HPV vaccine introduction in Mozambique: Generating knowledge from the demonstration project for national roll-out decision making and planning

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Abstract

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The studies in this dissertation describe an evaluation of the implementation of a HPV vaccination delivery demonstration project in Mozambique. Specifically, this work identifies the drivers of heterogeneous implementation performance during the 2-year project, by employing the Consolidated Framework for Implementation Research (CFIR) for analysis (*Aim 1*); tests the contribution of network structure on the added value of the project's implementation partnership (*Aim 2*); and describes the implementation strategy and cost estimates for the project and a fully immunized girl (FIG) (*Aim 3*).

In *Aim 1* we found that 18 CFIR constructs emerged from informants' responses as implementation influencers. Adaptability was identified as an important construct because delivery models needed to be adjustable to differing levels of girl school attendance. Expanding outside of school-based delivery was necessary in the lower performing district and was challenging. Available resources varied across the three sites, with one site receiving direct donor support, whilst others received primarily state-based support. These latter sites reported considerably more implementation bottlenecks, manifested

in the examples of weaker structural characteristics and insufficient organizational incentives. Health workers beliefs in vaccines' relative priority and organizational culture of personal sacrifice to undertake program activities drove performance. The positive drivers of implementation success can be capitalized on during country wide expansion of HPV vaccination.

In *Aim 2* Social Network Analysis (SNA) measures for partnership structure corroborated the perceived outcome survey results. They revealed a partnership network characterized by high overall connectivity scores of reachability 100% and average distance 2.5, features that are favorable for rapid and widespread diffusion of information, and also necessary for engaging and handling multiple implementation scales. High SNA effectiveness and efficiency measures for structural holes (85%) and low redundancy (30%) coupled with high mean perceived effectiveness (97.6%) and efficiency (79.5%) outcome scores were observed. Disparate institutions and organizations worked in a collaborative environment in which the comparative advantage of each entity was leveraged, thereby producing an effective and efficient partnership model that can be adapted during national scale up of HPV vaccination.

In *Aim 3* we found that total implementation costs for the whole project in the three pilot districts were $523,601, 99.4% of which were direct medical costs. Annual patterns and cost compositions of the aggregated costs provided insight into the factors contributing to changes in costs. They showed that important cost determinants were high vaccine price, number of administered doses, program startup costs and the necessity for rigorous demand generation. The cost per fully immunised girl of $54, amounts to more than 50% of Mozambique's current estimated health spending per capita of $92 making the vaccine extremely expensive to introduce. The country will need to consider strategies where savings can be achieved in order for national roll out of the HPV vaccine to be both feasible and sustainable.

The goal of the research in this dissertation, is to inform decision and policy making for national expansion of HPV vaccination in Mozambique, other low and middle-income countries, and global donors and implementing partner organizations.

Table of Contents

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Chapter 1: Introduction

Introduction

Human Papillomavirus (HPV) is the most common Sexually Transmitted Infection (STI) with a global average prevalence of approximately 11-12% in healthy women[1] and an 84.6% estimated lifetime infection risk for heterosexual individuals that have had least one partner[2]. Majority of the infections are asymptomatic and 90% will resolve spontaneously within two years, however those that persist can progress to pre-cancer or invasive cancers[3]. The virus is known as a causative carcinogen in six types of cancer: cervical, penile, vulval, vaginal, anal and oropharyngeal; amongst which cancer of the cervix account for the majority at 86.9%[4]. The attributable factor for HPV in cancer of the cervix has been found to be 100% with types 16 and 18 responsible for 70% of these as well as most of the other non-cervical HPV related cancers[5]. Approximately 530,000 cases of cancer of the cervix are reported annually making it the fourth most common cancer in women worldwide. Of these 266,000 progress to death with 87% occurring in low and middle income countries (LMICs)[6]. High age standardized incidence and mortality rates are observed in South East Asia, Latin America and sub-Saharan Africa [7]. East Africa, where Mozambique is situated, has the highest HPV incidence and mortality age standardized rates (ASR) at 27.6 and 42.7 per 100,000 respectively[4]. Mozambique is placed second on country rankings for cervical cancer burden with high ASRs of 65.0 and 49.2 per 100,000 for incidence and mortality respectively[6]. Research evidence from the country has demonstrated the relationship between HPV infection and cancer lesions. One study amongst 262 women aged 14-61 years found that 40% had HPV DNA, 19% abnormal cytology and 12% cervical neoplasia[8] while another study confirmed HPV 16 and 18 infection detection in cancer biopsies of 78% of cervical cancer cases that were evaluated[9].

The HPV vaccine became available in 2006 making it the first vaccine for the prevention of a sexually transmitted infection[10]. Three types are now available in the market, the bivalent that prevents against

HPV types 16 and 18, the quadrivalent against additional HPV types 6 and 11 and the 9-valent against five more additional HPV types 31,33,45,52 and 58 [11]. The vaccines have been widely utilized in many high-income countries with remarkable effectiveness results and high impact achieved against HPV related disease and widely documented. Surveillance data from sexual health services showed that less than 1% of women in 2011 compared to 10.5% in 2006 were diagnosed with genital warts[12]. Evidence of reduction in HPV sero-prevalence has also been documented with an overall decrease in HPV types 16 and 18 sero-prevalence of 64% in girls aged 13-19 years and 31% in women aged 20-24 years [13]. Evidence of the impact of HPV vaccines on cervical cytological and histological abnormalities have also recently emerged [14][15] as well as cross protection [16] and herd immunity effects [17].

Despite these remarkable achievements, the global difficulty has been on getting these vaccines to the low-income countries that need them most. Systematic reviews on global progress in implementation of HPV vaccination programs all raise the concern that the HPV mortality burden is highest in low income countries, more specifically sub Saharan Africa (SSA) and ironically these are the countries that have not benefitted from the vaccine [18][19]. This inequitable access to HPV vaccine[20] persists despite WHO recommending the introduction of the vaccine in LMICs[21] and Gavi, the Vaccine Alliance taking the decision to fund HPV vaccine introduction in these contexts in 2012 [22]. The Gavi program began in 2012, but first with demonstration projects in which countries were required to conduct pilot projects that would evaluate and prioritize possible HPV vaccination delivery models prior to national scale up. The rationale for piloting HPV vaccine delivery models was the lack of established health service delivery mechanisms for the novel target age group of 9 -14 years in these countries. The target age group for traditional routine national immunization program vaccines' is that of 9 -22 months[23]. Many LMICs undertook demonstration projects and by December 2017 thirty countries had implemented the pilots but a slow progress to national scaleup was noted with only six countries commencing national rollout [24]. Mozambique was one of the countries that completed a demonstration project in 2015 but to date has not

transitioned to a national HPV introduction program. A dearth of learnings from demonstrations projects has been cited as a problem amongst other issues [25] and specifically findings from the Mozambique project have not been published. This dissertation and the articles contained in it are an attempt to fill in this knowledge gap by generating knowledge from the Mozambique demonstration project that can be used to inform policy decision making and planning for the national roll out of the HPV vaccine in the country.

Chapter two entitled "*Consolidated Framework for Implementation Research (CFIR) identifies implementation performance drivers of Mozambique's HPV vaccine delivery demonstration project"* is a publishable manuscript in which the results of a post implementation interpretive evaluation are documented. The CFIR was employed as a lens to identify drivers of heterogeneous implementation performance in Mozambique's unique pilot project that included one Gavi funded site and another two funded by the Government of Mozambique. As a result, the demonstration project provided findings from three different districts representing three different contexts of economic resources, disease burden, health system capacity and cultural practices.

Chapter 3 entitled "*a mixed methods Case Study of Mozambique's Demonstration Phase Partnership Model"* documents the results of the utilization of the Gavi Full Country Evaluation (FCE) partnership framework, to test the contribution of network structure on the added value of the partnership. Specifically, the five partnership dimensions of contextual factors and prerequisites, partner performance, practices, partnership structure, and the perceived added-value in the form of effectiveness, efficiency and country ownership were assessed. The findings of this paper are particularly important to Gavi, the entity that funds new vaccine introductions in LMICs, because of its modus operandi of a Global Health

Partnership, whose model is based on the reliance of domestic and international partners to support implementation of immunization activities under its Partnership Engagement Framework mechanism.

Chapter 4 entitled *"An in-depth examination of the Mozambique HPV vaccine demonstration project implementation strategy and costs"* presents a comprehensive inquisition of the implementation strategy of Mozambique's HPV vaccine demonstration project that identified activities that were undertaken, the inputs of each activity and the cost of each input. The information was then used to estimate the total implementation cost for each year of the project, the cumulative costs for the whole project period and the cost per fully immunized girl (FIG). Annual patterns and cost compositions of the aggregated costs were explored so as understand the factors contributing to changes in costs. Furthermore, the cost per FIG was extrapolated to the whole country eligible population in order to demonstrate the total cost for a similar one year program. The paper provides a framework that other researchers can use to identify, measure and value costs of implementing HPV vaccine delivery strategies. Additionally, the results provide important cost information that can be utilized by Mozambique's Ministry of Health decision makers.

This dissertation represents an underpinning from which the Mozambique national immunization program can gather knowledge emanating from the demonstration project. The findings from our studies contain important lessons for not only the country but also the neighboring sub-Saharan region and for all LMICs in general. Additionally, other future implementation research, for program evaluation during scaleup, can be built from these studies.

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Chapter 2: Consolidated Framework for Implementation Research (CFIR) identifies implementation performance drivers of Mozambique's HPV vaccine delivery demonstration project

Title Page

Title:
Human Papillomavirus vaccine delivery in Mozambique: Consolidated Framework for Implementation Research (CFIR) identifies implementation performance drivers

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Abstract

Background
Since 2012 Gavi has provided financial support for HPV vaccine introduction in low and middle income countries (LMIC), however funding has been contingent on establishing a demonstration project prior to national scale-up, in order to gauge effectiveness of delivery models. Although by 2017, most beneficiary countries had completed demonstration projects, few have scaled up delivery nationwide. An important barrier is the dearth of published, country-specific implementation recommendations. We employed the Consolidated Framework for Implementation Research (CFIR) as a lens to identify drivers of heterogeneous implementation performance during Mozambique's 2-year demonstration project. Mozambique presents a compelling example as the country conducted demonstration projects in three different districts with extremely different resources, disease burdens, health system capacity and cultural mores.

Methods
A post implementation interpretive evaluation was undertaken. Forty key informant interviews were conducted with district and health facility immunization staff, Ministry of Education managers and teachers across the three demonstration districts as well as with central level key informants from MOH, research institutes and immunization program partners. We employed an analysis process previously described by Damschroder, et al. to explain the drivers and barriers to implementation success. Two researchers coded separately, and content analysis followed CFIR construct themes.

Results
18 constructs emerged from informants' responses as implementation influencers. Adaptability was identified as an important construct as delivery modalities needed to meet differing levels of girl school attendance. Expanding outside of school-based delivery was needed in the lower performing district and was challenging. Available resources varied across the three sites, with one site receiving direct Gavi support, whilst others received primarily state-based support. These latter sites reported considerably more implementation bottlenecks, manifested in the examples of weaker structural characteristics and insufficient organizational incentives. Health workers beliefs in vaccines' relative priority and organizational culture of personal sacrifice to undertake program activities drove performance. Advocacy and social mobilization through the right opinion leaders and champions generated higher demand.

Conclusion
Our findings demonstrate the expanding applicability of the CFIR in LMICs, with its breadth being a strength that allows for selection of relevant constructs within broader domains, without compromising robustness of results.

Key words
HPV vaccine, CFIR, LMIC, Mozambique, Gavi, demonstration project

Background

Human papillomavirus (HPV) is not a single virus, rather it is a group of different virus types, thirty of which can infect the anogenital tract and result in a variety of warts and carcinoma[1]. Of these, HPV types 16 and 18 have been proven to account for more than 70% of invasive cervical carcinoma; the fourth most prevalent cancer in women in the world[2]. Annually half a million women worldwide are diagnosed with cervical cancer and 50% amongst them die from the disease[3]. The burden is higher in low and middle-income countries (LMICs) where 85% of diagnosed cases and 87% of deaths occur due to late detection and limited treatment options[4]. The highest cervical cancer incidence and mortality rates are observed in sub Saharan Africa where HPV prevalence is high and screening programs lag behind those in other regions[2]. East Africa, where Mozambique is situated, has the highest HPV incidence and mortality age standardized rates (ASR) at 27.6 and 42.7 per 100,000 respectively[5]. Mozambique is placed second on country rankings for cervical cancer burden with high ASRs of 65.0 and 49.2 per 100,000 for incidence and mortality respectively[6]. Research evidence from the country has demonstrated the relationship between HPV infection and cancer lesions. One study amongst 262 women aged 14-61 years found that 40% had HPV DNA, 19% abnormal cytology and 12% cervical neoplasia[7] while another study confirmed HPV 16 and 18 infection detection in cancer biopsies of 78% of cervical cancer cases that were evaluated[8].

Cervical cancer prevention programs were traditionally based on screening and early diagnosis[9]. However the HPV vaccine which became available in 2006[10], has now become an integrated component of cervical cancer prevention programs in high income countries, because it is considered the most effective and efficient strategy[11]. Correspondingly the World Health Organization (WHO) recommended the adoption of the intervention by LMICs where prevention of cervical cancer and HPV related disease is of public health priority[12]. In support of this recommendation Gavi, the Vaccine Alliance, in 2011, made the decision to provide funding for eligible LMICs to introduce HPV vaccine

into their national immunization program (NIP) schedules. These countries were however first required to conduct demonstration projects that would evaluate and prioritize possible HPV vaccination delivery models prior to national scaleup[13]. The rationale for piloting HPV vaccine delivery models was the lack of established health service delivery mechanisms for the novel target age group of 9 -14 years in these countries. The target age group for traditional routine national immunization program vaccines' is that of 9 -22 months[14]. Demonstration projects rolled out quickly with 23 countries completing the pilots by the end of 2016. On the contrary national scale up failed to progress at the same pace and by December 2017 only three of these countries had successfully transitioned from the pilot to national roll-out[15][16][17].

Mozambique is one of these countries that have been in a long transition phase. The country completed the demonstration project in November 2015 with a plan of commencing national scale-up in January 2018, however by December 2017 a national rollout strategy was still lacking. One bottleneck is the lack of in-depth implementation phase knowledge from the three sites that implemented the demonstration projects. While most other countries implemented only Gavi funded pilots Mozambique is unique because it included two other sites funded by the Government. A feasibility study and post introduction evaluations were included as part of the Gavi funding for demonstration projects and these were conducted for the one Gavi site in Mozambique. Similar assessments were not achieved in the Government funded sites and our study is aimed at filling in this gap by providing salient implementation findings from all the three sites, information that will be pertinent for national scale up planning and decision making.

Several frameworks proposing theoretical bases for determinant factors in health programs' implementation success have been proposed in the literature[18][19][20]. With the aim of standardizing terminologies and approaches for identifying and documenting these implementation success determinants, the Consolidated Framework for Implementation Research (CFIR) was conceived through

the aggregation of content from a review of implementation science (IS) theoretical frameworks, conducted on more than 500 literature sources[21]. The CFIR is a meta-framework organized into five domains (*intervention characteristics, outer setting, inner setting, characteristics of individuals and process*) that are subdivided into 39 constructs and sub-constructs[22]. Due to its broad and generic nature, the provision of a support platform[23] by its developers and its continued revision and updates, the CFIR has proved appealing to researchers in the field with its utilization significantly expanding since it was first published in 2009[24]. A recent systematic review documented more than 25 empirical applications of the framework. The researchers found that the CFIR has mainly been applied to guide study planning, data collection and analyses, however an important area that the researchers identified that could benefit from more CFIR research is post implementation interpretive evaluation to explain success or failure [25]. Additionally, to date, (to the knowledge of the authors of this paper), the CFIR has not been utilized to study the implementation of vaccine delivery in LMICs. By utilizing the CFIR in our study we shall be adding to the growing body of knowledge of CFIR use in LMICs.

