could receive SQ-LNS regardless of whether scheduled vaccines were accepted."](#)

We also revised the Methods/Procedures section (page 22) to read:

“Participation in the SQ-LNS program was voluntary, and receipt of SQ-LNS was not conditional on receiving a scheduled vaccine. All caregivers first entered the vaccine circuit, where the child’s vaccination card or vaccination history was reviewed to determine whether any scheduled vaccines were due. When a vaccine was due and accepted, routine MoH staff administered the vaccine according to the national immunization schedule, either at the PHCC or at an HP, depending on facility catchment area. If a caregiver declined vaccination after counselling by a healthcare professional to address concerns, an otherwise eligible child could still receive the SQ-LNS ration at the PHCC. Thus, supplementation was not denied on the basis of vaccine refusal.”

Editors’ comment 2- The manuscript does not describe what nutrition services were routinely available to children in both arms outside the study intervention. For interpretability and ethical transparency, please briefly outline the standard nutrition services provided in the study setting and clarify whether these services were equally accessible to children in both the intervention and control clusters.

Reply from the authors: We thank the editorial team for raising this point. We agree that the manuscript should more clearly describe the routine nutrition services available outside the trial intervention and whether these services were accessible in both study arms. We have revised the Procedures section to clarify that standard of care nutrition services were routinely available through PHCCs and HPs in all clusters, independently of the NutriVax intervention and in accordance with national guidelines. These services included vitamin A supplementation during vaccination sessions at 6 and 12 months of age, as well as screening and treatment of children diagnosed with acute malnutrition with therapeutic or supplementary lipid-based foods. These services were available to children in both the NutriVax and control clusters.

Change made in the manuscript:

We revised the Methods/Procedures section page 22, by adding a new paragraph, as follows:

“Nutrition services were routinely available across all study clusters, independent of the trial intervention and in accordance with national guidelines. Vitamin A supplementation was provided during vaccination sessions at 6 months and 12 months of age. This was the only preventive nutritional supplementation routinely delivered in the study setting at PHCCs and HPs. Screening for acute malnutrition at PHCCs, HPs, and within communities was part of routine essential primary health-care activities and was conducted by MoH staff according to national guidelines across all clusters. Children diagnosed with acute malnutrition, were referred for nutritional treatment and received therapeutic or supplementary lipid-based foods according to the severity of malnutrition at PHCCs. These routine nutrition services were available to children in both the control and NutriVax clusters, and access to treatment for acute malnutrition did not differ between study arms.”

Editors’ comment 3- Justification of equipoise. The manuscript’s justification for equipoise remains underdeveloped, as the current explanation—that SQ LNS is not standard of care and not realistically scalable—does not sufficiently address the ethical implications of providing a potentially protective supplement to some eligible children but not others. Please expand clearly articulate why randomisation was ethically permissible in this context, how the study team weighed the known benefits of SQ LNS against the decision to withhold it from control clusters, and why universal provision was not considered feasible within the study’s operational or funding constraints. This clarification is essential for readers to understand the ethical foundation of the trial design.

Reply from the authors: We thank the Editorial Team for this important comment and for the opportunity to further clarify the ethical basis for randomization and equipoise underlying the trial design.

We have therefore expanded the Methods/Ethics section to make this justification explicit. The revised text clarifies that, at the time of the trial, SQ-LNS was not part of the routine standard of care in the study areas and that no SQ-LNS distribution programmes were planned or ongoing in either study arm. Accordingly, the trial did not withhold an intervention that was routinely available or otherwise accessible to the study population. All children in both arms continued to receive routine immunization and nutrition services according to national guidelines.

We also now clarify that the trial was not designed to re-establish the nutritional efficacy of SQ-LNS, for which an evidence base already exists, but to answer a distinct implementation question: whether integrating SQ-LNS distribution into routine primary health-care services could improve vaccination uptake under real-world operational and funding conditions. At the time of the trial, there was genuine uncertainty about the effectiveness, feasibility, and programmatic value of this paired delivery strategy.

Change made in the manuscript Methods/Ethics section page 25-26: “At the time of the trial, SQ-LNS was not part of the routine standard of care and no SQ-LNS distribution programs were planned or ongoing in the study areas. Although SQ-LNS has recognized nutritional benefits and is recommended by WHO in specific contexts, universal provision of SQ-LNS to all eligible children was not part of the existing MoH service package. The trial therefore did not withhold an intervention that was routinely available, planned, or otherwise accessible to children in control clusters. All children in both intervention and control clusters continued to have access to routine immunization and standard nutrition services according to national guidelines under real-world programmatic and funding conditions.

