Adolescent Wellness Visits in Tanzania (VITAA)

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CONTENTS

List of abbreviations

AIDS	Acquired Immune Deficiency Syndrome
AWV(s)	Adolescent wellness visit(s)
BMI	Body Mass Index
CEA	Cost effectiveness analysis
CEA	Cost Effectiveness Analysis
CFAR	Center For AIDS Research
CFIR	Consolidated Framework for Implementation Research
cRCT	cluster Randomized Controlled Trial
DHS	Demographic Health Survey
FGD	Focus Group Discussion
GEE	Generalized estimating equations
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HTC	HIV testing and counseling
ICER	Incremental Cost Effectiveness Ratio
KIIs	Key Informant Interview
LMICs	Low and middle-income countries
MOHCDGEC	Ministry of Health, Community Development, Gender, the Elderly & Children
MUAC	Mid Upper Arm Circumference
MUHAS	Muhimbili University of Health & Allied Sciences
NICHD	National Institute of Child Health and Development
NIMH	National Institute of Mental Health
PHQ-A	Patient Health Questionnaire for Adolescent
PrEP	Pre-exposure Prophylaxis
PTA	Parent-Teacher Association
QSR	Brand name Qualitative Software Developer
RCH	Reproductive and Child Health
RTI	Reproductive Tract Infections
SEM	Structural Equation Model
SRH	Sexual and reproductive health
SSI	Semi-structured Interview
STAG	Stakeholder Advisory Group
STI	Sexually transmitted infections
THMS	Malaria Indicator Survey
TWG	Technical Working Group
UNC	University of North California
USA	United States of America
VCT	Voluntary Counseling And Testing
WHO	World Health Organization
YAG	Youth Advisory Group

ABSTRACT
Getting adolescents in the door of a health facility is an entrenched health system problem, particularly for HIV and sexual and reproductive health (SRH) services. Adolescents in low-resource settings need a preventative health service platform applicable for all young people that promotes a culture of health-seeking behavior. In response to PAR-19-274 [Dissemination & Implementation Research in Health], this R01 will evaluate the impact of Adolescent Wellness Visits (AWVs), a new health service platform, for reaching young adolescents with HTC and other evidence-based prevention services which are clinic-based and school-facilitated. We posit that by coupling sexual and reproductive health (SRH) and non-SRH information and services, issues of self-risk assessment and access to services may be circumvented. AWVs could meet the SRH needs of at-risk adolescents and have a larger public health impact for all adolescents on access to traditionally neglected and untreated non-SRH issues such as poor nutrition, vision, dental, and mental health problems at the time of delivery as well as in the future as adolescents continue with more timely service utilization. The AWV is designed to be delivered during the last year of primary school when school attendance is high, and adolescents are on the cusp of puberty (mean age 13). This project is a collaboration between the University of North Carolina at Chapel Hill in the United States (prime), Muhimbili University of Health and Allied Sciences in Dar es Salaam, Tanzania, and Duke University in the United States.

Specific Aims are:
1) To assess the impact of Adolescent Wellness Visits on HTC (for all adolescents; primary outcome) and contraceptive uptake (for a sexually active subset) up to two years post-primary school via a cluster randomized controlled trial (20 school-clinic pairs: 10 intervention + 10 control; n=~1500 adolescents);
2) To evaluate factors that support or limit implementation of the AWV model and fidelity/adherence to implementation of the proposed package of evidence-based practices included in the AWV by utilizing 24 focus group discussions (FGDs) with implementers and up to **130 semi-structured interviews** (IDIs) with key informants and adolescents; and
3) To evaluate the cost-effectiveness of AWVs on two key health behavioral outcomes: uptake of HTC for all adolescents, and reductions in unmet need for contraception among sexually active adolescents.

Primary and Secondary outcomes: Our primary outcome is uptake of HTC for all adolescents; while the secondary outcome is reductions in unmet need for contraception among sexually active adolescents

Methodology:
Participants: Up to 1,500 adolescents in the seventh and final grade of primary school; and about 750 each from randomized intervention and control schools.
Study design: We will implement cluster randomized controlled trial with 10 intervention and 10 control school/health facility pairs; followed by exit qualitative interviews. The intervention will involve a single adolescent wellness visit to a public health facility within a walking distance (1 Km) that offers a package of evidence-based youth-friendly services on HIV testing uptake, and wider adolescent health concerns in Dar es Salaam and Pwani regions in Tanzania. All children will also be asked to read a Tanzania Commission for AIDS (TACAIDs) endorsed puberty book and encouraged to ask questions to teachers/parents, guardians and clinical staff during wellness visits for the intervention group. The intervention involves a single adolescent wellness visit to a public health facility within a walking distance (1 Km) to receive a package of evidence-based youth-friendly services on HIV testing uptake, and wider adolescent health concerns. The control condition will include exposure only to the puberty book. Direct observations coupled with exit FGDs and IDIs (with perspectives of parents, direct providers of health and education services, other key stakeholders, and adolescents), will describe factors that support or limit implementation of the AWV model including fidelity/adherence to components of the evidence-based package. This dissemination and implementation proposal aligns with the National Institute of Child Health and Development's (NICHD's) Research Theme #5: *Improving Health during the Transition from Adolescence to Adulthood* (NOT-HD-18-031), by facilitating behavior change through setting the tone for a 'culture of health and wellness' during this critical developmental period.

Budget Requested over five years of implementation: USD 1,060,561

DEFINITIONS OF KEY TERMS

Adolescent wellness visit (AWV): A youth-friendly one-time wellness visit, targeting young adolescents in the final year of primary school (mean age 13 years), that is coordinated by a public primary school and a public primary health care facility within about a kilometer distance from the school; and that lasts about 15-30 minutes. The assessments and information shared at the youth-friendly RCH clinic focus on seven priority health components (as defined by literature, parents and community leaders), including eye, dental, and mental health, as well as nutrition, puberty and contraception (for those sexually active) and an offer of HIV testing and counseling services (HTC) if requested and supported by feedback from HIV transmission risk assessments conducted by youth-friendly trained RCH nurses.

INTRODUCTION

Background and Literature Review.

In Tanzania, as in much of the world, very young adolescents are on the cusp of puberty, and for many, sexual and reproductive health (SRH) problems, including HIV, sexually transmitted infections (STIs) and unintended pregnancies, will increase as they age into adolescence.[1,2] Unfortunately, *adolescents are less likely* to access HIV testing and counseling (HTC), STI treatment, and contraceptive services than adults, yet they shoulder a disproportionate burden of these poor outcomes in many low and middle-income countries (LMICs). [1-6] In particular, HTC is a critical evidence-based intervention for reducing risky sexual behavior and for timely linkages to care for HIV-infected individuals.[4,7]

Getting adolescents in the door of a health facility is an entrenched health system problem.[3,8] For example, HTC requires either self-identification of risk for voluntary HTC or a leveraged opportunity for testing during a curative health visit, provider-initiated HTC. Neither approach adequately reaches adolescents who assess themselves as low risk, and who, as a group, are relatively healthy.[9-16] Likewise, global and national policies have emphasized adolescent-friendly reproductive health services but these static services are underdeveloped and underutilized since they usually require adolescent initiation.[17-20] Low utilization of health services among adolescents is an entrenched health system problem yet there is no routine adolescent health check-up platform in many low and middle-income countries (LMICs) on which to build. Adolescents are less likely to access HIV testing and counseling (HTC), sexually transmitted infection (STI) treatment, and contraceptive services than adults, and they shoulder a disproportionate burden of these poor sexual and reproductive health (SRH) outcomes, particularly in sub-Saharan Africa.[3-8] A health system paradigm shift is needed for adolescent health services to move from an opt-in/curative focus to a prevention-focused system that facilitates more regular interaction.

