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A pragmatic covariate-constrained cluster-randomised controlled trial of hybrid parents and health workers adaptive intervention for optimal (timely, cumulative age-appropriate) community-wide routine childhood immunisation coverage: the AGINTOPIC trial

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ABSTRACT

Introduction Vaccine-preventable infectious diseases (VPDs) covered by routine childhood immunisation programmes are major causes of morbidity/mortality as outbreaks continue to reoccur despite repeated efforts to increase immunisation coverage. This trial aimed at increasing optimal/timely immunisation coverage.

Methods The Adaptive Group Intervention for Optimal routine childhood Immunisation Coverage (AGINTOPIC) trial was conducted from 1 June 2022 to 31 May 2023 in Ebonyi state, Nigeria. 16 geographical clusters (where the primary healthcare facilities were providing weekly routine childhood immunisation) were covariate-constrained-randomised (1:1) to control arm (receiving no intervention) and intervention arm (receiving hybrid parents/health workers adaptive engagement to enlighten/facilitate regular communications/working relationships between them regarding optimal immunisation). The primary outcomes included the proportion of children aged 5–9 months who had optimal/timely (cumulative age-appropriate) receipt of every recommended birth to 14 weeks vaccine and the age-appropriate vaccines receipt (receipt timeliness) score. The outcomes were measured via baseline and end-of-study repeated cross-sectional surveys. All analyses were done using a cluster-level method on intention-to-treat basis, and randomisation-based inference was done via adjusted clustered permutation tests (aCPTs) to check the robustness/validity of the main findings.

Results A mean proportion of 6.0% (SD 8.1) of children aged 5–9 months in the control arm had optimal/timely receipt of every recommended birth to 14 weeks vaccine, vs 14.3% (11.7) in the intervention arm (adjusted prevalence difference 10.8%, 95% CI 0.8% to 20.9%, p=0.0376, aCPT p=0.0093). The mean age-appropriate vaccines receipt score was 75.1 (17.8) in the control arm, vs 85.5 (9.5) in the intervention arm (adjusted mean difference 9.5, 95% CI 1.0 to 17.9, p=0.0317, aCPT p=0.0155).

Conclusions The AGINTOPIC intervention significantly increased the optimal/timely (cumulative age-appropriate) community-wide routine childhood immunisation coverage, and the evidence illuminates the need for the exploration and adaptation of such pragmatic/dynamic/scalable community engagement intervention by routine childhood immunisation programmes in the global efforts to address the recurrent outbreaks of VPDs.

Trial registration number ISRCTN59811905.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The few rigorous and relevant randomised interventional trials were on timeliness of individual vaccines/doses at the recommended or appropriate ages (singular age-appropriate vaccinations) with various definitions of timeliness, without (clear) considerations for the cumulative intervals between the vaccines/doses, and most involved text message reminders while others involved financial incentives, phone call reminders, reminder bracelets and immunisation outreaches.

⇒ The existing evidence showed mixed results (significant and non-significant findings) across the trials regarding timely singular age-appropriate routine childhood immunisation coverage (for selected/representative vaccinations), assessed among the direct recipients of the interventions in most of the trials which used cohort survey design in their outcome assessments.

WHAT THIS STUDY ADDS

⇒ Our Adaptive Group Intervention for Optimal routine childhood Immunisation Coverage (AGINTOPIC) trial was the first on optimal/timely receipt of every recommended and due vaccine/dose at the recommended age and time-interval between doses (cumulative age-appropriate receipt of recommended doses) and involved the delivery of basic and adaptive intervention actions through the Promoters of Optimal Routine Childhood Immunisation Coverage group which reflects naturally existing social groups (traditional, community/village associations/meetings) in the study area and many other settings in and outside Nigeria.

⇒ Our findings demonstrate that, when fully received, the AGINTOPIC intervention significantly increased the actual optimal/timely (cumulative age-appropriate) community-wide routine childhood immunisation coverage (assessed via repeated cross-sectional surveys of all the eligible children in the communities irrespective of whether their parents were (direct) recipients of the intervention or not).

⇒ We understand the AGINTOPIC intervention (which is pragmatic, scalable and sustainable), as well as the community-wide impact (which perhaps reflects high positive externalities and cost-effectiveness of the intervention), to be of great public health and health policy value in the efforts to increase optimal/timely immunisation coverage for optimal protection against vaccine-preventable infectious diseases (VPDs).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our AGINTOPIC trial provides a pragmatic, dynamic and scalable approach to community engagement interventions which we understand can be adapted and sustainably applied by routine childhood immunisation programmes in order to significantly increase the actual optimal/timely (cumulative age-appropriate) community-wide routine childhood immunisation coverage in the global efforts to address the recurrent outbreaks of VPDs.

INTRODUCTION

The vaccine-preventable infectious diseases (VPDs) covered by routine childhood immunisation programmes continue to be major causes of morbidity and mortality among children younger than 5 years worldwide and particularly in Africa, including Nigeria and Ebonyi state. About 33% of the over 90 million global cases of VPDs among children younger than 5 years in 2015 occurred in Africa.[1] Every year over 30 million cases of VPDs and over half a million deaths from VPDs (about 58% of the global deaths from VPDs) occur among these children in Africa.[1] These VPDs include pneumococcal diseases (which cause lower respiratory infections), rotavirus infection (which causes acute diarrhoeal disease), diphtheria, pertussis (whooping cough), rubella, tetanus and measles.[1 2]

Routine childhood immunisation has made an invaluable contribution to the successful prevention and control of VPDs over the past decade, but the progress achieved has stagnated and is even reversing in many countries,[3 4] including Nigeria,[5–7] which had (about) the highest number of unimmunised children in the world (in 2018, 2019)[6 8] and where the state of routine immunisation has been considered a public health emergency.[6]

Outbreaks of VPDs continue to reoccur around the world[1 3 4 8] and in Nigeria.[9–11] These recurring outbreaks, particularly in Africa, could be as a result of poor coverage of childhood immunisations[1] but because delayed receipts of vaccinations increase the risks of VPDs and their outbreaks due to delays in vaccine-induced (herd) immunity,[12–15] suboptimal/untimely immunisation coverage could have also been contributing to these recurring outbreaks of VPDs.

There is low coverage of routine childhood immunisation and high mortality rate among children younger than 5 years in Ebonyi state, as the proportion of children aged 12–23 months who received all age-appropriate vaccinations was 26.3% in 2018[7] (before trial implementation) and 36.4% in 2024,[16] far below the national target of 80% by 2015[17] and the 10-year mortality rate among children younger than 5 years was 68 per 1000 live births by 2024,[16] far above the SDG 3.2 target of at most 12 per 1000 live births by 2030 as Nigeria appears not to be on course to achieve this target.[6] Outbreaks of VPDs continue to reoccur in Ebonyi state[9 10 18] despite repeated efforts to increase childhood immunisation coverage.[19] The foregoing situation perhaps indicates not only persistent wide gaps in routine childhood immunisation coverage in the state but also in the timeliness of the coverage, as the potential determinants of untimely receipt of vaccinations are also, understandably, determinants of non-receipt.[19] Such potential determinants include health services-related (eg, supply/provider-related) factors, sociodemographic factors (eg, educational level), socioeconomic factors (eg, household income), geographic factors (eg, travel distance), knowledge level and health care-seeking behaviour regarding other health services (eg, antenatal visit, health facility delivery).[12 13 20–23]

Routine childhood immunisation scheduling, guided by the scientific knowledge of vaccination immunology, local disease epidemiology and policy priorities, is designed to achieve optimal immunological response and high population coverage (herd immunity) in an affordable manner.[13 15] The ages at receipt of vaccine doses in routine immunisation programmes are important, but for multiple-dose vaccines, the recommended time-intervals between initial and subsequent doses (dosage timeliness) are more important than the ages at receipt of the subsequent doses when the initial doses were off schedule.[13 15] Thus, the receipt of all the recommended and due vaccine doses by the recommended ages and time-interval between doses (optimal/timely (cumulative age-appropriate/dosage-appropriate) receipt of the doses) will enhance the validity of vaccination coverage[24] and make the protection against VPDs optimal.

The identified previous and relevant rigorous randomised interventional trials on timeliness were on timeliness of individual or representative/selected vaccines/vaccine doses at the recommended or appropriate ages (singular age-appropriate receipt of the

vaccinations) with various definitions of timeliness but without (clear) considerations for the cumulative intervals between all the recommended and due vaccines/doses.[25–33] Most of the previous trials involved text message reminders to caregivers and others involved financial incentives to caregivers, phone call reminders to caregivers, reminder bracelets to infants/caregivers and immunisation outreaches. There is a need for optimal protection against the VPDs in immunisation programmes considering the recurrent global and local outbreaks of these VPDs and interventional studies to increase the optimal/timely (cumulative age-appropriate) receipt of every recommended and due vaccine dose would be of greater public health value. Such interventions would also increase the overall immunisation coverage in addition to increasing the timeliness of the coverage and are thus imperative.

Parents are the primary caregivers of their children and have the primary responsibility for their optimal/timely receipt of routine vaccinations. Primary healthcare (PHC) workers are local healthcare providers who are usually members of the communities they serve and who have regular contact with community members, including parents. It would be a veritable strategy to involve the PHC workers in context-specific community engagement interventions for immunisation coverage.[3] Moreover, the sensitisation of community groups, including parents, was effective in increasing the demand for malaria rapid diagnostic tests in Ebonyi state.[34]

Using a cluster design to prevent contamination between the study arms, we conducted a pragmatic covariate-constrained randomised interventional trial aimed at evaluating the effectiveness of hybrid parents and health workers adaptive intervention in increasing the optimal/timely (cumulative age-appropriate) community-wide routine childhood immunisation coverage.