The trial was not designed to test whether SQ-LNS has nutritional benefits. Rather, it was designed as a pragmatic trial to evaluate a policy-relevant question: whether co-delivering SQ-LNS distribution with routine immunization services could improve vaccination coverage under real-world operational conditions. At the time of the trial, there was no evidence that this pragmatic implementation strategy conducted under conditions of genuine non-availability of SQ-LNS would improve vaccination uptake, and there was real uncertainty regarding its feasibility, effectiveness, and programmatic value. Randomization was therefore considered ethically appropriate to rigorously assess the effectiveness and the acceptability of the intervention before any potential wider implementation.”

We also made a change in the Discussion section that we address in our reply to Reviewer number 5, comment 3.

Editors’ comment 4- The manuscript uses the phrase “updating vaccine status,” but it is unclear whether this refers to documenting vaccination history or administering vaccines. Please revise the text to explicitly define what this term means within the trial and remove any ambiguity that could lead readers to misinterpret the nature of the intervention.

Reply from the authors: We thank the editor for noting this ambiguity. We have revised the manuscript to remove the phrase “updating vaccine status” and to define explicitly what occurred within the trial procedures. In this context, the child’s vaccination card or history was reviewed to determine whether any scheduled vaccines were due. When vaccines were due and the caregiver accepted vaccination, they were administered by routine MoH staff according to the national immunization schedule. This process was part of routine vaccination services and did not constitute an additional trial-specific vaccination intervention.

Change made in the manuscript:

To remove any ambiguity, we revised the abstract by removing the phrase “updating vaccine status”.

To state explicitly what occurred within the trial procedures, we completed the Methods/Procedures section page 22 as mentioned in our reply to the first editor's comment:

“During immunization sessions, the child's vaccination card or history was reviewed to determine whether any scheduled vaccines were due. When a caregiver accepted the vaccination, MoH staff administered the vaccine.”

Page 22-23: “All caregivers first entered the vaccine circuit, where the child's vaccination card or vaccination history was reviewed to determine whether any scheduled vaccines were due. When a vaccine was due and accepted, routine MoH staff administered the vaccine according to the national immunization schedule, either at the PHCC or at an HP, depending on facility catchment area. If a caretaker declined a vaccination after counselling by a healthcare professional to address concerns, an eligible child could still receive their SQ-LNS ration at the PHCC. Thus, supplementation was not denied on the basis of vaccine refusal.”

Editors' comment 5- It is not currently explicit that all clusters assigned to the NutriVax arm were eligible to receive SQ LNS, whereas clusters in the control arm were not. Please revise the Methods to clearly describe the allocation of supplementation by arm, including whether any exceptions existed, how supplementation was operationalised at the cluster level, and how this distinction was communicated to communities.

Reply from the authors: We thank the editorial team for this helpful comment. We have revised the Methods section to clarify that all clusters assigned to the NutriVax arm were eligible for implementation of SQ-LNS distribution, whereas clusters assigned to the control arm did not receive SQ-LNS through the trial. No exceptions to this allocation were made.

Changes made in the manuscript:

We completed the Randomisation paragraph page 21 to read:

“All clusters assigned to the NutriVax arm were eligible for the SQ-LNS distribution program, whereas clusters assigned to the control arm did not receive SQ-LNS through the trial. No exceptions to this allocation were made.”

We also completed the Procedures paragraphs page 23 as follows:

“During standardized sensitization sessions, communities were informed about the services available in their cluster according to trial allocation. In NutriVax clusters, these sessions included additional messages on SQ-LNS eligibility criteria and appropriate use, both at PHCCs and within communities.”

Editors' comment 6- There is a discrepancy between the protocol—which appears to indicate that only malnourished children in the NutriVax arm were referred for treatment—and the rebuttal, which states that malnourished children in both arms were referred and treated. Please provide a definitive description of the screening procedures used in each arm, the referral pathways available to children identified as malnourished, and whether access to treatment differed in practice between intervention and control clusters. This clarification is necessary to assess the ethical conduct of the trial.

Reply from the authors: We thank the editorial team for identifying this discrepancy and agree that the manuscript should provide a definitive description of malnutrition screening, referral pathways, and access to treatment in both study arms. We have revised the Methods/Procedures section to clarify that routine nutrition services for acute malnutrition were available in all trial clusters through the existing MoH system, independently of the trial intervention.

As mentioned above in our answer to comment 2, in both arms, children identified as acutely malnourished through routine facility-based services or within communities were managed according

to national guidelines. Children with acute malnutrition were referred to the appropriate nutrition treatment program and received therapeutic or supplementary lipid-based foods according to the severity of malnutrition and routine programmatic practice. Access to treatment for acute malnutrition did not differ by trial arm.