Current HIV testing approaches are inadequate for reaching adolescents. HTC is an evidence-based practice that reduces risky sexual behavior and links HIV-infected individuals into care in a timely manner.[9-11] Early HIV care and treatment is paramount given that between 2005 and 2012, HIV-related deaths among adolescents increased by 50% while the global number of deaths decreased by 30%.7 Service provision strategies for HTC include voluntary counseling and testing (VCT) which requires a person to assess their risk for HIV and seek out HIV testing and provider-initiated HTC which leverages opportunities for HIV testing when individuals access non-HIV health services. Adolescents assess themselves at lower risk of HIV than adults, which influences VCT uptake, and as a group, adolescents are relatively healthy and do not routinely access health services as often as adults.[9-15] In Tanzania, as in much of the world, adolescents ages 15-19 years are less likely to have ever tested for HIV than young people ages 20-24, even after accounting for recent sexual activity.[2] Among young women ages 15-19 in Tanzania, only 31% had ever tested for HIV while almost 73% of young women ages 20-24 had been tested.[2] Testing is critical given that HIV prevalence in Tanzania by ages 23-24 is 6.6% for women and 2.8% for men.[2] Tanzanian officials have a target of 95% of people living with HIV knowing their status by 2023 and they acknowledge a current testing gap among adolescents, particularly because adolescents do not "interact regularly with the health system."[23,24]

Adolescents are also less likely to use contraception than adults, even though the risks and consequences of adolescent pregnancy are substantial and include a premature end to schooling, higher risk of maternal morbidity and mortality, and poor child health outcomes.[3,17-18] Pregnancy-related complications are the leading cause of death among girls ages 15-19 in low-income countries.[16] In Tanzania, 27% of women age 15-19 have begun childbearing—a stubbornly steady statistic for the last decade.1 Among 15-19-year-old sexually active women, only 8.6% currently use a modern contraceptive method.[1] Access to contraception besides condoms is particularly limited for unmarried adolescents who are less likely to access available family planning services, resulting in higher levels of unmet need for family planning.[18]

Baumgartner, formerly at Duke, now at UNC-Chapel Hill) and Kaaya (Muhimbili University of Health & Allied Sciences) have successfully pilot tested AWVs in Tanzania. First, health facilities are trained to provide high-quality adolescent-friendly services. Similar to the under-five child wellness visit model, AWVs are designed as clinic visits supported by the Ministries of Health and Education in Tanzania (*see letters of support*) for those in their last year of primary school (ages ~12-14) when school attendance is high. Escorted by school staff, each AWV (~20 min) includes health education and clinical screenings for SRH and non-SRH concerns. Future clinic visits, would be encouraged in subsequent years as needed.

Key findings, Pilot Study of Adolescents Wellness Visits in Dar es Salaam & Bagamoyo, Tanzania; 2016-2018. This Center For AIDS Research (CFAR)-funded pilot was conducted with two government primary schools matched to nearby public health facilities in Dar es Salaam & Bagamoyo. Our team demonstrated that AWVs are highly acceptable and feasible.[21] Of 173 potentially eligible Standard 7 students in two schools, 90% received the free-of-charge, clinic-based AWVs and completed exit surveys with medical record reviews (n=154; 92-girls, 62-boys; 102-Dar, 52-Bagamoyo). Forty-seven percent screened positive for a problem requiring immediate counseling and/or referral, and knowing one's HIV status was highly valued by adolescents. Among those who did not participate, two adolescents were assented/ consented but missed the AWV, 14 parents did not return consent forms, & three adolescents did not assent. Our team documented the feasibility of brief, school-facilitated field trips to nearby clinics whereby school staff escorted students in small groups (1 teacher per ~5-6 students). Each student had a confidential encounter with the primary care nurse and groups returned to the school together. Participants were surveyed immediately following administration of the AWVs which were held at two clinics. The mean age was 13 (range 11-18) years, half had reached puberty, none reported current sexual activity only five boys reported ever having had sex, but one girl screened positive for STI. Few adolescents thought they were at risk of HIV; however, many more wanted to know their HIV status than we anticipated.

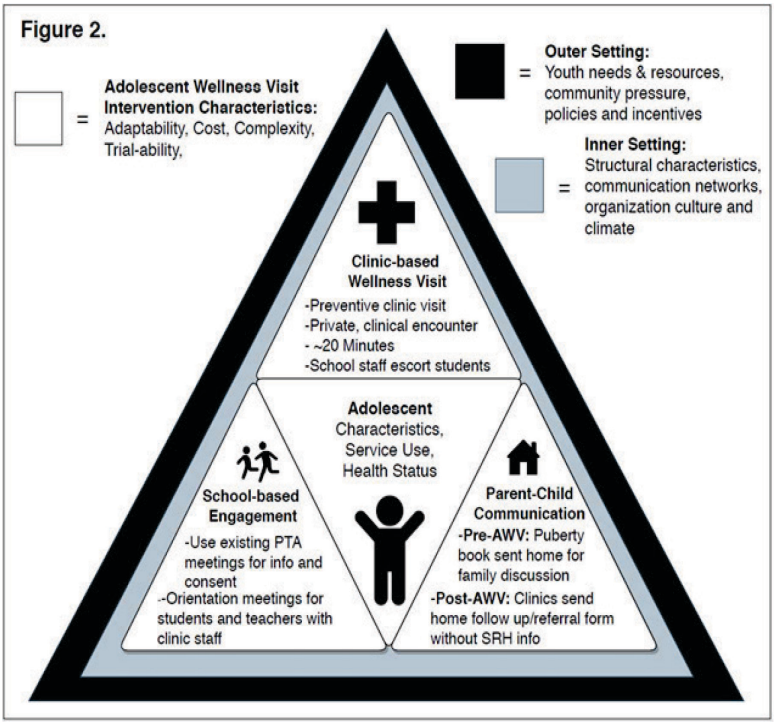
Adolescent Wellness Visit Components	Screening Results (n=154)	
Nutrition Assessment	Stunting (height-for-age)	14%
	Underweight (BMI)	12%
	Overweight (BMI)	12%
	Household Food Insecurity (self-report in survey)	11%
Eye Exam	Vision problem detected	17%
Dental Screener	Dental pain reported	14%
Mental Health Assessment	Risk of self-harm	3%
Puberty Information	Received Puberty Booklet	96%
Contraception	Received information about contraceptive methods	57%
	Received contraception	0%
HIV Testing and Counseling (HTC)	Requested HIV test from provider	29% (n=44)
	Received HIV Test (of those who requested)	7% (n=3)

There were also 60 key informant interviews (KIIs) with adolescents, parents, school staff, clinic providers, and government officials, both pre- and post-intervention. Ninety-seven percent of adolescent participants reported they would return to the clinic for health advice or a future AWV. When adolescents listed the top two most important or helpful aspects of the AWVs, 24% said HIV testing and counseling, followed by vision screening and puberty information. Among the KIIs, there were some concerns about the cost for following up on referred services. Some parents stated they were saving money for follow-up care; but overall, parents and school staff indicated that the AWV experience encouraged a culture of health and self-awareness among adolescents and they were eager for more collaboration. Escorted clinic visits with school staff were highly acceptable. Key stakeholders support testing AWVs at scale in the two regions in Tanzania.

Additional Evidence Base from Preliminary Studies: Adolescents are more likely to utilize HTC and contraception if the service environment is accessible, non-judgmental, friendly, and integrated, and the community supports adolescent SRH services.[32-34] Our team has published studies in both health and education with data illustrating that 1) integrated adolescent-friendly health services are feasible and acceptable, and 2) primary school-based sexuality education linked to health services is feasible and acceptable, and improves parent-child communication.

Conceptual framework

The Consolidated Framework for Implementation Research (CFIR) provides a cohesive structure for assessing the context, content and processes comprising a new health intervention.[22] This meta-theory identifies and explains how five major domains – the core components of the intervention itself, the inner and outer contexts, characteristics of the individuals involved, and the implementation processes – influence the success or failure of a complex intervention. Figure 2 illustrates core components of the AWV model plus key domains in the CFIR that will inform our study instruments and guide our data analyses. For example, attention to the outer setting includes collecting data on and understanding existing policies, guidelines and linkages between health services and primary schools at the local, district, regional and national levels to ensure that the Adolescent Wellness Visit model complements and enhances existing structural relationships. For the inner setting, the study will collect data from both health (clinicians and facility managers) and education (teachers, principals) sector key informants regarding functional skillsets before and after the intervention is implemented and absorptive capacity of schools and health clinics to change and include AWVs, among other factors. Attention to the intervention characteristics includes asking key informants and advisory groups (YAG & STAG) about the perceived relevant advantage of AWVs in primary school over existing adolescent services, cost of the model, and stakeholders' perceived ownership of the model and ability to try out and adapt various model components. Examining attitudes towards the AWV by adolescents themselves and other stakeholders (parents, teachers, clinicians, policy officials) falls under the domain of individual characteristics -- areas to consider based on the CFIR include the level of enthusiasm clinicians, teachers and adolescents have for the model, and the degree to which clinicians feel capable of delivering services, or the adolescents of receiving them. Finally, all domains are embedded in the process level which encompasses the incremental – and potentially recursive steps taken to plan, introduce, implement and sustain AWVs in this low-resource setting.



