A Pivotal Time in Global Cervical Cancer Prevention: Examining Young Women's Awareness about the Human Papillomavirus and Attitudes towards the HPV Vaccine in Durban, South Africa

by

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Abstract

It is a pivotal time in cervical cancer prevention for young South African (SA) women. Cervical cancer and infection with human immunodeficiency virus are both major public health concerns in SA. This study describes knowledge of female adolescents and young adults (AYA) about HPV, cervical cancer and explores predictors of HPV vaccine and HPV self-sample testing acceptability. In this cross-sectional study, questionnaires were administered to 122 female AYA who involved in a longitudinal study (AYAZAZI) which examined risk factors involved with HIV acquisition. Results indicated that although awareness and knowledge about these topics was very low among participants, as were perceptions of risk of acquiring HPV and developing cervical cancer, acceptability was very high towards HPV vaccines for self (97%) and (future) children (95%), as well for self-sample testing (85%). No significant variables were found to be associated with risk perception or self-sample acceptance. A significant difference was found between participants' perceived risk of acquiring HPV, HIV, and developing cervical cancer compared to the risk they felt other female AYA in their communities were at. The most influential sexual and reproductive health (SRH) information source and significant influences on HPV vaccine recommendations for participants were health care providers. Findings from this study are important in designing effective cervical cancer control programs that can attract more AYA for HPV vaccines and screening. As the HPV vaccine has only recently been introduced at a national level in SA, this study about awareness and vaccine acceptability is timely.

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Glossary

AAHS	Amorphous aluminum hydroxyphosphate sulfate adjuvant
AE	Adverse events
AIDS	Acquired immune deficiency syndrome
AYA	Adolescents and young adults
ART	Antiretroviral therapy
ARV	Antiretroviral medication
AYAZAZI	Adolescents and young adults “ZAZI” “Knowing ourselves”
CIN	Cervical intraepithelial neoplasia
HBM	Health belief model
HCP	Health care provider
HIC	High income country
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR-HPV	High risk human papillomavirus
LR-HPV	Low-risk human papillomavirus
IRR	Institute of race relations
KZN	Kwazulu-Natal
LMIC	Low and middle income country
LIC	Low income country
SA	South Africa
SAE	Serious adverse events
SRH	Sexual and reproductive health
STI	Sexually transmitted infection
VHM	Vaccine hesitancy model
VACCS	Vaccine and Cervical Cancer Screening Project
VIA	Visual inspection using acetic acid
WHIV	Women living with HIV
YE	Youth engagement approach

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Chapter 1: Introduction

It is a pivotal time in cervical cancer prevention for young South African (SA) women. It is a reality for many young women that they suffer from an array of sexual and reproductive health (SRH) challenges due to a lack of health services, low levels of awareness, and a health care system that is acute care than prevention focused. Cervical cancer and infection with human immunodeficiency virus (HIV) are both major public health problems in SA. As the HPV vaccine has only recently been introduced in SA, this study about awareness and vaccine acceptability is timely. This study describes knowledge of female adolescents and young adults (AYA) about HPV, cervical cancer and explores variables associated with HPV vaccine and HPV self-sample testing acceptability.

The first section of this chapter provides profiles of the country and city where this research takes place followed by a description of the burden of HPV infection and cervical cancer at a global and national level for SA. It then discusses the nature and epidemiology of HPV, its causal link to cervical cancer, and the relationship of the human immunodeficiency virus (HIV) to the HPV. Next primary and secondary prevention of cervical cancer is outlined, conceptual frameworks of the study as well as a statement of the problem and purpose of the study.

The Setting

South Africa has a population of approximately 56 million people with black African peoples as the majority at an estimated 80%; colored[1] and white people at 8.5% each of the total; Indian and Asian peoples 3%, and "other" populations representing the remaining 0.5% (Statistics South Africa, 2016). Figure 1 shows the ethnic populations in SA. The country has 9 provinces: Western Cape, Eastern Cape, Northern Cape, North West, Free State, Kwazulu-Natal, Gauteng,

[1] A person of mixed European ("white") and African ("black") or Asian ancestry, as defined by the SA government from 1950-1991. This term is still used to describe persons of mixed race.

Limpopo and Mpumalanga. The province where this research takes place is Kwazulu-Natal (KZN), which is the most highly densely populated area in the country (Figure 2). Within KZN there are 11 metropolitan municipalities and Durban is located the eThekwini district. The municipality spans an area of approximately 2 297km² and is home to approximately 3.5 million people. The main language spoken in this district is IsiZulu (62 %) followed by English at 26% (Statistics SA, 2016).

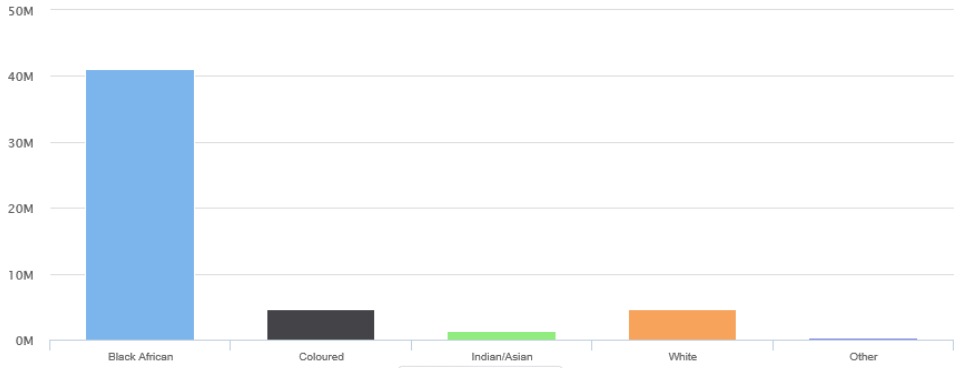

Figure 1. Ethnic Populations: South Africa
Note. From "Statistics by Place", by Statistics SA, 2016, http://www.statssa.gov.za

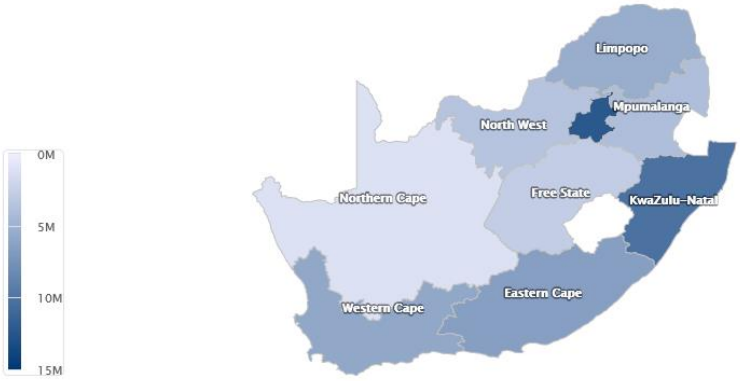

Figure 2. Provinces of South Africa: Population Density
Note. From "Statistics by Place", by Statistics SA, 2016, http://www.statssa.gov.za

The population in Africa is the youngest in age globally, with over 40% of its population under 15 years. South Africa's population is predominantly made up of young people with those below 35 years of age representing the largest group at an estimated 66%; 19 percent are between the ages 10-19 and 24 percent are aged 15-24 (United Nations Population Fund, 2016). Over two thirds of the young population (69%) reside in four provinces (Eastern Cape, KZN, Gauteng and Limpopo). Black African peoples have the youngest residents with 34% of the overall population under the age of 15 and 22% from 15-24 years of age with a median age of 21. The largest population represented in the eThekwini district is AYA aged 15-29. The district has more females (51%) than males (48%) and an overall mean age of 26.8 (Figure 3). The age and gender distribution in SA has important implications for cervical cancer prevention demonstrating the vital need to address prevention immediately.

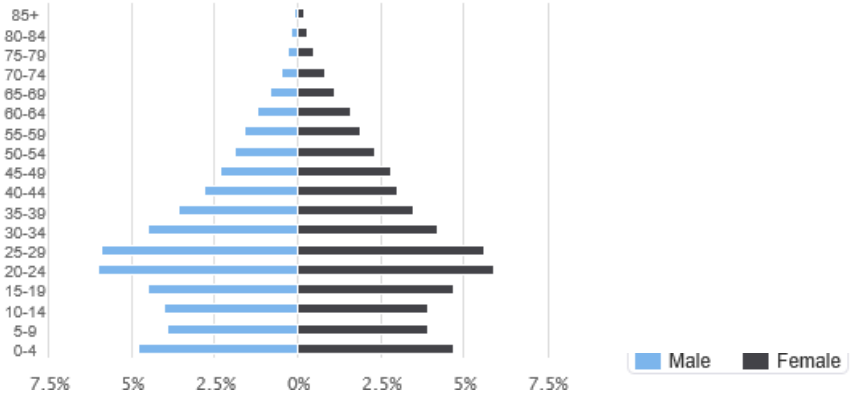

Figure 3. Sex and Gender Distribution: South Africa
Note. From "The People", by Statistics SA, 2016, http://www.statssa.gov.za/

Health Care System in South Africa

Healthcare is the responsibility of the SA Government, Department of Health (DoH) and is a two-tiered system with public- and private-sectors. An estimated 85% of the population utilizes public sector health services, private insurance or health schemes cover the remaining 15%

(Statistics South Africa, 2015). There are currently 87 registered medical schemes in South Africa with approximately 8.5 million beneficiaries. Predominantly, the DoH is responsible for the public-sector with the overall priority of improving the health status of the entire population with five priority areas including, increasing life expectancy; decreasing maternal and child mortality; combating HIV and AIDS; decreasing the burden of tuberculosis (TB); and strengthening the efficacy of the health-systems (Republic of South Africa: South Africa Government, 2017).

On September 12, 1978, the World Health Organization hosted the International Conference on Primary Health Care (PHC) with the goal of addressing the urgent need for all governments to protect and promote the health of their citizens. As defined by the conference in the Declaration of Alma Ata:

> "PHC is essential care based on practical, scientifically sound and socially acceptable methods and technology, made universally accessible to individuals and families in the community through their full participation, and at a cost that the community and country can afford to maintain at every stage of their development in the spirit of self-reliance and self-determination. It forms an integral part both of the country's health system, of which it is the central function and main focus, and of the overall social and economic development of the community" (World Health Organization, 1978, p. 3)

South Africa has struggled to fulfill this commitment due, in large part, to poor leadership and corruption resulting in a quadruple burden of disease of HIV and AIDS, TB, non-communicable diseases as well as exponentially high rates of maternal and child deaths (Mostert et al., 2015). This burden of disease translates into SA having considerably low life expectancy rates. According to the WHO (2015) the average global life expectancy is 63.1 years old, while South Africa is at 62.5. By contrast, high-income countries have an average life expectancy above 80 years of age. Currently the SA government is in the pilot stage of establishing national health insurance (NHI) program designed to "pool funds to provide access to quality affordable

personal health services for all South Africans based on their health needs, irrespective of their socioeconomic status" (Health Department: Republic of South Africa, 2015, p. 3). The long-term goal of this fourteen-year initiative is to eliminate the two-tiered system divided by socioeconomic lines and thus improve health outcomes for the majority of the population and those who need health services most.

Global and National Burden of Cervical Cancer

Cervical cancer is a preventable and significant global health concern with 80% of cases occurring in low- and middle-income countries (LMIC). The World Health Organizations (WHO) estimates that more than 1 million women globally are living with cervical cancer, many of whom are unaware of their status (World Health Organization, 2015). Internationally, the age standardized incidence rate of cervical cancer is 14 per 100,000 with the highest rates found in eastern (24.7), middle (30.6), and Southern Africa (31.5) (see Figure 4).

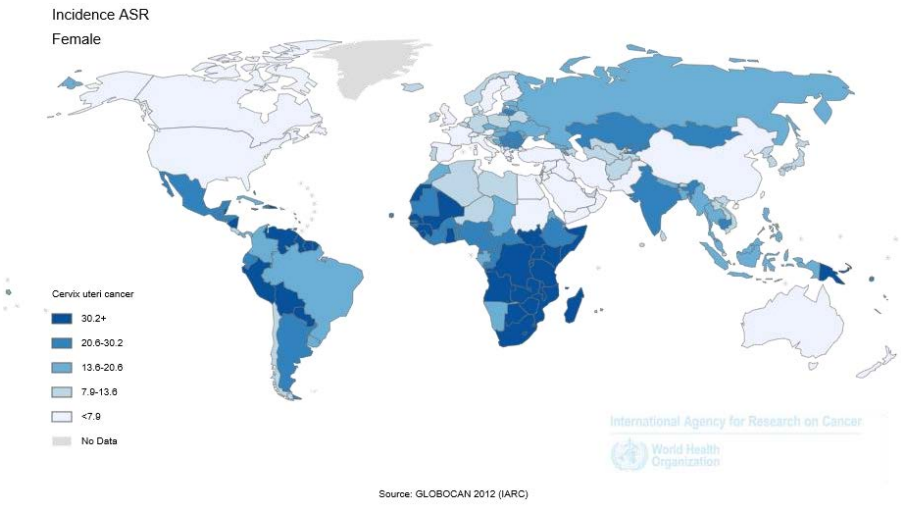

Figure 4. Global Age Standardized Incidence Rates: Cervical Cancer
Note. From "Simple Maps", by Ferlay et al., 2013, http://globocan.iarc.fr/Pages/Map.aspx

Annually, an estimated 260,000 women die worldwide from cervical cancer (Ferlay et al., 2013). It is postulated that by 2030 half a million women will die of cervical cancer with more than 98% of deaths occurring in LMICs (World Health Organization, 2014). Globally, the age standardized

mortality rate from cervical cancer is 6.8 per 100,000 (see Figure 5) with an estimated 60,000 deaths attributed to cervical cancer in Africa (17.5 per 100,000) annually (Ferlay et al., 2013). By contrast, Canada has significantly lower incidence and mortality rates at 7.4 and 1.7 per 100,000 (Canadian Cancer Society, 2016).

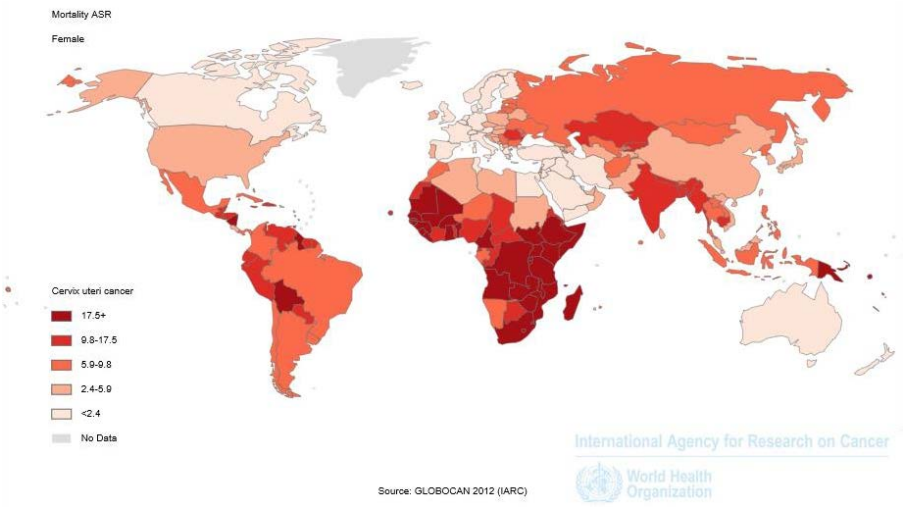

Figure 5. Global Age Standardized Mortality Rates: Cervical Cancer
Note. From "Simple Maps", by Ferlay et al. 2013, http://globocan.iarc.fr/Pages/Map.aspx

South Africa has some of the highest rates of cervical cancer in the world (see Table 1). Cervical cancer is the second leading cause of cancer for women with 7,735 new cervical cancer cases diagnosed annually at an incidence rate of 30.2 per 100,000. An estimated 4,248 women in SA die from cervical cancer annually making it a leading cause of cancer deaths among females at a mortality rate of 18 per 100,000 (Bruni et al., 2016; Ferlay et al., 2013).

Table 1. *Incidence and Mortality Rates: International Comparison*

Rates	Global	Less Dev.	High Dev.	South Africa
Incidence	14	15.7	9.9	30.2
Mortality	6.8	8.3	3.3	18

*per 100,000
Note. From ICO Information Centre on HPV and Cancer, 2016

The SA National Cancer Registry (NCR), first established in 1986, has not been updated since 2011 therefore current accurate cervical cancer incidence and mortality rates by ethnicity are difficult to obtain. However, historically, data has demonstrated that significant ethnic disparities in the incidence of cervical cancer exist nationally. For example, NCR data from 2011 showed that incidence rates of cervical cancer for all women was 21.67 per 100,000 (4,907 women). The ethnic breakdown for 2011 was: 21.67 (55) for Asian women; 25.49 (4,056) among black; 15.34 (359) among colored; and 14.49 (437) among white (National Cancer Registry: South Africa, 2011). Mortality rates were not reported by the NCR. Studies have estimated that of the approximately 80% of black African women who are diagnosed, 60% are latently diagnosed and die (Katz et al., 2016; Mqoqi, Kellett, Sitas, & Musa, 2004). However, there is currently no data available to support cases definitively.

Cervical cancer is currently the leading cancer at an incidence rate of 26.6 per 100,000 for young women in SA between the ages of 15 to 44 years (see Figure 6), many of whom are HIV positive (Bruni et al., 2016; Crosbie, Einstein, Franceschi, & Kitchener, 2013; Denslow, Rositch, Firnhaber, Ting, & Smith, 2014).

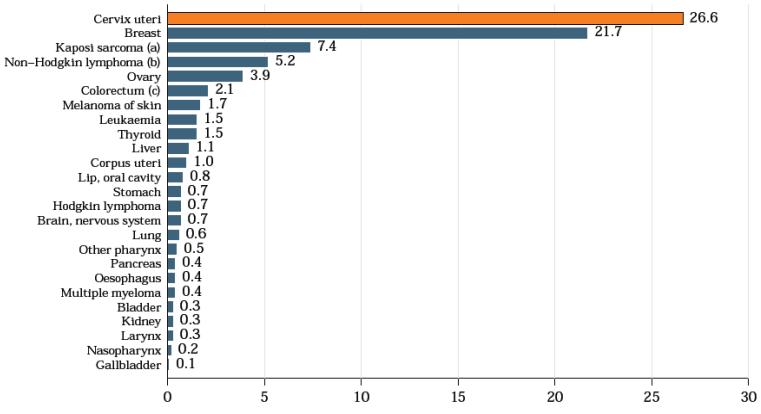

Figure 6. Incidence Female Cancers (age 15-44) in South Africa
Note. From "Human Papillomavirus and Related Diseases in South Africa: ICO Information Centre on HPV and Cancer", by Bruni et al., 2016, p.33

By contrast, breast cancer is the leading cancer for women of all ages in SA followed by cervical cancer and lung cancer (Bruni et al., 2016). Factors contributing to this high burden of cervical cancer include challenging socioeconomic conditions, competing health needs, disproportionate HIV rates, and health care infrastructure challenges (Denny, 2010; Finoacchario-Kessler et al., 2016; Katz et al., 2016; UNAIDS, 2015).

From a social determinants of health perspective, SA is faced with complex health issues stemming from a lack of access to the basic requirements of life including, affordable access to vital vaccinations, clean drinking water, adequate nutrition, reasonable housing conditions, education, and very low employment rates (Mayosi & Benater, 2014). South Africa has extreme levels of poverty with an estimated 31% of the population living on less than $2 per day (Republic of South Africa, 2016). Some of the largest economic disparities in the world are found in SA with the top 10% of the population earning 58% of the overall national income while the bottom 70% earn only 17% (Leibbrandt & Woolard, 2016).

A chronic shortage of health workers, funding, and infrastructure have contributed to the poor health outcomes of SA citizens. For example, while the public health sector serves more than 84% of the population (40 million), only 30% of the doctors in the country work in this sector while the remaining 70% work in the private-sector which serves the remaining 16% (8 million) peoples who can afford private health insurance either through employment or financial advantage (Coovadia, Jewkes, Barron, Sanders, & McIntyre, 2009; Mayosi & Benater, 2014).

The Nature and Epidemiology of the Human Papillomavirus

Papillomaviruses (PVs) are small DNA viruses identified to infect over 50 species of mammals, birds, and reptiles. Infectious cells are spread through close contact with infected skin cells or mucosal contact (Bonnez, 2014; Munoz, Castellsagué, de Gonzalez, & Gissmann, 2006).

There are 5 phylogenetic human associated PV's and over 170 identified types that infect the skin or mucosal membranes with new HPV types continuously being found (Bzhalava, Guan, Franceschi, Dillner, & Clifford, 2013). Of the strains that affect humans, types are categorized or identified as either high-risk (HR-HPV) or carcinogenic in nature, or low-risk (LR-HPV) (see Table 2). Non-carcinogenic types are commonly associated with the development of benign skin lesions or warts whilst HR-HPVs are associated with the development of cancer.

Table 2. *HPV Types: High- and Low-Risk*

HR-HPV	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, & 68
LR-HPV	6, 11, 42, 43, 44 & 45

The causal role of HPV in the development of cervical cancer is a well-established and universally accepted association (Crosbie et al., 2013; Schiffman, Castle, Jeronimo, Rodriguez, & Wacholder, 2007). Genital HPV is one of the most common occurring sexually transmitted infections in the world at an overall approximate prevalence rate of 10% (ranging from 6.1%-35%) (de Sanjosé et al., 2007). The HPV infection is the first documented necessary cause of human cancer, meaning that cervical cancer does not develop in the absence of persistent HPV infections (Bosch, Lorincz, Muñoz, Meijer, & Shah, 2002; Crosbie et al., 2013; Munoz et al., 2006). The HPV infection has been linked to six cancers to date: cervix, penis, vulva, vagina, anus and oropharynx (Bonnez, 2014; Dayyani et al., 2010; Munoz et al., 2006). The causal role of HPV infections in the aforementioned cancers has been documented beyond reasonable doubt.

Most women will acquire HPV at some point in their lives (70-90%), however many HPV's are asymptomatic and quite often the virus causes no harm and eventually regresses over time. Bruni and colleagues (2010) estimate that approximately 11% of the world population currently has an HPV infection. Between 5-10% of all women infected with HR-HPV will develop

persistent infections which can progress over decades into cervical cancer (Bosch et al., 2002; Munoz et al., 2006). Co-factors in the development of cervical cancer include smoking, multiple sexual partners, long-term hormonal contraceptive use, and co-infection with HIV (World Health Organization, 2014).

In 2008, the number of all new cancer cases worldwide attributed to HR-HPVs infections was 490,000 (30%) in lower income countries (LIC) and 120,000 (29%) in higher income countries (HIC), respectively. Notably, cervical cancer is associated with HPV types 16 and 18 in 70% of all cases worldwide (de Sanjosé et al., 2007; Walboomers et al., 1999). The most common HR-HPV types associated with invasive cervical cancer in sub-Saharan Africa are HPV16, 18, 45 and 35 (Bruni et al., 2016; Smith et al., 2007). In SA, the presence of HPV 16 and/or 18 in cervical cancer is estimated at 64% (see Table 3, Bruni et al., 2016). In SA, the highest rates of all HPV infections are among young women under the age of 25 (~43%) and decreases significantly after the age of 45 (~17%, ibid).

Recent research demonstrates a high presence of HPV infections in young women in SA. For example, a recent study conducted with 224 young women under the age of 30 in the province of KwaZulu-Natal enrolled in a prospective cohort study revealed an overall HPV prevalence rate of 76.3% with a 54% HR-HPV infection rate (Ebrahim et al., 2016). Similarly, in the Western Cape 332 young women (16-24 years) enrolled in a HPV vaccine trial demonstrated to have a HR-HPV rate of 49% (Sudenga et al., 2016). Research examining HPV prevalence according to age and HIV status conducted in Cape Town with 406 women (18-66 years) found an overall HPV rate of 36.7% among the 208 HIV-negative women and 61% among negative women aged 18-25. HPV prevalence in HIV-positive women was 74% with the highest prevalence (86.4%) in women between the ages of 18-24 (Mbulawa, Coetzee, & Williamson, 2015).

Cytology Result	*N*	HPV 16/18	95% CI
Normal	8661	3.2 %	2.8-3.6
Low-Grade Lesions	318	17.9	14.1-22.5
High-Grade Lesions	290	30.3	25.3-35.9
Cervical Cancer	488	63.9	59.6-68.1

Table 3. *Presence of HPV 16 & 18 in South African Cytology Results*
Note. From ICO Information Centre on HPV and Cancer, 2016

Giuliano and colleagues (2015) found similarly high HPV rates with young women in the Western Cape. From a total of 479 young women (16-24 years), 402 participants were HIV-negative, whereas 71% had more than 1 HPV type with rates highest among the youngest women (Giuliano et al., 2015). Finally, a larger scale study conducted in the Gauteng province testing 1,524 women attending public sector primary health clinics found that the overall HR-HPV prevalence was 74.6% with the age-specific prevalence showing a plateau-shaped curve (Richter, Becker, Horton, & Dreyer, 2013).

Overall, evidence from SA indicates that genital HPV infection is very common, particularly among young women. It is common for HPV infections to regress with age, however prolonged and multiple infections associated with suppressed immune activity (e.g., HIV), environmental factors in combination with latent diagnosis and treatment of cervical abnormalities are key contributors in the development of cervical cancer in SA. This is particularly the case among the most vulnerable populations of women with limited or challenging access to preventive health care services.

Cervical Cancer and HIV/AIDS

South Africa has 0.7% of the world's population and 17% of the global burden of HIV, which is the leading cause of death and illness among female adolescents and women of reproductive age (UNAIDS, 2015, 2016). The overall HIV/AIDS rate is 12% among children and 18.5% among adults, calculating to an estimated seven million people living with HIV with women representing over 60% of these infections (UNAIDS, 2015). In SA, HIV prevalence varies between regions. For example, in Kwazulu Natal, where this project took place, HIV prevalence is 12.2% compared 5.6% in Western Cape.

Globally, women are particularly vulnerable to HIV and acquire the virus younger than their male counterparts. A plethora of factors increase women's vulnerability to HIV acquisition including biological, behavioral, socioeconomic, cultural and structural risks (Ramjee & Daniels, 2013; UNAIDS, 2015, 2016; World Health Organization, 2016). Physiologically, women have a greater risk of acquiring HIV than men due to the larger mucosal surface of the vagina and higher likelihood of tissue injury during intercourse (Kalichman, Pellowski, & Turner, 2011). Adolescents and young women are particularly biologically vulnerable to HIV, as they have increased rates of asymptomatic and untreated STIs (linked to higher HIV acquisition rates) and immaturity of the inner vagina (cervix) to act as an effective barrier against these infections (Chersich & Rees, 2008; Kalichman et al., 2011; Wand & Ramjee, 2012).

Sociostructurally, women and girls are often treated as socially inferior (UNAIDS, 2016; World Health Organization, 2009). Gender inequities affecting health are particularly evident in LICs, such as SA, resulting in challenging access to health resources. Factors contributing to poor health outcomes and general well-being of women include, inequitable resource allocation, lower incomes, and reduced levels of education. In cultures that limit women's knowledge about

STIs and ability to negotiate safe sex further increase women's vulnerability to both HIV and STIs (WHO, 2009; WHO, 2015; UNAIDS, 2016). Violence against women is a well-recognized risk factor in the acquisition of HIV; for example, SA women who are exposed to intimate partner violence were found to be 50% more likely to acquire the virus compared to women who are not exposed to violence (Jewkes, Dunkle, Nduna, & Shai, 2010). It is estimated that 82% of new HIV infections among adolescents in SA occur in young women totalling over 4 million women. This gender imbalance is particularly evident in SA, where the incidence rate of HIV in young women aged 15-24 is up to four times higher than young men (UNAIDS 2015, 2016).

Cervical cancer is an AIDS-defining illness, meaning it develops much more rapidly and aggressively within a weakened immune system in women living with HIV (WHIV). For women with normal immune systems, cervical cancer can take between 15 to 20 years to develop, however for women with weakened immune systems it can take significantly less time at an estimated 5 to 10 years (Denslow et al., 2014). Research demonstrates that WHIV suffer from a wider range and higher rate of persistent cervical oncogenic HPV infections and as a result are 5-8 times more at risk for developing cervical cancer than those not infected; this is particularly the case for WHIV who are untreated, have high viral loads and low CD4 T-Cell[2] counts (Chen et al., 2014; Denslow et al., 2014). Conversely, genital inflammation as a result of HPV is associated with HIV acquisition at 3 times the rate for WHIV compared to uninfected women (Masson et al., 2015).

Antiretroviral therapy (ART) is a combination of antiretroviral drugs to help suppress the HIV virus and stop the progression of disease, first introduced in 1996 (Hammer et al., 1997). The WHO recommends ART for all individuals immediately following diagnosis of HIV.

[2] A CD4 count is a blood test that measures CD4 T lymphocytes (CD4 cells). For people living with HIV and a key indicator of how well the immune system is working and the strongest predictor of HIV progression.

Worldwide, the number of people currently on ART is 17.0 million. This number has vastly increased over the past 7 years, particularly in the hardest hit areas such as eastern and southern Africa reaching an estimated 10.3 million people and resulting in decreased mortality rates of up to 36% (UNAIDS, 2016). A national ART program was first introduced in SA in 2004 and now has the highest number of people on treatment globally (3.4 million) with women accounting for the majority of the infected population (WHO, 2015, 2016).

Although ART has demonstrated to have little if no beneficial effects in the development of cervical cancer for WHIV, women's life expectancy has increased exponentially as a result of increased access to treatment (De Vuyst, Lillo, Broutet, & Smith, 2008). With WHIV experiencing multiple and persistent HR-HPV infections, higher rates of cervical abnormalities, and living longer on ART, vaccinations, screening, and monitoring for cervical cancer is an essential component of preventive care for this group of women globally.

Primary and Secondary Cervical Cancer Prevention

In accordance with the WHO (2014), the goal of a comprehensive cervical cancer prevention and control program is to reduce the burden of cervical cancer by decreasing HPV rates, providing early detection and treatment, and access to timely treatment and palliative care (see Figure 7). Primary prevention is defined as *reducing the risk of exposure* by increasing resistance to infection, thereby avoiding the occurrence of infection (WHO, 2014). Primary prevention of cervical cancer also includes abstinence, mutual monogamy in virgins, condom use, and HPV vaccines (Manhart & Koutsky, 2002). Vaccines protecting against cancer-associated types of HPV are arguably one the most significant advances in the prevention of anogenital cancers (Bruni et al., 2016).

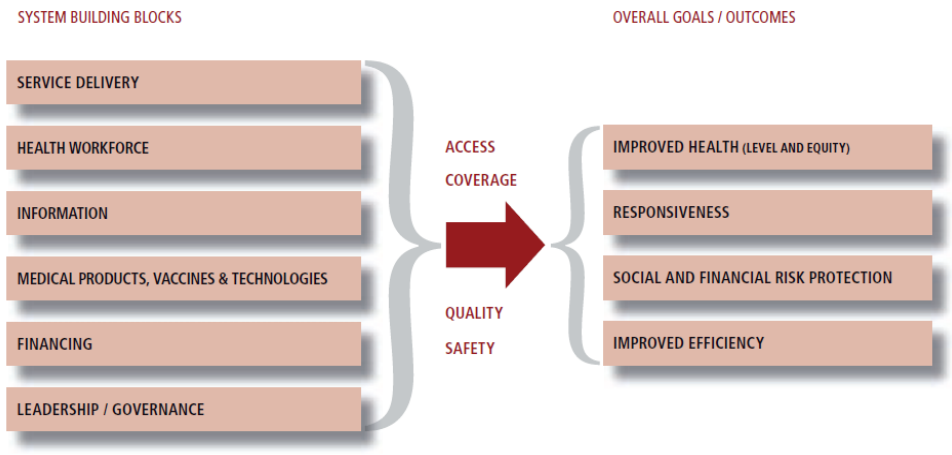

Figure 7. The WHO Health System Framework
Note. From "Health System Framework", 2016, http://www.wpro.who.int/health_services/health_systems_framework/en/

Worldwide, prophylactic bivalent (Cervarix), quadrivalent (Gardasil), and, more recently, nonavalent (Gardasil-9) vaccines are available for the prevention of HPV infections. The bivalent HPV vaccine is manufactured by GlaxoSmithKline and was released in 2007. The vaccine is based on virus-like particles (VLPs) of L1 (the major papillomavirus of the viral capsid or protein shell of the virus). The bivalent does not contain live virus therefore it does not infect the recipient, but rather neutralizes antibody response providing protection against the specific VLP types within the vaccine and strengthens immune response (Herrero, Gonzalez, & Markowitz, 2015). It is made up of HPV types 16 and 18 L1 proteins, two HPV types responsible for an estimated 70% of cervical cancer cases, and an AS04 adjuvant system[3] (Schiller, Casetlsague, & Garland, 2012; Schiller & Muller, 2015; Stanley, Pinto, & Trimble, 2012).