Editors' comment 7- The rebuttal indicates that individual consent was obtained only for household survey participants, not for the cluster randomised trial itself, and that caregivers in control clusters who requested SQ LNS were informed that it would not be provided. Please clarify who provided cluster level consent for trial participation, how communities were informed about the existence of two study arms, whether caregivers understood that supplementation was available in some clusters but not others, and how requests for SQ LNS in control clusters were handled. A fuller description of the consent and community engagement processes is needed to evaluate the ethical transparency of the study.

Reply from the authors:

We thank the editorial team for highlighting the need for greater clarification regarding the consent and community engagement processes at cluster level. Before trial implementation, meetings were conducted with stakeholders at state, Local Government Area (LGA), and ward (cluster) levels to present and discuss the study objectives, design, randomization procedures, and intervention modalities. In the administrative context of Nigeria, cluster-level agreement for trial participation was provided by the Ministry of Health primary health-care centre (PHCC) manager responsible for each cluster catchment area. During site opening visits, each PHCC manager across the 20 clusters signed a study participation agreement after reviewing all documents included in the investigator file, such as the protocol, study procedures, and memoranda of understanding between participating parties. All documents included in the investigator file were stored at each of the 20 participating PHCCs before implementation began. The PHCC manager is also responsible for community health activities and for overseeing community health policies at the ward level. In each ward, community mobilisers operate under the responsibility of the PHCC manager and are tasked with disseminating information within their communities. We described in the Methods/Procedures section they were trained to deliver standardised sensitisation sessions at PHCCs and within communities throughout the study period. To clarify the consent process at the cluster level, we have revised the Ethics section as follows.

Changes made in the manuscript:

For the sake of clarity, we added the following sentence in the Study Setting description, Methods section, page 21:

“Each LGA comprised ten administrative health zones, referred to as wards, each representing the smallest administrative unit used for planning and implementing health activities at facilities and in communities.”

The following sentence was added in the Methods/ Procedures section, page 23: “During standardized sensitization sessions, communities were informed about the services available in their cluster according to trial allocation.”

We also added the following sentence in the Ethics Approval and Inclusion paragraph page 25, to read:

“At the cluster level, a study participation agreement was signed by the MoH PHCC manager responsible for each ward catchment area (corresponding to a cluster for the trial), after reviewing the investigator file, including the protocol and study procedures.”

Page 26 “Community engagement was maintained throughout the study via regular meetings with health authorities and local leaders, including, in each LGA, Director or deputy Directors of Primary Healthcare department, Immunization and Disease Control officers, Monitoring and evaluation officers, Director of Family health, PHCCs managers and officers in charge, Nutrition officers, Local

Government Area facilitators, and village heads from participating clusters. Prior to trial implementation, formal meetings were held with state and LGA health authorities and community representatives to review and approve the trial design, and SQ-LNS distribution procedures. Randomization was conducted publicly and transparently, in the local Hausa language, with the active participation of village heads, as a deliberate safeguard to ensure acceptance of the cluster allocation process across both study arms. Engagement with stakeholders and community was further supported through a national steering committee, comprising representatives from federal, state, and local Ministry of Health, local and international nutrition and immunization partners, and community leaders. These activities ensured that community leaders and state authorities remained informed of the trial's progress throughout implementation and were among the first to receive preliminary study findings. Nigerian co-principal investigators participated in local and national meetings, international steering committee meetings, conducted regular monitoring investigation site visits and participated in dissemination activities of preliminary results at state and national levels. Following trial completion, Yobe State authorities allocated a dedicated SQ-LNS budget informed by the study findings, illustrating the sustained stakeholder engagement and research-to-policy translation underpinning this pragmatic trial."

Editors' comment 8- The manuscript notes substantial community engagement, involvement of community leaders, Ministry of Health officials and national investigators, in conducting core study activities as well as data ownership and authorship, yet none are listed as authors. Please clarify how authorship decisions were made and how contributions were evaluated according to authorship criteria.

Reply from the authors: We thank the editors for this important comment. Authorship decisions were made in accordance with the International Committee of Medical Journal Editors (ICMJE) authorship criteria. All listed authors made substantial contributions to the conception or design of the study, data acquisition, analysis or interpretation, participated in drafting or critically revising the manuscript, approved the final version, and agreed to be accountable for all aspects of the work. The proposed authorship list was shared with all co-authors, and comments and suggestions were requested when the first draft of the manuscript was circulated for review. National co-principal investigators are included as second first and second last authors, and all other national investigators who fulfilled authorship criteria are included among the co-authors.

The study also benefited from extensive engagement and support from community leaders, Ministry of Health officials, operational teams, and national collaborators throughout implementation and oversight. Their contributions were essential to the successful conduct of the trial and are acknowledged in the manuscript. However, not all contributors fulfilled the full ICMJE criteria required for authorship, particularly regarding participation in data analysis, manuscript drafting or critical revision, and approval of the final manuscript version.

