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**Prevention of cervical cancer in South Africa: opportunities
and challenges**

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Abstract

Cervical cancer is an important cause of morbidity and mortality in developing countries. This thesis examines the challenges to and opportunities for comprehensive (primary and secondary) prevention of cervical cancer in South Africa (SA), a middle-income country. Four questions were explored: a) can a cytology-based screening programme be effectively implemented in South Africa? ; b) what are the potential challenges to and opportunities for implementing a human papillomavirus (HPV) vaccination programme in South Africa? ; c) what is the association between human immunodeficiency virus (HIV), HPV, cervical cancer precursors and cervical cancer in South Africa and d) what is the prevalence of HPV and cervical cancer precursors, HPV types and HPV viral load in women initiating highly active antiretroviral therapy (HAART)?

Three provinces in SA were included in a study to design, develop and evaluate health system interventions for public sector cytology-based cervical screening services. A pre-and post-intervention cross-sectional study was conducted. Service organisation and service related outputs improved post-intervention. The proportion of staff who ever performed a Pap smear increased from 56% to 86% ($p < 0.001$); and 68% of staff agreed with the screening policy after, as opposed to 23% before the intervention ($p < 0.001$). The number of Pap smears performed increased by 76%, with 90% of these smears done on women in the appropriate target age group. However, the overall Pap smear coverage targets were not met and timely treatment for women with high-grade squamous intraepithelial lesions (HSIL) was a problem. Efforts to improve referral, feedback and health information systems proved challenging. Although there were some improvements in client knowledge of cervical cancer and Pap smears, this did not translate into an increase in the number of Pap smears among women interviewed post-intervention.

A qualitative study was conducted to explore key challenges to and opinions about HPV vaccination introduction in South Africa. A total of 50 in-depth interviews and 6 focus group discussions were conducted at policy, health service provider and community levels of enquiry. All respondents indicated support for the HPV vaccine. Policy makers and providers expressed concern about the implementation of the current cervical cancer screening programme. The high

cost of the vaccine was perceived as a barrier by policy makers. Providers and policymakers noted that the Department of Health had sufficient experience with managing vaccines, but recognised that the HPV vaccine would need to reach a different target age group compared to that usually served by the Expanded Program on Immunization. The most appropriate form of delivery was considered to be through schools, but concern was expressed about the capacity of the current school health system to deliver the vaccine. Most respondents did not anticipate that opposition to the HPV vaccine would be a major problem. The limited knowledge of the HPV vaccine, cervical cancer prevention and the current cervical cancer screening policy suggest that the introduction of the vaccine will need to be accompanied by a strong information, education and communication strategy that addresses issues of HPV vaccine side-effects and efficacy as well as provides ongoing education on cervical cancer.

Two studies were conducted to determine the role HIV plays in the risk of cervical cancer and cervical cancer precursor lesions in South Africa. The first, a case control study conducted at an early stage in the HIV epidemic and prior to the introduction of HAART in the public sector in South Africa, showed no association between HIV and invasive cervical cancer (adjusted odds ratio 1.0, 95% confidence interval (CI) 0.7 - 1.7). An analysis of the controls was undertaken to determine the association between HIV and cervical cancer precursors and HPV. Fifty percent of the HIV positive controls had an abnormal Pap smear. HIV positive women were nearly 5 times more likely to have high-risk HPV (HR-HPV) present compared to HIV negative women (prevalence ratio (PR) 5.1, 95% CI 3.3 - 7.7). Women infected with both HIV and HR-HPV were at a higher risk of squamous intraepithelial lesions (SILs) than women infected with neither of these viruses (adjusted PR 19.8, 95% CI 11.0 - 35.7).

The second study was a cross-sectional survey conducted at a public sector ART clinic in Cape Town. The median age of the 109 participants was 31 years and the median CD4 count was 125 cells/ μ L. Sixty six percent of women had an abnormal Pap smear, the HR-HPV prevalence was 78.9 % and the median HPV viral load was 181.1 relative light units (RLU). The most prevalent HR-HPV types among women with SILs were HPV types 18 (24.0%), 35 (22.0%) and types 16, 45 and 58 all with a prevalence of 20.0%. Multivariate regression was carried out to determine independent risk factors for SILs. HPV viral load and smoking were associated with an

increased risk of SILs. The adjusted PR for SILs was 5.0 (95% CI 1.2 - 20.6) for those that were HC2 positive and a viral load of ≤ 181.1 RLU (the median HPV viral load) and 7.6 (95% CI 1.9 - 30.8) for those that were HC2 positive with a HPV viral load > 181.1 RLU, with HC2 negative women as the reference group. Smokers were 1.5 times more likely to have SILs compared to non-smokers (PR 1.5, 95% CI 1.1 - 2.1).

The final chapter reflects on the main findings and discusses opportunities for and challenges to preventing cervical cancer in SA. The thesis concludes that without strong leadership, improved management capacity and a strengthened health system, implementation of a comprehensive cervical cancer prevention programme is unlikely to succeed.

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Preface

This thesis is based on four research projects. The role of the candidate in each of the projects is outlined below.

Implementing a cytology-based cervical cancer screening programme in South Africa (Chapter 4)

This was a collaborative project between the Women's Health Research Unit, University of Cape Town (Dr J Moodley, Professor M Hoffman, Ms V Daries), the Women's Health Project, University of Witwatersrand (Dr M Kawonga, Ms Robertson, Ms Silo) and EngenderHealth, USA (Ms J Bradley, Dr M Barone). The research team met on a regular basis to discuss all aspects of the project. The candidate was a co-principal investigator in the project and was involved in the design of the study; managed one of the three research sites; led the development of the health worker training intervention, posters and pamphlets and the Pap smear register; participated in the development of the cytology request and report forms and the referral and feedback forms; was co-responsible for data management, data analysis, data interpretation and dissemination of results.

Preparing for HPV vaccination in South Africa (Chapter 5)

This was a collaborative project between the Women's Health Research Unit, University of Cape Town (Ms J Harries, Dr J Moodley, Ms S Mall) and EngenderHealth, USA (Dr M Barone). The candidate was a co-principal investigator and was involved in development of the study proposal; was co-responsible for the development of the interview guides; supervised data collection; was co-responsible for analysis and interpretation; and was co-responsible for dissemination of results.

HIV, cervical cancer precursor lesions and cervical cancer among South African women (Chapter 6)

This study was based upon a secondary analysis of data collected as part of a case-control study conducted to determine the association between hormonal contraceptives and cervical cancer. The candidate was not part of the original case-control study, but was the principal

investigator of the study reported in chapter 6 which determined the association between HIV, cervical cancer precursor lesions and cervical cancer. This latter study was a collaborative project between Women's Health Research Unit, University of Cape Town (Dr J Moodley, Professor M Hoffman, Professor S Shapiro, Dr D Cooper, Mr H Carrara), the Institute of Infectious Disease and Molecular Medicine, University of Cape Town (Professor A-L Williamson, Mr B Allan), the Slone Epidemiology Unit, Boston University (Professor L Rosenberg) and the Department of Obstetrics and Gynaecology, University of Cape Town (Professor L Denny). The candidate was responsible for designing the study; co-responsible for data analysis and was responsible for dissemination of results.

HPV infection and cervical cancer precursor lesions in women initiating HAART (Chapter 7)
This was a collaborative project between the Women's Health Research Unit, University of Cape Town (Dr J Moodley, Professor M Hoffman, Ms D Constant), the Institute of Infectious Disease and Molecular Medicine, University of Cape Town (Professor A-L Williamson, Ms A Salimo, Mr B Allan) and the Department of Molecular and Cell Biology, University of Cape Town, Cape Town (Professor E Rybicki, Dr I Hitzeroth). The candidate was the principal investigator and designed the study; supervised data collection; analysed the data and disseminated the study results.

The work presented in this thesis has resulted in the following peer-reviewed publications:

Moodley, J., Kawonga, M., Bradley, J. & Hoffman, M. 2006. Challenges in implementing a cervical screening program in South Africa. *Cancer Detection and Prevention*, vol. 30, no. 4, pp. 361-368.

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Harries, J., Moodley, J., Barone, M.A., Mall, S. & Sinanovic, E. 2009. Preparing for HPV vaccination in South Africa: key challenges and opinions. *Vaccine*, vol. 27, no. 1, pp. 38-44.

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Moodley, J., Harries, J. & Barone, M. 2009 Misinformation and lack of knowledge hinder cervical cancer prevention. *South African Medical Journal*, vol. 99, no. 3, pp. 128.