The quadrivalent vaccine manufactured by Merck was approved in 2006, and is similarly based on VLP technology, but rather contains an amorphous aluminum hydroxyphosphate

[3] Trade name for combination of adjuvants or agents that modify the effect of the VLPs

sulfate (AAHS) adjuvant and VLPs for two additional HPVs (types 6 and 11) than the bivalent vaccine and is therefore also protecting also against genitals warts (McCormack, 2014; Schiller et al., 2012; Stanley et al., 2012). The most recent prophylactic vaccine developed was approved in 2014 and manufactured by Merck. The nonavalent vaccine uses the same VLP and adjuvant system as the quadrivalent with protection against nine HPV types (6, 11, 16, 18, 33, 45, 52, and 58), which are responsible for close to 90% of cervical cancers and large proportion of cervical abnormalities (Joura et al., 2015; Schiller & Muller, 2015).

Currently, HPV vaccines are available globally through publicly funded immunizations programs in 64 countries, four countries sub-nationally, and 12 overseas territories, targeting a total of approximately 118 million women (See Figure 8). In SA the bivalent and quadrivalent are currently approved and available, however the nonavalent vaccines are not yet available (Medicines Control Council, 2008).

Figure 8. Global National and Pilot HPV Vaccine Programs: 2016

Note. From "Global Progress in Cervical Cancer Prevention", by Cervical Cancer Coalition, 2016, http://www.cervicalcanceraction.org/comments/maps.php

Large clinical trials have shown both the bivalent and quadrivalent vaccines to prevent an estimated 90%-100% of HPV 16 and 18 infections and associated precancerous lesions among previously uninfected women (Herrero et al., 2015). Both vaccines have also been shown to induce partial cross-protection against related HR-HPV types in previously uninfected recipients (HPV 31, 33, 45, & 51) (ibid). However, the bivalent or quadrivalent HPV vaccines have not been shown to change clearance rates of HPV 16 and 18 when the infection is present (Haupt et al., 2011; Szarewski et al., 2012).

The newest HPV vaccine (nonavalent) demonstrates similar results with 99% reduction in seroconversion or HPV acquisition rate following immunization also preventing infection or diseases related to HPV 31, 33, 45, 52, and 58, however in terms of cross-protection did not prevent infection or disease beyond the nine HPV types the vaccine protects against (Joura et al., 2015). Overall, all three prophylactic HPV vaccines are well researched and have demonstrated to be highly efficacious in the prevention of anogenital cancers associated with HR-HPV infections.

The HPV vaccine is a critical and effective primary prevention measure against HPV-related cancers particularly in low resource settings with limited screening resources and high HIV and HPV prevalence rates (De Vincenzo, Conte, Ricci, Scambia, & Capelli, 2014; Nakalembe, Mirembe, & Banura, 2015). The WHO (2016) currently recommends the primary target group for HPV vaccination is girls between the ages of 9-13, as young women have a most robust immune system and it is more efficacious as a prophylactic (i.e., before acquiring HPV). Efficacy trials have shown that the anti-body response of adolescents and young women (15-26 years) for both the bivalent and quadrivalent vaccines are similar to that of girls aged 9-15 years, however concentration of the antibody or immune response in the younger group of women was

found to be significantly higher compared to older group (McCormack, 2014; Schwarz et al., 2012). A secondary target population of older adolescents and young women as catch-up cohorts are important in reducing HPV rates among the general population (Bruni et al., 2016; Garland et al., 2016).

Robust evidence indicates that HPV vaccines have a favourable safety profile (Stillo, Santisteve, & Lopalco, 2015). A recent global review examining data of over 1 million recipients of the quadrivalent vaccine from 2006-2015 found no serious adverse events (SAE) in recipients (Vichnin et al., 2015). Similarly, a review of the safety of the bivalent and quadrivalent vaccines by Stillo and colleagues (2015) found that although SAEs such as appendicitis, abdominal pain, spontaneous abortion, ovarian cysts, venous thromboembolisms, and Guillain-Barre syndrome had been reported, not one case had been found to be directly related to the vaccine by investigators but rather were due to pre-existing conditions and risk factors. For example, reports of most SAEs were shown to have occurred equally between both the control and active groups. Fatal outcome rates reported for the bivalent vaccine had virtually the same incidence rates between the vaccine (<0.06%) and control groups (0.07%) while the quadrivalent vaccine had one reported death that was attributed to a pre-existing cardiac condition. The most common adverse events (AE) documented within the literature for both vaccines included syncope, local reactions at the inject site, fever, and nausea (Vichnin et al., 2015). Evidence overwhelmingly shows that HPV vaccines are a highly efficacious and safe option in the prevention of infections and diseases caused by HPV and vital in locales with limited secondary screening, high HIV and HPV rates.

As HIV significantly increases the risk of acquiring persistent HPV infections, it is also important to discuss the safety and efficacy of HPV vaccines within this population. For WHIV,

favourable safety profiles have been reported to be equal for both the bivalent and quadrivalent vaccines when compared to HIV negative women (Denny et al., 2013; Levin et al., 2010; Stillo et al., 2015). Further to this, a recent trial conducted with HIV positive and negative women in Canada demonstrated the quadrivalent vaccine to be well tolerated and effective for both groups of women. Post vaccination patients underwent follow-up at 24 months and although higher general seroconversion was found among WHIV, findings indicated that optimal response to the vaccine was among WHIV with a suppressed viral load. This meaning that HIV viral suppression was associated with higher antibody response against HPV infections. Findings from this study demonstrate the need to ensure ideal timing of the HPV vaccination for WHIV, with administration of the HPV vaccine following virologic suppression (Money et al., 2016).

The HPV vaccine is a highly cost-effective health intervention and the WHO (2015) postulates that in LMICs the HPV vaccine could prevent an estimated 4 million cervical cancer related deaths among women over the next decade if a 70% vaccination coverage rate was achieved. However, many countries face significant financial and political barriers in achieving optimal uptake rates (Wigle, Coast, & Watson-Jones, 2013). While many eligible women from high-income and upper-middle income countries have received a full course of the HPV vaccination by the end of 2014 (33.6%), only a small portion of women (2.7%) had received the vaccine in less developed areas of the world (Bruni et al., 2016). Many women living in countries with the highest burden of HIV and cervical cancer cases with challenging access to screening remain unprotected.

In 2014, a public school-based HPV vaccination program was rolled out by the SA Health Department using the bivalent vaccine (Cervarix) aiming to reach girls in grade 4 (aged 9 and older) in 80% of the poorest public schools targeting just under 500,000 girls. No private schools

were included in the program. Vaccinations were performed by Ministry of Health nursing staff once parental consent was received. To date, the targeted vaccination coverage rates for girls in grade 4 was reported at 92% with 412,617/454,652 girls receiving the first round and 422,000/454,652 receiving two doses. The overall estimated coverage rate for children (male and female) born in 2004 due to this program is at an estimated 39% (Botha & Richter, 2015).

South Africa's Deputy Director-General of Strategic Health Programmes in the National Department of Health, Dr. Yogan Pillay, recently reported (2016) that the number of grade 4 girls who had completed the required two doses of HPV vaccination reached 649,330. The goal, Pillay states, is to eventually reach all 18,000 primary schools across the country, as opposed to focus strictly on the poorest schools. With the wealthiest 20% of schools not covered in the HPV vaccination program, Health Minister Aaron Motsaeledi called on medical schemes to pay for the vaccines to help parents in for all learners to be covered by the program. HPV vaccines, however, have not been a priority for medical schemes to cover and have had unimpressive uptake rates to date.

Private sector data from 2015 demonstrated that the HPV vaccine uptake rate in SA have been slow. Data estimates that of the 16 million women eligible for HPV vaccines between the ages of 9-45, only 50,000 received vaccines through private health schemes between 2009 and 2014 (Richter, 2015). An article in the Mail & Guardian reported three of the largest medical schemes, Bonitas, Discovery Health, and Fedhealth's reactions to the Health Ministers message to have all medical aide schemes in the country pay for the HPV vaccine to help all parents be able to afford to have their daughters vaccinated. Bonita responded that they were considering looking into the HPV vaccine for upcoming years but urged its members to access Pap testing with their benefits package. With Discovery Health, the vaccine can be paid for using member savings accounts and

not widely accessed, as 3,578 of its 1.228-million female plan members received the HPV vaccine within the last year. When speaking about the high-cost of the HPV vaccine, a Discovery Health representative stated:

> "Vaccines are typically regarded as a public service or public goods in the sense that it benefits not only individuals who are vaccinated but also society at large, and ultimately the broader healthcare system. We believe that the department of health should consider making vaccines available in the private sector at state tender prices. These prices are well below current private sector vaccine prices, and access to state tender prices would make vaccines significantly more affordable for medical schemes and their members. This would also have the very positive effect of reducing the burden of patients attending public sector clinics" (Green, 2013).

Fedhealth expressed similar concerns about the financial feasibility of offering the HPV vaccine in a benefits package, nothing that "it is unlikely that private patients will be able to get the vaccine at the same price as government can procure it. Legislation states there can only be one single exit price so it is illegal to negotiate prices in the private sector" (Green, 2013). In summary, the government feels the HPV vaccine, specifically for those young women in the 20% of higher income schools and private schools, should be the responsibility of the private sector while the health schemes distinctly feel that the Ministry of Health should be responsible for vaccinating all young women or at the least be able open to negotiating cost-share pricing for the vaccine[4].

Secondary prevention refers to the *early detection and treatment* of diseases using interventions strategies such as screening (WHO, 2014). Current recommended cervical cancer approaches recommended by the WHO (2014) include cytology (Papanicolaou or Pap test), visual inspection using acetic acid (VIA) and HPV testing. The intention of cytology and VIA screening tests are to identify cervical dysplasia or abnormalities while HPV testing aims to detect the presence of HR-HPV types most commonly associated with anogenital cancers. Using

[4] Within the private health sector and with extended insurance the vaccine cost is R650. While in the public sector with no insurance, to buy the vaccine from a pharmacy would cost approximately R2300.

cytology, abnormal changes are categorized by the extent of the dysplasia or cervical intraepithelial neoplasia (CIN) from mild (CIN1) to severe (CIN3). VIA, on the hand, uses acetic acid and a health care professional can visually examine abnormal cellular changes (ibid).

A recent systematic review comparing test accuracy of the HPV test, cytology, and VIA in women over the age of 18 years and HIV negative (or undiagnosed) women found HPV testing to have the highest sensitivity compared to cytology or VIA screening for diagnosing CIN2+. The findings also indicated that the most common form of overtreatment occurred using VIA. The pooled estimates for VIA sensitivity and specificity were 0.77 and 0.82, respectively, and for cytology-based screening was 0.84 and 0.88 while HPV testing was 0.95 and 0.84 (Mustafa et al., 2016). Similarly, a cross-sectional study evaluating screening methods among WHIV in South Africa demonstrated HPV testing to be the most sensitive screening method for detecting CIN 2+, however it was less specific than cytology and VIA. The estimated sensitivity and specificity for VIA was 0.65 and 0.69, respectively, while cytology-based screening was 0.76 and 0.84 and HPV testing 0.92 and 0.51 (Firnhaber et al., 2015).

In SA, cytology-based screening is currently the most common screening tool followed by VIA, with HPV testing being used in pilot projects. A National Cervical Screening Program was established in 2000 and every woman within the public sector over the age of 30 is eligible for 3 free Pap tests administered at 10 year intervals. Despite the free screening, uptake rates in the public health sector are poor and estimated by the SA government to be at 54% for the 2014/15 time period (Ministry of Health, South Africa, 2015). However, uptake rates of Pap tests by Bruni et al. (2015), using multiple small scale studies, are significantly lower averaging annual overall rates of an estimated 14%. Challenges to cytology based screening also include a significant loss to follow-up after receiving abnormal results, competing national and local

healthcare priorities (e.g., tuberculosis; HIV/AIDS), inadequate numbers of health care professionals, and a lack of awareness about HPV and cervical cancer among women (Botha & Richter, 2015; Chidyaonga-Maseko, Chirwa, & Muula, 2015; Francis et al., 2011).

The WHO (2014) notes that cervical cancer prevention efforts in SA are significantly hindered by the absence of an active national cancer registry (which as mentioned earlier was last updated in 2011) and screening program stating that, "irrespective of how good a screening test is, it will have no impact unless introduced as part of a well-planned and implemented program" (p. iv). The central success of a cancer registry and screening program begins with political will, as it requires significant national planning and adequate funding. Creating linkages between vaccine administration and cervical screening and cancer registries would be beneficial for monitoring and needs to be a national priority. Cancer control planning and monitoring is vital for SA; an area of the world with the highest rates of cervical cancer (Bray et al., 2014).

The relationship of HPV in the development of cervical cancer is well-established and therefore HR-HPV testing, which can be clinician-administered or self-administered, is a well-researched and highly recommended approach for underserved and under-resourced areas of the world as an alternative to cytology-based screening. It has also been demonstrated to be a highly accurate and acceptable screening method among women worldwide (Gravitt, Belinson, Salmeron, & Shah, 2011; Racey, Withrow, & Gesink, 2013; Verdoodt et al., 2015). Currently only 6 countries have national HPV testing programs including, Argentina, Italy, Mexico, Netherlands, Spain and the United States with pilot programs in 11 additional countries (see Figure 9).

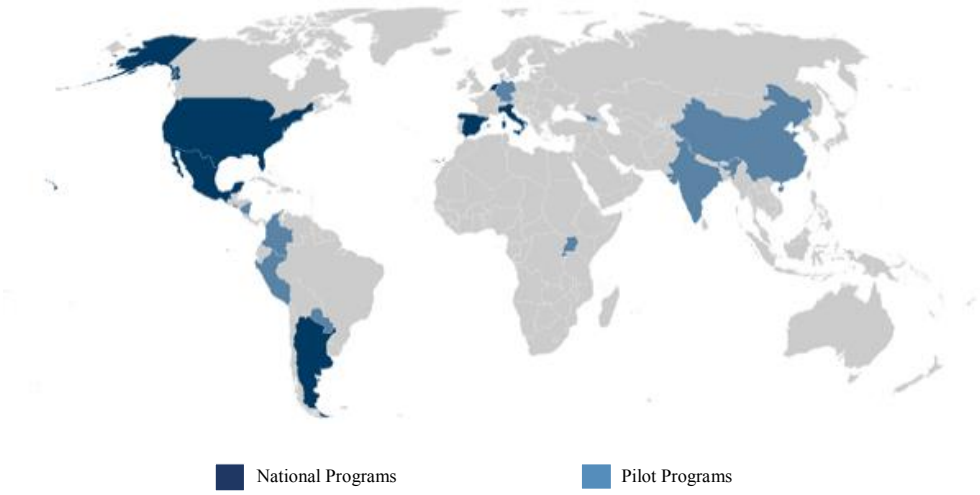

Figure 9. Global Progress in HPV Testing for Cervical Cancer Screening

Note. From "Global Progress in Cervical Cancer Prevention", by Cervical Cancer Coalition, 2016, http://www.cervicalcanceraction.org/comments/maps.php

From a macro perspective, political will and dedicated financing are greatly required to expand HPV vaccination and screening to achieve and maintain a reduction in cervical cancer incidence in SA (Botha & Richter, 2015; Harries, Moodley, Barone, Mall, & Sinanovic, 2009). On an individual level, the global literature from LMICs demonstrates that women's knowledge about these topics is generally poor (Cunningham, Davison, & Aronson, 2014). Additional key factors in the willingness to vaccinate or promote vaccination in SA include being able to better understand the infection and its link to cancer, having a healthcare provider recommend the vaccine, and integrating traditional healers as educators. Within the literature, awareness and knowledge about these topics were positively associated with HPV vaccine acceptance and uptake. Therefore, a successful HPV vaccine campaign would largely benefit from better understanding women's awareness and knowledge, as these factors play a key role in making informed health decisions (Chidyaonga-Maseko et al., 2015; Cunningham et al., 2014; Perlman et al., 2014).

Conceptual Frameworks

This research was designed with the health belief (HBM) and vaccine hesitancy (VHM) models in mind. The HBM is one of the commonly used theories in health behaviour research and identifies contributors that are predictive of health behaviours (i.e., vaccine acceptance or Pap testing) including: risk susceptibility, risk severity, benefits to actions, barriers to action, self-efficacy, and cues to action (Glanz & Bishop, 2010). More specific to my research, and personally preferential, is the VHM[5] which considers not only individual but also historical, political and socio-cultural factors influencing vaccine uptake (Dubé et al., 2013). The model also recognizes the important role that trust in vaccine safety, health care professionals, and policy makers as well as the messages women receive, play in vaccination decision-making (Figure 10). Overall, understanding vaccine acceptance is complex and involves many factors that are not purely cognitive in nature but also emotional, cultural, social, spiritual and political. This research was influenced by both conceptual frameworks by inclusion of these variables in the questionnaire and analysis of covariates in vaccine and self-sample acceptability.

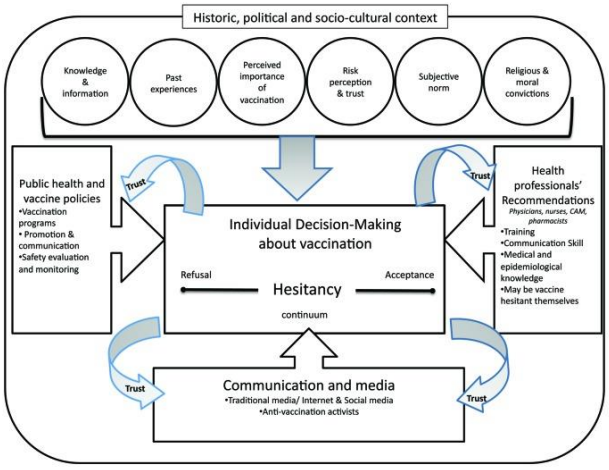

Figure 10. Vaccine Hesitancy Model
Source: Dubé et al. 2013

[5] It is important to note that although the VMH accounts for a variety of factors the play a role in decision-making about vaccines, it has not been adapted for LMICs and does not account for factors such as socioeconomic status.

Social Determinants of Health Perspectives

Disease and health conditions, using this perspective, are thought to be a result of social, economic, as well as political forces, collectively referred to as social determinants of health (Wilkinson & Marmot, 1998). Social determinants of health perspectives outline the remarkable sensitivity to and relationship of health to our social environment. These factors are recognized on both an international (e.g., WHO) and national level (e.g., Public Health Agency of Canada; PHAC) as contributors to health. Many diseases determined by networks of interacting determinants, all of which have the ability to contribute to or negatively affect one's health. Organizations have different ideas about what constitutes a social determinant. For example, the WHO identifies ten main social determinants while the PHAC identifies twelve (see Table 4). By asking questions about social determinants, this research examined these factors and whether they influenced awareness about HPV, cervical cancer, and ultimately acceptance the HPV vaccine.

Table 4. *Social Determinants of Health: WHO & PHAC*

	Determinants
WHO	Social Status; Stress; Early Life; Social Exclusion; Work; Unemployment; Social Support, Addiction; Food; Transportation.
PHAC	Income & Social Status/Support; Education & Literacy; Employment/ Work Conditions; Social Environments; Physical Environments; Personal Health Practices; Coping Skills; Child Development; Biology/Genetics; Health Services; Gender; Culture

Youth Engagement Approaches

The aforementioned conceptual frameworks and perspectives are complimentary to a youth engagement (YE) approach, which was integrated into the project by the AYAZAZI Research Team before my HPV, cervical cancer, and vaccines section of the survey was introduced. The

AYAZAZI research team has a cohort of AYA in Soweto and Durban, SA to identify, understand and link socio-behavioural, clinical, and biomedical patterns of risk for HIV acquisition and vaccine trial preparedness using a mixed method approach. The rationale behind using a YE approach was because the topics being studied were highly personal with the team recognizing the need to collaboratively develop innovative, creative, and culturally appropriate HIV interventions with and for AYA; those most affected by HIV. The AYAZAZI research team believes that AYA voices need to be integrated into SRH health research and policy programming, as they know best. Youth engagement recognizes young people's right to participate in decisions that impact them and recognizes the knowledge and skills they bring to the table. In a research setting, youth engagement involves leadership that is able to see the potential and impact of adults and young people working together (Powers & Tiffany, 2006). This means that youth are included as partners in the design and implementation of research involving key issues that affect their lives thus generating key knowledge to inform future interventions and community mobilization. This project relied on the knowledge of and direction from AYA throughout all stages; from planning to dissemination. Research assistants for this project were two female AYA who assisted in conducting an awareness workshop, questionnaire design and pilot testing, as well as knowledge translation (KT) activities.

Statement of the Problem

Globally, the highest HIV rates are found in SA and more particularly within the province of KwaZulu-Natal where this research takes place. AIDS and related illnesses are currently the leading cause of death among adolescents (10-19) in SA with young women most acutely affected. Cervical cancer is a preventable and significant global health concern. Globally, SA has some of the highest rates of cervical cancer in the world and is currently the leading cause of

cancer among young women in SA, many of whom are HIV positive. HIV/AIDS and cervical cancer are the most serious health challenges faced by South African adolescents and young adolescents (AYA) requiring an immediate global response.

Purpose of the Study

The aims of this study were to describe the knowledge, awareness, and beliefs about HPV infection, cervical cancer, and HPV vaccine among a cohort of AYA and explore factors associated with vaccine acceptability.

Summary

Cervical cancer is a preventable and significant global health concern. South Africa and, in particular, the province of KwaZulu-Natal with the highly dense population and extremely high rates of HIV, is the 'epicentre' of both the HIV and cervical cancer epidemic. Young women specifically are at a significant risk of acquiring HIV and HPV infections, resulting in disproportionately high rates of cervical cancer nationally. It is a pivotal time in global cervical cancer prevention. The HPV vaccine is a safe and efficacious prevention tool with promising outcomes for women of all ages, particularly WHIV. It is the only vaccine available worldwide that has been demonstrated to prevent cancers. Although 'elite responders[6]' to the HPV vaccine are young women, many factors demonstrate the importance of increasing the uptake of vaccine to all women in SA.

The severity of the HPV crisis among young women stems partly from the barriers and disconnection between primary and secondary prevention measures. Lack of education, access to screening services (including follow-up of abnormal results), and low rates of HPV vaccination acceptability and uptake warrants an immediate response from the global research community.

[6] A child/youth with a robust immune system that has not yet engaged in sexual activity and acquired HPV.

Unlike treatments such as ART that do not provide a long-term solution, HPV vaccinations are preventative and have been shown to have cross-protection benefits with minimal adverse outcomes.

Despite national efforts in SA to rollout the HPV vaccines, the uptake remains alarmingly low, particularly among those at the highest risk of acquiring and developing HPV related cancers. It can be argued that governmental approaches alongside embedded societal and cultural barriers contribute to low vaccine uptake. First, government needs to make HPV education and vaccination a national priority that should be seen as a public health investment. Second, barriers to social determinants of health experienced by a significant proportion of vulnerable populations must also be addressed; education, employment, poverty and access to health care services are a few of the factors that must be considered by when developing future health policy and vaccine initiatives in this part of the world. It is also important to have research examine the target population of young women, specifically assessing levels of education around efficacy and safety of vaccinations in general as well as link between HPV and cancer. Further, with the use of the VHM conceptual framework, causal links can be made between societal structures and public trust in vaccinations and recommendations from health care professionals. Finally, closer examination of predictive factors associated with primary and secondary prevention in an area of the world with the highest HIV and cervical cancer rates is required.

This study will address gaps in the literature, help inform preventive health policy, and assist in expansion of the national vaccine initiative in SA by better understanding awareness of HPV and cervical cancer and acceptability of the HPV vaccine among the most vital and affected group of women globally.

Chapter 2: Literature Review

Background

Cervical cancer is the leading cause of cancer deaths among young women in SA. Contributors in the disproportionate morbidity and mortality associated with cervical cancer in this area of the world include high HPV infection rates, high HIV endemicity, challenging access to primary and secondary preventive services, competing health priorities, high levels of sexual violence and poverty and an overall lack of awareness about HPV and its relationship to cervical cancer. Since the introduction of the HPV vaccine worldwide, the availability of and subsequent uptake rates of the HPV vaccine in South Africa remain alarmingly low. Only a small proportion of the population have access to private medical insurance, leaving the majority (~80%) most at risk for HPV acquisition unable to access the vaccine. In 2014, the Health Department in South Africa began a national rollout of HPV vaccines among girls in grade 4 in some public schools, however the overall national coverage rate for eligible females currently remains inadequately low. The greatest public health impact of HPV vaccination will be in countries with limited or no access to screening. The high rate of cervical cancer combined with the current lack of access to the HPV vaccine warrant the expansion of vaccine availability to those who need it most in South Africa, which will ultimately require a better understanding factors influencing women's decision to be vaccinated.

Key Global Reports

Two key reports about HPV vaccine delivery strategies in LMICs exist: one was authored by the World Health Organization (WHO; 2011) and the second by the Program for Appropriate Technology in Health (PATH; 2015). Both are important starting points or background for this literature review. Both reviews provide details of large-scale demonstration projects and provide insight on HPV vaccine program development for informing decision makers. PATH routinely

provides HPV vaccines at a subsidized rate for LICs. It is important to note that while PATH provides vaccines for a variety of LICs, SA does not qualify for their subsidy programs due to its designation as a middle-income country. However, lessons learned in areas with low resources and high rates of HPV and cervical cancer are beneficial to compare and can serve as examples for South Africa's current National HPV vaccination program.

Since 2006, PATH and GAVI Alliance have worked with these four countries to better understand how to most efficiently deliver the vaccine; reasons behind acceptance or refusal of the vaccine; and on outcomes which are used to inform government and aid in the development or scale-up of HPV vaccine programs. The first report, by PATH, was conducted with parents of girls eligible for HPV in LICs in four countries, including Peru (264 schools and 161 health facilities), Uganda (417 schools and 69 health facilities), India (537 schools and 672 health facilities), and Vietnam (38 schools and 72 health facilities) (LaMontagne et al., 2011). Findings showed from the cross-sectional study included the uptake rate for 7,269 young women between the ages of 9-14 and response surveys with parents, most of whom were mothers. Overall, findings demonstrated moderate HPV vaccination coverage within the demonstration projects, with the exception of one program in Uganda that coupled with an existing Child Days Plus program (52.6%). School-based programs uptake ranged from 88.9-96.1% in Peru, Uganda, and Vietnam. The combination approach used in India (delivered in schools and health centres) averaged from 77.2% to 87.8% (urban vs. rural). Solely health-centre based HPV vaccine delivery approaches in Vietnam had the highest coverage rates at 98.6%. Parent responses indicated that they had a positive perception about the HPV vaccine and its benefits to their daughter's health in general, despite a lack of awareness about cervical cancer or HPV. A belief in and support of vaccines in general was associated with HPV vaccine acceptance. Finally, the

messaging surrounding the vaccine was a factor in parent decision-making. Barriers reported by parents included absenteeism of students, limited awareness about the vaccination program; lack of knowledge about cervical cancer, HPV and vaccine; as well as challenges in determining girl's eligibility. The authors conclude that "more attentive planning and communication" (p.8) could help to address some of the barriers faced in the demonstration projects.

A recent report by PATH (2016) in collaboration with the London School of Hygiene and Tropical Medicine outlines lessons learned from HPV demonstration projects and national programs in LMICs. The objectives of the report were to synthesize lessons learned, generate recommendations on vaccine delivery strategies and best practices for both demonstration and national programs. A variety of HPV vaccine support programs are available for low-resource countries through Merck & Co, GARDASIL® Access Program (GAP), GAVI Vaccine Alliance, the Australian Cervical Cancer Foundation and PATH (funded by the Bill and Melinda Gates Foundation). This cross-sectional retrospective review includes 46 countries, a systematic review (72 articles), unpublished literature (188 reports) and key informant interviews (56) from 40 different countries. Delivery experiences were reviewed from 12 national programs; 66 demonstration projects or pilots with a total of 92 distinct experiences within the countries. Overall, findings demonstrate that the delivery of the HPV vaccine is feasible and highly acceptable resulting in impressive coverage rates in LMICs. The total number of young women vaccinated through the projects and programs is ~1.8M, with 1.4M achieving full vaccination status (all three doses). Findings were organized by general topics including, national decision-making and planning, service delivery, health workforce, monitoring and evaluation, financial support and sustainability, and scale-up. Given the scope of the project and literature review, all

factors mentioned will be reported and considered, however findings regarding acceptance or refusal of the HPV vaccine and successful delivery strategies will be reviewed in greater detail.

Key findings and lessons learned from the demonstration projects and national programs include adequate preparation, communication, and delivery strategies. This meaning that high-level political commitment plays a vital role in the success of any project or program and that time has to be allotted to gain acceptance with proper education and stakeholders prior to the administration of the vaccine while recognizing that each locale has unique needs needing to be addressed. An intersectoral planning approach is key to successful implementation and sustainability of the HPV vaccine program. In addition, the integration of the HPV vaccine with other routine vaccination programs also proved to be an effective way to increase participation. In terms of the most effective delivery strategies, projects or programs that included school-based HPV vaccine delivery had higher uptake rates. Knowledge about HPV and its association to cervical cancer, as well as the vaccine throughout countries involved in demonstration projects was generally low. However, messaging that focused on the safety profile and efficacy of the vaccine, and endorsement the vaccine by national government and international standards (WHO), contributed to more successful uptake rates of the vaccine. The most influential individuals in the delivery of the HPV vaccine are health workers, teachers, and community leaders. Community mobilization activities are vital to introduce prior to vaccination by both health workers and community leaders with appropriate messaging. Face-to-face communication with community members and parents helped to decrease the spread of misinformation regarding the vaccine and program thus improving acceptance of the vaccine.

Overall, the lessons learned in the development and implementation of HPV vaccination strategies include the benefit of integrating HPV vaccines in a school setting, identifying eligible

girls based on grades or class rather than age, and integrating the HPV vaccine to other national immunization schedules. Adequate preparation, coordination, monitoring and supportive supervision within the health and education system, as these factors facilitate higher HPV vaccine uptake. Evidence-based education and outreach needs to begin at least one month before rollout with locale specific materials to help raise community awareness. Findings outline the low levels of awareness and knowledge about these topics in all areas of the world and the importance of reframing the message from HPV as an STI to receiving the HPV vaccine as a means of preventing cervical cancer and HPV related cancers.

Factors Associated with HPV Vaccine Acceptability and Uptake: Literature Search

The objective for the remainder of the chapter is to provide an examination of peer-reviewed literature about factors associated with HPV vaccine acceptability and uptake among AYA and parents (caretakers) in LMICs. A search was conducted in the electronic database: Ovid MEDLINE, to identify studies related to strategies used to increase HPV vaccination uptake and vaccine acceptability in LMICs with specific focus on females with a total of 198 articles first identified (see Appendix A for the search strategy). Based on the key questions, inclusion and exclusion criteria were determined. Included were full articles written in English. Articles written before the year 2000 were excluded. Studies conducted with male participants were excluded with the exception of articles about health care professionals in training. Articles that were not research based were also excluded (e.g., opinion papers). Because understanding perspectives, knowledge, and awareness about these topics from future health care professionals is important to answering questions about acceptability of the vaccine among female AYA, studies about medical and nursing students with male participants were also reviewed. If a study had parents or caregivers paired with daughters receiving vaccines, the articles were reviewed. Articles

including parental attitudes and acceptance towards the HPV vaccine were also included. Inclusion criteria for the review included: research measuring uptake and acceptability (actual and theoretical) of the HPV vaccine among female adolescents (16-19 years) and young adults (15-29 years). Due to the 'elite responder' age of 9-13, articles including all young women 9- 29 years were included. The review did not explore studies with cohorts of females older than 29 years of age (unless it was a parent or caregiver study). If a study had groups of women ranging in ages, only studies with cohorts of women with a mean age of 23 years (median of ages of interest 15-29) and younger were included.

Two review articles, including one systematic review about factors associated with HPV vaccine acceptability in African countries and a general review about contributory factors associated with cervical cancer prevention strategies in LMICs were reviewed. Eleven articles featuring the work of seven teams working to better understand factors influencing or associated with HPV vaccine uptake among adolescents and caregivers in LMICs were reviewed. Seventeen studies regarding attitudes, perceptions, and acceptability (theoretical) of the HPV vaccine among AYA were reviewed. Although literature about parental or caregiver's attitudes towards and acceptance of the HPV vaccine for daughters is not directly related to the topic of this dissertation research and AYA acceptability specifically, twenty eight articles about this subpopulation were reviewed and a brief summary is provided to give context and better understand the educational needs and correlates or predictors of HPV vaccine acceptance among parents and caregivers who are, in some cases, the decision-makers for children and adolescents. Although a total of 198 articles were identified, once inclusion and exclusion criteria was implemented and articles were reviewed, a total of 140 articles were excluded (see Appendix B for search strategy flow diagram).