As indicated by letters of support from WHO and Tanzanian government officials in the health and education sectors, multiple stakeholders are eager for new approaches to enable adolescents to utilize SRH services. Developing a feasible, effective and sustainable strategy is paramount. Our implementation research approach engages wide stakeholder participation throughout the project. Some AWV logistics are purposefully left open (e.g., clinic visit escort timing) so local schools/clinics can finalize together in partnership (with our team facilitating and documenting process) to create the most sustainable implementation design. Youth Advisory Groups (YAG), composed of ~10 youth ages 15-19, and Stakeholder Advisory Groups (STAG), composed of ~10 stakeholders including parents, educators, clinicians, and policy officials including a local WHO representative, will be created for each study district, starting in Year 1. The YAGs and STAGs will hear updates from the study team and provide insights on the AWV implementation and its acceptability within the communities. Based on previous use of YAGs by Baumgartner & Kaaya, we anticipate that members will assist on issues such as study retention strategies, and how to prepare for local dissemination activities. The STAGs may inform national policymaking for adolescent health services as some members will be involved in the following mechanisms which are already in place: participation in the two key Technical Working Groups (TWG) of the MOHCDGEC dealing with adolescents and school health—the quarterly TWG within the Section of Reproductive, Maternal, Child and Adolescent Health with a formal TWG whereby quarterly

stakeholders and donors meet with management of the Reproductive Maternal Child and Adolescent Health Section which includes the Adolescent Health Unit to exchange lessons learned from research and practice, review policies, guidelines etc. Similarly, the Section of Health Promotion with its school health unit has a TWG which meets quarterly as well. Both TWGs may opt to have specific task forces to probe in depth specific issues for policy making.

Statement of the Problem

Adolescent–friendly Sexual and Reproductive Health (SRH) services are a proven effective strategy for providing SRH services to adolescents. In recognition of the multiple SRH burdens faced by young women and men, there is broad and widely supported global guidance that HIV, contraceptive, and other SRH services such as STI screening and treatment should be offered as a package of integrated adolescent-friendly services.[19,20, 25] Standards for adolescent-friendly SRH services include provision that is accessible, equitable, appropriate, and effective.[19] Tanzania has had national standards and a training curriculum on adolescent-friendly reproductive health services since 2006.[26,27] However, there is an evidence gap on how to best implement these services, especially for younger adolescents.[28] Evaluations of youth-friendly HIV-contraceptive integrated services across East Africa have highlighted limitations of current approaches, but there is now enough cumulative global evidence to conclude that in order to increase service use, interventions must address both the supply and demand sides of adolescent-friendly services, be linked to schools and communities, and be prevention-focused as opposed to solely problem-focused.[28-34] In addition, it is not enough to improve service quality and general information about services—interventions must include sustainable provider trainings, facility adjustments, and broad demand generation/community acceptance approaches to promote adolescent-friendly health service use.

Bundling SRH services with non-SRH services to address adolescents' broader health needs may prove effective in further increasing adolescent uptake of HTC and other SRH services. Demand for and community acceptance of SRH services for adolescents is improving but is still fraught with issues of stigma related to adolescent sexuality. There is also global guidance that youth would benefit from additional non-SRH prevention services. In the United States, the American Academy of Pediatrics and the American Academy of Pediatric Dentistry recommend annual physical and dental check-ups throughout adolescence; however, no such national guidance exists for Tanzania or most low and middle-income countries (LMICs).[39,40] The World Health Organization recommends selected preventive health services for adolescents, often through school-based services, but there is no global guidance for annual check-ups or wellness visits—this is a current evidence gap acknowledged by WHO (*see Letters of Support*). Traditionally, wellness visits for adolescents have not been a priority in LMICs due to limited human and financial resources for non-curative visits. In Tanzania, some school-based initiatives exist such as deworming campaigns, and there are new efforts to reach adolescents with the HPV vaccine;[41] but beyond these vertical programs, there are no current examples of comprehensive prevention-focused check-ups for adolescents in low-resource settings.

Tanzanian adolescents would benefit from multiple non-SRH health services. Tanzanian adolescents experience both under-nutrition (~12-21%) and/or over-nutrition (~12-25% overweight or obese).[21,42-43] There are education programs and nutrition resources available in Tanzania, but few are integrated into routine care.[41] Adolescents also experience visual impairments that can impact schooling and educational success (2-17%).[21,44-45] Vision is easily screened for and glasses are available in Tanzania. Good dental health can prevent a myriad of problems such as dental caries and tooth loss.[47] WHO estimated that among 12-year-olds in school in Tanzania, 78% had signs of gum disease.[47] A recent study found that among schoolchildren, the prevalence of dental caries was 17%, dental pain was 36%, and oral problems was 54%.[44] Dental hygiene education paired with screening for dental problems by non-specialists with follow-up with dentists as needed is a low-resource strategy. Finally, Tanzanian adolescents experience poor mental health, including suicidal ideation, with higher rates among those exposed to risk factors such as HIV and violence (~12-27%).[49-52] Mental health screening, counseling and referrals for specialized care within a primary care setting is feasible per our pilot study experience and supported by WHO guidelines.[53]

Adolescent Wellness Visits (AWV) is a new health service delivery platform implemented during the last year of primary school. Given the evidence that adolescents underutilize clinic-based services, even when they are adolescent-friendly and high quality (supply), a new structural implementation strategy is needed whereby services become routine healthcare for adolescents (demand). We propose to evaluate the impact of an innovative strategy for reaching adolescents with HTC and other screening services —Adolescent Wellness Visits that are coordinated with primary schools and delivered at health facilities that offer a package of evidence-based services appealing to adolescents, parents, and communities. Similar to the under-five child wellness visit model, the AWVs we will test are supported by both the Ministries of Health and Education in Tanzania for those in their last year of primary school (ages ~12-14 years) [*see letters of support in Appendix 1*]. This preventive visit would include both SRH and non-SRH health education, counselling and clinical services. Our Theory of Change is that exposure to an AWV in early adolescence will not only have immediate service utilization and health impacts, but also future impacts. For example, the AWV model changes the current paradigm of self-referral or provider-initiated HTC by bringing all adolescents into the clinic setting for an initial wellness visit via a school-facilitated "field trip" to an adolescent-friendly clinic. We posit that exposure to and familiarity with adolescent-friendly services will not only increase immediate HTC for high-risk adolescents, but that adolescent will return to the clinic for HTC in the future due to higher health literacy, increased awareness of their personal risk, familiarity with the clinics and/or better understanding of available services.

AWVs target adolescents in the last year of primary school (Standard 7) when they still have access to a strong structural institution. The end of primary school is an opportune moment. More than 85% of Tanzanian adolescents attend Standard 7 nationally but only 29% attend secondary school. Because some Standard 7 students do not graduate, AWVs will be timed early in the school year which aligns with stated school preferences from our pilot study. Standard 7 students are ages ~12-14, right on the cusp of puberty when many higher risk adolescents initiate sexual activity. Tanzanian primary schools have a standard health curriculum that we will build upon and extend for this intervention based on an intervention our team has already tested in Dar es Salaam).[54-56] Public education sector officials (*see letters of support*) see this project as an opportunity for improving the health, school attendance and academic performance of their students. Tanzanian girls and boys need basic information on puberty, contraception and HIV prior to sexual debut. The AWV approach is prevention-focused and provides information to all adolescents, regardless of sexual activity. AWVs could also identify adolescents who are exposed to violence and abuse and link them to appropriate child protection services if needed. This study will contribute to scientific evidence gap on how best to engage and deliver adolescent-friendly health services to young adolescents, including HIV testing services.

Study justification

This project is innovative in several important ways. First, the AWV model bundles sexual and reproductive health (SRH) and non-SRH health needs to de-stigmatize adolescent health services, which have traditionally been SRH-focused. By combining SRH and non-SRH health services, there will be a range of services valued by adolescents, parents, and communities. Parents/guardians will be informed that all adolescents, regardless of sexual activity, should have preventive check-ups to address their health needs, thus creating demand for services. Second, AWVs are clinic-based and school-linked prevention services for adolescents—a model not previously tested in Africa for its impact on either continued health service utilization or health outcomes. Initiating wellness visits for both girls and boys when the vast majority are not yet sexually active (age ~12-14 years) provides an opportunity for education on HTC and contraception prior to self-assessing a need for such services. This new routine health service platform can also be used to introduce new prevention technologies and vaccines as they become available for adolescents (e.g. PrEP, HPV vaccine).

Third, adolescents who test positive for HIV during the AWV will receive facilitated referrals to ensure they are enrolled in HIV care and treatment in a timely, efficient, and adolescent-friendly manner. Our team has previously tested a 7-step model for facilitated referrals in HIV care settings with promising results.[57] Fourth, the AWV model was developed with sustainability in mind—it is a multi-sectoral structural approach

requiring collaboration from both health and education sectors and it builds on existing adolescent-friendly standards and policies using school and health facility resources, within a school health programme where actors from both health and education are available at primary health care levels. In other words, this is a "real world" pragmatic implementation trial with significant promise for scale-up if found to be effective. Finally, we will use a cluster randomized pragmatic trial design including the geographical disposition of the clusters as a metric for our stratified randomization. Although this approach has been increasing in global health implementation studies, our study will innovate this approach by including geographical metrics in our randomization such as distance between school and health clinic and geo-economic indicators.

