# Improving HPV Immunization Coverage Among Adolescent Girls in Mali and Côte d'Ivoire Through an Innovative Community-Based Follow-Up: A Randomized Controlled Trial Protocol

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## *ABSTRACT*

### *Background*

Human papillomavirus (HPV) vaccination is one of the most effective strategies for preventing cervical cancer, yet coverage among adolescent girls in West Africa, including Mali and Côte d'Ivoire, remains far below the World Health Organization (WHO) target of 90% coverage by age 15. Barriers include limited community awareness, weak follow-up systems, and sociocultural constraints that contribute to missed vaccination opportunities. Muso Health has previously demonstrated the potential effectiveness of an innovative community health worker (CHW)-led, digitally supported follow-up model for improving childhood immunization coverage; this model has now been adapted to address HPV vaccination among adolescent girls in the same communities.

### *Objective*

To evaluate the effectiveness of a community-based CHW follow-up intervention, supported by a digital tool, in increasing HPV vaccination coverage and reducing time-to-vaccination among adolescent girls in Mali and Côte d'Ivoire, using a randomized controlled trial (RCT) design with a waitlist.

### *Methods and analysis*

This is a multi-site, pragmatic, parallel-group RCT with a waitlist (delayed-intervention) design, implemented across Muso Health catchment areas in Mali and Côte d'Ivoire. Eligible participants are adolescent girls who are, or will become, eligible for HPV vaccination during the study period (aged 10 years in Mali; 9-14 years in Côte d'Ivoire). Eligible girls are randomized 1:1, stratified by country, site, and CHW supervision zone, to: (i) a control arm receiving standard community mobilization; or (ii) an intervention arm receiving proactive CHW home visits guided by a digital tool with real-time data visualization and automated task reminders. Twelve weeks after launch, the control arm crosses over to receive the intervention (waitlist activation). The primary outcome is HPV vaccination coverage (proportion vaccinated among eligible girls with known status) compared between arms at 12 weeks. The secondary outcome is the time (in days) from study initiation to vaccination within 12 weeks. Exploratory outcomes compare coverage and time to vaccination between the original arms at 25 weeks, after both arms have received the intervention.

The planned total sample size is 17,188 adolescent girls (9,550 intervention; 7,638 control), with minimum detectable effects estimated separately for Mali (baseline coverage 4.95%) and Côte d'Ivoire (baseline coverage about 93%), because baseline coverage differs sharply between the two countries. The primary analysis will use mixed-effects logistic regression and the secondary analysis Kaplan-Meier, Cox proportional hazards, and restricted mean survival time methods, all accounting for clustering by CHW supervision zone, as detailed in the study's Statistical Analysis Plan.

***Ethics and dissemination***

Verbal informed consent was obtained from participants (or their parents/guardians, given participants' minor status) prior to vaccination status assessment, in view of low literacy rates in the study population. The protocol has been submitted to the relevant national and institutional ethical review boards in Mali and Côte d'Ivoire for approval or exemption. Findings will be disseminated through peer-reviewed publication, stakeholder workshops, and policy briefs to inform HPV immunization strategies in comparable low-resource settings.

**Clinical Trial registration: NCT07807202**

***Keywords***

Human papillomavirus (HPV); adolescent vaccination; Professional Proactive Community Health Workers; Randomized Controlled Trial; waitlist design; digital health; Mali; Côte d'Ivoire;

## Background

Cervical cancer remains a leading cause of cancer-related morbidity and mortality among women globally, with nearly 90% of deaths occurring in low- and middle-income countries (LMICs)(1, 2). Persistent infection with high-risk human papillomavirus (HPV) types is the primary cause of cervical cancer, making HPV vaccination a critical component of prevention strategies(2, 3). Sub-Saharan Africa bears a disproportionate burden of disease due to high HPV prevalence and limited access to screening and treatment services.

In response, the World Health Organization (WHO) has set a global strategy for cervical cancer elimination, including a target of 90% HPV vaccination coverage among girls by age 15 years(4). Progress toward this target, however, remains uneven across countries, particularly in West Africa(5-7).

In Côte d'Ivoire, the HPV vaccine was introduced into the national immunization program in 2019 and is provided free of charge to eligible girls. Despite this, vaccination coverage has remained below national targets: national estimates indicate coverage of approximately 8.5% in 2020, rising to about 27% in 2021, still far below the national target of 95%(8). More recent large-scale campaigns supported by Gavi have aimed to accelerate uptake, targeting up to 3.5 million girls aged 9-18 years, including both in-school and out-of-school populations(9). That campaign achieved remarkable HPV vaccine coverage of 93% in April 2025 (10). Nevertheless, barriers such as lack of awareness and parental hesitancy were reported(10).

In Mali, HPV vaccination was introduced more recently, in 2024. Early implementation data indicate that over 145,000 ten-year-old girls were vaccinated within the first nine months of 2025, including both school-attending and out-of-school girls(11). While this demonstrates promising initial uptake, challenges remain: misinformation (particularly concerns about infertility), geographic barriers, and limited access to health services in remote regions have been identified as key obstacles to achieving high coverage(12). Earlier evidence from Mali also highlights low levels of knowledge about HPV and cervical cancer despite high stated willingness to accept vaccination, suggesting that demand-side barriers such as awareness and decision-making autonomy may significantly influence uptake(13).