List of abbreviations

ART	antiretroviral therapy
ASC-H	atypical squamous cells cannot exclude high-grade squamous intraepithelial lesions
ASC-US	atypical squamous cells of undetermined significance
ASIR	age-standardised incidence rate
ASMR	age-standardised mortality rate
ATP	according-to-protocol
CCTMM	City of Cape Town Metropolitan Municipality
CI	confidence interval
CIN	cervical intraepithelial lesion
DHC	District Health Council
DHS	district health system
DNA	deoxyribonucleic acid
DNHPD	Department of National Health and Population Development
DOH	Department of Health
DVI	direct visual inspection
ELISA	enzyme-linked immunoabsorbant assay
EM	Ehurkhuleni Municipality
EPI	Expanded Program on Immunisation
GAVI	Global Alliance for Vaccination and Immunization
HAART	highly active antiretroviral therapy
HC2	Hybrid Capture second generation
HER	HIV Epidemiology Research
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR-HPV	high- risk human papillomavirus
HSIL	high-grade squamous intraepithelial lesions

IARC	International Agency for Research on Cancer
ICC	invasive cervical cancer
ICPD	International Conference on Population and Development
IEC	information, education and communication
IQR	interquartile range
ITT	intention-to-treat
KAP	knowledge, attitudes and practice
LBC	liquid based cytology
LSIL	low-grade squamous intraepithelial lesions
MITT	modified-intention-to-treat
NBS	New Bethesda System
NCR	National Cancer Registry
NDOH	National Department of Health
NGO	non-governmental organisation
NHI	National Health Insurance
NHLS	National Health Laboratory Service
OR	odds ratio
Pap	Papanicolaou
PCR	polymerase chain reaction
PGWC	Provincial Government of Western Cape
PHC	primary health care
PMTCT	prevention of mother to child transmission
PR	prevalence ratio
RLU	relative light units
SA	South Africa
SASOG	South African Society of Obstetricians and Gynaecologists
SIL	squamous intraepithelial lesions
STI	sexually transmitted infection

VIA	visual inspection with acetic acid
VILI	visual inspection with Lugol's iodine
VLP	virus like particle
WHO	World Health Organization
WHP	Women's Health Project
WHRU	Women's Health Research Unit
WIHS	Women's Interagency HIV Study

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Chapter 1: Introduction

Chapter 1 provides background information about the research field, outlines the aims and objectives of the thesis, briefly describes the research methods and provides an outline of the thesis chapters. The chapter is structured as follows:

- 1.1. Background
- 1.2. Aim
- 1.3. Objectives
- 1.4. Synopsis of methods
- 1.5. Thesis structure

1.1 Background

Cervical cancer continues to be an important women's health problem (Parkin et al. 2005; Ferlay et al. 2010b). Until recently, the only option for prevention of cervical cancer has been to screen and treat precursor lesions i.e. through secondary prevention. In developed countries¹ the implementation of organised cervical screening programmes, most commonly by means of Papanicolaou (Pap) smears, has resulted in a decline in cervical cancer incidence and mortality (Miller et al. 2000; Peto et al. 2004; International Agency for Research on Cancer (IARC) 2005). By contrast, cervical cancer remains a problem in developing countries because of ineffective or absent screening programmes (Lazcano-Ponce et al. 1999; Sankaranarayanan, Budukh & Rajkumar 2001; IARC 2005). There are no organised cytology-based programmes in low-income countries. It has been suggested that these countries should focus their efforts and resources on improving diagnostic and treatment services for clinically manifest cervical cancer before embarking on a screening programme for precursor lesions (Sankaranarayanan, Budukh &

¹ The World Bank classifies countries as low, middle (subdivided into lower middle and upper middle) or high income. The classification is based on the gross national income (GNI) per capita and is as follows: low income, \$995 or less; lower middle income, \$996 - \$3,945; upper middle income, \$3,946 - \$12,195; and high income, \$12,196 or more. High income countries, with the exception of Hong Kong (China), Israel, Kuwait, Singapore, and the United Arab Emirates are sometimes referred to as developed countries. Low-income and middle-income countries as well as Hong Kong (China), Israel, Kuwait, Singapore, and the United Arab Emirates are sometimes referred to as developing countries (The World Bank 2009).

Rajkumar 2001). Some middle-income countries have implemented cytology-based screening programmes in the past 30 years. However they have achieved limited success, largely due to programmatic challenges (Lazcano-Ponce et al. 1999; Sankaranarayanan, Budukh & Rajkumar 2001; IARC 2005; Garland et al. 2008b; Murillo et al. 2008). It has been suggested that middle-income countries should consider implementing an organised programme in a limited geographical area before expanding to cover the country (Sankaranarayanan, Budukh & Rajkumar 2001; Sepulveda, Prado 2005). Programmes should emphasize high coverage of older women rather than offer frequent smears to women in a wide age range. Competing health care priorities and poorly functioning health care systems have made it difficult for sub-Saharan African countries to implement cervical cancer screening programmes and currently no comprehensive cervical cancer screening programme exist in this region (IARC 2005).

South Africa (SA) is a middle-income country with a relatively well-developed health infrastructure compared to other developing countries. Cervical cancer is the second most common cancer among South African women with an age-standardised incidence rate (ASIR) of 25.5 per 100 000 women and is the leading cause of cancer mortality amongst women (age-standardised mortality rate (ASMR) of 21 per 100 000 women) (Norman et al. 2006; National Health Laboratory Service 2009). The impact of the gross inequities in terms of health status and access to health care during the apartheid era can be seen in the differences in cervical cancer incidence and mortality rates by race group. The South African National Department of Health (NDOH) has identified cervical cancer as a national health priority and in 2000 introduced a screening policy stating that every woman is entitled to three free Pap smears (in the public sector) in her lifetime at 10-year intervals, starting at the age of 30 years (Department of Health 2000). Studies in South Africa have indicated that barriers to an effective screening programme exist both at community and health service level (Leiman 1987; Abrahams, Wood & Jewkes 1997; Smith, Moodley & Hoffman 2003; Moodley et al. 2006; Moodley, Harries & Barone 2009). This policy thus presents a considerable challenge to reproductive health programme managers charged with translating national policy into action at provincial, district and facility level.

It is now well established that infection with certain types of human papillomavirus (HPV) is a necessary but not sufficient cause of cervical cancer (Walboomers et al. 1999; Bosch et al. 2002). This is of considerable public health importance and has led to new possibilities for the prevention of cervical cancer. There are 15 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) classified as high-risk (HR) types or oncogenic for cervical cancer. HPV16 and HPV18 are the dominant oncogenic types worldwide, consistently detected in 70% of all cancers of the cervix (Munoz et al. 2003).

The recent development of two prophylactic HPV vaccines (Harper et al. 2006; FUTURE II Study Group 2007), a bivalent vaccine that targets HPV16 and HPV18 and a quadrivalent vaccine that targets HPV types 16, 18, 6 and 11, offers potential for primary prevention of cervical cancer in SA. However implementing a HPV vaccine programme presents several unique challenges: for example, to obtain maximum effectiveness the vaccine needs to be administered prior to the onset of sexual activity. This means vaccinating young adolescents, a target group not usually included in public sector immunization programmes. Experience with introducing new health technologies has demonstrated the importance of understanding the local context before innovations are introduced and incorporating the perspectives of a broad range of stakeholders, including those of users, providers, managers, policy makers and community groups (Simmons et al. 1997). Studies in developed countries have examined the knowledge and attitudes of health providers, parents and young women, and have assessed what factors may play a part in uptake of the HPV vaccine (Giles, Garland 2006; Noakes, Yarwood & Salisbury 2006; Zimet et al. 2006; Ogilvie et al. 2007). Little work has been done in developing countries, where these issues may be different (Harries et al. 2009).

Whilst recognizing the potential impact of the vaccines on the incidence of HPV and cervical cancer, secondary prevention of cervical cancer remains important because, not all women will be vaccinated, some cervical cancers are caused by HPV types that the vaccines do not protect against, and the vaccines are not effective in women who already have HPV infection (Jacob, Bradley & Barone 2005; Franco et al. 2006). An effective cervical cancer prevention programme will need to be comprehensive, and consider both primary and secondary strategies.

SA is confronted by one of the worst human immunodeficiency virus (HIV) epidemics in the world and it is estimated that there are currently 5.4 million people with HIV or acquired immune deficiency syndrome (AIDS) in SA, with a greater number of women, compared to men, affected (Department of Health 2008). The HIV epidemic has impacted on health service delivery in many ways in South Africa: the workload of health service providers, particularly nurses has increased, health workers have been infected by HIV, and overall increased health resources are needed to address the burden of HIV-related illness (Benatar 2004; Shisana et al. 2004; Schneider et al. 2006). HIV also has a direct impact on cervical cancer and its precursor lesions. Immune-suppression plays an important role in conferring increased risk and is associated with an increase in incidence and prevalence of HPV infection (Wright et al. 1994; Ellerbrock et al. 2000; Palefsky, Holly 2003). There may also be a direct interaction between the two viruses at a molecular level (Palefsky, Holly 2003). Studies have shown that women infected with HIV have a higher prevalence of HPV and are at a greater risk of developing cervical cancer and its precursor lesions compared to HIV negative women (Sun et al. 1997; Minkoff et al. 1998; Massad et al. 1999; Massad et al. 1999; Palefsky et al. 1999; Ahdieh et al. 2000; Duerr et al. 2001; Jamieson et al. 2002; Hawes et al. 2003; Schuman et al. 2003; Moodley et al. 2006; Rowhani-Rahbar et al. 2007). An increase in HPV viral load has been shown to be associated with increasing severity of cervical lesions (Lillo et al. 2005). HIV positive women are infected with a broader range of HPV types and are more likely to have multiple HPV types present, compared to HIV negative women (Clifford et al. 2006). HPV type is a strong risk factor for progression from persistent HPV infection to cancer (Schiffman et al. 2007). Worldwide there is considerable variation in regional HPV type distribution in HIV positive women (Clifford et al. 2006). Limited information is available on the prevalence and distribution of HPV types and on HPV viral load among HIV positive women in South Africa (Denny et al. 2008; Moodley et al. 2009). In developing a comprehensive cervical cancer prevention strategy for South Africa, it is important to determine the role HIV plays in the risk of cervical cancer and cervical cancer precursor lesions.

Highly active antiretroviral therapy (HAART) has been shown to decrease HIV viral loads, increase CD4 cell counts and decrease most opportunistic infections (Hogg et al. 1998; Palella et al. 1998). Since the introduction of HAART there has been a decline in certain malignancies in

HIV infected individuals (Jacobson et al. 1999; Ledergerber, Telenti & Egger 1999). HAART has the potential to influence the relationship between HIV and cervical cancer in two contrasting ways. Firstly, by prolonging life HAART lengthens exposure to HPV infection thereby increasing the likelihood of cervical precursors and cancer. Conversely, because HAART restores immune-competence, it may reduce the risk of cervical precursors and cancer (Palefsky 2003; Palefsky 2006). However, it has also been suggested that HPV-specific immunity may not recover fully after immune response is restored (Palefsky 2003; Palefsky 2006). Studies on the impact of HAART on the natural history of cervical cancer have produced mixed results, with some studies showing benefit and others no effect (Heard et al. 1998; Orlando et al. 1999; Lillo et al. 2001; Minkoff et al. 2001; Heard et al. 2002; Moore et al. 2002; Ahdieh-Grant et al. 2004; Heard, Palefsky & Kazatchkine 2004; Heard, Potard & Costagliola 2006; Omar et al. 2011). As HAART becomes increasingly available in the public sector in SA, the life expectancy of HIV positive women will increase. The important question of whether the benefits of HAART will or will not be partially offset by an excess risk in cervical cancer remains to be answered. Long-term longitudinal studies of the natural history of cervical lesions in women initiating HAART will be critical to inform the development of locally relevant, rigorous screening protocols. Data on the prevalence of cervical cancer precursor lesions amongst HIV positive women initiating HAART will assist in estimating resources and planning cervical cancer prevention and treatment services.