Change made in the manuscript (Acknowledgements paragraph page 16): "We sincerely thank the children, caregivers, and communities who participated in this study. We are deeply grateful to the health-care workers, community mobilizers, primary health-care centre managers, Local Government Area authorities, and the Yobe State Ministry of Health directors and officers for their commitment and support throughout the study, as well as the ALIMA operational teams who contributed to trial implementation and support. We also acknowledge the valuable support and guidance provided by the members of the national steering committee throughout the NutriVax project."

Editors' comment 9- Please describe what happened to participating children and communities after the trial ended or whether any provisions were made for continued access to SQ LNS or related services. Please briefly outline post trial plans, including any transition, handover, or sustainability measures, so readers understand the longer-term implications for participants.

Reply from the authors:

While the study was still ongoing, we made several unsuccessful advocacies attempts towards international donors to finance SQ-LNS post-trial in the study areas. International donors, though, are reluctant to finance health and nutrition programming in Nigeria because it is a middle-income country perceived as having enough resources to cover its population's needs. This perception does not account for the disparities found in the northern part of the country, but it is a perception nevertheless. Donors are, however, willing to finance policy-relevant research, as evidenced by the investment made in NutriVax-Measles by the Eleanor Crook Foundation (ECF) and Gavi, the vaccine alliance.

We have also continuously advocated for the mobilization of domestic resources for SQ-LNS at the State and National levels. Our efforts were small in comparison to a successful international initiative by UNICEF called the Child Nutrition Fund (CNF). Philanthropists have donated financing to the CNF for matching any governments' investment in nutritional commodities. So if a state or national government purchases 1,000 cartons of SQ-LNS or RUTF, the CNF will purchase an additional 1,000 cartons, basically making this a two-for-one deal. This played a large role in convincing the government of Nigeria and World Bank to include >600 000 cartons of SQ-LNS in the Accelerating Nutrition Results in Nigeria (ANRiN) 2.0 which was announced after the NutriVax study was completed.

While ANRiN 2.0 was deliberated, in September 2025, ALIMA was invited to participate in the week-long Yobe State 2026 Health Sector Annual Operational Plan (AOP) Finalization and Validation Workshop. This is an annual meeting jointly run by the Ministry of Health and Ministry of Finance to validate the upcoming year's health sector budget. One of the national co-PIs, Dr. Baba Waru Goni, presented the preliminary results of NutriVax and led the advocacy for including SQ-LNS in the 2026 state budget. And because there was a strong desire to also take advantage of the CNF matching program, the government committed to include the purchase of 58,000 cartons of SQ-LNS in the 2026 health budget.

In terms of transition and handover, throughout the study, we made sure to include refresher trainings with MoH staff managing the program at health centers, as well as to have joint supervision visits with the LGA nutrition and NPI focal points as well the national Co-PIs in order to build local capacity for setting up and co-delivering SQ-LNS with routine vaccinations. At handover, we made sure to provide stakeholders with electronic copies of all operational documents created for the study and program (standard operating procedures, registries, ration cards, M&E plans, etc.). Finally, once ANRiN 2.0 was announced, we successfully obtained financing from the Child Relief International (CRI) Foundation for ALIMA to provide operational support to the MoH in terms of running NutriVax outside of research.

In the long term, sustainability will depend on dedicated financing, the experience of running such a program by MoH staff, and knowledge sharing from international groups like ALIMA. While we were not successful in obtaining financing for continuing the SQ-LNS program immediately after the study ended, advocacy efforts, including ours, have led to some substantial investments in SQ-LNS by the national government and several state governments.

Change made in the manuscript:

We added the following paragraph to the Ethics Approval and Inclusion subsection of the Methods section page 26:

“Even though SQ-LNS has strong scientific evidence, the lack of international and domestic investment has led to slow uptake. The study team advocated for financing of SQ-LNS to continue post-trial, but could not secure the funding. The Yobe State government did, however, commit to purchasing SQ-LNS in their 2026 budget, in large part due to an initiative led by UNICEF called the Child Nutrition Fund (CNF) in which international donors match domestic investments in nutritional commodities. After the

trial ended, the government of Nigeria and World Bank also announced the Accelerating Nutrition Results in Nigeria (ANRiN) 2.0, which includes substantial financing for SQ-LNS, some of which will be allocated to the areas where NutriVax was conducted. Sustainability of SQ-LNS programming will depend on dedicated financing like this as well as building the capacity of MoH staff to manage such distribution programs.”