Across both countries, HPV vaccination programs rely heavily on school-based delivery strategies, which may fail to reach out-of-school girls and those in marginalized settings. Weak follow-up systems, limited tracking of eligible adolescents, and insufficient community engagement further contribute to missed opportunities for vaccination. These systemic gaps are compounded by sociocultural factors, including parental influence, gender norms, and misinformation.

Community-based approaches have emerged as a promising strategy to address these challenges(14-16). Muso Health has previously launched an innovative community-based follow-up model that leverages the proactivity of community health workers (CHWs) and digital tools to improve childhood immunization coverage in the communities it serves(17). Muso's programmatic data suggest this model may be effective in improving children's vaccination coverage: for example, a 90% reduction in zero-dose children aged 0-23 months was observed 24 months after the intervention began. Given this potential, Muso Health has adapted the model to improve adolescent HPV vaccination coverage in the same communities.

This study, therefore, aims to assess the effectiveness of an innovative, CHW-led, digitally supported community-based follow-up intervention in improving HPV immunization coverage among adolescent girls in Mali and Côte d'Ivoire, using a randomized controlled trial with a waitlist design.

## Objectives

### *Primary objective*

To evaluate the effectiveness of the community-based CHW follow-up intervention in increasing HPV vaccination coverage among eligible adolescent girls, compared with standard community mobilization, at the phase 1 endline, 12 weeks after launch.

### *Secondary objective*

To evaluate whether the intervention reduces the time elapsed from study initiation to HPV vaccination within 12 weeks among eligible adolescent girls, relative to the control arm.

### *Exploratory objective*

To compare HPV vaccination coverage and time to vaccination between the original arms 25 weeks after launch, after the control arm had received the intervention from week 12, to assess whether the delayed-start group caught up with the early-start group.

## Methods

### *Trial design*

This is a multi-site, pragmatic, two-arm, parallel-group randomized controlled trial with a waitlist (delayed-intervention) design and a 1:1 allocation ratio, stratified by country. All eligible girls are randomized at baseline to an intervention or a control arm; following the phase 1 assessment, the control arm crosses over to receive the intervention, so that all participants ultimately have access to the intervention by the end of the study (see Participant timeline).

### *Study setting*

The trial is implemented in existing Muso Health program catchment areas: in Mali, the health areas of Bankas, Yirimadio, and Bakorobabougou; and in Côte d'Ivoire, the Madinani health district and the Diape catchment area. These sites were originally established for a community-based follow-up intervention targeting childhood immunization (0-23 months) described in Sandie et al. (2025)(17), and have now been adapted to additionally support adolescent HPV vaccination follow-up.

## Eligibility criteria

### *Inclusion criteria*

- Adolescent girls residing within a participating Muso Health catchment area in Mali or Côte d'Ivoire.
- Age eligible for HPV vaccination per national guidelines during the study period: 10 years in Mali; 9 to 14 years in Côte d'Ivoire.
- Girls not yet age-eligible at study launch but expected to become eligible during the study period are also included (see Participant timeline and Sequence generation for the allocation rules for this subgroup).

### *Exclusion criteria*

- Girls residing outside the defined catchment areas or not identifiable through the Community Health Toolkit (CHT) programmatic data system.

## Intervention description

The intervention builds on the existing Muso Health community-based follow-up model, adapted for adolescent HPV vaccination. Professional CHWs (ProCHWs) use a purpose-built digital workflow, integrated into their mobile application, to identify eligible girls, verify vaccination status, and follow up with unvaccinated girls and their parents or guardians. Figure 1 summarizes the CHW workflow for both study arms.

### *Control arm: standard community mobilization*

CHWs in the control arm conduct home visits using a digital form that identifies eligible girls and documents their current HPV vaccination status. This baseline identification and status-verification workflow reflects standard practice but does not include proactive invitation or follow-up prompts for unvaccinated girls.

### *Intervention arm: CHW follow-up with digital decision support*

In addition to the status-verification workflow described above, CHWs in the intervention arm actively invite unvaccinated eligible girls (through their parents or guardians) to attend HPV vaccination, and receive automated, digitally scheduled follow-up prompts. Specifically:

- An automated vaccination status verification form is systematically triggered in the CHW mobile application for every eligible girl.
- Where a girl has not yet been vaccinated, CHWs document a planned vaccination date in consultation with the parents or guardians.
- A vaccination follow-up form is automatically generated 2 days before the planned vaccination date, prompting the CHW to remind the parents or guardians and to document whether vaccination occurred.
- The follow-up form remains active in the mobile application until submitted by the CHW, ensuring continuity of follow-up for each beneficiary.
- An in-app analytics dashboard displays each CHW's real-time HPV vaccination coverage performance within their catchment area.
- All data synchronize to a supervisor-facing, Looker Studio-based programmatic dashboard, supporting real-time monitoring of coverage, identification of underperforming areas, and data-driven supervisory action.

The digital intervention package was deployed progressively at the start of the trial. From launch (8-9 April 2026, depending on country) to 19 May 2026, the CHW workflow in the intervention arm comprised home visits for identification of eligible girls, vaccination status verification, invitation to vaccinate, and follow-up of unvaccinated girls. From 19 May 2026 onward, this workflow was complemented with the supervisor dashboard, enabling supervisors to monitor CHW progress and provide targeted support. This phased rollout reflects the operational reality of digital tool deployment in the field and is described transparently here for completeness (see Participant timeline).