The goal of this paper is to present the results of the utilization of the CFIR, for the determination of salient constructs that discern the performance of HPV vaccine demonstration sites in Mozambique. The sites were classified as high, intermediate or low performing based on the HPV vaccination coverage results that they achieved during the project (Figure 1).

Methods

In this study the CFIR was utilized to perform a qualitative post implementation interpretive evaluation[26]. A semi structured interview guide was developed based on each CFIR construct description and used to conduct 36 key informant interviews (KIIs), on selected individuals who had directly or indirectly been involved in providing the HPV vaccine in the three demonstration sites in Mozambique. These individuals included; health facility immunization staff, district immunization staff,

district education staff, provincial immunization staff, provincial medical heads, national level immunization program staff, staff from research institutions and non- governmental organizations (NGOs) that had supported the national immunization program during all the implementation phases. The interviews were conducted in person in the interviewee's venue of choice. Interviews lasted between 1 and 2 hours and voice digital recordings of all the KIIs were obtained. These audio recordings were then transcribed verbatim and the five steps described below were followed in order to apply the CFIR taxonomy and tools to the analysis;

Step 1: Defining the innovation

While the HPV vaccine itself is an innovation, the focus of this study was on the demonstration project vaccine delivery model design as the innovation. One of the donor demonstration project requirements was for the country to show that the tested HPV vaccine delivery model could reach at least 50% of the target group[27]. The country chose to explore a school based vaccine delivery model based on the rationale that this is where most of the girls in the target age group can be found. These school based vaccination campaigns would be complemented with mobile outreach visits to the communities where the vaccine would be provided for girls that were not enrolled in school.

Step 2: Defining the unit of analysis, site inclusion and performance criteria

The unit of analysis for this study was the district. There were only three district pilot sites and all three sites were compared. The rationale for including all the districts was the fact that the sites were few and therefore it was relevant to include all of them. Furthermore, each district was chosen to represent distinct geographical, disease burden and economic realities in the country. The three districts are Manhiça, Manica and Mocímboa da Praia representing Maputo, Manica and Cabo Delgado provinces respectively. Each province also represents the three regions of Mozambique which are the South, Central and Northern regions. Provincial health and socio-economic parameters in the three provinces where HPV vaccine demonstration projects were implemented are shown in table 1.

Step 3: Initial CFIR construct selection.

In this step the CFIR description for each domain (*intervention characteristics, outer setting, inner setting, characteristics of individuals and process*) was used to identify the Mozambique HPV vaccine demonstration project setting equivalent. Given that the descriptions are construct specific within each domain, all the 39 CFIR constructs descriptions were read through and linked to the Mozambique HPV vaccine demonstration project setting. 13 constructs that were deemed not to be relevant were excluded at this point. We excluded the whole domain of *characteristics of the individual* because the innovation in the study was primarily a service delivery intervention, and data was not collected from the girls who were the recipients of the HPV vaccine. For this reason, all the five sub constructs within the domain were not relevant.

Step 4: Final CFIR construct selection

The final constructs for rating were selected through the coding process. Nvivo software, version 11, was used to facilitate coding of interview transcripts. The CFIR codebook template which provides codebook descriptions for each construct guided the development of our study codebook. Responses to the research questions that we had come up with for each of the remaining CFIR constructs were sought and given their own code. A team of two researchers separately conducted the coding and the kappa statistic was used to measure inter coder reliability at a threshold of 80%[29]. Following coding, a report of each code was produced, read, and re-interpreted in order to create a synthesis of findings related to each code[30]. We removed constructs that were not reflected in our transcripts and we ended up with a total of 19 constructs for the next step.

Step 5: CFIR construct valence and strength rating

Ratings were performed for the valence, which assesses whether the construct had a positive, neutral or negative influence, and the strength, the degree of the influence on implementation success or failure. For this purpose, the valence construct rating rules shown in table 2 were utilized together with the strength

ratings described on cfir.com website[23]. For interpretation, a comparison of ratings across the units of analysis (the HPV vaccine demonstration districts) was conducted using an excel based rating matrix. Finally, the pattern and strength of the ratings were established and in so doing each construct was distinguished based on each implementation site.

Results

A total of 19 constructs were evaluated, 12 were distinguishing (11 strongly and 1 weakly), five were not distinguishing but positively influencing, one not distinguishing and negatively influencing, and one was neutral, neither distinguishing nor influencing implementation (Table 3).

Details of the findings are described below categorized by each construct that was rated for valence and strength.

A. Innovation Characteristics

1. Adaptability (Strongly Distinguishing Construct)

The delivery model for the HPV vaccine demonstration project was designed at the national level to be primarily school based. The design did not consider or address existing differences in the proportion of girls enrolled in schools in the three demonstration sites, each of which was representing one of the three different regions of the country. Guidance provided to districts was detailed on the orientation for the administration of the HPV vaccine in the schools but not on the community outreach component which was left ambiguous, with all three demonstration sites in the different regions of country expected to carry out vaccination activities for the same number of days and in the same manner. There was no distinction to cater for varying proportions of girls not enrolled in school. For this reason, the model was limited and did not provide for flexibility for districts to adapt to their local context's situation. Interviewed key informants from the intermediate and low performing districts expressed the need for a delivery model that could cater for such differences. These key informants (KIs) stated that districts with a significantly

larger proportion of girls out of schools may require a different approach to conduct community outreach activities to reach such girls, for example they may need more days which would mean a larger budget. They also said that the model should allow for the vaccine to be provided in different locations.

> *"Here in Cabo Delgado we have a significant proportion of girls that are not in schools. Early marriages are the norm, so we have to be able to offer the vaccine in the schools, community and health facility for a longer period than the time that was stipulated for us during the demonstration project".*

2. *Complexity (Strongly Distinguishing Construct)*

Three aspects of the HPV vaccine demonstration project were mentioned as complex by the KII respondents from the low and intermediate districts and not by those from the high performing district. These are, the non-health facility based nature of the delivery model, the necessity to closely collaborate with the ministry of education and other non-health sector structures and finally the target age group. While all respondents from all sites found that the delivery model was complex, the respondents from the intermediate and low and performing sites had additional aspects of complexity beyond those described by those from the higher performing site. For all respondents, the necessity to leave the health facility to go and vaccinate eligible girls where they could be found, was deemed more complex compared to the existing routine vaccines health facility based model. The respondents from the low and intermediate performing sites described additional challenges posed by the significantly larger number of girls not enrolled in schools. Finding these girls in the community was a complex task because it was difficult to locate them and this hampered the achievement of a higher vaccine coverage rate in these sites. The district had to decide the best place and methods to reach the girls. While some community outreach activities had been considered within the demonstration project school based delivery model, these were limited with none or minimal orientation to the district on the methodology of locating the girls.

Furthermore, no budget had been allocated for the possibility of a district needing to conduct outreach activities outside of the one week vaccination period.

> *"Another principle challenge for HPV vaccine demonstration, was the difficulty in accessing the target group. While I agree that we should offer the vaccines in schools, we also have to find the girls in the community and that became very complex for us".*

The health workers in the high performing district did not have difficulty in locating the very few girls not attending school in their district.

> *"For us it was not difficult, we managed to find all the girls even those who had not been registered"*

The second complexity created by the non-health facility based nature of the model was the need to collaborate with non-health care system individuals for vaccination process activities; teachers for the school based and community leaders for the community based vaccination. The health workers had to depend on these individuals to conduct certain activities such as pre-vaccination registration of the girls as well as the identification of the vaccination venue; in some instances, the teachers took on the role of filling in the girls' vaccination card or (and) the vaccination registration book. This according to the respondents from the low and intermediate performing sites was complex because they were forced to innovate methods of collaborating with the teachers and community leaders in a way that was new to them, and they were not always successful.

> *"Vaccinating in schools it is not an easy job because the social mobilization we have to conduct is different from what we normally do for vaccination. In this case we had to depend on the teachers to communicate to the girls, register them and also to organize the girls on the day of the vaccination. I had to keep calling the teacher using my mobile*

phone all the time which is different from what we do for the usual vaccines we give to babies here in the health facility"

The gender specific and novel target age group was difficult for social mobilization. They said they found that it took longer for the parents and the community as a whole to understand why it was only girls, of an age higher than the usual under two years old immunization age group they are used to. This challenge was peculiar to the low performing district, with the key informants from this district describing how they had to talk to the girls' parents many times in order to make them understand the reasons for the selected age group and gender for HPV vaccination eligibility.

"The HPV age group was a bit difficult for mothers to understand and we had to talk to them many times for them to understand"

3. *Design Quality & Packaging (Not a Distinguishing Construct)*

All the districts received the same materials from the national level. For this reason, this was not a distinguishing construct.

B. Outer Setting

1. *Needs & Resources of those Served by the Organization (Strongly Distinguishing Construct)*

This construct, which describes barriers to reaching those served by the organization, strongly distinguished performance because the low and intermediate performing districts' health worker respondents reported a failure of the delivery model design to address some elements, that subsequently compromised their ability to reach all the eligible girls in their districts. Two main issues were raised, first, was the lack of knowledge of the exact location of girls who were not in school. While they were cognizant that these girls were in the community, not knowing their precise location became a barrier to reaching them for vaccination. They said they would need to rely on community and neighborhoods leaders to assist them in identifying where these girls are and similarly where best to locate community

outreach vaccine delivery points. They didn't consult the community leaders during the demonstration project because as stated earlier the delivery model had been designed at national level without the flexibility for these sites to adapt to the reality of their context.

> *" Girls not in school, where are they? It will be best to collaborate with community leaders to have them identify the best locations to offer the vaccine so that we can reach most girls out of school."*

On the contrary health worker key informants from the high performing site said they did not have a problem locating the few girls who were not enrolled in schools in their district.

Another barrier to reaching the eligible target group was the scheduling of the vaccination date during a period when children were not in school because it was a local public holiday (school stay at home day). Cities and districts in Mozambique occasionally have local specific holidays such as city commemoration days. The HPV vaccination day that was selected at national level during the demonstration project vaccination campaign was applied uniformly to all districts with no consideration of the occurrence of a local public holiday and this according to KIIs from both the intermediate and low performing sites contributed to their sites' sub optimal performance. The higher performing district health workers did not encounter this problem when they went to administer the HPV vaccine to girls in the schools in their district.

> *"we had a problem of having planned for HPV vaccination to happen when children were not in school because it was a holiday"*

C. Inner setting

1. *Structural Characteristics (Strongly Distinguishing Construct)*

Some of the structural characteristics of the intermediate and low performing districts were stated by KIIs as factors that negatively affected the ability of the project demonstration site to achieve the target

coverage of the girls eligible for HPV vaccination. Specific examples described by key informants from these districts were the total number of schools in the districts, the states of roads and other transportation infrastructure such as the existence or lack of bridges. Bridges are an important part of infrastructure in Mozambique because rivers and other water bodies are common features in most of the country. An underlying factor to the state of the transportation network in these districts is the economic development status and the intermediate and lower performing districts are economically less developed than the higher performing districts (Table 1). These natural and infrastructural challenges contributed significantly to the inaccessibility of some pockets of the population in these districts. Fewer schools meant that there were a higher number of girls not enrolled in schools and further distances to be covered by the health workers to reach the schools. Additionally, key informants from the high performing district said that they noted vaccination coverage differences with the arears in their district that were more economically developed attaining better rates that economically poorer areas.

> *"even though the overall coverage here in the district was 70%, when we stratify, we find that the areas that are economically advantaged had higher coverage rates"*

2. *Networks & Communications (Weakly Distinguishing Construct)*

The intermediate and low performing districts' respondents from the health directorate mentioned a non-transparent communication from MOH central level regarding funds as one of the problems that they encountered. The central level managers were vague on when they would receive the funding allocated for their demonstration project activities. They kept being told that the funds would arrive in the following few days and finally they didn't receive the fuds at all. The health directorate workers in the high performing districts did not experience this challenge because their funding which came from Gavi was disbursed on time for them to initiate the implementation project activities.

> *"The central level kept telling us the funds will be in the province tomorrow, but we didn't' receive anything and finally we managed to get some funds for fuel but not per diems for the workers"*

3. *Culture (Not a Distinguishing Construct)*

Organization culture was not a distinguishing factor. In the directorates of health at all levels in the Mozambique health system there is culture of doing the best to make things work under the circumstances including sacrificing when a matter is deemed to be a priority or of national interest. According to the KII respondents from all the demonstration sites, health interventions are viewed to be beneficial for the population and for this reason they did their best under the circumstances and went out of their way to meet the set targets. Respondents from all the three demonstration sites talked of having been selected as the pioneer sites was an honor to them. Organization culture was therefore not a distinguishing factor, however it was strongly positive in influencing implementation.

> *"I don't know all the details because I am not the one managing funds here in the province but we managed to get some fuel from the transport people and continue with activities as we waited for funds from central level"*

> *"It was an honor for us to be chosen as the pioneer district for something like this so we did all possible in terms of resources for social mobilization and community involvement to make it successful. We interacted with the district governor so that he could gather the other district leaders (eg permanent secretary) and neighborhood heads"*.

> *"We tried to explain to them (community leaders and teachers) that this was something that was going to benefit the population and our province had been selected for the demonstration project that we just had to sacrifice by being a bit patient and doing what we can to make it work"*.

4. *Relative Priority (Not a Distinguishing Construct)*

This was not a distinguishing factor. All health workers in all the implementation sites said that vaccination was a priority for the improvement of the health of the population.

5. *Organizational Incentives & Rewards (Strongly Distinguishing Construct)*

This was a strong distinguishing factor. The vaccination coverage rate of the girls eligible for the HPV vaccine in the districts which incentives were not paid was much lower compared to the districts where funds were available to pay individuals involved in conducting activities related to the demonstration project. A major repercussion was specifically experienced with the community leaders who were also opinion leaders in the lowest performing district. They were disgruntled and lost trust in the local health directorate because they thought that the directorate had received money from the central level but did not want to pay them. Consequently, they not only failed to complete the tasks that they had agreed on (pre-vaccination registration of girls), but went farther and used their important positions as opinion leaders, to discourage parents from allowing their daughters to be vaccinated. According to the KIIs the impact of this counteractive negative social mobilization on the achievement of the target vaccination coverage rate was significant.

> *"The non-payment of some of those involved led to, discontent, dissatisfaction and even mistrust. Mistrust because they thought that we (the provincial health directorate) had received the money and had not paid them. Especially the non-health people such as the teachers and community leaders who were helping us implement the program".*
>
> *"One thing that can be improved next time…specifically for me…. I had to call the teachers about the vaccination day and the ministry didn't give me air time so I had to use my own money to buy airtime. They should give us airtime next time"*
>
> *"You know our mentality, the personnel and the people are used to receiving the payment before the work. Next time they should guarantee the availability of incentives for teachers'.*

6. *Learning Climate (Strongly Distinguishing Construct)*

The district that had an evaluation component performed better compared to the districts that were not required to conduct an evaluation as a key deliverable for future financial support. This district was being funded by Gavi and a local research institution was tasked with conducting a coverage survey as we as a feasibility study. One criteria for future funding was the ability for the country to demonstrate that a coverage of 50% of eligible girls.

> *"we (the central level technical working group) were always concerned about Manhiça because this is the district that Gavi would evaluate us (the country) on"*

7. *Available Resources (Strongly Distinguishing Construct)*

This was a strong distinguishing factor because the best performing district had more financial resources than the medium and poor performing districts for implementation of HPV vaccination activities. These sites, which had received insufficient money for the demonstration project, could not afford to fund all the activities that would have been ideal for the vaccination campaign to be successful. They had to compromise and do what they could with the fewer financial resources that they had. On the contrary the district that had higher levels of funding could undertake more activities and this strongly influenced the ability of the site to achieve a higher vaccination coverage rate of the eligible girls. One activity that clearly demonstrated the disparity in the resources available to the sites was the social mobilization. The high performing site's social mobilization strategy included an extra component, beyond the regular methods that were being implemented in all the demonstration sites. The regular methods were in the form of television and radio spots, health worker talks and community leader talks while the extra social mobilization strategy involved engagement of community volunteer activists who conducted door to door educational visits. Because theses activists received remuneration a similar strategy could not be adapted in the sites that had less funding. Respondents also talked about shortage of vehicles to transport the health workers to schools as another significant problem that they faced within the available resources category. The transportation problem encompassed shortages in available vehicles as well as fuel and driver per diems.