METHODS

Study design

This study was a pragmatic, two-arm, parallel, open-label, covariate-constrained cluster-randomised controlled trial with 1:1 allocation. A cluster was the nearest catchment area (geographical community(ies)/village(s)/settlement(s)) for at least one public PHC facility with at least 500 households or a population of 3000. This Adaptive Group Intervention for Optimal routine childhood Immunisation Coverage—AGINTOPIC trial—involved hybrid parents and PHC workers' adaptive engagement in the intervention arm to enlighten the parents and PHC workers and facilitate regular communications and working relationships between them regarding optimal receipts of routine childhood immunisation. There was no intervention in the control arm which had only the usual practice of PHC facilities providing routine childhood immunisation services. A repeated cross-sectional survey design (in contrast to a cohort survey) was adopted to assess the community-wide impact of the intervention. This trial was conducted according to a protocol[19] which was developed with the guidance of the Standard Protocol Items: Recommendations for Interventional Trials 2013 checklist. The reporting of this trial is according to the Consolidated Standards of Reporting Trials statement: extension to cluster randomised trials.[35]

Participants

This AGINTOPIC trial was conducted in Ebonyi state in the southeast geopolitical zone of Nigeria. The participants were clusters, and within each cluster, PHC workers and parents were participants in the intervention while mother–child pairs were participants in the household surveys. Those eligible were the clusters where the PHC facilities were providing maternal and child healthcare services including weekly routine childhood immunisation and which were at least 10 km apart or separated by a buffer area/natural barrier (to prevent contamination between clusters),[36] PHC workers in the PHC facilities, parents of infants aged 0–2 months and mother–child pairs in which the children were aged 5–23 completed months (subdivided into 5–9, 10–11 and 12–23 completed months). The 5–9 and 10–11 age groups were chosen because they were the most appropriate age groups for respectively assessing the full and partial impact of the 10 months intervention, as they were respectively aged 0–2 months at the start of the intervention. Thus, only parents of infants aged 0–2 months were eligible for the intervention. Only the participants who gave oral informed consent were included. Using a multistage sampling technique, eligible clusters were randomly selected, and all the eligible participants within the selected clusters were selected. Details of the eligibility criteria, schedule of enrolment, intervention and assessment of outcomes and the sampling technique are in the trial protocol.[19]

Before this trial, the routine childhood immunisation schedule in Ebonyi state for infants was: At birth (BCG, birth dose of hepatitis B vaccine (HBV-0), birth dose of oral polio vaccine (OPV-0); 6 weeks (OPV-1, first dose of pneumococcal conjugate vaccine (PCV-1), first dose of pentavalent vaccine (Penta-1), first dose of inactivated polio vaccine (IPV-1); 10 weeks (OPV-2, PCV-2, Penta-2); 14 weeks (OPV-3, PCV-3, Penta-3, IPV-2); 6 months (vitamin A-1) and 9 months (first dose of measles containing vaccine (MCV-1), yellow fever vaccine, meningitis vaccine).

Sample size

Based on the 26.3% of the children in Ebonyi state who received all the recommended vaccinations appropriate for their ages[7] and assuming 50% of them (13.15%) had optimal/timely receipt of all the vaccinations,[12] the proportion of children aged 10–11 months who had optimal/timely receipt of every recommended birth to 9 months vaccine dose (based on vaccination data from their vaccination cards) could plausibly be estimated to be 13.15% in the control arm. With an intracluster

correlation coefficient of 0.05, a cluster size of 15 eligible children aged 10–11 months whose vaccination data were collected from their vaccination cards, 80% power at 5% probability of type I error, the trial would require 8 clusters per arm to detect a 20 percentage point increase in the outcome in the intervention arm (an increase from 13.15% to 33.15%). This gave a total of 16 clusters, a minimum of 120 children aged 10–11 months per arm and 240 in total. The same sample size estimates were also applied for the children aged 5–9 and 12–23 months.

Procedures and intervention

A baseline household survey was conducted to assess the study outcomes using structured interviewer-administered questionnaire written in English. The electronic version of the questionnaire was programmed using the KoBoToolbox software and installed in KoBoCollect in Android devices before it was administered by interviewers who were trained for that purpose.[19] During the survey, vaccination data of children aged 5–23 months were collected from their vaccination cards and through recall from their mothers/primary caregivers. Data were also collected on the following background characteristics: gender, age, place of delivery and birth order of the children; number of ante-natal visits by the mothers, age, marital status, educational level and occupation of the mothers; age, educational level and occupation of the husbands of the mothers; household income and the travel time to catchment immunisation facility. The baseline survey was followed by random allocation of clusters and then the delivery of the intervention. An end-of-study household survey was then conducted to assess the study outcomes after the intervention. The questionnaire items and the conduct of the end-of-study survey were the same as those of the baseline survey. Refresher training was conducted for the interviewers before the end-of-study survey 10 months after the baseline survey. Details of the schedule of enrolment, intervention and assessment of outcomes are in the trial protocol.[19]

The intervention was a composite action consisting of two broad strategies, basic and adaptive intervention actions (table 1) and was delivered from 25 July 2022 to 26 April, 2023. The basic intervention action involved the formation of the Promoters of Optimal Routine Childhood Immunisation Coverage (PORCHIC) group and three to four physical PORCHIC group discussions/meetings, including brief enlightenment discussions with parents during the weekly routine immunisation clinics (table 1). The PHC workers identified eligible parents at and outside the PHC facilities and registered them as PORCHIC group members over 5 months or up to 5 months before the end-of-study survey. Community resource persons (CORPs) were also tasked with identifying eligible parents outside of the health facilities and referring them to the PHC workers for registration as PORCHIC members. The physical PORCHIC group discussions/meetings were generally held in about every alternate month and preferably at the health facilities on immunisation days. Each discussion was semistructured into two parts—determinants with solutions/strategies and enlightenment—moderated by an investigator and lasted about 1–2 hours.

The first PORCHIC group discussions/meetings were mainly focused on identifying determinants of untimely vaccinations and readily available, feasible and affordable solutions via focus group discussions and on enlightening the participants via enlightenment group discussions (details in online supplemental appendix pp 2–4). The second, third and fourth PORCHIC group discussions/meetings were mainly focused on getting the views of the new PORCHIC members (who were registered after the previous discussion(s)), reinforcing the knowledge and perceptions of the old PORCHIC members and implementing the identified solutions/strategies, based on the findings from the earlier engagement(s)/discussion(s), as part of the adaptive intervention.

The adaptive intervention action (table 1) involved cluster-specific and non-cluster-specific actions, including modifications of and improvements in the engagement strategy and messages, informed by the (proximal) determinants and feasible solutions identified during the basic intervention from participants' experiences and perceptions and from observations of the investigators. The cluster-specific and non-cluster-specific modifications were based on determinants identified particularly within clusters or generally across clusters. For example, while most of the identified determinants (table 1) cut across all the intervention clusters, missed opportunities due to non-opening of multidose vials for very few clients were particular to some clusters. Also, the modifications practically varied among the clusters in line with the extent of the identified determinants and the particular context of clusters. The detail is in online supplemental appendix pp 2–4.

Outcomes

Optimal/timely routine childhood immunisation coverage was conceptualised as the receipt of every recommended vaccine dose at the recommended age and time interval between doses by the target population. This was the cumulative age-appropriate or cumulative dosage-appropriate receipt of recommended vaccinations. In our concept, optimal/timely immunisation coverage was about the actual optimal/timely receipt of every recommended and due vaccine dose and, unlike previous studies, we did not use the optimal/timely receipt of only one of the doses usually given together (representative/selected vaccine doses) in assessing optimal/timely immunisation coverage. For example, Penta-1, Penta-2 and Penta-3 were not representatives of the other 6, 10 and 14 weeks vaccines. Every dose was assessed and contributed to the cumulative assessment because of pragmatic considerations and our understanding that there were vaccine dose-specific supply-side (eg, stockout) and demand-side (eg, personal experiences and perceptions regarding side effects of specific