## Outcomes

### *Primary outcome*

HPV vaccination coverage, defined as the number of adolescent girls with a documented completed HPV vaccination per 100 eligible adolescent girls (aged 10 years in Mali; 9-14 years in Côte d'Ivoire) with known vaccination status. The primary endpoint is the between-arm difference in HPV vaccination coverage (intervention versus control) at the phase 1 endline, 12 weeks after launch (1 July 2026). A girl counts as vaccinated if her documented vaccination date is on or before 1 July 2026. Time frame: 12 weeks.

### *Secondary outcome*

Time to HPV vaccination, defined as the number of days elapsed between study initiation and receipt of the HPV vaccine. The secondary endpoint is the between-arm difference (intervention versus control) in mean time to vaccination within 12 weeks, estimated as the difference in restricted mean survival time at 84 days, among girls unvaccinated at launch (girls vaccinated before launch have no event during follow-up). Time frame: 12 weeks.

### *Exploratory outcomes (phase 2)*

Four exploratory outcomes compare the original arms after both had received the intervention: (1) HPV vaccination coverage 25 weeks after launch (1 October 2026), defined as for the primary outcome but counting vaccinations dated on or before 1 October 2026; because the control arm began receiving the intervention at week 12, this compares an early with a delayed start of the

intervention; (2) the change in coverage between 12 and 25 weeks within each arm, and whether the gap between arms narrowed after the crossover; (3) time to HPV vaccination over 25 weeks, summarized as the restricted mean time to vaccination and as hazard ratios before and after the week-12 crossover; and (4) vaccination uptake by 25 weeks among girls unvaccinated at launch, overall and by country. Time frame: 25 weeks.

### *Outcome measurement*

All outcomes are ascertained from routine programmatic data recorded by CHWs in the Community Health Toolkit (CHT) platform during scheduled home visits and follow-up contacts. No additional data collection instrument or participant-facing survey is used; outcome ascertainment relies entirely on programmatic vaccination-status verification, consistent with the pragmatic, routine-data-based design of this trial. Vaccination status at each endline is derived from the documented vaccination date. Because not every girl could be visited by 1 July 2026, CHWs continued to verify vaccination status, including the vaccination date, until 1 October 2026. The timing of a verification visit therefore affects only whether a girl's status is known, not the period over which she can be counted as vaccinated. Girls reported as vaccinated without a documented date are treated as having unknown status.

## Participant timeline

Version 1.0 of this protocol (March 2026) planned a study launch on 1 April 2026, with a phase 1 evaluation at 3 months (1 July 2026) and a phase 2 evaluation at 6 months (1 October 2026). In practice, the intervention launched on 8 and 9 April 2026 in Mali and Côte d'Ivoire, respectively, and the intervention package was deployed in two stages, as described under Intervention description. The realized timeline is summarized in Table 1.

**Table 1: Study timeline**

| Milestone | Date | Description |
|---|---|---|
| Trial launch | 8-9 April 2026 | Randomization and launch of CHW workflows in Mali (8 April) and Côte d'Ivoire (9 April) |

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| Intervention package stage 1 | Launch - 19 May 2026 | Intervention arm: identification, status verification, invitation, and follow-up of unvaccinated girls. Control arm: identification and status verification only. |
| Intervention package stage 2 | From 19 May 2026 | Supervisor dashboard activated in the intervention arm, enabling real-time monitoring and support of CHWs |
| Phase 1 endline (both arms) | 1-Jul-26 | Vaccination status on this date, 12 weeks after launch, is the phase 1 (primary) outcome; a girl counts as vaccinated if her documented vaccination date is on or before 1 July 2026 |
| Waitlist crossover | 2-Jul-26 | Former control arm begins receiving the full intervention package (waitlist activation) |
| Verification window (both arms) | 2-Jul-26 to 1-Oct-26 | CHWs verify each girl's vaccination status, including the vaccination date, at home visits; status on 1 July 2026 (phase 1) and on 1 October 2026 (phase 2) is derived from the documented dates |
| Phase 2 endline (both arms) | 1-Oct-26 | Vaccination status on this date, about 25 weeks after launch, is the phase 2 (exploratory) outcome, based on documented vaccination dates recorded at each girl's |

| | | |
|---|---|---|
| | | last CHW visit on or before 1 October 2026 |

**Sample size**

The trial includes 17,188 adolescent girls: 8,823 in Mali (5,365 intervention; 3,458 control) and 8,365 in Côte d'Ivoire (4,185 intervention; 4,180 control). The intervention-arm totals include 2,110 girls (1,945 in Mali and 165 in Côte d'Ivoire) who were expected to age out of eligibility within the first three months and were therefore allocated to the intervention arm without randomization (see Sequence generation); they are included in the calculations below, consistent with the primary analysis. Because the number of girls was fixed by the eligible population of the catchment areas rather than chosen to reach a target power, we report the minimum detectable effect (MDE): the smallest true difference in coverage the trial can detect with 80% power, using a two-sided test at $\alpha = 0.05$.

Baseline HPV vaccination coverage differs sharply between the two countries, so the MDE is estimated separately for each country rather than from a single pooled baseline. Baseline coverage is 4.95% in the Mali study population. In Côte d'Ivoire, the April 2025 national multi-age campaign reached about 93% of eligible girls (10), so baseline coverage is assumed to be 93%. For each country, the MDE is the absolute difference $\Delta = p_1 - p_0$ that solves $\Delta = z_{1-\alpha/2}\sqrt{[\bar{p}(1-\bar{p})(1/n_1 + 1/n_0)]} + z_{1-\beta}\sqrt{[p_1(1-p_1)/n_1 + p_0(1-p_0)/n_0]}$, where $p_0$ is baseline coverage, $p_1$ is coverage in the intervention arm, $n_1$ and $n_0$ are the numbers of girls in the intervention and control arms, and $\bar{p}$ is the average of $p_1$ and $p_0$ weighted by arm size.