A wide range of literature exists about knowledge of HPV, vaccines, and women's acceptability (intention) of the HPV vaccine, however very few articles are available which specifically examine the direct role of interventions in or specific factors associated with HPV vaccine uptake among female AYA and caretakers in LMICs. Findings from this review indicates a common theme among AYA and parents that knowledge about HPV and its associated diseases are very low in LMICs despite cervical cancer being a leading cause of death among women in these areas of the world. Acceptability of the vaccine among both AYAs and parents and willingness to participate in interventions which aid in the prevention of cervical cancer, despite having very little awareness about these topics, was consistently very high throughout all studies; this was the similar for both acceptability in-theory and actual uptake studies. Comprehensive education campaigns which included a wide variety of stakeholders (nurses; educators; policy-makers, media and parents) for periods of time prior to the administration of the vaccine, demonstrated to be an important contributor to successful acceptability and uptake rates for AYA and parents. Key features cited in the literature commonly associated with reluctance towards the HPV vaccine include: confusion or misinformation regarding the safety profile of the vaccine; a lack of awareness about how cervical cancer can be prevented; challenging medical infrastructure and quality of vaccine program; affordability of the vaccine; and the stigma associated with HPV being a STI. Health care provider attitudes towards, opinions about, and recommendation to patients demonstrated to play a critical role in the willingness to participate in the HPV vaccine for both the female AYA and parents.

Review Articles

A recent review article examined contributing factors of cervical cancer prevention services in LMICs and categorized barriers as individual, community, and health system-related (Chidyaonga-Maseko et al., 2015). From the 31 articles reviewed by the authors, the most common individual barrier in cervical cancer prevention services was inadequate knowledge about HPV and cervical cancer in general. More particularly, a lack of awareness about the association of HPV to cervical cancer and a familiarity with preventive health. Other notable contributory individual factors included challenging economic circumstances and geographic inaccessibility to preventive services. Cultural beliefs and embarrassment were also cited as important factors in the decision to participate in screening and HPV vaccination. Community-related factors include social norms, gender roles, and women's predominantly subordinate positions in LMICs. The way in which HPV is viewed (social stigma) and sex education is offered, plays a role in women's willingness to participate in preventive measures. Finally, health system-related factors such as having an organized cervical cancer prevention program requires adequate financial resources, infrastructure, health care professionals, and surveillance. The political will of a country and national prioritization is arguably one of the most significant factors in the uptake of preventive cervical cancer services for women living in LMICs.

A systematic review about HPV vaccine acceptability from a parental perspective by Cunningham and colleagues (2014) and included fourteen studies from ten sub-Saharan African countries. Overall, acceptability of the vaccine was high (59-100%) however similar to the previous review, awareness and knowledge about the topic of HPV, cervical cancer, and HPV vaccines were low and strongly associated with acceptability of the vaccine. Using a health belief model framework, the authors found that perceived personal risk of acquiring HPV

infection and developing cervical cancer was low and corresponded with a lower vaccine acceptance rate. Conversely, the higher the perceived severity associated with cervical cancer the more likely women were to accept the vaccine. In terms of perceived effectiveness and benefits of the HPV vaccine, the literature demonstrated higher acceptability among participants with previous positive experiences with vaccines and in areas with higher levels of sexual violence towards young women. The perceived barriers ranged in the literature from cost, availability or accessibility, and uncertainty about the safety profile of the vaccine, however these factors did not deter participants from accepting the vaccine. Finally, recommendations from health care professionals played an important role in vaccine acceptance in over half of the studies reviewed. Most importantly, public endorsements by the government and community attitudes were also found to be key factors in HPV vaccine acceptance among women in Africa.

Uptake of the HPV Vaccine: South Africa

Six articles about three demonstration studies related to uptake of the HPV vaccine among adolescents in South Africa were reviewed. The HPV vaccine demonstration teams conducted research in KwaZulu-Natal, Gauteng, and Western Cape provinces. The first demonstration project conducted was in 2011 (before the national rollout in 2014) and included 31 primary schools (1000 learners aged 9-14 in grades 4 and 5) in the province of KZN (Moodley, Tathiah, Mubaiwa, & Denny, 2013). The demonstration sites were based in settlements characterized by high HIV rates, poverty, and poor access to services. A working group was established prior to the project that included various key stakeholders such as provincial and district health and education representatives. Information sessions were held with a wide array of community members including principals, teachers, school governing bodies, parents, community and religious leaders, traditional leaders, traditional healers, school health teams, hospital nurse and

doctors and private practitioners prior to the administration of the program. Training, education, and administration of the vaccines was offered by teams consisting of a nursing sister, a registered nurse, and 2 enrollment nurses. Results from the study indicate successful vaccine uptake rates, with 963 of the learners receiving the first dose, 943 (97.9%) the second, and 938 (97.8%) the third, respectively. With educational materials provided about cervical cancer screening and prevention the authors hoped to promote Pap testing at the local clinics. A school-based setting for HPV vaccination programs are ideal and it is very important to begin planning well before the implementation of the program. This project demonstrates high acceptance rates of the HPV vaccine, credited in part to the inclusion of the community in the discussion about outreach and educational messaging and effective training strategies.

A qualitative study conducted by Katz and colleagues (2013) in Soweto, the province of Gauteng, examined factors influencing HPV vaccination (bivalent) uptake among a sample of low-income South African adolescents between the ages of 12-19 years (*N*=224) and their female caregivers (*N*=39). Of the youth recruited, 201 agreed to partake in the HPV vaccine and received the first dose; 192 (95.5%) received a second; and 164 (81.6%) completed all three doses. Adolescents and caregivers of youth who had accepted the vaccine were chosen randomly to participate in a semi-structured interview to better understand perspectives regarding their decision-making. All but two caregivers identified as single-parents with many women not having a steady source of income. Four themes emerged from this study including, single-headed households lead to adolescent autonomy in decision-making; the role of health care providers (HCP) and peers in influencing vaccine uptake and providing support; STI vaccination as a harm-reduction strategy in the setting of endemic gender-based violence; and the influence of the HIV epidemic in understanding of the HPV vaccine. Caregivers expressed concerns about not

being able to keep their children safe and the vaccine represented a way in which they could better protect their daughters against cervical cancer. High levels of sexual violence against and exploitation of young women was also important drivers for caregivers and adolescents in vaccine uptake. Adolescents described having a high degree of autonomy in their health-decision making and commonly educated the caregivers about sexual health matters, in particular about the benefits of vaccination. Both caregivers and adolescents described the role of and relationships with the health care professionals as essential in providing sexual health education in this setting which significantly influenced decisions about health. Peers also played a role in encouraging one another to initiate the vaccine (Katz et al., 2013).

The Vaccine and Cervical Cancer Screen (VACCS) project (4 articles) was conducted in a total of 34 low resource schools in rural Gauteng and Western Cape and focused on multi-generational learning, educating female caregivers of adolescents being offered the HPV vaccine for females in grades 4-7 (Dreyer et al., 2015; Snyman, Dreyer, Botha, & van der Merwe, 2015; Snyman, Dreyer, Botha, van der Merwe, & Becker, 2015). The demonstration studies were coordinated in a way that first educated all key stakeholders, educators, administrators of schools, and then placed focus on parents and adolescents. The school-based approach gave an opportunity to increase knowledge about cervical cancer therefore also improving acceptance of preventive measures for both mothers and daughters. A key focus was also on messaging to the community about the vaccine, as a preventive vaccine rather than STI related. Findings overall demonstrated an improvement in screening (using HPV testing and cytology) among the mothers involved in the projects and uptake of the vaccine was very high. The first project, conducted in 19 primary schools (2,000 school girls) administered both the Cervarix and Gardasil vaccines with girls younger than 10 receiving Gardasil and all others Cervarix. The first dose of the

vaccine to 2,030 girls (99.2% of invited cohort) with a total of 1,859 (91.6%) considered 'adequately' vaccinated. For the purpose of this study, girls who had received at least 2 doses 6 months apart and those who received 3 doses were considered sufficiently vaccinated. Findings demonstrated that parents who attended the information night were significantly more likely to have their children vaccinated, however girls aged 12 and over were eligible to participate in the vaccine without parental consent. Offering the vaccine throughout one school calendar year also improved uptake completion rates. Education is a key ingredient in the roll-out of the vaccine and school-based settings are the ideal place in which multi-generational learning can occur[7].

In the second paper by the VACCS team (2015), HR-HPV self-screening and vaccine uptake rates are reported for girls and their mothers in 10 schools across the province of Gauteng. This implementation study was conducted among 1,654 eligible girls and mothers. Of the invited girls for vaccine, 1,053 girls received the first vaccine and 941 (89.4%) were considered adequately vaccinated or completed two doses within 6 months or three full doses. Findings demonstrated a significant completion rate difference between schools with vaccination schedule completed within the same calendar year compared to over two calendar years. Consent for vaccination was higher among the parents who attended the education seminar about cervical cancer. Uptake of the test for HR-HPV was offered to 596 parents or guardians who attended the education events at schools and 795 test kits were handed out. A total of 253 (44%) kits were returned. The presence of HR-HPV was found in 75 (29.6%) of the samples tested with 23 (9.1%) positive for HPV 16 and/or 18. A significant portion of women (45) reported not participating in cervical cancer screening for 5+ years despite the mean age of 38 years. The authors measured knowledge and behaviour following education sessions with pre- and post- findings

[7] It is important to note that an estimated 4% of children between the ages of 7-13 years are not enrolled in school in South Africa; therefore strategies also need to exist for outreach to these special populations.

demonstrating the key elements of education, communication, and team involvement make a difference in effective delivery of the HPV vaccine. It also shows the interest and acceptability of hrHPV self-collection testing (an approach with increased sensitivity and predictive value) among a group of women with high rates of HPV and limited access to screening services.

The project was offered in two stages using lessons learned in VACCS1 to inform VACCS2 (Snyman, Dreyer, Botha, & van der Merwe, 2015). The second project involved five schools in the province of Gauteng. From the 965 girls invited for vaccination 519 (53.7%) consented and 518 (99.8%) of these received the first dose and 495 (95.4%) completion rate. For this study, the project provided a two-dose schedule of the vaccine, taking into account preliminary data showing sufficient immunogenic response from the two-dose schedule (when administered within a 6-month time period between doses). Similar to stage one of the project, the aim was to also link feasibility of offering HPV self-testing for female caregivers of girls (grade 4-7) receiving the vaccine. A total of 1,135 self-screening kits were given out to caregivers and 575 (50.7%) were returned. Results showed that 27 (16.9%) of women tested positive for oncogenic HPV while 15 (9.4%) were positive for HPV 16 and/or 18. Findings demonstrate the benefits of offering self –testing with HPV vaccination, or a multi-generational approach, as it increases acceptability and yields high uptake rates. All studies suggest that school-based programs can be implemented quite successfully in a range of urban and rural locales and should be designed to target those most at-risk of acquiring HPV and related cancers in South Africa.

Uptake of the HPV Vaccine: Low- and Middle-Income Countries

Five articles related to factors influencing HPV vaccine uptake among AYA in other LMICs published from 2012-2015 were included in the literature review. The studies were conducted in Uganda, Brazil, Peru, Tanzania, and Cameroon. Participants in these articles ranged between the

ages of 9 – 19 years. Vaccine uptake rates for completion were found to be fairly high ranging from 65-88% within the articles. The study designs were all demonstrations/interventions. Studies were conducted from 2012-2015 and sought to describe factors involved in uptake or refusal of the vaccine and/or lessons learned from projects.

A study examining the feasibility of HPV vaccines for girls in Uganda, interviews and focus groups were conducted with key informants including health workers, teachers, and national health officials. The goal of the cross-sectional study was to better understand the most appropriate HPV vaccine (bivalent) delivery strategy for young women aged 10-15 years (Mugisha et al., 2015). Vaccine uptake and acceptability rates were reported and evaluated for two different delivery strategies in two Ugandan districts: grade-based (grade 5) and age-based (10-year-olds). Vaccines in both strategies were administered during an existing national child program distributing medications and vitamins. Findings from this study indicated the difficulty with both establishing eligibility using an age-based delivery strategy but also higher dropout rates between dose 1 and dose 3 of the HPV vaccine. For age-based the drop out between doses was as high as 27%, while in the grade-based strategy, the dropout rate was only 12%. Interviews and focus groups with key informants were then conducted to better understand factors involved in the success and obstacles in both strategies. Further to this, interviews with key informants demonstrated that several key factors contributed to the successful delivery of the HPV vaccine including: coordination between health workers and teachers; appropriate delivery strategy designs based on synergistic working relationships; positive responses and actions from teachers in delivery; and visible government endorsements and ownership of the program.

Lessons learned included the need to administer all three doses to students within the same school year, as the loss to follow-up was identified to be problematic due to students moving to

new districts the following year. A challenge identified by teachers was absenteeism during days which vaccines were being administered which was more easily able to be addressed within the grade-based strategy as teachers knew their students and could follow up for missed does. With a limited workforce the authors posit that delivery of the HPV vaccine be co-administered with routine national vaccines and a grade-based rather than age-based strategy be implemented.

A unique demonstration project took part in the Peruvian jungle examining the role of pairing mothers and daughters in a screen, treat, and vaccination program (Abuelo et al., 2013). Using a community-based participatory research approach, community health leaders were hired and trained to educate and collect data in rural and urban areas along the Amazon, Peru. The health leaders were given 2.5 days of training prior to recruiting participants. In total, 320 women (30-45 years) and their daughter, niece, granddaughter, or "child of the community" (aged 10-13 years) were recruited from soup kitchens, schools, and health posts in 175 rural areas and 145 in the city. Girls aged 10-13 were administered the quadrivalent vaccine while mothers were given an HPV self-sample test to perform at home. Results demonstrated that 37 (11.5%) women tested positive for HR-HPV with most (30; 80%) attending follow-up (colposcopy, biopsies, and cryotherapy). A total of 312 (98%) girls received the first dose of the HPV vaccine, 280 (90.6%) the second, and 200 (71.5%) the third or final dose. Issues cited as barriers to completing the three-dose schedule included, not being able to locate participants, pregnancy, or parent refusal. Challenging retention was also due to a severe flood in the areas involved in the study and participants needing to be relocated. Evaluations of the program indicated that participants were highly satisfied with self-sample testing (99.7%) and most felt competent and comfortable conducting HPV self-sample tests without assistance (97%). The author's stated that the concept of a mother-daughter program is appealing however may be less effective for vaccination

compared to a stand-alone school-based vaccination program. This is particularly the case because the study encountered problems of vaccine retention and challenging terrain, and many health leaders were conducting research door-to-door. Having a program within an organized system would achieve higher HPV vaccination uptake and completion rates. The authors also note the need to vaccinate girls early in this area of the world, due to higher than usual pregnancy rates among 11-year olds. Using a community based preventive care model, this study displays the need for community specific researchers, materials, and awareness campaigns. Ultimately, the need for buy-in from educators, community, parents, and girls themselves was essential in the successful uptake of the vaccine in this project.

Acceptability, feasibility, and best delivery strategies for the HPV vaccine were explored in an HPV vaccine demonstration project in Cameroon to inform the government in the rollout of the vaccine nationally. An HPV vaccine demonstration project that took place in the capital city, Yaoundé, Cameroon (Ogembo et al., 2014). At the start of the study, there was reluctance to offer the vaccines in schools for fears of adverse reactions due to misinformation. The authors note that once no adverse events were reported at the first stages of the project after vaccinating the first 1,600 girls in a clinic setting (to best monitor for events), the vaccine was then moved in schools and communities (using mobile clinics and door-to-door or peer-tracking approaches). The study group was given donations of the vaccine (19,200 doses) by the International Gardasil Access Program and offered the HPV vaccine to girls aged 9-13 years in a variety of settings. Awareness campaigns were delivered in schools, churches, clinics, and community gatherings prior to the administration of the vaccine. Nursing staff designed print materials for their local clinics to educate girls in their own communities. The initial goal was to enroll 6,400 girls while a total of 6,851, 6,517 and 5,796 girls received the first, second, and third doses of the vaccine,

respectively. The authors note the very challenging circumstances they had to work with, including the publication of an inflammatory local newspaper article about the harms of the HPV vaccine during the time of the project. The project shows that with adequate information to stakeholders, HPV vaccination is feasible and if fears continue to persist in a community about the safety profile of the vaccine, ensuring a setting within a clinic is accessible to first administer the vaccine may help as a starting point. The success noted in this project can be attributed to "training, commitment, and leadership" (p. 4402) of the health facility staff, better understanding religious and socio-cultural conflicts related to the HPV vaccine, and that high uptake is directly linked to education of parents, caregivers, teachers, traditional and religious leaders, and communities.

In a school-based HPV vaccination demonstrative study in Brazil, Frehnani and colleagues (2013) evaluated the uptake and completion rate for girls in the sixth and seventh grade (mean age of 11.9 years). The study included two public and six private schools in the rural town of Barretos with 1,574 eligible adolescents for vaccination. One month prior to the administration of the HPV vaccine (quadrivalent) the study was advertised throughout the community using a variety of approaches including billboards, television, newspaper, internet, and local radio stations. All educators involved in the project were scheduled for an education week with nursing staff. An education week was also offered to eligible female students to discuss sexual health, STIs, and the vaccine. Students were then also encouraged to have their parents attend a parent meeting. The parent meeting was led by physicians and nursing staff and parents were asked to fill out a questionnaire. Most parents reported being informed of the vaccine demonstration project by the school followed by local media and medical professionals. The parents of 124 girls refused the vaccine (~9%). The most commonly cited reason for refusal was

incorrect information about the vaccine and fear of adverse events (28.4%), undisclosed personal reasons (20.2%), and the child not wanting the vaccine (14.5%). Other reasons included feeling the child was too young, health problems, a belief that vaccines are not necessary, physician advise against it, no knowledge or trust of the vaccine and difficulties travelling to receive the vaccine. Overall, parent acceptance was 91.8% (1,389). Vaccine uptake rates for the first, second, and third doses were 87.5%, 86.3%, and 85.0%, respectively. This study demonstrates the feasibility of school-based HPV vaccination as a prime vaccine administration site. It also outlines the importance of information being made available through the education system and ensuring that educators, girls, and their parents are properly educated prior to the rollout of HPV vaccines.

A cluster-randomized trial conducted in Mwanza, Tanzania by Watson-Jones and colleagues (2012) aimed to better understand the most ideal delivery strategy for the HPV vaccine for girls in grade 6 or 14 years of age at the time of the study. The study compared two strategies, class- versus age-based, in 134 schools (60 urban, 60 rural, and 14 private schools) among 5,532 young women. Vaccines (quadrivalent) for the demonstration project were provided by Axios Healthcare Development and administered by government nursing staff in selected schools. Prior to vaccination rollout, teachers, parents/guardians, and girls were given verbal and written information about the vaccine in community meetings. Awareness was also raised using pamphlets and posters, radio messages, and community drama groups in Mwanza. The project used an opt-out consent approach whereby parents not wanting their daughters to receive the vaccine were given the opportunity to indicate this prior to administration. In total, 67 schools used an age-based approach and 67 schools were selected for class- or grade-based vaccination. Three private schools refused to participate in the project. Vaccine coverage rates were 84.7%

for the first dose, 81.4% for the second dose, and 76.1% received all 3 doses. Class-based vaccination uptake was significantly higher than age-based for all three doses (78.7% vs. 72.1%).

Among the 848 (15.3%) girls who did not receive the first dose parent refusal and absence from school on the day of vaccinations were the main cited reasons. Parent refusal was particularly evident in private schools and several urban government schools. As the first randomized trial to examine delivery strategies for HPV vaccination, evidence indicates the efficacy of using a class-based delivery strategy due to logistical advantages of having all girls in one location and being able to work closely with school staff and parents in one class rather than multiple classrooms. The reluctance of parents in private schools was, in part, attributed to teacher responses and refusal to hold parent-teacher meetings prior due to fears about losing income from parents who did not approve. The author's noted that a national campaign of information about cervical cancer and the benefits of HPV vaccination would be needed which specifically addressed staff and parents in private schools. The study demonstrates that the HPV vaccine is highly acceptable in the population with class-based delivery strategies having higher coverage rates (Watson-Jones et al., 2012).

Findings from all studies demonstrate that appropriate education about the virus and its association to cervical cancer as well as dispelling myths about the safety of the vaccine were key factors in the decision to participate in vaccination. Studies also examined the delivery strategy of the vaccine and found the most successful uptake rates were in a school-based or multiple delivery site approaches (i.e., school and clinic based). A common theme among all articles was the vital role that HCPs, educators, and government or social media messaging played in women's decisions to both screen and vaccinate. Finally, the involvement and education of various stakeholders (i.e., school staff; parents; government) plays a critical role in

the acceptance of the HPV vaccine in multiple settings. In addition, areas with high levels of HIV, sexual violence, poverty and predominantly female single-headed household's interventions need to focus on ensuring that adolescents receive extensive education about cervical cancer prevention.

School-based vaccination programs are effective way to ensure three dose completion and ability to track young women by grade. Reasons for refusal include questions about the safety profile, mistrust, the belief that girls were 'too young', and a lack of knowledge about HPV and cervical cancer. Credible information sources play a critical role in HPV vaccine uptake and needs to be done well in advance to administration of the vaccine in both demonstrative projects and programs. Ensuring the messaging regarding the vaccine is focused on cancer prevention rather than STI and normalizing the topic within the community with locally curtailed awareness campaigns (*e.g.,* radio advertisements; television; internet; posters and adverts). Highest uptake rates are found in school-based program rather than clinic or door-to-door approaches. CBPR designs and community involvement can contribute to successful recruitment and ensure locale specific approaches are used in the implementation of the project. High satisfaction was reported using a community-based approach with the added bonus of having high vaccine uptake rates, this was particularly reported to be the case in challenging locales. Careful planning needs to be done prior vaccine programs being implemented, in any setting and adequate training needs to take place with all staff involved in the program, applicable government officials, and community members.

HPV Awareness HPV Vaccine Acceptability among AYA

A total of seventeen articles were reviewed about attitudes, perceptions, and acceptability of the HPV vaccine among young women in LMIC's and are organized by area of the world the

research was conducted in. Six studies that met search criteria took place in Africa (South Africa; Nigeria; Cameroon; and Uganda), ten studies were conducted in Euroasia (Turkey; Thailand; India; Lebanon; China; and Malaysia), and one in South America (Argentina). Of the six studies conducted in Africa, four studies had female University students as participants and two recruited adolescent females from high schools. Of the ten studies from Euroasia, three were conducted with medical and nursing students, five of the studies recruited undergraduate students, one study was with middle school students and one study recruited female AYA from community clinics. The research conducted in Argentina, South America, was conducted with young women in a hospital setting.

A cross-sectional study conducted with female undergraduate students in Durban (*N*=440), SA, examined correlates of HPV vaccine acceptance (Hoque, Ghuman, & Van Hal, 2013). The mean age of respondents was 20.39 years with 63% of participants reporting to have engaged in sexual activity of which the majority, 79.4%, had only one prior sexual partner. Among female university students who had never had sex, many (58.9%) had heard of cervical cancer prior to the study and only 12 women were aware that a sexually transmitted virus caused cervical cancer. Many participants (36.5%) believed cervical cancer to be a disease that is inherited. Despite the low rates of awareness about HPV and cervical cancer, of the 163 (37%) participants with no prior sexual history, 125 (77.3%) reported that they would be willing to receive the HPV vaccine. The most common reasons for refusal of the vaccine included being afraid of the injection and fears about side effects and pain. Acceptance of the vaccine was significantly associated with family members having been diagnosed with HPV or cervical cancer. Women who reported to know about the Pap smear test and were informed about risk factors associated

with cervical cancer (multiple partners; early sexual debut; smoking and STIs) were more likely to accept the vaccine compared to others (Hoque et al., 2013).

Similarly, a study conducted in Lagos, Nigeria among female University students also found low levels of knowledge about HPV, cervical cancer, and vaccines (Makwe, Anorlu, & Odeyemi, 2012). The mean age for the 362 respondents was 21.5 years with 41.4% reporting to have engaged in sexual activity with 21% having one prior sexual partner. A total of 56.4% women were aware of cervical cancer and 17.7% knew about HPV prior to the study. The connection between HPV and cervical cancer was reported to be known by only 11.1% of the participants. Overall, from the 15 true or false questions about HPV, the median score was 2. Perceived risk for acquiring HPV infection and developing cervical cancer was low at 6.25% and 6.9%, respectively. Of the 362 participants, 14% were aware that an HPV vaccine existed, 57.7% of which reported to be willing to receive the vaccine. Reasons for refusal of the vaccine were not reported nor was the relationship between knowledge and/or risk perception in vaccine acceptability.

Two studies were conducted in Nigeria examining knowledge about HPV and acceptance of vaccination among university students. The first study took place at a University in Kano, northern Nigeria with 375 female undergraduate students recruited from various academic departments (Iliyasu, Abubakar, Aliyu, & Galadanci, 2010). Participants had a mean age of 22.7 years with 21% reporting to have previous sexual experience with 67.1% having sexual relations with only one partner. A total of 202 (53.9%) women were aware of cervical cancer and 133 (35.5%) knew about HPV prior to the study. The relationship between HPV and cervical cancer was reported to be known by 18.4% of the participants. Many respondents reported they thought cervical cancer was inherited (39%). A total of 277 (74%) of participants reported HPV vaccine

acceptance with significant predictors including age (older women more likely to engage), medical education (compared to other education departments), and having higher levels of HPV knowledge and awareness about cervical cancer. Documented reasons for refusal of the vaccine were most commonly because of fear of side effects and controversies around vaccines.

A more recent cross-sectional study (2015) was conducted in Southwest Nigeria to determine knowledge of HPV and cervical cancer as well as acceptance of the HPV vaccine among 169 female medical students (Adejuyigbe, Balogun, Sekoni, & Adegbola, 2015). The authors note the importance of gauging medical students as future healthcare providers who will inevitably play an important role in patient decisions about the HPV vaccine. The mean age of participants was 20.8 years with most reporting to never have had sex before (77.1%). Most women reported having between 1-5 sexual partners in their lifetime (81%). Most participants had heard of cervical cancer (95.4%), HPV (85.4%), but fewer had heard about the HPV vaccine (69.3%) prior to the study. Of the cohort of students, 95.9% had never received the HPV vaccine. Most of the women (75.7%) would accept the vaccine if it was free, 3.6% were not willing and 20.7% said they were unsure about the vaccine. Participants noted that barriers to the vaccine include inadequate information, high cost, challenging access, worry regarding the safety and efficacy, and religious reasons. The factors found to be significantly associated to HPV vaccination acceptance were having good knowledge about HPV and the HPV vaccine and age, with older participants significantly more knowledgeable about the topics.

Evidence demonstrates that a significant number of elite responders exists in university settings with a fair proportion of young women who have had sexual relations with only one partner. HPV vaccine acceptability, therefore, is important to explore among this group of women. Overwhelmingly data shows that awareness and knowledge about HPV, cervical cancer,

and vaccines is fairly low as is the self-perceived susceptibility of acquiring the virus or related cancers. The studies conducted in medical schools outline how imperative it is that medical students have adequate knowledge about cervical cancer, HPV, and vaccines, as they provide counsel and recommendations for cervical cancer prevention. With the low levels of knowledge found in all of the studies, a key take home message is the need to provide better education about HPV, cervical cancer and vaccines. Many of the young women in university settings have not yet had sexual relations (with many only reporting one previous partner), therefore are prime candidates for the HPV vaccine.

Two studies looked at awareness, knowledge and acceptability of the HPV vaccine among adolescent females in educational settings. The first study, conducted in five schools in North West Cameroon, was a cross-sectional study with 553 AYA aged 12-26 years (Ayissi et al., 2012). The mean age of participants was 17.2 years with most (78%) reporting to not yet had sexual relations. Prior to the study, the study team organized an awareness campaign targeting adolescents, parents, principals, teachers and the community in general. Pamphlets and posters were distributed to the school, churches and among community members and awareness talks were hosted at various venues. Participants were administered a questionnaire following the educational campaign. Compared to the previously reported studies, awareness about HPV (87%), cervical cancer (82%) and HPV vaccines (76%) reported in this Cameroonian study using awareness sensitization strategies prior to the survey, is much higher. Similar to other studies, age (older) and education were found to be associated with HPV knowledge. However, no sociodemographic characteristics or any other factors (risk perception or knowledge) were found to predict (prior) uptake or acceptability of the HPV vaccine in this study. A total of 34% of respondents had been vaccinated against HPV prior to the survey. The adolescents who were not

yet vaccinated (76%) most reported to “agree” (29.5%) or “strongly agree” (46.8%) about their willingness to be vaccinated against HPV infections.

In 2014, Turiho and colleagues assessed adolescent females’ knowledge about cervical cancer and HPV vaccines and acceptance of the vaccine in Ibanda and Mbarara districts, Uganda. Adolescents in Ibanda had been part of previous HPV vaccine demonstration projects with sensitization strategies used before vaccine rollout, while Mbarara did not yet have access to vaccines therefore was used as a comparison district. Using a comparative cross-sectional mixed methods approach, 777 young women (mean age of 13.4 years) completed a questionnaire and five focus groups with 8-12 participants from the vaccinated districts were conducted with adolescents from the cohort. Findings showed that knowledge levels about cervical cancer and the HPV vaccine were significantly higher among vaccinated girls with 85% considered knowledgeable compared to the unvaccinated at 15%. However, knowledge levels among unvaccinated participants were not found to make a significant difference in the role of HPV vaccine acceptance nor did perceived susceptibility or severity. Overall, most respondents (91%) supported HPV vaccination for their daughters and friends. Results from the focus groups indicated that girls’ primary motivation for receiving the HPV vaccine was to protect against cervical cancer. Other motivations included protecting their bodies to be able to bear children in the future and having a clear understanding that no side effects existed that would harm reproductive health. Deterrents reported by attendees to the focus groups in the acceptability of the HPV vaccine included negative rumours and anxiety about infertility and unknown side effects (Turiho et al., 2014).

From the twelve studies conducted in Euroasian areas, three studies examined HPV awareness and acceptance of the vaccine among medical and nursing students, six were conducted with

post-secondary students from a range of programs, two within a community clinic setting, and one with female secondary school students. Studies took place in Turkey, India, China, Lebanon and Malaysia. The first article with health care professionals in training took place in Ankara, Turkey with 752 female postsecondary students (*n*=520 nursing students; 232 control group). The purpose of this cross-sectional study was to assess the awareness and knowledge regarding HPV, HPV-related conditions and the vaccine among nursing students versus a control group of undergraduate students in various programs (Uzunlar et al., 2013). The average age of the participant in both groups was 20.4 years. Nursing students were found to have significantly higher awareness rates than the control group with 86% of them having heard about HPV compared to 24% among the other participants. Knowing the HPV virus was associated with cervical cancer was reported to be known for 88% of the nursing students compared to 31% among the control group. Of the entire cohort vaccination status was 3.8%. Among unvaccinated participants, however, the percentage of willingness to be vaccinated was 50%, 66%, and 13% among all the participants, nursing students and control group, respectively. Vaccine willingness for future daughters was 67%, 76% and 48% for the aforementioned groups. Significant factors related to acceptability of the vaccine included previous knowledge about the HPV vaccine and being a health care provider student. Age and having an understanding of the relationship between HPV and cervical cancer demonstrated to be related to the acceptance of the vaccine among the cohort of nursing students.

Two cross-sectional studies were conducted with medical and para medical students regarding knowledge about HPV, cervical cancer, and willingness to receive the HPV vaccine in India with AYA aged 17-25 years (Pandey, Vanya, Bhagat, Binu, & Shetty, 2012; Swarnapriya, Kavitha, & Reddy, 2015). The first study, conducted in 2012 looked at awareness and attitudes among 618

students at Karturba Medical School. While no mean age is reported, the majority of participants were between the ages of 20-22 (49%) and 17-19 (37%) years. Similar to the nursing study previously reviewed, the study stratified recently accepted medical students (55% in control group) and those in the final year of medical school (45%) to look at the role medical education played in awareness and acceptance. A total of 258 (43%) of participants were male and 350 (57%) were female. Overall, most participants knew about HPV and that it was a necessary factor in the development of cervical cancer (89%) with no differences found between sexes but a significant difference found between the education control (83%) and test group (97%). The protective efficacy was also reported to be significantly higher among the late stage medical students (84%) compared to group of new medical students (70%). The acceptance rates for the HPV vaccine was 68% for all participants with female students significantly more likely to accept the vaccine the males (79% vs 53%). Education levels did not play a role in HPV vaccine acceptance. Obstacles to HPV vaccination reported by participants included high cost (21%), fear of complications (17%0 and worry about efficacy (17%).