Research Questions:

This study evaluates a new service delivery platform for reaching adolescents in Tanzania with HTC and other evidence-based screening services via clinic-based 'Adolescent Wellness Visits' (AWVs) coordinated between primary schools and health facilities that offers a package of youth-friendly services. Because adolescents are less likely to access prevention-oriented health services such as HIV testing and counseling (HTC) and contraception than adults, yet they bear a disproportionate burden of poor HIV and reproductive health outcomes in many low-resource settings, we pose the following overarching research questions:

a) Will coupling sexual and reproductive health (SRH) services with non-SRH services such as nutrition, vision, dental, and mental health screenings that are applicable for all school-based young adolescents increase their use of adolescent health services, including contraception, HTC, and prompt access to HIV care and treatment services in the future?
b) From the perspectives of key informants and direct health care providers, what factors would support or limit the implementation of the AWVs model and fidelity/adherence to the proposed package of evidence-based practices included in the AWVs model?

Study Objectives

a) Broad Aim:

This real-world pragmatic implementation trial will evaluate the impact of AWVs on multiple health service use outcomes for adolescents in Tanzania. The primary outcome is having any HTC up to two years post-primary school (~ages 14-16). In addition to contributing to knowing one's HIV status, HTC is a great indicator for preventive service use since it is applicable for all adolescents in Tanzania. Secondary outcomes for subpopulations include contraceptive use, linkages to HIV care and treatment, and treatment for health problems identified during screening.

b) Specific Aims and primary hypothesis to be tested:

1) To assess the impact of Adolescent Wellness Visits on HTC (for all adolescents; primary outcome) and contraceptive uptake (for sexually active subset; secondary outcome) up to two years post-primary school via a cluster randomized controlled trial (20 school-clinic pairs: 10 intervention + 10 control; n=~1200 adolescents)

   Primary Hypothesis: Randomization to the intervention arm will result in an improved HTC uptake up to two years after primary school, relative to those in the control arm.
2) To evaluate factors that support or limit implementation of the AWV model and fidelity/adherence to implementation of the proposed package of evidence-based practices included in the AWV by utilizing 24 focus group discussions with implementers and **up to 90** semi-structured interviews with key informants; and **up to 40 in-depth interviews with participating adolescents** and

   Illustrative Implementation outcome: Fidelity to the AWV model and acceptability by parents and other key stakeholders. (Fidelity is measured the proportion of observed visits that implemented core evidenced based components of the AWV; acceptability of AWV components will be described from the narrative data from interviews with parents/guardians)
3) To evaluate the cost-effectiveness of AWVs on two key health behavioral outcomes: uptake of HTC for all adolescents, and reductions in unmet need for contraception among sexually active adolescents.

The study team: A diverse team of experts has been assembled to meet project objectives. The team is led by Dr. Joy Noel Baumgartner at UNC-Chapel Hill (PI) and Dr. Sylvia Kaaya at Muhimbili University of Health & Allied Sciences (MUHAS) (local PI), who have a long history of collaboration and both of whom have prior experience developing and evaluating health interventions. At MUHAS, their most recent collaborations include the AWV pilot study, a NIMH R34 pilot clinical trial, and an NICHD R01 that was a mixed methods longitudinal adolescent cohort study assessing the challenges of adolescent women's participation in HIV prevention trials.[57] This study revealed that sexually active adolescents aged 15-17 faced similar pregnancy and STI risks to those aged 18-21 yet they had lower perceived HIV risk and less use of health services compared to older adolescents. Baumgartner and Kaaya have collaborating since 2002 when Baumgartner spent a year at MUHAS conducting her dissertation fieldwork. The MUHAS team includes two promising junior investigators-- Mr. Isaac Lema (co-I), a clinical psychologist with extensive experience working with adolescents who was the Study Coordinator for the AWV pilot study, and Dr. Happiness Saronga (co-I), a health economist who will support the cost effectiveness analysis (CEA) study aim and lead local cost data collection activities.

At the Duke Global Health Institute (DGHI), Kaaya and Baumgartner are joined by Dr. Joseph Egger (co-I), an epidemiologist in the Research Design & Analysis Core (RDAC) who will lead the study analyses with support from RDAC staff. RDAC has extensive experience with designing and conducting trials in LMICs and Baumgartner has had multiple previous grants in collaboration with RDAC including cluster randomized trials. Egger will lead the analysis ensuring the blinding of the PI without impacting the integrity of the administration of the trial. In addition, Dr. Marisa Domino (co-I) is an economist at UNC-Chapel Hill who work on the CEA with MUHAS colleagues. Baumgartner and Kaaya have worked in adolescent health research for many years including school-based projects. Besides our AWV pilot study, Kaaya completed a 4-year European Union-funded study, Project Prepare, that evaluated a school-based intervention to promote SRH among adolescents aged 12-14 in Dar es Salaam primary schools. In sum, our team is well prepared to carry out this paradigm-shifting model of Adolescent Wellness Visits to increase HTC and other health services.

We also note that a crucial part of our implementation research is significant involvement by Tanzanian Ministry of Health and Education officials at district and regional levels (*See letters of support*). We are fully cognizant of the policy and planning issues for implementing AWVs within the public health sector and we have already laid much of the groundwork for stakeholder engagement during our pilot study which culminated in a high-level dissemination meeting in Dar es Salaam in October 2018. Related to policy, we have Dr. Eric van Praag as an advisor. Van Praag is a resident of Tanzania and very involved in policy recommendations at the nexus of school health and community health workers which could have implications for our AWV model and sustainability so we want to stay engaged on this topic. Baumgartner and Kaaya have collaborated with Van Praag previously.

MATERIALS AND METHODS

This 5-year study fills a critical void in understanding how to organize and deliver evidence-based adolescent-friendly preventive health services in a low-income country. In particular, we will identify opportunities to strengthen the Tanzanian health system to support increased adolescent HTC, contraceptive use, and linkages to care for HIV-positive adolescents through Adolescent Wellness Visits. This project will be guided by the Consolidated Framework for Implementation Research (CFIR) as it evaluates the impact of this paradigm-shifting approach to adolescent healthcare in Tanzania. An economic analysis will determine whether this new public health approach is financially feasible and sustainable in a low-resource setting.

Pilot study data assessing feasibility and acceptability of the AWV model, as summarized in our background and literature review [See page 6-7], prepares us to conduct a cluster randomized controlled trial (cRCT) with 20 Tanzanian primary schools to evaluate the impact of AWVs on HTC uptake among adolescents up to two years post-primary school (median age 15 years) [Aim 1], within an implementation research framework. Student cohorts will be followed up for ~2.5 years after completing the AWV and leaving primary school.

The *primary study outcome* is the difference between intervention and control groups in HTC uptake measured up to two-years post-primary school (~ages 15-16 years) inclusive of the initial AWV; *secondary outcomes include* contraceptive use at last sex among those who have initiated sexual activity, and any other health service utilization. During the cRCT, we will evaluate factors that support or limit uptake of the AWV evidence-based preventive health services (Table 1) [Aim 2], and conduct an economic analysis of the model [Aim 3]. Selected primary schools and geographically matched health facilities will jointly implement AWVs.

Study Setting

This project will be conducted in two sites in Tanzania: Kinondoni District in Dar es Salaam region (urban) and Bagamoyo District in the Pwani region (rural/peri-urban). The two districts were involved in the pilot study, and this implementation study is in response to a request by the two districts to conduct a trial to evaluate the effects of the AWVs on future access to services related to reproductive health. District health and education officers have re-confirmed support for allowing us to administer the AWVs within their catchment areas. Final identification of a list of matched school-clinic sites will be in collaboration with government officials prior to randomization, and site visits will confirm distances and other key eligibility factors. District enrollment data from schools was collected in 2019 for Standard 6, which indicates varying class sizes, and this will be taken into account for constrained randomization. For Kinondoni district, Dar es Salaam region, there were 10,645 Standard six students across 46 schools which average 231 students per class cohort. For Bagamoyo district, Pwani region, there were 2,988 Standard six students across 37 schools which average 80 students per class cohort. Randomization will occur at the school level, stratified by region.

The AWV intervention

Selected primary schools and geographically matched health facilities will jointly implement AWVs. Most components of the wellness visits will occur at the health facilities, but schools and clinics will work together to establish the mechanisms for school-clinic linkages. The AWV will be free of charge during the project period because the proposed activities are well within the services that should be readily and freely available in government health clinics—our team has support from district health offices to ensure services, materials, and commodities are in place. We have support from the local health authorities to test this model, and we will cost the intervention to assess the potential burden of increased client volume on the health system. In theory, the standard of care is that all students who attend primary care health services and who are not covered by the Community Health Fund (national health insurance scheme) should be able to receive health services for free, if available.