The MDE is 1.42 percentage points in Mali (from 4.95% to 6.37%, a 29% relative increase; odds ratio 1.31) and 1.48 percentage points in Côte d'Ivoire (from 93.0% to 94.5%; odds ratio 1.29). Because about 93% of girls in Côte d'Ivoire are expected to have been vaccinated already, the intervention can raise coverage there only among the remaining 7%: an increase of 1.48 points corresponds to vaccinating an additional 21% of the girls who were unvaccinated at baseline. In the sensitivity analysis restricted to randomized girls (excluding the 2,110 girls allocated by the age-out rule), the MDEs are 1.57 points in Mali and 1.50 points in Côte d'Ivoire.

The primary analysis pools both countries in a model adjusted for country. Assuming a common intervention odds ratio in both countries and combining the country-specific variances of the log odds ratio by inverse-variance weighting, the trial has 80% power to detect an odds ratio of 1.20, equivalent to an increase of about 0.9 percentage points in Mali and 1.1 points in Côte d'Ivoire. Because randomization is individual and stratified by CHW supervision zone, no design effect for clustering is applied. These estimates replace the earlier calculation (MDE of 0.94 percentage points, a 19% relative increase), which applied the Mali baseline of 4.95% to the full sample of 17,188 girls.

Because the high baseline in Côte d'Ivoire dilutes any effect on coverage, a pre-specified supplementary analysis compares vaccination uptake by 12 weeks among girls unvaccinated at launch. Its MDE depends on uptake in the control arm, which is not known in advance. Assuming that about 95% of girls in Mali and 7% in Côte d'Ivoire were unvaccinated at launch, the MDE in Mali ranges from 1.5 to 2.6 percentage points for control-arm uptake between 5% and 20%. In Côte d'Ivoire, with about 590 unvaccinated girls, only increases of 6 to 10 percentage points could be detected, so the country-specific uptake estimate there will be imprecise. The observed baseline coverage in each country's trial cohort will be reported, and the MDEs recalculated with it.

Given the pragmatic, routine-data-based design, some missingness in verified vaccination status is anticipated at each evaluation point, arising from girls' emigration out of the study site or from time constraints preventing verification for all girls (particularly at the phase 1 evaluation). To limit this, CHWs continued to verify vaccination status until 1 October 2026 (see Outcome measurement). Figure 2 shows how the MDE in each country changes with the proportion of girls whose vaccination status is unknown, assuming status is missing at random within each arm. At the attrition targets of 10% in the control arm and 20% in the intervention arm, the MDE rises to 1.54 percentage points in Mali and 1.61 points in Côte d'Ivoire, about 8% above its value with complete data. The MDE stays within 15% of its complete-data value as long as unknown status is below about 22% in both arms in Mali and 25% in Côte d'Ivoire. In Mali, unknown status in the control arm costs more precision than in the intervention arm, because the control arm is smaller. The attrition targets of 10% (control) and 20% (intervention) are therefore retained. Full sample size and power methodology are provided in the study's Statistical Analysis Plan (SAP), available as a supplementary document.

**Recruitment**

No individual recruitment procedures are required beyond routine CHW household enumeration, since the trial uses existing Muso Health catchment-area registers maintained in the CHT platform. All adolescent girls identified as eligible within a participating catchment area are considered for randomization; there is no self-selection or opt-in enrollment step, consistent with the pragmatic, programmatic nature of this trial.

**Sequence generation**

Randomization is performed centrally using a computer-generated allocation sequence, stratified at the country level (Mali and Côte d'Ivoire analyzed and randomized separately). Within each country, eligible girls, including those not yet age-eligible at the time of randomization but expected to reach the required age during the study period, alongside those already age-eligible, are randomized 1:1 to the control and intervention arms, with additional stratification by site, catchment area, and CHW supervision zone to ensure balance across these operationally important strata.

Girls expected to age out of HPV vaccination eligibility within the first three months of the study (i.e., before the phase 1 evaluation) are systematically allocated to the intervention arm rather than randomized, to avoid assigning girls with limited remaining eligibility windows to a delayed-intervention (waitlist) arm. This allocation rule is applied transparently and uniformly. It concerns 2,110 girls (1,945 in Mali and 165 in Côte d'Ivoire), who are included in the primary analysis; that analysis is read together with the same analysis restricted to randomized girls (see Statistical methods and Discussion).

**Allocation concealment mechanism**

Group allocation is generated and stored centrally within the CHT platform's back-end configuration and is not accessible to CHWs, supervisors, or participants prior to a girl's registration in the system. Once a girl is registered as eligible, her arm assignment is automatically applied by the platform and determines which digital workflow (control or intervention) is triggered on the CHW's mobile application, preventing manual selection or foreknowledge of allocation by field staff.

**Implementation**

The randomization sequence is generated by the study statistician (A.B. Sandie) and implemented in the CHT platform by the Muso Health data systems team. CHWs and their supervisors enroll and follow up with participants according to the workflow triggered by the platform for each girl's assigned arm; field staff do not have discretion over allocation and are informed only of the workflow relevant to the girls in their caseload.