The second study was conducted in 2015 in Southern Indian with 957 medical and para medical students. The mean age of student participants was 19 years with mostly female (72%). Participants were recruited from medical, dental, and nursing departments. Knowledge, attitude and practices regarding HPV vaccination were examined with an overall 45% reporting to have good knowledge about the topics. Specifically, 60% of participants had heard about HPV and knew that the causal relationship between the infection and cervical cancer. The age of participant nor gender made a significant influence on the knowledge about HPV and the vaccine however medical and nursing students had significantly better knowledge levels about these topics than dental students. Despite the reported high levels of awareness about HPV among the

medical and para medical students, only 7% (65) students reported to be HPV immunized. Of those unvaccinated 51% said they would be willing to receive the vaccine. From the group unwilling to be vaccinated the top reasons for unwillingness included doubts regarding the efficacy, fear of side effects (26%), cost (22%), and minimal risk reception of developing cervical cancer (15%).

A total of six articles were reviewed about knowledge and attitudes towards HPV and vaccination among female postsecondary students in the Euroasia region. In 2010, a cross-sectional study was conducted with 650 ethnically diverse female students from a public university in Kuala Lumpur, Malaysia (Wong & Sam, 2010). The mean age of participants in this study was 21.4 years. Most respondents had not previously heard about HPV prior to the study with 22% reporting not to have heard of HPV and only 10% reported knowing about a vaccine for HPV. Age was the only factor to significantly correlate with knowledge. Across the entire sample, the mean awareness score was 3.25 out of the 14 questions (*SD*=2.41) indicating very low levels of awareness. Despite the low levels of knowledge, 48% of participants reported willing to receive the HPV vaccine. The intention to receive the vaccine was significantly related to reported awareness levels. The most commonly cited reasons for HPV vaccine refusal was concern about the safety and efficacy (51%), low risk perception (42%) and embarrassment related to receiving vaccine for an STI (11%). A study conducted by Juntasopeepun and colleagues (2012) in Chiang Mai, Thailand with 738 female college students (*M*=19.9 years). Using an online questionnaire, the cross-sectional study examined factors influencing acceptance of the HPV vaccine. A large proportion (64%) of students did not have a history of sexual experience. Only 9 women (1.2%) reported to have received the HPV vaccine previous to the study. A total of 65% participants knew about HPV and how it was contracted while 60%

reported understanding the link between HPV and cervical cancer. Overall acceptability rates for the vaccine was 55% with high intention significantly related to age, previous sexual experience, received a recommendation to be vaccine, and be more knowledge about these topics than the low intention group. Other significant variables found to be associated with vaccine acceptability were perceived susceptibility to cervical cancer and perceived benefits of vaccination (Juntasopeepun, Suwan, Phiamongkhol, & Srisomboon, 2012).

Dany and colleagues (2015) examined knowledge, attitudes, and intentions of 215 female college students in Beirut, Lebanon. The mean age of participants was 22.7 with equal ratios of undergraduate and graduate students and most reporting no previous sexual experience (68.3%). Only 17% of participants reported to have received the HPV vaccine with many never having heard of HPV (37%) prior to the study. The mean knowledge score for knowledge questions about HPV and vaccination of 52.7 (from a possible score of 160) demonstrated poor overall awareness among students. Many of the participants reported they did not feel at risk for acquiring HPV (60%) however believed that all college females should have the vaccine (62%) (Dany, Chidiac, & Nassar, 2015). Again, similarly to previous research with post-secondary students a significant predictor of acceptability of the HPV vaccine is knowledge scores and that despite low levels of knowledge there is still a general positive attitude and high acceptability towards the vaccine. A similar cross-sectional study was conducted in Changsha, China with 117 university students with a mean age of 21 years (Gu, Niccolai, Yang, Wang, & Tao, 2015). Most participants (90%) reported that they had heard of HPV and cervical cancer (78%) prior to the study. HPV vaccine acceptability rates for this study are lower than previously reported studies, at 44%. In terms of correlates or predictors of acceptability the only variable significantly related to intention to vaccinate was knowledge levels about cervical cancer and vaccines. Among the

women who did not have an intention to receive the vaccine, most reported possible side effects (60%) as the reason for declination. The top influencers reported to make a difference in participants' decision to uptake the HPV vaccine included doctors (48%) and parents (13%).

The last study with female post-secondary students in LMICs reviewed was conducted in Turkey (undisclosed city) with 800 university students in a variety of departments (Koc & Cinarli, 2015). The mean age of participants was 20.4 years with 28% reporting having no previous sexual experience. Only 12% of students had heard of HPV previous to the study with 10% reporting knowing the relationship between HPV and cervical cancer. A small portion of students knew that an HPV vaccine existed (9%). Overall and similar to previously reviewed studies, low levels of knowledge were found among participants but dissimilar was the low acceptance HPV vaccination rates reported (33%). The most commonly cited reasons for declination of the vaccination were: not having enough information about the vaccine (38); not feeling it is necessary (23%); possibility of adverse events following vaccination (21%); and the cost associated with the HPV vaccine (7%). No correlates or predictors of acceptability were reported in this study. Findings outline the urgent need for post-secondary educational programs to increase awareness about cervical cancer prevention, particularly because a large proportion of AYA are sexually inexperienced and therefore would be prime candidates for the HPV vaccine.

One article was reviewed with secondary school girls in Euroasia (Al-Naggar, Bobryshev, Al-Jashamy, & Abdulghani, 2012). The cross-sectional study was conducted in Melaka, Malaysia with 612 school girls aged 13-17 (M=13.9) and examined factors associated with prior HPV vaccination uptake. The prevalence of HPV vaccination was 80% with the majority of girls reporting to have received the vaccination from their schools (77%). Most participants reported to have heard about HPV (78%) and cervical cancer (69%) prior to the study. Cited reasons for

vaccination uptake were being encouraged by a health care professional or teacher (49%), parent influence (29%), and encouragement from friends (0.2%). Reported significant factors in the uptake of the HPV vaccine included income of the parent, parent education level, having knowledge about HPV and cervical cancer, and receiving the vaccine in a school setting. Again, findings from this study echo all previous findings in the literature that recognize knowledge as a significant factor influencing HPV vaccination acceptability and uptake among AYA.

The last article reviewed from Euroasia was conducted in a research hospital in Ankara, Turkey (Ozyer et al., 2013). A total of 408 young women with a mean age of 18.5 years were administered questionnaires examining awareness about HPV and attitudes about vaccination. A large proportion of the cohort (98.5%) reported not to have previous sexual experience. Of the young women participating in the study, 42% had heard about HPV with 33% knowing that HPV can cause cervical cancer. Young women were significantly more likely to know about HPV that older participants, which is contrary to findings from the previous studies with older AYA being more knowledgeable about these topics. Only 1.4% of the cohort had been vaccinated while only 11.2% were willing to receive the HPV vaccine. Cited reasons for declining or reporting to be disinterested in receiving vaccination were a lack of information (66%), being unmarried (20%), and doubts about the safety and efficacy of the vaccine (3.4%). Findings from this study are unique, in that knowledge about HPV and cervical cancer were high however acceptability rates very low.

The last study reviewed was conducted in Maipu, Argentina and examined HPV vaccine acceptability among 174 young women with a median age of 23 years. The cross-sectional study took place in a hospital setting and explored correlates of HPV vaccine acceptance. Only 3 participants reported never having engaged in sexual activity. A small proportion of young

women had heard of HPV (17%) while 19% reported to have heard of cervical cancer prior to the study. Altogether 95% of young women reported to be willing to receive the HPV vaccine. Statistically significant correlates in participants' HPV vaccination acceptability was the belief that the vaccine is safe with lower confidence about safety associated with lower acceptance. The authors also found that most women (75%) reporting to be vaccine acceptant were willing to pay for vaccination, despite low socioeconomic status of many of the participants. The authors conclude that high acceptance of the HPV vaccination whether free or out-of-pocket for young women in the study. Perceived safety of the HPV vaccine in this study was found to be an important correlate of acceptability as opposed to previously significant factors associated to knowledge or awareness about these topics (Alder et al., 2013).

Parent Awareness about HPV and Acceptability of the HPV Vaccine for Daughters

Parents are critical decision makers for vaccine delivery in young children and adolescents. A literary review of 28 articles, subdivided into the geographical categories of Africa, Euroasia and South America, found that rates of parental acceptability of the HPV ranged from 44%-96%. The majority of these articles examined parental acceptability for daughters getting vaccinated, with a predominant portion also examining the opinions and knowledge of mothers. Overall, despite the majority of articles reporting limited knowledge about HPV and the HPV vaccine, most parents were found to be highly accepting of having their daughters receive the vaccine. A dominant theme throughout this global review, rightly so, is that all parents just want to keep their children safe and healthy. Concerns over vaccine efficacy and safety were prominent reasons why reluctant parents were not interested in having their children vaccinated.

When examining literature from Africa, the nine articles reviewed on parental acceptability to get their child vaccinated included studies from Cameroon, multiple areas in Kenya, Nigeria,

South Africa, Morocco, Tanzania, Malawi and Botswana. Of these articles, parent acceptability ranged from 67%- 95%, with responses varying based on the convenience of vaccine administration (Becker-Dreps, Otieno, Brewer, Agot, & Smith, 2010; DiAngi, Panozzo, Ramogola-Masire, Steenhoff, & Brewer, 2011; Ezeanochie & Olagbuji, 2014; Francis et al., 2011; Mouallif et al., 2014; Ports, Reddy, & Rameshbabu, 2013; Vermandere et al., 2014; Wamai et al., 2012). The three most common variables associated with parental acceptability throughout all studies were higher education, having higher levels information around the disease and the HPV vaccine, as well as increased perceived risk. Respondents that had higher education were more likely to have at least heard of cervical cancer and thus were able to more easily acknowledge the potential severity of the disease. Of the articles that did examine uptake, acceptance was associated with uptake, but education level as well as disease-specific knowledge were more significant correlates. Additional correlates to uptake also included convenience of vaccination administration and knowledge of when and where the multiple doses would be offered.

The most prominent predictors reported in HPV vaccine acceptability among parents and caregivers were education level and specific understanding of the disease and vaccine. Lower education and respondents living in rural areas were found to be more unaware of the preventative measures available including screening and vaccination. Participants most commonly cited the unknown side effects of the vaccination as a reason for declining their child's participation. Specifically, reasons for the distrust with the HPV vaccine included concerns of causing infertility, that the vaccine would not be administered safely or that it would not be effective. Additionally, three articles cited parental beliefs that their daughters would be more likely to become sexually active if vaccinated against HPV (DiAngi et al., 2011; Mouallif

et al., 2014). Cost, comparatively, was not a dominant drawback for parental acceptability or uptake but many survey respondents reported a maximum willingness to pay: the highest amount from all the articles was equivalent to $5 USD.

Sixteen Eurasia-based studies on parental acceptability of vaccinating their child with the HPV vaccine were reviewed. The countries included: Turkey, Vietnam, Fiji, Malaysia, Indonesia, Eastern India, Thailand and China. From all articles in this geographical area, parental acceptability ranged from 44%-96%, with significant increases in acceptability in China, Fiji and Vietnam if some sort of government program was established in support specifically for the HPV vaccination (Alsaad, Shamsuddin, & Fadzil, 2012; Basu & Mittal, 2011; Dinh et al., 2007; Jaspers, Budiningsih, Wolterbeek, Henderson, & Peters, 2011; Kilic, Seven, Guvenc, Akyuz, & Ciftci, 2012; Kruiroongroj, Chaikledkaew, & Thavaorncharoensap, 2013; Madhivanan et al., 2009; Madhivanan et al., 2014; Mairaing, Suwannarakark, THaweekul, & Poomtavorn, 2012; Songthap, Pitisuttithum, Kaewkungwal, Gungladda, & Bussaratid, 2012; Vincente et al., 2015; Wang et al., 2015; Wong, 2009; Zhang et al., 2013). The most dominant predictor for parental acceptability in these countries was higher education and increased knowledge specifically around HPV, cervical cancer and protective measures the vaccine offers. Multiple articles in this geographic category also examined the impact of HPV and cervical cancer knowledge campaigns and parental acceptability, seeing a positive correlation. One interesting finding to this correlate was found in China where a study by Wang and colleagues discovered that prior knowledge increased parental acceptability but higher education actually decreased parental acceptability. Among reasons why parents would not accept getting their child vaccinated, the two dominant predictors mentioned in most articles were vaccine efficacy and safety. Included under efficacy, there were varying opinions on when adolescents should actually receive the

vaccination. Two other drawbacks worth noting were cost and the need for greater information around the disease and the vaccination.

Three studies about parental acceptability of HPV vaccination in South America were examined from the countries of Argentina, Honduras and Brazil. Parental acceptability rates were at 74% in Argentina, 91% in Honduras and 95% in Brazil. All three studies referenced the correlate of increased knowledge as well as increased education as predictors to parental acceptability (Arrossi, Maceira, Paolino, & Sankaranarayanan, 2012; Osis, Duarte, & Sousa, 2014; Perkins, Langrish, Cotton, & Simon, 2011). In Argentina, there was a mass media campaign put on by a cancer Non-Governmental Organization followed by a government-initiated vaccination program significantly contributed to the public's general knowledge base around HPV the vaccination (Arrossi et al, 2012). In Honduras, a majority of study participants knew about the preventative measures for cervical cancer but were unaware of specific knowledge around HPV. Tied to education and knowledge, socio-economic status of these South America countries also showed to be a predictor of parental acceptability. When examining drawbacks on reasons why parents would not accept getting their child vaccinated, the dominant predictor was perceived low risk; either participants believe their daughters were not yet sexually active and/or they also believed they will only have one sexual partner in their lifetime (Perkins et al, 2011).

Summary

Vaccine readiness is important to understand among AYA females. Although most studies were not conducted with "elite responder" age group (9-13 years), the literature outlines that many AYA in LMICs have not yet engaged in sexual relations even up to university level. This has important implications because these populations are not currently being targeted,

particularly in South Africa. The literature demonstrates the importance of implementing effective sensitization strategies prior to the administration of the HPV vaccine for adolescent females. Misinformation and rumours need to be counteracted and addressed upfront. Primary prevention of HPV for adolescents includes using creative and responsive education strategies to teach about HPV, cervical cancer, and the HPV vaccine. Improved understanding of AYAs knowledge about these topics and factors that influence the acceptance of the HPV vaccine will help inform HPV vaccination programs. The literature also demonstrates the effectiveness of using well organized community-based awareness programs with key stakeholders. It is important that decision-makers in education, parents, and adolescents are well-informed, as this will promote participation in HPV vaccination programs. It is imperative that individuals on all levels are well-prepared and involved. A better understanding about how women with diverse ethnicities and religious beliefs feel about HPV and vaccination will help to create more effective immunization strategies. In terms of literature about awareness and vaccine acceptability among health care professionals in training, overall rates of awareness compared to other groups of AYA was generally higher. However, some gaps still exist in the understanding or application, as even these groups had fairly low HPV vaccine uptake and acceptability rates. There is room for improvement in education for nursing and medical student because of the critical role they play in patients' acceptability of and adherence to screening and vaccination. Medical training will have a definitive impact on the understanding of this important public health issue.

The major obstacles reported within the literature regarding the implementation of the HPV vaccine include cost, acceptability, perceived susceptibility for infection and cervical cancer, lack of public awareness or sensitization programs and infrastructure, worries regarding the safety profile and efficacy of the vaccine as well as social and religious aspects. It is important

that programs address individual, community, and health system related factors in attempts to increase the uptake, and accessibility of the HPV vaccine in parts of the world with highest prevalence and mortality rates associated with HPV related cancers. In South Africa, arguably one of the largest barrier has been the lack of accessibility to the HPV vaccine, as it is unaffordable for the majority of women with no access to health schemes or private insurance.

SA women suffer disproportionately higher rates of cervical cancer and have some of highest mortality rates compared to women in the rest of the world. Young women in SA are a particularly vulnerable population given high rates of HIV and urgently need to be targeted in the expansion of the HPV vaccine. The conversation about extending the HPV vaccine program in South Africa requires immediate action at the National and Global level, as it is the most effective solution to reduce the incidence of cervical cancer for women who are most at-risk. HPV vaccination is a safe, effective, ethical, and acceptable solution to the global cervical cancer crisis in LMICs, particularly in areas coping with high HPV and HIV infection rates and challenging access to screening services.

Chapter 3: Methods

Introduction

Previous research conducted in LMICs has demonstrated that very low levels of knowledge exist about HPV and the viruses' relationship to cervical cancer (Abdullahi et al., 2014; Cunningham et al., 2014; Tsu, Cernuschi, & LaMontagne, 2014). Prevention of the virus and cervical cancer is also poorly understood with concerns voiced by both recipients and parents about the safety profile of the HPV vaccine. Overwhelmingly, literature shows the efficacy of including an educational component with community prior to any HPV vaccine program rollout, as normalizing the topic of HPV, reframing the message about vaccine being an "STI prevention" to a "cervical cancer prevention" tool, and ensuring that stakeholders such as leaders and influencers in the community are made well aware of the safety and benefits concerning the HPV vaccine, as to decrease misinformation and ensure appropriate dissemination for AYA and parents. Despite the reported low levels of awareness about HPV, cervical cancer, and the HPV vaccine the acceptability and uptake rates of the vaccine in studies are surprisingly high, which was more so the case when education components were built in to the program (Cunningham et al., 2014; Snyman, Dreyer, Botha, van der Merwe, et al., 2015).

Cervical cancer is an entirely preventable disease and we now have the tools to protect girls globally. The recent development of HPV vaccines offers great potential for primary prevention of cervical cancer in SA. The questions guiding this study are:

- What are female AYAs awareness and attitudes towards HPV, cervical cancer, and HPV vaccines;
- What correlates, if any, exist between AYA who are and are not HPV vaccine acceptant; how do female AYA feel about HPV self-sample testing;

Based on the literature and geographical context, the hypothesis for the study is that participants will have low-levels of awareness about these topics but despite the lack of knowledge will report high acceptability rates for the HPV vaccine and self-sample testing. From a HBM perspective, key predictors for acceptability of the vaccine include higher perceived likelihood of developing HPV infection and cervical cancer, severity of the diagnosis, and perceived benefits and efficacy of the vaccine in reducing the risk of HPV and cervical cancer. While this is found in higher income countries, these themes were not reported to be predominant factors in LMICs. The most commonly cited barrier to the HPV vaccine in the literature for both AYA and parents was apprehension due to concerns over the safety profile and side effects of the vaccine as well as community perceptions (Abdullahi et al., 2014; Chidyaonga-Maseko et al., 2015; Dreyer et al., 2015). Cost barriers were also reported in some of the articles if a project did not cover the cost of the vaccine. Cues to action are situational and social factors that contribute to vaccination acceptability or uptake.

Based on the aforementioned factors, the author proposes that AYA who feel at higher risk for HPV infection and cervical cancer and those that rated having an infection or associative cancer as more 'severe' will be more likely to engage in primary and secondary prevention strategies. In addition, participants who view the vaccine as beneficial and highly efficacious will be more likely to be vaccine acceptant. The cost of the vaccine (as it is not covered in SA for AYA) is also proposed to play a significant role in HPV vaccination acceptance.

Broadly speaking, the aim of the study is to address gaps in the literature, help inform preventive policy, and assist in the introduction and propagation of HPV vaccination in SA. Being able to better understand correlates of acceptability of the HPV vaccine and innovative screening strategies such as HPV self-sample testing among the most acutely affected group of

women globally is the main goal of this work. Based on the literature and geographical context, the hypothesis for the study is that participants will have low-levels of awareness about these topics but despite the lack of knowledge will report high acceptability rates for the HPV vaccine and self-sample testing. Further to this, participants with higher levels of awareness, perceived severity and likelihood of viral acquisition are proposed to have higher vaccine acceptance rates.

Research Questions

With the enormous burden of cervical cancer among young women in SA, a focus needs to be placed on research about primary prevention for oncogenic HPV infections. Effective screening and preventive technologies exist to reduce the risk of cervical cancer and this project examines acceptability and correlates of these technologies: the HPV vaccine and HPV self-sample testing, in an area of the world with the highest HIV and HPV rates. The research questions for this study were:

- What do female AYA in Durban know about HPV, cervical cancer, and the HPV vaccine;
- What determinants (socioeconomic and behavioural factors) are related to AYAs acceptability of the HPV vaccine and HPV self-sample testing;
- What are female AYAs attitudes towards the HPV vaccine for (future) children;
- Where do female AYA receive sexual and reproductive health information from;
- What are female AYAs perceptions (risk; severity) of the HPV infection and cervical cancer?

Sampling

This research was conducted collaboratively with a youth-centered study entitled, "AYAZAZI: Investigating Patterns of Behavioural and Biomedical Risk for HIV Acquisition and Vaccine Trial Preparedness among Adolescents and Young Adults in a priority setting". AYAZAZI, an HIV prevention study, is a multi-site, inter-disciplinary, prospective cohort study focused on understanding linked patterns of socio-behavioural and biomedical HIV risk among youth in Soweto and Durban, SA using a youth engagement approach. The AYAZAZI research

team consisted of two AYA research assistants, a social worker, a registered nurse, a coordinator, a medical doctor, a local principle investigator and two AYA HIV counsellors. The team's objective was to better understanding how to help AYA make informed decisions about their sexual health and offer them access to testing for sexual and genital tract infections and counselling services.

A relationship was formed with a principle investigator (PI) on the AYAZAZI study through course work attended, as well prior relationships and collaborative work between the PI, A.K, and the PhD co-supervisor, G.O. As a result of the similarities in topics, relevance of HPV prevention to this particular cohort of AYA females, and former positive working relationships, an HPV sub-section was collaboratively created and imbedded into the existing AYAZAZI questionnaire. The HPV sub-section was administered to 122 females who had formerly participated in the study and were returning for follow-up 12-month visits in Durban and was administered at the end of the AYAZAZI survey.

Participant Recruitment

Participants in Durban were recruited through though active community recruitment via locations such as schools, tertiary institutions, community centres, clinics, and hostels, through posters, flyers and pamphlets, and face-to-face recruitment. Individuals enrolled for the AYAZAZI study at the Commercial City Centre MaTCH Research Unit (MRU) site[8]. Inclusion criteria for enrollment in the study at baseline included:

- Reside in Durban;
- Aged 16-24 years (at baseline);
- Are either known to be HIV-negative or do not know their HIV status;
- Willing to undergo HIV testing as specified according to the visit schedule;

[8] MRU is a Division of the Wits Health Consortium (Pty) Ltd in the Department of Obstetrics and Gynaecology in the Faculty of Health Sciences at the University of the Witwatersrand.

- Able and willing to provide written informed consent and assent for minors for socio-behavioural assessments and biological specimen collections.

Individuals were excluded from the study if they meet any of the following criteria:

- Have an obvious psychological/psychiatric disorder that would invalidate the informed consent process or otherwise contraindicate participation in the assessment;
- Minors (under age 18) without written informed consent from a parent or legal guardian;
- Are shown to be participating in clinical or observational studies as determined by finger-print co-enrolment system[9].

Study Area Description

The province of KZN, where this research took place, is the most highly densely populated area in SA. Durban is located the eThekwini district and home to approximately 3.5 million people. South Africa's population is predominantly made up of young people with those below 35 years of age (66%). Black African peoples have the youngest residents with 34% of the overall population under the age of 15 and 22% from 15-24 years of age with a median age of 21. The largest population represented in the eThekwini district is AYA aged 15-29. The district has more females (51%) than males (48%) and an overall mean age of 26.8 (Statistics South Africa, 2015, 2016). Currently, cervical cancer is the leading cause of death among young women in SA, therefore the age and gender distribution have important implications for cervical cancer prevention and outline the vital need to better understand attitudes and acceptability towards the HPV vaccine, particularly in KZN.

Procedure and Time Frame

The AYAZAZI survey was administered at baseline, 3-, 6-, and 12-month time points. At baseline 132 female AYA were enrolled and at 12-month 128 (97%) were retained, with a total of 122 participants who were willing to complete the HPV questionnaire. Both the AYAZAZI and HPV survey were administered by AYAZAZI research assistants in isiZulu or English. The

[9] The finger-print enrolment system is used at the MRU to determine participants eligibility based on prior enrolment with studies.

HPV questionnaire was administered to participants after the AYAZAZI survey and took approximately 15 minutes. Before data collection, the author facilitated a two-day arts-based workshop about HPV, cervical cancer, and vaccines with all AYAZAZI staff members with the goal of equipping the research team with awareness about the topics. This also was helpful to mirror what would happen as part of an HPV intervention program to identify gaps in knowledge, receive input from the research team about contextually appropriate wording regarding the topics, and how to best work with the female AYA to raise awareness about a highly prevalent health issue. During this time pilot testing and training on the questionnaire also took place with the research assistants who were working on the study. Data collection took place between September 30th, 2016 and May 3rd, 2017 at the MRU site in the central business district of Durban. For AYA 18+ years, consent was from the participant and those under 18, an assent form was signed by the participant and a consent form was signed by the parents of guardian prior to data collection at baseline (Appendix C, D, & E). The lead institutions for the AYAZAZI study were Simon Fraser University, the University of Witwatersrand, and the University of KwaZulu-Natal. Ethical approval for this study was obtained from Research Ethic Boards from all participating institutions prior to the commencement of the study. An additional harmonized ethics proposal (to add HPV and cervical cancer section) was approved by all institutions as well as institution of the researcher, the University of Northern British Columbia (see Appendix F).

Instrumentation

Using a HBM and VHM lens, the HPV survey was compiled by the author and her committee and organized into four sections including, **Section I**: HPV and Cervical Cancer Awareness; **Section II**: Risk Perception and Impact; **Section III**: HPV Vaccine Awareness & Acceptability;

and **Section IV**: Cervical Cancer screening (Appendix G). The survey has a total of 30 questions. Half of the questions (15) are standardized questions related to screening, treatment, and vaccines from a core module from the WHO (2016) *Improving Data for Decision Making in Global Cervical Cancer Programs Toolkit* (IDCCP). Seven questions were from the *Knowledge and Perceptions Survey* (KAPs), a standardized questionnaire designed by McPartland and colleagues (2005) and examine perceived severity, susceptibility, and knowledge of HPV. The remainder of the questions examined awareness about the existence of HPV and cervical cancer and the sources of knowledge about these topics, locale specific barriers (availability and cost), as well as questions examining perceived barriers and benefits.

Questions and scales from the 12-month AYAZAZI survey were merged with the HPV survey data. Self-efficacy was measured using validated perceived stress and resiliency scales in the AYAZAZI questionnaire. The *Perceived Stress Scale* (PSS) is one the most widely used psychological instrument for measuring the perception of stress (Cohen, Kamarck, & Mermelstein, 1983). The scale measures the degree to which one appraises and deals with stress in their lives. It is also determines how unpredictable, uncontrollable and overloaded respondents find their lives overall. Questions 1-10 were coded for response options ranging from 'never' (0), to 'very often' (4). Four items of the scale were reverse coded and the total was calculated with scores possibilities ranging from 0-40. The higher the PSS-10 score, The higher the PSS-10 score, the most likely it is the participant perceives their environmental demands to exceed their ability to cope indicating higher levels of stress.

The *Connor-Davidson Resiliency Scale 10* (CD-RISC-10) was used to measure resiliency levels among participants. The CD-RISC-10 is one of the best-known instruments in the field of resilience assessment (Connor & Davidson, 2003). Responses from the 10-items ranged from

'never' (0), to 'very often' (4). When the items are added the score should be between 0-40 with higher scores reflecting greater resilience or ability to endure difficult experiences, including "change, personal problems, illness, pressure, failure, and painful feelings". The higher the CD-RISC score, the more likely the individual demonstrates resilient behaviours despite being faced with adversities and possess positive coping skills.

As part of pilot testing with representative individuals, the HPV survey underwent revisions to ensure that the questions were locale appropriate and easily translatable for the AYA. Once the survey was finalized, the research assistant's conducted pilot testing with seven members of the MRU team in both English and isiZulu. All HPV survey data was collected using paper format and later entered into a template in Excel by the research assistants and on the project. Data quality checks were performed by the research assistants routinely and then double checked by the PI (VR) and later entered into a SPSS for analysis. Pre-determined variables from the AYAZAZI questionnaire (12-month time point) were extracted and merged with the HPV survey data and analyzed by the author.

Data Analysis

Descriptive statistics were used to analyze characteristics at the 12-month time point, frequencies and proportions to describe categorical variables and medians and interquartile ranges for continuous variables. Socio-demographic variables included: the age of participant; dichotomized age categories youth (16-19) and young adults (20-25); sexual orientation (heterosexual vs. LGBTQ); relationship status (in a relationship/living together vs. in a relationship/not living together vs. single); student status (current student vs. not a student); type of student (high school vs. post-secondary); type of housing (formal vs informal housing, which

included RDP housing[10], shacks, hostels and informal settlements); head of the household (females vs. males); monthly income (<400 ZAR[11] vs. 401-1600 vs. 1601+); parental status (have child(ren) vs. do not have child(ren)); the number of children; and pregnancy status (currently pregnant vs. not currently pregnant). Finally, the current clinical HIV status of participants was also reported (HIV + vs. HIV-).

Health behaviour descriptors were chosen based on factors associated in the development of cervical cancer including, smoked cigarettes over the past 30 days (smoked 1-10 cigarettes per day on average vs. did not smoke in past 30 days); non-medicinal drug use[12] (ever used drugs vs. never used drugs). Sexual health behaviours included, age (*M; SD*) at first consensual sex defined as oral, vaginal or anal sex; number of consensual sexual partners ever; dichotomized sexual partners categories (1 sexual partner vs. ≥ 2 sexual partners); whether a condom used at time of first consensual sexual experience (used a condom vs. did not use a condom); and consistency of condom use (consistent use "always", vs. inconsistent use "sometimes and never").

Healthcare utilization descriptors were chosen based on whether participants would have access to cervical screening or vaccines and whether services specific to women's needs were needed and accessed by participants. The level of violence towards women in SA is an important determinant of women's SRH outcomes and therefore was also reported. The descriptors included, whether participants had access to medical aid (have health insurance vs. do not have health insurance); whether participants had i) needed and ii) received services for: mental health, physical and sexual violence, addiction, faith-based or traditional healers ("yes/no"); and

[10] Reconstruction and Development Programme (RDP) is subsidized government housing.
[11] 400ZAR is roughly equivalent to $40CND. For scale the average monthly income in SA for 2017 was 19608ZAR.
[12] AYAZAZI questionnaire defined "drugs" as substances used for recreational/enjoyment (non-medicinal) purposes, including marijuana/dagga, other street drugs, over-the-counter drugs (available at pharmacies without a prescription) taken in excess of directions or prescribed drugs taken in excess of prescription.

experiences with sexual or physical violence over the past 6-months (experienced sexual or physical violence vs. did not experience sexual or physical violence vs. prefer not to answer).

Mental Health: mental health descriptives included a perceived stress (PSS-10) and resiliency (CD-RISC 10) scales and were chosen based on literature about the role of self-efficacy in health behaviours. In accordance with both a HB and VH models, self-efficacy plays a role in health decisions. The PSS-10 had 10 statements with responses ranging from, Never = 0; Almost Never = 1; Sometimes = 2; fairly often = 3; and Very often = 4. Scores were obtained by reversing the scores on the four positive items (questions d, e, g and h): 0=4, 1=3, 2=2, 3=1, 4=0 and then summing across all 10 items with score range possibility of 0-40. The higher the score the higher perceived stress the participant was experiencing. Overall mean and standard deviations for all participants are reported are dichotomized low (score of 0-20) vs. high (20+) stress scores. Similarly, the CD-RISC 10 scale consisted of 10 statements and scores with responses ranging from, Never = 0; Almost never, 1 or 2 days = 1; Sometimes, between 3 and 10 days = 2; fairly often, between 11 and 20 days = 3; Very often, over 20 days = 4. The scores of responses were added with a score potential ranging from 0-40 and obtained by adding questions (all positive) with the higher score reflecting higher levels of resilience. The overall mean and standard deviation as well as dichotomized scores, low (scores of 0-20) vs. high (20+), resilience scores are reported.

Outcomes

Objective 1: SRH information sources and influences were measured by asking participants about where they received information about these topics from. Women were asked if they were aware of the following topics: i) contraceptives, ii) HPV, iii) cervical cancer, iv) HPV vaccine, and v) cervical cancer screening. Responses were collapsed into four groups: (1)

friends and family (mother, father, aunt, sibling, grandmother, partner, or friend) vs. (2) health care professional (doctor or nurse), vs. (3) media (television, internet, or radio), vs. (4) school (school and counsellors) vs. (5) AYAZAZI and other community groups vs. *I don't know* or *never heard of it* (99). Frequencies for each 5 topics are reported.

Recommendation sources and cost factors about decisions to vaccinate against HPV were measured by asking women, "would you consider getting the HPV vaccine if, i) it cost you 2300ZAR to purchase, ii) it was free, iii) it was recommended by your doctor or a nurse, and iv) it was recommended by family or friends". A 4-point Likert scale for all questions ranged from "definitely would not (1); probably would not (2); neutral (3); definitely would (4); and I don't know (97)".