Little is known about the burden of HPV associated disease in HIV positive women in SA and about the implications of the HIV epidemic for cervical cancer prevention programmes.

This thesis sets out to examine the challenges and opportunities in preventing cervical cancer in a middle income, African country. It will examine four related questions:

- Can a cytology-based based screening programme be effectively implemented in South Africa?
- What are the potential challenges to and opportunities for implementing an HPV vaccination programme in South Africa?

- What are the associations between HIV, HPV, cervical cancer precursors and cervical cancer in South Africa and what are the implications of the associations for cervical cancer prevention programmes?
- What is the prevalence of HPV and cervical cancer precursors and the HPV types and HPV viral load in women initiating HAART?

Issues relating to cost-effectiveness and competing health priorities are important in developing a comprehensive cervical cancer preventive strategy but are not included within the confines of this thesis.

1.2 Aim

The overall aim is to identify challenges in comprehensive prevention (primary and secondary prevention) of cervical cancer in South Africa and make recommendations for an optimal cervical cancer prevention strategy.

1.3 Objectives

1. To design, implement and evaluate health system interventions for public sector cytology-based cervical screening services in South Africa. This includes:
 - a. Identifying service-delivery barriers to a cytology based screening programme.
 - b. Developing appropriate and replicable interventions to strengthen cervical cancer prevention services.
 - c. Evaluating the effectiveness of these interventions. In this context effectiveness was defined as the extent to which the organisation and functioning of cervical cancer screening services; staff knowledge, attitude and practice (KAP), client KAP, service utilisation and Pap smear coverage improved post-intervention.
2. To understand key opinions about, challenges to, and opportunities for, the potential introduction of the HPV vaccine in the public sector in South Africa.
3. To determine the association between HIV, cervical cancer precursor lesions and cervical cancer among South African women.

4. To determine HPV prevalence, types and viral load and the prevalence of cervical precursor lesions among women initiating HAART.

1.4 Synopsis of methods

The studies contributing to this thesis utilise quantitative, health systems and qualitative research methods. This mix of methods was chosen in order to provide a more complete assessment of the challenges inherent in implementing a comprehensive cervical cancer preventive strategy. The methods used to address each of the research questions are briefly summarised below.

To design, implement and evaluate health system interventions for public sector cytology-based screening services in South Africa.

To address the first objective, three of nine provinces in South Africa were included in a study to identify health system barriers and facilitators, and to design, develop and evaluate interventions to address these challenges. In consultation with respective provincial health authorities, one sub-district per province was purposively selected to represent different socio-economic, geographical and health system contexts in the country. The research sites represent the different range of challenges that are likely to be experienced in various contexts within the country viz. urban vs. rural, middle vs. low income populations and varying levels of health system infrastructure. Baseline surveys, consisting of facility audits, staff KAP surveys, client KAP surveys and a review of laboratory data were conducted at primary care facilities in the project districts in 2001. Information on aspects of service functioning and on clients' and provider's knowledge, attitudes, and practices was collected. Meetings were held with stakeholders to discuss baseline findings and to further identify programmatic strengths and weaknesses. Based on these findings a number of health system (e.g. Pap registers, data collation sheets) and community awareness interventions (e.g. posters and pamphlets at clinics and community sites, radio and newspaper slots) were developed and implemented. Surveys were undertaken once again in 2002/2003. Pre- and post-intervention data were compared to determine changes in service structure, functioning and utilisation.

To understand key opinions about, challenges to, and opportunities for, the potential introduction of the HPV vaccine in the public sector in South Africa

A qualitative study that explored key challenges and opinions towards HPV vaccination introduction in South Africa was conducted between February 2007 and March 2008. Qualitative methods were used as they are particularly useful in exploring a topic about which little is known. Experienced fieldworkers trained in qualitative research methods conducted in-depth interviews with 24 health care providers and 26 policy makers and key policy informants at national and provincial levels. Six focus group discussions were carried out with female community members and in total forty-three women were included in these discussions. Key issues explored included: views and experiences on current cervical screening policy and programmes; views on vaccination as a method of cervical cancer prevention; HPV vaccine delivery mechanisms and possible opposition to the HPV vaccine. Data were analysed using a thematic analysis approach in which main themes and categories were identified and analysed.

To determine the association between HIV, cervical cancer precursor lesions and cervical cancer among South African women

Two studies were undertaken to determine the role that HIV plays in the risk of cervical cancer and cervical precursor lesions. The first, a case-control study was conducted to determine the risk of cervical precursor lesions and cervical cancer among HIV positive women in South Africa. This study was conducted at an early stage of the HIV epidemic and at a time HAART was not available in the public sector services. Data were derived from a case-control study conducted in the Western Cape, between January 1998 to December 2001 that examined the association between hormonal contraceptives and invasive cervical cancer. In 2004 anonymous HIV testing was done on stored serum samples, using the enzyme-linked immunoabsorbant assay (ELISA). The relationship between HIV, cervical cancer precursor lesions and cervical cancer was then explored. For the association between HIV and cervical cancer, HIV prevalence in the cases (n= 486) were compared with that in the controls (n= 1365). Adjusted HIV odds ratios (OR) and 95% confidence intervals (CI) were calculated using multiple logistic regression. For the association between HIV and cervical cancer precursor lesions, the analysis was restricted to the control group which consisted of 103 women with atypical squamous cells of undetermined significance (ASC-US), 53 with low-grade squamous intraepithelial lesions (LSIL), 50 with

high-grade squamous intraepithelial lesions (HSIL) and 1159 with normal cytology women. Women with normal cytology were used as a reference group. Adjusted prevalence ratios (PR) for HIV and 95% confidence intervals (CI) were calculated using log-binomial regression.

To determine HPV prevalence, types and viral load and the prevalence of cervical cancer precursor lesions among women initiating HAART

The second study conducted to provide information on the role of HIV in cervical cancer and precursor lesions of the cervix was undertaken at a later stage of the HIV epidemic in the Western Cape Province. A cross-sectional survey was conducted at an antiretroviral therapy (ART) clinic in Cape Town, South Africa, between January and May 2007, to determine the prevalence of high-risk HPV (HR-HPV), HPV viral load, HPV types and cervical cancer precursor lesions in 109 HIV positive women initiating HAART. A research nurse collected data on socio-demographic status and sexual and reproductive history; conducted a pelvic examination; took a Pap smear and collected cervical samples for HPV testing. Descriptive statistics (medians and proportions) were used to characterise the variables. Adjusted prevalence ratios and 95% confidence intervals for predictors of squamous intraepithelial lesions (SILs) were determined using Poisson regression with robust variance.

1.5 Thesis structure

Chapter 2 is a literature review on the prevention of cervical cancer. It explores the burden of cervical cancer, describes the natural history of cervical cancer as a basis for preventive strategies, describes methods of screening, discusses issues related to implementation of cytology-based screening programmes, discusses primary prevention through HPV vaccination and the association between HIV and cervical cancer. Chapter 3 provides information on the context of the problem. It describes the unique challenges that South Africa faces as a middle-income country with a relatively well developed infrastructure, a fragmented health system and a huge HIV/AIDS burden. It also describes cervical cancer prevention efforts in South Africa. The next 4 chapters present the methods, results and discussion for each of the study objectives namely: implementing a cytology-based secondary screening programme in SA i.e. a secondary preventive strategy (chapter 4), key opinions about, potential challenges to and opportunities for,

the introduction of HPV vaccination in South Africa i.e. a primary preventive strategy (chapter 5), HIV, cervical cancer precursor lesions and cervical cancer among South African women (chapter 6) and HPV infection and cervical cancer precursor lesions among women initiating HAART (chapter 7). Chapter 8 considers the implications of the main findings and discusses the feasibility of preventing cervical cancer in SA.

University of Cape Town

Chapter 2: Literature review

The literature review provides information on the burden of cervical cancer, describes the natural history of cervical cancer as a basis for preventive strategies, describes methods of secondary prevention of cervical cancer, discusses issues related to implementation of cytology-based screening programmes, discusses primary prevention through HPV vaccination and the association between HIV and cervical cancer. The structure of the chapter is as follows:

2.1. Burden of cervical cancer

2.1.1. Global burden of disease

2.1.2. Burden of disease in South Africa

2.2. Natural history of cervical cancer

2.2.1. HPV as the causative agent

2.2.2. Progression of HPV infection to cervical cancer

2.2.3. Aspects of epidemiological findings pertinent to preventive strategies

2.3. Secondary prevention

2.3.1. Screening tests

2.3.2. Experience with cytology-based screening programmes

2.3.3. Summary of challenges in implementing cytology-based screening programmes in middle-income countries

2.4. Primary prevention through HPV vaccination

2.4.1. Features of current vaccines

2.4.2. Experience in introducing HPV vaccine in developed countries

2.4.3. Issues for HPV vaccine introduction in developing countries

2.5. HIV and cervical cancer

2.5.1. HIV and HPV infection

2.5.2. HIV and cervical cancer precursor lesions

2.5.3. HIV and invasive cervical cancer

2.5.4. The impact of HAART on cervical lesions

2.5.5. Prevention of cervical cancer in HIV positive women

2.6. Summary

2.1 Burden of cervical cancer

2.1.1 Global burden of disease

Cervical cancer is the third most common cancer among women worldwide, comprising 8.8% of all cancers in women (Ferlay et al. 2010b). In 2008 it was estimated that there were 529 000 new cases and 275 000 deaths from cervical cancer worldwide (Ferlay et al. 2010b). Cancer is responsible for 13% of all deaths worldwide (Boyle, Levin 2008; World Health Organization 2009), with cervical cancer accounting for 8.6% of all cancer deaths (Ferlay et al. 2010a). Global prevalence estimates suggest that there are 1.4 million cases of clinically recognised cervical cancer annually (Sankaranarayanan, Budukh & Rajkumar 2001). The current available information however probably underestimates the true burden of disease, as for several developing countries good quality incidence and mortality data are not available. In developing countries many women do not receive medical care and are therefore not included in cancer registries, where these exist.