In preparation for implementing the AWVs, study health facilities will receive three main training components with associated ongoing supportive supervision: 1) Adolescent-friendly health service standards (Tanzania's Ministry of Health, Community Development, Gender, Elderly & Children [MoHCDGEC] has national guidelines and trainers) which include HTC and contraception.[26,27]; 2) Additional non-SRH health screenings and treatments led by the study team and government district trainers; and 3) How to deliver facilitated referrals for adolescents who test positive for HIV.[53] Not only will facility-based health providers attend the relevant training, but ~2 school teacher counselors from each matched school in the health facility's catchment area will also attend so they are a resource for their students on what is included in Adolescent Wellness Visits and can serve as a link between schools and facilities (e.g., communication activities, follow-up on referrals).

In preparation for the adolescent survey, we will pretest the instrument with about 20 Standard 7 students to make sure the questions and response categories are well understood by young people. Survey wording will be revised accordingly prior to data collection. Students involved in pre-testing will include girls and boys and be selected from a school that is not part of the main trial.

All Standard 7 students (median age 13) will have one facilitated clinic-based Adolescent Wellness Visit that includes a set of prevention-focused services (Table 1). Trained adolescent-friendly primary care nurses will visit their matched primary schools to discuss some health topics and explain elements of the AWV prior to students' first visits. There will also be outreach and communication activities with parents/guardians about

the AWVs during the regular Parent-Teacher Association (PTA) meetings at the beginning of the year, at which time parental consent will be obtained. Adolescent assent will be obtained during school hours after distribution of government-published Puberty Books (https://www.growandknow.org/books.html) and a nurse school visit. These books are approved by the Ministry of Education and complement the school health curriculum. Distribution prior to the AWVs provides an opportunity for adolescents to ask confidential SRH-related questions when they visit the AWV nurse.

Table 1. Evidence-Based Services included in Adolescent Wellness Visit for Standard 7 Students

Screenings & Tests	Clinical Follow-up	Refs
Vital Signs & Nutritional Status: Blood pressure; Height, Weight, BMI; Mid-upper arm circumference (MUAC)	Follow-up for BP >140/90 mmHg; If BMI <18 or >30, or MUAC outside normal, refer to nutrition services; Nutrition/exercise counseling for all	39, 61-63
Dental Dental Pain screener question	Refer to a dentist for problems; Counsel on dental hygiene	64-66
Vision Visual Acuity Test (Snellen eye chart)	Refer for follow-up/glasses if visual acuity <6/12	67
Mental Health Assessment Depression assessment using Patient Health Questionnaire (PHQ-A)	If suicidal ideation item endorsed, immediate facilitated referral to psychiatric nurse, and/or social worker for assessment of imminent suicide risk. Same day counseling if moderate/severe depression per WHO's mhGAP Intervention Guide for care in primary care settings.	53,68, 78
Puberty: Swahili Puberty Booklets distributed in schools before AWV. Clinician answers questions, condom model demonstration.	Girls & Boys: discuss pregnancy risk; info/counseling on contraception (regardless of sexual activity)--provision if needed. Condoms available in clinic.	69-72
STI/RTI symptom screening: Ask about any itching; sores; discharge; pain	Syndromic management of STIs	73, 76, 77
Information about HIV testing and counseling (HTC) Info on HIV, risks, prevention, HTC	Uptake of HTC if desired by client Facilitated referral to Care & Tx if HIV-positive	23,24, 35-36
*Other health problems you want to discuss? Possible probes: skin problems, alcohol use, smoking, abuse/violence, etc.	Brief counseling and follow-up as indicated; referral to 'gender focal person' staffed at gov't health center level available for gender-based violence issues.	58, 37
* Evidence-based guidelines for standardized screening/treating for substance use and violence among adolescents in clinic settings in Tanzania is accumulating but not yet ready for implementation. AWVs will provide a clinic-based platform when/if such interventions are recommended.		

Study Design

AIM 1: **To assess the impact of Adolescent Wellness Visits on HTC uptake among adolescents up to two years post-primary school utilizing a cluster randomized controlled trial**

Study Design*:* To evaluate the impact of the Adolescent Wellness Visit model on HTC and other study endpoints, we will conduct a cluster randomized controlled trial (cRCT) with randomization at the primary school level. To determine if the AWV model will improve HTC and other health service utilization behaviors in adolescents, we will test the primary hypothesis that randomization to the intervention arm will result in improved any HTC uptake up to 2 years after primary school, relative to those in the control arm.

We will randomize 20 schools, divided into control and intervention arms and follow each arm for two years post-primary school to measure their use of HTC and other endpoints over time. Baseline exit interviews will be conducted after the AWV sessions at the intervention schools and interviews at control schools will be

conducted at roughly the same time to ensure age matched cohorts. The intervention arm will receive the AWV intervention, as described earlier. Both intervention and control adolescents will be recruited at the school level, at the beginning of their final year of primary school in Standard 7 (age range 12-14 years). With school level randomization, to achieve comparability of arms in baseline school-level characteristics, a constrained approach will be used taking into account school size, proportion of boys and girls, socioeconomic indicators of the school neighborhood, rural vs. urban area and distance from clinics. All students from a school's Standard 7 cohort will be invited to participate in the study, assigned to control or intervention according to their respective school randomization. Although the likelihood of contamination between arms is low due to the characteristics of our cRCT design (distance between clusters makes it unlikely that an adolescent from the intervention arm will interact with another from the control arm), we acknowledge that some control participants may be exposed to health communications about AWVs post-primary school if clinics publicize AWV services more widely and thus may access services due to this outreach. While we consider this risk low based on the pilot study experience, we will collect information from all participants on their exposure to community messages from our project and ask what prompted any use of health services to account for this influence.

Randomization Procedure: Each participant who has their consent properly obtained to be part of the study will be randomized at the school level. We will randomize the two arms in one block. Due to the nature of the interventions, it is not possible to blind participants and research assistants to the allocation received. Study statisticians will be blinded during the analysis phase.

Study Participants and Sample Size Estimation

For aim 1, we are powering on the difference in proportion of uptake of HTC between intervention and control arms. For this cRCT, the sampling unit within a cluster is students at the beginning of their final year of primary school--Standard 7. The study will recruit a *total sample size of 1200 (up to 1500 max)* adolescents (600 each in intervention and control arms, average 60 per school-cluster). The average age is likely 13 years old but we will limit the age eligibility to 10-17 years at time of enrollment. Our sample power estimates were calculated to test the primary hypothesis that randomization to the intervention arm will result in higher HTC uptake up to the two-year post-primary school assessment, relative to those in the control arm. We used a conservative estimate for intra-cluster correlations of 0.05, based on prior behavioral intervention studies and DHS data, and an estimated coefficient of variation of 0.65 based on anticipated school characteristics. Based on survey-weighted analysis of the 2011-2012 Tanzania HIV/AIDS and Malaria Indicator Survey (THMIS) for 15-17 year old's (the youngest age group with available data), we assume an estimate of 20% for HTC uptake in the control arm.[2] Thus, a total of 960 students would be needed to detect 40% (20% increase in relation to control) of HTC uptake in the intervention arm at follow-up, and assuming 20% of participants drop out of the study, with 95% power and a type I error rate of 5% (see Table 2). Assuming that we recruit 10 schools per arm, we will need to recruit 1200 students across these 20 schools in order to detect this effect. Therefore, our proposed sample of up to 1500 (influenced by size of class cohorts) is more than enough to identify our hypothesized effect of the AWV intervention, assuming 20% of participants drop out. Given the cRCT design, over-sampling of clusters is vital as the loss of a single school/cluster due to unforeseen reasons would compromise the rigor of the study. As a real-world, pragmatic trial, we erred on the side of being conservative with our selection of 20 clusters.

Table 2: Aim 1 Sample Size Calculations

- Difference in proportions with HTC uptake between arms = .20
- Proportion in Control with HTC uptake= .20
- Proportion in Intervention with HTC uptake=.40
- Coefficient of variation of cluster sizes = 0.65
- alpha = 0.05
- Intra-cluster correlation (ICC) = 0.05

Power	***Clusters (schools) per arm***	ICC	Participants per cluster	Participants per cluster (inflated 20%)	Total number of participants	Total number of participants (inflated 20%)

Assuming 60 students per school at the beginning of the study						
0.97	***12***	0.05	48	60	1152	1440
0.96	***11***	0.05	48	60	1056	1320
0.95	***10***	**0.05**	**48**	**60**	**960**	**1200**
0.92	***9***	0.05	48	60	864	1080
0.89	***8***	0.05	48	60	768	960
0.85	***7***	0.05	48	60	672	840

Intervention fidelity

A traditional pragmatic trial might not include intervention fidelity, but based on prior critiques of pragmatic trials, we want to ensure a negative result is not due to low intervention fidelity.[78] Our study team will ensure that each intervention school/clinic pair receives all informational meetings and clinical trainings in order to deliver the AWVs. However, provider adherence to the AWV components and quality of the clinical encounter could vary by site. Data on intervention fidelity will also be used in the analysis as potential effect modifier. Intervention fidelity will be measured with both patient and provider self-reports about receipt of core AWV components, referrals and use of same-day follow-up services. Direct observations will be conducted for at least 5 sessions with boys and 5 sessions with girls from each smaller and larger class sizes (N=20) at the intervention sites across districts during one of the days when the AWV will be conducted.