Reviewers' Comments:

Reviewer #2 (Remarks to the Author):

I thank the authors for their revisions and attention to the comments of the reviewer. I think that this manuscript has been strengthened, especially in its clarity of reporting. I find the statistical analyses to be justified, appropriate, and properly reported, and have no additional recommendations.

Reply from the authors: We thank Reviewer #2 for the careful re-evaluation of the revised manuscript and for the positive assessment of the statistical analyses and overall reporting. We are pleased that the revisions have strengthened the manuscript to his/her satisfaction, and we are truly thankful for the time and expertise invested in reviewing our work, and helping us improve the manuscript.

Reviewer #4 (Remarks to the Author):

The authors have presented a heavily-revised version of their manuscript, which I have reviewed along with the comments of the other reviewers.

In general, the revised manuscript has been "toned down" and the conclusions/interpretations no longer go beyond the findings, which is an improvement.

The authors have responded adequately to my original concerns, though I still have some disagreements with them, particularly the documentation of community consent. The authors say permission was granted by health and LGA authorities, but still only discuss "community representatives" as "approving study procedures". There are two distinct issues here for me. First, how was this approval documented? I didn't see any information sheets, etc., that would allow for gatekeepers to have a standard set of information before giving their permission for inclusion of their LGA or village. Second, who were these "community representatives" and how were they chosen? On what basis did they speak for their "communities"? What was their legitimacy, and how might they have influenced (for good or for bad) participation of caregivers of children who were participating in the trial?

Reply from the authors: We thank reviewer 4 for highlighting the need for greater clarification regarding the consent and community engagement processes at cluster level. Please see our response to editors' comment 7 and to reviewer 5 comment 4 which raised the same issue on stakeholders and community engagement. We revised the Ethics and inclusion paragraph (page 25-26) to better present who were the stakeholders and community representatives involved.

Likewise, I do think that the authors maintain the most optimistic interpretations possible of their results. I will not belabor this point - but I remain skeptical that the addition of SQ-LNS is "worth it" as a way to increase vaccination coverage - particularly when it's so low to begin with. The authors have at least addressed the low (in absolute terms) vaccination coverage, even post-intervention, which is the most important thing for this manuscript. I look forward to seeing their additional analyses, particularly those related to cost-effectiveness. Obviously vaccinating any unvaccinated child, or feeding any hungry child, is a good thing, but it will be interesting to see how this strategy works out as a matter of policy.

Reply from the authors:

We thank the reviewer for these comments. Our cost efficiency analysis is underway and the manuscript is being prepared. We fully agree that consideration of added costs will be a big factor for countries or donors in deciding to move forward with a strategy like NutriVax. We have also added the following sentences to the Discussion (page 13) to further contextualize the issue of costs:

“Many countries like Nigeria use mass vaccination campaigns and other supplemental immunization activities (SIAs) to achieve temporarily high coverage, but at significant costs in terms of financial and human resources (REF). NutriVax would not eliminate the need for SIAs, but if it contributed to steady gains in coverage in the routine immunization program, it could reduce their frequency and scale.”

REF: Auzenberg M, Fu H, Abbas K, Procter SR, Cutts FT, Jit M. Health effects of routine measles vaccination and supplementary immunisation activities in 14 high-burden countries: a Dynamic Measles Immunization Calculation Engine (DynaMICE) modelling study. *Lancet Glob Health*. 2023 Aug;11(8):e1194-e1204. doi: 10.1016/S2214-109X(23)00220-6. PMID: 37474227; PMCID: PMC10369016.

Finally, I read with interest the comments of the additional reviewer (or whatever the "comments received on April 1" were) and the responses of the authors. At times, I found the tone of both the reviewer in their comments and the authors in their response to be unfortunate. I think that some of the fundamental questions posed by the reviewer ("was this trial necessary?") are valid, even if posed in an unnecessarily confrontational way. Likewise, the authors, even if they felt attacked, showed little self-awareness in their responses. Beginning with their first sentence "We would like to respectfully emphasize that as scientists from the North and the South, we do not find appropriate the way this reviewer is addressing his/her comments," they are skating on thin ice. As a white European global health researcher myself, I don't want to claim that I am in any way perfect in this regard, but I was gobsmacked to see the logo/slogan "Global Health in the Global South" on every page of the authors' rebuttal - for a trial that was conducted and largely run by Nigerian clinicians and researchers - but for which all 3 of the first and joint last authors are French. As the ancient Greeks said, "know thyself"...

Reviewer #5 (Remarks to the Author):

April 20th, 2026

Response to Editor

I was asked to assess the revised manuscript specifically with respect to the appropriateness of the control arm, the standard of care provided to participants, and whether equipoise was adequately maintained. My assessment takes into account the authors' responses to prior reviewer comments and is based on the revised manuscript as currently presented. The trial is ethically defensible as designed and conducted, but the manuscript continues to under-articulate its ethical justification, particularly with respect to equipoise, in ways that require revision before publication.