Developing countries, where 85% of all cases occur, bear a disproportionate burden of the disease. Cervical cancer accounts for 11.4% of all cancer deaths in developing countries compared to 2.7% of cancer deaths in developed countries (Ferlay et al. 2010a). The cumulative risk for developing cervical cancer before age 74 years in developing countries is almost double that in developed countries (1.9% vs. 0.9%) (Ferlay et al. 2010b). Table 2.1 shows the marked

differences in age-standardised cervical cancer incidence and mortality rates for different regions. All cancer incidence and mortality rates have been included in Table 2.1 to illustrate the comparative burden posed by cervical cancer and all cancers.

The highest cervical cancer incidence rates occur in the low and medium income regions of sub-Saharan Africa, South-Central Asia, Latin America, Melanesia and the Caribbean, where there are few cervical cancer prevention programmes. The East African region has the highest ASIR for cervical cancer with cervical cancer accounting for nearly one third of all cancer cases. By contrast the Australia/New Zealand region has the highest all cancer ASIR, with cervical cancer accounting for less than 2% of the cancer cases. East Africa also has the highest ASMR for cervical cancer with cervical cancer responsible for almost a quarter of all cancer deaths. By contrast in the Australian/New Zealand region cervical cancer accounts for less than 2 % of cancer deaths.

There is considerable variation in the incidence rates among countries in the various regions. For example, in a review of the incidence and mortality rates for cervical cancer in 21 Latin American countries very high rates were reported in Haiti (ASIR 93.9 per 100 000), whilst much lower rates were reported in Uruguay (ASIR 13.3 per 100 000) (Arrossi, Sankaranarayanan & Parkin 2003). Cervical cancer is the most common cancer among women in Africa, comprising 25.4% of all female cancers (Parkin et al. 2008). Eastern and Southern Africa have the highest cervical cancer incidence rates in the African region and worldwide, while North Africa has a much lower ASIR, similar to that seen in some developed regions.

Table 2.1: Age-standardised incidence and mortality rates per 100 000 for cervical cancer and all cancers in 2008 (world standard population)

Region/Country	Cervical cancer incidence	All cancers incidence	Cervical cancer mortality	All cancer mortality
Eastern Africa	34.5	125.3	25.3	95.9
Southern Africa	26.8	161.1	14.8	108.1
Western Africa	33.7	123.5	24.0	91.2
Middle Africa	23.0	96.7	17.0	75.6
Northern Africa	6.6	98.9	4.0	68.2
Caribbean	20.9	153.5	9.4	86.2
Central America	22.2	134.4	11.1	80.6
South America	23.9	162.9	10.7	88.2
Northern America	5.7	274.4	1.7	91.5
South Central Asia	24.6	110.8	14.1	71.7
Eastern Asia	9.6	158.1	3.9	87.3
Western Asia	4.5	119.5	2.1	74.3
South-Eastern Asia	15.8	141.7	8.3	89.4
Central and Eastern Europe	14.5	184.2	6.3	94.0
Southern Europe	8.0	212.2	2.5	81.2
Western Europe	6.9	250.9	2.0	84.3
Northern Europe	8.3	249.4	2.4	99.7
Australia / New Zealand	5.0	276.4	1.4	86.0
Melanesia	23.7	133.4	16.6	95.9
Micro/Polynesia	13.4	184.0	4.9	79.9

Source: (Ferlay et al. 2010b)

Time trends in cancer incidence and mortality need to be interpreted with caution due to changes in data quality and methodology of estimation over time (Parkin et al. 2005). With cervical cancer an additional complexity relates to changes in the proportion of deaths coded as “uterine cancer not otherwise specified” and time trends need to be interpreted with this caveat in mind. In general cervical cancer incidence and mortality rates have decreased in most developed countries in the past 20 to 40 years (IARC 2005). Most of this decline is credited to the implementation of effective screening programmes.

The limited data on time trends of cervical cancer in developing countries indicate that incidence and mortality rates have been relatively stable with some small declines which have been attributed to socio-demographic changes rather than to prevention efforts (Sankaranarayanan, Budukh & Rajkumar 2001). This assumes reliable and valid data in these countries. Cancer registration systems are relative uncommon in Africa and limited data is available on time trends for cervical cancer (Parkin et al. 2008). Data from the Kampala Cancer registry, set up in 1954, shows an increase in the incidence of cervical cancer between the 1960 and 1997 from 17.1 per 100 000 to 45.8 per 100 000 (Wabinga et al. 2000). The reasons for the increase are not understood and have not been investigated. No increase in incidence over time has been documented in Harare (Zimbabwe) or Nigeria (Parkin et al. 2003; Parkin et al. 2008). In most Latin American countries cervical cancer mortality has remained relative unchanged since 1960 except for declines documented in Puerto Rico and Chile (Robles, White & Peruga 1996; Sankaranarayanan, Budukh & Rajkumar 2001; Arrossi, Sankaranarayanan & Parkin 2003; IARC 2005). Cervical cancer continues to be an important cause of morbidity and mortality in developing countries.

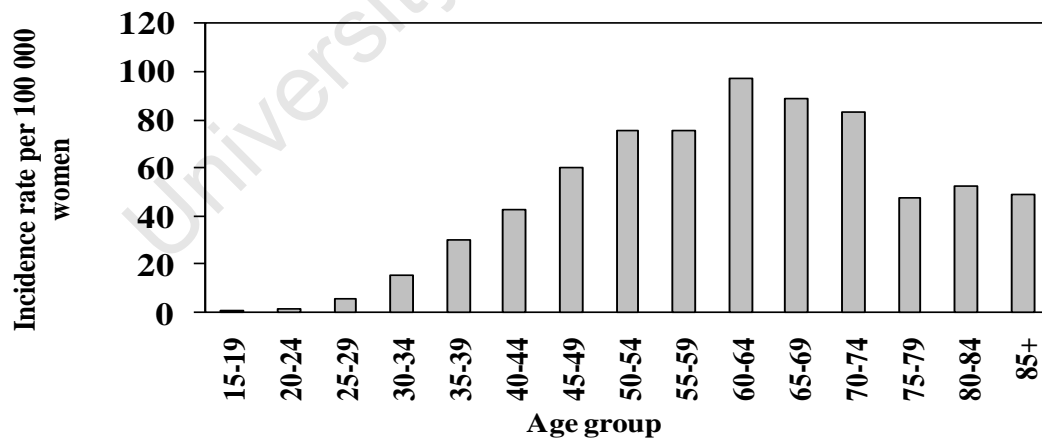
2.1.2 Burden of disease in South Africa

South Africa does not have a national population-based cancer registry. The main source for cancer statistics is the National Cancer Registry (NCR). The registry was established in 1986 and relies on histology reports from public and private pathology laboratories nationwide. As a pathology-based registry it is prone to under reporting.

Data on the ASIR of cervical cancer, as with many other diseases in South Africa, describes the distribution of the disease among the four race groups that formed the legal basis of apartheid regulation viz. Black (African), White (Caucasian), Coloured(mixed race) and Asian (Indian). A problem with the use of these categories is the implication that phenotypic differences between races are coterminous with genetic differences which determine predisposition to disease. This has been shown to be incorrect (Diamond 1994; Ellison et al. 1996; Ellison, de Wet 1997). In South Africa apartheid resulted in sharp social, economic and geographic divisions between the races. Differences in health status reflect these socio-economic divisions.

According to the most recent NCR statistics (2001), cervical cancer is the second commonest cancer among all South African women with an ASIR of 25.5 per 100 000 women (National Health Laboratory Service 2009). Overall one in thirty five women in South Africa is at risk of developing cervical cancer. Figure 2.1 shows the age-specific incidence rate for cervical cancer in 2001. The incidence rate rose steadily with age with women aged 60 to 64 years having the highest rate (ASIR 97.0/ 100 000 women).

Figure 2.1: Age-specific incidence rate for cervical cancer, South Africa 2001



Source: (National Health Laboratory Service 2009)

The marked difference in the ASIR for cervical cancer in the different population groups in South Africa are shown in Table 2.2. These differences could be related to differential access to

cervical screening and differences in HPV infection rates. Among Black South African women cervical cancer is the commonest cancer with an ASIR of 30.6.