Outcomes

Our primary outcome is HTC uptake and our main secondary outcome is contraceptive uptake among those who are sexually active. HTC uptake will be measured as a binary outcome, with a positive value being attribute to any participant who reports any HTC uptake after enrollment and up to our two years post primary school. Any HTC uptake includes testing done at the initial AWV session or after the AWV session. HTC is the only SRH-based intervention that is regulated and standardized for adolescents in Tanzania. Thus, HTC uptake is the best proxy for SRH health seeking behavior with less barriers to access than other indicators such as contraception. HTC uptake will be collected as part of a survey.

Mediators and moderators:

We will evaluate potential mediation and moderation influences over the effect of the intervention on HTC and contraception uptake. To do this, we will examine the pathways through which the intervention impacts adolescents risk behavior. See Table 3 for pre-defined mediators and moderators

Table 3. List of selected mediators and moderators of study outcomes

Documented exposure to all components of AWV
Use of AWV and general health services; perceptions of quality; out of pocket expenses
Knowledge and attitudes on contraception
Treatment Self-Regulation Questionnaire *(to measure Health Self Determination)*
HIV risk self-assessment
Puberty milestones (e.g., menstruation; boys' voice)
Sexual behavior/risks (sexual activity, # partners, IPV, etc.)
Child Labor Questions
Household Hunger
Tanzania Equity Tool
Strengths and Difficulties Questionnaire
Selected/Modified questions from Child Exposure to Domestic Violence Questionnaire
Questions About Puberty Books
HIV Knowledge and Attitudes questions
HIV testing norms
Mental health (PHQ-9 and GAD)
Substance Use

Additional survey items related to health and mental health domains:
We have incorporated new questions to the endline survey that fall within the predetermined outcome areas of health and mental health. The additional survey domains include food insecurity, diet quality, climate anxiety, collectivism, and adolescent empowerment. The new instruments include the Diet Quality Questionnaire, Climate Anxiety Scale, and Utu Scale.

Data Collection
Up to 1500 study participants (intervention and control) will be interviewed at 4 timepoints: baseline and three follow-up time points (at 12, 18 and 24 months after the end of Standard 7). Interviews can be completed by phone or in-person on the grounds of their (former) school or near their home depending on their preference. Interviews will comprehensively assess knowledge, attitudes and behavioral data, plus HTC and health service utilization. Multiple interviews help maintain contact and support study retention. As part of informed consent, we will ask all participants in the intervention group for permission to access their medical records (for most, this will only be their AWV record). Our Pilot Study indicates that this is acceptable to adolescents and their parents. Medical records will provide valuable information on health status and health service utilization measures and will serve as supplemental confirmation of HTC services received for the intervention group only (we will not have access to medical records for the control group so the primary outcome is still based on self-reported HTC). Although the primary outcome measure for Aim 2 is ever HTC, current contraceptive use for those who are sexually active (sex in last 3 months) and current enrollment in HIV care and treatment services for those who have previously tested HIV-positive are also key secondary outcomes of interest at 12 and 24 months of follow-up. Given the increased sample size, high retention rate of the sample thus far, and higher than expected length of time for each round of data collection, the study will conduct adolescent surveys at three follow-up time points instead of four (removing a round in the middle). This change still allows us to maintain the original timing for the endline data collection that is tied to our trial outcomes and all other scientific objectives.

Aim 2: To evaluate factors that support or limit implementation of evidence-based health services via Adolescent Wellness Visits
To complement the cRCT on the impact of the Adolescent Wellness Visits, we will collect qualitative data on factors that support or hinder health service utilization and the AWV experience more specifically. This is necessary for an implementation research study such as this one in which the value of HTC and contraception is already known but in which the scientific goal is to determine ways to effectively get adolescents to reach providers and use these services. Qualitative data is the best way to determine barriers and facilitators and to identify solutions. Data will be collected in years 2-4, during the key intervention implementation years.

In Year 2, study staff will conduct 24 post-AWV debrief focus group discussions (FGDs) with 10 schools and 10 clinics, plus 2 FGDs with head teachers in each district and 2 FGDs for mop up if needed (6-8 per FGD, ~160 participants total) split across the AWV intervention sites in Dar and Pwani. Participants will be selected from key informants previously identified in the pilot study (district education and medical officers (n=4); district school health coordinators (n=2) and district RCH coordinators (n=2; total n=8 and 1 FGD). From schools, we will interview the following: a) Head teachers and/or academic masters/madams (n=20) b) Teacher counselors (n=20) c) Class and science teachers (20; total n=60 and nine FGDs); and from clinics a) direct providers in AWVs implementing RCH clinics (n=30) b) facility-based eye health nurses involved in AWVs training or implementation (n=10) c) facility based mental health nurses or practitioners involved in AWVs training or implementation (n=10) d) facility based or district level nutritionists involved in AWVs training or implementation (n=10; total n=60; or nine -10 FGDs) will assess implementation processes and perceived fit of the intervention within school and clinic procedures.

In Year 3, study staff will also conduct up to 50 semi-structured interviews (SSIs) with parents of adolescents from both the intervention and control groups to ascertain their perceptions of their children's health status, use of services, and acceptability of the AWV model. These parents will be selected on a range of factors to gain a broad perspective, including whether the child had a referral or not, whether the parent(s) consented

early, delayed, or declined to participate, or were in the control group or intervention group (n=40) , and 10 additional SSIs if needed to reach saturation (total N=50). All attempts will be made to balance parents/guardians' sex to allow for gendered perspective during analysis. As referenced earlier, parental support is crucial for maximal uptake of the model. In Years 3 to 5 , up to 40 semi-structured interviews (SSIs) with government officials representing the health, education, and social welfare sectors at district, regional and national levels, as well as other relevant stakeholders will be conducted; these will include school health coordinators from both the district education and health offices (n=4); ward education focal persons (n=4); district AIDS coordinators (n=2); district academic officers (n=2) district
education officers (n=2), district health officers (n=2); district social workers (n=2) and a few miscellaneous others (total N=40). Meetings with government liaisons on adolescent health policy issues will be held in Years 1, 3, and 5 so these SSIs will partially reflect that policy engagement work as well as their feedback on preliminary findings.

In year 4, we will conduct up to 40 in-depth interviews with adolescents already participating in the study. The purpose of these in-depth interviews will be to gain a deeper understanding of the adolescents' experience of and impact of the intervention, decisions to get tested for HIV at AWV or after, norms and comfort accessing healthcare for contraception or HIV testing. For adolescents living with HIV and/or who are pregnant/parenting, we will ask additional questions to better understand their experiences and their autonomy over their health and health care access. We will also be asking several questions about adolescents' understanding of climate change as well as its impact on their health and mental health.

Qualitative Data Collection Summary

Methods	# of Participants
24 Focus Group Discussions (1 per intervention school and 1 per intervention clinic)= 10 schools and 10 clinics, plus a separate FGD with head teachers in each district (n=2), and additional FGD(s) to mop up (n=2) if needed	24 FGDs * ~8 people per FGD = 160 participants
Interviews with Parents	= 50 participants
Interviews with Government Officials and other Stakeholders	= 40 participants
Interviews with adolescents	= 40 participants

Aim 3: To evaluate the cost-effectiveness of AWVs on uptake of HTC for all adolescents, and reductions in unmet need for contraception among sexually active adolescents.

Trial-based cost effectiveness analysis (CEAs) are useful for their high internal validity and timeliness(1). They also provide the necessary information to guide decision makers seeking to adopt a particular program. For these reasons, we will conduct a CEA alongside the AWV effectiveness trial. Furthermore, the social, economic, and political environment in Tanzania presents an opportunity to assess some potentially important downstream effects of the proposed AWV intervention. Although the national policy in Tanzania promotes easy access to HIV testing, current evidence suggests that adolescents between ages 15 to 19 years are less likely to test for HIV. This age range also corresponds to the period with a high risk of HIV transmission, especially when the adolescent is out-of-school. Adolescents also use contraceptives less frequently than adults living in Tanzania. As a result, early pregnancy among school-age girls occurs quite frequently with recent estimates showing that 25% of adolescents in Tanzania have begun childbearing.[79-80] Girls bear the brunt of teenage pregnancy as the current laws in Tanzania require a pregnant girl to be expelled from school. In addition, recent statements from the government suggests that girls who were expelled for being pregnant will not be allowed to return to school after delivery of their baby. Therefore, the lifetime health and economic consequences of failure to use contraceptives among adolescents in Tanzania can be significant and disproportionally impactful on girls in the society.