"The main challenge for the HPV project was the insufficient funds which led to non-payment of the health workers and the other participants' that is teachers and community leaders per diems".

"Lack of transport to access the schools especially in the areas that were hard to reach. We had to manage with the few resources that we had for example even using vehicles that were not in the best condition"

"Any activity here in the province such as supervision depends on the availability of a car which means fuel and per-diem for the driver. For us to go and vaccinate the girls in schools we needed a car and this was a challenge because we have few cars here in the district"

"What needs to be improved most is the availability of funds. Until today health workers who took part in the demonstration have not been paid their per diems".

8. Access to Knowledge & Information (Strongly distinguishing Construct)

Respondents from the intermediate and poor performing districts talked about a lack of training for the teachers as an important issue that affected the implementation of activities. Teachers in the high performing site received training to execute various activities during the preparation and implementation phases of HPV vaccination. These activities included pre-registration of eligible girls, educating them and their parents about the upcoming vaccination campaign, organizing the vaccination venue in their schools, organizing the girls for vaccination (for example into queues) and assisting the health workers to complete the registration in the girl's cards. An additional key role for the teachers was the monitoring of the girls for side effects after the health workers had left to go to another school. KIIs from the intermediate and low performing site reported that the non-training of teachers impacted on ensuring that all girls were in schools on the day of vaccination and subsequently on the ability of their district to achieve the target vaccination coverage rate. This construct was therefore strongly distinguishing.

"In the second year we were better organized and were able to train teachers and they performed better in informing the girls and their parents and we performed better on the coverage".

"Next time we have to train all teachers"

D. Process

1. Planning (Not a Distinguishing Construct)

This construct was not distinguishing because the respondents from all sites reported a delay in the initiation of preparatory activities, a factor that negatively influenced implementation. They blamed the MOH central level for sending information, funds and materials too late, when the selected vaccination date was approaching, leaving them with limited timelines to conduct preparatory activities in their districts.

"The problem with the late arrivals of funds was with central level and this didn't improve even in the second year. The funds should arrive before, at least 3 weeks in advance in order for us to organize our teams better".

"What needs to be improved is to start social mobilization early…..the information arrived late to the population because we received the social mobilization materials from the central level late"

2. Opinion leaders (Strongly Distinguishing Construct)

This construct was strongly distinguishing and was reported by the respondents from the low performing site. They stated the problem of having inadvertently excluded an important group of opinion leaders, the mosque imams. This had a negative repercussion because the imams in this district are very important opinion leaders to the extent that what they say is taken as an order by their followers. In addition, majority of the population in the region are Muslims and this negatively impacted on implementation

success. The high and intermediate performing districts did not experience similar problems with religious leaders.

> *"Religious leaders were more important because our community is largely Muslim. We heard people say that they only heard the message from the radio and not from their religious leaders in the mosque. We have learnt that it is not enough to pass the message through the radio and community leaders. We have to involve all opinion leaders including the mosque imams."*

3. *Champions (Not a Distinguishing Construct)*

The HPV vaccine demonstration project in all the sites was largely influenced by the interest of Mozambique's first lady who at the time had identified cancer of the cervix as one of her legacy campaigns. Her involvement was the driver behind the inclusion of the non-Gavi funded districts in the demonstration project and the motivation for the successful realization (/completion) of the demonstration in these districts despite limited funding. Her involvement also gave the vaccine a high visibility and largely contributed to generation of demand due to higher coverage by the media during the launch ceremony that she officiated

4. *Key stakeholders (Strongly distinguishing construct)*

Role of Gavi as the donor was a strongly distinguishing construct. This is because Gavi was behind the exclusion of the moderate and poor performing districts from their funding. which consequently resulted in a worse performance compared to the district that had funds from Gavi available for HPV vaccination related activities.

5. *Innovation Participants (Strongly distinguishing construct)*

The engagement of the innovation participants was compromised by the community beliefs in the low performing district. According to the KIs from these districts people did not understand why the vaccine

was being offered to only girls instead of to all children as is done with the other vaccines that are offered to children and which the population are familiar with.

> *There was a misbelief that we were vaccinating girls to make them sterile not be able to have children. It even reached a point when the girls were no longer going to school.*

> *Beliefs that the vaccine would make the girls sterile. Even when we went to the community there were some mothers who were hiding their children to avoid getting the HPV vaccine*

6. *Executing (Neither a distinguishing nor an influencing construct)*

Despite a number of challenges, all HPV doses expected to be delivered during the demonstration project were accomplished within the planned timelines and the objectives of project were met. The country was able to implement a pilot in 3 different districts that represent three different contexts.

7. *Reflecting and evaluating (Not a distinguishing construct)*

KII participants from all sites talked about having used learnings from the first-year implementation to improve during the second year of the project.

> *"Comparing the first and second years of HPV vaccination we got better in the second year because we learnt from our experience. We had created a mechanism for mobilizing the community and we had better results than in the first year"*

> *"In implementation there is always some problem in the beginning and we observe these and then we usually try to improve the next time and avoid repeating the same mistakes. So in comparison with last year we improved. For example, we avoided planning for vaccination when children were on holidays…"*

Discussion

Our study has revealed eight key significant drivers of implementation success or failure emerging from this CFIR construct analysis. These are; adaptability, complexity, financial resources, positive organizational culture and workers beliefs about the innovation, training, intervention recipient's perceptions, engaging the right opinion leaders and decentralization of planning and other processes.

The first two key drivers emerged from the two strongly distinguishing constructs *adaptability* and *complexity* from the first CFIR domain of *innovation characteristics.* The delivery model that was designed at national level was a school based model that did not cater for differing proportions of school enrollment of the target group of adolescent girls eligible for the vaccine. The vaccination guidelines that all the three demonstration districts received from the national level allocated a one week period for the conducting of school based vaccination and community outreach too. There was no possibility for the districts that had fewer girls enrolled in school to deviate from these timelines. The lower performing district had only 40% of girls enrolled in school and health workers here cited the lack of sufficient timelines and guidance on how to reach girls out of school as a key barrier to achieving higher vaccination coverage. An adaptable model that could allow such districts to allocate more time and resources to community outreach visits is desirable. The other innovation characteristic domain that impacted on performance was complexity. While a complex intervention poses challenges for the health system it also offers an opportunity for the nurturing and creation of new implementation ideas. Complexities that were highlighted by health workers were those of having to administer the HPV vaccine predominantly out of the health facility and therefore having to rely on non-health workers, teachers in schools and leaders in communities, in order to reach out of school girls. This brought on new types of challenges, an example being the unclear communication channels. While it may not be possible to eliminate complexity due to the vaccine target group and lack of an established health service delivery

model for the group, it could be minimized by for example addressing how health workers should collaborate with teachers and community leaders.

The *inner setting* CFIR domain produced the next set of factors that influenced implementation performance. Three strongly distinguishing constructs *structural characteristics, available resources and organizational incentives and rewards* were all about insufficient financial resources curtailing the ability of the intermediate and poor performing districts to achieve higher vaccination coverage. Implementation performance varying based on either the availability of funding for the demonstration project or the economic development of the district. This finding underscores the need to address inequity during national scale up. Poorer districts will require more financial resources than the districts that are relatively economically stronger. Organizational workers' values, work ethic and beliefs which were evaluated by the *inner setting* constructs of *culture* and *relative priority*. While they were not distinguishing they strongly influenced implementation in all the sites. Health workers' beliefs in the importance of vaccines as a high health priority coupled with the organizational culture in the Mozambican health sector, of doing whatever it takes even when in non-ideal circumstances to ensure that eligible populations can access health interventions, were pertinent in driving the completion of all the demonstration project activities despite existing challenges. These positive organizational implementation success drivers should be leveraged during national scaleup. The final significant CFIR inner setting domain construct was access to knowledge and information which was strongly distinguishing. The non-training of teachers in the intermediate and poor performing districts compromised their ability to perform that activities that were expected of them during the pilot and consequently impacted negatively on vaccination coverage. In going forward training should be planned for all individuals that shall be expected to carry out any activities related to the vaccination process.

Constructs that delve into the recipients of the intervention also stood out in our study. While we had excluded the *characteristics of individual* domain from our evaluation due to the organization centric nature of the study, interestingly the importance and relevance of innovation recipients manifested itself through other CFIR domains. The construct *needs and resources* from the outer setting domain and the *innovation participants* from the process domain, both strongly distinguished performance in the different demonstration project sites. Social mobilization will need to be informed by finding from studies that have captured recipients' perceptions, beliefs and attitudes. Additionally, the identification of the right opinion leaders is key to implementation success. Failure to engage Muslim religious leaders in the low performing site undermined social mobilization. Community members informed health workers in this site that they had not taken their girls for vaccination because they only heard the messages about HPV vaccination on the radio but not from their *imams* in the mosques. In addition a longer period of social mobilization will be required compared to what was done during the demonstration project.

While planning was found to be important from our results it was more pertinent at the higher level of the health system. The units in our study were the frontline and also peripheral health service provision segments and even though planning negatively influenced performance, the impact at this level was not very profound because all the districts largely accomplished the demonstration project objectives despite their late involvement in planning activities. However, based on the study participants observations earlier involvement of districts in planning activities is likely to improve implementation performance and is highly recommended.

Conclusion

We conclude that the CFIR is a useful and practical tool for researching health system implementation success determinants. A salient characteristic which made it a preferable IS framework, as well as a rationale for us to recommend it to other health intervention researchers, is its unique methodology that

allows for the comparison of constructs across different implementation efficiencies. This feature ensures that researchers do not just list determinants but are compelled to delve deeper and understand them in the context of implementation success or failure. Furthermore, its broadness makes it a comprehensive framework that ensures that an extensive range of implementation determinants are considered. This usually manifests itself during the exercise of assessing all the 39 constructs and subsequently narrowing down and selecting those relevant to the evaluation. As such researchers are pushed beyond being narrow minded irrespective of their context or nature of their intervention, be it a health system or community based intervention. Additionally, it allows for flexibility without compromise, for example in our study we found it was possible to indirectly explore innovation recipients, despite excluding the *characteristics of individual* domain from the evaluation.

Finally, due to its widespread application researchers are able to compare results with other studies that have applied the CFIR to implementation research evaluations. We were able to compare our findings with those of other studies that utilized the CFIR for similar evaluations. Our findings were similar to those of other studies undertaken in resource limited setting and developed countries too.

Table 1: Provincial health and socio-economic parameters in the HPV demonstration project provinces

Parameters	**Maputo**	**Manica**	**Cabo Delgado**
Proportion of girls aged 6 years or more who enrolled in primary schools	64.7	63.5	46.8
Under-five mortality	96	114	116
Contraceptive prevalence rate among women 15-49 years old (married or in union)	32.8	12.5	2.9
Proportion of households with access to potable water	85.1	84.1	37.1
Proportion of households with access to electricity	60.3	22.2	5.0
Wealth quintile (proportion in poorest quintile)	1.2	5.5	23.8

Source: INE et al. 2013 (DHS 2011)[28]

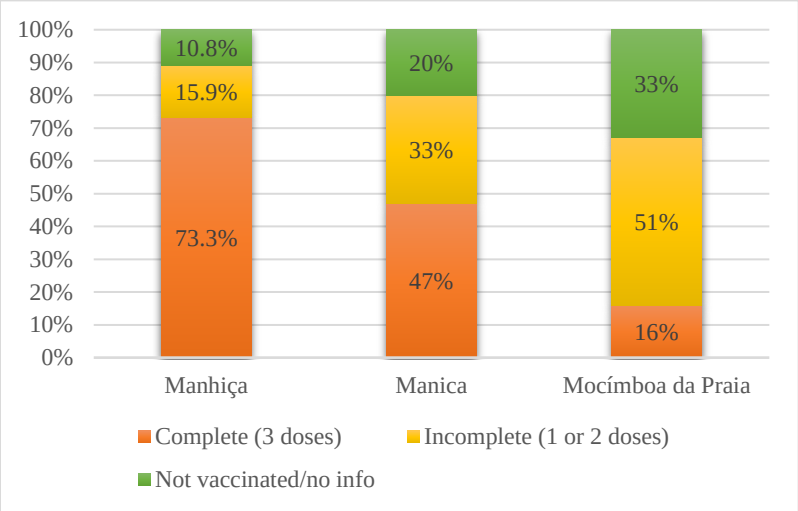
Table 2. CFIR construct rating rules[21]

Rating	Criteria
-2	The construct is a negative influence in the organization, an impeding influence in work processes, and/or an impeding influence in implementation efforts. The majority of respondents describe explicit examples of how the key or all aspects (or the absence) of a construct manifests itself in a negative way
-1	The construct is a negative influence in the organization, an impeding influence in work processes, and/or an impeding influence in implementation efforts. Respondents make general statements about the construct manifesting in a negative way but without concrete examples: (1) the construct is mentioned only in passing or at a high level without examples or evidence of actual, concrete descriptions of how that construct manifests; (2) there is a mixed effect of different aspects of the construct but with a general overall negative effect; (3) there is sufficient information to make an indirect inference about the generally negative influence; and/or (4) judged as weakly negative by the absence of the construct.
0	A construct has neutral influence if: (1) it appears to have neutral effect (purely descriptive) or is only mentioned generically without valence; (2) there is no evidence of positive or negative influence; (3) credible or reliable respondents contradict each other; and/or (4) there are positive and negative influences that balance each other out, the construct has some positive influence whereas other influences are negative and, overall, the effect is neutral.
+1	The construct is a positive influence in the organization, a facilitating influence in work processes, and/or a facilitating influence in implementation efforts. Respondents make general statements about the construct manifesting in a positive way but without concrete examples: (1) the construct is mentioned only in passing or at a high level without examples or evidence of actual, concrete descriptions of how that construct manifests; (2) there is a mixed effect of different aspects of the construct but with a general overall positive effect; and/or (3) there is sufficient information to make an indirect inference about the generally positive influence.
+2	The construct is a positive influence in the organization, a facilitating influence in work processes, and/or a facilitating influence in implementation efforts. The majority of respondents describe explicit examples of how the key or all aspects of a construct manifests themselves in a positive way.
Missing	Respondent(s) were not asked about the presence or influence of the construct or, if they were asked about a construct, their responses did not correspond to the intended construct and were instead coded to another construct. Respondent(s)' lack of knowledge about a construct does not necessarily indicate missing data and may instead indicate the absence of the construct.

Table 3: Mozambique HPV vaccine demonstration project CFIR construct valence rating

		Valence		
Evaluated Constructs	**Distinguishing**	**High**	**Intermediate**	**Low**
Innovation Characteristics				
Adaptability	Strongly	+2	-2	-2
Complexity	Strongly	-1	-2	-2
Design Quality & Packaging	Not	+2	+2	+2
Outer setting				
Patient Needs & Resources	Strongly	+2	-2	-2
Inner Setting				
Structural Characteristics	Strongly	+2	-2	-2
Networks & Communications	Weakly	-1	-2	-2
Culture	Not	+2	+2	+2
Relative Priority	Not	+2	+2	+2
Org. Incentives & rewards	Strongly	0	-2	-2
Learning Climate	Strongly	+2	0	0
Available Resources	Strongly	0	-2	-2
Access to knowledge and info	Strongly	+2	-1	-1
Process				
Planning	Not	-1	-2	-2
Opinion leaders	Strongly	+2	-2	-2
Champions	Not	+2	+1	+1
Key stakeholders	Strongly	+2	0	0
Innovation participants	Strongly	+2	0	-2
Executing	Neutral	0	0	0
Reflecting &Evaluating	Not	+2	+2	+2

Figure 1: Mozambique demonstration project HPV vaccination coverage



Source, National Immunization Program, 2015

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Chapter 3: A mixed methods Case Study of Mozambique's Demonstration Phase Partnership Model

Title Page

Title:
Delivering human papillomavirus vaccine in Mozambique: A mixed-methods partnership evaluation

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Abstract

Background
Gavi, the Vaccine Alliance, is a Global Health Partnership whose model is based on the reliance of domestic and international partners to support implementation of immunization activities under its Partnership Engagement Framework mechanism. We applied the Gavi Full Country Evaluation (FCE) partnership framework to test the contribution of network structure on the added value of the Mozambique HPV vaccine demonstration phase partnership.