**Blinding**

Given the nature of the intervention (a visible difference in CHW household visit and follow-up practices), blinding of CHWs and participants to arm assignment is not feasible, consistent with most pragmatic, community-delivered public health interventions. Outcome assessment relies on objectively documented vaccination status recorded in the CHT platform rather than on subjective participant- or CHW-reported measures, which mitigates (but does not eliminate) the risk of observer bias. The study statistician conducting the primary analyses will not be blinded to arm assignment, as unblinded analysis is required to implement the pre-specified statistical models; however, the analysis code and Statistical Analysis Plan were finalized before endline data access, limiting the potential for analytic bias.

**Data collection methods**

All outcome and covariate data are extracted from the Community Health Toolkit (CHT) platform, an open-source digital health platform used by CHWs for routine household visits and follow-up. Vaccination status is recorded by CHWs at the point of care during home visits, using a structured digital form; no additional data collection tool, questionnaire, or biological sample is required from participants. Data completeness is supported by the automated triggering and persistence of follow-up forms until submission, and by supervisor dashboard monitoring of missing or overdue assessments.

**Data management**

Data are entered directly into the CHT platform by CHWs using mobile devices and synchronize automatically to a central, access-controlled database when network connectivity is available.

Range and consistency checks are built into the digital forms (valid age ranges, valid vaccination dates) to reduce data entry error at the point of collection. Access to the raw programmatic database is restricted to designated Muso Health data management staff; the study statistician receives a de-identified analytic extract for the purposes of this evaluation.

**Statistical methods**

Full statistical methods are pre-specified in a dedicated Statistical Analysis Plan (SAP), finalized prior to endline data access and provided as a supplementary file to this protocol. In brief:

- Primary outcome: HPV vaccination coverage at 12 weeks will be compared between arms using a mixed-effects logistic regression model, adjusted for country and age (months remaining in the national eligibility window at launch), with a random intercept for CHW supervision zone to account for clustering. The primary analysis includes the girls allocated to the intervention arm by the age-out rule and is read together with the same analysis restricted to randomized girls; the same pairing applies to the secondary and supplementary analyses. Results will be reported as an adjusted odds ratio (OR), average marginal effect (absolute risk difference), and relative risk, each with 95% confidence intervals (CI).
- Supplementary uptake analysis: the primary model is refitted among girls unvaccinated at launch, with vaccination by 12 weeks as the outcome, overall and by country, because the high baseline coverage in Côte d'Ivoire dilutes any effect on coverage.
- Secondary outcome: Time to HPV vaccination within 12 weeks, among girls unvaccinated at launch, will be analyzed using Kaplan-Meier estimation and a Cox proportional hazards model (clustered robust standard errors at the CHW zone level), reported as an adjusted hazard ratio with 95% CI. The secondary endpoint, the between-arm difference in mean time to vaccination, will be estimated as the difference in restricted mean survival time (RMST) at 12 weeks (84 days).
- Missing data: The primary analysis uses complete cases (girls with known vaccination status). Unknown status is classified by cause (deactivated or deceased; no information source; not visited because the girl aged out, because of an age or sex data correction, or because she was not reached in time), and the sensitivity analyses are conditioned on cause: multiple imputation for girls not reached in time, a delta-adjusted (tipping-point)

imputation for girls with no information source, and bounding analyses for causes that cannot be imputed. Age or sex data corrections are resolved through a blinded post-randomization eligibility review rather than treated as missing data.

- Type I error: The primary hypothesis is tested once, after verification of vaccination status at 1 July 2026 closed on 1 October 2026, at a two-sided α of 0.05. The phase 2 comparisons address a different question (early versus delayed start of the intervention) and are exploratory.
- Country-specific and sensitivity analyses: Pre-specified country-specific analyses and sensitivity analyses (unadjusted model; model including site and an arm × country interaction; Kaplan-Meier estimate of coverage at 12 weeks; verification timing; and retention of girls excluded at the eligibility review) are detailed in the SAP.
- Phase 2 (exploratory): coverage at 25 weeks by original arm (mixed-effects logistic regression and Kaplan-Meier estimate), change in coverage between 12 and 25 weeks (generalized estimating equations with an arm × time interaction), time to vaccination over 25 weeks (RMST and a Cox model with hazard ratios before and after the crossover), and uptake by 25 weeks among girls unvaccinated at launch (the same model as the supplementary 12-week uptake analysis, with a Kaplan-Meier estimate alongside).

All analyses will be conducted in R (version ≥ 4.3), with analysis code version-controlled and locked prior to endline data access. Any deviation from the pre-specified SAP will be reported as a post hoc analysis and justified in the final study report.

**Harms**

Because this trial evaluates a follow-up and reminder workflow rather than the vaccine itself, and does not alter vaccine administration procedures, no additional vaccine-related adverse events are anticipated beyond those associated with routine, nationally recommended HPV vaccination, which are monitored through each country's existing vaccine pharmacovigilance system. Potential intervention-related harms are limited to the low risk of social or psychological discomfort from repeated CHW follow-up contact; CHWs are trained to discontinue follow-up at the request of the parent or guardian. Any such concerns raised to CHWs or supervisors will be logged and reported to the principal investigators and the relevant ethical review board.

## Auditing

The trial is conducted under the oversight of the Muso Health research team, led by the principal investigators. Data quality audits are performed periodically by the data management team through automated consistency checks and random spot-checks of CHW-entered data against dashboard-reported indicators. The statistical analysis code and locked SAP provide an auditable record of pre-specification, distinct from any post hoc analytic decisions.

Research ethics approval

This protocol has been submitted for review to the relevant national and institutional ethical review boards in Mali and Côte d'Ivoire, for approval or exemption as appropriate given the study's reliance on routine programmatic data and a licensed, nationally recommended vaccine.