Our CEA aims to estimate the health and economic benefits of investing in the roll-out of Adolescent Wellness Visits (AWVs) in Tanzania. Our study will take both the health system and societal perspectives as recommended by the 2nd US panel of cost-effectiveness analysis, and cover two periods of interest: 1) First

two-years of implementation of the study using project data, and 2) a post-study period of 10 to 15 years to link outcomes observed during the period of the study to long-term health and economic outcomes.

Data Management & Analysis

Data Management: Data collection activities will be in English or Kiswahili, per participant preferences. Interview and discussion guides and cohort study instruments will be translated into Kiswahili. For qualitative data collection (semi-structured key informant interviews, FGDs), interviews and discussions will be audio recorded (per consent received), and transcribed directly into English by bilingual study staff. Using a HIPAA-compliant qualitative software (e.g. QSR NVivo 12 Dedoose, etc) memos and summaries of qualitative text will be prepared to aid in analyses for Aim 2. The software will support coding and finer level re-coding of text and enables the researcher to explore how theoretical concepts (such as the CFIR) fit together by developing and modifying a hierarchical coding index.

For the cRCT which collects primarily quantitative data, we will utilize mobile data capture and verification. Mobile data collection has been used successfully for health surveys in low-resource settings and the benefits such as reduced data entry time are substantial. We will use open-source Android tablets with the exact data collection platform to be used is still to be determined, so we can consult with local partners. Precautions will be in place to protect confidentiality of the data, including collecting data offline and only uploading on secure password-protected office WIFI and encrypting and password-protecting files prior to transfer to Duke [See Human Subjects]. This will be supported by a data sharing agreement between MUHAS, the University of North Carolina at Chapel Hill, and Duke University provided by the Tanzanian National Institute for Medical Research.

Data Analysis

Aim1**:** To assess the impact of Adolescent Wellness Visits on HTC (for all adolescents; primary outcome) and contraceptive uptake (for sexually active subset) up to two years post-primary school via a cRCT.

Analysis on aim 1 will test the primary hypothesis that randomization to the intervention arm will result in improved HTC up to two years after primary school (~2.5 years after baseline assessment), relative to those in the control arm. We will use an intention to treat design with a generalized estimating equations (GEE) model to estimate the intervention effect at 24-months for each binary outcome separately. A log-link will be used with an assumed binomial distribution for the outcome, in order to obtain risk ratios. If this log-binomial model does not converge, we will use a modified Poisson model.[81] Models will include an exchangeable correlation structure to account for the correlation of outcomes among adolescents within the same cluster. We will also use Kauermann-Carroll bias-corrected variances to account for the relatively small number of clusters in our study.[81] To ensure the rigor and validity of the effect estimates, we will include in the statistical model any additional baseline covariates (Table 1) that predict missing outcome data or which are imbalanced across arms at baseline. In addition, all variables used in the constrained randomization will be included in the primary statistical models. We will perform sensitivity analyses using multiple imputation to assess robustness of our findings to different response patterns, utilizing covariates hypothesized to influence missingness in the imputation model.[82,83]

Mediation and moderation analysis**:** Mediation analysis will be conducted to evaluate the theoretical assumptions that health status, sex, documented exposure to the AWV, knowledge and attitudes on contraception, health literacy HIV risk-self-assessment and sexual behaviors might individually influence the effect of the intervention on outcomes and the extent to which of these individual variables mediate the effect, conditional on the presence of other mediators in the model. A set of structural equation modeling will be fit to evaluate the direct and indirect (mediated) effects of the Adolescent Wellness Visit model intervention on HTC and contraceptive use at last sex. The indirect effect of the intervention on outcomes via each individual mediator will be the product of the path from intervention to mediator and the path from mediator to outcome, with a bootstrapping correction that has shown improve the rigor of this approach. The impact of all mediators included in the model will be expressed as the total indirect effect of intervention on outcome. We will also

evaluate the modifying effect of sex, puberty milestones, and sexual behaviors on the intervention effect over HTC and contraceptive uptake. For this moderation analysis, we will separately include interaction terms between intervention and our pre-defined potential modifiers using a similar SEM model approach, evaluating the changes in the effect on HTC and contraceptive uptake.

Aim 2**:** To evaluate factors that support or limit implementation of evidence-based health services via Adolescent Wellness Visits An iterative process of data collection and analysis will begin as soon as the qualitative research is initiated and proceed through a series of four interrelated steps: reading; coding; data display; and data reduction.[84] Our analyses will be organized by domains of the Consolidated Framework for Implementation Research (CFIR). Meeting notes from individual/group consultations plus YAG and STAG meeting notes will be summarized, coded, and reviewed in order to finalize logistical procedures for the Adolescent Wellness Visits (e.g., strategies for escorting students to first clinic visit) and to ensure that our planned complementary activities (health communication, stakeholder meetings) are fully considering all CFIR domains prior to implementation. Transcripts from the 24 FGDs and up to 90 SSIs (50w/parents + 40 w/gov't), **up to 40 adolescent interviews** will be analyzed similarly—reading; coding; data display; and data reduction.[76] Data from FGDs and SSIs, plus the YAG activities, will be presented to the STAGs for feedback on barriers and facilitators to the Adolescent Wellness Visits. The information will be used to help inform a set of recommendations that will be developed for dissemination meetings in Year 5 for those who are in positions to influence scale-up, pending positive results. Note that throughout the intervention phase, Mr. Lema (co-I) will be responsible for monitoring fidelity to the Adolescent Wellness Visit model to ensure that the intervention is being implemented as planned (checklist on availability of services, adherence to adolescent-friendly guidelines, etc.) and to document gaps in services that may affect our testing aspects of the model (e.g., stock-outs).

Aim 3**:** To evaluate the cost-effectiveness of AWVs: uptake of HTC for all adolescents, and reductions in unmet need for contraception among sexually active adolescents. Table 4 summarizes our approach for the CEA and our parameters of interest.[85-87] Aim 3 will evaluate cost per HIV test received among all adolescents between baseline assessment through ~2.5 years of follow-up, and cost for one behavioral outcome among sexually active adolescent girls (i.e., use of contraception at last sex). AWVs will be compared against the status-quo in Tanzania, which, in most situations, is equivalent to no access. Data for our analysis will be collected from AWV program documents, clinic records, and school records as described in the Impact Inventory (see Appendix). Costs will be measured in local currency units and converted to USD at an exchange rate to be specified. For each outcome, we will estimate Incremental Cost Effectiveness Ratios (ICERs) as well as the probability that AWVs are cost-effective using a range of hypothetical thresholds for Tanzania. We will address sampling uncertainty by analyzing within and between-group variance in costs and effectiveness to create confidence intervals for our cost-effectiveness ratios, and we will conduct sensitivity analysis to address parameter uncertainty.

Table 4. Parameters for the Cost-effectiveness analysis

Population considered	Adolescents aged 15 to 19 years in Tanzania
Perspective	Health sector and societal
Intervention	Adolescent Wellness Visit in last year of primary school
Comparator	Status quo (No AWV)
Costs considered	Health & Education sectors
Benefits/effects considered	Health and economic
Period of interest	Program duration (2 yrs) & Long-term (10-15 yrs) for social/economic benefits

Anticipated challenges and solutions

Our pilot study established the feasibility and acceptability of AWVs but following up an adolescent cohort over time could be challenging as youth move for both education and job opportunities. Our team has experience tracking adolescents over time [49,79] and we will use a variety of retention strategies including assented WhatsApp study participant groups and timing interviews with holidays/breaks when participants are most likely to be home with relatives to help mitigate these risks.

Project timeline	July 2021 to June 2022	July 2022 to June 2023	July 2023 to June 2024	July 2024 to June 2025
IRB clinical trial approvals (UNC, Duke, MUHAS, NIMR)	X			
Youth Advisory Group (YAG) & Stakeholder Advisory Group (STAG) meetings	X	X	X	X
Policy review/ liaison with district/national health & education government sectors	X		X	
Preparation for AWVs at 10 intervention schools: • Orient schools, clinics, communities • Student/Teacher/Nurse meetings for info and adolescent assenting • Parent-school meetings for info and parental consenting • Train providers and ensure facility readiness	X			
Baseline data collection from adolescent cohorts at 20 schools	X	X		
Implement AWVs at 10 intervention schools during academic year (Jan to Sept for 2022 academic school year)		X		
Follow-up data collection for 12, 18 and 24 months post primary school from adolescent class cohorts		X	X	X
Data management, analysis, reporting and manuscript prep		X	X	X
Dissemination Activities				X

Capacity Building

Strengthening the Tanzanian team in implementation research is a core component of this project. Co-investigator Mr. Lema is a promising researcher with deep clinical expertise at MUHAS as a Clinical Psychologist. He was the study coordinator for the AWV pilot study and will be again for this R01. We propose that he be supported to complete his PhD at MUHAS in public health by using the R01 data for his dissertation. By virtue of being a team member, Lema will receive in-person and virtual training and support in protocol development, data analysis, and manuscript preparation. Baumgartner & Kaaya have had ongoing collaborations for more than a decade including weekly USA/Tanzania team calls. These calls, in addition to monitoring visits, serve as supportive supervision for the team with reinforcement of previous trainings (ethics, data management/analysis). We also envision master's level global public health trainees at MUHAS and UNC/Duke under the supervision of our Co-Is working as research assistants, using data for their theses. Lema and Baumgartner have already jointly supervised one Duke master's student on the pilot study which resulted in a manuscript submission, highlighting the bidirectional learnings between the MUHAS and US-based university sites.