Methods
Mixed methods were utilized to measure five partnership dimensions. Qualitative tools described the contextual factors and prerequisites, partner performance and practices; social network analysis (SNA) the partnership structure, and a survey measured the perceived added-value in the form of effectiveness, efficiency and country ownership. Forty key informant interviews were conducted with frontline ministry of health workers, ministry of education staff and supporting partner organization members with 34 of these additionally responding to the social network and perceived outcomes surveys.

Results
SNA measures for partnership structure corroborated the perceived outcome survey results. They revealed a partnership network characterized by high overall connectivity scores of reachability 100% and average distance 2.5, features that are favorable for rapid and widespread diffusion of information necessary for engaging and handling multiple implementation scales. High SNA effectiveness and efficiency measures for structural holes (85%) and low redundancy (30%) coupled with high mean perceived effectiveness (97.6%) and efficiency (79.5%) outcome scores were observed. Additionally, the tie strength average score of 4.056 on a scale of 5 denoted high professional trust. These are all markers of a partnership where disparate institutions and organizations worked in a collaborative environment in which the comparative advantage that each entity had to offer was leveraged. Lower perceived outcome scores for country ownership (24%) were found with the challenges of working with out-of-country partners being prominently cited by study participants as reasons.

Conclusions
While there is room for improvement on the country ownership aspects of the partnership, the expanded, diverse and inclusive collaboration of institutions and organizations that implemented the Mozambique HPV vaccine demonstration project was effective and efficient and we recommend that the country adapt a similar model during the national scale up.

Key Words
Partnership, HPV vaccine, SNA, Mozambique, Gavi, Global health, demonstration project

Background

Health program implementation by nature, and especially in low-and middle-income countries (LMICs), requires the involvement of different types of players from different sectors[1]. Disparate individuals spanning different health system levels such as community, health facility, regional, national and international and from different types of organizations and institutions all have a role to play[2]. This diversity in actors relies on various relationships and interactions amongst the players during operationalization of the programs. Partnership, which is defined as a collaboration with the mission of accomplishing a common goal either contractually or non-contractually, is a key type of such relationships[3]. Partnerships, have traditionally existed at the country level amongst different implementing entities, however the phenomenon of global health partnerships (GHPs), is more recent, having emerged in the last two decades[4]. Nevertheless, GHPs have expanded rapidly and gained broader relevance to the extent that they are now considered a salient feature of health program implementation in LMICs[5]. Consequently, partnership has gained prominence as a health program implementation determinant in these settings [6]. Additionally, the broader implementation science (IS) field recognizes the study and measurement of partnerships as a core component of implementation research with emphasis on its pertinence being highlighted in different forms in IS frameworks [7] [8] [9].

Gavi, the Vaccine Alliance, is a GHP that was set up with the agenda of increasing the availability and accessibility of new and underutilized vaccines in low income countries (LICs)[10]. Founded in 1999, the public private partnership brought together four founding organizations, the Bill and Melinda Gates Foundation (BMGF), World Bank, World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) in a set up designed to leverage each organization’s unique technical expertise in the global arena. Additionally, pharmaceutical companies that manufacture vaccines, donor and recipient governments, civil society organizations, research and technical institutes are also members of the alliance[11]. In this partnership model, Gavi does not place implementation support teams for its

sponsored programs in countries but instead relies on both in- and out- of country partners under its Partnership Engagement Framework (PEF) mechanism. WHO and UNICEF are the principal in country implementation partners undertaking the majority of PEF activities, with other organizations' involvement depending on countries' immunization programs' capacity needs [12].

Gavi financial support for new vaccine introductions (NVIs) began in 2000, with the roll out of the diphtheria, pertussis (whooping cough), and tetanus and Hepatitis B (DPT-HepB) vaccine. Subsequently the number of supported vaccines increased to the current eleven; one of which is the Human Papillomavirus (HPV) vaccine[13]. Its inclusion in 2011, was however marked by an unprecedented requirement for countries to first implement a demonstration project prior to national scale-up, in order to gauge effectiveness of possible delivery models. The demonstration project was deemed necessary due to the novel target age group of 9 -13 years that falls out of the routine country national immunization program (NIP) target age group of 9 -24 months. Most LICs do not have an adolescent specific health care service and therefore lack a health service delivery system for this target group[14]. HPV vaccine introductions were thus being conducted in two phases, the demonstration project and the national roll out, each with its own set of decision making, planning and execution processes [15]. While Gavi has had a record of success in accelerating the national adoption of the other new vaccines[16], HPV vaccine introduction has encountered the challenge of slow adoption. Only three of 23 countries that had completed demonstration projects by December 2016, advanced to the national scale up phase, a stark contrast to Gavi's planned target of eight nationwide HPV vaccine introductions by 2015[17]. While the reason for the lagged uptake is multifactorial, one important barrier is the dearth in published country specific HPV vaccine demonstration project evaluation findings in the literature[18].

This paper is one in a series of three (in progress), that seek to fill this gap by describing findings from three case studies conducted on the Mozambique HPV vaccine demonstration project. The study was embedded within the larger Gavi Full Country Evaluation (FCE), taking place in four countries [19] . In

this article, we apply the Gavi FCE partnership framework (Figure 1) [20] to test the contribution of network structure on the added value of the Mozambique HPV vaccine demonstration phase partnership.

Methods

The Gavi FCE Partnership Framework

The Gavi FCE partnership framework was developed by the FCE team, through the integration of concepts from public administration, organizational science and network analysis resulting in a theoretical framework that proposes the measurement of network structure using social network analysis (SNA). The network structure of organizational partnerships tends to be more decentralized than traditional organizational structures; ensuring effective partnership networks require an element of supporting the appropriate structure of relationships. The framework describes five partnership evaluation dimensions (Table 1) that are causally related and additionally provides for the empirical measurement of network structure using SNA metrics[20].

In line with social network diffusion theory, we hypothesized that the 'structure' dimension of the framework will be highly predictive of a partnership's performance and this paper puts additional analytic emphasis on partnership structure through the application of social network analysis methods. Social network diffusion theory explains how network structures act as either facilitators or barriers to the adoption of novel practices. Network-level structure and outcomes are determined by the relationships between network actors. These relationships usually involve the exchange of any content, for example information or resources between two actors [21]. In this study we measured the exchange of technical assistance information between network actors and collaboration through working together relationships. We assume the effective implementation of the HPV vaccine demonstration project occurred in part due to the effective structure of collaboration relationships and the effective diffusion of information through the network.

The Gavi FCE partnership framework included outcome measures of perceived efficiency, effectiveness, and country ownership of the partnership, as well as network diffusion theory hypotheses relating network structure to these outcomes (see Table 2). We augmented these hypotheses with a similar framework relating network connectivity to health systems governance. We used the WHO health system framework governance characteristics approach as described by Blanchet et al[22]. In this approach, specific SNA hypotheses and measures are linked to three governance capacity characteristics that the framework recommends for the health care delivery collaborations that commonly exist in LMICs. A frequent feature of these collaborations is the engagement of diverse actors including governments, research institutes and various types of global health organizations. The approach was deemed suitable because the Mozambique HPV vaccine demonstration project implementation constituted a similar group of partner stakeholders. Listed in table 2 are the hypotheses and summary of SNA measures, including those described by Blanchet et al and considered under each of the three capacity characteristics.

Study design

Mixed methods were utilized to measure each of the five dimensions of the partnership evaluation framework detailed in table 1. Qualitative tools described the contextual factors and prerequisites, partner performance and practices; social network analysis (SNA) the partnership structure, and finally a survey measured the perceived added-value in the form of effectiveness, efficiency and country ownership.

Study Setting

The Gavi FCE is a prospective evaluation that began in 2013 in four countries: Mozambique; Uganda; Zambia; and Bangladesh. The study was commissioned by Gavi with the aim of linking inputs, outputs, outcomes and impact to the support provided by Gavi. A key evaluation question is the role of the Gavi partnership model in decision making, planning, implementation and financial support. The findings presented in this paper were from one the studies that sought to respond to this research question.

The case

The Mozambique HPV vaccine demonstration project was conducted during two years with the objective of testing a HPV vaccine delivery model for girls aged between 9 and 13 years. It was implemented in three districts that were chosen to represent the three diverse geographical regions of Mozambique. These were Manhiça, Manica and Mocímboa da Praia in the Southern, Central and Northern regions respectively. Funding was obtained from Gavi for Manhiça district while the Government of Mozambique (GoM) funded the project in the other two districts. The delivery model that was tested was primarily school based whereby health workers delivered the vaccine to girls in schools. Periods of one week were predetermined and utilized for the delivery of each dose. In the first year (2014) three doses were delivered in May, June and November in alignment with the then WHO recommended schedule of administration of a dose at 0, 1 and 6 months. In the second year (2015) the WHO guidelines had changed to two doses at 0 and 6 months and the vaccine was administered in June and November[23]. Data was collected by a team of Gavi FCE researchers in all the three demonstration districts during the two years of the project.

Data Collection

Qualitative data

Three methods were used to gather qualitative data *i) document review ii) direct observations iii) key informant interviews (KIIs).* A broad range of documents were reviewed including all Mozambique HPV vaccine demonstration project vaccine grant proposals, HPV demo project budgeted plans, Mozambique Gavi business plan and partnership engagement framework, Gavi HPV vaccine demonstration project guiding documents, minutes of meetings held by the NIP and partners, notes from direct observations, terms of reference for the different HPV vaccine demonstration project related committees/working groups, NIP programmatic evaluation documents, NIP strategic plans, NIP audits and financial reports. Information gathered from document review were used to refine the questions in the KII topic guide.

Direct observations were conducted through participation in all HPV vaccine demonstration project meetings ranging from NIP technical working group meetings; subcommittee meetings focusing on, for example, cold chain management; national immunization technical advisory group meetings; and Inter Agency Coordination Committees (ICC) meetings. Additionally, events such as trainings, supervision visits, the official launch and all implementation activities for HPV vaccine demonstration project in the three demonstration districts were tracked. Information gathered from direct observations that respond to the evaluation aspects of the five dimensions of the partnership framework were used to further refine the questions in the KII topic guide.

The sampling approach for the KIIs was two pronged. First, was the comprehensive approach targeting all known NIP stakeholders and second the chain referral (snow ball) approach targeting other key informants (KIs) as they were referred by those that are already sampled[24]. Known institutions and organizations that were identified through document review and direct observations. Samples were drawn from the following groups within the identified entities: health facility immunization staff, district immunization staff, district education staff, provincial immunization staff, provincial medical heads, central MOH level immunization program staff, staff from research institutions, non-Governmental organizations (NGOs), bilateral and multilateral institutions that supported the NIP during all the HPV vaccine demonstration project phases.

A semi-structured open ended interview guide was developed for KIIs. The key informants were being interviewed repeatedly over the lifespan of the Gavi FCE and interviewee fatigue was an encountered limitation. In order to mitigate this the number of questions was minimized by eliminating questions from the KII topic guide that already had responses from document review and previous KIIs of the FCE. A generic topic guide was used for all KIIs with probing techniques applied whenever the need arose.

Interviews were conducted in the place of convenience to the key informant, usually their office. Appointments were arranged over email and phone and consent form and topic guide shared with the key informant prior to the interview. Note taking and audio recording were both used to document the interview. It was foreseen that audio recording was likely to modify what people said and probing techniques were used to elicit information during these instances.

Social Network and Perceived Outcomes data

A two-section structured survey questionnaire was utilized for the collection of both the network and perceived outcomes data. Boundary specification of the network was made using the positional strategy[21]. Actors were identified based on their positions in the institutions and organizations involved in the implementation of the HPV vaccine demonstration project. The network survey was then administered to them with the aim of identifying the individual professionals the actors had interacted with during the HPV vaccine demonstration project processes, activities or events, and the actors' working relationships with them. The actor was asked: "With whom did you work with on the HPV vaccine demonstration project?" This is known as a 'name generator' in social network analysis[21]. They were subsequently asked to rate their level of professional trust and satisfaction with the provided or received technical assistance from a scale of one to five. Professional trust was defined as "expectations when working with the individual you have named, do you trust that he/she has the ability to respond to what you requested for and to do and complete what they have promised to do?" The perceived outcomes section contained a set of questions about the KIs' perceptions of the outcomes of their working relationships with the other organizations. These questions were adapted from Provan et al.[25] and organized according to perceived benefits and drawbacks of working together. The KI was asked to choose if the benefit or drawback occurred or did not occur. In addition, probing was employed to capture reasons for the choice provided by the informant.

Data Analysis

The units of analysis for the qualitative segment of our study, were the individuals, institutions and organizations directly involved in the implementation of the Mozambique HPV vaccine demonstration project. Audio recorded data was transcribed into texts by known professional transcribers with experience in transcribing other audio recorded data in the Mozambique Gavi FCE. Nvivo software was used to facilitate a theme based analysis as per the five dimensions of the partnership conceptual framework. A preliminary codebook was developed and responses to the partnership framework dimension's research questions sought and given their own code. Following coding, a report of each code was produced, read, and re-interpreted in order to produce a synthesis of findings related to each code. The results from this analysis informed the understanding of the partnership context, how and why partners perform as they do and how and why partnership practices are what they are**.**

The individual was the unit of analysis for the social network and perceived outcome analyses. The data collected from the network survey was entered into a spreadsheet matrix in MS Excel. Each reported working relationship, or "tie," was weighted according to the key informant's reporting of relationship trust. Technical assistance exchange tie was entered as binary. The resulting spreadsheet contained three asymmetrical, undirected network matrices. These network matrices were imported into UCINet software[26] for analysis. Descriptive network maps were created using the NetDraw[27] application within UCINet software. Nodes were color coded according to node attributes from the survey. UCINet was used to describe the structural properties of the identified networks which were treated as independent variables in comparison to the outcomes measures. Data from the perceived benefits and drawbacks survey section was also entered into the same excel spreadsheet as the network data and the scores aggregated and analyzed for effectiveness, efficiency and country ownership of the partnership.

We employed an iterative triangulation process in which all the three types of data were analyzed and reanalyzed in order to construct patterns and facilitate interpretation.

Results

Descriptive statistics

A total of 40 KIIs were conducted at national, provincial, district and health facility level in the three HPV vaccine demonstration district sites in the country (Table 3). Thirty-four of these study participants additionally responded to the social network and perceived outcomes surveys. All the interviews were conducted during the second year of the implementation phase of the HPV vaccine demonstration project. Majority of those interviewed were from the Ministry of Health (MOH) (55%) and the Ministry of Education (MOE) (15%) with a larger proportion (35%) being from the district level.

Detailed results are presented below within the five Gavi FCE partnership framework dimensions.

Contextual factors and prerequisites

While the Gavi Alliance plays a key role in driving Mozambique's national immunization program and in turn the HPV vaccination delivery partnership, other important contextual factors that emerged as key drivers of the partnership were the country's first lady's involvement as a champion, Gavi's requirement for the NIP to carry out assessments to demonstrate the feasibility of the vaccination delivery model and the delivery of the vaccines in schools.

The Gavi Alliance partnership is the main driver of the country's national immunization partnership which according to interviewed informants historically stemmed from when the country first became a beneficiary of Gavi grants in 2001. The two core Gavi partners WHO and UNICEF, whose roles within the alliance are the provision of in-country implementation support, were referred to by NIP staff as the "traditional partners" that had been relied on since the inception of Gavi support. Furthermore each partner was known for specific roles, WHO for technical guidance and UNICEF for logistics and supplies.