## Protocol amendments

This document is Version 2.1 of the study protocol (7 October 2026). Version 1.0 (March 2026) described the trial as an adaptive A/B testing evaluation. Version 2.0 (August 2026) clarified the design as a randomized controlled trial (RCT) with a waitlist and incorporated the realized implementation timeline and an explicit description of the consent process. It aligns the protocol with version 2.1 of the Statistical Analysis Plan: it defines the phase 1 outcome as vaccination status on 1 July 2026 (12 weeks after launch), with verification continuing until 1 October 2026; adds 12-week time frames for the primary and secondary outcomes and exploratory phase 2 outcomes at 25 weeks; replaces the interim alpha-spending approach with a single confirmatory test; and specifies cause-specific handling of unknown vaccination status and a post-randomization eligibility review; adds a supplementary analysis of vaccination uptake among girls unvaccinated at launch, and specifies that the primary analysis, which includes girls allocated by the age-out rule, is read together with the analysis restricted to randomized girls; it also adds uptake by 25 weeks among girls unvaccinated at launch as an exploratory phase 2 outcome. These changes were made before any outcome data were accessed. Any future amendments will be dated, summarized in a version history, and communicated to the relevant ethical review boards and trial registry.

## Consent or assent

Given low literacy rates in the study population, verbal informed consent was obtained from participants (or, given participants' status as minors, from their parents or guardians on their behalf,

with assent sought from the adolescent girl herself where developmentally appropriate) prior to vaccination status assessment. Consent was sought by the CHW at the time of the household visit, following a standardized verbal script explaining the purpose of the assessment, the voluntary nature of participation, and the right to decline without consequence for access to routine immunization services. Verbal consent was documented by the CHW in the CHT platform at the time it was obtained.

**Confidentiality**

All participant data are collected and stored within the access-controlled CHT platform, identifiable only to authorized CHWs, supervisors, and designated Muso Health data management staff for operational and clinical follow-up purposes. The analytic dataset used for this evaluation will be de-identified prior to transfer to the study statistician, retaining only the minimum variables necessary for analysis (arm, country, site, CHW zone, age, and outcome variables), with no participant names or other direct identifiers included.

**Declaration of interests**

ABS, YK, VZG, MA, MB, BT, ID, JAK, NC, OG, GA, AM, TM, MC, BT, LG, and AJ were Muso employees during the study implementation and investigation.

**Access to data**

The study Principal Investigator (A.B. Sandie) will have full access to the final analytic dataset. Aggregated, de-identified results will be made available to co-investigators, national immunization program partners, and, subject to data-sharing agreements and institutional approval, to other researchers upon reasonable request, as detailed in the Data Availability Statement.

**Ancillary and post-trial care**

As this trial involves a licensed, nationally recommended vaccine administered through standard health system channels (not experimentally introduced by the study team) and a non-invasive follow-up workflow, no ancillary or post-trial care provisions beyond routine national immunization and pharmacovigilance services are applicable. All participants, including those in

the control arm, receive the intervention by the end of the study period through the waitlist crossover design, ensuring equitable access to the CHW follow-up support by trial completion.

**Dissemination policy**

Findings will be disseminated through peer-reviewed publication, presentations at relevant regional and international conferences, stakeholder workshops with national immunization program partners in Mali and Côte d'Ivoire, and policy briefs targeted at program managers and funders working on HPV immunization in comparable low-resource settings. There are no publication restrictions; authorship will follow the contributions outlined under Contributors and Guarantor and will conform to International Committee of Medical Journal Editors (ICMJE) authorship criteria.

## Discussion

### *Anticipated strengths*

- This trial leverages an existing, previously validated community-based follow-up platform (17), increasing the feasibility and external validity of implementation at scale.
- The pragmatic design, using routinely collected programmatic data rather than a bespoke research data collection system, minimizes participant burden and better reflects real-world implementation conditions relevant to policymakers.
- The waitlist design ensures all eligible girls, including those initially randomized to the control arm, ultimately have access to the intervention, addressing an important ethical consideration in community-level public health trials.
- Stratified randomization by country, site, and CHW supervision zone, together with a pre-specified, clustering-aware statistical analysis plan, supports robust and generalizable effect estimation.
- The large sample (N = 17,188) supports precise estimation of the intervention effect, with minimum detectable effects reported separately for each country.

### *Anticipated limitations*

- Blinding of CHWs and participants to arm assignment is not feasible given the nature of the intervention, introducing a risk of performance and, to a lesser extent, ascertainment bias, although outcome ascertainment relies on objectively documented vaccination status rather than subjective report.
- As a pragmatic trial relying on routine programmatic data, some vaccination status is expected to be unknown at each evaluation point (see Sample size). Pre-specified sensitivity analyses conditioned on the cause of unknown status (multiple imputation, tipping-point and bounding analyses) are planned, but residual bias from informative missingness cannot be entirely excluded.
- Vaccination status on 1 July 2026 was verified for some girls up to three months later, so classification depends on documented vaccination dates. Girls without a documented date

are treated as having unknown status, and a sensitivity analysis restricted to girls verified by 30 August 2026 checks whether later verification affected the results.