1. Appropriateness of the control arm - The control arm is ethically appropriate. At the time of the trial, SQ-LNS had never been distributed in either study LGA, and there were no Ministry of Health plans for its distribution. The manuscript states clearly that “there had never been any SQ-LNS distribution program in either LGA nor were there any MoH plans to do so.” Participants in the control arm were therefore not denied access to an intervention they would otherwise have received. All clusters received the full National Programme on Immunization (NPI) schedule, standard nutrition services including referral and treatment for acute malnutrition per national guidelines, and community sensitization activities on vaccination and infant and young child feeding. The control arm was not a placebo arm it represented genuine, fully operational standard care for this setting. This is an important ethical distinction. However, this argument is not made explicitly as an ethical principle anywhere in the

manuscript. The non-availability of SQ-LNS in the study area is mentioned in passing across sections but is never articulated as the formal ethical rationale for the control arm design. The manuscript would benefit from a clearly stated non-deprivation statement, ideally in the Ethics subsection or early in the Methods, affirming that the control arm was not deprived of an accessible intervention and framing the study explicitly as a pragmatic implementation trial conducted under conditions of non-availability rather than a classical deprivation-based design.

Reply from the authors: We warmly thank Reviewer 5 for this important insight and the opportunity to better articulate the ethical rationale underlying the control arm design and the non-deprivation principle in the manuscript. We have revised the Ethics subsection of the Methods (pages 22-23) to clarify explicitly that the control arm reflected routine standard care in the study setting and that participants were not deprived of an intervention that was otherwise available or accessible. We also frame the study as a pragmatic implementation trial evaluating a policy-relevant delivery strategy under real-world conditions of non-availability, rather than a deprivation-based design. We now state clearly that, at the time of the trial, SQ-LNS had never been distributed in either study LGA and that no Ministry of Health SQ-LNS distribution programmes were planned or ongoing in the study areas.

Change made in the manuscript Methods/Ethics section page 22-23: “At the time of the trial, SQ-LNS was not part of the routine standard of care and no SQ-LNS distribution programs were planned or ongoing in the study areas. Although SQ-LNS has recognized nutritional benefits and is recommended by WHO in specific contexts, universal provision of SQ-LNS to all eligible children was not part of the existing MoH service package. The trial therefore did not withhold an intervention that was routinely available, planned, or otherwise accessible to children in control clusters. All children in both intervention and control clusters continued to have access to routine immunization and standard nutrition services according to national guidelines under real-world programmatic and funding conditions.”

The trial was not designed to test whether SQ-LNS has nutritional benefits. Rather, it was designed as a pragmatic trial to evaluate a policy-relevant question: whether co-delivering SQ-LNS distribution with routine immunization services could improve vaccination coverage under real-world operational conditions. At the time of the trial, there was no evidence that this pragmatic implementation strategy conducted under conditions of genuine non-availability of SQ-LNS would improve vaccination uptake, and there was real uncertainty regarding its feasibility, effectiveness, and programmatic value. Randomization was therefore considered ethically appropriate to rigorously assess the effectiveness and the acceptability of the intervention before any potential wider implementation.”

To begin the second paragraph in the Discussion section (page 13), we made the following changes:

“While there is strong evidence for the impact of SQ-LNS on child growth, it was not standard of care in the study area at the time of the trial. To the best of our knowledge, NutriVax-Measles is the first randomized controlled trial assessing whether a pragmatic implementation strategy of co-delivering SQ-LNS with routine immunizations leads to improved vaccination coverage.”

2. Standard of care provided -The standard of care was preserved in both arms throughout the trial. I note that the revised manuscript has addressed a key concern from prior review: it now explicitly states in the Methods that SQ-LNS provision was not contingent on vaccination acceptance, and that caregivers could receive SQ-LNS even after declining vaccines. This is an important ethical safeguard against coercion and undue inducement, and its inclusion represents a meaningful improvement. What remains problematic is the continued use of the term “incentive” throughout the manuscript appearing in the abstract, introduction, and results without qualification. This creates an interpretive inconsistency with the Methods section and leaves the paper open to misreading, particularly in a vulnerable population. The authors should either (a) qualify each use of “incentive” by explicitly cross-referencing the non-conditionality described in the Methods, or (b) replace “incentive” in the abstract and

introduction with more neutral language such as “co-delivered intervention” or “attendance facilitator,” reserving “incentive” for the Discussion where the mechanism is being interpreted.

Reply from the authors: We again thank the reviewer for these very helpful comments. We have removed “incentives” from most of the paper and reserved it mainly for the Discussion where we are interpreting the mechanism.