"We are used to working with WHO for technical guidance. UNICEF they usually support us for vaccine logistics and supply" NIP

Two other organizations, VillageReach an international non-governmental organization(NGO) and Fundação para o Desenvolvimento da Comunidade (FDC) a local organization were also considered as "usual" NIP partners and had supported immunization activities for more than five years prior to the HPV vaccine demonstration project launch. Further investigation revealed that that these two organizations had strong ties to Gavi. VillageReach is an American based organization whose funding comes from the BMGF a founding partner of the Gavi Alliance, and whose founding board member was at one time the Gavi board president. Coincidentally, FDC`s founding president had also previously been the head of the Gavi board for a decade, from its inception in 2001 until 2009. Qualitative data results demonstrated the importance of these Gavi links to their participation as partners in the HPV vaccine delivery demonstration project.

"Invitation for VillageReach (to be NIP partner) was explicit. Especially after the head of NIP understood VillageReach`s work and its relationship with GAVI. She (NIP head) was new initially. The president of Gavi used to be board member of VillageReach from the inception of VillageReach. We were more invited when they realized the relationship we had with GAVI and the information that VillageReach had with regard to Gavi" (Civil Society Organization)

"….for example FDC was already interested (in HPV vaccination introduction) from before because their president Machel was a member of the Gavi board for many years" (Research Institute)

In the year prior to the launch of the HPV vaccine demonstration project, Mozambique's then first lady assumed the leadership of the Forum of African First Ladies Against Breast & Cervical Cancer and

hosted a conference in Maputo[28], the country's capital. This position propelled her to become a HPV vaccination champion in both the continent and the country with subsequent impact on the HPV vaccination pilot partnership. The NIP and MOH were compelled to take on a leadership role as opposed to the participatory role that both entities had assumed during the HPV grant application writing period. Significant results of this new MOH role in the HPV vaccination pilot project partnership saw the demonstration project expanded to two more districts instead of only the one district that Gavi had approved for funding, with the MOH using its own funds to carry out demonstration activities in the two additional districts. Another outcome of this MOH leadership, was the disbursement of HPV vaccine introduction grant (VIG) funds from Gavi through MOH and not to Gavi in country partners WHO and UNICEF as had happened previously with pneumococcal vaccine (PCV) introduction grant and as had been agreed on during the HPV vaccination grant signing. The MOH having assumed a leadership role was able to negotiate with Gavi to receive the funds.

A couple of contextual factors unique to HPV vaccination led to an expanded partnership that was compositionally different from that observed during the introduction of other vaccines. First was Gavi's requirement for the country to include an assessment component in the pilot in order to demonstrate the feasibility of the delivery model that would be tested. For this purpose two research institutions, the Manhiça Research Center (CISM) and the country's National Institute of Health (INS) were included in the partnership to lead assessments in the Gavi and Government funded districts respectively. The second factor was the nature of delivering the vaccine in schools that necessitated the involvement of the ministry of education in the partnership. Subsequently ministry of education personnel were involved in HPV vaccination activities at all levels from national to provinces, districts and schools.

Partnership Structure

The SNA results for distance, reachability, centralization, betweenness, density, structural holes, homophily and average trust are shown in table 4. The network structure was found to contain a total of 50 actors and 164 ties. The reachability score is 100% meaning that there is at least one path connecting all actors in the network and each can be reached from whichever point the network you start at (figure 2).

The distance score which is defined as the average number of edges in the shortest path between pairs at 2.52 is short. Shorter distance in SNA is commensurate with faster and more accurate information flow. Combining these two scores with our first WHO health system governance first characteristic hypotheses (Table 2) we can infer a partnership that has the capacity to effectively engage with and handle multiple scales. The perceived outcome survey scores corroborate this finding (Table 5). The effectiveness average score of 97.6% was the highest in the outcome survey and includes scores of 100% agreement in three questions in which respondents were asked about the HPV vaccination partnerships ability for better execution, better quality and improved response to challenges when they worked with multiple types of entities and organizational hierarchical levels.

For the second WHO health system governance characteristic hypotheses the centralization score was found to be neither low or high at 48% and the average betweenness was 37.24 with a large standard deviation of 110.1. This is not surprising given that the outdegree statistics identified three outlier actors numbers 2, 5 and 24 (figure 2) around which the network is centralized with actor number 2 possessing the highest outdegree score. The partnership is not highly centralized around 1 focal actor (e.g. EPI program). Despite this, effective relationships between three key actors ensured that the partnership could coordinate and respond effectively to challenges. Supporting this finding were the perceived outcomes survey results in which 100% of respondents agreed that the HPV partnership had a high capacity to respond to existing challenges that arose during the process (Table 5) and qualitative data too (quotation below).

"The involvement of many organizations was very advantageous because we as the district directorate of health would not have been able to undertake all the activities within the short time that we had to prepare. The partners and their support helped us to reach where we would not have reached, for example sometimes they gave us fuel when we didn't have and even one hired a boat to reach some islands" (District Health Directorate)

The third WHO health system governance characteristic is the capacity to combine and integrate different forms of knowledge whose hypotheses (Table 2) are based on density and reachability across different spheres and entities. Actors in very dense networks have difficulty in accessing diverse forms of knowledge; however density is important for the effective transfer of complex knowledge[29]. This network has a low density score of 0.1338, which taken together with the observed diversity of types of entities in the network, distinguished by different colors in figure 2, as well as the 100% reachability across entities, lead us to conclude that actors in this partnership are well positioned to receive new types of information.

Further support for this finding comes from the contextual qualitative data in which respondents observed that the implementing partnership for the HPV vaccine that targets a novel age group is compositionally different from that implementing the vaccines that target the traditional infant age group.

"The target group for HPV vaccine is different so we have to work with different collaborators, for example the ministry of education and partners in the community that helped us to pass the message" (District Health Directorate)

Partnership performance, practices and outcomes

Given that the Gavi FCE partnership framework is a pathway and prior studies[30] [20] have demonstrated that a partnership's structure determines its performance, practices and consequently the outcomes, the last three dimensions are interpreted here jointly. SNA measures have so far revealed a

network characterized by high overall connectivity and that is favorable for rapid and widespread diffusion of information. In addition trust within the partnership is very high as evidenced by the high tie strength average score of 4.056 which is very close to the upper limit of five on the scale that respondents had been asked to rate professional trust on. These results are further supported by the network outcome SNA measures that unveil an efficient network characterized by a high number of structural holes and less redundancy. Majority (85%) of the nodes in the network require only 2 or 3 paths to reach them and 70% have only one way to connect with other nodes. The network was also found to be heterogenous with and E-I index scores of 0.195.

On triangulation with qualitative and perceived outcomes data so as to facilitate interpretation we found that these topological features of the network influenced partnership practices and subsequently the outcomes.

The partnership structure heterogeneity significantly influenced partnership practices. The avoidance of duplication of activities or partner organizations focusing on the same activities in the same geographical area emerged as very key to the effectiveness and efficiency of this partnership. Respondents at all levels emphasized the role of regular meetings in the form of a formalized NIP technical working group (TWG) at national level and regular meetings chaired by the head of health at provincial and district levels. Specific roles for specific partner organization was another attribute that respondents repeatedly stated. Remarkably each partner organization was known for a specific role in this partnership. Beyond WHO and UNICEF's earlier stated roles VillageReach was known as a logistical support partner, FDC for community mobilization and GlaxoSmithKline (GSK) usually supported printing of training material and health worker job aids. Perceived outcomes survey scores added strength to these findings with 88% of respondents agreeing that the partnership leveraged each partner organizations' comparative advantages.

> *"……the duplication of activities does not occur because each organization presents its activities to the directorate and the directorate tells them where they can work. Apart from that we have regular coordination meetings"* MOH provincial Directorate

Lower agreement perceived outcome scores were noted for the questions on country ownership (79%), reduction in financial cost of process (74%) and better allocation of each organization's financial resources (62%), consistent with a similar study in Uganda[20]. Many district level respondents expressed their dissatisfaction in the sufficiency of funding that had been availed to the districts for HPV vaccination activities with the situation being worse in the districts that were not funded by Gavi and had to depend on only MOH funds. While some respondents noted that partner organizations had stepped in and helped a lot especially with in kind donations many expressed the lack of funding especially for outreach activities when they had to visit communities to look for non-school attending girls.

Correspondingly the highest drawback score was that of country ownership at 24%. Several issues were mentioned regarding country ownership but featuring prominently was the preference for a country based partner organization. Respondents expressed their unhappiness on the inclusion of a non-country based partner in the HPV implementation partnership. Language barrier and lack of contextual knowledge were mentioned as some of the problems of the specific technical assistance that was provided by the particular partner who was considered foreign. The lack of participation in the regular technical working group meetings was also noted as a hindrance to an individual based outside the country contributing effectively to the partnership. This is because TWG meetings was the forum where most of the partnership communication took place with updates on progress on processes being made, important discussions taking place and key decisions being made during the meetings. Short visits to the country to provide technical assistance were said to be ineffective and were even blamed for having largely contributed to the delay in the accomplishment of some HPV vaccination pilot implementation phase deliverables.

Discussion

Delving into the Mozambique HPV vaccination implementation stakeholder relationships in this case study, has revealed the importance of balance between donor and government influence, the necessity for adaptability to changing needs and the value of country ownership for an effective vaccine delivery partnership.

We observed a partnership that was equally driven by the MOH as well as the influence of the global Gavi partnership model. The balance between Gavi and Government of Mozambique influences during the implementation of this pilot led to remarkable effectiveness and efficiency results. The perceived outcome survey mean effectiveness score was quite high at 97.6% and the mean efficiency was 79.5%. Partnership composition and practices were equally driven by both entities resulting in a complementary relationship that engendered a favorable collaborative environment in which the best that each institution had to offer was leveraged. The Gavi partnership model of having specific core partner roles guided the HPV partnership to adapt these principals resulting in optimization of each organizations competencies and avoidance of redundancies in terms duplication of partner activities. These conditions created a conducive environment for the successful testing of a challenging vaccine delivery model for a novel target group in three different Mozambican contexts with the outcome of important knowledge being gained for the planning for national scale up. Had Gavi's influence been dominant and the original Gavi decision followed, the HPV vaccination pilot would have taken place in only one district representing only one Mozambican economic and religious context and learnings from the different contexts that the other two districts offered, would have been missed.

Another salient finding emerging from this study is the importance of a flexible partnership to adequately respond to unpredictable events and evolving priorities. The expansion of the Mozambique demonstration project that was originally planned for just one district to three districts happened in a short period of

time, within just six months prior to the launch of the demonstration project. The ability for the partnership to adapt and bring on and integrate new members to the implementation collaboration was outstanding. This finding not only agreed with the SNA hypotheses that we had adapted from Blanchet et al regarding the second characteristic of the WHO health system governance characteristic number two (table 2) but with our SNA results too. Our results clearly demonstrate that a partnership whose structure is moderately centralized, around few key diverse players, has a higher capacity to coordinate actors and provide rapid response. Similarly rapid response occurs when the key diverse players have the ability to reach all actors across the different entities in the network. In addition, another learning was the function of an innovative intervention requiring additional roles and further leading to the expansion of the partnership. Again the partnership was malleable and successfully integrated the necessary research institutions and ministry of education for the purpose.

The third and final outcome measure of our study was the country ownership for which the perceived outcome survey score at 79.5% at was among the lower scores. A salient factor that was elucidated was how the location, in or out of country, of a technical assistance provider affects the outcome of their support. The specific barriers that were encountered by the out of country international partner and which we have highlighted in our results section, are particularly informative and relevant for Gavi to consider when assessing potential technical assistance providers for countries in the current era of the partnership engagement framework (PEF).

Strengths and Weaknesses

Our study's participation rate was quite high with 40 individuals from different entities and different health system levels responding to both the network and perceived outcomes survey. This is a relatively large sample size especially for the qualitative data component; however, the accuracy of network data rely on a full census of a network and this study's response rate may lead to underestimations of network density in particular. Ties beyond the set boundary were not explored and there might be missing data that

was not captured. Mixed methods captured different types of data that were triangulated and this facilitated interpretation. The generalizability of our findings may be limited to low and middle-income countries whose socioeconomic features are similar to those of Mozambique.

Conclusion

In applying the Gavi FCE partnership framework we have found it to be a particularly useful tool for conducting a comprehensive partnership evaluation. This is because unlike previous predecessor partnership evaluation frameworks, namely the traditional and Brinkerhoff[31], the FCE framework takes a more holistic approach resulting in the consideration of an expanded set of partnership characteristics that influence partnership performance outcomes. While all three frameworks invariably describe the causal chain nature of the partnership characteristic from the contextual factors and prerequisites in a sequence all the way to the outcomes, the inclusion of the partnership structure together with the provision for the use of SNA tools to study it, highly enhanced the framework. These components of the FCE framework offer the possibility of unmasking partnership attributes that may not be overt. SNA theory provides the basis for looking at a partnership as a constellation of relationships that make up a network and the metrics a way to measure its effectiveness and efficiency. Furthermore the utilization of mixed methods that the FCE framework also provides for, allowed for a broader analysis and exploration of the partnership. For these reasons we recommend the use of the Gavi FCE framework to evaluate global health partnerships.

While there is room for improvement on the country ownership aspects of the partnership, the expanded, diverse and inclusive collaboration of institutions and organizations that implemented the Mozambique HPV vaccine demonstration project was effective and efficient and we recommended that the country adapt a similar model during the national scale up.

Table 1: Gavi FCE partnership framework dimensions' description

1. Contextual factors and prerequisites: Identification of the governmental and non-governmental institutions and organizations as well as the individuals that are involved in the implementation of the Mozambique HPV vaccine demonstration project. The origins of the partnership and how the broader political environment and the global Gavi Alliance partnership has influenced this. Other Mozambique contextual factors that have facilitated or blocked the successful formation and performance of this partnership.
2. Partnership structure: Understanding the composition of actors and their relationships with each other as well as the connections between the implementers of the HPV vaccine demonstration project in the country.
3. Partner performance: Exploration of how effectively partners meet their deliverables and the mechanisms for accountability.
4. Partnership practices: Investigation of the functionality of the whole partnership in terms of professional trust. Additionally, any formal and informal rules and processes that govern the partnership; partners' competencies, capacities, roles and responsibilities, the partnership coordination mechanisms and management of the partnership.
5. Partnership's added value: Determination of the outcomes namely efficiency, effectiveness and country ownership of the HPV vaccine demonstration project partnership in Mozambique;

Table 2: Social Network Analyses hypotheses and metrics

Theory of network diffusion hypotheses and measures for network efficiency and effectiveness

Structural holes: Network with more structural holes is more efficient for the diffusion of information

Redundancy: Less redundancy means a more efficient network for the relaying of information

Homophily: Novel information is more likely to enter heterogeneous networks while homophily in a network can be a barrier to accessing new information

WHO health system framework governance characteristics hypotheses and measures for network connectivity

Characteristic 1: Capacity to effectively engage with and handle multiple scales (e.g. levels and sectors of the health system)

Reachability: Networks with a high level of reachability have the ability to access various sources of information.

Distance: The shorter the distance between the actors the faster the diffusion of information. Networks with short average path length are more likely to facilitate the widespread diffusion of information

Characteristic 2: Capacity to anticipate and cope with uncertainties and surprises

Centralization: A centralized structure has a higher capacity to coordinate actors and provide rapid response

Betweenness: Rapid response occurs when the key actors have the ability to reach all the players in the network

Characteristic 3: Capacity to combine and integrate different forms of knowledge

Reachability: The diversity of technical knowledge can be achieved through relationships with actors that belong to other spheres or other subnetworks.