Frequencies will be calculated for consideration factors in decisions to receive the HPV vaccine and t-tests will be used to examine mean differences in the importance of cost (paying 2300 ZAR vs. receiving the HPV vaccine for free) and recommendation source (receiving a recommendation from a health care provider vs. friend and family) in AYA participants' consideration of receiving the HPV vaccine.

Objective 2: HPV, cervical cancer, and HPV vaccine awareness was measured by first asking participants if they had heard of HPV, cervical cancer, the HPV vaccine, or cervical cancer screening prior to the study, using a "yes/no/I don't know" response. A series of 8 true or false statements about HPV, cervical cancer, and the HPV vaccine formed an awareness scale with possible scores ranging from 0-8. Awareness scores were summed, with the mean and standard deviation reported. Participants will also be stratified into two groups based on the median calculated from awareness scores (0-2 = 'little to no awareness'; 2+ = 'some awareness').

Objective 3: HPV vaccine and vaginal self-collection acceptability was measured by asking participants, "Would you be willing to receive a vaccine to help prevent HPV infections and cervical cancer?" (Yes vs. No vs. I don't know) and, "Would you want your child/ren (or future children) to receive the HPV vaccine?" (Yes vs. No. vs. I don't know). Cross-tabs will be run to examine current mothers and pregnant participant's acceptability of the HPV vaccine for children. Acceptability rates for the HPV vaccine and self-collection, as well the preferred location of testing (clinic vs. home) will be reported (count; percentage). Women were also asked to rate the level of importance regarding whether the HPV vaccine protected against cancer and genital warts. This is important because currently the rollout for government program is administrating Cervarix (bivalent) protecting against only HPV 16 and 18, strains associated with cervical cancers but not genital warts. A Likert scale ranging from, (1) not important at all, (2) of little importance, (3) moderately important, (4) important, and (5) very important, was used. Frequencies and distributions will be reported about prevention priorities.

Objective 4. Risk Perceptions for acquiring HPV, HIV and developing cervical cancer were measured using 4-point Likert scales. Participants were asked, "How much at risk do you think you are of becoming infected with, i) HIV, ii) HPV, and iii) cervical cancer". The scale ranged from, (1) not at all at risk of becoming infected with HIV/HPV/Cervical cancer, (2) low risk, (3) medium risk, or (4) high risk. Scores were dichotomized to low (1-2) and high (3-4) risk groups and frequencies will be reported. Participants were then asked "how much at risk do you think other women in your community are of becoming infected with i) HIV, ii) HPV, and developing iii) cervical cancer". The same Likert scale was used as described above with answers dichotomized into low and high perceived risk categories.

Objective 5. Risk Perceptions of Self Compared to Other AYA Females. In accordance with literature about perceived STI risk, AYA commonly have lower perceived levels of risk associated with themselves acquiring viruses and developing diseases in comparison to how they perceive others to be at risk for the same infections and diseases. Therefore, t-tests were run to examine the mean differences between participants' risk perception of self vs. risk perception of other women in the community to acquire HIV and HPV as well as to develop cervical cancer.

Objective 6. Perceptions of severity and vaccine efficacy beliefs were measured asking participants "how much of a negative impact would having i) HPV and ii) cervical cancer have on you and your life?" A Likert scale with responses ranging from (1) no impact at all, (2) low impact, (3) medium impact, and (4) high impact, were used to gage perceptions of severity. Similarly, **HPV vaccine effectiveness beliefs** were measured asking, "how likely do you think the HPV vaccine would reduce your chance of, i) getting infected with HPV, and ii) developing cervical cancer". The response scale ranged from "(1) very likely, (2) fairly likely, (3) not likely, and (4) very unlikely. Both severity and efficacy belief variables will be dichotomized and frequencies reported.

Objective 7. Factors associated with perceived risk. Risk perceptions can be affected by a variety of mediating factors such as sociodemographic and sexual health behaviours. A Chi-square test of independence will be calculated to compare the frequency of risk perception (high vs. low) of 1) acquiring HPV and 2) developing cervical cancer with: age (16-19 vs. 20-25); sexual orientation (heterosexual vs. LGBTQ); income level (<400ZAR vs. 401-1600 vs. 1601+); student status (student vs. not a student); housing type (formal vs. informal); head of household (female vs. male); stress scale score (high vs. low); resiliency scale score (high vs. low); HIV

status (HIV+ vs. HIV-); condom use consistency (consistent vs. inconsistent; and sexual partners (1 vs. 2+).

Objective 8. Factors influencing willingness to participate in self-sample collection are related to a variety of social, contextual, and personal factors in the literature. A Chi-square test of independence was run to compare the frequency of HPV self-sample collection acceptability (yes vs. no) with: age (16-19 vs. 20-15); sexual orientation (heterosexual vs. LGBTQ); income level (<400ZAR vs. 401-1600 vs. 1601+); student status (student vs. not a student); housing type (formal vs. informal); HIV status (HIV+ vs. HIV-); sexual partners (1 vs. 2+); sources of information about 1) HPV, 2) cervical cancer and 3) cervical screening (friends/family vs. HCP's vs. media vs. school vs. AYAZAZI/community groups); knowledge or awareness about topics (none to low vs. some to high); perceptions of 1) risk and 2) severity (high vs. low); stress scale score (high vs. low); and resiliency scale score (high vs. low). Where associations were found with bivariate analysis, binomial logistic regression analysis will be used to identify predictors of willingness to participate in HPV self-sample testing.

Objective 9. Uptake of cervical cancer prevention services included questions asking women, "Have you received the cervical cancer vaccine" (yes vs. no. I don't know) Women were also asked, "Has a healthcare provider ever tested you for cervical cancer" with a "yes", "no", or "I don't know" response. Frequencies for participation in HPV vaccines and cervical cancer screening were calculated and cross-tabulated by HIV status in accordance to current guidelines following HIV diagnosis that a woman receive cervical screening. Reasons for receiving a test for cervical cancer included, (1) following up on abnormal or inconclusive results, (2) recruited for testing by a HCP, (3) experiencing pain or other symptoms, and (4) heard about test and wanted to get tested. Results for the most recent test were reported with

response options, (1) did not receive a result, (2)normal/negative, (3) abnormal/positive, (4) suspect cancer, (5) inconclusive and (6) "I don't know". Frequencies for reasons for receiving cervical screening and results will be reported.

Summary

The objectives of the research were to determine the level of awareness about HPV infection, cervical cancer, and vaccines among female AYA in an area of the world with the highest HIV and HPV rates; describe attitudes and beliefs of female AYA towards the HPV vaccine, evaluate the acceptability of vaginal self-sample testing for HPV, and analyze associations and/or predictors of HPV vaccine and self-sample testing acceptability. The most commonly cited barriers in the literature to receiving the HPV vaccine, a part from cost, were misconceptions about the efficacy and safety of the vaccine. Low levels of awareness are attributed to a lack of appropriate education campaigns prior to the administration of the HPV vaccine in both school and clinic settings for young women and parents. This research about acceptability of the HPV vaccine and innovative preventative cervical cancer screening tools will help to inform cervical cancer prevention initiatives.

This study was a collaborative project with a youth centered study examining HIV acquisition in Durban, SA. The age of the cohort (16-26) are key to focus on for cervical cancer prevention efforts in SA. Data analysis included descriptive statistics, health behaviour descriptors, health care utilization descriptors, and mental health measures. Outcome objectives included, AYA SRH information sources; HPV, cervical cancer, and HPV vaccine awareness; HPV vaccine and vaginal self-collection acceptability; risk perceptions for acquiring HPV, HIV and developing cervical cancer (self-versus other women); perceptions of severity and vaccine efficacy beliefs;

factors associated with perceived risk; factors influencing willingness to participate in self-sample collection; and uptake of cervical cancer prevention services.

Chapter 4: Results

Introduction

The findings of '*A Pivotal Time in Global Cervical Cancer Prevention*" study on HPV vaccine and screening awareness and acceptability are presented in this chapter. Descriptive data will first be presented followed by the nine outcomes: SRH information sources and influences; HPV, cervical cancer, and HPV vaccine awareness; HPV vaccine and self-sample acceptability; perceptions of risk for acquiring HIV, HPV and developing cervical cancer; perceptions of risk for acquiring HIV, HPV and developing cervical cancer for self, compared to other women in the community; perceptions of severity associated with HPV and cervical cancer as well as efficacy beliefs about the HPV vaccine; factors associated with perceived risk; factors associated with willingness to participate in self-sample collection; and uptake of cervical cancer prevention services.

Descriptives

Of the 132 female AYA enrolled in the AYAZAZI study at the Durban site, 122 completed the HPV questionnaire at the 12-month collection point. Characteristics are shown in Table 5. Participants ranged from 17-25 years of age (M = 20.16; SD = 2.05) with 55 (45%) adolescents (16-19 years) and 67 (55%) young adults (20-25 years). Participants were mostly heterosexual (113; 92.6%), with six (4.9%) reporting to be lesbians, and three bi-sexual (2.5%). Most participants were currently in a relationship but not living with their partner (100; 82%), while 19 (15.6%) reported to be single and three (2.5%) currently lived with their partner. Most participants reported attending school (78 or 63.9%), enrolled in high school (14; 11.5%) or post-secondary education (63; 51.6%). The amount of monthly income participants reported was most commonly between 401-1600 ZAR (45%).

Table 5. Descriptive Characteristics

Characteristics (n = 122)	n (%)
Socio-demographics	
Age category, years	
16 to 19	55 (45.1)
20 to 25	**67 (54.9)**
Sexual orientation	
Heterosexual	**113** (92.6)
LGBTQ	9 (7.4)
Currently in school	
Yes	**78** (63.9)
No	44 (36.1)
Relationship Status	
In relationship	**103** (84.5)
Single	19 (15.5)
Housing	
Formal	**88** (72.1)
Informal	34 (27.9)
Head of Household	
Female	**84** (68.9)
Male	35 (28.7)
More than one	3 (2.5)
Have Children	
Yes	34 (27.8)
No	**88** (72.1)
Monthly personal income	
<400 ZAR	31 (25.4)
401-1600 ZAR	**55** (45.1)
1601+ ZAR	3 (2.5)
Sexual history, behaviours, and violence	
Ever had consensual sex	
Yes	**98** (80.3)
No	24 (19.7)
≥2 Sexual partners in lifetime	
Yes	**67** (68.4)
No	31 (31.6)
Condom use in past 6 months	
Consistent (“always”)	0 (0)
Inconsistent (sometimes/never)	**48** (100)
Condom use first consensual sex	
Yes	30 (31.3)
No	**66** (68.8)
Ever experienced physical/sexual violence	
Yes	3 (2.5)
No	**113** (92.6)
Prefer not to say	6 (4.9)
HIV Status	
Positive	8 (6.6)
Negative	**106** (93.4)

Overall, most participants reported to be living in formal housing (72.1%) while the remainder in informal housing situations this included RDP housing[13] (20.5%), shacks in informal settlements (4.1%), and hostels (3.3%). Participants' homes were mostly headed by women (68.9%). The head of the household most often was an adult female (18-60 years) at 49.2%, followed by males (18-60) 24.6%, and older females (<60) at 12.3%, respectively. Of the 122 women, 34 (28%) were mothers with most having one child (33) and one mother had two children. Seven women (5.7%) were currently pregnant. Of the 122 AYA participants, 8 (6.6%) were HIV positive and been diagnosed by the AYAZAZI team at a prior point of contact[14].

Health Behaviour Descriptors

Most women (85.2%) had not smoked cigarettes in the past 30 days, while 18 (14.8%) smoked 1 or more cigarettes on average per day. The majority of women reported to have participated in non-medicinal drug use (64.8%) at least once in their lifetime. Sexual health behaviours including whether AYA had engaged in consensual sex, the age of first consensual sex, use of condoms during first sexual encounters, number of sexual partners, and male condom use and frequency, as well as any experiences with sexual or physical violence. Of the 122 participants, 98 (80.3%) said they had engaged in consensual sexual activity. The age of first sexual activity ranged from 14-21 (M = 17.48; SD 1.54). Many participants (68%) reported to have had consensual sex with ≥ 2 sexual partners throughout their lifetime. The number of sexual partners ranged considerably from 1 – 25 (M = 3.27; SD = 3.69), with participants most often reporting having had one (N = 31; 25.4%), two (N = 25; 25.5%), or three partners, respectively (N = 15; 12.3%). One participant reported having 21 and another 25 consensual sexual partners.

[13] Reconstruction and Development Programme (RDP) is subsidized government housing.
[14] All participants in the study were either diagnosed HIV- or undiagnosed at time of enrollment.

Participants were asked if they used a condom during their first consensual sexual encounter, most 68 (68.8%) said “no” while 30 (31.2%) said “yes”. Women who reported to be sexually active, 67 (54.9%) stated that they use male condoms ever, while only 1 woman reported to use female condoms. No participants reported using condoms consistently (every time) and all women who answered the question (48) reported to use male condoms inconsistently. Of the 48 (39.3%) females who used male condoms, all said they used them only ‘sometimes’.

Healthcare Utilization Descriptors

Very few participants reported having access to medical aid (health insurance programs) at 16.4% ($N = 20$) which means very few had access to health services above and beyond basic coverage. However, when asked about health services that AYA needed 18 (15%) reported needing services for mental health, physical and sexual violence, addictions and faith- or traditional-based healers over the past 6 months. Four women stated that since their last visit, they had required services for gendered-based violence, while 3 of those women received services. Many of the participants (12%) needing additional services reported having received them from the aforementioned health care services providers. Table 6 details healthcare services examined for need and whether women received.

Table 6. *Health Services Needed and Received*

Type of Service	**Needed (*N*)**	**Received**
Mental Health	2	1
Physical Violence	1	2
Sexual Violence	3	1
Addictions	1	2
Faith-Based	6	5
Traditional Healers	5	4

Overall, three women reported to have experienced sexual or physical violence over the past 6 months with six women stating they "prefer not to say". Two participants reported to be physically hurt or threatened by a sexual partner and three selected "prefer not to answer". Similarly, one woman stated that she had been forced to have sex with someone when she didn't want to over the past six months, while six women said they preferred not to answer the question. Not surprisingly, there are incongruences between services required, particularly for physical and/or sexual violence support, and those received among this cohort of young women.

Mental Health Descriptors

Mental health scale findings measuring perceived stress and resiliency are presented next. From a possible score of 40, participant PSS-10 scores ranged from 0-30 and were normally distributed (M =15.7; SD =6.59). Scores higher than 20 indicated higher levels of stress. The data was stratified for high- (score > 20) versus low-levels (0-20) of perceived stress. Findings showed that most of participants reported feeling low levels of perceived stress (N = 85; 69.7%) compared to higher levels (N = 37; 30.3%). Scores for the CD-RISC-10 measuring resiliency ranged from 7-40 yielding a mean score of 27.96 (SD = 7.3) with a positively skewed distribution. Scores higher than 20 indicated higher levels of resilience. Stratified scores showed that most AYA women had high levels of resilience (105; 86.1%) compared to those with low levels. This finding indicates that most participants reported having fairly high levels of adaptability, coping skills, and positive outlooks on life.

Sexual and Reproductive Health Information Sources and Influences

Participants were asked if they had heard about and where they received SRH information such as contraception, HPV, cervical cancer, cervical cancer screening, and the HPV vaccine and social influences (friends/family vs HCP's) in their decision to receive the HPV vaccine. Results

about affordability of the vaccine for participants are also presented. Results showed that few participants had heard about HPV ($N = 7$) or the HPV vaccine ($N = 20$), while AYA more frequently had heard about contraception ($N = 119$) and cervical cancer ($N = 109$). Table 7 shows SRH topics and where participants learned about each from. When all SRH topics were combined, the most influential sources of information about SRH for AYA females in order were, health care professionals, communications/social media, family/friends, and AYAZAZI/community groups. The least reported source for information about these topics was in a school setting.

Table 7. *SRH Information Sources: Frequencies*

	Contraception	Cervical Cancer	HPV	HPV Vaccine	Screening
Family/Friends	21	20	-	1	25
Communication/Media	13	**44**	**4**	7	12
Health Care Professionals	38	31	3	**8**	**37**
AYAZAZI/Other Group	**44**	4	-	-	5
School	12	22	-	3	8

*Groups are not mutually exclusive

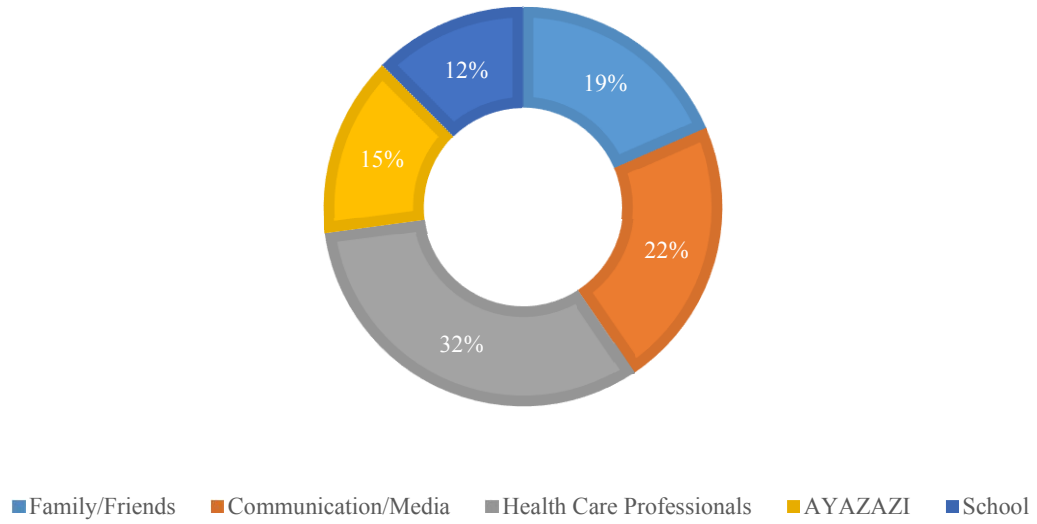

Figure 11. Sources of Information about SRH Topics

Participants were asked how likely they would have the HPV vaccine if recommended by a health care professional compared to friends/family members. Most stated they "definitely would" if recommended by a HCP (77.9%), whereas fewer women said they "definitely would" receive the vaccine if recommended by friends/family members (20.6%; see Table 8). Health care professionals (*M*=4.69; *SD*=.69) played a significant role in influencing AYA females to consider the receiving the HPV vaccine compared to recommendation from family or friends (*M* = 3.38*; SD*=1.37) at t (120) = 74.48, p = .000.

Table 8. *Likelihood of Receiving HPV Vaccine from Recommendations*

	Doctor or Nurse	**Friends or Family**
	%	**%**
Definitely would not	.80	15.6
Probably would not	1.6	11.5
Neutral	3.3	10.7
Probably would	15.6	38.5
Definitely would	77.9	20.5

The role of affordability in acceptance of the HPV vaccine was also explored. Two questions were asked about the importance of affordability including, 1) how likely would you consider the HPV vaccine if it cost you 2300ZAR to purchase? And, 2) how likely would you consider the HPV vaccine if it was free? Questions were measured on Likert scales with importance of affordability ranging from, 1 -"Definitely would not receive the vaccine" to 5 - "Definitely would receive the vaccine". Most participants were significantly more favourable towards the vaccine if it was free (M = 4.84; SD = .50) then if the vaccine cost 2300 ZAR (M = 2.17: SD = 1.55) at t (112) = -19.39, p = .000. The inverse relationship between cost variables is shown below in Figure 12.

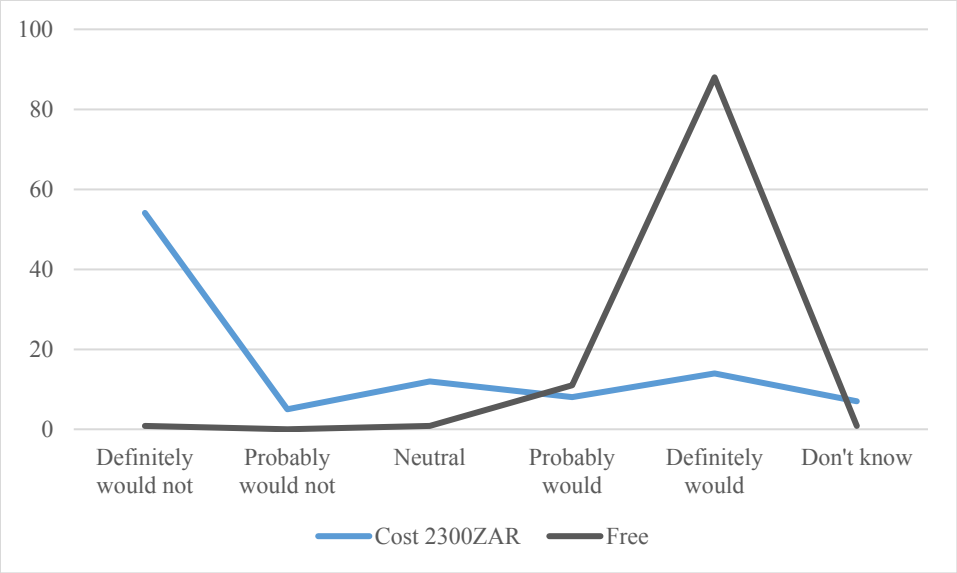

Figure 12. Fiscal Considerations for Receiving the HPV Vaccine

Awareness about HPV, Cervical Cancer, Vaccines, and Screening

Awareness about HPV, cervical cancer, and screening, as well as the HPV vaccine was examined by first asking women if they had ever heard about these topics prior to the study. Women were then administered an awareness scale, to measure levels of awareness. Of the 122 women, very few (6.6%) had heard of HPV or the HPV vaccine (16.4%), prior to participation in the study. However, most women had heard of cervical cancer (89.3%) and a test to check for cervical cancer (61.5%). The participants were asked to mark a series of eight statements about HPV, cervical cancer, and the HPV vaccine as 'true' or 'false'. If participants said "I don't know" or the incorrect answer they were marked with a score of zero whereas correct statements were worth a score of one.

Statements were combined for a total knowledge and awareness score (0-8). Women's scores ranged from 0-7 (M = 1.71; SD = 1.89), with just under half scoring "0" (42.6%). When scores were stratified (0-2 = 'little to no awareness'; 2+ = 'some awareness') most AYA women (66.2%) had 'little to no awareness' about these topics. Importantly, most women indicated they

did not know that an HPV vaccine was available (87%) nor were aware of most of the statements about HPV and cervical cancer presented to them (See Figure 13).

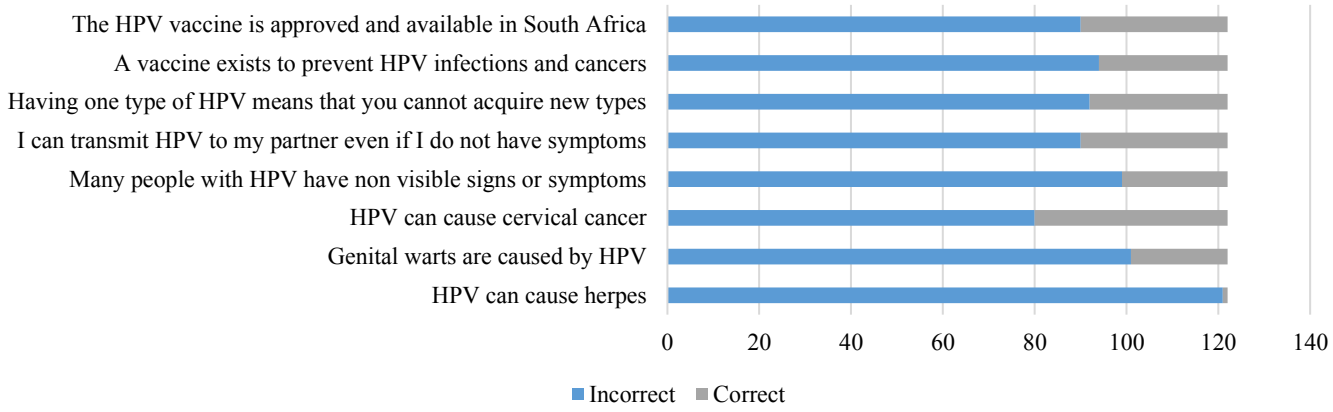

Figure 13. Awareness Scores: HPV, Cervical Cancer and Vaccine

HPV Vaccine & Self-Collection Acceptability

Participants were asked about HPV vaccine acceptability for self and children (or future) children as well as their willingness to participate in vaginal self-sample testing or collection. AYA women were also asked about the importance that the HPV vaccine reduces warts and/or cervical cancer. Most women (N = 118; 96.7%) said they would be willing to receive the vaccine, while three women stated "I don't know". Acceptability for children and future children was also high at 95.1% (N = 116), with four participants declining the vaccine and two stating "I do not know". A cross tabulation was run to explore whether current mothers and those who were pregnant were HPV vaccine acceptant for their children. All mothers in the cohort (N = 34) and women who were currently pregnant (N =7) stated they would want the HPV vaccine for their child (ren).

The acceptability of vaginal self-collection (for HPV) was measured by asking women if they would be willing to collect a sample by themselves to test for cervical cancer if they were given instructions on how to collect the sample. Most women stated they would be willing to

participate in self-collection (*N* = 103; 85.1%), with 15 (12.4%) would not, and the remaining 3 (2.5%) women stating, "I don't know". Just over half of the women indicated they would prefer to collect the self-sample at a clinic (*N* = 68; 61.8%) while 35 (38.2%) women said they would prefer to collect the sample in their homes and two said they would participate in self-collection, but did not know where they would prefer to collect the sample.

Last, women were asked to rate the level of importance regarding whether the HPV vaccine protected against cancer and/or genital warts. Most AYA rated the importance of the HPV vaccine to prevent genital warts as "Important" or "Very Important" (*N* = 118; 96.7%). Similarly, the importance of the vaccine to prevent cancer was rated as "Important" or "Very Important" by 119 participants (97.5%). This indicates equal level of importance for participants that the HPV vaccine protect against both genital warts and cancers.

Risk Perceptions for Acquiring HPV, HIV, and Developing Cervical Cancer

Participants were asked to rate their perceived risk of acquiring HIV, HPV, and cervical cancer. A Likert scale was used to rate perceived risk with responses ranging from, 1 'not at all at risk of becoming infected'; 2 'low-risk'; 3 'medium-risk'; and 4 'high-risk of becoming infected'. Risk perception scores for self for all three categories (HIV, HPV and Cervical Cancer) were then recoded and dichotomized into low- and high-risk groups (See Table 9).

Table 9. *Stratified Perceived Risk Scores: Self*

Perceived Risk	**HPV**	**Cervical Cancer**	**HIV**
	N (%)	***N (%)***	***N (%)***
Low Risk	49 (43)	42 (39.6)	84 (75)
High Risk	65 (57)	64 (60.4)	28 (25)

The perceived risk that participants felt other AYA females in their communities was rated and similarly dichotomized into low- and high-risk groups (See Table 10).

Table 10. *Stratified Perceived Risk Scores: Other AYA Females*

Perceived Risk	HPV	Cervical Cancer	HIV
	N (%)	*N (%)*	*N (%)*
Low Risk	5 (4.4)	12 (10.8)	13 (11.1)
High Risk	108 (95.6)	99 (89.2)	104 (88.9)

Consistently for all categories, participants perceived themselves to be at much lower risk of acquiring HIV and HPV as well as developing cervical cancer compared to other AYA females in their communities. Figure 14 shows a comparison of participants who perceived themselves to be at high-risk for acquiring HIV and HPV as well as developing cervical cancer in relation to other AYA females in their community.

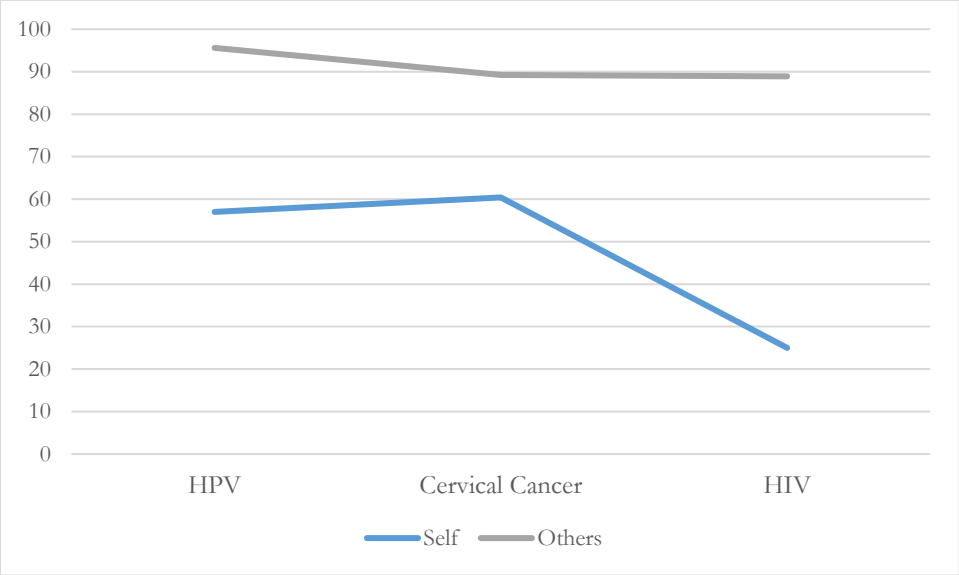

Figure 14. Perceptions of Risk (High): Self vs. Others

Risk Perceptions of Self Compared to Other AYA Females

In all three domains, participants rated other young women as being at a much higher risk compared to themselves of acquiring HIV, HPV, and cervical cancer. The means and standard deviations for perceived risk of self compared to others is below in Table 11.

Table 11. *Perceived Risk for HIV, HPV, and Developing Cervical Cancer: Self vs. Others*

Perceived Risk	Self	Other AYA Females
	M (SD)	***M (SD)***
HIV	2.2 (.79)	3.5 (.69)
HPV	2.7 (.95)	3.6 (.60)
Cervical Cancer	2.8 (.95)	3.5 (.71)

Participants commonly have lower perceived levels of risk associated with themselves acquiring viruses and developing diseases in comparison to how they perceive others to be at risk for the same infections and diseases. Results demonstrate that participants believed that other young people in their community were at a significantly higher risk than themselves of acquiring HIV at t (116), = 55.2, p = .000, HPV at t (112), =64.2, p =.000 and developing cervical cancer at t (110), = 51.73, p = .000.

Perceptions of Severity and Vaccine Efficacy Beliefs

The perceived severity or impact of HPV and cervical cancer was measured using a Likert scale ranging from 1 – no impact on my life, to 4 – high impact. Women rated the perceived severity of acquiring HPV and cervical cancer as similarly high, M = 3.39 (SD = .86) and M = 3.68 (SD = .68), respectively. When data was dichotomized by 'no to low impact" vs "some to high", 9 (8.3%) participants felt HPV would have no to low impact while 11 (9.8%) stated that cervical cancer would have no to low impact on their lives. Overall, the severity or negative impact that acquiring HPV or developing cervical cancer was rated very high by participants.

Effectiveness beliefs were measured regarding the HPV vaccine. A Likert scale ranging from 'Not Very likely' to 'Very likely' was used for this question. When asked how likely the participants thought the HPV vaccine would reduce their chances of becoming infected with HPV and developing cervical cancer, most women expressed believing the vaccine to be highly

efficacious with preventing both HPV (*M*=3.53; *SD* = 82) and cervical cancer (*M* = 3.47; *SD* = .816). Data was dichotomized to "no/little belief "vs "fairly/high belief" that the HPV vaccine will prevent HPV and cervical cancer, demonstrating that 100 (91.7%) and 101 (90.2%) participants had fairly high efficacy beliefs about the preventive properties of the vaccine against HPV and cervical cancer.

Factors Associated with Perceived Risk

Chi-square tests of independence were used to calculate and compare the frequency of risk perception (high vs. low) of both 1) acquiring HPV and 2) developing cervical cancer with age, sexual orientation, income level, student status, housing type, head of household, HIV status, condom use consistency, stress and resiliency scores, and number of sexual partners. No factors listed were found to be significantly associated to risk perception for acquiring HPV or developing cervical cancer.

Factors Influencing Willingness to Participate in Self-Sample Collection

Most participants said they would be willing to participate in self-sample collection (*N* = 103; 85.1%), with 15 (12.4%) would not, and the remaining 3 (2.5%) women stating, "I don't know". A Chi-square test of independence was run to compare the frequency of HPV self-sample collection acceptability (yes vs. no) with: age, sexual orientation, income level, student status, housing type, stress and resiliency scores, HIV status, sexual partners, sources of information about 1) HPV, 2) cervical cancer and 3) cervical screening, knowledge or awareness about topics, and perceptions of 1) risk for HPV and cervical cancer and 2) perceived severity of HPV and cervical cancer. However, no significant associations were found in the analysis, therefore binomial logistic regression analysis was not used to explore predictors in HPV self-sample testing acceptability.