Table 1 Basic and adaptive intervention actions

	Basic intervention action	Main activities
1	Formation of the Promoters of Optimal Routine Childhood Immunisation Coverage (PORCHIC) group	► By investigators: Engagement of the key community members in the formation of the PORCHIC group ► By PHC workers: Registration of eligible parents, who were either seeking care at the PHC facilities or identified outside the facilities, as PORCHIC group members ► By CORPs: Identification of eligible parents outside the facilities and referring them to the PHC workers for registration as PORCHIC group members
	► Primary members: Investigators, parents, PHC workers ► Other members: Key community members (such as the cluster heads, community resource persons (CORPs), traditional birth attendants (TBAs))	
2	Physical PORCHIC group discussions	
	► Regarding non-receipt and untimely receipt of routine childhood vaccinations ► To identify the (proximal) determinants and feasible solutions/strategies to addressing them during the study ► To enlighten the PORCHIC group members and by extension other community members ► To facilitate regular communications and working relationships between parents and PHC workers (and between PORCHIC group members)	First PORCHIC group discussion/meeting ► Part 1: Focus group discussions (FGDs) on the determinants and feasible solutions ► Female FGD: Involved the investigators, female parents, PHC workers, CORPs, TBAs, etc as necessary ► Male FGD: Involved the investigators, male parents, PHC workers, CORPs, village heads, etc as necessary ► Expressions of perceptions and sharing of experiences ► Part 2: Enlightenment group discussion ► Introduction of the research problem and purpose of the study ► Expressions of knowledge and perceptions regarding vaccines/vaccinations and routine childhood immunisation schedule by participants ► Explanations of key facts about vaccines/vaccinations, routine childhood immunisation schedule, and optimal/timely receipt of vaccinations, by the investigators ► Highlighting of key life-saving actions to practise and promote (used as summary message) ► Discussion of comments, questions and answers
	Second to fourth PORCHIC group discussions/meetings ► To get the views of the new PORCHIC members (registered after the previous discussion(s)) on the determinants of non-receipt and untimely receipt of routine childhood immunisations and feasible solutions ► To enlighten the new members and by extension other community members ► To reinforce the knowledge and perceptions of the old PORCHIC members ► To implement other solutions/strategies informed by the findings from the previous discussion(s)/engagement(s)	Second to fourth PORCHIC group discussions/meetings ► Part 1: Group discussion on determinants and feasible solutions ► Part 2: Enlightenment group discussion ► Introduction of the research problem and purpose of the study to the new participants ► Expressions of knowledge and perceptions, as above, by the old participants ► Expressions of knowledge and perceptions, as above, by the new participants ► Explanations of key facts, as above, by the investigators ► Highlighting of key life-saving actions, as above, by the old participants ► Highlighting of key life-saving actions, as above, by the investigators ► Discussion of comments, questions, and answers
3	Subsequent registration of eligible parents as new members of the PORCHIC group up to 5 months before the end-of-study survey	► By PHC workers: Continued registration of eligible parents as above with brief enlightenment discussion during registration ► By CORPs: Continued identification and referral of eligible parents as above
4	Enlightenment discussions with parents during the weekly routine immunisation clinics ► To reinforce the knowledge and perceptions of the PORCHIC members attending the immunisation clinics ► To enlighten the other parents attending the clinics	► By PHC workers: Facilitation of brief enlightenment discussions with parents, using abridged PORCHIC group discussion format, during the health talk sessions in the weekly immunisation clinics

Continued

Table 1 Continued

Adaptive intervention action	Main solutions (actions and messages) targeted at identified determinants
► Modification of the engagement strategy and the PORCHIC group discussion messages based on the (proximal) determinants and feasible solutions identified during the basic intervention ► Involved cluster-specific and non-cluster-specific modifications based on determinants identified particularly within clusters or generally across clusters	Missing of appointment dates due to forgetting by mothers/caregivers ► Always (re)writing or pasting the next appointment date on the door post or wall ► Regularly checking the appointment date on the vaccination card ► Keeping the vaccination card where it would always be visible but out of children's reach, for example, hanging it on the wall instead of putting it under a box/clothes in a box ► Setting reminders using mobile phones or paper-based calendars, and its demonstration ► Neighbours (with the same appointment dates) reminding each other Delayed receipt of birth doses & missing of appointment dates due to illness of mothers or children ► Ensure to deliver at a health facility ► Get advice from health workers ► Get relatives or friends to take the children for vaccinations Missing of appointment dates due to lack of transport fare ► Prioritising and making financial preparations for appointment dates Missing appointment dates due to the bad attitude of some health workers ► Sensitisation of health workers and giving reassurance to the parents Missing appointment dates due to missed opportunities because of non-opening of multi-dose vials for very few clients ► Collaborating with other PHC facilities to share multi-dose vials when clients were very few Other actions and messages ► Modification of the 'key life-saving actions' to 'disease outbreak prevention actions' as summary message ► Highlighting of disease outbreak prevention actions to practice and promote ► Discussion of comments, questions, and answers

PHC, primary healthcare.

vaccines/doses) determinants of optimal/timely vaccination receipt.

Our conceptualisation and operationalisation of optimal routine immunisation coverage and the categorisation and scoring of the receipt of vaccinations are presented in online supplemental appendix (pp 5–6) and greater details are in the trial protocol.[19] Briefly, optimal/timely receipt of a vaccine dose was the receipt of the dose on the scheduled date, with a 7-day forward acceptable window for birth, 6 weeks and 9 months doses and a 7-day backward window for 9 months doses. The receipt of each recommended vaccine dose was categorised as optimal/timely, suboptimal/untimely (early and delayed/late) and non-receipt. The optimal receipt of a multidose vaccine was the optimal receipt of every dose of the vaccine. Overall, the optimal receipt of all the recommended vaccines in an immunisation schedule was the optimal receipt of every recommended vaccine in the schedule. The suboptimal receipt of a multidose vaccine was the delayed or early receipt of at least one dose of the vaccine or non-receipt of less than the total number of doses. Non-receipt of a multidose vaccine was the non-receipt of all the vaccine doses.

The receipt of each recommended vaccine dose as a continuous variable was scored from the maximum of 100 for optimal receipt to the minimum of 0 for non-receipt. The scores progressively reduced by seven for each succeeding week's delay, from a score of 93 for 1 week delay, 86 for 2 weeks delay, 79 for 3 weeks delay, down to 2 for 14 weeks or more delay. The score for early receipt was 2. The vaccine receipt score for a multidose vaccine was the average of the dose receipt scores for all the doses of that vaccine. The overall or cumulative vaccine receipt score for all the recommended vaccines in the immunisation schedule was the average of the vaccine receipt scores for all the vaccines.

Our trial had primary, coprimary and secondary outcomes. The outcomes among the children aged 5–9

months during the end-of-study survey were to assess the full impact of the intervention regarding the birth to 14 weeks vaccine doses, as these children were born in months 1–5 of the intervention and their parents were expected to have full exposure to the intervention in the intervention clusters. The outcomes among the children aged 10–11 months during the end-of-study survey were to assess the partial impact of the intervention regarding the birth to 9 months vaccine doses, as these children were born in months −1 to −2 of the intervention and their parents were expected to have partial exposure to the intervention, only after the 6 weeks vaccinations. The outcomes among the children aged 12–23 months during the end-of-study survey were to assess the 'catch-up' effect of the intervention on their vaccination status.

The primary outcomes were the proportion of children aged 5–9 months who had optimal/timely (cumulative age-appropriate) receipt of every recommended birth to 14 weeks vaccine; the age-appropriate vaccines receipt (receipt timeliness) score for the recommended birth to 14 weeks vaccines by children aged 5–9 months; the proportion of children aged 10–11 months who had optimal/timely (cumulative age-appropriate) receipt of every recommended birth to 9 months vaccine; and the age-appropriate vaccines receipt (receipt timeliness) score for the recommended birth to 9 months vaccines by children aged 10–11 months. The coprimary outcomes were the proportion of children aged 5–9 months who had optimal/timely receipt of the recommended individual birth to 14 weeks vaccines/doses; the individual birth to 14 weeks vaccines/doses receipt scores among children aged 5–9 months; the proportion of children aged 10–11 months who had optimal/timely receipt of the recommended individual birth to 9 months vaccines/doses; and the individual birth to 9 months vaccines/doses receipt scores among children aged 10–11 months.

The secondary outcomes were the proportion of children aged 5–9 months who had received every recommended birth to 14 weeks vaccine (were up to date); the proportion who did not receive Penta-3 among the children aged 5–9 months who received Penta-1 (Penta-1 to Penta-3 dropout rate); the proportion of children aged 10–11 months who had received every recommended birth to 9 months vaccine; the proportion who did not receive Penta-3 among the children aged 10–11 months who received Penta-1; the proportion of children aged 10–11 months who had optimal/timely receipt of vitamin A-1, who had received vitamin A-1, the vitamin A-1 receipt score among children aged 10–11 months; the proportion of children aged 12–23 months who had received every recommended birth to 9 months vaccine, who had received every recommended birth to 9 months vaccine by 12 months of age, and who received Penta-1 but not Penta-3.

The trial logic framework (figure 1) for the hypothesised effect of the intervention on the study outcomes incorporated the '3Cs' vaccine hesitancy model.[37] The performance of PHC workers in engaging parents regarding timely receipt of routine childhood immunisation and the parents' actions regarding timely receipt of the immunisation by their children were expected to remain the same in the control arm. The intervention was expected to enlighten parents and PHC workers, including the other PORCHIC group members and by extension other community members, about optimal/timely receipt of routine childhood vaccinations and increase effective communication and working relationships between them.

The intervention was expected to specifically increase their awareness and knowledge and enhance their perceptions about the VPDs, the routine childhood vaccines/vaccinations, and the vaccination process/system, including immunisation schedules and its rationale; sensitise them about the importance of the receipt and timely receipt of the vaccinations, determinants of non-receipt and untimely receipt of the vaccinations, and the readily available and affordable solutions/strategies; and increase their commitment, planning and actions towards optimal/timely receipt of the vaccinations by the children. These were expected to, respectively, lead to a decrease in complacency about the vaccinations (increase in the perceived risk of the VPDs and in the perceived importance of the vaccinations), increase in confidence in the vaccinations (regarding safety and effectiveness) and increase in convenience in the vaccinations (increase in the perceived availability and accessibility of the vaccinations) and thus increase in the optimal/timely (cumulative age-appropriate) coverage and coverage timeliness score of routine childhood immunisation in the intervention arm.