Density: Dense networks are more likely to facilitate the transfer of information however actors in a dense network have difficulty in accessing diverse forms of knowledge

Table 3: Organization affiliation of study participants

Organization Type	Number	%
MOH NIP	22	55
National	*5*	*12.5*
Provincial	*6*	*15*
District	*11*	*27.5*
MOE	6	15
National	*1*	2.5
Provincial	*2*	5
District	*3*	7.5
Multilateral	3	7.5
CSO/NGO	4	10
Research Institute	3	7.5
Bilateral	1	2.5
Pharmaceutical	1	2.5
Gavi	0	0
Total	40	100%

Table 4: Network Survey Statistics

Metric	Value	Hypothesis (from Table 2)
Nodes	50	
Ties	164	
Distance (average path length)	2.5	Networks with short average path length are more likely to facilitate the widespread diffusion of information
Reachability	1	Networks with a high level of reachability have the ability to access various sources of information
Centralization	0.483	A centralized structure has a higher capacity to coordinate actors and provide rapid response
Betweenness	37.24	Rapid response occurs when the key actors have the ability to reach all the players in the network
Density	0.1338	Dense networks are more likely to facilitate the transfer of information however actors in a dense network have difficulty in accessing diverse forms of knowledge
Structural holes	85%	Network with more structural holes is more efficient for the diffusion of information
Redundancy	70%	Less redundancy means a more efficient network for the relaying of information
Homophily E-I index	0.195	Novel information is more likely to enter heterogeneous networks while homophily in a network can be a barrier to accessing new information
Average tie weight	4.06	

Table 5: Perceived benefits of partnership (n=34)

Benefits:	**% of respondents who agreed**
Effectiveness	
Better able to execute activities	100%
Planned activities were executed with greater quality	100%
Better able to identify the need for, and to acquire additional support	97%
Better able to respond to existing challenges, or those that arose during the process	100%
Increased sustainability of immunization program	91%
Mean Effectiveness	97.6%
Efficiency	
More timely execution of planned activities	94%
Leveraged each organizations' comparative advantages	88%
Reduction in financial cost of process	74%
Better allocation of each organization's financial resources	62%
Mean Efficiency	79.5%
Country Ownership	
Increased country ownership	79%
Increased transparency among partners	91%
Increased accountability among partners	74%
Increased legitimacy of decisions made	94%
Increased fairness of decisions made	91%
Mean country ownership	85.8%
Drawbacks:	
Effectiveness	
Strained relations within my organization	9%
Created competition and conflict among member organizations	6%
Mean Effectiveness drawbacks	7.5%
Efficiency	
Unnecessary management burden on my organization	24%
Loss of control/autonomy over decisions	6%
Forced us to make decisions in a way which was not natural/typical for our organization	21%
Mean Efficiency drawbacks	17%
Country Ownership	
Not enough credit given to my organization	24%
Total Country Ownership drawbacks	24%

Figure 1: Gavi FCE partnership framework[20]

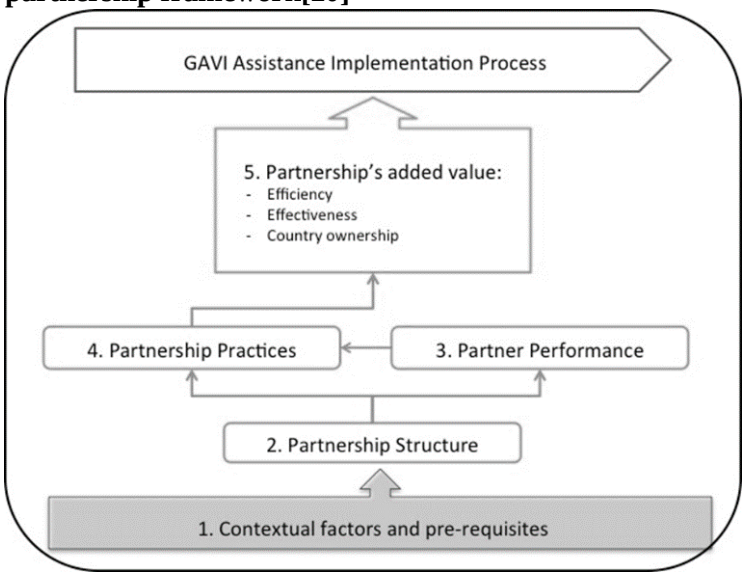
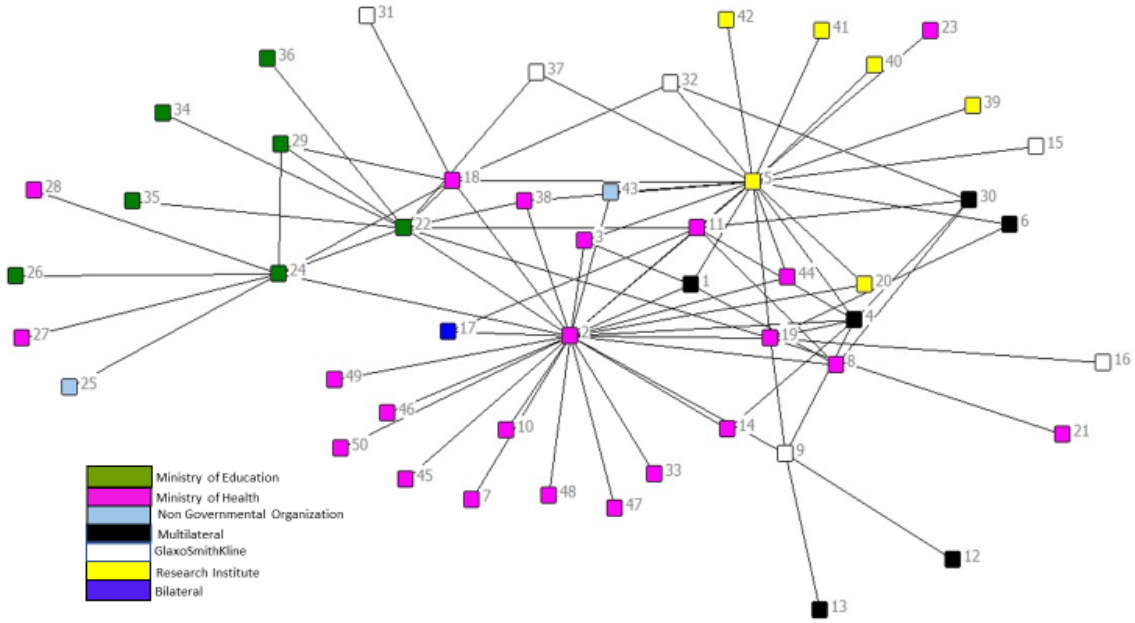


Figure 2: Mozambique HPV vaccine demonstration project partnership network structure



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Chapter 4: Mozambique HPV demonstration project delivery strategy and estimated costs

Title Page

Title:
An in-depth examination of the Mozambique HPV vaccine demonstration project implementation strategy and costs

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Abstract

Background
Cost is recognized as an important health program implementation determinant. In this study, a comprehensive inquisition of the implementation strategy of Mozambique's HPV vaccine demonstration project identified activities that were undertaken. Standardized methods were then utilized to estimate implementation costs and the cost per fully immunized girl (FIG).

Methods
Primary data was collected through document review, participatory observations and key informant interviews with project implementers at national immunization program central offices, provincial and district health directorates as well as in health facilities. The principle of the production function of a health program was used to identify resources and their quantities. Their costs were then valued using a mix of both micro and gross costing and subsequently aggregated. The overall cumulative costs were divided by the number of fully immunized girls to find the cost per FIG which was then extrapolated to the whole country eligible population in order to demonstrate the total cost for a similar one year program.

Results
Total project implementation costs were $523,601. Annual patterns and cost compositions of the aggregated costs provided insight into the factors contributing to changes in costs. They showed that important cost determinants were high vaccine price, number of administered doses, program startup costs and the necessity for rigorous demand generation. The cost per FIG was $72 (95% CI: $62 - $83) in year one, $38 (95% CI: $37 - $40) in year two and $54 (95% CI: $49 - $61) for the whole project period. The cost of a FIG when the first year third dose implementation costs were excluded were, Year 1: $60 (95% CI: $50 - $72), Year 2: $38 (95%CI: $31 - $46) and for the whole two year period $48 (95%CI: $42 - $55). The projected estimated costs for a one year 2 dose program targeting all 10 year old girls in the country were $18,156,549 ($15,865,384 - $20,748,196).

Conclusion
Adapting the current school-based implementation strategy for national scale up of HPV vaccination in Mozambique would be an expensive endeavor.

Background

Cost is an important implementation determinant factor that has been recognized by implementation research frameworks and outcomes guides [1][2]. The emphasis on the need for the inclusion of implementation strategy is pertinent because cost effectiveness studies undertaken during controlled trials may generate biased results that may not adequately inform efforts to deliver proven interventions [3]. Costs can be incurred during different implementation phases, and measuring and documenting them at any particular phase provides useful information for national policy makers and health program managers engaged in decision making for the adoption of health services' innovations [4]. Such cost information is also useful to researchers attempting to standardize implementation research costing methods in order to facilitate the production of generalizable study findings [5].

Human Papillomavirus (HPV) is a common sexually transmitted infection with a prevalence of 10% in healthy women globally[6]. The pathogen is not one single virus but a group of more than 100 strains, 30 of which can infect the anogenital tract to cause warts and cancers[7]. Of these, HPV types 16 and 18 have been proven to account for more than 70% of invasive cervical carcinoma (ICC), the most significant cancer caused by the HPV[8]. About 530,000 cases of cervical cancer occur in the world annually with 50% progressing to death[9]. Low and middle-income countries (LMICs) whose screening programs are underdeveloped and treatment options are limited, bear the brunt of the ICC burden with 85% of diagnosed cases and 87% of deaths occurring in these settings [10]. Globally, the highest rates of age standardized HPV incidence and mortality of 27.6 and 42.7 per 100,000 respectively, are found in East Africa [11]. Mozambique, with very high age standardized rates of 65.0 and 49.2 per 100,000 for incidence and mortality respectively, falls in second place on global ranking of cervical cancer burden[12]. Studies conducted in the country have established the high HPV prevalence as well as its relationship with cancer of the cervix. One study amongst 262 women aged 14-61 years found that 40% had HPV DNA, 19% abnormal cytology and 12% cervical neoplasia[13]. A second one confirmed HPV

types 16 and 18 infection in cancer biopsies of 78% of cervical cancer cases that were examined in the study[14].

The HPV vaccine which became available in 2006, is considered highly efficient as a prevention tool for cancer of the cervix [15]. Three types of the vaccine, bivalent, quadrivalent and nonavalent have been widely used in many high-income countries with notable consequent decline in HPV related disease [16] [17][18]. The World Health Organization (WHO) recommends adoption of the vaccine in LMICs where cervical cancer is of high public health priority[19]. Correspondingly Gavi, the Vaccine Alliance , in 2011, included HPV vaccine on the list of vaccines that it supports with funding for introduction into LMIC national immunization programs' (NIP)[20]. A challenge, however, was encountered: girls ages 9 - 13, the target group for HPV vaccination, are not usually targeted for routine immunization and don't usually interface with the health system because adolescent specific health services seldom exist in these settings[21]. As such Gavi's initial HPV vaccine introduction strategy required countries to conduct a demonstration project to test possible delivery mechanisms prior to national rollout[22]. Many low and middle income countries leveraged this opportunity and to date, thirty countries have conducted demonstration projects [23]. However, a slow progress to national scaleup of HPV vaccination was observed as only six countries had commenced national HPV vaccination programs by December 2017[24][25]. One identified barrier is the higher delivery costs due the complexity of setting up a new delivery model for the 9 -13 year old target age group[26] .

A recent study that reviewed HPV introduction costs from LMICs concluded that country specific HPV cost data were lacking and there was a need for more information from country demonstration projects[27]. The aim of this study is to fill this gap in knowledge by describing the results of an in-depth analysis of the implementation costs of the demonstration project that was conducted in Mozambique.

Specifically, we determined the cost of a fully immunized girl (FIG) and subsequently estimated the costs of rolling out a similar program nationally. We achieved these objectives, by examining the demonstration project vaccine delivery strategy, assessing the incurred implementation costs and extrapolating these costs to the national level.

Methods

This costing study was nested within the Mozambique Gavi, Full Country Evaluation (FCE), a six year prospective program evaluation that began in 2013. With the aim of linking Gavi funded immunization program inputs and outputs to outcomes and impact, the FCE is comprised of a process evaluation, household survey and a resource tracking component. The HPV vaccine demonstration project specific data collection period was from January 2014 to March 2017. Data was collected within the FCE process evaluation component through document review, participatory observation, and key informant interviews (KIIs).

Implementation Costing Approach

The study was performed from the payer perspective, in this case the Government of Mozambique through the Ministry of Health[28]. The costing approach followed the three steps of *identification*, *measurement* and *valuation*[29]. The resource items necessary for HPV vaccination were identified using the principle of the production function of a health care program[30]. WHO guidelines for estimating costs of introducing new vaccines into the national immunization program[31] and HPV scaling up guidelines[32] as well as HPV vaccine costing literature[33][34] were also used to ensure a comprehensive description of all the resource items. These resource items were then organized into into direct medical and direct non-medical cost categories[35]. For the identification and the measurement of the quantity of resource use in terms of the physical units required in each cost category[36], primary data was collected from the demonstration project documents and the NIP strategic document referred to as the

comprehensive multiyear plan (cMYP). Additionally, activities were documented during process evaluation participatory observations and finally key informant interviews were conducted (KIIs). Subsequently a mix of both micro and gross costing was used to value the costs[37]. The sources for unit and lump sum costs were primary cost data from Mozambique including Ministry of Health (MOH) values for salaries, travel allowances, fuel and other activities implemented by the NIP.

Mozambique's HPV vaccine demonstration project delivery strategy

The demonstration project sites were three districts Manhiça, Manica and Mocímboa da Praia, each selected to represent the three socioeconomically diverse regions of the country; south, central and northern regions respectively (Figure 1).

The Government received Gavi funding for Manhiça district in the south but not for the other two districts, with the consequence that Manhiça implemented slightly more activities in comparison to the other two districts. The HPV vaccine was delivered through a periodic school based model; periods of one week were predetermined and utilized for the delivery of one dose of the vaccine, in an outreach format to schools. Additionally some community outreach visits were made in the days after the vaccine had been administered in the schools. In order to simplify the identification and reach of adolescent girls, the 10 year age group was selected based on the rationale that a one age cohort was likely to be found in one grade at schools. As such during implementation only one grade rather than multiple ones were targeted in the schools, a strategy that limited disruption of school activities in the other grades not involved in the vaccination exercise. In the first year of the project, each eligible girl received three doses of the bivalent Cervarix™ vaccine, administered one each in May, June, and November in order to fulfill the WHO recommended schedule of 0,1 and 6 months. In the second year, following revised WHO guidelines, the number of doses were reduced to two, scheduled at 0 and 6 months. These were administered in June and November to a new group of eligible 10 year old girls.

For the outreach visits, teams composed of a health worker and an auxiliary staff member from all health facilities in the district made visits to up to three schools and two community spots during the course of the five weekdays of the vaccination week. The teams spent about 6 hours in each school and 6 hours in each community outreach spot. In each school, one identified responsible teacher arranged a vaccination venue, registered the girls prior to the vaccination day, and organized them in queues ready for vaccine administration by the health workers. The same teacher was in addition tasked with observing the girls for any symptoms of adverse effects after immunization (AEFI) for a period of up to 48 hours after vaccination. Overall supervision was provided by two provincial and two district supervisors for each of the three demonstration districts. Additionally, two supervisors from the national level, visited each district during the vaccination week to provide oversight and technical support.

Preparatory activities that were undertaken prior to the commencement of the administration of the vaccines included vaccine procurement, social mobilization, trainings, development and revision of monitoring tools. Vaccines and injection materials were procured and distributed through the existing national immunization cold chain system from the national warehouse in Maputo to health facilities in the three demonstration districts. Social mobilization messages were developed, piloted and then finalized. Different types of information, education and communication (IEC) materials were developed and produced including brochures, radio and television media spots. Additionally, community leaders were engaged to provide community talks in all districts and community activists made door to door visits in one district. A call-in educational service was further leveraged for community members to call in and ten telephone operators were trained and provided services during the demonstration project. The three districts each conducted a launching ceremony in which costs were incurred for promotional material items such as banners, T-shirts and caps. Trainings were conducted in a cascade manner for the health workers and ministry of education staff. Monitoring tools that were developed and printed included tally sheets, registration books and vaccination cards. A post introduction evaluation (PIE) was conducted in the one district where the Ministry of Health had received Gavi financial support.