For example, we changed this initial description of the study in the following ways, page 4:

“We conducted an open-label pediatric, pragmatic, superiority, two-arm, parallel, cluster-randomized, controlled trial with baseline measurements in northern Nigeria to evaluate whether **co-delivering** SQ-LNS to children aged 6–23 months alongside the routine National Program of Immunization (NPI) - the NutriVax strategy - at primary health care centres (PHCCs) could **lead to increased vaccine uptake** compared to routine NPI.”

3. Whether equipoise was maintained -This remains the primary unaddressed ethical issue. The manuscript cites high-certainty WHO evidence for the benefits of SQ-LNS and notes that it is strongly recommended in food-insecure settings. It also documents a substantial burden of acute malnutrition among enrolled children. Yet the study randomizes access to SQ-LNS across clusters without explicitly reconciling this strong evidence base with the decision to “withhold” access from half of the clusters during the study period. The ethical justification that SQ-LNS was not part of the available preventive package in the study setting is sound, but it is only implied. For a study of this nature, implication is not sufficient; the argument needs to be made explicitly. The key distinction that needs to be articulated is that the trial was not designed to test whether SQ-LNS has nutritional benefit that question has been answered. Rather, it was designed to test whether delivering SQ-LNS through immunization platforms, in a specific operational and programmatic context, improves vaccination coverage at scale. This is a distinct question. Genuine uncertainty about this implementation question, combined with the non-availability of SQ-LNS in the setting, is what justifies randomization. This distinction is central to establishing equipoise and is currently missing from the manuscript. The authors should transfer the equipoise language from their rebuttal into the manuscript specifically a brief a dedicated paragraph in the Ethics subsection of the Methods or early in the Discussion that:

- a) Acknowledges the strong evidence base for SQ-LNS and existing WHO recommendations
- b) States that at the time of the trial, there was no evidence that SQ-LNS could improve vaccination coverage
- c) Confirms that SQ-LNS was not available in the study setting at the time of the trial
- d) Affirms that the trial did not withhold an accessible or a routinely provided intervention
- e) Frames the study explicitly as a pragmatic implementation trial evaluating a policy-relevant delivery strategy under real-world conditions, situating it within an implementation ethics framework rather than a classical clinical equipoise framework. This will further affirm that the trial therefore did not withhold an accessible intervention and was conducted under conditions of clinical and programmatic equipoise.

Reply from the authors:

We thank the reviewer for these comments, which has really helped us better articulate this important aspect. We have made several changes to the manuscript.

To begin the second paragraph in the Discussion section (page 13), we made the following changes:

While there is strong evidence for the impact of SQ-LNS on child growth, it was not standard of care in the study area at the time of the trial. To the best of our knowledge, NutriVax-Measles is the first randomized controlled trial assessing whether a pragmatic implementation strategy of co-delivering SQ-LNS with routine immunizations leads to improved vaccination coverage.

We also made several changes in the Methods section and Ethics section that we detailed in response to the Editors' comment 3. The same section was also edited to address your first comment related to Appropriateness of the control arm.

Regarding terminology, we agree that the study evaluates a policy-relevant delivery strategy under real-world conditions. The primary objective of the present article is to report the effectiveness of the strategy on vaccination outcomes within a cluster-randomized trial framework. To the best of our knowledge, pragmatic trials are primarily designed to determine the effectiveness of interventions under the usual conditions in which it will be applied, which is the case of the NutriVax-Measles trial. We have therefore framed our study as a "pediatric pragmatic superiority parallel cluster-randomized trial", consistent with the published protocol, trial registration and ethics approval. As specified in the present article, the acceptability, feasibility, and cost-related components of the broader evaluation are planned for separate publications. For these reasons, we did not modify the formal description of the trial design to add the word "implementation" to that already long framing of the trial design. However, we have strengthened the manuscript to more clearly emphasize the policy-relevant and real-world nature of the delivery strategy being evaluated, and we would be happy to further revise the terminology should the Editors consider it preferable.

4. Community engagement and stakeholder involvement - The rebuttal provides considerably more detail on community engagement than the manuscript presents, and this strength should be more fully reflected in the paper (can go into the supplementary and be cited in the main manuscript if word count limits present a constraint). The authors conducted formal meetings with State and LGA health authorities and community representatives before the trial, obtaining community-level approval of the trial design, cluster allocation, and SQ-LNS distribution procedures. Randomisation was conducted transparently and publicly, with the active participation of community leaders a critical safeguard given that the absence of SQ-LNS in control clusters could otherwise have generated community tension or pressure. A national steering committee was in place throughout, comprising representatives from federal, state, and local Ministry of Health, international nutrition and immunization actors, and community leaders. Community leaders were kept informed of the trial's progress in real time and were the first to receive preliminary results. The Yobe State authorities' decision to allocate SQ-LNS budget in 2026 directly informed by those results exemplifies the kind of sustained stakeholder engagement and research-to-policy translation that is the hallmark of well-conducted pragmatic implementation trials. The Scientific Committee also included the lead researcher from analogous SQ-LNS cluster-randomised trials in Mali, who advised on methodology and ethical standards, an additional layer of external ethical scrutiny. I commend the multidisciplinary team for ensuring that local input was not a formality but a core and ongoing component of the trial. This depth of engagement substantially enhances the ethical legitimacy of the study and its potential for sustainable impact.