Randomisation and masking

16 clusters were assigned to the two study arms (1:1) via covariate-constrained randomisation technique. Using a programme written in Stata,[38] the principal investigator generated the randomisation/allocation schemes based on 10% cut-off of the balance score and l2 balance metric as overall balance was sought on important baseline covariates among children aged 5–9 and 10–11 months whose vaccination data were collected from their vaccination cards. The baseline covariates were the primary outcomes; delivery at health facility, birth order of the child; number of ante-natal visits by the mother and educational level of the mother; educational level of the husband of the mother; household income; travel time to catchment immunisation facility and the location of cluster (rural and urban/semiurban). After running the programme, an allocation scheme was automatically chosen but it was not used, rather, an independent statistician randomly selected the final scheme from the dataset of the constrained randomisation space (permutation matrix of acceptable allocations). The final scheme was then entered into the input dataset and the balance across study arms was summarised in a table using the table 1 command and the result

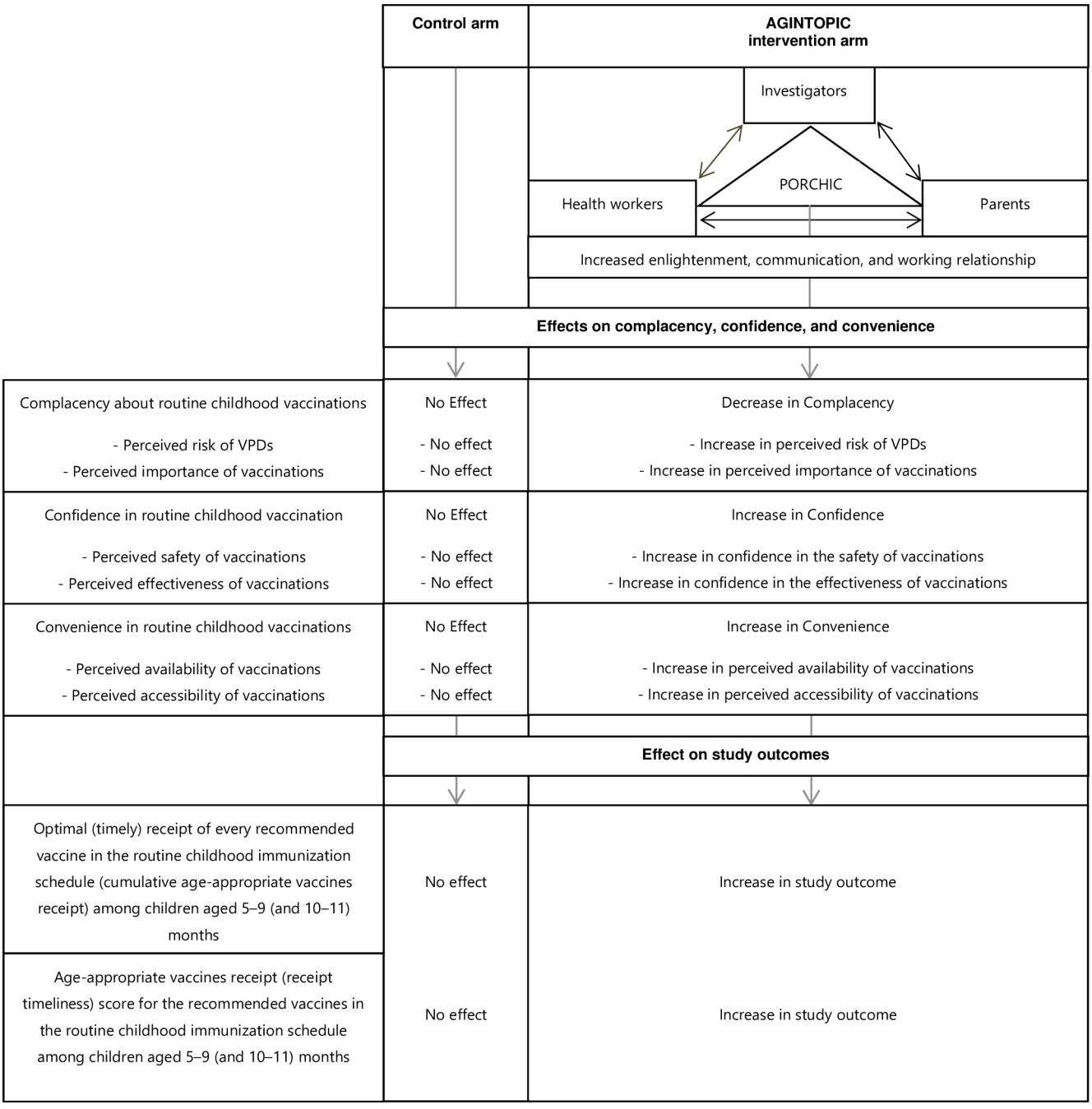

Figure 1 Trial logic framework. AGINTOPIC, Adaptive Group Intervention for Optimal routine childhood Immunisation Coverage; PORCHIC, Promoters of Optimal Routine Childhood Immunisation Coverage; VPDs, vaccine-preventable infectious diseases.

showed that reasonable overall balance was achieved between the control and intervention arms for all the covariates (online supplemental appendix p 7).

The automatically 'chosen scheme' variable in the constrained randomisation space dataset was updated to reflect the final chosen allocation scheme. The validity of the constrained randomisation was assessed by observing the number of restricted allocation schemes (in the constrained space) to make sure they were not too few (less than a 100 for example) compared with the unrestricted allocation schemes[36 38] and by creating a 16×16 matrix of cluster allocations to observe the percentage of times out of the total number of acceptable allocations (in the constrained space) that each pair of clusters was allocated to the same treatment arm (whether any pair was never or always allocated to the same arm).[36] There were 1288 acceptable allocations in the constrained space, and no pair of clusters was ever or always allocated to the same treatment arm, as the percentage of times each pair of clusters was allocated to the same treatment arm ranged from 20.0% to 66.9% (online supplemental appendix p 8). The constrained randomisation was considered to be reasonably valid.

It was not possible to mask the investigators, participants and interviewers because of the pragmatic and open nature of the intervention.

Data quality control

More details are in the protocol.[19] Briefly, two anonymous photographs of the vaccination evidence on the vaccination card of each child were taken and transmitted to the online record along with the other data. The photographs were used to double-check on errors/inconsistencies in the date data because the entry of 'dates' is particularly prone to error due to the number of digits involved, and this fact, with the need to be very careful when collecting data, was emphasised and re-emphasised during the training of the interviewers. The errors in the date variables assessed, using Stata and Excel, and corrected included errors in the digits of the dates; inconsistencies between date of birth and completed age in months (with the date of interview); discrepancies between vaccine doses usually given together such as the birth, 6, 10 and 14 weeks doses and 9-month doses; and inconsistencies in the chronology of the dates such as the chronology between the dates of birth and dates vaccination doses were given and between the dates the birth, 6, 10 and 14 weeks doses, and 9 months doses were given, respectively. The few cases of obvious errors in the transmitted photographs were corrected after communicating with the respective interviewers who cross-checked with the respective respondents and in the very few instances where corrections could not be made, such as illogical chronology between the dates of birth and dates vaccination doses were given, the data were discarded as appropriate.

Statistical analyses

Data were analysed using Stata/SE V.15.1 (Stata). All analyses were on intention-to-treat basis and were done using a cluster-level method of analysis for cluster randomised trials with small number of clusters per treatment arm.[36] Prevalence difference in the intervention arm compared with control was computed from the cluster-level summaries (proportions for dichotomous outcomes and medians for continuous outcomes) in each study arm. Unadjusted analysis was via bivariate linear regression of the cluster-level summaries of the outcome measures on the study arms to obtain the corresponding p value and 95% CI of each prevalence difference, while adjusted analysis was via multivariate linear regression, controlling for cluster-level summaries of baseline covariates of interest including the most appropriate and predictive subsets of the covariates used for the constrained randomisation.[38 39] Based on expert judgement, and as prespecified in the trial protocol, the covariates were the respective outcomes, delivery at health facility, number of ante-natal visits by the mother and travel time to catchment immunisation facility.[19]

For the primary outcomes, additional adjusted analysis via a two-stage procedure[36] was also done as exploratory analysis. The first stage involved multivariate linear regression of the outcome measure on the cluster-level summaries of the baseline covariates excluding the intervention effect. The differences between the observed outcomes (cluster-level summaries) in the clusters and the predicted outcomes in the absence of intervention effect were the difference-residuals (covariate-adjusted residuals) which replaced the observed cluster-level summaries in a bivariate linear regression in the second stage in estimating the intervention effect (prevalence difference), corresponding p value and 95% CI which were thus adjusted for the covariates in the first stage.

To check the robustness/validity of the main findings, randomisation-based inference was done via adjusted clustered permutation tests (aCPTs) (which controlled for the respective outcomes, delivery at health facility, number of ante-natal visits by the mother and travel time to catchment immunisation facility) that incorporated the constrained randomisation schemes.[36 38 39] The aCPTs were done at the individual level using a programme written in Stata.[38] The balance between the study arms was assessed via comparative analysis of baseline data. This trial is registered with ISRCTN, number ISRCTN59811905.

Patients and public involvement

Patients or the public were not involved in the design, conduct or reporting of this study.

RESULTS

The AGINTOPIC trial was implemented from 1 June 2022 to 31 May 2023. Eligibility screening and recruitment of clusters occurred from 1 June 2022 to 1 July 2022. Of the 115 clusters screened, 56 met the eligibility criteria and 16 were then randomly selected to participate in the trial (figure 2). Baseline household questionnaire survey was conducted from 2 July 2022 to 16 July 2022. Out of the 3108 submissions received, 2961 (95.3%) were valid submissions of which 2428 (82.0%) had vaccination records from vaccination cards (figure 2). All the submissions with vaccination cards, and only such submissions, were included in the analysis of baseline balance across study arms and in the adjusted analysis at the end of the study (figure 2).

The allocation of the 16 clusters (8 clusters per study arm) was constrained on baseline covariates. After the intervention, the end-of-study household questionnaire survey was conducted from 1 May 2023 to 31 May 2023. Overall, out of the 1792 submissions received for the control arm, 1728 (96.4%) were valid submissions of which 1434 (83.0%) had vaccination records from vaccination cards, and out of the 1676 submissions received for the intervention arm, 1608 (95.9%) were valid submissions of which 1448 (90.0%) had vaccination records from vaccination cards (figure 2). All the submissions with vaccination cards, and only such submissions, were included in the end-of-study analysis (figure 2).