Uptake of Cervical Cancer Prevention Services

The cohort of AYA women (16-24 years) in our study are part of an extraordinarily important group of women who are at the highest-risk of developing cervical cancer. Whether participants had ever received the HPV vaccine or cervical screening was measured and further cross tabulated with HIV status[15]. Out of the entire cohort of AYA participants, only 2 (1.6%) had received an HPV vaccine, while 2 stated they did not know if they had. Eight (6.6%) women said they had received testing or screening for cervical cancer. Several reasons were listed for having screening including, experiencing pain and/or other symptoms ($N = 5$), because they had heard about the test and wanted to get checked ($N = 2$), and follow-up from abnormal results (1). The eight women were living with HIV (WHIV) and ranged from 19-24[16] years. None of the WHIV had received an HPV vaccine, with one saying she did not know if she had. Only 1 out of 8 WHIV had received Pap testing because of reported pain and other symptoms.

Participant Feedback

Participants were asked to provide feedback of the AYAZAZI youth study at the 12-month point (at time of HPV survey). The AYA were asked, 1) what have you liked about the AYAZAZI study overall, and 2) If we received additional funding to continue AYAZAZI, what services would you like use to offer. When asked what they liked about the study, from the 76 participants (male and female) who filled out the survey, 47 (61%) identified AYAZAZI as being a direct and key source of health (SRH; emotional; physical) support, education and services. Below are some of the responses from participants about how AYAZAZI (and using a youth engagement approach) had benefitted their lives:

[15] The WHO recommends cervical screening directly following HIV diagnosis. HPV vaccination also recommended.
[16] Half of the WHIV were 19 years of age (N=4)

1. Everything especially the way they treat us and the knowledge we are getting as youth;
2. AYAZAZI staff members are very kind and friendly. I have learned a lot in terms of my health;
3. The care and patience towards my health and the fact that I get regular checkups;
4. It encouraged the youth to continue protecting themselves from unprotected sex and free from STIs. Furthermore it helps one to know his/her status (HIV);
5. They make sure we are find and they treat us as the member of the study. The services are very good;
6. Everything about AYAZAZI is amazing! I like the friendly stuff and the information they provide for us as youth is quite amazing;
7. It changed my lifestyle;
8. The fact that the staff is very friendly and makes it easier for us to open up about our health problem;
9. Each time I come in to visit they just seem to amaze me with all the information I did not know about;
10. I have liked everything about AYAZAZI the staff is amazing they treat their clients with care and love;
11. AYAZAZI study is more helpful to the youth and really helped me a lot about my life they teach me everything about how to take care of my personal life;
12. Everything how you guys treat clients and care you have about youth health;
13. I learned how to keep myself healthy and I love the way you treat us as youth you keep us free from stress.

One participant stated they she "liked that they taught me about HPV, I didn't know about it". In terms of what participants would want for services if additional funding was given to AYAZAZI, 8 (11%) of respondents said they would want to see HPV vaccines or further cancer studies:

1. Include a cancer study;
2. Cancer testing;
3. It shouldn't be just about HIV & STI. I would like others services like checking for cancer etc.;
4. Cancer services and still HIV;
5. Pap smears for under 30 years because they are also sexually active;
6. Cancer testing, youth book clubs and support groups;
7. Vaccines for HPV, more studies about it;
8. The machine to check for cervical cancer.

Findings from the post-survey with participants demonstrate the important role that trust plays in optimal SRH services for AYA involved in this study. This research study and team made it possible for many of the AYA to access SRH services they may not have otherwise, gain

awareness and feel empowered about SRH topics, and feel well-supported in a youth-engaged project where they were able to become active participants in their own health care. AYA expressed wanting to not only know more about HPV, but also to have cancer related studies and testing and HPV vaccines if they were to participate in future research studies.

Summary

Participants in this study were female AYA enrolled in a study site in downtown Durban. The cohort of 122 AYA were mostly heterosexual and in relationships. Many AYA were currently students and working towards post-secondary credentials. Formal housing was most common housing situation with many participants reporting, on average, low monthly personal income amounts. Homes of participants were predominantly headed by females with a considerable number of AYA females with a child or children and/or currently pregnant. A small portion of participants were living with HIV at the time of survey administration. Both mothers, who are making decisions for their children about HPV vaccines, and WHIV, those at highest-risk of acquiring HPV and developing cervical cancer, are particularly important women to focus on.

A small portion of AYA reported smoking cigarettes and just over half had experimented with non-medicinal drugs at some point in their lives. Most AYA reported being sexually active, with most saying they did not use a condom during their first consensual sexual experience and all said they inconsistently used condoms. Ages of first consensual sex and number of partners ranged considerably within this cohort. However, most participants who were sexually active had been with ≥ 2 sexual partners with a couple AYA saying they had been with 20+ partners. The inconsistent condom use among all participants paired with higher numbers of sexual partners are alarming findings, as this population of young women are at the highest-risk from suffering from an array of unfavourable SRH health outcomes. Despite the high numbers of STI's locally

and among the population, the data demonstrated that participants have a considerably low perceived level of risk for acquiring HPV, HIV, or developing cervical cancer perhaps explaining why AYA are engaging in unusually risky sexual health behaviours.

Most of the women reported to have no medical aid, however reported needing unique health services including services for mental health, sexual and physical assault, traditional and spiritual healing services. As sexual assault and assault in general tends to be highly underreported in SA, the low rates of reporting these incidents within the cohort may not reflect realistic rates. Some participants said "prefer not to answer" to questions pertaining to violence, therefore higher rates than what are reported in the cohort are assumed. Mental health indicators reported were perceived stress and resiliency scales, with most women reporting to have low-levels of stress and high-levels of resilience or ability to adapt, cope, and have a positive outlook on life.

Sources for SRH knowledge ranged considerably, however the most influential sources for information overall were health care professionals, communication/media, and family/friends. However, AYAZAZI was most influential in teaching AYA about contraceptives compared to any other sources. When it comes to recommendations for receiving the HPV vaccine, health care professionals played a significant role in women's considerations to receive the vaccine compared to friends/family. An additional significant factor in the decision to receive the HPV vaccine was affordability, as it is a tremendous cost currently in SA. Most women said that if the vaccine was free they would get it, however with the current cost (2300ZAR), which translates to roughly $230CND, and very few participants having access to medical aid the HPV vaccine is not currently a reality for most women. Recommendation sources for and affordability of the HPV vaccine mattered to women.

Awareness about HPV and its association to cervical cancer as well as the HPV vaccine was very low among women in this study. Few women had heard about HPV prior to the study, and few knew that an HPV vaccine existed to protect them against genital warts and cancers. As previously stated, despite very low knowledge levels the acceptance rate of the HPV vaccine remained very high. Beliefs about effectiveness regarding the HPV vaccine were also high. This is important because although AYA women in the cohort had very little practical awareness about these topics, they still believed the vaccine would be effective and all expressed interest in receiving or having their (future) children receive it to protect against HPV. There are several plausible factors for a favourable attitude towards the HPV vaccine including the trust that had been established with the AYAZAZI staff and HCPs prior to the questionnaire as well as the high-levels of cervical cancer locally. HPV vaccine acceptance for self and (future) children was very high. All current mothers and pregnant women stated they would have their child receive the HPV vaccine. Most women said they would prefer to collect their sample at a clinic as opposed to at home. Almost all of the AYA stated they would want the HPV vaccine to protect against genital warts as well as cancers. The protective factors were equally important to women which is important given the current HPV vaccine being rolled out in SA only protects against 2 oncogenic HPV types but not genital warts. In general, risk perception for acquiring HPV, HIV, and developing cervical cancer was low among participants compared to how they perceived risk levels for other women in their communities. This factor did not, however, play a role in women's acceptance of the HPV vaccine or self-sample testing. HPV vaccine efficacy beliefs were rated high by participants. There were no significant associations found in relation to perceived risk level of acquiring HPV or developing cervical cancer. Similarly, no factors were found to be associated with participants' willingness to participate in HPV self-sample

collection. The reported uptake of cervical cancer prevention services (Pap testing and HPV vaccines) were almost non-existent among this cohort, this was also the case among WHIV who are most at-risk for cervical cancer.

Finally, the post-questionnaire survey overwhelmingly showed that AYAZAZI played an important, if not key, role in AYA's understanding and awareness about SRH topics. AYA expressed feeling valued, loved, listened to, and trusting of staff for education and STI testing needs. AYA expressed wanting to not only know more about HPV, but also to have cancer related studies and testing as well as HPV vaccines, if they were to participate in future research studies with the AYAZAZI team. It was clear from the feedback that this study and team really mattered to participants.

Chapter 5: Discussion

In this chapter AYA women's awareness about HPV and attitudes towards the HPV vaccine as well as self-sample acceptability are discussed. After a concise introduction, a discussion of the outcomes is presented in a way that addresses the proposed research questions for this study. The sections will include: description of the cohort; knowledge about HPV, cervical cancer, and the HPV vaccine; acceptability of the HPV vaccine (self and children) and HPV self-sample testing; acceptability; SRH information sources; and perceptions of risk. A summary and implications are presented to end the chapter.

Introduction

Cervical cancer is an entirely preventable disease. It is a pivotal time in cervical cancer prevention for young South African women. It is a reality for many young women to suffer from array of SRH challenges, this is particularly the case for cervical cancer (Ebrahim et al., 2016; Richter, 2015). HPV related cancers and HIV/AIDS are major public health problems in SA (Bruni et al., 2016; UNAIDS, 2015). One of the most important advances in cervical cancer prevention is the HPV vaccination, and will have a significant impact in countries like SA with high HPV prevalence rates, low screening rates and limited resources to manage HPV associated lesions and cancers. Secondary prevention, including innovative approaches such as HPV self-sample testing, are equally important to invest in and focus on in areas of the world with high rates of cervical cancer. Due to the fact that the HPV vaccine has only recently been rolled out in SA at a national level, this study about awareness and vaccine acceptability is timely and will contribute to policy and decision making moving forward for a population at the highest-risk of acquiring HPV. This study aimed to describe AYA females' awareness about HPV and cervical

cancer, as well as explore associations and predictors of HPV vaccine and self-sample acceptability.

Description of the Cohort

Women who participated in this study were representative of a population at the highest risk of HPV, HIV, and cervical cancer in SA. The demographics of study participants were representative of the SA reality, with many AYA already having begun childbearing, with 27% of mothers overall in the study. Youth mothers (16-19 years) represented 10% of the overall cohort, 7% of whom already had children and 3% currently pregnant. This is comparable to the most recent *SA Demographic and Health Key Indicator's Report* (2017), showing that 16% of women age 15-19 in South Africa have begun childbearing: 12% have given birth, and another 3% were pregnant at time of survey collection.

Sexual health behaviours, such as number of partners and condom use, were also found to be similar between our cohort and the national average. The sexual practices that AYA females in this study reported to be participating in show cause for concern, as these behaviours put them at a considerable higher-risk for acquiring STIs. For example, over half of the participants in this study reported not to use a condom the first time they had consensual intercourse and all reported inconsistent condom use over the past six months. Further to this, many AYA reported having multiple sexual partners (68%) with a mean of 3.27 lifetime partners. These findings are also consistent with national data showing that 39% of the female AYA (15-24 years) reported not to use a condom the last time they had intercourse. Data also showed that 4.6% of the participants had ≥2 sexual partners (over the past year) with a mean of 2.9 lifetime partners (NDoH, Stats SA, SAMRC, & ICF, 2017).

Finally, in comparison to the overall AYAZAZI cohort in both Soweto and Durban (*N*=425) the female AYA who participated in this study were fairly representative in terms of age, student status, and sexual behaviours. The AYAZI cohort in both sites consisted of 40% males and 60% females, with the most common age group between 18-21 years (60%). This is similar to the AYA females in this study with a mean age of 20.3 year with a slightly larger representation of young adults (20-25 years) at 55%. Most participants in the HPV study were currently attending school (*N*=78; 78%), which was also the case for most participants in the AYAZAZI study at 71% (303/425). Reported sexual behaviours of the female AYA in this study did differ from the overall cohort, with 70% reporting to be sexually active in Soweto and 76% in Durban, respectively. However, 80.3% of HPV study participants reported to have been sexually active with most stating they had been with more than 2 sexual partners (68%) in comparison to the overall AYAZAZI cohort at 21% in Soweto and 17% in Durban. In addition, consistent condom use was not reported by any female AYAs in the HPV study, while this it was reported by 30% of participants in Soweto and 30% in Durban. These comparisons tell us several things about the AYA females participating in this sub-study, 1) many are currently enrolled in formal education, 2) sexual practices (number of partners and inconsistent condom use) were vastly different between the HPV sub-study and AYAZAZI participants, and 3) due to sexual health practices participants are at the greatest risk-for acquiring HIV and developing problematic SRH outcomes. Education level can play a role in health decision-making, however in this sub-cohort despite comparable ages and education levels, sexual health behaviours did not reflect this.

HIV rates found in our study were slightly lower at 7%, compared to the estimated national average for young women (15-24 years) at 10.4% (UNAIDS, 2016). Of the 8 WHIV in the cohort, half were youth (16-19 years) and half young adults (20-15). There were 3 WHIV in our

study who were mothers and none who were currently pregnant. In comparison, 30.8% of all women nationally who participated in antenatal care were HIV positive (National Department of Health, 2015). Although the inclusion criteria upon enrollment for the AYAZAZI study was HIV negative status or unknown, a plausible explanation for the lower rates of HIV among AYA in our study, for some, was their early involvement with the AYAZAZI research team at a pivotal time in their lives for HIV acquisition. Having the opportunity to learn about SRH topics from a health team that they trusted, have access to STI testing and being empowered to play a role in managing their own health, all could have contributed to the lower HIV rates found among our participants.

In terms of types of healthcare utilization descriptors, very few AYA females in our study had access to medical aid (16.4%). Similarly, the Institute of Race Relations (IRR) reported in 2017 that 17.4% of the overall SA population had access to private medical aid programs. AYA females in SA face unique and challenging health circumstances, often requiring access to an array of health services. Within our cohort, participants reported experiencing physical and sexual violence and requiring health services for assault, as well as mental health and addictions services. Keeping in mind that an estimated 1 in 9 assaults are reported, this calculates to an unacceptable number of women who have experienced assault. The 2016 Demographic and Health Survey reports that 1 in 5 women in SA have experienced physical violence. In particular, young women (18-24 years) experienced highest rates of violence, with 17% of respondents reporting to have been survivors of abuse. The high levels of violence towards women is a major public health concern in SA and needs to be considered in SRH services for young women.

Knowledge about HPV, Cervical Cancer, and the HPV Vaccine

Results from this study demonstrated that participants' awareness about HPV and the HPV vaccine was very low, with most AYA stating they had never heard of HPV prior to the study. Further to this, most participants did not know that an association existed between HPV, cervical cancer and genital warts, they could transmit HPV to their partner if they were asymptomatic, and were unsure if HPV caused herpes. The HPV vaccine has been available in SA since 2010, however most AYA did not know that a vaccine existed that protected against HPV or HPV related cancers, nor were they aware that it was available locally. These findings are consistent with previous studies where awareness about these topics were generally low among both AYA females and caregivers, particularly in relation to the lack of awareness about HPV and its association to cervical cancer (Cunningham et al., 2014; Perlman et al., 2014).

In contrast, most AYA participants had heard of cervical cancer prior to this study. Several factors that were not measured on the survey can be attributed to AYA's having heard about cervical cancer including knowing someone with cervical cancer and the influence of a television series. The research assistants for this study reported that participants commonly spoke about knowing or hearing about someone or having a family member who had been diagnosed with cervical cancer. In addition to the personal effect that cervical cancer had in some of the women's lives, a number of participants also reported that a local popular television series had recently featured a character who was diagnosed with cervical cancer with the story line including her treatment and recovery. These findings are consistent with communications and media being the main source of information about cervical cancer for AYA. Even though awareness was low, participants indicated on the post-survey they wanted to learn more about HPV as well as have the opportunity to engage in screening and have access to HPV vaccines.

Acceptability of the HPV Vaccine: Self

Acceptability reported for the HPV vaccine among this cohort of female AYA (97%) was comparable to previously reported studies about acceptability in an African setting ranging from 59-100% (Cunningham et al., 2014). With such high acceptability rates, finding associative or predictive factors as originally proposed was not feasible. Factors associated with acceptability of the HPV vaccine according to Health Belief and Vaccine Hesitancy Models, as well as the literature, measured in this study included: knowledge and awareness, beliefs about susceptibility, perceptions of HPV vaccine efficacy, family/parental attitudes, HCP influence, knowing someone with cervical cancer, and the quality or comprehensiveness of a vaccination program (Dubé et al., 2013; Perlman et al., 2014; Turiho et al., 2014).

A number of studies have shown awareness, risk perception, and vaccine efficacy beliefs to be significant factors in the acceptance of the HPV vaccine (Chidyaonga-Maseko et al., 2015; Gu et al., 2015; Perlman et al., 2014; Wamai et al., 2012). This was not the case in this study, where AYA had very little, if any, awareness about these topics prior to the study and relatively low perceptions of risk of acquiring HPV and developing cervical cancer. This finding could be attributed to the high rates of cervical cancer seen locally as well as because the information about these topics was relayed by trusted health care staff (AYAZAZI team). Efficacy beliefs, however, regarding the HPV vaccine were very high among our participants with HCP's being the most common source of information about the vaccine. Opinions and recommendation from HCPs in this study played a significant role in participants' consideration to receive the HPV vaccine. A considerable amount of research conducted in LMICs demonstrated similar findings, that HCP opinions and recommendation mattered and played an influential role for both AYA

and caretakers in making decisions about their health, this included decisions about receiving the HPV vaccine (Gallagher et al., 2017; Tsu et al., 2014).

Finally, knowing someone with cervical cancer was also found to be associated with HPV vaccine acceptance (Cunningham et al., 2014). Although this factor was not captured on the questionnaire, feedback from the research assistants on this study was that participants regularly reported knowing or hearing about someone who had been diagnosed with cervical cancer and/or had watched a popular local television series that had recently featured a character with cervical cancer. Knowing about cervical cancer was commonly associated with knowing someone who had been diagnosed. Additional locale specific factors driving HPV vaccine acceptability in SA are the high rates of HIV, sexual violence, and poverty as well as households predominantly led by women (Katz et al., 2013).

In this study, a mentionable number of our AYA reporting to have experienced sexual and/or physical violence, low monthly incomes, and predominantly female-headed households. Keeping in mind that sexual violence has been found to be highly underreported in SA, rates reported in this study should be interpreted with caution. The aforementioned locale specific factors were also plausible contributors in the high HPV vaccine acceptance rates found.

It is important to note that although acceptability rates for the HPV vaccine for this cohort of AYA women was very high, with many living with low income and having no access to health insurance benefits, access to the vaccine would be very challenging for most participants. In this study, cost was found be play a significant role in participants decisions to receive the vaccine, with most stating they would receive it if it were free and significantly fewer if the vaccine cost current the current local market price of 2300ZAR. Cost as a barrier to the HPV vaccine has also been reported as a barrier in a variety of other studies (Cunningham et al., 2014; Harries et al.,

2009). South Africa is unique in an African context, as it is classified as a middle-income country therefore does not qualify for GAVI or other International HPV vaccination subsidization programs[17].

With the national roll-out of the HPV vaccine involving only some girls in public education schools, this does not include a public health component or free distribution of the vaccine for those outside the chosen schools or grades. Cost, therefore, remains a very real issues for AYA females in this cohort, as well as in general throughout SA. A mentionable number of participants had not yet had sexual intercourse (20%) in this cohort. Similar studies about HPV vaccine acceptability have also shown that a number of AYA had not yet engaged in sexual activity and therefore were still ideal candidates to receive the HPV vaccine (Dreyer et al., 2015; Mugisha et al., 2015). Findings from this study demonstrate favourable acceptability towards the HPV vaccine among a population who are at the highest risk of developing HPV related cancers and unable to afford the vaccine. This study outlines the urgent need to expand the national HPV vaccine program in SA, in particular to include AYA who have not yet been exposed to HPV.

Acceptability of HPV Vaccine: Children

Parents and caretakers are critical decision-makers in health care decision-making processes, this is particularly the case for the HPV vaccine as it is recommended to be administered between 9-12 years. Participants in this study reported having highly favourable attitudes about the HPV vaccine, with most (95%) stating they would have their children or future children vaccinated against HPV. All participants who were currently mothers (*N*=34) or pregnant (*N*=17) said they would have their children vaccinated against HPV, if it were available to them. Due to high acceptance rates, no factors could be determined to be associated with HPV vaccine acceptance. Research conducted in similar settings demonstrated caretaker HPV vaccine

[17] https://www.gavi.org/support/sustainability/countries-eligible-for-support/

acceptance for their daughters between 44-96%. The most common reasons for caregivers (predominantly female) to refuse the HPV vaccine for their daughters included, fears about vaccine efficacy and safety, low education and awareness about HPV and its association to cervical cancer and the high cost of the vaccine (Mouallif et al., 2014; Perkins et al., 2011; Vincente et al., 2015; Zhang et al., 2013).

Efficacy beliefs about the HPV vaccine were high among participants in this study, however awareness about HPV and cervical cancer were very low as was perceived risk for acquiring HPV and developing cervical cancer. It is also important to note that AYA reported living in predominantly female headed households (69%), this is a higher proportion than the reported national average of 41.36% of households headed by women in the '*Living Conditions of Household Survey 2015*' (Statistics South Africa, 2017). These findings outline the important role and central influence that mothers and grandmothers play in the lives of young women. As outlined in the previous section, cost was also an important factor in HPV vaccine acceptability with most participants in the study reporting not be able to afford to purchase the vaccine. With the national roll-out of the HPV vaccine involving only select schools, there is a chance that participants' children attend or will attend a participating school. Now that participants have information about HPV and its connection to cervical cancer from this study, there is the hope that this will influence their decisions about HPV vaccination for their children in the future.

Acceptability of HPV Self-Sample Testing

In a wide variety of settings, HPV self-sample testing has been demonstrated to not only be highly efficacious, but also an acceptable alternative to cytology-based screening (Farmer et al., 2010; Mustafa et al., 2016). This is particularly the case in areas with challenging access to health and screening services such as SA (Phiri et al., 2016; Tsu et al., 2014). In this study,

participants were highly favourable towards collecting a sample by themselves if given directions, with most women reporting to feel most comfortable taking the sample at the clinic rather than in their homes. Diffidence and feelings of embarrassment among women was also a theme found in the literature about self-collection (Mitchell et al., 2011; Sievers & White, 2016). This may partially explain why women in this study said they would prefer to collect the sample in a clinic setting, to ensure proper collection techniques and privacy that they may not otherwise have in their homes.

A variety of sociodemographic and behavioural variables have been found to influence testing acceptance, therefore tests were run to examine associations, but no variables were found to be significantly associated with acceptance. Similar to HPV vaccine acceptance, knowledge and awareness was the most significant predictor in the literature found to be associated with women's participation in cervical cancer screening services (Bukirwa et al., 2015; Chidyaonga-Maseko et al., 2015). Despite AYA participants in this study reporting to have very little awareness about these topics, most still reported to be HPV self-sample acceptant with a few stating they were unsure. Self-sample acceptability rates in this study are comparable to those found in the literature among women living in similar low-resource settings (Moses et al., 2015; Ogilvie et al., 2013). Again, the high level of acceptance towards self-sample testing could be associated with the level of trust established prior within this AYAZAZI cohort with staff and HCPs.

Finally, all WHIV in this study reported to be self-sample acceptant, which is also consistent with the literature about the success of integrating cervical cancer prevention tools, such as HPV self-collection, with existing HIV health services (Adamson, Huchko, Moss, Kinkel, & Medina-Marino, 2015; Mahomed et al., 2014; Mitchell et al., 2017; Moses et al., 2015). This is an

extremely important target population for cervical cancer screening, as WHIV generally present with cervical cancer and pre-cancer approximately a decade earlier than HIV negative women, quite often beginning to present in their late twenties (Denny et al., 2012). The high acceptance of vaginal self-sample testing, particularly among WHIV, shows that an excellent opportunity exists to integrate cervical cancer prevention services into existing primary care structures.

Sexual and Reproductive Health Information Sources

Both questionnaire data and post-questionnaire survey results demonstrated that AYA relied heavily on the knowledge they received about SRH, in particular contraceptives, from the AYAZAZI team. Youth engagement approaches for health interventions or health research projects have proven to be a successful way to involve youth and ensure retention as well as adherence to the intervention or health research projects (Powers & Tiffany, 2006; Wood et al., 2014). Involving those who are most affected by the issue being studied is key to successful outcomes. AYA participants in our study reported to be highly trusting of AYAZAZI staff for STI testing and health information needs and expressed feeling valued, listened to, and well informed by the research study staff.

Most AYA females in this study had heard about cervical cancer most commonly from the internet, television, and radio. As previously discussed, many participants related to the researchers that they had become aware of cervical cancer from a local television series popular among young people. Health care professionals were also very influential sources of information for AYA about cervical cancer, screening, and although most participants had not heard about the HPV or the vaccine prior to the study, if they had, HCPs were the most common source of information. When all SRH topics were combined, the most influential information source in this study overall was HCPs. These findings are consistent with other studies about HPV vaccine and

cervical cancer screening acceptance in LMIC's, where HCPs are noted to play an instrumental role in education and health decision making for women, this was particularly the case for sensitization campaigns prior to the administration of the vaccine (Chidyaonga-Maseko et al., 2015; Gallagher et al., 2017; Perlman et al., 2014).

A multigenerational approach to cervical cancer prevention efforts within this population could also be advantageous. A range of studies in similar settings indicate the important role that both mothers and grandmothers play in the health care decision-making process (Francis et al., 2011; Perlman et al., 2014). Cervical cancer prevention programs combining pubescent vaccination with screening for older women (caregivers) have been found to be somewhat successful (Dreyer et al., 2015; Snyman, Dreyer, Botha, van der Merwe, et al., 2015). Richter (2015), an HPV specialist in SA, calls these types of multigenerational programs "crucial" (p.3) to decreasing HPV related cancers nationally, as both HPV vaccines and screening are needed synergistically to effectively decrease cervical cancer rates. These approaches would need to be combined, as they will not be effective for all populations. This is also why effective community engagement strategies are critical to better understand what a community needs prior to education campaigns and the rolling out of any health program, particularly for vaccines.

Perceptions of Risk

This study demonstrated that AYA women had fairly low perceptions of risk for acquiring HIV, HPV, and developing cervical cancer. However, participants rated other women in their community to be at a significantly higher risk than themselves in all three domains. Our findings about AYA females having low perceptions of risk acquiring STI's is consistent with the literature about AYA in similar settings (Maughan-Brown & Venkataramani, 2018; Sychareun, Thomsen, Chaleunvong, & Faxelid, 2013). Sociodemographic and behavioural variables were

tested to explore associations between high- and low-risk perceptions groups and yielded nothing reportable. This lack of significance between the two groups could be attributable to the small sample size. Despite participants' perceptions of risk being generally low, most still reported wanting to participate in HPV self-sample testing and receive the HPV vaccine. Perceptions of risk did not appear to play a role in health behaviour decision-making for our cohort of women, as hypothesized at the onset of this study. However, the low risk perception may cause AYA to engage in high-risk behaviours which are likely to endanger their sexual and reproductive health.

Summary

The vast inequities in cervical cancer outcomes between women from LMICs and HICs demonstrates the need for innovative, creative, and regional appropriate efforts in global cancer control. Cervical cancer is a preventable global health concern. South Africa and, in particular, KZN with the highly dense population of female adolescents and young adults in combination with the extremely high rates of HIV and cervical cancer demonstrate the urgent need for research to better understand acceptability of primary and secondary prevention efforts among this population. With young women at a significant risk of acquiring HIV and HPV infections, it is a pivotal time in global cervical cancer prevention. HPV vaccine uptake rates remain despairingly low in SA.

Participants in this study represented those highest at-risk for acquiring HPV and developing cervical cancer: AYA females in childrearing age and WHIV. Sexual health behaviours reported by participants are alarming and similar to those reported nationally. Although high rates of acceptability were found for the HPV vaccine for self and (future) children as well as HPV self-sample collection, no variables originally proposed were found to be associated with acceptability. Findings from this study also outline the important role that HCP's, trusted

interventions such as AYAZAZI, and female caretakers play as sources for SRH information and in guiding health decision making. Cervical cancer prevention approaches that use a multigenerational approach have been found to improve screening and vaccine uptake, particularly among women who would not have otherwise participated in these prevention efforts. This study outlines the urgent need to expand the HPV vaccination program to a wider variety of ages, particularly for those who have not yet been exposed to HPV, enhance HPV self-sample testing for WHIV as it is highly acceptable, and design interventions that help to increase adolescents' perceived risks. Several important implications of this study follow.

Recommendations

Expansion of the HPV Vaccine Program – Investing in Primary Prevention

Expanding the HPV vaccine program in SA is an ethically and fiscally responsible next move in addressing the cervical cancer epidemic. Cervical cancer is eminently preventable and utilizes a considerable amount of health resources. The HPV vaccine is the most cost effective, safe, and efficacious prevention tool with promising outcomes and the only vaccine available worldwide shown to prevent cancers, however in SA uptake (due to lack of availability) remains despairingly low. In an area of the world with the highest deaths associated with cervical cancer, it is imperative the government consider expanding the existing national HPV vaccine program. The reality is that 70% of the population will need to be vaccinated to see an effect within the population, or 'herd immunity'(Brisson et al., 2016). SA is far away from achieving this goal currently, with a current roll-out plan involving select schools and covering only a small percentage of eligible females.

The significantly influential role of HCPs in AYA's consideration to receive the HPV vaccine in this study is a very important finding. Due to the fact that the HPV vaccine is still fairly new

in SA, the recommendations from HCPs will be pivotal in encouraging women to receive that vaccine. It is therefore important that HCP's are first well educated about the HPV vaccine and able to relay appropriate information to patients. Evidence overwhelmingly demonstrates the need to include a wider range of ages eligible to receive the HPV vaccine and particularly targeting: WHIV or those most vulnerable to acquire HIV (low SES, education, areas with high rates of gender-based violence), AYA who are pre-coitus and have therefore not yet acquired HPV, and AYA of childbearing age. All groups have demonstrated to be highly acceptant of the HPV vaccine (in theory and actual uptake). AYA females in these populations face number of contextual barriers to accessing the HPV vaccine for themselves and their children. Sadly, the reality is that the HPV vaccine is not accessible for most SA women, largely due to the high cost locally and challenging access to health care services in general and very few women have access to medical aid for vaccine benefits.

Expansion of the HPV vaccine program in SA will require a concerted political commitment and allocated resources, both of which are challenging in a country with competing health priorities (HIV/AIDS & tuberculosis), and high levels of poverty and inequality. Cervical cancer prevention should not be viewed as separate from HIV/AIDS care, as the two are inextricably linked. As a result of national efforts to diagnose HIV and improve the uptake and adherence of ART medications, women are living longer and therefore are at a greater risk for developing cervical cancer (Ghebre, Grover, Xu, Chuang, & Simonds, 2017). In addition to the reduction of cervical cancer, the HPV vaccination also offers a chance to provide other SRH services targeted by AYA, such as HIV prevention efforts. The alarming cervical cancer rates, particularly among young women and often mothers, in SA calls for the government to prioritize and strengthen cervical cancer primary prevention efforts. We have the tool to protect girls from suffering

needlessly and dying from an entirely preventable disease. It is pivotal time in cervical cancer prevention and the global health community needs to help mobilize appropriate resources.

Self-Sample Testing Options – Investing in Secondary Prevention

Given the current climate in SA, investing in screening options for cervical cancer is also imperative. While the HPV vaccine is currently a primary prevention method for cervical cancer, the impact of the vaccine will not be seen for another 2-3 decades, nor does it cover those who are already infected with HPV. HPV vaccine coverage is still so low in SA that effects on the population will be minimal for quite some time. For these reasons, secondary prevention must be strengthened and women, particularly those most vulnerable, must be given options on how they would prefer to participate in screening. Currently the predominantly used screening method in SA is the Pap test, which is resource intensive and difficult to access for women with low follow-up rates. Vaginal self-sample testing has proven to be an effective and acceptable alternative for women who are vulnerable due to histories of violence, feel embarrassed, have limited access to HCP's and health services, and want to play a more active role in managing their health (Mitchell et al., 2017; Racey et al., 2013).

Similar to the HPV vaccine, improving secondary prevention or screening programs will take considerable investment from the government. An additional issue is that currently SA does not have an active cancer registry or reporting system and careful tracking and monitoring will be a key first step to addressing the cervical cancer epidemic. Nationally, all female residents are eligible to receive three Pap tests per lifetime beginning at 30 years of age however, 1) many women don't know they are eligible for these tests, 2) WHIV require screening at a much earlier age than HIV negative women, 3) few women have access to screening due to financial and geographical constraints, and 4) a pelvic exam (Pap test) is a highly invasive procedure and often

one performed by a male HCP. There are a plethora of reasons for the low uptake of Pap testing in SA, however it is clear that new innovative, acceptable, effective, and more affordable testing option exists and needs to be explored as a screening option at a national level.