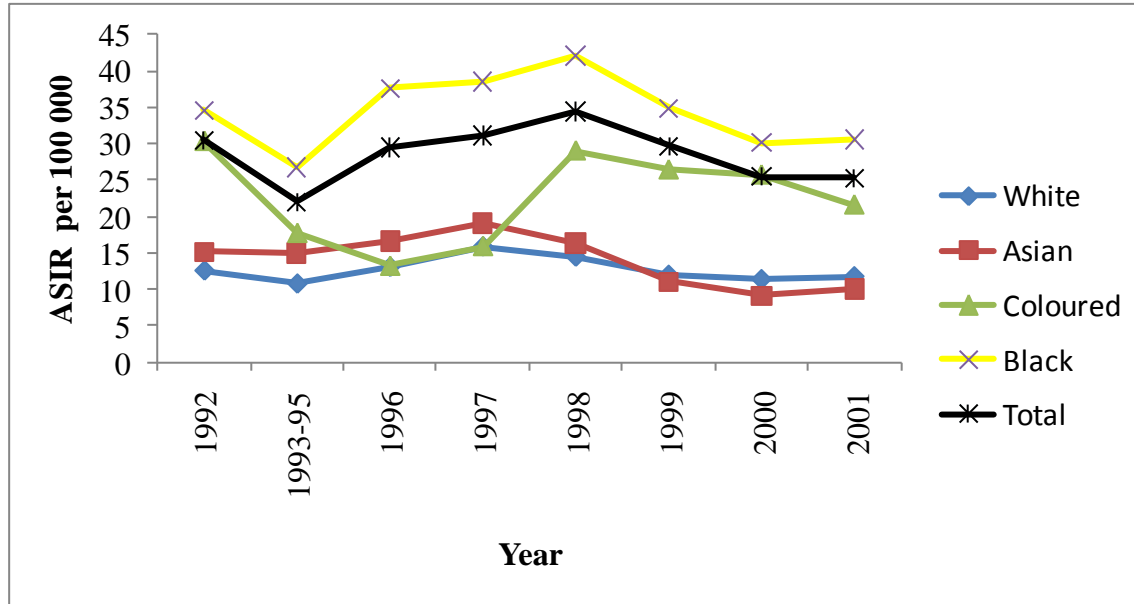
Table 2.2: Age-standardised incidence rates for cervical cancer, 2001 (world standard population)

Population group	Age standardised incidence rates per 100 000
Asian	10.0
African	30.6
Coloured	21.6
White	11.8
Total	25.5

Source: (National Health Laboratory Service 2009)

The ASIR for the different population groups over a 10 year period are shown below (Figure 2.2). There has been a small decline in the overall ASIR from 1992 to 2001. Over time there has been a modest decline in the ASIRs in the Coloured and Black population, however these rates remain unacceptably high, and are similar to the high rates seen in developing countries in Africa. ASIRs among the Asian and White population are similar to those seen in developed countries.

Figure 2.2: Age-standardised incidence rates for cervical cancer 1992 - 2001 (world standard population)



Source: (Sitas et al. 1997; Sitas, Madhoo & Wessie 1998; Mqoqi et al. 2003; Mqoqi et al. 2004; National Health Laboratory Service 2009)

Trends in age standardised cervical cancer mortality rates in South Africa for the period 1949 to 1990 showed that the overall trend for Coloureds increased in this period, the trend for Asians decreased from the mid 1970's whilst that for Whites decreased (Bailie et al. 1996). Trends in the African population could not be studied because of deficiencies in mortality data for that population group. The authors ascribe the contrasting mortality patterns between Coloureds and Whites to differences in access to screening services, with Whites mostly having access to Pap smears in the private sector and Coloureds reliant on opportunistic Pap smear screening in the public sector services.

Cervical cancer is the leading cause of cancer deaths amongst women in South Africa (Norman et al. 2006). In a burden of disease study conducted in South Africa in 2000, cervical cancer was ranked as the 15th highest cause of loss of life among females, accounting for 50 027 premature years of life lost (Bradshaw et al. 2003). Table 2.3 shows the all cause mortality rates and the cervical cancer mortality rates for the different population groups. The all cause mortality rate

was 1.7 times higher for African compared to White South African women, whilst for cervical cancer the mortality rates were 5.4 times higher for African compared to White women (Bradshaw et al. 2006).

Table 2.3: All cause and cervical cancer age-standardised mortality rates per 100 000 population by population group 2000 (world standard population)

	African	Coloured	Indian	White	South African
All cause	1613	1394	1172	937	1468
Cervical cancer	27	22	8	5	21

Source: (Bradshaw et al. 2006; Norman et al. 2006)

In summary cervical cancer remains an important cause of morbidity and mortality among women in South Africa, underscoring the need for a comprehensive prevention strategy.

2.2 Natural history of cervical cancer

2.2.1 HPV as the causative agent

Epidemiological studies have shown strong and consistent associations between HPV infection and cervical cancer (Walboomers et al. 1999; Munoz 2000; Bosch et al. 2002). Studies include cross-sectional surveys, case-control studies, cohort studies, intervention studies, experimental studies and natural history investigations (Bosch et al. 2002; IARC 2005). The strength of association is the strongest ever observed for human cancer, with a pooled odds ratio for squamous cell cervical cancer associated with HPV positivity of 158.2 (95% CI 113.4 - 220.6) (Munoz et al. 2003). The worldwide prevalence of HR-HPV in cervical cancer specimens is 99.7% and HPV is now recognised as a necessary cause of cervical cancer (Walboomers et al. 1999). This is of considerable public health relevance as it not only enables identification of a high-risk group of women (those with persistent HR-HPV infection), but it also raises the possibility of primary prevention by vaccination against this known aetiological agent.

Infection with HPV is not a sufficient cause of cervical cancer and among women persistently infected with HPV additional cofactors increase the risk of progression to cervical cancer. These cofactors include exposure to tobacco smoke, a parity of greater than five, immune-suppression including infection with HIV, the use of oral contraceptives for greater than five years, infection with *Chlamydia Trachomatis* and *Herpes Simplex type 2* (Castellsague, Munoz 2003; IARC 2005). Other cofactors that have been identified in studies in Africa include poor genital hygiene and alcohol (Parkin et al. 2003). From a public health perspective women exposed to any of these cofactors constitute a group at increased risk of cytological abnormalities compared to women in the general population. Evidence for the role of diet in cervical cancer remains inconclusive (Castellsague, Munoz 2003; IARC 2005).

HPV is a non-enveloped, double-stranded deoxyribonucleic acid (DNA) virus that infects epithelial cells. Papillomaviruses are relatively stable and resistant to desiccation. Over 100 types of the HPV have been identified and approximately 40 of these affect the anogenital area. Fifteen HPV types are classified as high-risk or oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) and these are frequently associated with cervical cancer. Three HPV types (26, 53, and 66) are classified as probable high-risk types (Munoz et al. 2003). HPV16 is the dominant type associated with more than half of the cervical cancers world-wide, followed by HPV18 (10% - 15%), HPV45 (7%), and HPV31 (3%) (Bosch, de Sanjose 2003; Clifford et al. 2003; Munoz et al. 2003). Twelve HPV types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89) have been classified as having a low-risk of association with cervical cancer and are referred to as benign or non-oncogenic types (Munoz et al. 2003). Low-risk types 6 and 11 are most often associated with genital warts (Munoz et al. 2003; Trottier, Franco 2006).

HPV is a common sexually transmitted infection. Results from a global meta-analysis on HPV prevalence in women with normal cytology indicate a point prevalence of 10.4% (95% CI 10.2–10.7) with a higher prevalence in less compared to more developed countries (15.5% vs. 10.0%) (de Sanjose et al. 2007). HPV prevalence is highest in young women (approximately 20% in women < 25 years) and decreases with age. In all regions except Asia a second peak in prevalence is seen in older women. In Africa this 2nd peak occurs after the age of 54 years. Possible explanations for this second peak include an impaired immune response triggered by

hormonal changes resulting in reactivation of latent HPV, changes in sexual behaviour and that of their partners in middle age, or a result of cohort effects.

There is considerable variation in HPV prevalence worldwide, with the highest HPV prevalence rates reported in Africa (22.1%; 95% CI 20.9 - 23.4) (de Sanjose et al. 2007). An IARC population-based survey conducted in 15 613 cytologically normal women aged 15 -74 years from eleven countries around the world also demonstrated a variation of nearly 20 times in prevalence across the countries (Clifford et al. 2005). In the latter pooled analysis only one African country viz. Nigeria was included and these women had the highest HR-HPV and HPV16 prevalence. Worldwide HPV16 is the most common HPV type with an estimated point prevalence of 2.6% (95% CI 2.5 -2.8). Studies indicate that in Europe, and Central and South America HPV18 is the second most frequent type, whilst in Africa, HPV52 is the second most frequent type and HPV18 the third. In Asia the commonest types in order of decreasing frequency are types 16, 52, 58 and then 18. In Northern America, HPV18 is also the fourth most common type after HPV16, HPV53 and HPV52 (Bosch et al. 2008; WHO/ICO Information Centre on HPV and Cervical Cancer 2010).

Relatively few studies have looked at HPV prevalence and type distribution in South African women. A study conducted among women attending public sector health services in the Western Cape reported a high HPV prevalence (20.4%) in women with normal cytology (Allan et al. 2008). In this study the commonest types seen in women with normal cytology were HPV16 (2.0%) and HPV52 (1.9%). In women with HSIL types 16 and 35 were the commonest both with a prevalence of 18.9%, followed by types 52 and 31 both with a prevalence of 11.3%. Two small studies reported on HPV types in women with invasive cervical cancer and concurred with results elsewhere that HPV16 was the most prevalent type (Williamson et al. 1994; Kay et al. 2003). The prevalence of HPV types in South Africa will be important in assessing the possible impact of HPV vaccines.

2.2.2 Progression of HPV infection to cervical cancer

An understanding of the natural history of cervical cancer is important in developing preventive strategies and in managing cervical cancer and its precursors. It is useful to note that several classifications exist for reporting cervical cancer precursor lesions (National Cancer Institute 1989; Solomon et al. 2002). The original classification used by Papanicolaou, was replaced by a descriptive one (using the dysplasia terminology), and later by the cervical intraepithelial neoplasia (CIN) classification. Since 1988, the Bethesda classification, using the terminology squamous intraepithelial lesion (SIL)) has been introduced. The 1988 Bethesda system also introduced the term atypical squamous cells of undetermined significance (ASCUS) which is an equivalent cytological diagnosis that denotes cellular changes that are more marked than reactive inflammatory changes but are not diagnostic of SILs. In 2001 atypical squamous cells were divided into those that were of undetermined significance (ASC-US) and those with atypical squamous cells but where HSIL could not be excluded (ASC-H). The changes in nomenclature are summarized in Table 2.4.