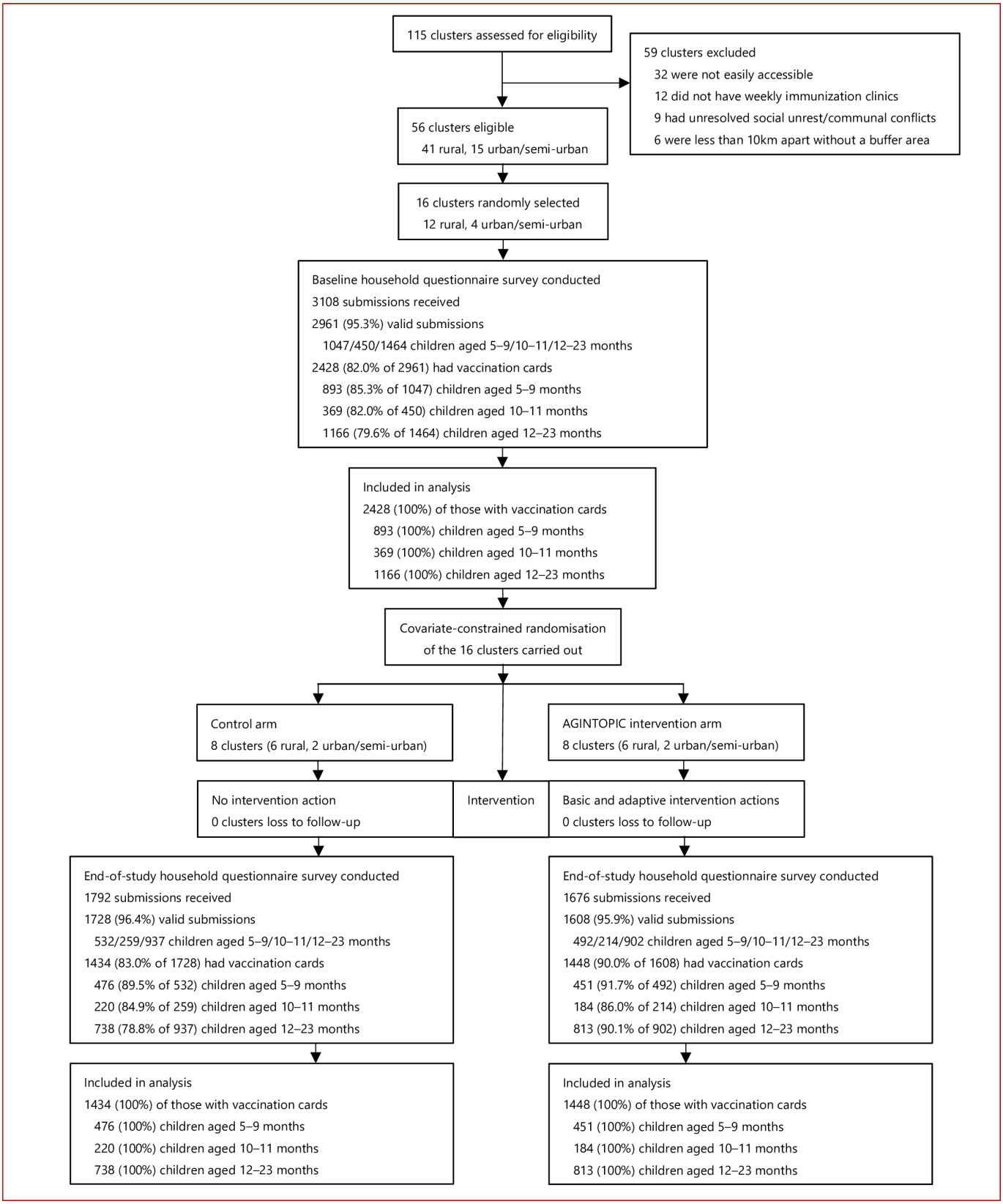

Figure 2 Trial profile. AGINTOPIC, Adaptive Group Intervention for Optimal routine childhood Immunisation Coverage.

There was reasonable overall balance between both study arms with respect to important baseline characteristics, particularly the baseline covariates of interest used for the constrained randomisation (table 2).

The crude and adjusted results of the full effects of the intervention on the primary outcomes among the children aged 5–9 months are presented in table 3. The adjusted results are similar in the main and additional/

Table 2 Cluster-level summaries* of important baseline cluster-level and individual-level† characteristics, by study arm

	Control arm	AGINTOPIC intervention arm
Cluster level		
Number of clusters	8	8
Location of clusters		
Rural	6	6
Urban or semi-urban	2	2
Number of participants, median (range)†		
Children aged 5–9 months	45.5 (40–101)	60 (34–89)
Children aged 10–11 months	22.5 (14–32)	23 (16–36)
Individual level†		
Median age of participants, months		
Children aged 5–9 months	7.1 (0.6)	6.6 (0.5)
Children aged 10–11 months	10.7 (0.5)	10.3 (0.5)
Proportion of participants by gender		
Children aged 5–9 months		
Male	50.6% (10.8)	47.1% (8.6)
Female	49.4% (10.8)	52.9% (8.6)
Children aged 10–11 months		
Male	56.1% (11.5)	47.8% (13.0)
Female	43.9% (11.5)	52.2% (13.0)
Proportion of participants delivered at a health facility‡	75.1% (26.1)	85.2% (11.5)
Median birth order of participants	3.1 (0.7)	2.6 (0.7)
Median age of mothers of participants, years	28.3 (1.3)	28.9 (1.6)
Proportion of participants' mothers who completed secondary or higher education	58.7% (19.7)	56.3% (15.8)
Proportion of participants' mothers whose husbands completed secondary or higher education	68.9% (17.0)	67.3% (14.3)
Proportion of participants in households with higher monthly household income§	25.5% (24.0)	32.5% (28.2)
Median number of ante-natal visits by mothers of participants	4.9 (1.2)	5.5 (1.5)
Median travel time to vaccination facility, minutes	27.3 (10.5)	25.3 (11.2)
Primary outcomes		
Children aged 5–9 months		
Proportion who had optimal receipt of every recommended birth to 14 weeks vaccine¶	7.0% (12.6)	4.1% (4.2)
Median age-appropriate vaccines receipt (receipt timeliness) score for the recommended birth to 14 weeks vaccines¶	75.5 (12.9)	76.6 (8.8)
Children aged 10–11 months		
Proportion who had optimal receipt of every recommended birth to 9 months vaccine**	11.6% (29.4)	4.5% (5.6)
Median age-appropriate vaccines receipt (receipt timeliness) score for the recommended birth to 9 months vaccines**	70.1 (23.9)	70.8 (15.8)

Data are mean (SD) unless otherwise stated.
*Only cluster-level summaries of baseline characteristics are presented because the study used a repeated cross-sectional design and baseline and follow-up data were not necessarily on the same individuals.
†Refers to the primary participants (children aged 5–9 and 10–11 (5–11) months whose vaccination data were collected from their vaccination cards).
‡Public and private health facility in contrast to other places (home, traditional birth attendant).
§Monthly household income of 81 000 Nigerian Naira or more.
¶The recommended and due vaccines
**The recommended and due vaccines.
AGINTOPIC, Adaptive Group Intervention for Optimal routine childhood Immunisation Coverage.

Table 3 Effects of the AGINTOPIC intervention on the primary outcomes compared with the control

	Number of clusters (number of participants)	Cluster-level prevalence or median score, mean (SD)	Crude results*		Adjusted results†		Additional adjusted results‡		Adjusted clustered permutation test§
			cPD (95% CI) or cMD (95% CI)	P value	aPD (95% CI) or aMD (95% CI)	P value	aPD (95% CI) or aMD (95% CI)	P value	P value
Children aged 5–9 months¶									
Had optimal receipt of every recommended birth to 14 weeks vaccine**									
Control	8 (476)	6.0% (8.1)	0.0	–	0.0	–	–		–
AGINTOPIC intervention	8 (451)	14.3% (11.7)	8.3% (–2.5 to 19.1)	0.1210	10.8% (0.8 to 20.9)	0.0376	9.4% (1.5 to 17.3)	0.0236	0.0093
Age-appropriate vaccines receipt (receipt timeliness) score for the recommended birth to 14 weeks vaccines**									
Control	8 (476)	75.1 (17.8)	0.0	–	0.0	–	–		–
AGINTOPIC intervention	8 (451)	85.5 (9.5)	10.4 (–4.9 to 25.6)	0.1678	9.5 (1.0 to 17.9)	0.0317	8.6% (1.9 to 15.4)	0.0156	0.0155
Children aged 10–11 months¶									
Had optimal receipt of every recommended birth to 9 months vaccine††									
Control	8 (220)	2.0% (4.3)	0.0	–	0.0	–	–		–
AGINTOPIC intervention	8 (184)	2.2% (4.8)	0.2% (–4.7 to 5.1)	0.9354	1.3% (–3.1 to 5.8)	0.5216	1.1% (–2.2 to 4.5)	0.4820	0.3292
Age-appropriate vaccines receipt (receipt timeliness) score for the recommended birth to 9 months vaccines††									
Control	8 (220)	69.0 (23.1)	0.0	–	0.0	–	–		–
AGINTOPIC intervention	8 (184)	70.9 (10.6)	1.9 (–17.4 to 21.2)	0.8369	0.7 (–10.4 to 11.8)	0.8954	0.6% (–8.0 to 9.3)	0.8808	0.9969