Base-case cost assumptions

A summary of the base-case costs, assumptions and sources are shown in Table 1. Given that the vaccines were delivered to schools and communities where the eligible girls were located, recipients and their caregivers did not incur any costs to seek for the services. As such patient costs were not considered in this study.

The direct medical costs comprised of procurement of vaccines and vaccine injection supplies, vaccine distribution, cold chain costs, social mobilization, personnel, outreach visits, and monitoring and evaluation (M&E). The calculation for the total annual vaccine cost was made by taking into consideration the cost per vaccine dose of $5.70, achieved vaccination coverage for years one and two converted to the number of girls vaccinated, number of doses per girl (three in year 1 and two in year 2), the observed wastage rate of 5% and a buffer stock of 25%. Vaccines were procured at the beginning of the two year demonstration period. Vaccine injection supplies which were procured together with the vaccines included syringes and safety boxes. Syringe quantities were assumed to be of the same amount as the vaccine doses while each five liter safety box can hold 100 syringes. The syringe wastage rate used was the standard 10% utilized by the Mozambique NIP.

Vaccine distribution consisted of air and road transport costs. Cold chain cost was based on the national immunization standard storage costs and were calculated for the period that the HPV vaccines were stored prior to their utilization. Vaccines arrived in country six months prior to the vaccination date and required storage until the all vaccines were used up after the administration of the last dose in the second year. The required cold chain space volume in liters per month was estimated and multiplied by the storage unit cost. The decrease in vaccine volume over the months as the vaccines got used up with each administered dose, as well as the amounts of time that the vaccine spent at national, provincial, district and health facility, were taken into account. HPV vaccine did not require a different distribution timeline from that of other NIP vaccines and was integrated into the routine monthly mechanism existing at all health system

levels. For social mobilization, unit costs for trainings of community leaders and volunteers as well as the incentives for the community volunteers were available from project documents and were used to calculate total costs. Units costs were used for all IEC materials calculations while lump sum quantities were used for the television and radio spots development, production and broadcasting costs.

Personnel costs included training costs and the time that health workers spent on outreach visits calculated in hours spent at schools and community outreach spots multiplied by the wages per hour. Outreach visit costs comprised of health worker per diems and fuel. For monitoring and evaluation supervisor per diems, air tickets for national level supervisors and fuel costs were considered. The PIE costs included per diems and fuel costs. Lump sum costs were utilized for the monitoring tools development and printing. All fuel cost calculations are estimated using the kilometers that were travelled and the amount of fuel required in liters. Training costs are comprised of travel per diems, training materials and venue costs and were based on actuals values incurred during the demonstration project. Education workers training costs and time spent during vaccination activities and post vaccination observations for adverse effects were calculated in hours and then by the wage cost per hour.

Direct non-medical costs were the overhead administrative costs. These were estimated by taking the overall annual provincial and district immunization program overhead costs and dividing them by the 52 weeks in a year, then calculating the costs needed during the 5 weeks that HPV vaccine was administered plus another 6 weeks for preparatory activities (2 weeks prior to the initial dose and 1 week for each of the remaining 4 doses that were administered throughout the demonstration project).

Estimation of the cost of a fully immunized girl (FIG) and extrapolation to a one year national program

In order to estimate the cost of a FIG, all the total costs for the two years in all the cost categories and at all levels were added up. They were then divided by the total number of girls who completed the dosing

schedule of three and two vaccine doses in years one and two respectively. Ninety five percent credibility intervals (CIs) around all estimated FIG costs were calculated (38). Upper and lower bound values for the model input parameters were determined through an assumption of a 20-30% standard deviation from the baseline costs values. Subsequently maximum likelihood was used to obtain a gamma distribution for each parameter and then 10,000 simulations were run so as to generate possible random costs. The resulting cumulative totals were depicted in histograms and the 2.5 and 97.5 statistical percentiles were utilized to set the confidence intervals endpoints on the graphs.

These costs for a FIG were then extrapolated to a one year program that would target all 10 year old girls in Mozambique. For this projection, new FIG costs were estimated using model input parameters that excluded the first year third dose costs, so as to accommodate the current two dose HPV vaccine schedule that is recommended by WHO. The target 10 year old girl population was calculated from the Mozambique 2007 census data from which the 2017 projected population was selected(39).

All costs were collected in Mozambican Meticais and converted to US dollars using official exchange rates(40). Analyses were conducted in Microsoft Excel 2017 (Microsoft, Redmond, WA, USA) and R software version 3.43 (RStudio, Boston, MA, USA).

Results

Interviews were conducted at all levels of the health system from the central to the service delivery level. A total of 45 respondents participated in the study of whom 55% were Ministry of Health staff and included immunization program, health directorate and finance and administration managers at health facilities, districts, provinces and national level office. Ministry of Education accounted for 15% of the study participants and were sampled from staff at national, provincial and district levels as well as in

schools. The remaining participants were drawn for the organizations supporting the immunization program in the implementation process with 10% being NGOs, 7% multilaterals, 7% research institutes, 3% bilateral organizations and 3% from a pharmaceutical company.

A summary of the number of health facilities, schools, and target population of eligible girls in each district are shown in table 2. Of the three districts Manica had the largest number of health facilities (20) and schools (114) while Mocímboa da Praia had the fewest with just 7 health facilities and 50 primary schools. Similarly, Manica had the larger target population of eligible girls than the other two districts during the two years of the demonstration. These were 3,952 in year 1 and 4,095 in year 2 compared to Mocímboa da Praia's 1,254 in year 1 and 1,452 in year 2 and Manhiça, 3,350 in year 1 and 3,588 in year 2. The proportion of eligible girls who received the full vaccine dose regimen, was higher in the second year of the project in all the three districts. This is presented as percentage coverage for years one and two respectively in each district as follows: Manhiça 73% and 77%; Manica 47% and 51%; Mocímboa da Praia 16% and 21%.

The total implementation costs for the whole project in the three pilot districts were $523,601, 99.4% of which were direct medical costs. In Table 3 the costs of implementing the HPV vaccine demonstration project strategy activities are presented as total costs and additionally they are categorised into annual costs. Year one total project implementation costs were significantly higher than year two costs. The largest proportion (23.8%) of the total project implementation costs incurred in year one was spent on personnel, while in year two most spending was on procurement which accounted for 34% of total project implementation costs.

When costs were categorized by amounts spent in the different project locations including the central level and the three districts the largest proportion were incurred in Manhiça accounting for 36.3% of total costs. Costs expended in Manica also amounted to a large proportion at 31.% while those spent at the

central level and Mocimboa da Praia were the least and amounted to just 16.7% at each of the locations. At the central level the largest implementation cost spending was on M&E activities which accounted for 52% of the total costs, while procurement costs were the larger cost components in the districts accounting for 27%, 34% and 27% in Manhiça, Manica da Mocimboa da Praia respectively.

The cost per FIG was $72 (95% CI: $62 - $83) in year one, $38 (95% CI: $37 - $40) in year two and $54 (95% CI: $49 - $61) for the whole project period. The cost of a FIG in each of the project districts in year 1, year 2 and whole project period were; Manhiça: $53 (95% CI: $41 - $63), $32.74 (95% CI: $29 - $43) and $42 (95% CI: $38 - $47); Manica: $66 (95%CI: $55 - $74), $33 (95%CI: $22 - $46) and $49 (95%CI: $40 - $54) and Mocimboa da Praia $373 (95%CI: $252 - $427), $123 (95%CI: $79 - $225) and $222 (95% CI: $136 - $361).

The cost of a FIG when the first year third dose implementation costs were excluded were, Year 1: $60 (95% CI: $50 - $72), Year 2: $38 (95%CI: $31 - $46) and for the whole two year period $48 (95%CI: $42 - $55). The projected estimated costs for a one year 2 dose program targeting all 10 year old girls in Mozambique are presented in table 4.

Discussion

This study presents the resources and costs that were expended on the Mozambique HPV vaccine demonstration project. The analysis was accomplished through delving into the implementation strategy and identifying the activities that were undertaken during the project cycle starting from planning and preparations through to project realization up to the conclusion. The results show that important cost determinants were high vaccine price, number of administered doses, program startup costs and the necessity for rigorous demand generation. In addition, the implementation cost per FIG is high and if a similar mainly school-based implementation strategy were to be adapted during national scaleup, introducing the HPV vaccine in Mozambique would be a very expensive undertaking.

Annual patterns and cost compositions of the aggregated costs provided insight into the factors contributing to the cost per FIG found in this study. Total costs in all cost categories except the procurement category decreased in the second year of the project. Further exploration of its cost components revealed that the HPV vaccine's dose price of $4.60 was notably much higher than dose prices for older vaccines such as Bacillus Calmette–Guérin (BCG) at $0.11 and measles at $0.24. Even recently introduced pneumococcal conjugate (PCV) and rotavirus vaccines dose prices of $3.50 and $2.55 respectively, while higher than those for traditional vaccines, are lower than the HPV vaccine dose price (41). Similar findings of the high HPV vaccine price making up a large proportion of its high introduction costs in LMICs have been previously documented (42)(43)(44). Given that 50% of vaccine economic costs for national immunization programs are usually due to vaccine procurement (45), the findings from the current study raise concerns on the sustainability of HPV vaccines for Mozambique and other LMICs. Global level strategies to lower the HPV vaccine price are needed in order to facilitate the vaccine's adoption in these LMIC settings.

Other substantial proportions of the estimated total costs in this study were from the cost categories of personnel and vaccination campaign. Both decreased significantly during the second year because of the reduction in vaccine dosing to two instead of the three doses that had been administered in the first year, which resulted in the exclusion of a whole week of vaccination campaigns activities costs. Staff time costs accounted for 59% of personnel category costs, with most costs emanating from the amount of time that health workers spent out in a school or community outreach point administering the vaccine. The workers were typically spending a whole day out of the health facility, completely dedicated to administering just one vaccine, a process that significantly increased the cost when valued in terms of health worker wages. Costs in the vaccination campaign category were composed of amounts spent on transportation and incentives for the health workers who had to travel to schools to administer the vaccine. These findings are important because of the possibility of a single dose scheduling in the future,

due emerging evidence of sufficient protection from one dose of the vaccine(46)(47). The current study findings show that an additional decrease in the HPV vaccine dose regimen, would lower the operational costs of delivering the vaccine and lead to savings on costs, a situation that would make the vaccine's introduction more feasible for Mozambique.

Higher year one costs in personnel, social mobilization and M&E cost categories reflect the start-up costs that go into initiating a program. Given the intensity of activities during the demonstration project for a small number of girls and the fact that the unit cost for all start-up activities will remain the same in the case of a national scale up, in which a larger number of girls is expected to be reached, the cost of a FIG is expected to decrease over time due to the economies of scale. Additionally, social mobilization costs were higher in the district with the highest vaccination coverage, meaning that if resources are available, such costs can be considered as an investment for increased vaccine uptake. These findings are consistent with those of a study from Rwanda, (48) the first country to roll out the HPV vaccine nationally in Africa. One strategy to fund social mobilization activities that the Mozambique Ministry of Health could explore is to seek for other non-Gavi financial resources.

The high cost per FIG of $54, observed in this study is consistent with costs per FIG found in other costing studies conducted within the context of HPV vaccine demonstration project implementation in LMICs(27)(33)(34). Such expenditure on an individual recipient of the vaccine would amount to more than 50% of Mozambique's current estimated health spending per capita of $92(49). Furthermore, when the cost per FIG in the current study was extrapolated to a one year country wide program, the total estimated cost of $18,000,000 ($15,865,000 - $20,748,000) was found to be relatively higher compared to annual costs for recently introduced new vaccines in Mozambique. Specifically, the PCV at$11,000,000 and rotavirus vaccine $16,000,000 that target a whole cohort of boys and girls while the HPV vaccine targets half the cohort because it is administered to girls only.

The weaknesses in this study stem from the assumptions that had to be made. While most cost inputs were obtained from observed data, some were based on information from the interviews of health workers and teachers. Specifically, the amount of time that the health workers spent at schools was estimated and not measured. The same pertains to the amount of time that teachers dedicated to the HPV vaccination process in the schools and the time that they expended on observing the vaccinated girls for adverse effects after immunization. Wages for both teachers and health workers were based on central level salary recommendations rather than actual district level salaries. Fuel cost calculations were made using the national immunization program methodology that did not distinguish the different distances to be covered in the different districts, but rather allocated the same amounts of fuel to all districts irrespective of number of schools or health facilities. A flat local to dollar currency exchange rate that did not account for inflation fluctuations that may have occurred during the period of the demonstration project was assumed in the study. All these limitations may have led to both over and under estimation of the costs calculated in the study.

Conclusion

Program implementation is complex, and cost is a known implementation factor. This study applied standard methods and principles to calculate implementation costs for a HPV vaccine delivery strategy. It thus provides a framework that other researchers can use to identify, measure and value costs of implementing HPV vaccine delivery strategies. Additionally, the results provide important cost information that can be utilized by Mozambique's Ministry of Health decision makers. Introducing the HPV vaccine in Mozambique will be a costly endeavor. The country will need to consider strategies where savings can be achieved in order for the national roll out of the HPV vaccine to be both feasible and sustainable.

Table 1: Base-case costs assumptions and sources

Cost Component	Assumptions	Cost Source
	Direct Medical	
Procurement	HPV bivalent vaccines and vaccine injection supplies. Calculated based on cost per vaccine dose $5.70, achieved vaccination coverage for years one and two (Manhiça 73.3%,77%; Manica 47%,51%; and Mocímboa da Praia 16%,21%), the number of girls vaccinated, number of doses per girl (three in year 1 and two in year 2), the observed wastage rate of 5% and a 25% buffer stock Syringe quantities were assumed to be the same as the vaccine doses while each five liter safety box was assumed to hold 100 syringes. The syringe wastage rate used was the standard 10% utilized by the Mozambique NIP	NIP cost records, cMYP, HPV vaccination project documents and reports
Cold chain and vaccine distribution	The required cold chain space volume in liters per month was estimated and multiplied by the storage unit cost. 25 months of storage were assumed given that the vaccines arrived 6 months prior to the first dose. The decrease in vaccine volume over the months as the vaccines got used up with each administered dose, as well as the amounts of time that the vaccine spent at national, provincial, district and health facility, were taken into account HPV vaccine did not require a different distribution timeline as such the routine monthly mechanism existing at all health system levels was utilized. To revise	NIP cost records, cMYP, HPV vaccination project documents and reports
Social Mobilization	Actual costs as reported during the demonstration project were used for all social mobilization activities including message development, unit costs for trainings of community leaders and volunteers; Incentives for the community volunteers and leaders for door to door campaigns. Units costs for all IEC materials and lump sum quantities for the television and radio spots development, production and broadcasting costs	NIP cost records, HPV vaccination project documents and reports
Personnel	Actual training costs as reported during the demonstration project were utilized for training costs calculation while for outreach it was assumed that health workers spent about 6 hours in each school and 6 hours in each community outreach spot. These hours were multiplied by the wage cost.	NIP cost records, HPV vaccination project documents and reports, KIIs with health workers, MOH salary scales
Vaccination outreach visits to schools and communities	Outreach visit costs comprised of health worker per diems and fuel.	NIP cost records, HPV vaccination project documents and reports
Monitoring and Evaluation including PIE	Supervisor per diems, air tickets for national level supervisor and fuel costs were considered. The Post Introduction Evaluation costs included per diems and fuel costs. Lump sum costs were utilized for the monitoring tools development and printing.	NIP cost records, HPV vaccination project documents and reports
Education workers training and time costs	Actual training costs as reported during the demonstration project were utilized for training costs calculation and for vaccination it was assumed that teachers spent about 6 hours in vaccination activities for each dose and 48 in observing girls for symptoms of vaccination adverse effects.	NIP cost records, HPV vaccination project documents and reports, KIIs with teachers, Ministry of Education salary scales
	Direct non-medical	
Overhead administrative costs	Overhead administrative costs were estimated by taking the overall annual provincial and district overhead costs and dividing them by the 52 weeks in a year, then calculating the costs needed during the 5 weeks that HPV vaccine was administered plus another 6 weeks for preparatory activities (2 weeks prior to initial dose and 1 week each of the remaining 4 doses)	NIP cost records, cMYP, Interviews with KIIs Other MOH docs