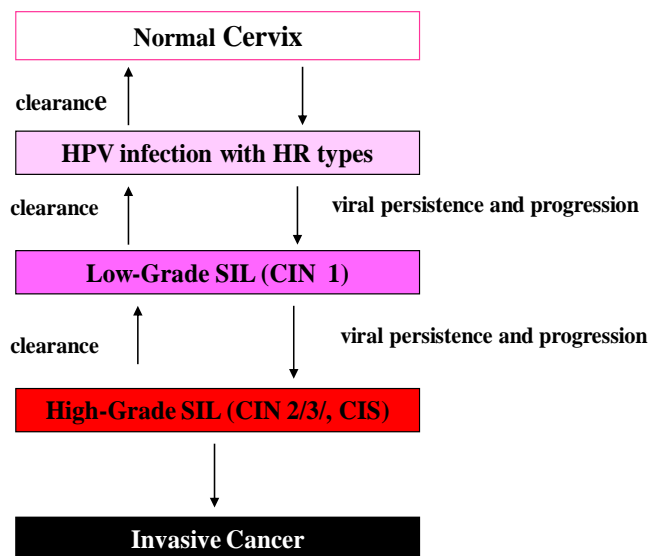
Table 2.4: Cytology nomenclature

Descriptive classification	CIN Classification	Bethesda 1988	Bethesda 2001
Atypia	Atypia	ASCUS	ASC-US ASC-H
Mild dysplasia	CIN grade 1	LSIL	LSIL
Moderate dysplasia	CIN grade 2	HSIL	HSIL
Severe dysplasia	CIN grade 3	HSIL	HSIL
CIS	CIN grade 3	HSIL	HSIL

CIS, carcinoma in situ; CIN, cervical intraepithelial neoplasia; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion ; HSIL, high grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells cannot exclude HSIL

The main steps in cervical carcinogenesis include: HPV transmission and infection of the epithelium (Holowaty et al. 1999; Schiffman, Kjaer 2003; Moscicki et al. 2006)of the transformation zone of the cervix, viral persistence, progression to precursor lesions and invasion of the basement membrane of the epithelium (invasive cancer) (Holowaty et al. 1999; Schiffman, Kjaer 2003; Moscicki et al. 2006; Schiffman et al. 2007) and are depicted in Figure 2.3.

Figure 2.3: Natural history of cervical cancer



CIS, carcinoma in situ; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR, high-risk LSIL, low-grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion

Adapted from (PATH 1997)

Penetrative sexual intercourse is the primary route of HPV infection. Transmission through non-penetrative sexual contact does occur but is rare (Winer et al. 2003; Burchell et al. 2006). HPV is highly transmissible. The median probability of HPV transmission per act was estimated in a

computer simulation study to be 40% (range 5 – 100%) (Burchell et al. 2006). Winer, et al. (2003) followed up a group of university students and reported a cumulative 24-month incidence of HPV of 38.9 % (95 % CI: 29.4 - 50.3) among virgins that initiated sexual activity. Risk factors for HPV transmission include number of sexual partners, partner's sexual behaviour and early sexual debut (Schiffman, Kjaer 2003; Burchell et al. 2006). Evidence for male circumcision as a risk factor for HPV infection is conflicting (Burchell et al. 2006). Condom use appears to offer some protection against HPV infection, however HPV can still be transmitted through contact with areas not protected by condoms (Burchell et al. 2006).

The majority of cervical HPV infections are cleared spontaneously or suppressed within one to two years of exposure by cell-mediated immunity (Stanley 2006). Persistence (defined as the detection of the same HPV type over a time period of several months to a year) is uncommon, but the longer the virus persists the greater is the risk of cervical cancer developing (Schiffman, Kjaer 2003). Persistence is commoner in older women (Schiffman et al. 2007). Reasons why some women infected with HPV develop persistent infection are not fully understood, but are thought to include viral type, differences in cell-mediated immune responses, individual host factors and possible environmental factors such as smoking and oral contraceptives (IARC 2005; Schiffman et al. 2007). HPV16 has been shown to persist longer than other oncogenic types (Franco et al. 1999). Persistent HR-HPV infection can lead to precursor lesions of the cervix. Women infected with multiple HPV types are also at a greater risk of cervical cancer precursor lesions compared to women infected with a single type, although it is not clear whether the risk is greater than the sum of risks posed by individual HPV types (Herrero et al. 2005).

Studies have shown that the majority of LSILs regress (Ostor 1993; Holowaty et al. 1999; IARC 2005). A review of studies reporting on the natural history of CIN1 concluded that 57% of CIN1 lesions regressed (Ostor 1993). Progression and regression rates were studied in a large historical cohort study in Canada, where Pap smear histories were recorded at a laboratory in a time when cervical squamous lesions were managed conservatively. In this study the majority (87.7%) of cases with mild dysplasia regressed to normal cytology within 10 years, with most of the regression occurring in the first 2 years. Approximately half of those with moderate dysplasia

regressed to normal cytology. Progression from mild dysplasia to severe dysplasia or worse occurred in 10.0% of women within 10 years, and from moderate to severe dysplasia in 32.0% of women within 10 years. It is not possible to study the progression of HSIL to invasive cancer, as this would be ethically unacceptable. Crude estimates from early studies suggest the risk of invasion is 30% within 5- 10 years (Kinlen, Spriggs 1978; Chang 1990).

HPV type is also a strong risk factor for progression from persistent HPV infection to cancer (Khan et al. 2005; Schiffman et al. 2007). Identifying which HR-HPV types preferentially progress from precursor lesions to cancerous lesions is important in informing the development of type-specific HPV vaccines. A meta-analysis that compared the prevalence of HPV types in HSIL (the immediate precursor lesion to cervical cancer) and invasive cancer concluded that HPV16, 18 and 45 were most likely to progress to invasive cervical cancer compared to other types (Clifford et al. 2003). A similar study conducted in Taiwan showed that HPV16 followed by HPV33 and 18 was most likely to progress from subclinical infection to invasive cervical cancer (Ding et al. 2008). The oncogenic potency of types 16 and 18 was confirmed in a study that followed up 20 810 women and reported the risk of developing CIN3 or cancer 10 years after HPV infection was 17.2% for HPV 16 and 13.6% for HPV 18, whilst the risk for women who had other HR-HPV types present was 3% (Khan et al. 2005; Schiffman et al. 2007). Although there is variation in the HPV types in women with normal cytology across regions, similarities in HPV type-specific distribution in invasive cervical cancer across the regions worldwide have been recorded (Clifford et al. 2003).

Progression from HPV infection to invasive cancer is slow, usually taking decades. The peak prevalence of transient HPV infections occurs in young women (teens to early 20s) after sexual debut. The peak in precancerous lesions occurs approximately 10 years later and the peak prevalence of invasive cervical cancer (ICC) at 40 to 50 years of age (Schiffman, Castle 2005).

2.2.3 Aspects of epidemiological findings pertinent to preventive strategies

Knowledge of the natural history and epidemiology of cervical cancer provide important information for the development of cervical cancer preventive strategies. The identification of HPV as a necessary cause of cervical cancer raised the possibility of primary prevention by vaccination. HPV infection is common with worldwide variation in prevalence and types. Fifteen high-risk HPV types have been identified. Vaccines against cervical cancer must provide protection against types that have demonstrated the greatest oncogenic potential, with the ideal being a polyvalent vaccine. Prophylactic vaccines will need to be administered prior to sexual debut. The impact of the vaccine at a country level will depend on prevalent HPV types and vaccine coverage. HPV-type specific data are therefore important in estimating the potential impact of an HPV vaccine strategy. Condoms offer some protection against HPV and should be promoted, however, consistent condom use is a challenge and condom use is unlikely to impact significantly on cervical cancer rates.

Criteria have been developed to assist when trying to determine whether or not screening is a suitable prevention strategy for a given disease (Wilson, Junger 1968). Cervical cancer meets all of the disease characteristics described: it is a common disease with serious consequences if left untreated; the natural history is well understood and it has a long latent period allowing time to detect and treat precancerous stages.

In summary natural history data provide guidance on when best to initiate screening. Cervical cancer most often develops in women after the age of 40 years. The immediate precursor lesion, HSILs, peak in women in their mid-30s. To achieve the maximum benefit from screening, countries with limited resources should aim to identify and treat women with HSILs by directing screening efforts at women in their thirties. As cervical cancer develops slowly screening can take place relatively infrequently and still have a significant impact on morbidity and mortality. HPV infection is common in young women and most infections clear spontaneously, hence screening by HPV testing should target older women who are more likely to have persistent HPV infection. As most LSILs (57% - 88%) regress spontaneously (Ostor 1993; Holowaty et al. 1999), women with these lesions can be monitored and only treated if the lesions fail to regress.

Programmes should focus on active treatment of HSILs as a significant proportion of these lesions (estimated 30%) progress to invasive cancer (Kinlen, Spriggs 1978; Chang 1990).

2.3 Secondary prevention

2.3.1 Screening tests

Conventional cytology

The first cytology test was developed by George Papanicolaou in the 1920s. Conventional cytology testing involves the collection of cervical cells from the transformation zone of the cervix using a spatula or brush, slide preparation and staining, and then microscopic examination of the cells. The accuracy of the test has been reviewed in several cross-sectional studies that have compared the Pap smear results to a reference standard of histology or colposcopy (Fahey, Irwig & Macaskill 1995; Nanda et al. 2000; IARC 2005; Sankaranarayanan et al. 2005). Histology results report the absence or presence of CIN of different degrees (CIN1, CIN2 or CIN3) or invasive cervical cancer. Pap smear results are categorized as abnormal (positive) or normal (negative) at various thresholds (ASC-US, LSIL or HSIL). The reference standards (histology or colposcopy) are not perfect diagnostic tests and are themselves subject to inaccuracy, which can lead to an underestimate of sensitivity and specificity. If studies do not verify normal Pap smear results with the reference standard this can lead to a biased study sample. This verification bias can result in elevated estimates of sensitivity and lower estimates of specificity.