*From analysis (bivariate linear regression) adjusting for clustering.
†From analysis (multivariate linear regression) adjusting for clustering and the baseline covariates of interest (cluster-level summaries of the respective outcomes, delivery at health facility, number of ante-natal visits by mother, travel time to catchment immunisation facility).
‡From analysis adjusting for clustering and the baseline covariates of interest in a two-stage procedure involving covariate-adjusted residuals (considered exploratory).
§Adjusting for the baseline covariates of interest.
¶Those whose vaccination data were collected from their vaccination cards.
**The recommended and due vaccines and a measure of the full impact of the intervention.
††The recommended and due vaccines and a measure of the partial impact of the intervention.
AGINTOPIC, Adaptive Group Intervention for Optimal routine childhood Immunisation Coverage; aMD, adjusted mean difference; aPD, adjusted prevalence difference; cMD, crude mean difference; cPD, crude prevalence difference.

exploratory analyses. The mean proportion of children aged 5–9 months who had optimal/timely (cumulative age-appropriate) receipt of every recommended birth to 14 weeks vaccine significantly increased from 6.0% (SD 8.1) in the control arm to 14.3% (11.7) in the intervention arm (adjusted prevalence difference (aPD) 10.8%, 95% CI 0.8% to 20.9%, p=0.0376). The aCPT p value of 0.0093 indicated the validity of the main finding. Similarly, the mean age-appropriate vaccines receipt (receipt timeliness) score for the recommended birth to 14 weeks vaccines by children aged 5–9 months significantly increased from 75.1 (17.8) in the control arm to 85.5 (9.5) in the intervention arm (adjusted mean difference 9.5, 95% CI 1.0 to 17.9, p=0.0317, aCPT p=0.0155).

The crude and adjusted results of the partial effects of the intervention on the primary outcomes among the children aged 10–11 months are presented in table 3. The adjusted results are similar in the main and additional/exploratory analyses. We observed no significant difference between both study arms with respect to the mean proportion of children aged 10–11 months who had optimal receipt of every recommended birth to 9 months vaccine and the mean age-appropriate vaccines receipt score for the recommended birth to 9 months vaccines by children aged 10–11 months.

The crude and adjusted results of the full effects of the intervention on the coprimary outcomes among the children aged 5–9 months are presented in table 4. Regarding the mean proportion of children aged 5–9 months who had optimal receipt of the recommended individual vaccines and vaccine doses, only the optimal receipt of HBV-0, OPV-0 and IPV was significantly increased in the intervention arm compared with the control arm in the main results. The mean proportion of children aged 5–9 months who had optimal receipt of OPV, PCV and Penta had statistically non-significant increase in the intervention arm compared with the control arm in the main results (respectively: aPD 8.7%, 95% CI −1.7% to 19.1%, p=0.0916; aPD 7.9%, 95% CI −1.8% to 17.6%, p=0.0986; and aPD 8.8%, 95% CI −1.2% to 18.7%, p=0.0771). However, the aCPT p values were, respectively, 0.0171, 0.0202 and 0.0155, indicating that the non-significant findings in the main results might not be valid or that there were significant intervention effects in the randomisation-based inference.

Regarding the mean age-appropriate vaccines receipt score for the recommended individual vaccines and vaccine doses by children aged 5–9 months, only the receipt scores for OPV, PCV and Penta were significantly increased in the intervention arm compared with the control arm (table 4).

The crude and adjusted results of the partial effects of the intervention on the coprimary outcomes among the children aged 10–11 months are presented in table 4. We observed no significant difference between both study arms with respect to the mean proportion of children aged 10–11 months who had optimal receipt of the recommended individual vaccines and vaccine doses such as MCV-1, yellow fever vaccine and meningitis vaccine and the mean age-appropriate MCV-1, yellow fever vaccine and meningitis vaccine receipt scores by those children.

The crude and adjusted results of the intervention on the secondary outcomes are presented in online supplemental appendix (pp 9–12). Briefly, among the children aged 5–9 months, the increase in up-to-date vaccination for every recommended birth to 14 weeks vaccine was not statistically significant, but the aPD of 17.8% was of public health significance. The increase in up-to-date vaccination for OPV, PCV and Penta was, respectively, statistically significant. The decrease in the dropout rate between Penta-1 and Penta-3 was statistically significant. No significant increase was observed among the children aged 10–11 and 12–23 months.

DISCUSSION

The AGINTOPIC trial evaluated the full impact of hybrid parents and health workers' adaptive intervention on the optimal community-wide routine childhood immunisation coverage among children aged 5–9 months in Ebonyi state, Nigeria. We found that the intervention significantly increased the proportion of children aged 5–9 months who had optimal/timely (cumulative age-appropriate) receipt of every recommended birth to 14 weeks vaccine and significantly increased the age-appropriate vaccines receipt (receipt timeliness) score for the recommended birth to 14 weeks vaccines by those children. The intervention also significantly increased the optimal receipt of individual vaccines and vaccine doses such as HBV-0, OPV-0 and IPV (and OPV, PCV and Penta in randomisation-based inference) and the age-appropriate vaccines receipt scores for individual vaccines like OPV, PCV and Penta by those children.

The trial also evaluated the partial impact of the intervention on the optimal community-wide immunisation coverage among children aged 10–11 months and we found that the intervention did not significantly increase the proportion of children aged 10–11 months who had optimal receipt of every recommended birth to 9 months vaccine and did not significantly increase the age-appropriate vaccines receipt score for these vaccines by those children. The intervention also did not significantly increase the optimal receipt of each individual vaccine (MCV-1, yellow fever vaccine and meningitis vaccine) and the age-appropriate vaccine receipt score for each of the vaccines by those children.

Our findings demonstrate that, when fully received, the intervention was more effective in increasing the optimal/timely (cumulative age-appropriate) routine childhood immunisation coverage and in increasing the timeliness score of the coverage compared with the control. Our findings also show that, when partially received, the intervention was not more effective in increasing the optimal routine childhood immunisation coverage and in increasing the timeliness score of the coverage compared with the control.

Table 4 Effects of the AGINTOPIC intervention on the coprimary outcomes compared with the control

	Number of clusters (number of participants)	Cluster-level prevalence or median score, mean (SD)	Crude results*		Adjusted results†		Adjusted clustered permutation test‡
			cPD (95% CI) or cMD (95% CI)	P value	aPD (95% CI) or aMD (95% CI)	P value	P value
Children aged 5–9 months§							
Had optimal receipt of BCG							
Control	8 (476)	46.7% (18.3)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	58.8% (11.7)	12.1% (–4.4% to 28.5%)	0.1376	8.5% (–7.3% to 24.4%)	0.2573	0.2547
Had optimal receipt of birth dose of hepatitis B vaccine (HBV-0)							
Control	8 (476)	49.8% (17.5)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	68.9% (11.9)	19.1% (3.1% to 35.1%)	0.0229	14.5% (0.2% to 28.8%)	0.0472	0.045
Had optimal receipt of oral polio vaccine (OPV)							
Control	8 (476)	9.4% (10.8)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	16.5% (11.9)	7.2% (–5.0% to 19.4%)	0.2283	8.7% (–1.7% to 19.1%)	0.0916	0.0171
Had optimal receipt of OPV-0							
Control	8 (476)	44.7% (14.9)	0	–	0	–	–
AGINTOPIC	8 (451)	64.8% (10.8)	20.1% (6.2% to 34.1%)	0.008	17.3% (2.5% to 32.2%)	0.0264	–
Had optimal receipt of OPV-1							
Control	8 (476)	39.5% (14.7)	0	–	0	–	–
AGINTOPIC	8 (451)	56.0% (20.4)	16.5% (–2.5% to 35.6%)	0.0842	14.7% (–1.4% to 30.8%)	0.0698	–
Had optimal receipt of OPV-2							
Control	8 (476)	50.5% (25.3)	0	–	0	–	–
AGINTOPIC	8 (451)	50.5% (19.2)	–0.01% (–24.1% to 24.1%)	0.9992	3.2% (–14.4% to 20.9%)	0.6926	–
Had optimal receipt of OPV-3							
Control	8 (476)	39.2% (26.3)	0	–	0	–	–
AGINTOPIC	8 (451)	43.9% (13.7)	4.6% (–17.9% to 27.1%)	0.6671	4.3% (–12.9% to 21.5%)	0.5884	–
Had optimal receipt of pneumococcal conjugate vaccine (PCV)							
Control	8 (476)	15.6% (14.7)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	22.0% (15.1)	6.4% (–9.6% to 22.4%)	0.4061	7.9% (–1.8% to 17.6%)	0.0986	0.0202
Had optimal receipt of PCV-1							
Control	8 (476)	41.1% (14.4)	0	–	0	–	–
AGINTOPIC	8 (451)	59.3% (21.7)	18.2% (–1.6% to 37.9%)	0.0685	14.3% (–2.5% to 31.2%)	0.0871	–
Had optimal receipt of PCV-2							
Control	8 (476)	50.4% (25.3)	0	–	0	–	–
AGINTOPIC	8 (451)	50.8% (20.1)	0.4% (–24.1% to 24.9%)	0.9747	2.5% (–15.6% to 20.6%)	0.7658	–