Dissemination and transition to policy plans

This project will determine the impact of AWVs on HTC and health service utilization more broadly for adolescents. It will provide evidence to both the government of Tanzania and WHO as they contemplate the value of this new service delivery investment. The study will also move the field of prevention science forward as one of the first studies in Africa to develop and evaluate a platform for both SRH and non-SRH health services for young adolescents, the implications of which could inform annual health check-up strategies for U.S. populations which are currently underutilized. This D&I proposal creates and leverages a new population level health service for adolescents that aligns with NICHD's Research Theme #5: Improving Health during the Transition from Adolescence to Adulthood (NOT-HD-18-031). A prevention-focused adolescent health service in LMICs can set the tone for a 'culture of health and wellness' during this critical developmental period.

Ethical Considerations:

Informed consent process per participant type:

Adolescents: The study participants will include children below the age of 18 years who are technically minors. Students will hear about the study more broadly as a class during school hours when our research team visits the school. They will then be taken one by one for individual assent on school grounds at a private location for additional questions and signature. Whether they choose to assent or not will not visible to their classmates. If an adolescent does not assent, we will not pursue parent/guardian consent. All staff that will be involved in consenting child participants are bilingual in English and Swahili and will be involved in the consenting process. During a study staff school visit, students in standard 7 classes that have been randomized to participate in the control and AWVs arms will be provided information about the study and invited to participate in the study. All children that assent to participate will be provided with a study brochure, to take home to their parents or guardians. Each parent study information sheet will provide contact information in terms of a contact number of the study PI and/or co-PI in case they have any questions before they provide consent. Parents will also be requested to provide their contact phone numbers on the information sheet and to attend with the study information sheet a parent teachers study information meeting at the school, that will be called by the head teacher on behalf of the study team (PTA meeting). Only children that assent and also have parental consent will be recruited in the study to attend AWVs and/or complete surveys. Parents will also be an important contact person for scheduling follow-up surveys with the child.

Adolescents involved in Pretesting Activities Only: Standard 7 students at a school that is not part of the main study, will but purposefully selected to participate in pretesting the survey. The study team will work with the school principal to obtain permission first and both adolescent and their parents/guardians must assent and consent (new forms are attached).

Parents/guardians: Parents/guardians will hear about the study more broadly at a PTA meeting coordinated by the schools and attended by our research team. They will then be taken one by one for individual consent at a private location for additional questions and signature. If either the adolescents or parents/guardians want more time to consider participation (or they missed the school visit/PTA meeting), the research team may visit their homes at a later date to discuss the study and seek assent/consent. Alternatively, the research team may set up additional school-based visits to meet with adolescents/parents/ guardians until everyone is reached. The above procedures were used for our CFAR pilot study at two schools and this strategy was acceptable and feasible to the schools and communities. At this meeting more information will be provided to parents about the study by both the head teacher and the study team and any questions that are raised by parents answered. Parents will then be invited to permit their children to participate. At this stage two each consent forms will be circulated and parents requested to sign whether they give their child permission to participate or not and submit one copy either at the meeting or to the headteachers office within a few days; and to keep the second copy for their own record. Parents that accept to participate will be informed that the study team will contact them by phone likely twice every year (4 times in 2 years) to ensure that their phone number has not changed and consenting parents will also be provided a study card with the study logo and a contact number in the event they change their phone number so they can contact the study team and provide us with an update phone contact number.

Some parents will also be invited to participate in in-depth interview—we will purposely select up to 50 parents/guardians (balanced by sex, district, intervention/control) using their contact information from the consenting process for their child. Because the parents themselves are not being consented for their own participation in data collection at baesline, we will document on an excel tracking form during the parental consent process whether they are open to being re-contacted in the future for possible study participation in in-depth interviews. Only parents with confirmed acceptance for being re-contacted, will be reached by phone to set up their consent and date for a scheduled in-depth interview. Only parents that had consented to participate in in-depth interviews will hence be contacted and invited to attend a study-based location or a location of their preference for the in-depth interview.

Key informants: Key Informants are largely targeted for participation based on particular expertise (health provider, school staff member, parent of VITAA participant) and we will consent these adults at their place of employment for the professionals or at their homes/child's school for the parents. For these adult participants office visits will be made at the health facility, schools and different levels of education and health departments from ward to district in order to inform potential participants about the study. They will be invited to ask any questions and once these questions have been answered, they will be invited to participate. Only participants that consent to participate will be scheduled for FGDs or IDIs, as with parents and adolescents, these participants will be invited to keep a copy of the consent form.

Informed consent process- all participants

Multiple points for information giving and improving understanding: We anticipate that most adolescents (assent) and parents/guardians (consent) and FGD and IDI adult participants (consent) will agree to hear about the study and consent or assent on the same day; however, we will allow at least two days for them to review and contemplate as needed. The official informed assent/consent process is expected to take approximately 20 minutes per person. However, prior to obtaining individual assent/consent most adolescents (via school-based information sessions) and parents/guardians (via PTA meetings) will have already had the opportunity to learn more broadly about the study and ask questions. Individual participants will be still be given individual time to ask questions and must sign without their respective matched adolescent and/or parent/guardian present in order to avoid undue influence from the other. Before requesting participants' signature on the assent /consent form, study staff will make every effort to ensure that the participants questions have been answered.

Minimizing undue influence/coercion: To minimize the possibility of coercion or undue influence, the participants will be informed of all aspects of the study and any questions will be answered. The voluntary nature of the study will be emphasized. The participants will also be told that their decision to accept or decline participation in the study will not impact their ability to receive education services for their children or standard of care health services at the health facility. A copy of the assent /consent form will be provided to participants with a contact phone number to call in case they have questions or concerns about the study. For the adolescents in particular, the team will first seek assent before seeking parental/guardian consent. If adolescent assent is not obtained, then the team will not seek parental consent in order to put the rights of the adolescent first. However, if the adolescent requests that parental consent be sought before they sign the assent, we will accommodate this request. Our first priority is the adolescent and we do not want them to feel any undue influence to participate from the research team, their school or their parents.

Informed parental consent and adolescent assent for recontact

We are adding optional parent consent and adolescent consent forms requesting permission to recontact study participants for a potential follow-on study. Research Assistants will discuss and obtain consent and assent from parents and adolescents during the endline data collection process, ensuring participants that whether they agree or not, it does not affect their final survey nor their ability to participate to dissemination activities for the current study.

Data Safety and Monitoring

To ensure the safety of our research participants and to protect the validity and integrity of our study data for this clinical trial, the following activities will be implemented:

- Assent/Consent Forms for the study participants (adolescents + parents) will include a section highlighting that study confidentiality will be broken if participants reveal verbally or by interviewer observation an intent to harm themselves or others (suicidal or homicidal risk; reports of child abuse) during a study interview and/or as part of an AWV. Depending on the type of harm identified, the study team may need to contact a supervisory health provider (on-call psychiatrist) and/or protection/social work services for follow-up. The Assent/Consent Forms will also include a section describing that their de-identified data may be shared with other researchers once the study has ended.

- All procedures that will be administered during the Adolescent Wellness Visit at the clinic (vital signs, nutritional assessment, dental pain screening, vision test, mental health screening, STI syndromic questions, and assessments for needing contraception or HTC) are all evidence-based, non- invasive, and in line with Tanzanian health policies. If an adolescent and the provider agree that HTC is warranted, standard national guidelines will be followed for all aspects of the testing and counseling session.
- The investigators will make all study related documents, including consent forms, readily available for inspection by the study's IRBs, NIMR and its authorized site monitors, and the Office for Human Research Protection (OHRP).
- The study will be conducted in full compliance with the protocol. With the exception of modifications required to eliminate immediate participant safety concerns, the protocol will not be amended without approval from the principal investigators. Protocol amendments will be aligned and submitted to all the relevant IRBs including UNC IRB, Duke IRB, MUHAS IRB, and the National Institute of Medical Research (NIMR) IRB. All IRBs must approve the amendment prior to implementation of the amendment

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