Reply from the authors: We sincerely thank Reviewer 5 for this thoughtful and generous assessment of the community engagement and stakeholder involvement processes. We are pleased that the depth and quality of these efforts are recognised. We agree that these activities were insufficiently described in the manuscript and have strengthened the Ethics and Community engagement sections accordingly.

Changes made in the manuscript (Ethics approval and inclusion paragraph (pages 23)) : "Community engagement was maintained throughout the study via regular meetings with health authorities and local leaders, including, in each LGA, Director or deputy Directors of Primary Healthcare department, Immunization and Disease Control officers, Monitoring and evaluation officers, Director of Family health, PHCCs managers and officers in charge, Nutrition officers, Local Government Area facilitators, and village heads from participating clusters. Prior to trial implementation, formal meetings were held with state and LGA health authorities and community representatives to review and approve the trial design, and SQ-LNS distribution procedures. Randomization was conducted publicly and transparently,

in the local Hausa language, with the active participation of villages heads, as a deliberate safeguard to ensure acceptance of the cluster allocation process across both study arms. Stakeholders and community engagement was further supported through a national steering committee, comprising representatives from federal, state, and local Ministry of Health, local and international nutrition and immunization partners, and community leaders. These activities ensured that community leaders and state authorities remained informed of the trial's progress throughout implementation and were among the first to receive preliminary study findings. Nigerian co-principal investigators participated in local and national meetings, international steering committee meetings, conducted regular monitoring investigation sites visits and participated in dissemination activities of preliminary results at state and national levels. Following trial completion, Yobe State authorities allocated a dedicated SQ-LNS budget informed by the study findings, illustrating the sustained stakeholder engagement and research-to-policy translation underpinning this pragmatic trial."

We also revised the following sentence in the Acknowledgments section (page 16) :

"We are also indebted to the members of the scientific committee for the NutriVax-Measles trial: Kathryn Dewey (University of California, USA), Indi Trehan (University of Washington, USA), Lieven Huybregts (International Food Policy Research Institute - IFPRI, USA), Saskia de Pee (World Food Program - WFP, Italy), Alison Connor (IDinsight, Kenya), whose extensive experience conducting individual and cluster randomized control trials, including some with SQ-LNS, provided valuable methodological and ethical guidance before and during the study."

I recommend additional revision. The study addresses an important and underfunded area of child health, the design is scientifically sound, and the ethical safeguards are substantively in place. The issues identified by reviewers 1 and 5 are not fundamental design flaws but rather deficiencies in how the ethical rationale is articulated. With targeted revisions to the Ethics subsection, abstract, and relevant Methods language, the manuscript can meet the ethical and equipoise standards expected. The core argument that this was a pragmatic implementation trial conducted under conditions of genuine non-availability, with standard carefully preserved is defensible and simply needs to be stated explicitly and with appropriate rigor. I also note the substantial involvement of local stakeholders, including the Ministry of Health, in the planning and implementation of the study. This is a strong feature of pragmatic implementation trials of this nature. The authors should be commended for ensuring that local input was a core component of the study design and execution.

Reply from the authors:

We want to sincerely thank the reviewer for the time and expertise devoted to such a careful reading of our manuscript and our rebuttal letter. We are particularly grateful for the clear articulation of the ethical and equipoise considerations that were insufficiently expressed in earlier versions of the manuscript. We appreciate the reviewer's recognition that the study was conducted with appropriate ethical safeguards and meaningful local stakeholder involvement. In response, we have made several targeted revisions along the lines suggested in the relevant sections of the manuscript. This second revision now states more explicitly that the study was designed as a pragmatic trial conducted under conditions in which SQ-LNS was not routinely available in the study setting, that standard immunization and nutrition services were maintained in both arms, and that the trial evaluated a policy-relevant delivery strategy rather than the nutritional efficacy of SQ-LNS itself. We also expanded the description of community engagement, cluster-level approvals, and the involvement of Ministry of Health and community stakeholders throughout the study. We are grateful for the reviewer's constructive guidance, which substantially improved the clarity and rigor of the manuscript.