Continued

Table 4 Continued

	Number of clusters (number of participants)	Cluster-level prevalence or median score, mean (SD)	Crude results*		Adjusted results†		Adjusted clustered permutation test‡
			cPD (95% CI) or cMD (95% CI)	P value	aPD (95% CI) or aMD (95% CI)	P value	P value
Had optimal receipt of PCV-3							
Control	8 (476)	40.7% (25.7)	0	–	0	–	–
AGINTOPIC	8 (451)	45.7% (16.4)	5.0% (–18.1% to 28.1%)	0.6496	4.1% (–10.3% to 18.4%)	0.5391	–
Had optimal receipt of pentavalent vaccine (Penta)							
Control	8 (476)	14.9% (14.8)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	21.9% (14.8)	7.0% (–8.9% to 22.9%)	0.3628	8.8% (–1.2% to 18.7%)	0.0771	0.0155
Had optimal receipt of Penta-1							
Control	8 (476)	40.3% (14.3)	0	–	0	–	–
AGINTOPIC	8 (451)	58.5% (21.6)	18.2% (–1.4% to 37.8%)	0.0663	15.6% (–1.0% to 32.3%)	0.0627	–
Had optimal receipt of Penta-2							
Control	8 (476)	50.4% (25.3)	0	–	0	–	–
AGINTOPIC	8 (451)	51.4% (19.9)	1.0% (–23.4% to 25.4%)	0.9307	4.0% (–13.9% to 21.9%)	0.6303	–
Had optimal receipt of Penta-3							
Control	8 (476)	40.1% (26.4)	0	–	0	–	–
AGINTOPIC	8 (451)	45.0% (16.6)	4.8% (–18.8% to 28.5%)	0.6668	4.3% (–10.8% to 19.4%)	0.5388	–
Had optimal receipt of inactivated polio vaccine (IPV)							
Control	8 (476)	11.0% (12.2)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	19.5% (14.3)	8.6% (–5.7% to 22.8%)	0.2174	9.1% (0.04% to 18.2%)	0.0491	0.0171
Had optimal receipt of IPV-1							
Control	8 (476)	31.3% (13.6)	0	–	0	–	–
AGINTOPIC	8 (451)	50.3% (22.0)	19.0% (–0.7% to 38.6%)	0.0575	8.2% (–10.6% to 26.9%)	0.3552	–
Had optimal receipt of IPV-2							
Control	8 (476)	22.1% (19.9)	0	–	0	–	–
AGINTOPIC	8 (451)	26.1% (17.7)	4.1% (–16.2% to 24.4%)	0.6727	3.7% (–9.3% to 16.6%)	0.5426	–
Age-appropriate vaccine receipt (receipt timeliness) score by children aged 5–9 months§							
For BCG							
Control	8 (476)	96.1 (3.5)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	99.1 (2.5)	3.1 (–0.2 to 6.3)	0.0615	2.7 (–1.1 to 6.5)	0.1398	0.663
For HBV-0							
Control	8 (476)	96.5 (3.7)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	99.1 (2.5)	2.6 (–0.8 to 6.0)	0.1202	1.0 (–2.2 to 4.3)	0.496	0.6646

Continued

Table 4 Continued

	Number of clusters (number of participants)	Cluster-level prevalence or median score, mean (SD)	Crude results*		Adjusted results†		Adjusted clustered permutation test‡
			cPD (95% CI) or cMD (95% CI)	P value	aPD (95% CI) or aMD (95% CI)	P value	P value
For OPV							
Control	8 (476)	76.4 (22.7)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	87.7 (10.5)	11.3 (–7.7 to 30.3)	0.2232	12.7 (0.4 to 25.0)	0.0448	0.0047
For OPV-0							
Control	8 (476)	96.5 (3.7)	0	–	0	–	–
AGINTOPIC	8 (451)	99.1 (2.5)	2.6 (–0.8 to 6.0)	0.1202	2.0 (–1.9 to 5.9)	0.288	–
For OPV-1							
Control	8 (476)	77.0 (34.9)	0	–	0	–	–
AGINTOPIC	8 (451)	86.9 (34.4)	9.9 (–27.3 to 47.0)	0.5775	–2.3 (–33.9 to 29.3)	0.8741	–
For OPV-2							
Control	8 (476)	84.9 (34.7)	0	–	0	–	–
AGINTOPIC	8 (451)	96.9 (3.5)	12.1 (–14.4 to 38.5)	0.3441	–1.3 (–8.1 to 5.6)	0.688	–
For OPV-3							
Control	8 (476)	77.4 (34.4)	0	–	0	–	–
AGINTOPIC	8 (451)	87.8 (20.7)	10.3 (–20.2 to 40.8)	0.4799	15.1 (–10.3 to 40.6)	0.2145	–
For PCV							
Control	8 (476)	75.4 (32.7)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	87.6 (12.3)	12.2 (–14.3 to 38.7)	0.3395	9.9 (0.01 to 19.7)	0.0498	0.014
For PCV-1							
Control	8 (476)	77 (34.9)	0	–	0	–	–
AGINTOPIC	8 (451)	86.9 (34.4)	9.9 (–27.3 to 47.0)	0.5775	–4.5 (–36.8 to 27.8)	0.7633	–
For PCV-2							
Control	8 (476)	84.9 (34.7)	0	–	0	–	–
AGINTOPIC	8 (451)	96.9 (3.5)	12.1 (–14.4 to 38.5)	0.3441	–1.1 (–6.1 to 3.9)	0.6278	–
For PCV-3							
Control	8 (476)	79.6 (33.8)	0	–	0	–	–
AGINTOPIC	8 (451)	88.2 (20.9)	8.6 (–21.6 to 38.7)	0.5521	5.5 (–3.4 to 14.3)	0.1995	–
For Penta							
Control	8 (476)	75.3 (32.6)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	87.8 (12.4)	12.5 (–13.9 to 38.9)	0.3278	12.3 (1.4 to 23.2)	0.031	0.0093
For Penta-1							

Continued

Table 4 Continued

	Number of clusters (number of participants)	Cluster-level prevalence or median score, mean (SD)	Crude results*		Adjusted results†		Adjusted clustered permutation test‡
			cPD (95% CI) or cMD (95% CI)	P value	aPD (95% CI) or aMD (95% CI)	P value	P value
Control	8 (476)	77 (34.9)	0	–	0	–	–
AGINTOPIC	8 (451)	86.9 (34.4)	9.9 (–27.3 to 47.0)	0.5775	–2.0 (–32.5 to 28.5)	0.8873	–
For Penta-2							
Control	8 (476)	84.9 (34.7)	0	–	0	–	–
AGINTOPIC	8 (451)	96.9 (3.5)	12.1 (–14.4 to 38.5)	0.3441	–1.1 (–6.1 to 3.9)	0.6278	–
For Penta-3							
Control	8 (476)	79.6 (33.8)	0	–	0	–	–
AGINTOPIC	8 (451)	88.2 (20.9)	8.6 (–21.6 to 38.7)	0.5521	5.5 (–3.4 to 14.3)	0.1995	–
For IPV							
Control	8 (476)	53.3 (32.4)	0	–	0	–	–
AGINTOPIC intervention	8 (451)	74.5 (22.6)	21.2 (–8.8 to 51.1)	0.1517	17.8 (–8.6 to 44.2)	0.1633	0.0901
For IPV-1							
Control	8 (476)	63.0 (35.9)	0	–	0	–	–
AGINTOPIC	8 (451)	78.6 (36.4)	15.6 (–23.2 to 54.4)	0.404	9.7 (–39.4 to 58.8)	0.6686	–
For IPV-2							
Control	8 (476)	49.5 (42.7)	0	–	0	–	–
AGINTOPIC	8 (451)	75.9 (31.7)	26.4 (–13.9 to 66.8)	0.1818	22.7 (–22.4 to 67.8)	0.2874	–
Children aged 10–11 months§							
Had optimal receipt of first dose of measles-containing vaccine (MCV-1)							
Control	8 (220)	27.3% (22.1)	0	–	0	–	–
AGINTOPIC intervention	8 (184)	26.9% (17.6)	–0.5% (–21.9% to 20.9%)	0.9617	2.4% (–12.5% to 17.2%)	0.7285	0.5714
Had optimal receipt of yellow fever vaccine (YFV)							
Control	8 (220)	25.1% (22.1)	0	–	0	–	–
AGINTOPIC intervention	8 (184)	26.9% (17.6)	1.8% (–19.6% to 23.2%)	0.8616	5.2% (–10.0% to 20.4%)	0.4662	0.3556
Had optimal receipt of meningitis vaccine (MV)							
Control	8 (220)	24.9% (23.0)	0	–	0	–	–
AGINTOPIC intervention	8 (184)	25.5% (18.7)	0.6% (–21.9% to 23.1%)	0.9573	3.4% (–11.2% to 17.9%)	0.6181	0.4922
Age-appropriate vaccine receipt (receipt timeliness) score by children aged 10–11 months§							
For MCV-1							
Control	8 (220)	50.2 (44.6)	0	–	0	–	–
AGINTOPIC intervention	8 (184)	51.8 (40.1)	1.7 (–43.9 to 47.0)	0.9423	–7.9 (–46.1 to 30.2)	0.6533	0.6801

Continued

Table 4 Continued

	Number of clusters (number of participants)	Cluster-level prevalence or median score, mean (SD)	Crude results*		Adjusted results†		Adjusted clustered permutation test‡	
			cPD (95% CI) or cMD (95% CI)	P value	aPD (95% CI) or aMD (95% CI)	P value	P value	
For YFV								
Control	8 (220)	48.1 (42.4)	0	–	0	–	–	
AGINTOPIC intervention	8 (184)	51.8 (40.1)	3.8 (–40.5 to 48.0)	0.8583	–8.8 (–50.1 to 32.4)	0.6436	0.6522	
For MV								
Control	8 (220)	49.8 (44.1)	0	–	0	–	–	
AGINTOPIC intervention	8 (184)	52.7 (40.1)	2.9 (–42.4 to 48.1)	0.8935	–6.7 (–44.1 to 30.7)	0.6987	0.7469	

*From analysis adjusting for clustering.
†From analysis adjusting for clustering and the baseline covariates of interest (cluster-level summaries of the respective outcomes, delivery at health facility, number of ante-natal visits by mother, travel time to catchment immunisation facility).
‡Adjusting for the baseline covariates of interest.
§Those whose vaccination data were collected from their vaccination cards.
AGINTOPIC, Adaptive Group Intervention for Optimal routine childhood Immunisation Coverage; aMD, adjusted mean difference; aPD, adjusted prevalence difference; cMD, crude mean difference; cPD, crude prevalence difference.