Nanda et al. (2000) reviewed 12 studies conducted in women undergoing Pap tests for screening and in which verification was done on all, or a random sample of patients with negative Pap smear results. For a Pap smear threshold of LSIL, the sensitivity in detecting CIN2 or worse lesions ranged from 44% to 99% and specificity from 91% to 98% (Nanda et al. 2000). In four studies conducted in South Africa sensitivity in detecting CIN2 or worse lesions ranged from 53% to 78% and specificity from 88% to 97% (Denny et al. 2000; Wright et al. 2000; Denny et al. 2002; Cronje et al. 2003). The study by Cronje et al. (2003) was the only study in which all normal Pap smears were verified (sensitivity 53%, specificity 95%).

Both sampling and reading/detection errors are thought to contribute to the low-moderate sensitivity of Pap smears. Training and quality control measures (such as workload limits, proficiency testing, review of abnormal smears by a pathologist and cytology-histology correlations) are important in reducing these errors.

Liquid-based cytology

The liquid-based cytology (LBC) technique involves transferring cells collected on a sampling device to a fluid preservation medium and then processing the suspension in the laboratory. The cells remain well preserved in the suspension at room temperature for several weeks. Excess blood and mucus can be removed from the suspension and a small aliquot of suspension is then deposited in a thin layer onto a slide. The advantages of LBC include fewer unsatisfactory test results, the slides are quicker and easier to screen than conventional slides and remaining cell suspension is suitable for additional tests such HPV test (IARC 2005; Sankaranarayanan et al. 2005; Cuzick et al. 2008). LBC is however more expensive than conventional cytology. A recent meta-analysis of studies comparing conventional and liquid cytology showed that LBC is neither more sensitive nor more specific than conventional cytology in detecting HSIL (Arbyn et al. 2008a). The pooled sensitivity and specificity in detecting CIN2 or worse lesions was 57% and 97% respectively.

HPV testing

It is established that cervical cancer is caused by persistent HR-HPV types. The direct detection of HPV in cervical specimens thus could be used as a screening tool. HPV cannot be reliably cultured in the laboratory. HPV testing relies on molecular techniques that detect HPV DNA in cervical samples collected by a cone shaped brush. The two HPV DNA tests that have been validated in large studies are the hybrid capture second-generation (HC2) and polymerase chain reaction (PCR) based methods.

HC2 uses a signal amplification technique and is based on hybridizing long synthetic RNA probes in solution. One RNA probe (A) detects five low risk HPV types namely 6, 11, 42, 43 and 44 and the other probe (B) detects 13 high risk types namely 16, 18, 31, 33, 35, 39, 45, 51, 52,

56, 58, 59 and 68. The HPV DNA-RNA hybrids are captured by antibodies and detected by a series of reactions that produce a luminescent product that can be measured. The recommended cut-off value for test positive results is 1 relative light unit and is equivalent to 1pg of HPV DNA per 1 ml of buffer solution. The intensity of emitted light is proportional to the amount of DNA present in the specimen, so it is also able to provide a semi-quantitative measure of HPV viral load (Iftner, Villa 2003; IARC 2005; Sankaranarayanan et al. 2005). Studies have documented an increase in HPV viral load with increasing severity of cervical lesions (Heard et al. 2000; Sun et al. 2001; Sun et al. 2002; Dalstein et al. 2003; Levi et al. 2004; Wu et al. 2006). HPV viral load could therefore be useful in differentiating women at a higher risk of SIL. HC2 testing requires equipment ranging from basic laboratory supplies to advanced equipment such a luminometer integrated with a personal computer. These requirements make the use of HC2 costly. The HC2 is unable to provide information on specific individual HPV types.

The PCR-based method produces highly concentrated samples of a specific DNA genetic sequence through target amplification. Analysis of the amplified product can be done in different ways such as gel electrophoresis, dot blot or line assays. The strength of the PCR method lies in its capacity to detect very small amounts of HPV DNA. Strict laboratory procedures are critical to reduce contamination. Distinction of 40 types can be achieved using type-specific probes. Quantification of HPV viral load is possible, and the Real-Time PCR assay is considered to be one of the most accurate assays to quantify HPV viral load. However, the equipment and costs involved make PCR HPV tests inappropriate for large scale screening programmes.

A number of cross-sectional studies have evaluated the accuracy of HC2 as a screening test (IARC 2005; Sankaranarayanan et al. 2005). The sensitivity of HC2 in detecting CIN 2 or worse lesions varied from 66-100% and the specificity from 61% - 96% (IARC 2005; Sankaranarayanan et al. 2005). In a number of the studies Pap smear accuracy was also evaluated and, in general, the HPV test had a higher sensitivity and lower specificity than the Pap smear. Generally the accuracy was lower in studies that used self-sampling specimens by clients, compared to clinician sampling studies. The HC2 test has been evaluated in two studies in SA. In a study by Denny et al (2000) the sensitivity of the HC2 to detect CIN2 or worse lesions was 73% and specificity 88% and in a study by Wright et al (2000) the sensitivity was 84% and

specificity 85%. Studies have shown that screening strategies that incorporated HPV testing were cost-effective alternatives to cytology-based screening programmes in developing countries (Goldie et al. 2005; Vijayaraghavan et al. 2009). HPV testing by HC2 is an approved technique for cervical screening and triage of unequivocal cervical abnormalities in many developed countries.

The effect of a single round of screening by HPV testing, cytology testing, or visual inspection of the cervix with acetic acid (VIA) on the cervical cancer incidence and mortality rate was recently assessed in a randomised controlled trial in India (Sankaranarayanan et al. 2009). Clusters of villages were randomly assigned to undergo screening by HPV testing (34 126 women), cytology testing (32 058 women), VIA (34 074 women) or to receive standard care (31 488, control group). In India standard of care is no screening. Women who had positive results on screening underwent colposcopy and directed biopsies, and those with cervical precancerous lesions or cancer received appropriate treatment. Women were between 30 and 59 years old and were followed up for 8 years. The study found that a single round of HPV testing was associated with a significant decline in the rate of advanced cervical cancers and associated deaths, as compared with the unscreened control group. In the HPV-testing group, cervical cancer was diagnosed in 127 subjects as compared with 118 subjects in the control group, hazard ratio for the detection of advanced cancer (stage II or higher) in the HPV-testing group was 0.5 (95% CI 0.32 - 0.69). There were 34 deaths from cervical cancer in the HPV-testing group, as compared with 64 in the control group, hazard ratio, 0.5 (95% CI 0.33 - 0.83). No significant reductions in the numbers of advanced cancers or deaths were observed in the cytology-testing group (54 deaths, hazard ratio 0.9, 95% CI 0.62 - 1.27) or in the VIA group (56 deaths, hazard ratio 0.9, 95% CI 0.66 - 1.25), as compared with the control group (Sankaranarayanan et al. 2009).

The use of HC2 in developing countries has been hampered by the cost of the test, laboratory requirements and logistics involved. To overcome some of these problems a new test, the *careHPV*, has been developed for use in developing countries. The test uses signal amplification and can detect 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). It does not require electricity or running water and can be performed by technical staff in two and a half hours. A cross-sectional study of the clinical accuracy of the *careHPV* was conducted

in China. The accuracy of the test in detecting CIN2 or worse lesions was as follows: sensitivity of 90% (95% CI 83.0-97.0%) and a specificity of 84% (82.7 – 85.7%). Further studies are needed to test reproducibility in populations with different HPV prevalence (Qiao et al. 2008).

Visual inspection with acetic acid (VIA)

VIA involves examination of the cervix with the naked eye under a bright light source, one minute after acetic acid (3-5% dilution) has been applied to the cervix using a cotton swab or spray. This method is also referred to as “direct visual inspection” (DVI). The presence of aceto-white areas in the transformation zone of the cervix indicates a positive result. Aceto-whitening is not specific to cervical cancer and may also occur in immature squamous metaplasia and inflamed cervical epithelium. A number of studies have evaluated the test characteristics of VIA and have reported a sensitivity of between 67% to 79% and a specificity between 49% and 86% in detecting CIN2 or worse lesions (IARC 2005; Sankaranarayanan et al. 2005; Arbyn et al. 2008b). In part this wide variation can be explained by the subjective nature of VIA. Three studies have evaluated the accuracy of VIA in the South African setting and results are similar to those reported elsewhere with sensitivity ranging between 67% and 79% and specificity between 49% and 85% (Denny et al. 2000; Denny et al. 2002; Cronje et al. 2003). The main advantages of VIA are that it is cheap, quick and requires a low level of infrastructure and results are available immediately, all important issues in low-resource settings. However the test is subjective and provider supervision and quality assurance mechanisms are necessary to ensure reliable results. Limited information is available on how VIA will perform as a routine screening test in real health service settings.

VIA also offers the possibility of immediate treatment, referred to as the “see and treat” approach. In this approach women who are VIA positive are treated immediately with cryotherapy, without confirmatory tests such as colposcopy and histology. A concern with this approach is the possibility of high rates of overtreatment. The safety and efficacy of the approach was assessed in a randomized controlled trial in South Africa where 6555 women aged 35 to 65 years were screened using the HC2 test and VIA (Denny et al. 2005). Women were subsequently randomized to one of three groups: a group that received cryotherapy if the HC2 test was positive; a group that received cryotherapy if the VIA test was positive and a delayed

evaluation group (control group). At 6 months all women had a colposcopy assessment and women with biopsy confirmed CIN2 or worse lesions were treated. The prevalence of CIN2 or worse lesions at 6 months was lower in both see-and-treat groups compared to the control group (prevalence of 0.8% in the HC2 group, 2.2% in the VIA group and 3.6% in the control/delayed evaluation group). The see-and-treat approach using HC2 thus resulted in a 77% lower prevalence in CIN2 or worse lesions at 6 months, and the VIA a 37% lower prevalence when compared to the control group. However given the known low specificity, particularly of VIA, of the tests in detecting CIN2 or worse lesions it is likely that a fair proportion of women were unnecessarily treated with cryotherapy. The results of the VIA group in this study are in disagreement with those reported by the study in India where no reduction in advanced cervical cancer or cervical cancer mortality was observed after VIA (Sankaranarayanan et al. 2009), which could be due to a higher rate of treatment in the South African study.