- Baseline HPV vaccination coverage in Côte d'Ivoire is high (about 93% after the 2025 national campaign), so the intervention can raise coverage there only among the few girls still unvaccinated, and the coverage comparison in that country can detect only effects that vaccinate a substantial share of them. The supplementary analysis among girls unvaccinated at launch addresses this dilution, but its precision in Côte d'Ivoire is limited by the small number of unvaccinated girls.
- Girls expected to age out of eligibility within the first three months (2,110 girls; 1,945 in Mali, 36% of the Mali intervention arm) were allocated to the intervention arm without randomization, so they have no counterparts of the same age in the control arm. The primary analysis includes them and adjusts for age, but this adjustment relies on extending the age relationship observed in randomized girls. The primary estimate will therefore be read together with the analysis restricted to randomized girls; if the two diverge, the randomized-girls estimate will take precedence for causal interpretation.
- The intervention and evaluation were designed and implemented by the same organization (Muso Health), which may introduce a risk of investigator bias in both delivery and interpretation of results; this is mitigated by pre-registration of the SAP and by involvement of independent national immunization program and academic co-investigators, but should be transparently acknowledged.
- The staged rollout of the digital intervention package (see Intervention description) means that girls enrolled earlier in phase 1 experienced a less complete intervention (without supervisor dashboard support) than those enrolled later; while this is accounted for descriptively, it introduces a degree of within-arm heterogeneity in intervention intensity.
- As the trial is implemented in a specific set of Muso Health catchment areas already served by an established community health worker program, findings may have limited generalizability to settings without an existing CHW infrastructure or digital health platform.

***Generalizability***

If effective, this community-based, digitally supported follow-up model could offer a scalable complement to school-based HPV vaccination delivery strategies, particularly relevant for reaching out-of-school adolescent girls and those in marginalized or hard-to-reach settings across West Africa and other low-resource contexts with comparable CHW infrastructure. Results will be interpreted with attention to the specific health system, digital infrastructure, and community engagement conditions present at the Muso Health study sites.

**Trial Status**

This protocol (Version 2.1, dated 7 October 2026) describes a trial whose data collection is complete. Randomization and launch of the CHW workflows took place on 8-9 April 2026; the control arm crossed over to the full intervention package on 2 July 2026; and verification of vaccination status continued until 1 October 2026, which was also the phase 2 endline. At the time of this version, no outcome data had been analyzed.

**Contributors and Guarantor**

*Conceptualization*: ABS, YK, AJ

*Methodology:* ABS, YK, AJ

*Formal analysis*: ABS

*Investigation*: ABS, YK, VZG, MA, MB, BT, ID, JAK, NC, OG, GA, AM, TM, MC, BT, LG, RC, YC, HD, FS, YT, BB, OSS, KK, ID, AJ

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*Supervision*: ABS, YK, AJ

**Data Availability Statement**

De-identified individual participant data underlying the results reported in this study will be made available upon reasonable request to the corresponding author, subject to a data-sharing agreement and approval by the relevant national immunization program authorities in Mali and Côte d'Ivoire, beginning 3 months after publication. The full statistical analysis code will be made available via the Muso Health data catalog (https://musodatacatalog.org/?page=1&ps=15) upon publication.