Generally, findings of our trial show similarities with some previous randomised interventional trials but with notable differences. Compared with our findings, the results of a randomised trial in northwest Ethiopia showed that text message reminders intervention significantly increased the on-time full vaccination (within 4 days before to 4 weeks after the scheduled dates) and on-time individual vaccinations at 6, 10 and 14 weeks of age (for Penta-1, Penta-2 and Penta-3, respectively) and at 9 months of age (for measles vaccine) compared with the control,[26] however, the participants assessed at 9 months had fully received the intervention, unlike in our trial. In a randomised trial in Guatemala, the results showed that text message reminders significantly increased the timeliness of the second scheduled visits (on the scheduled date) (but not the third scheduled visits) to the immunisation clinics compared with the control.[29] A randomised trial in Northern Ghana reported that voice call reminders (with sensitisation) to caregivers and conditional financial incentives to caregivers and community health volunteers significantly increased the timely receipts of both BCG (within 4 weeks of birth) and OPV-0 (within 2 weeks of birth) and of OPV-0, but not of BCG, compared with the control.[30]

Household visits by trained community volunteers followed by targeted immunisation outreaches by catchment health facilities did not significantly increase timely receipt of BCG vaccination within the first month after birth compared with the control in the results of a randomised trial in West Cameroon.[33] In the results of a randomised trial in Pakistan, reminder bracelet interventions had no significant effect on the time-to-receipt of Penta-3 and that of MCV-1 compared with the control,[27] and another randomised trial in Pakistan reported that text message reminders did not significantly increase the timely receipts of 6, 10 and 14 weeks vaccines within the scheduled time compared with the control.[31] In another randomised trial in Pakistan, the results showed that financial incentives (conditional cash transfers) to caregivers significantly increased the timely receipts of Penta-3 and of MCV-1 (within 4 weeks of the scheduled dates) while text message reminders only significantly increased the timely receipt of MCV-1, not of Penta-3, compared with the control, however, timeliness was a secondary outcome in that trial.[32]

The results of a randomised trial in Zimbabwe also showed that text message reminders intervention significantly increased the receipt of individual vaccinations without delays at 6, 10 and 14 weeks of age compared with the control, but this was a secondary outcome.[28] Text message reminders and text message reminders plus conditional financial incentives to caregivers significantly increased the timely receipt of measles vaccine (within 2 weeks of the scheduled date), but not of Penta-1, Penta-2 and Penta-3, compared with the control in the results of a randomised trial in western Kenya.[25] But the timeliness was a secondary outcome in that trial.

The foregoing evidence shows mixed results regarding randomised interventional trials to increase the timeliness of routine childhood immunisation coverage. Although the specific interventions and timeliness measures and assessments vary among the trials which were conducted in different contexts, the evidence emphasises the importance of and need for such interventions in improving timely immunisation coverage, in addition to highlighting the challenges in modifying health behaviour in this regard.

In our trial, the hybrid parents and health workers' adaptive engagement significantly increased the optimal community-wide immunisation coverage among the children aged 5–9 months via the mechanism illustrated in figure 1 and explained in the methods section. 'Community-wide' reflects the fact that the impact of the AGINTOPIC intervention on the outcomes was assessed among all the eligible children in the communities irrespective of whether their parents were (direct) recipients of the intervention or not. This community-wide impact was assessed through the repeated cross-sectional survey design of our trial and is in contrast to the observed impact of most of the previous trials which were assessed by cohort survey designs. We understand this community-wide impact of our AGINTOPIC intervention (eg, adjusted prevalence difference of 10.8%) to be very conservative and of public health significance. The absolute impact of a 10.8 percentage point increase cannot be reasonably compared with the relative impact (risk ratios) reported by the other relevant trials. Notwithstanding, we understand the community-wide impact of a 10.8 percentage point increase to be significant from a public health perspective, considering the fact that the AGINTOPIC trial largely targeted behavioural determinants (which are often difficult to address) amidst systemic and socioeconomic determinants of optimal/timely receipt of routine childhood immunisations which were beyond the scope of the trial.

Perhaps the impact of our trial could have been more significant if not for some observed challenges like the unexpected delays in the formation of the PORCHIC group (in identifying and registering a reasonable number of eligible members before commencement of the first PORCHIC group discussion) and the lower than expected rate of participation in the PORCHIC group discussions/meetings by the registered parents, both of which reduced the number of exposures to the intervention before the subsequent immunisation appointments/due dates. The partial impact of the intervention on optimal community-wide immunisation coverage among the children aged 10–11 months was not significant as the above observed challenges were more pronounced among these children who were 1–2 months old before we started the formation of the PORCHIC group.

There were some limitations in our trial. Because of limited resources, the trial was implemented over 1 year with the delivery of the intervention spanning about 10 months. Hence, the children who were born in about months 1–5 of the intervention were aged about 5–9 months during the end-of-study survey, and the recommended and due vaccine doses which were appropriate for timeliness assessment were the birth to 14 weeks vaccinations. It is thus not easy to predict how the full impact of the intervention would have differed from what was observed if these children were up to at least 10–12 months old and their receipts of the 9 months vaccinations were part of the timeliness assessment. This limitation should be addressed in subsequent trials. Also, it is not clear how (extent/direction) the systemic and socioeconomic determinants of optimal/timely vaccination receipts identified in the intervention clusters during the PORCHIC group discussions (stockouts, poverty, long distance and lack of transport fares etc), which were beyond the scope of our intervention, could have affected our findings. Although these determinants were assessed only in the intervention clusters during the trial, we believe the situation was similar in the control clusters based on the fact that all the clusters were within the same socioeconomic and geopolitical environment and health system and based on our previous experience in the study setting. Thus, coupled with the covariate-constrained allocation of clusters, we understand that the effects of such determinants, if any, would be minimal.

Our trial had many strengths. The PORCHIC group in our trial reflects the popular and naturally existing social groups (various traditional, community, or village associations or meetings) in the study area and many other settings in and outside Nigeria, and the delivery of the basic and adaptive intervention actions through the PORCHIC group thus provides a pragmatic, dynamic and scalable approach to community engagement interventions which can be adapted by routine childhood immunisation programmes. Due to the nature of our concept of optimal immunisation coverage and the outcome measures, achieving optimal routine immunisation coverage in our trial was perhaps relatively demanding, and the observed impact thus reflects the robustness and strong performance of the AGINTOPIC intervention. Because of the pragmatic, scalable and sustainable nature of the intervention, as well as the community-wide impact which perhaps reflects high positive externalities and cost-effectiveness of the intervention, we understand the AGINTOPIC intervention to be of great public health and health policy value in the efforts to increase optimal/timely immunisation coverage for optimal protection against VPDs in order to reduce outbreaks.

Because date variables are particularly prone to errors during data documentation and entry, we took rigorous measures to enhance date data quality as clearly stated in the methods section. This, together with the high availability of vaccination cards with valid date data as shown in the trial profile, reflects the robustness and validity of the timeliness assessment in our trial and of the observed impact. Our trial involved both rural and urban clusters, the intervention involved eligible parents in the communities and not only those visiting health facilities, and the

outcome measurement involved mother–child pairs (in the communities and not only those visiting health facilities) in a repeated cross-sectional household survey to assess the community-wide effect of the intervention. All these enhanced the generalisability of our trial findings. Again, the random allocation of clusters was constrained on baseline covariates, and we confirmed the validity of the covariate-constrained randomisation and also confirmed the robustness and validity of the main findings by randomisation-based inference through aCPTs. Moreover, our trial was transparently implemented with fidelity based on a prospectively registered protocol.[19]

We recommend that future trials of this nature should not only assess the community-wide impact of the intervention but also assess the impact on the direct recipients of the intervention (eg, the children whose parents/caregivers were registered as PORCHIC members and/or those who actually participated in the PORCHIC group discussions) and on those who were not (direct) recipients of the intervention (positive externalities). If the outcome is observed to be significantly higher among the non-recipients, or non-direct recipients, of the intervention compared with the control, it will mean that there are significant positive externalities; otherwise, there are no significant positive externalities.

CONCLUSIONS

The AGINTOPIC trial has demonstrated that, when fully received, the hybrid parents and health workers adaptive intervention significantly increased the actual optimal/timely (cumulative age-appropriate) community-wide routine childhood immunisation coverage, including completeness of the coverage, in Ebonyi state, Nigeria, and the evidence also illuminates the need for such pragmatic, dynamic and scalable community engagement intervention which we understand can be adapted and sustainably applied by routine childhood immunisation programmes in the global efforts to address the recurrent outbreaks of VPDs.

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Contributors UIO is the lead author and was the principal investigator, conceptualised and designed the trial, designed the data collection tool and programmed the software, wrote the protocol and directed the implementation of the trial, oversaw data quality control, did the statistical analyses and interpretations, wrote the manuscript and is the guarantor. RLE, CIA, COI, GEN, CCI and LCE contributed to the development of the study design, data collection tool and protocol. COI and LCE contributed to the implementation of the trial and data quality control. All authors contributed to the revision of the manuscript and read, edited and approved the final manuscript.

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