Table 2: Schools and health facilities in the HPV vaccine demonstration districts

	Manhiça	Manica	Mocímboa da Praia
Health Facilities	13	20	7
Primary Schools	90	114	50
Necessary Teams	21	28	13
Target population Year 1	3350	3952	1254
Fully immunized girl year 1	73.3%	47%	16%
Target population year 2	3588	4095	1452
Fully immunized girl year 2	77%	51%	21%

Table 3: Year one versus year two demonstration project implementation costs

Direct Medical	**Year 1**	**Year 2**	**Total**
Cold Chain	$2,000	$2,000	$4,000
Education Staff	$29,993	$15,826	$45,819
M&E	$56,050	$35,350	$91,400
Personnel	$77,543	$21,324	$98,867
Procurement	$58,387	$67,387	$125,774
Social Mobilization	$33,500	$24,500	$58,000
Vaccination Campaign	$66,975	$29,767	$96,742
Direct Non-Medical			
Overhead	$1,500	$1,500	$3,000
Grand Total	**$325,948**	**$197,654**	**$523,602**

Table 4: Projected costs for a one year two dose HPV vaccination program

Province	Total
Maputo Provincia	$1,164,263.00 ($1,017,345 - $1,330,448)
Maputo Cidade	$660,112 ($576,813 - $754,336)
Gaza	$1,030,906 ($900,816 - $1,178,056)
Inhambane	$1,149,800 ($1,004,707 - $1,313,921)
Sofala	$1,533,068 ($1,339,611 - $1,751,897)
Manica	$1,495,776 ($1,307,024 - $1,709,281)
Zambezia	$3,482,485 ($3,043,032 - $3,979,571)
Tete	$1,894,574 ($1,655,498 - $2,165,003)
Nampula	$3,362,016 ($2,937,765 - $3,841,906)
Niassa	$1,111,315 ($971,078 - $1,269,942)
Cabo Delgado	$1,272,236 ($1,111,693 - $1,453,834)
Grand Total	**$18,156,549 ($15,865,384 - $20,748,196)**

Figure 1: Mozambique HPV vaccine demonstration project sites

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Chapter 5: Conclusion

Conclusions

This dissertation is a compilation of three publishable manuscripts, that present findings from an evaluation of the Mozambique HPV vaccine delivery demonstration project. They aim to provide knowledge to inform decision making and planning for countrywide scale up of the vaccine. Additionally, other LMICs in similar phases of HPV vaccine introduction, donors and entities involved in the expansion of access to HPV vaccine globally, can benefit from the results.

Important findings have emerged from the set of three of studies conducted in this research. In chapter two, we found eight key significant drivers of implementation success or failure from the CFIR guided post interpretive evaluation. These are; adaptability, complexity, financial resources, positive organizational culture and workers beliefs about the innovation, training, intervention recipient's perceptions, engaging the right opinion leaders and decentralization of planning and other processes. The school based model designed at national level did not cater for differing proportions of school enrollment of the target group of adolescent girls eligible for the vaccine. An adaptable model that could allow districts with lower school enrollment to allocate more time and resources to community outreach visits is desirable. Insufficient financial resources compromised the ability of the intermediate and poor performing districts to achieve higher vaccination coverage. Poorer districts will require more financial resources than the districts that are relatively economically stronger thus necessitating equitable distribution of resources during national scaling up. Health workers' beliefs in the importance of vaccines as a high health priority coupled with the organizational culture in the Mozambican health sector, of doing whatever it takes even when in non-ideal circumstances to ensure that eligible populations can access health interventions, were pertinent in driving the completion of all the demonstration project activities despite existing challenges. These positive organizational implementation success drivers should be leveraged during national scaleup. For social mobilization, important opinion leaders were missed in one district and the social mobilization period was too short in all demonstration sites. Given

the non-traditional target age group of the vaccine a more robust social mobilization campaign addressing these problems will be required. Our study provides one of the early experiences of the utilization of the CFIR in LMICs and we found the CFIR to be a useful and practical tool for researching health system implementation determinants in this setting. Its broadness in the form of 39 constructs does not only make it a comprehensive framework that provides for researchers to consider numerous factors but also one that allows for flexibility so that researchers can select constructs that are relevant to their studies.

Chapter three revealed the importance of balance between donor and government influence, the necessity for adaptability to changing needs and the value of country ownership for an effective vaccine delivery partnership. The Mozambique HPV demonstration partnership composition and practices were equally driven by Gavi, the Vaccine Alliance and the Government of Mozambique. The Gavi partnership model of having specific core partner roles guided the HPV vaccine's implementation partnership to adapt these principals in the avoidance of duplication of activities. Consequently, a favorable collaborative environment in which different entities' competencies could be leveraged was created. Had Gavi's influence been dominant, and the original Gavi decision been followed, the HPV vaccination pilot would have taken place in only one district representing only one Mozambican economic and religious context. This would have resulted in learnings from the different contexts that the other two districts offered, being missed. Another pertinent finding in this chapter is the importance of a flexible partnership that can adequately respond to unpredictable events and evolving priorities. The partnership structure was key for this attribute. Our results showed that a partnership whose structure is moderately centralized, around few key diverse players, has a higher capacity to coordinate actors and provide rapid response. We also learnt that a novel intervention may compel additional roles and further lead to the expansion of the partnership underscoring the importance of flexibility and the capability to absorb new members in such a partnership. Country ownership was the partnership feature that study participants were dissatisfied with because of two main reasons. One was the selection by Gavi, of organizations not based in the country, to

provide technical assistance and the other was the termination of program activities when organization completed projects. These call for improvement on these partnership qualities, however overall the expanded, diverse and inclusive collaboration of institutions and organizations that implemented the Mozambique HPV vaccine demonstration project was effective and efficient. A similar partnership model is recommended for national scaling up of the HPV vaccine in Mozambique.

In chapter four, study findings show that important cost determinants were high vaccine price, number of administered doses, program startup costs and the necessity for rigorous demand generation. In addition, the implementation cost per FIG is high. Cost components revealed that the HPV vaccine's dose price of $4.60 was notably much higher than dose prices for older vaccines such as Bacillus Calmette–Guérin (BCG) at $0.11 and measles at $0.24. Even recently introduced pneumococcal conjugate (PCV) and rotavirus vaccines dose prices of $3.50 and $2.55 respectively, while higher than those for traditional vaccines, are lower than the HPV vaccine dose price. Staff time costs and vaccination costs decreased significantly during the second year because of the reduction in vaccine dosing to two instead of the three doses that had been administered in the first year, which resulted in the exclusion of a whole week of vaccination campaigns activities cost. This observed trend of a decrease in these two costs categories, when number of doses is decreased, is especially important given the possibility of a one dose scheduling in the future. Higher year one costs in personnel, social mobilization and M&E cost categories reflect the introduction costs that go into starting up a program. Given the intensity of activities during the demonstration project for a small number of girls, and the fact that the unit cost for all start-up activities will remain the same in the case of a national scale up in which a larger number of girls is expected to be reached, the cost of immunizing a girl is expected to decrease over time due to the economies of scale. The high cost per FIG of $54 observed in our study is not unique as it is comparable to other estimated costs for FIG from studies conducted in LMICs. However, such expenditure on an individual health service recipient would amount to more than 50% of Mozambique's current estimated health spending per

capita of $92. Furthermore, when this cost per FIG was extrapolated to a one year countrywide program, the total estimated cost of $18,000,000 ($15,865,000 - $20,748,000) was found to be relatively higher compared to annual costs for recently introduced new vaccines in Mozambique. These findings emphasize the need for drug access advocacy, campaigns and negotiations as well as other strategies to reduce the price of HPV vaccine to make it accessible to the populations that need it most. Overall, introducing HPV vaccine in Mozambique will be a very expensive endeavor and the country will need to consider strategies where savings can be achieved in order for the national roll out of the vaccine to be both feasible and sustainable

The goal of frameworks in implementation science is to guide the process of identifying factors that are believed to influence the process of adoption of evidence-based interventions into health programs and policy. In this field frameworks focus on identifying and specifying these implementation determinants. The research in this dissertation has demonstrated the salient relationships between implementation determinants through delving into the CFIR as an overarching framework and two specific components those of costing and networks and communications.

The key recommendations that have arisen for policy decisions during scaling up of HPV vaccine delivery in Mozambique and other LMICs are:

- Design an adaptable HPV vaccine delivery model that can reach non-school going girls
- Define and clarify roles for non-health system individuals involved in the vaccine delivery such as teachers and community members
- Allocate sufficient resources in lower socio-economic regions with poor road infrastructure networks and few schools
- Leverage positive health worker organizational norms such as the belief in relative priority of vaccines in prevention of diseases of public health priority

- Provide training for non-health system implementers such as teachers and community members
- Mobilize additional non-Gavi resources in order to implement a rigorous demand generation exercise aimed at behaviour change
- HPV vaccine delivery implementation partnerships should be flexible in bringing on new members in order to adequately respond to unpredictable events and evolving priorities
- Aim for a balance between donor and government influence during implementation so as to create a favourable collaborative environment
- Gavi's should appoint country based implementing partners to provide technical assistance during the implementation process
- Develop strategies to engender country ownership of HPV vaccination program and encourage sustainability of the program
- HPV vaccine price reduction strategies should be developed and implemented

Appendix: Questionnaires

Mozambique HPV demonstration project research questions for each CFIR construct

Domain	Constructs	Research questions for the Mozambique study
Intervention characteristics	Intervention Source	To what extent was the HPV vaccine demo project developed externally?
	Evidence Strength & Quality	To what extent were you provided with or made aware of the evidence supporting the introduction of HPV?
	Relative Advantage	Do you feel HPV is better than screening for cervical cancer in women in Mozambique?
	Adaptability	How adaptable was the HPV vaccination demo project implementation model for the different contexts in Mozambique? Were there different implementation strategies used in the three sites sites?
	Trialability	Do you feel the ability to implement first using a demo project was helpful? If so, why?
	Complexity	Please describe whether the implementation of the HPV vaccine demo was complex in your district (or nationally)?
	Design Quality & Packaging	What did you think about the way in which HPV vaccination demo results were presented to policy makers here in country?
	Cost	What is the cost of providing full HPV vaccination to a girl in Mozambique (To be tackled in aim 3)
Outer setting	Patient Needs & Resources	To what extent have patient needs been taken into consideration during the implementation of the HPV demo project?
	Cosmopolitanism	Did the cosmopolitanism of the specific district, impact implementation effectiveness at each of the sites?
	Peer Pressure	To what extent have other countries in the region implemented HPV demo project and national roll outs? Has this impacted how Mozambique's implementation of HPV demo?
	External Policy & Incentives	What kind of international policies, mandates have influenced the decision to implement HPV vaccine in the country?
Inner Setting	Structural Characteristics	How did the infrastructure (maturity, size and coverage) of the NIP affect the implementation? Was there be need for changes in any of these?
	Networks & Communications	What was the HPV demo project implementing stakeholder network structure?
	Culture	What were there cultural differences in the three districts?
	Implementation Climate	Were the health managers and health workers in your district open to implementing this vaccine as a pilot? At the national level was there interest or hesitation to implement? Please describe your perspective on this.

Domain	Constructs	Research questions for the Mozambique study
	Readiness for Implementation	(Leadership and resources)What has been the level of support from leaders? Did your site/district receive sufficient human and financial resources to support the implementation of the HPV demo?
Characteristics of individuals	Knowledge & Beliefs about the Intervention	What knowledge and beliefs about the HPV vaccine impacted implementation? At facility, district, national, levels ?
	Self-efficacy	Not relevant
	Individual Stage of Change	Not relevant
	Individual Identification with Organization	Not relevant
	Other Personal Attributes	Not relevant
Process	Planning	How was planning for implementation of the HPV demo carried out at each district?
	Engaging	Who were the key people engaged in the HPV demo in each district and nationally?
	Executing	Did the demo project implementation go according to plan? Why or why not?
	Reflecting &Evaluating	How was the demo project monitored and evaluated? How is this informing the national roll out?

SNA and Perceived outcome survey questionnaires

Respondent's name: _____Respondent's organization: _____

Respondent's job title: _____Location (city): _____

Is respondent's organization an international, national, or sub-national organization? : _____

Number of years respondent has been at his/her present organization: _____

Interview Date: _____Name of Interviewer: _____

Introduction

My name is ……..... I am a member of the Gavi evaluation team that is evaluating the processes, networks and systems for the delivery of vaccines in country.

The topic we would like to address in today's interview is:
Mapping of the networks of those involved in the implementation of Gavi funded streams (Rotavirus vaccine (RV), IPV, MSD, HPV and HSS) in the last 12 months.

1. Can you tell me the names of the people that you worked together with in the implementation of Gavi funded streams in the last 12 months. The streams we are referring to are RV, IPV, MSD HPV and HSS. List the name of the individual, organization or government ministry (MOH, MOF etc) and the department and title of the person as well as the Gavi stream you worked together on.
   [Allow respondent to list all names, giving them time and silence to think of additional names. By the end of the listing if Ministry of Education and provinces have not been mentioned, probe about these where appropriate].

2. I would like you to reflect on the overall "professional trust" you have for each listed individual and give scores in the sheet below. When we say 'professional trust,' we mean your confidence that he/she can respond to what you have requested, that they will complete what they have agreed to do and that they will perform it well. Mark with a circle the appropriate number on the provided survey form.
   1 = no confidence; 2 = some confidence; 3= satisfactory confidence; 4 = high confidence; 5 = very high confidence

3. Now I would like to know if you provided or received technical assistance (TA) from the individuals you have listed. By technical assistance we mean the transfer of knowledge or competencies. Circle a "P" for "I provided" or an "R" for "I received".

4. Next we would like to know your level of satisfaction with the provided or received technical assistance. Mark with a circle the appropriate number in the provided survey form.

1 = High dissatisfaction; 2 = dissatisfaction; 3 = fair satisfaction; 4= high satisfaction; 5 = very high satisfaction.

When the respondent completes filling in the form, probe around negative TA satisfaction and professional trust scores. Ask them to give reasons for negative scores. Find out how the given negative example has impacted on the partnership

Individuals the respondent worked with	**New**	**HPV**	**HSS**	**Professional trust**	**I provided/requested technical assistance to/from them**	**Satisfaction with TA provided/received**
(Name, organization, department, title)	(Mark with an X)			(Circle)	(P/R)	(Circle)
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Nome: Org: Departamento:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5

Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5
Name: Org: Department:				1 2 3 4 5		1 2 3 4 5

I would like to know the benefits and drawbacks of working together with other individuals, organizations, or departments in a group / (NIP partnership). Mark in the box below whether you think that the listed benefit or drawback occurred. Check only one box for each benefit or drawback

Benefits:	**Occurred**	**Did not occur**
a. Better able to execute activities	☐	☐
b. More timely execution of planned activities	☐	☐
c. Planned activities were executed with greater quality	☐	☐
d. Better able to identify the need for, and to acquire additional support	☐	☐
e. Better able to respond to existing challenges, or those that arose during the process	☐	☐
f. Better allocation of each organization's financial resources	☐	☐
g. Reduction in financial cost of process	☐	☐
h. Leveraged each organizations' comparative advantages	☐	☐
i. Increased sustainability of immunization program	☐	☐
j. Increased country ownership	☐	☐

k.	Increased transparency among partners	☐	☐
l.	Increased accountability among partners	☐	☐
m.	Increased legitimacy of decisions made	☐	☐
n.	Increased fairness of decisions made	☐	☐
o.	Other benefits:		

Drawback:		**Occurred**	**Did not occur**
p.	Unnecessary management burden on my organization	☐	☐
q.	Created competition and conflict among member organizations	☐	☐
r.	Loss of control/autonomy over decisions	☐	☐
s.	Strained relations within my organization	☐	☐
t.	Not enough credit given to my organization	☐	☐
u.	Forced us to make decisions in a way which was not natural/typical for our organization	☐	☐
v.	Other drawbacks:	☐	☐