HPV self-sample testing is a breakthrough in self-care and provides access to lifesaving testing for women in low-resource areas and investment in this type of testing will not only reduce costs to both women and the health system, but also save the lives of millions of women who are already infected with HPV. This study adds to the already comprehensive literature demonstrating highly favourable acceptance towards HPV self-sample testing among populations who are most vulnerable. Evidence also overwhelmingly shows how community- and youth-engagement approaches and integrating HPV services into existing SRH programs can be a highly successful and help to influence positive health behaviours, this is particularly the case among AYA as they are highly influential (Huchko, Maloba, Nakalembe, & Cohen, 2015; Phiri et al., 2016; Powers & Tiffany, 2006; Tsu et al., 2014). Investment into the expansion of both primary and secondary cervical cancer prevention efforts are required to address this global health crisis. Local and international financial investment and political commitment is paramount in the expansion of HPV prevention health services for SA women.

Education about HPV: Investing in a Multigenerational Approach

Findings from this study reinforce the urgent need for appropriate education about HPV and its association to cervical cancer while recognizing the key role that female caregivers play in the lives of young women. It's important to recognize that AYA have special SRH needs that often remain unmet, commonly due to lack of knowledge, social stigma, and judgmental attitudes among service providers (Abdullahi et al., 2014; Bukirwa et al., 2015; Katz et al., 2013). HCPs are also highly trusted sources for information and recommendations and play an important role

in women's decisions to participate in HPV vaccines and screening and SRH decisions in general. Awareness campaigns need to be culturally and age appropriate, engage multiples generations of women, as well as involve well informed HCPs and health team members who are non-judgemental and interested in developing positive relationships with women to help empower them to take ownership over their SRH.

A challenge will be creating a campaign that addresses the needs of the local community. In some cases, this may mean outlining the benefits of the HPV vaccine using cancer prevention messaging, as opposed to STI focused messaging. Raising awareness and normalizing HPV will to help to change the conversation about HPV and reduce the social stigma attached to it. Mothers and grandmothers are highly influential in the younger generations' health care decision-making and are an equally important group of women needing to be targeted for screening. Young women need support from their families and communities and access to nonjudgmental SRH services in order to make responsible choices and have safe and healthy sexual experiences.

Individual barriers to engaging in HPV vaccines and testing is largely associated with a lack of awareness and knowledge about risk factors and prevention cervical cancer. Despite this study showing no association between awareness and acceptability, it is important to remember that our participants do not necessarily represent the general population of women in SA, as they have already had extensive (12+months) of engagement in a SRH research study and as a result had higher levels of trust with information they were receiving. A significant investment needs to be towards developing awareness programs and education materials that are locally and appropriately designed prior to the scale-up of HPV vaccine and testing programs.

The next chapter is a summary of the study. Study limitations and recommendations for further research are also presented.

Chapter 6: Conclusion

Study Questions and Methods

This study explored the knowledge and awareness about HPV, cervical cancer, and the HPV vaccine as well as acceptability of HPV vaccine and self-sample testing among a highly vulnerable population of female AYA living in the epicentre of the HIV crisis, Durban, SA. There was a special focus on finding determinants related to awareness, acceptability, and risk perception for participants and to assess the most influential sources of SRH information. The research method involved RA's administering surveys to a cohort of female AYA involved in a longitudinal research study examining risk factors involved with HIV acquisition among AYA. A total of 122 AYA females participated in the study and quantitative analysis was performed after merging the data set with select variables from the 12-month AYAZAZI survey.

Key Findings

Findings from this study are important in designing effective cervical cancer control programs that can attract more AYA for HPV vaccines and screening. This study contributes to the field of cervical cancer prevention research by providing three main themes including, 1) awareness and knowledge about HPV and the vaccine were generally poor, 2) encouragingly high rates of acceptability towards the HPV vaccine and self-sample testing, and 3) key sources of SRH information and influences. The results indicate that awareness and knowledge about topics were generally low, as were perceptions of risk, and no personal and contextual factors played a role in the acceptability of either HPV vaccine or self-sample testing for AYA.

The most influential sources SRH was HCPs, communication/media, and family/friends. AYAZAZI was most influential in teaching AYA about contraceptives. Professionals played a significant role in women's considerations to receive the vaccine compared to friends/family.

Affordability was also rated as a significant factor in AYA's decisions to receive the vaccine. Recommendation sources for and affordability of the HPV vaccine mattered to women. Awareness about HPV or it association to cervical cancer, as well as the HPV vaccine were very low among women in this study. In fact, most women had never heard about HPV or the vaccine prior to the study. All mother and pregnant women stated they would have their child receive the HPV vaccine.

In general, risk perception for acquiring HPV, HIV, and developing cervical cancer was low among participants compared to how they perceived risk levels for other women in their communities. This factor did not, however, play a role in women's acceptance of the HPV vaccine or self-sample testing. HPV vaccine efficacy beliefs were rated high by participants. There were no significant associations found in relation to perceived risk level of acquiring HPV or developing cervical cancer. Similarly, no factors were found to be associated with participants' willingness to participate in HPV self-sample collection.

Anecdotally and feedback surveys indicated that AYA wanted to know more about HPV, be involved in cervical cancer prevention related studies and access to HPV vaccines and testing. It was clear from that this study mattered to participants and AYAZAZI was a safe space for AYA to receive information, receive STI testing and counselling, and have the opportunity to access non-judgemental HCPs and services.

The population of AYA in this study were not overly representative of the general AYA population in SA, largely due to the fact that many were attending or had access to education as well were living in formal housing. The fact that the female AYA had built trusting relationships with HCPs and the AYAZAZI research team also put them at an advantage in comparison to many other AYA in SA for access to SRH services and health education, both of which could

have played a critical role in the acceptability of the HPV vaccine and self-sample testing. Ensuring AYA have access to appropriate health education in a setting where they feel welcomed, valued, and listened to, despite their education or income level, will play a pivotal role in SRH decision making.

Limitations

The results from this study may not be generalized to all contexts or all SA women, since women in this study were mostly from an urban setting and participants were predominantly Zulu. Limitations to this study also include the small sample size. The information provided by participants may have been under-reported, particularly concerning personal details such as sexual health behaviours or experiences with violence, due to being uncomfortable in sharing sensitive information. This may have been minimized because participants had long term and trusting relationship with the research assistants on the AYAZAZI team who were asking these sensitive questions. However, being a survivor of assault is a sensitive topic that many young women, even if they trust someone, may be difficult to discuss due to factors such as the consequences of disclosure or fear of repercussions. Finally, a factor that emerged from anecdotal discussion with research assistants was the role that knowing someone with cervical cancer had on participants' acceptability of prevention options and risk perception however unfortunately this was not captured in the questionnaire.

Recommendations for Future Research

Based on findings from this study, recommendations for future research include:

- Expansion of the current project to include a larger and more geographically diverse sample of AYA females to explore predictors of actual HPV vaccine uptake and SRH testing preferences;

- Interventions aimed at educating the general public as well as key populations about HPV, cervical cancer, and the HPV vaccine that are locally developed and culturally as well as age appropriate;
- Increased involvement of AYA in projects relating to SRH services and needs;
- Better understanding how to create and implement multigenerational cervical cancer prevention projects;
- Modelling studies assessing HPV vaccine and testing expansion using a cost-benefit lens.

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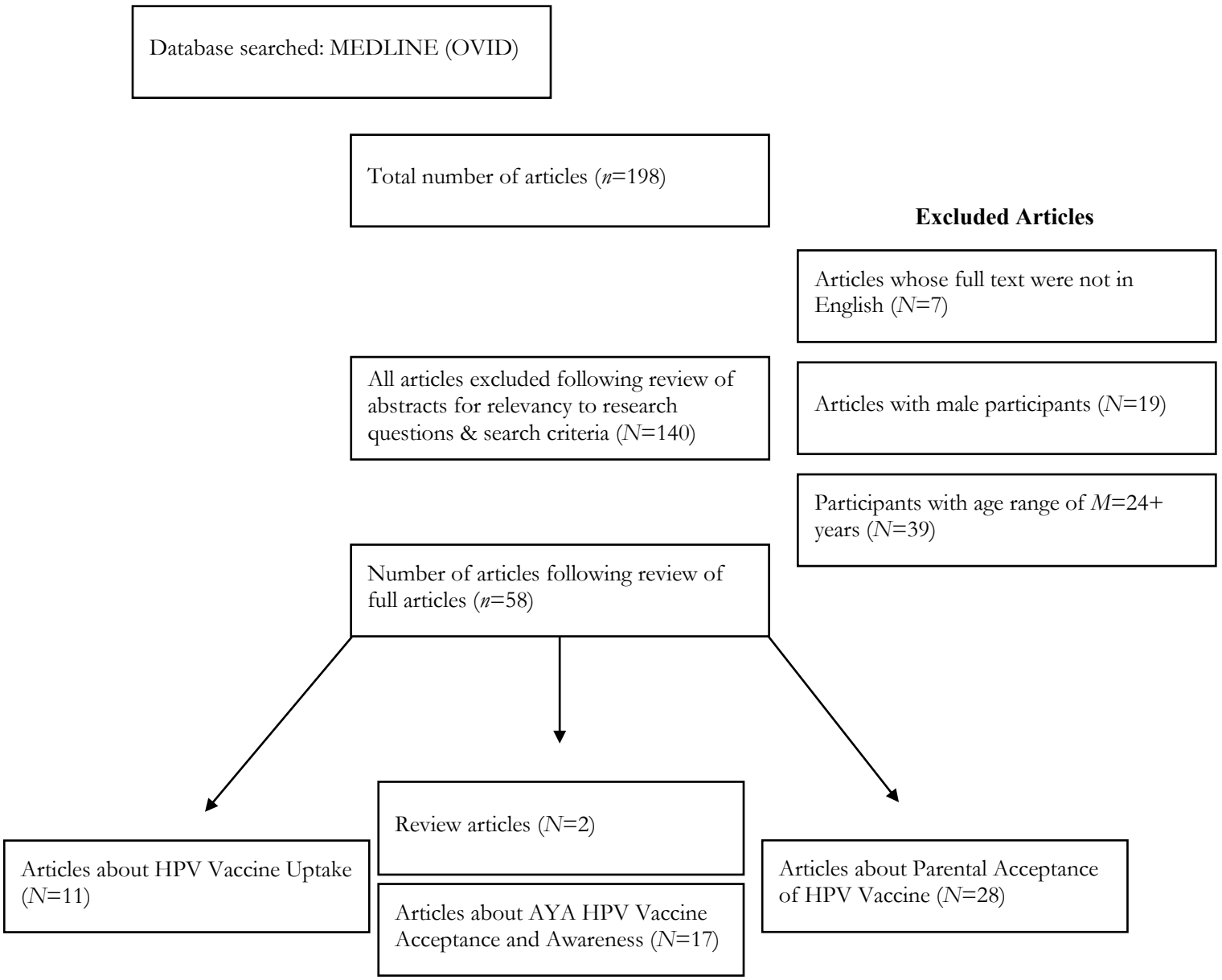
Appendix A: MEDLINE (OVID) Literature Review Search Strategy

Steps	Key Search Terms	Articles Yielded
1	Immunization/	
2	Immunization Schedule/	
3	Immunization, Secondary/	
4	Immunotherapy, Active/	
5	Mass Immunization/	
6	Immunization Programs/	
7	Vaccination/	
8	or/1-7	14,3349
9	Papillomavirus Infections/	
10	(human papilloma* or HPV).tiab.	
11	or/9-10	44,066
12	8 AND 11	3281
13	Papillomavirus vaccines/	
14	12 OR 13	7133
15	exp Young Adult/	
16	Adolescent/	
17	Women/	
18	Men/	
19	or/15-18	2,186,170
20	14 AND 19	3371
21	(human papilloma* or HPV) adj ((vaccinat* or revaccinat* or immunization or immunisation) adj3 (“adolescent”[MeSH Terms] OR “young adult”[MeSH Terms] OR “women”[MeSH Terms] OR “men”[MeSH Terms] OR “child”[MeSH Terms] OR child OR children OR boy OR boys OR girl OR girls OR adult OR men OR male OR female OR women OR teenager OR adolescent OR adolescence)).ti,ab.	
22	((human papilloma* or HPV) adj (immunization or immunisation or vaccination) adj (program* or rate* or coverage or adher* or uptak*)).ti.	
23	20 or 21 or 22	7137
24	Developing Countries.sh,kf.	
25	(Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America).hw,kf,ti,ab,cp.	
26	(Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Brasil or Bulgaria or	

	Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or Sudanor or South Africa or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).hw,kf,ti,ab,cp.	
27	((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab.	

28	((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab.	
29	(low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.	
30	(low adj3 middle adj3 countr*).ti,ab.	
31	(lmic or lmics or third world or lami countr*).ti,ab.	
32	transitional countr*.ti,ab.	
33	or/24-32	3,300,152
34	23 and 33	647
35	decision making/ or choice behaviour/	
36	patient acceptance of health care/	
37	health promotion/	
38	Patient Education as Topic/	
39	Health Education/	
40	school health services/	
41	(human papilloma* or HPV) adj ((vaccinat* or revaccinat* or immunization or immunisation) adj2 (prevent* OR protect* OR "public health" OR educat* OR program* OR train* OR support* OR project*)	
42	or/35-41	326, 803
43	34 AND 42	198

Appendix B: Search Strategy Flow Diagram



Appendix C: Consent Form

AYAZAZI: Investigating Patterns of behavioural and biomedical risk for HIV acquisition and vaccine trial preparedness among adolescents and young adults in a priority setting

INFORMED Consent form for Participants 18 years and older

This study is funded by: The Canadian HIV Vaccine Initiative (CHVI), in collaboration with the Canadian Institutes of Health Research.

The doctor in charge: Prof. Glenda Gray (Perinatal HIV Research Unit)

Site Telephone Number: 011 989 9752

To the potential Participant: *This informed consent form may contain words that you do not understand. Please ask the study staff to explain them or re-phrase words or phrases to help you understand the information. We encourage you to take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.*

Introduction

Hello, my name is……..…; I am part of a research team from the Perinatal HIV Research Unit (PHRU) at the University of the Witwatersrand doing a study, called AYAZAZI, in partnership with Simon Fraser University in Canada to understand HIV risk among South African adolescents and young adults and to find ways to improve participation of young people in HIV vaccine research studies in South Africa.

We would like to invite you to take part in this research study. The study will take place at the PHRU, Chris Hani Baragwanath Academic Hospital, Soweto and you are invited to participate in this study because you live in this community and are between the ages of 16-24 years.

VOLUNTARY PARTICIPATION AND/OR WITHDRAWAL

This consent form provides information about the study procedures and allows you the opportunity to decide if you are interested or not interested in taking part in this study. Before you agree to take part, you should understand this information. Please ask the study staff to explain any sections that are unclear to you and answer any questions you may have. If you agree to take part in this study, we will ask you to sign this consent form and you will get a copy to keep. Your participation is entirely voluntary. You may decide not to participate or withdraw from the study at any time. Thank you for taking time to hear about our research.

BACKGROUND

HIV risk among adolescents and young adults remains high and is likely influenced by various social, behavioural, historical/cultural and biological factors. However, a lack of research that links social, behavioural and clinical data, particularly in a priority setting and for populations most likely to be at risk of HIV, have hampered efforts to identify these factors in detail.

PURPOSE OF THE STUDY

The purpose of this study is to assess socio-behavioural and biological factors that may affect HIV risk among adolescents and young adults in South Africa. This study will continue for a period of 6 years for each participant and will include visits every 6 months for the duration of the 6 years. The data collected from this study will be used to try and understand:

Social and behavioural factors that place young people at risk of acquiring HIV

Sexually acquired infections and/or biological processes that increase the risk of acquiring HIV in young people

Ways to improve participation of young people in HIV vaccine research studies

STUDY PROCEDURES

This study will enrol up to 400 adolescents and young adults from Soweto that are both HIV-positive and HIV-negative and follow them over 6 years. If you agree to participate in this study, you will be asked to come into the AYAZAZI clinic at PHRU every 6-months to fill out a questionnaire, undergo a physical exam to screen for sexually transmitted infections and provide biological samples. The first visit will consist of the following activities:

First you will be asked to fill out a demographic form with your contact information (cell phone number or telephone number) in order for study staff to contact you throughout the study.

Next you will be asked to complete an online social and behavioral questionnaire that will include questions about your demographics (e.g., age, education, where you live), lifestyle (e.g. drug-use), reproductive health, mental health, sexual health and orientation, thoughts around HIV vaccine research and use of health care and social services. The questionnaire will take place in a private room at the AYAZAZI clinic and will take approximately 60 to 90 minutes to complete. During this time a trained study staff member will be present to answer any questions you may have about the wording or content in the questionnaire. Data from the questionnaire will be captured on a secure/password protected online database that does not contain any personal identifying information such as your name. Only people involved in this research will have access to the database. You are not required to answer any questions that may make you feel uncomfortable, and you are welcome to skip questions or stop at any time.

Following completion of the questionnaire, a project nurse will take you into a private examining room and ask you to fill out a medical history form. The nurse will then perform a short visual exam of your genitals to look for symptoms of sexually transmitted infections and collect a biological sample to test for the following sexually transmitted infections: *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, and *Mycoplasma genitalium*. Females will also be tested for Bacterial Vaginosis and Yeast infection. For females collecting a biological sample will consist of gently swabbing the inner wall of the vagina and for males this will consist of a urine sample. Additionally, the nurse will draw a sample of your blood (approximately 50 ml or 5 tubes or 12 1/2 teaspoons). Both genital swabs and urine samples will be transported to protocol approved laboratories laboratory where trained laboratory staff will test for HIV/sexually transmitted infections. The collected blood samples will be used for testing to explore biological factors that may put young people at risk of infection with HIV and other diseases. These tests will also be done at protocol approved laboratories. If you agree, the nurse will also perform a rapid, on-site HIV test (for HIV-negative participants) and a pregnancy test (for female participants). Pre-test counselling will be provided before the rapid HIV test is performed and post-test counselling will be provided after the results are available. Counselling will cover the meaning of a positive or negative HIV and/or sexually transmitted infection test result, methods for preventing HIV and/or sexually transmitted infections for yourself and others, referral in the event of a positive test and treatment information for HIV and/or STIs. Again you are not required to take part in any tests that make you feel uncomfortable, and you are welcome to ask the nurse to stop at any time.

After your first visit, appointments for follow-up visits will be scheduled for every 6 months. During follow-up visits you will again be asked to fill out a questionnaire, undergo a physical exam to screen for symptoms of sexually transmitted infections and provide biological samples for laboratory testing. Laboratory results for HIV tests and/or tests for sexually transmitted infections will be made available to you within two weeks after your visit at the AYAZAZI clinic. Throughout the duration of the study you will be assigned a unique study ID that will be used to collect test results. This will ensure that personal identifying information such as your name will not be linked to your results. Only the nurse who examined you and collected your samples will know your results. Again you will be provided with voluntary counseling when receiving your laboratory test results. Over the duration of the study you will also be asked to keep your contact information up-to-date so study staff can keep in contact with you about your next visit.

GENETIC TESTING USING BLOOD SAMPLES

Biological testing using your blood samples may also involve genetic testing. This part of the study is entirely voluntary and if you agree to participate in this part of the study, it will be explained to you and you will be required to sign a separate consent form.

BENEFITS TO PARTICIPATING IN THIS STUDY

This study may not benefit you directly. However, your participation and the information learned may help explain the socio-behavioural and biological factors that put young people at risk of HIV and ways to improve participation of young people in HIV vaccine research studies.

RISKS OR DISCOMFORTS ASSOCIATED WITH PARTICIPATING IN THIS STUDY

There are very few risks associated with participating in this study. However, some participants have reported stigmatization as a result of being in a research study. Family or friends may worry about you or get upset that you have agreed to participate. They may assume that if you are participating in this study that you have been infected with HIV and stigmatize you. If this happens to you, we can discuss the situation and how best to handle it moving forward.

You may also find some of the questions that we ask in the questionnaire are personal and make you feel uncomfortable or embarrassed. You are not required to answer any questions that make you feel uncomfortable, and you are welcome to skip questions or stop the questionnaire at any time. Additionally, you may feel uncomfortable or nervous during the physical examination and biological sample collection. This will involve exposing your genitals to a medical professional and drawing blood, which may make you feel awkward. The risks of drawing blood may also include feeling dizzy, being sore or having a bruise or swelling at the site where blood is drawn. Again you are not required to take part in any procedures that make you feel uncomfortable and may stop at any time. Lastly, you may feel nervous or scared waiting for results from HIV/STI laboratory tests. If you are feeling this way, please tell us. The study staff and nurses are always here to help make you feel more comfortable and discuss any concerns you have about the study or procedures at any time. We will additionally have a trained counsellor/social worker available if you need any further support.

RESEARCH RELATED INJURIES

If you are injured as a result of participation in this study, the study clinic will give you immediate access to necessary treatment and the cost of this treatment will not be charged to you. You will then be told where you may receive additional treatment for these injuries.

ALTERNATIVES TO PARTICIPATING IN THIS STUDY

The alternative to participating in this study is not to participate. If you choose not to participate in this study, you will still be offered free Voluntary Counselling and Testing at the AYAZAZI clinic. Your decision will have no impact on your health care at this or other facilities.

COSTS AND COMPENSATION

There are no financial costs to you or your family for taking part in this research study. To compensate you for your time, you will receive R150.00 for each scheduled visit that you attend. The payment for scheduled visits is to cover the cost for transport, refreshments and possibly some of the time spent in the clinic.

STATEMENT OF CONFIDENTIALITY

All information collected during this study will be kept strictly confidential. To protect your personal identity, all information you share will be identified using a unique study ID. Your name and other personal information will not appear on the questionnaire, on laboratory test results or in any publications or reports produced by this study. You will also use your unique ID number when you go to collect your laboratory test results. Only authorized research personnel will have access to all study materials over the course of the study.

NEW FINDINGS

The study staff will share with you any new research findings that may develop while you are participating in this study.

RIGHT TO DECLINE/WITHDRAW FROM THIS STUDY

Your participation in this research study is completely voluntary. Even if you decide to participate now, you have the right to withdraw from this research study at any time. Your decision to participate or withdraw from this study will have no impact on your access to services at PHRU's clinics or other health care facilities.

WHAT HAPPENS IF YOU DECIDE TO DISCONTINUE PARTICIPATION

If you decide to withdraw early from the study you have a right to choose whether you want your questionnaire information and biological samples to be kept or destroyed. Your decision to stop taking part in this study will not have any negative consequences.

WHO TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS

If you have any questions, comments, or concerns about participation in this study, feel free to talk to the study staff or contact any of the investigators listed below. We are here to support you.

Contacts for questions or problems: Throughout the duration of the study, if you do not understand something that is being done or have any questions please do not hesitate to contact one of the following:

Prof. Glenda Gray, Principal Investigator, PHRU, Soweto, South Africa; Telephone: (011) 989-9703

Dr. Janan Dietrich, Co-investigator, PHRU, Soweto, South Africa; Telephone: (011) 989-9757

Contacts at Simon Fraser University: If you have any additional questions, comments, or concerns about this research you may contact our collaborators in at the Simon Fraser University in Canada:

Prof. Mark Brockman, Principal Investigator, Simon Fraser University, Burnaby, Canada; Telephone: (+1) 778-782-3341; Email: mark_brockman@sfu.ca

Dr. Angela Kaida, Co-investigator, Simon Fraser University, Burnaby, Canada; Telephone: (+1) 778-782-9068; Email: angela_kaida@sfu.ca

Dr. Jeffrey Toward, Director, Office of Research Ethics, Simone Fraser University; Telephone: (+1) 778-782-6593; Email: jtoward@sfu.ca

Who can I call for Information about my Rights?

This clinical study protocol has been submitted to the University of the Witwatersrand Human Research Ethics Committee (Wits HREC - Medical) and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2013) which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

If you want any information regarding your rights as a research participant, or have complaints regarding this research study, you may contact:

Johannesburg:

Prof. Cleaton-Jones, Chairperson

The University of the Witwatersrand

Human Research Ethics Committee

Telephone number: (011) 717 2301

This independent committee is established to help protect the rights of research participants and gave written approval for the study protocol.

SIGNATURE PAGE

I have read this informed consent form and understand that signing this form means that:

I have had the opportunity to ask questions and all my questions have been answered to my satisfaction.

I have been given sufficient time to consider the above information regarding the purpose of this study, the procedures as well as the possible benefits and risks.

I can withdraw from this study at any point should I not want to continue and this decision will have no negative consequences for me.

I have not waivered any of my human rights.

I have voluntarily made an informed decision to participate in this study without being forced to do so in any way.

Participant's Name and Surname (Print)	Participant's Signature	Date	Time

Clinic Staff conducting consent discussion Name and Surname (Print)	Clinic Staff Signature	Date (dd/mmm/yyyy)	Time

**For individuals who are unable to read or write, also complete the signature block below:*

Witness' Name and Surname (Print)	Witness' Signature	Date	Time

**Witness is impartial and was present for the consent process.*

As part of this study we will be doing a number of smaller research studies. Would it be okay for staff from AYAZAZI to contact you in the future about these sub-studies?

Yes

No

Don't know

Prefer not to answer

Appendix D: Adolescent Assent Form

AYAZAZI: Investigating Patterns of behavioural and biomedical risk for HIV acquisition and vaccine trial preparedness among adolescents and young adults in a priority setting

Adolescent assent form

This study is funded by: The Canadian HIV Vaccine Initiative (CHVI), in collaboration with the Canadian Institutes of Health Research.

The doctor in charge: Prof Glenda Gray (Perinatal HIV Research Unit)

Site Telephone Number: 011 989 9752

To the potential Participant: *This assent form may contain words that you do not understand. Please ask the study staff to explain them or re-phrase words or phrases to help you understand the information. We encourage you to take home an unsigned copy of this assent form to think about or discuss with family or friends before making your decision.*

Introduction

Hello, my name is……..…; I am part of a research team from the Perinatal HIV Research Unit (PHRU) at the University of the Witwatersrand doing a study, called AYAZAZI, in partnership with Simon Fraser University in Canada to understand HIV risk among South African adolescents and young adults and to find ways to improve participation of young people in HIV vaccine research studies in South Africa.

We would like to invite you to take part in this research study. The study will take place at the PHRU, Chris Hani Baragwanath Academic Hospital, Soweto and you are invited to participate in this study because you live in this community and are between the ages of 16-24 years.

VOLUNTARY PARTICIPATION AND/OR WITHDRAWAL

This is an assent form and provides information about the study procedures and allows you the opportunity to decide if you are interested or not interested in taking part in this study. Before you agree to take part, you should understand this information. Please ask the study staff to explain any sections that are unclear to you and answer any questions you may have. If you agree to take part in this study, we will ask you to sign this assent form and you will get a copy to keep. Your participation is entirely voluntary. You may decide not to participate or withdraw from the study at any time. Because you are younger than 18 years, we will also need your parent/legal guardian to give permission for you to take part in this study until you are 18 years and sign a separate consent form. Both you and your parent/legal guardian need to be in agreement in order for you to be enrolled in this study. Thank you for taking time to hear about our research.

BACKGROUND

HIV risk among adolescents and young adults (AYA) remains high and is likely influenced by various social, behavioural, historical/cultural, and biological factors. However, a lack of research that links social, behavioural and clinical data, particularly in a priority setting and for populations most likely to be at risk of HIV, have hampered efforts to identify these factors in detail.

PURPOSE OF THE STUDY

The purpose of this study is to assess socio-behavioural and biological factors that may affect HIV risk among adolescents and young adults in South Africa. This study will continue for a period of 6 years for each participant and will include visits every 6 months for the duration of the 6 years. The data collected from this study will be used to try and understand:

Social and behavioural factors that place young people at risk of acquiring HIV

Sexually acquired infections and/or biological processes that increase the risk of acquiring HIV in young people

STUDY PROCEDURES

This study will enrol up to 400 adolescents and young adults from Soweto that are both HIV-positive and HIV-negative and follow them over 6 years. If you agree to participate in this study, you will be asked to come into the AYAZAZI clinic at PHRU every 6-months to fill out a questionnaire, undergo a physical exam to screen for sexually transmitted infections and provide biological samples. The first visit will consist of the following activities:

First you will be asked to fill out a demographic form with your contact information (cell phone number or telephone number) in order for study staff to contact you throughout the study.

Next you will be asked to complete an online social and behavioral questionnaire that will include questions about your demographics (e.g., age, education, where you live), lifestyle (e.g. drug-use), reproductive health, mental health, sexual health and orientation, thoughts around HIV vaccine research and use of health care and social services. The questionnaire will take place in a private room at the AYAZAZI clinic and will take approximately 60 to 90 minutes to complete. During this time a trained study staff member will be present to answer any questions you may have about the wording or content in the questionnaire. Data from the questionnaire will be captured on a secure/password protected online database that does not contain any personal identifying information such as your name. Only people involved in this research will have access to the database. You are not required to answer any questions that may make you feel uncomfortable, and you are welcome to skip questions or stop at any time.

Following completion of the questionnaire, a project nurse will take you into a private examining room and ask you to fill out a medical history form. The nurse will then perform a short visual exam of your genitals to look for symptoms of sexually transmitted infections and collect a biological sample to test for the following sexually transmitted infections: *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, and *Mycoplasma genitalium*. Females will also be tested for Bacterial Vaginosis and Yeast infection. For females collecting a biological sample will consist of gently swabbing the inner wall of the vagina and for males this will consist of a urine sample. Additionally, the nurse will draw a sample of your blood (approximately 50 ml, or 5 tubes, which is 12 1/2 teaspoons). Both genital swabs and urine samples will be transported to protocol approved laboratories where trained laboratory staff will test for HIV/sexually transmitted infections. The collected blood samples will be used for testing to explore biological factors that may put young people at risk of infection with HIV and other diseases. These tests will also be done at protocol approved laboratories. If you agree, the nurse will also perform a rapid, on-site HIV test (for HIV-negative participants) and a pregnancy test (for female participants). Pre-test counselling will be provided before the rapid HIV test is performed and post-test counselling will be provided after the results are available. Counselling will cover the meaning of a positive or negative HIV and/or sexually transmitted infection test result, methods for preventing HIV and/or sexually transmitted infections for yourself and others, referral in the event of a positive test and treatment information for HIV and/or sexually transmitted infections. Again you are not required to take part in any tests that make you feel uncomfortable, and you are welcome to ask the nurse to stop at any time.

After your first visit, appointments for follow-up visits will be scheduled for every 6 months. During follow-up visits you will again be asked to fill out a questionnaire, undergo a physical exam to screen for symptoms of sexually transmitted infections and provide biological samples for laboratory testing. Laboratory results for HIV tests and/or tests for sexually transmitted infections will be made available to you within two weeks after your visit at the AYAZAZI clinic. Throughout the duration of the study you will be assigned a unique study ID that will be used to collect test results. This will ensure that personal identifying information such as your name will not be linked to your results. Only the nurse who examined you and collected your samples will know your results. Again you will be provided with voluntary counseling when receiving your laboratory test results. Over the duration of the study you will also be asked to keep your contact information up-to-date so study staff can keep in contact with you about your next visit.

GENETIC TESTING USING BLOOD SAMPLES

Biological testing using your blood samples may also involve genetic testing. This part of the study is entirely voluntary and if you agree to participate in this part of the study, it will be explained to you and you will be required to sign a separate assent form.

BENEFITS TO PARTICIPATING IN THIS STUDY

This study may not benefit you directly. However, your participation and the information learned may help explain the socio-behavioural and biological factors that put young people at risk of HIV and ways to improve participation of young people in HIV vaccine research studies.

RISKS OR DISCOMFORTS ASSOCIATED WITH PARTICIPATING IN THIS STUDY

There are very few risks associated with participating in this study. However, some participants have reported stigmatization as a result of being in a research study. Family or friends may worry about you or get upset that you have agreed to participate. They may assume that if you are participating in this study that you have been infected with HIV and stigmatize you. If this happens to you, we can discuss the situation and how best to handle it moving forward.

You may also find some of the questions that we ask in the questionnaire are personal and make you feel uncomfortable or embarrassed. You are not required to answer any questions that make you feel uncomfortable, and you are welcome to skip questions or stop the questionnaire at any time. Additionally, you may feel uncomfortable or nervous during the physical examination and biological sample collection. This will involve exposing your genitals to a medical professional and drawing blood, which may make you feel awkward. The risks of drawing blood may also include feeling dizzy, being sore or having a bruise or swelling at the site where blood is drawn. Again you are not required to take part in any procedures that make you feel uncomfortable and may stop at any time. Lastly, you may feel nervous or scared waiting for results from HIV/sexually transmitted infection laboratory tests. If you are feeling this way, please tell us. The study staff and nurses are always here to help make you feel more comfortable and discuss any concerns you have about the study or procedures at any time. We will additionally have a trained counsellor/social worker available if you need any further support.