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# Figure

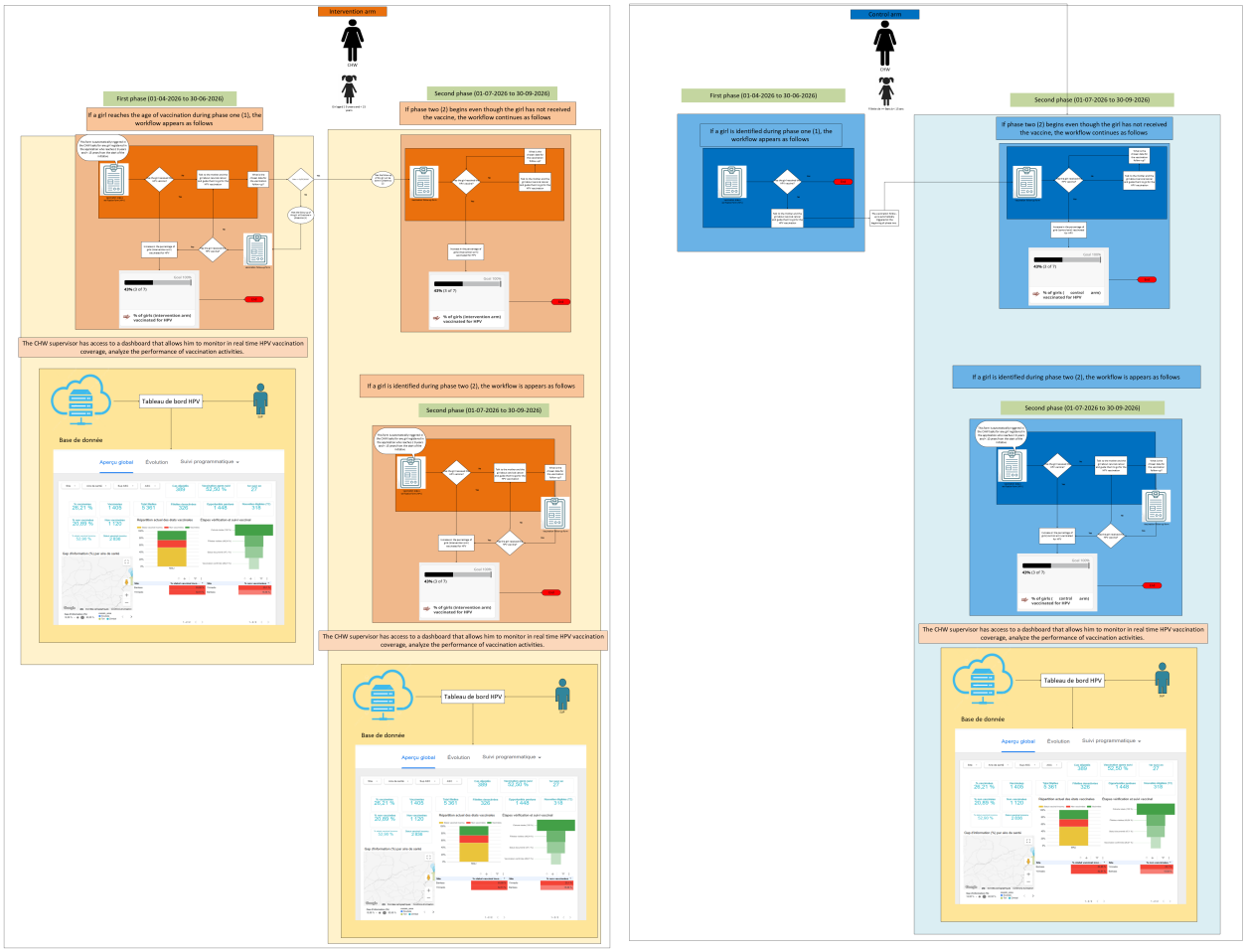



**Figure 1. Summary of the CHW workflow in both the intervention (orange) and control (blue) arms, across phase 1 and phase 2 of the trial.**

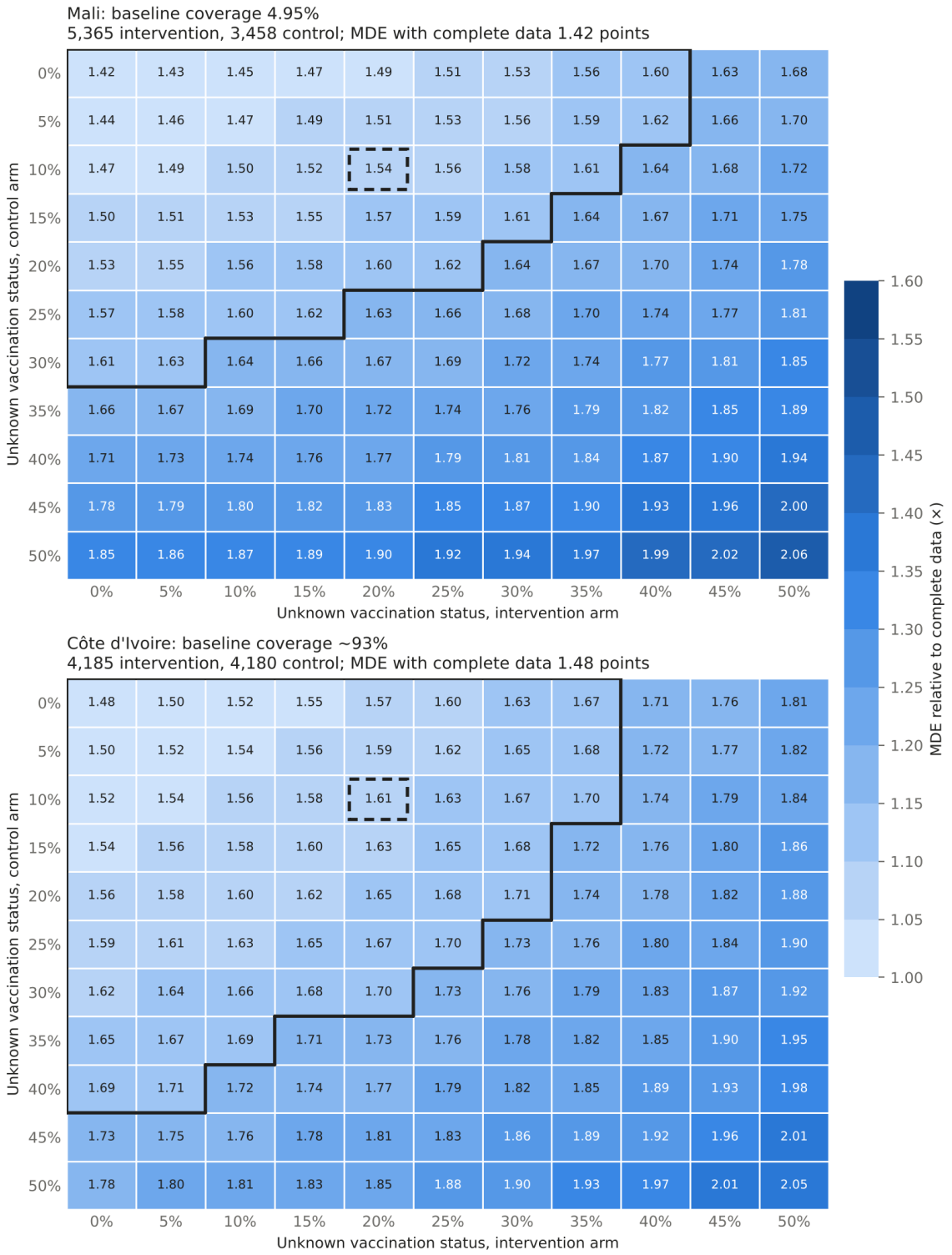



**Figure 2. Minimum detectable effect (percentage points) by proportion of girls with unknown vaccination status in the intervention and control arms, in Mali and Côte d'Ivoire. Solid outline: MDE within 15% of its complete-data value; dashed box: attrition targets (20% intervention, 10% control).**