RESEARCH RELATED INJURIES

If you are injured as a result of participation in this study, the study clinic will give you immediate access to necessary treatment and the cost of this treatment will not be charged to you. You will then be told where you may receive additional treatment for these injuries.

ALTERNATIVES TO PARTICIPATING IN THIS STUDY

The alternative to participating in this study is not to participate. If you choose not to participate in this study, you will still be offered free Voluntary Counselling and Testing at the AYAZAZI clinic. Your decision will have no impact on your health care at this or other facilities.

COSTS AND COMPENSATION

There are no financial costs to you or your family for taking part in this research study. To compensate you for your time, you will receive R150.00 for each scheduled visit that you attend. The payment for scheduled visits is to cover the cost for transport, refreshments and possibly some of the time spent in the clinic.

STATEMENT OF CONFIDENTIALITY

All information collected during this study will be kept strictly confidential. To protect your personal identity, all information you share will be identified using a unique study ID. Your name and other personal information will not appear on the questionnaire, on laboratory test results or in any publications or reports produced by this study. You will also use your unique ID number when you go to collect your laboratory test results. Only authorized research personnel will have access to all study materials over the course of the study.

We will keep the information listed below, private and will not share this information with your parents/legal guardian:

Your attitudes towards sexual behaviour and reasons for staying in the study.

Your answers to questions in the questionnaire, including questions about sexual behaviour and whether you are having sex.

The results of laboratory sexually transmitted infection/HIV tests and treatments that you receive over the duration of the study.

The results of pregnancy tests that you receive over the duration of the study (females).

However, to protect you from harm, we will ask you to tell a trusted adult (not necessarily your parents/legal guardian) if you test positive for HIV or an sexually transmitted infection or if you become pregnant (females). The study staff are here to provide you with support and counsel you in the event that these situations arise. Additionally, the law requires us to tell authorities if you are being sexually or physically abused. The law also requires us to report sexual offenses like rape. The authorities can help you get out of that situation. We will tell you if we are going to inform the authorities about any situations. In all cases the study staff are there to provide you with support and help. We also encourage you to talk to your parents/legal guardian so that they can help you deal with these situations.

NEW FINDINGS

The study staff will share with you any new research findings that may develop while you are participating in this study.

RIGHT TO DECLINE/WITHDRAW FROM THIS STUDY

Your participation in this research study is completely voluntary. Even if you decide to participate now, you have the right to withdraw from this research study at any time. Your decision to participate or withdraw from this study will have no impact on your access to services at PHRU's clinics or other health care facilities.

RE-CONSENTING AT AGE 18

Because you are younger than 18 years, we also need your parent/legal guardian to give permission for you to take part in this study and sign a separate consent form; however, when you reach 18 years of age you no longer need your parent/legal guardian to give permission for you to participate. At that time we will ask you to sign a separate consent form and you will have the opportunity to decide if you are still interested or not interested in continuing to participate in this study as an adult.

WHAT HAPPENS IF YOU DECIDE TO DISCONTINUE PARTICIPATION

If you decide to withdraw early from the study you have a right to choose whether you want your questionnaire information and biological samples to be kept or destroyed. Your decision to stop taking part in this study will not have any negative consequences.

WHO TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS

If you have any questions, comments, or concerns about participation in this study, feel free to talk to the study staff or contact any of the investigators listed below. We are here to support you.

Contacts for questions or problems: Throughout the duration of the study, if you do not understand something that is being done or have any questions please do not hesitate to contact one of the following:

Prof. Glenda Gray, Principal Investigator, PHRU, Soweto, South Africa; Telephone: (011) 989-9703

Dr. Janan Dietrich, Co-investigator, PHRU, Soweto, South Africa; Telephone: (011) 989-9757

Contacts at Simon Fraser University: If you have any additional questions, comments, or concerns about this research you may contact our collaborators in at the Simon Fraser University in Canada:

Prof. Mark Brockman, Principal Investigator, Simon Fraser University, Burnaby, Canada; Telephone: (+1) 778-782-3341; Email: *mark_brockman@sfu.ca*

Dr. Angela Kaida, Co-investigator, Simon Fraser University, Burnaby, Canada; Telephone: (+1) 778-782-9068; Email: *angela_kaida@sfu.ca*

Dr. Jeffrey Toward, Director, Office of Research Ethics, Simone Fraser University; Telephone: (+1) 778-782-6593; Email: jtoward@sfu.ca

Who can I call for Information about my Rights?

This clinical study protocol has been submitted to the University of the Witwatersrand Human Research Ethics Committee (Wits HREC - Medical) and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2013) which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

If you want any information regarding your rights as a research participant, or have complaints regarding this research study, you may contact:

Johannesburg:

Prof. Cleaton-Jones, Chairperson
The University of the Witwatersrand
Human Research Ethics Committee
Telephone number: (011) 717 2301

This independent committee is established to help protect the rights of research participants and gave written approval for the study protocol.

SIGNATURE PAGE: ASSENT FOR PARTICIPATION

I have read this assent form and understand that signing this form means that:

I have had the opportunity to ask questions and all my questions have been answered to my satisfaction.

I have been given sufficient time to consider the above information regarding the purpose of this study, the procedures as well as the possible benefits and risks.

I can withdraw from this study at any point should I not want to continue and this decision will have no negative consequences for me.

I have not waivered any of my human rights.

I have voluntarily made an informed decision to participate in this study without being forced to do so in any way.

Participant's Name and Surname (Print)	Participant's Signature	Date	Time

Clinic Staff conducting assent discussion Name and Surname (Print)	Clinic Staff Signature	Date (dd/mmm/yyyy)	Time

**For individuals who are unable to read or write, also complete the signature block below:*

Witness' Name and Surname (Print)	Witness' Signature	Date	Time

[#] *Witness is impartial and was present for the assent process.*

As part of this study we will be doing a number of smaller research studies. Would it be okay for staff from AYAZAZI to contact you in the future about these sub-studies?

Yes
No
Don't know
Prefer not to answer

Appendix E: Parental Consent Form

AYAZAZI: Investigating Patterns of behavioural and biomedical risk for HIV acquisition and vaccine trial preparedness among adolescents and young adults in a priority setting

Parent/ Legal guardian Informed consent form

This study is funded by: The Canadian HIV Vaccine Initiative (CHVI), in collaboration with the Canadian Institutes of Health Research

The doctor in charge: Prof. Glenda Gray (Perinatal HIV Research Unit)

Site Telephone Number: 011 989 9752

To the Parent/ Legal Guardian: *This informed consent form may contain words that you do not understand. Please contact/ask the study staff to explain them or re-phrase words or phrases to help you understand the information. We encourage you to think about or discuss this form with family or friends before making your decision.*

INTRODUCTION

Hello, my name is……..……; I am part of a research team from the Perinatal HIV Research Unit (PHRU) at the University of the Witwatersrand doing a study, called AYAZAZI, in partnership with Simon Fraser University in Canada to understand HIV risk among South African adolescents and young adults and to find ways to improve participation of young people in HIV vaccine research studies in South Africa.

We would like to invite your child to take part in this research study. The study will take place at the PHRU, Chris Hani Baragwanath Academic Hospital, Soweto and your child is invited to participate in this study because he/she lives in this community and is between the ages of 16-24 years. You have been given this consent form because your child is younger than 18 years and as a parent/legal guardian your permission is required for your child to participate.

VOLUNTARY PARTICIPATION AND/OR WITHDRAWAL

This consent form provides information about the study procedures and allows you the opportunity to decide if you are interested or not interested in consenting to your child's participation in this study. Before you agree to allow your child to take part, you should understand this information. Please ask the study staff to explain any sections that are unclear to you and answer any questions you may have. If you agree to your child's participation in this study, we will ask you to sign this consent form and you will get a copy to keep. Your child's participation is entirely voluntary. Your child may decide not to participate or withdraw from the study at any time. Because your child is younger than 18 years of age we will need your consent along with their assent in order for him/her to take part in this study until he/she is 18 years old. Both you and your child need to be in agreement in order for him/her to be enrolled in this study. Thank you for taking time to hear about our research.

BACKGROUND

HIV risk among adolescents and young adults (AYA) remains high and is likely influenced by various social, behavioural, historical/cultural and biological factors. However, a lack of research that links social, behavioural and clinical data, particularly in a priority setting and for populations most likely to be at risk for HIV, have hampered efforts to identify these factors in detail.

PURPOSE OF THE STUDY

The purpose of this study is to assess socio-behavioural and biological factors that may affect HIV risk among adolescents and young adults in South Africa. This study will continue for a period of 6 years for each participant and will include visits every 6 months for the duration of the 6 years. The data collected from this study will be used to try and understand:

Social and behavioural factors that place young people at risk of acquiring HIV

Sexually acquired infections and/or biological processes that increase the risk of acquiring HIV in young people

Ways to improve participation of young people in HIV vaccine research studies

STUDY PROCEDURES

This study will enrol up to 400 adolescents and young adults from Soweto that are both HIV-positive and HIV-negative and follow them over 6 years. If you agree to your child's participation in this study, he/she will be asked to come into the AYAZAZI clinic at PHRU every 6-months to fill out a questionnaire, undergo a physical exam to screen for sexually transmitted infections and provide biological samples. The first visit will consist of the following activities:

First, your child will be asked to fill out a demographic form with their contact information (cell phone number or telephone number) in order for study staff to contact him/her throughout the study.

Next your child will be asked to complete an online social and behavioral questionnaire that will include questions about your child's demographics (e.g., age, education, where he/she lives), lifestyle (e.g. drug-use), reproductive health, mental health, sexual health and orientation, thoughts around HIV vaccine research and use of health care and social services. The questionnaire will take place in a private room at the AYAZAZI clinic and will take approximately 60 to 90 minutes to complete. During this time, a trained study staff member will be present to answer any questions your child may have about the wording or content in the questionnaire. Data from the questionnaire will be captured on a secure/password protected online database that does not contain any personal identifying information such as your child's name. Only people involved in this research will have access to the database. Your child is not required to answer any questions that may make him/her feel uncomfortable, and he/she is welcome to skip questions or stop at any time.

Following completion of the questionnaire, a project nurse will take your child into a private examining room and ask him/her to fill out a medical history form. The nurse will then perform a short visual exam of your child's genitals to look for symptoms of sexually transmitted infections and collect a biological sample to test for the following sexually transmitted infections: *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, and *Mycoplasma genitalium*. Females will also be tested for Bacterial Vaginosis and Yeast infection. For females collecting a biological sample will consist of gently swabbing the inner wall of the vagina and for males this will consist of a urine sample. Additionally, the nurse will draw a sample of your child's blood (approximately 50 ml or 5 tubes or 12 1/2 teaspoons). Both genital swabs and urine samples will be transported to protocol approved laboratories where trained laboratory staff will test for HIV/sexually transmitted infections. The collected blood samples will be used for testing to explore biological factors that may put young people at risk of infection with HIV and other diseases. These tests will also be done at protocol approved laboratories. If your child agrees, the nurse will also perform a rapid, on-site HIV test (for HIV-negative participants) and a pregnancy test (for female participants). Pre-test counselling will be provided before the rapid HIV test is performed and post-test counselling will be provided after the results are available. Counselling will cover the meaning of a positive or negative HIV and/or sexually transmitted infection test result, methods for preventing HIV and/or sexually transmitted infections for your child and others, referral in the event of a positive test and treatment information for hiv and/or sexually transmitted infections. Again your child is not required to take part in any tests that make him/her feel uncomfortable, and your child is welcome to ask the nurse to stop at any time.

After your child's first visit, appointments for follow-up visits will be scheduled for every 6 months. During follow-up visits your child will again be asked to fill out a questionnaire, undergo a physical exam to screen for symptoms of sexually transmitted infections and provide biological samples for laboratory testing. Laboratory results for HIV/sexually transmitted infections tests will be made available to your child at the AYAZAZI clinic within two weeks after his/her visit. Throughout the duration of the study your child will be assigned a unique study ID that he/she will use to collect test results. This will ensure that personal identifying information such as your child's name will not be linked to their test results. Only the nurse who examined your child and collected your child's samples will know his/her results. Again your child will be provided with voluntary counseling when receiving his/her laboratory test results. Over the duration of the study your child will also be asked to keep their contact information up-to-date so that study staff can keep in contact about their next visit.

GENETIC TESTING USING BLOOD SAMPLES

Biological testing using your blood samples may also involve genetic testing. This part of the study is entirely voluntary and if you and your child agree to participate in this part of the study, it will be explained to you and you will be required to sign a separate consent form.

BENEFITS TO PARTICIPATING IN THIS STUDY

This study may not benefit your child directly. However, your child's participation and the information learned may help explain the socio-behavioral and biological factors that put young people at risk of HIV and ways to improve participation of young people in HIV vaccine research studies.

RISKS OR DISCOMFORTS ASSOCIATED WITH PARTICIPATING IN THIS STUDY

There are very few risks associated with participating in this study. However, some participants have reported stigmatization as a result of being in a research study. Family or friends may worry about your child or get upset that they have agreed to participate. They may assume that if your child is participating in this study that they have been infected with HIV and stigmatize them. If this happens to your child, we can discuss the situation and how best to handle it moving forward.

Your child may also find some of the questions that we ask in the questionnaire are personal and make him/her feel uncomfortable or embarrassed. Your child is not required to answer any questions that make him/her feel uncomfortable, and he/she is welcome to skip questions or stop the questionnaire at any time. Additionally, your child may feel uncomfortable or nervous during the physical examination and biological sample collection. This will involve exposing your child's genitals to a medical professional and drawing blood, which may make your child feel awkward. The risks of drawing blood may also include feeling dizzy, being sore or having a bruise or swelling at the site where blood is drawn. Again your child is not required to take part in any procedures that make him/her feel uncomfortable and may stop at any time. lastly, your child may feel nervous or scared waiting for results from HIV/sexually transmitted infection laboratory tests. If your child is feeling this way, please tell us. The study staff and nurses are always there to help make your child feel more comfortable and discuss any concerns he/she has about the study or procedures at any time. We will additionally have a trained counsellor/social worker available if your child needs any further support.

RESEARCH RELATED INJURIES

If your child is injured as a result of participation in this study, the study clinic will give him/her immediate access to necessary treatment and the cost of this treatment will not be charged to you. Your child will then be told where he/she may receive additional treatment for these injuries.

ALTERNATIVES TO PARTICIPATING IN THIS STUDY

The alternative to consenting to your child's participation in this study is not to consent to their participation. If you choose not to consent to your child's participation in this study, your child will still be offered free Voluntary Counselling and Testing at the AYAZAZI clinic. Your decision will have no impact on your child's health care at this or other facilities.

COSTS AND COMPENSATION

There are no financial costs to you or your family for taking part in this research study. To compensate your child for their time, he/she will receive R150.00 for each scheduled visit that he/she attends. The payment for scheduled visits is to cover the cost for transport, refreshments and possibly some of the time spent in the clinic.

STATEMENT OF CONFIDENTIALITY

All information collected during this study will be kept strictly confidential. To protect your child's personal identity, all information he/she shares will be identified using a unique study ID. Your child's name and other personal information will not appear on the questionnaire, on laboratory test results or in any publications or reports produced by this study. Your child will also use his/her unique ID number when he/she goes to collect his/her laboratory test results. Only authorized research personnel will have access to all study materials over the course of the study.

We will keep the information listed below, private and will not share this information with you:

Your child's attitudes towards sexual behaviour and reasons for staying in the study.

Your child's answers to questions in the questionnaire, including questions about sexual behaviour and whether your child is having sex.

The results of laboratory sexually transmitted infection/HIV tests and treatments that your child receives over the duration of the study.

The results of pregnancy tests that your child receives over the duration of the study (females).

However, to protect your child from harm, we will encourage him/her to tell a trusted adult (not necessarily yourself) if he/she tests positive for hiv or an sexually transmitted infection or if she becomes pregnant (females). The study staff are there to provide your child with support and counsel your child in the event that these situations arise. Additionally, the law requires us to tell authorities if your child is being sexually or physically abused. The law also requires us to report sexual offenses like rape. The authorities can help your child get out of that situation. We will tell your child if we are going to inform the authorities about any situations. In all cases the study staff are there to provide your child with support and help. We will also encourage your child to talk to you so that you can help them deal with these situations.

NEW FINDINGS

The study staff will share with you and your child any new research findings that may develop while your child is participating in this study.

RIGHT TO DECLINE/WITHDRAW FROM THIS STUDY

Your child's participation in this research study is completely voluntary. Even if he/she decides to participate now, he/she has the right to withdraw from this research study at any time. Your decision to consent to your child's participation or your child's decision to withdrawal from this study will have no impact on his/her access to services at PHRU's clinics or other health care facilities.

RE-CONSENTING AT AGE 18

Because your child is younger than 18 years of age we also need your consent along with their assent in order for him/her to take part in this study, however, when your child reaches 18 years of age he/she no longer needs your permission to participate. At that time we will ask your child to sign a separate consent form and he/she will have the opportunity to decided if he/she is ll interested or not interested in continuing to participate in this study as an adult.

WHAT HAPPENS IF YOUR CHILD DECIDES TO DISCONTINUE PARTICIPATION

If your child decides to withdraw early from the study he/she has a right to choose whether he/she wants his/her questionnaire information and biological samples to be kept or destroyed. Your child's decision to stop taking part in this study will not have any negative consequences.

WHO TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS

If you have any questions, comments, or concerns about participation in this study, feel free to talk to the study staff or contact any of the investigators listed below. We are here to support you.

Contacts for questions or problems: Throughout the duration of the study, if you do not understand something that is being done or have any questions please do not hesitate to contact one of the following:

Dr. Glenda Gray, Principal Investigator, PHRU, Soweto, South Africa; Telephone: (011) 989-9703

Dr Janan Dietrich, Co-investigator, PHRU, Soweto, South Africa; Telephone: (011) 989-9757

Contacts at Simon Fraser University: If you have any additional questions, comments, or concerns about this research you may contact our collaborators in at the Simon Fraser University in Canada:

Prof. Mark Brockman, Principal Investigator, Simon Fraser University, Burnaby, Canada; Telephone: (+1) 778-782-3341; Email: *mark_brockman@sfu.ca*

Dr. Angela Kaida, Co-investigator, Simon Fraser University, Burnaby, Canada; Telephone: (+1) 778-782-9068; Email: *angela_kaida@sfu.ca*

Dr. Jeffrey Toward, Director, Office of Research Ethics, Simone Fraser University; Telephone: (+1) 778-782-6593; Email: jtoward@sfu.ca

Who can I call for Information about my Rights?

This clinical study protocol has been submitted to the University of the Witwatersrand Human Research Ethics Committee (Wits HREC - Medical) and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2013) which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

If you want any information regarding your rights as a research participant, or have complaints regarding this research study, you may contact:

Johannesburg:

Prof. Cleaton-Jones, Chairperson
The University of the Witwatersrand
Human Research Ethics Committee
Telephone number: (011) 717 2301
This independent committee is established to help protect the rights of research participants and gave written approval for the study protocol.

SIGNATURE PAGE

I have read and understood the participant information sheet and I hereby agree and I understand that:

My child is participating freely and without being forced in any way to do so.

I have had the opportunity to ask questions and all my questions have been answered to my satisfaction.

I have been given sufficient time to consider the above information regarding the purpose of this study, the procedures as well as the possible benefits and risks.

My child can withdraw from this study at any point should he/she not want to continue and this decision will have no negative consequences for me/my child.

I can withdraw my child from this study at any point should I not want to continue and this decision will have no negative consequences for me/my child.

I have not waivered any of my human rights.

I have voluntarily made an informed decision to allow my child to participate in this study without being forced to do so in any way.

_____

Participant's Name and Surname (Print)

Parent/Legal Guardian's Name and Surname (Print)	Parent/Legal Guardian's Signature	Date	Time

Clinic Staff conducting consent discussion Name and Surname(Print)	Clinic Staff Signature	Date (dd/mmm/yyyy)	Time

**For individuals who are unable to read or write, also complete the signature block below:*

Witness' Name and Surname (Print)	Witness' Signature	Date	Time

Appendix F: Research Ethics Board Approval

Simon Fraser University

Certificate of Ethical Approval for Harmonized Minimal Risk Behavioural Study

Simon Fraser University
Office of Research Ethics
8888 University Drive
Burnaby, BC V5A 1S6
Tel: 778-782-3447

Also reviewed and approved by:

- **UBC Behavioural Research Ethics Board (BREB)**
- **University of Northern British Columbia**

Principal Investigator:	Primary Appointment:	Board of Record REB Number:	UBC REB Number:
Gina Ogilvie	UBC/Medicine, Faculty of/School of Population and Public Health		H16-02132

Study Title:
Study Module Title Under Review: KNOWLEDGE, AWARENESS, AND BELIEFS ABOUT HPV, CERVICAL CANCER, SCREENING & VACCINES AMONG YOUNG WOMEN IN DURBAN, SOUTH AFRICA

Study Approved: September 12, 2016 **Expiry Date: September 12, 2017**

Research Team Members:	Angela Kaida Sheona Mitchell Mark A. Brockman
Sponsoring Agencies:	- Canadian Institutes of Health Research (CIHR) - "Integrated global control and prevention of HPV related diseases and cancer"

Documents included in this approval:

Document Name	Version	Date
Protocol:		
AYAYZAZI: HPV, Cervical Cancer, Screening, and Vaccines Module: Research Proposal	1	August 15, 2016
Consent Forms:		
AYAZAZI: Consent Form (Parental/Guardian)	1	March 18, 2015
AYAZAZI: Consent Form (Participants 18+)	1	March 18, 2015
Assent Forms:		
AYAZAZI: Adolescent Assent Form	1	March 18, 2015
Questionnaire, Questionnaire Cover Letter, Tests:		
AYAZAZI 12-month Questionnaire	1	August 12, 2016
HPV, Cervical Cancer, Screening, and Vaccine Module	1	August 12, 2016
Other Documents:		
Original University of Witwatersrand HREC	1	September 1, 2014
Original AYAZAZI SFU Ethics Approval	1	March 16, 2013

AYAZAZI Research Protocol	1	September 15, 2015

This ethics approval applies to research ethics issues only and does not include provision for any administrative approvals required from individual institutions before research activities can commence.

The Board of Record (as noted above) has reviewed and approved this study in accordance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2, 2014).

The "Board of Record" is the Research Ethics Board delegated by the participating REBs involved in a harmonized study to facilitate the ethics review and approval process.

The application for ethical review and the document(s) listed above have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

This study has been approved either by the Board of Record's full REB or by an authorized delegated reviewer.

Appendix G: Study Questionnaire

Section 13: HPV & Cervical Cancer Awareness (All AYA Women)

Q1. Have you heard of the Human Papillomavirus or HPV?

- ❑ Yes → **Skip to S13-Q2**
- ❑ No → **Skip to S13-Q3**
- ❑ Don't know
- ❑ Prefer not to answer

Q2. Where did you hear about HPV? *Allow participant to respond without reading options. (Check all that apply):*

- ❑ Mother
- ❑ Father
- ❑ Aunt
- ❑ Sibling
- ❑ Grandmother
- ❑ Boyfriend/partner
- ❑ School
- ❑ Doctor or nurse
- ❑ Counsellor
- ❑ Online/Internet
- ❑ TV
- ❑ Other (specify): _____
- ❑ Don't Know
- ❑ Prefer not to answer

Q3. Have you heard of cervical cancer?

- ❑ Yes → **Skip to S13-Q4**
- ❑ No → **Skip to S13-Q5**
- ❑ Don't know
- ❑ Prefer not to answer

Q4. Where did you hear about Cervical Cancer? *Allow participant to respond without reading options. (Check all that apply):*

- ❑ Mother
- ❑ Father
- ❑ Aunt
- ❑ Sibling
- ❑ Grandmother
- ❑ Boyfriend/partner
- ❑ School
- ❑ Doctor or nurse
- ❑ Counsellor
- ❑ Online/Internet
- ❑ TV
- ❑ Other (specify): _____
- ❑ Don't Know

- ❑ Prefer not to answer

Q5. Awareness about HPV	Agree	Disagree	Don't Know
i. HPV can cause herpes	❑	❑	❑
ii. Genital warts are caused by HPV	❑	❑	❑
iii. HPV can cause cervical cancer	❑	❑	❑
iv. Many people with HPV have no visible signs or symptoms	❑	❑	❑
v. I can transmit HPV to my partner even if I do not have symptoms	❑	❑	❑
vi. Having one type of HPV means that you cannot acquire new types	❑	❑	❑
vii. A vaccine exists to prevent HPV infections and cervical cancer	❑	❑	❑
viii. The HPV vaccine is approved and available in South Africa	❑	❑	❑

HPV is short for human papillomavirus. HPV is a group of more than 150 viruses. HPV can cause genital warts and some HPVs can lead to cancer, particularly cervical cancer. There are more than 40 HPV types that can infect the genital areas of males and females. You can get HPV by having vaginal, anal, or oral sex with someone who has the virus. HPV is a very common sexually transmitted infection (STI). Anyone who is sexually active can get HPV, even if you have had sex with only one person. HPV is so common that nearly all sexually active men and women get it at some point in their lives. HPV can be passed even when an infected person has no signs or symptoms. You can develop symptoms years after you have sex with someone who is infected, making it hard to know when you first became infected.

Q6. How much at risk do you think <u>you</u> are of becoming infected with HPV?

- ❑ Not at all at risk of becoming infected with HPV
- ❑ Low risk
- ❑ Medium risk
- ❑ High risk
- ❑ Don't know
- ❑ Prefer not to answer

Q7. How much at risk do you think <u>other young women</u> in your community are of becoming infected with HPV?

- ❑ Not at all at risk of becoming infected with HPV
- ❑ Low risk
- ❑ Medium risk
- ❑ High risk
- ❑ Don't know
- ❑ Prefer not to answer

Q8. How much at risk do you think <u>you</u> are of developing cervical cancer?

- ❑ Not at all at risk of developing cervical cancer
- ❑ Low risk
- ❑ Medium risk
- ❑ High risk
- ❑ Don't know
- ❑ Prefer not to answer

Q9. How much at risk do you think <u>other young women</u> in your community are of developing cervical cancer?

- ❑ Not at all at risk of developing cervical cancer
- ❑ Low risk
- ❑ Medium risk
- ❑ High risk
- ❑ Don't know
- ❑ Prefer not to answer

Q10. How much of a negative impact would <u>having an HPV infection</u> have on you and your life?

- ❑ No impact at all
- ❑ Low impact
- ❑ Medium impact
- ❑ High impact

- ❑ Don't know
- ❑ Prefer not to answer

Q11. How much of a negative impact would <u>having cervical cancer</u> have on you and your life?

- ❑ No impact at all
- ❑ Low impact
- ❑ Medium impact
- ❑ High impact
- ❑ Don't know
- ❑ Prefer not to answer

Section 14: Vaccine Awareness & Willingness

Q12. Have you heard of the HPV or cervical cancer vaccine?

- ❑ Yes → **Skip to S14-Q13**
- ❑ No → **Skip to S14-Q14**
- ❑ Don't know
- ❑ Prefer not to answer

Q13. Where did you hear about HPV or cervical cancer vaccine?

Allow participant to respond without reading options. (Check all that apply):

- ❑ Mother
- ❑ Father
- ❑ Aunt
- ❑ Sibling
- ❑ Grandmother
- ❑ Boyfriend/partner
- ❑ School
- ❑ Doctor or nurse
- ❑ Counsellor
- ❑ Online/Internet
- ❑ TV
- ❑ Other (specify): _____
- ❑ Don't Know
- ❑ Prefer not to answer

Q14. How likely do you think the HPV vaccine will reduce your chance of getting infected with HPV?

- ❑ Very likely
- ❑ Fairly likely
- ❑ Not likely
- ❑ Very unlikely
- ❑ Don't know
- ❑ Prefer not to answer

Q15. How likely do you think the HPV vaccine would reduce your chance of developing cervical cancer?

- ❑ Very likely
- ❑ Fairly likely
- ❑ Not likely
- ❑ Very unlikely
- ❑ Don't know
- ❑ Prefer not to answer

Q16. Would you be willing to receive a vaccine to help prevent HPV infections and cervical cancer?

- ❑ Yes
- ❑ No
- ❑ Don't know
- ❑ Prefer not to answer

Q17. How *important* is it to <u>you</u> that the HPV vaccine:

	Very Important	Important	Moderately Important	Of Little Importance	Not important at all	Don't Know
a) Prevent cancer	❑	❑	❑	❑	❑	❑
b) Prevent genital warts	❑	❑	❑	❑	❑	❑
c) Prevent both genital warts and cancer	❑	❑	❑	❑	❑	❑
d) Be recommended by your doctor or a nurse	❑	❑	❑	❑	❑	❑
e) Be recommended by family or friends	❑	❑	❑	❑	❑	❑
f) Is affordable	❑	❑	❑	❑	❑	❑

Q18. Would you consider getting an HPV vaccine if:

	Definitely would not	Probably would not	Neutral	Probably would	Definitely would	Don't Know	Prefer not to answer
a) It cost you R2300 to purchase	❑	❑	❑	❑	❑	❑	❑
b) It was free	❑	❑	❑	❑	❑	❑	❑
c) It was recommended by your doctor or a nurse	❑	❑	❑	❑	❑	❑	❑
d) It was recommended by family or friends	❑	❑	❑	❑	❑	❑	❑

Q19. Would you want your child/ren (or future children) to receive the HPV vaccine?

- ❑ Yes
- ❑ No
- ❑ Don't know
- ❑ Prefer not to answer

Q20a. Have you received the cervical cancer vaccine?

- ❑ Yes → **Skip to S14-Q20b**
- ❑ No → **Skip to S14-Q21**
- ❑ Don't know
- ❑ Prefer not to answer

Q20b. How many shots/doses did you receive?

- ❑ 1
- ❑ 2
- ❑ 3
- ❑ Don't know
- ❑ Prefer not to answer

Q20c. At what age did you receive your first vaccination for HPV/cervical cancer? ☐

- ❑ Don't know
- ❑ Prefer not to answer

Section 15: Cervical Cancer Screening

Q21. Have you heard of a test to check for cervical cancer?

- ❑ Yes → **Skip to S15-Q22**
- ❑ No → **Skip to S15-Q23a**
- ❑ Don't know
- ❑ Prefer not to answer

Q22. If you have heard about a test to check for cervical cancer, or Pap test, where did you hear about it?
Allow participant to respond without reading options. (Select all that apply):

- ❑ Mother
- ❑ Father
- ❑ Aunt
- ❑ Sibling
- ❑ Grandmother
- ❑ Boyfriend/partner
- ❑ School
- ❑ Doctor or nurse
- ❑ Counsellor
- ❑ Online/Internet
- ❑ TV
- ❑ Other (specify): _____
- ❑ Don't Know

Q23a. Would you be willing to collect a sample by yourself to test for cervical cancer if you were given instructions on how to collect the sample?

- ❑ Yes → **Skip to S15-Q23b**
- ❑ No → **Skip to S15-Q24**
- ❑ Don't know
- ❑ Prefer not to answer

Q23b. Where would you feel most comfortable collecting a sample?

- ❑ Healthcare clinic
- ❑ Your home
- ❑ Don't know
- ❑ Prefer not to answer

Q24. Has a healthcare worker ever tested you for cervical cancer?

- ❑ Yes → **Skip to S15-Q25**
- ❑ No → **Survey completed**
- ❑ Don't know
- ❑ Prefer not to answer

Q25. At what age were you first tested for cervical cancer? ☐

Q26. When was your last (most recent) test for cervical cancer? ☐ Year ☐ Month

- ❑ Don't know

- ❑ Prefer not to answer

Q27. What is the MAIN reason you had your last test for cervical cancer?

- ❑ Following up on abnormal or inconclusive result
- ❑ Recruited for testing by health care provider
- ❑ Experiencing pain or other symptoms
- ❑ Heard about the test and wanted to get tested
- ❑ Other _____
- ❑ Don't Know
- ❑ Prefer not to answer

Q28. Where did you receive your last test for cervical cancer?

- ❑ Mobile clinic
- ❑ Community clinic
- ❑ Government hospital
- ❑ Private hospital/private clinic
- ❑ Other (specify): _____
- ❑ Don't know
- ❑ Prefer not to answer

Q29. What was the result of your last (most recent) test for cervical cancer?

- ❑ Did not receive result
- ❑ Normal/Negative
- ❑ Abnormal/Positive
- ❑ Suspect cancer
- ❑ Inconclusive
- ❑ Don't know
- ❑ Prefer not to answer

Q30. Did you have any follow-up visits because of your test results?

- ❑ Yes
- ❑ No
- ❑ Don't know
- ❑ Prefer not to answer

Thank you for your time. The survey is now complete.