Visual inspection with Lugol's iodine (VILI)

In this visual inspection method, Lugol's iodine is applied to the cervix and then examined for mustard-yellow areas. A pooled analysis of eleven studies that concurrently evaluated five cervical cancer screening tests including VILI and VIA showed that VILI had a higher pooled sensitivity than VIA in detecting CIN 2 or worse lesions (91% compared to 79%) with a similar pooled specificity (85%) (Arbyn et al. 2008b). There was wide inter-study variation of both VIA and VILI accuracy parameters, reflecting the subjective nature of these tests and the need for training and supervision.

The accuracy of the screening tests described above is summarized in Table 2.5.

Table 2.5: Range of sensitivity and specificity values for different screening methods in detecting CIN2 or worse lesions

Screening method	Sensitivity	Specificity
Conventional cytology	44% - 99%	91% - 98%
Liquid based cytology	57%*	97%*
HPV testing using hybrid capture 2	66% - 100%	61% - 96%
HPV testing using <i>careHPV</i>	90%	84%
Visual inspection with acetic acid	67% - 79%	49% - 86%
Visual inspection with Lugols iodine	74% - 98%	73% - 92%

*pooled value

Combined screening methods

As no current screening method has sufficient sensitivity and specificity to detect HSIL or worse lesions, combinations of tests are being investigated. Combinations can be applied in a single stage, such as LBC and HPV testing, or in sequential stages. Evidence suggests that screening women with both cytology and HPV tests increases sensitivity for detection of prevalent CIN3 or cancer (IARC 2005; Bulkman et al. 2007). HPV testing followed by triage with cytology for HPV test positives has been suggested as a rational approach for older women because of the higher sensitivity of HPV testing and the higher specificity of cytology (IARC 2005; Cuzick et al. 2006). For lower resource settings possible future combinations could include a rapid HPV test followed by VIA for HPV test positives (Cuzick et al. 2006; Cuzick et al. 2008).

Emerging technologies

Newer technologies with better sensitivity and specificity than existing tests are being investigated as screening tools. Technologies include: HPV typing, HPV mRNA, HPV viral load, HPV integration, methylation markers and cell proliferation markers (Cuzick et al. 2006). Prior to introduction into the health services, these tests will need to be clinically validated.

2.3.2 Experience with cytology-based cervical screening programmes

Cytology-based screening programmes are the mainstay of cervical screening programmes in developed countries. In most developed countries women have their first Pap smear soon after initiating sexual activity and subsequently once every one to five years, with a move toward less frequent screening intervals (three to five years).

Observational case-control and cohort studies have demonstrated the effectiveness of cytology screening in reducing the incidence and mortality of cervical cancer (IARC 2005). Cohort studies conducted in Canada, Finland, Iceland, Denmark, Norway and Sweden all showed a protective effect of cytology-based screening programmes. Relative risk estimates for invasive cancer ranged from 0.17 in the Canadian study to 0.77 in the Norwegian study (IARC 2005). Studies relating trends in incidence and mortality to cervical screening have also provided ecological evidence of the effectiveness of cytology based screening programmes. Mortality rates in the Nordic countries have declined since the introduction of organised cervical screening programmes in the 1960's. The greatest reduction was seen in Iceland (80% between 1965 and 1982), which had the widest target age range. Decline in mortality was related to population coverage, with greater declines seen in those Nordic countries that had higher coverage rates (Laara, Day & Hakama 1987). A review of mortality trends in the UK showed that since the introduction of the national screening programme the previous rising trend of cervical cancer mortality was reversed (Peto et al. 2004). Declines in cervical cancer incidence and mortality have also been seen in Europe, USA, Japan and Oceania and have been related to the introduction of cervical screening programmes (Sankaranarayanan, Budukh & Rajkumar 2001; IARC 2005). Organised screening programmes have shown a greater effect than opportunistic screening (Sankaranarayanan, Budukh & Rajkumar 2001; IARC 2005).

In most low-income countries, screening for cervical cancer is non-existent (Chirenje et al. 2001; Sankaranarayanan, Budukh & Rajkumar 2001; IARC 2005). Sub-Saharan Africa and India account for a substantial proportion of the global cervical cancer burden. However, South Africa is the only sub-Saharan African country that has a cervical screening policy and there is no national organised cervical screening programme in India. Many low-income countries do not have the resources and capacity to implement a sustainable cytology-based screening programme

and it has been suggested that low-income countries should rather focus on improving their capacity to diagnose and treat cervical cancer (Chirenje et al. 2001; Sankaranarayanan, Budukh & Rajkumar 2001). Screening technologies such as VIA and rapid HPV tests are being explored as alternatives for low-resources countries.

Cytology-based screening programmes have been introduced in some middle-income countries with mixed results. The Chilean programme is an example of a successful cytology-based screening programme in Latin America and offers instructive lessons for other middle-income countries. Annual Pap smear screening was introduced in the 1970's. However screening tended to focus on young women and the programme was poorly organised and managed (Sepulveda, Prado 2005; Salas 2006). The programme was re-organised in 1987 with the aim of screening 80% of women aged 25 to 64 years every 3 years. Screening was first implemented in a demonstration area and later expanded to the entire country. Key strategies included co-ordination at national, regional and community levels with a focus on increasing management capacity, monitoring Pap smear quality, implementing a quality assurance programme at cytology laboratories and timely diagnosis and treatment of abnormal Pap smears (Salas 2006). Pap smear coverage increased from 40% in 1990 to 66% in 1996 and 98% of women with abnormal Pap smears were followed-up. The ASMR rate decreased from 12.8% in 1980 to 6.8 per 100 000 women in 2001 (Sepulveda, Prado 2005; Salas 2006).

Puerto Rico established a cervical screening programme in the 1960s, offering Pap smears to women 15 years and older. A survey conducted in 2002 showed that 72% of women over the age of 18 years had had a Pap smear in the preceding 3 years (Murillo et al. 2008). A decrease in cervical cancer incidence and mortality rates over the last 30 years has been documented (Sankaranarayanan, Budukh & Rajkumar 2001; Arrossi, Sankaranarayanan & Parkin 2003). The ASIR decreased from 38 per 100 000 women during 1950 - 1954 to 19.9 per 100 000 women in 1990. During the same period the cervical cancer mortality rate decreased from 19.2 per 100 000 women to 5.2 per 100 000 women.

Since the 1970's Costa-Rica has had opportunistic screening mainly through family planning services. In 1995 a national cytology programme was introduced in which women 20 years and

older are offered Pap smears every 2 years (Murillo et al. 2008). Coverage has varied across regions in the country. A national survey in 2000 showed that the Pap smear coverage among women aged 18-44 years was low (37%). The incidence rate of cervical cancer in 2000 was 18.2 per 100 000 women and there had only been a 9% decline in incidence since the implementation of the national screening programme (Murillo et al. 2008). Mortality rates have remained unchanged (Sankaranarayanan, Budukh & Rajkumar 2001; Arrossi, Sankaranarayanan & Parkin 2003). Colombia has had a cervical screening programme since the 1970s. In the 1990s the programme focussed on screening women aged 25-69 years every 3 years. Although the mortality rates have remained unchanged, a decrease in incidence rate has been seen in Cali, Colombia (Aristizabal et al. 1984; Sankaranarayanan, Budukh & Rajkumar 2001).

Cytology based programmes have also been implemented in Cuba and Mexico. Cuba offers women 20 years and older Pap smears every 2 years and Mexico screens women aged 25-65 years annually. However there has been no reduction in cervical cancer incidence and/or mortality rates in either of these countries (Sankaranarayanan, Budukh & Rajkumar 2001; Arrossi, Sankaranarayanan & Parkin 2003). An evaluation of the programme in Mexico showed that there was low screening coverage (40% over a 3 year period), the quality of the cytology services was sub-optimal, there was poor co-ordination of the programme and the country had insufficient resources to conduct annual Pap smears (Hernandez-Avila et al. 1998; Sankaranarayanan, Budukh & Rajkumar 2001; Flores et al. 2003). In Cuba cytology quality and follow-up of clients with abnormal Pap smears, both important aspects of a screening programme, is reported to be good, however, coverage is low (54% in 1993/1994). A review of cervical cancer screening programmes in Latin America and the Caribbean identified a number of issues that need to be addressed to improve the impact of cytology-based programmes. These include follow-up of screened positives, quality of Pap smears, participation rates, monitoring and evaluation systems (Murillo et al. 2008).

Malaysia, a middle-income country with a significant burden of cervical cancer, has offered free Pap smears to women aged 20-65 years every 3 years since 1995. Barriers to programme implementation in Malaysia include, poor co-ordination, long waiting times for Pap smears, absence of a call-recall system and poor access in rural areas (Othman, Rebolj 2009). The

coverage rate remains low at 47%. A pilot project that addresses these challenges has been initiated in two districts in Malaysia and the impact of this are expected in 2010/2011.

The key elements of a successful cytology-based screening programme include: a policy on the target age and frequency of smears, trained staff (smear takers, cytotechnologist, pathologists, colposcopists and programme managers), a good laboratory infrastructure with quality assurance mechanisms, transport systems to get smears to the laboratory, a system for communicating the results to women, a mechanism to ensure all women with abnormal smears are followed-up and treated, high population coverage and a system to monitor and evaluate the performance of the programme.

2.3.3 Summary of challenges in implementing cytology-based screening programmes in middle-income countries

Key challenges to implementation of cytology-based screening programmes in middle-income countries have been identified and include: competing health priorities, lack of organisation, poor coverage, poor access to services particularly for rural women, limited cytology laboratory capacity and quality, poorly developed health infrastructure, limited human and financial resources, inadequate staff training, loss to follow-up of women with abnormal smears and inadequate monitoring and evaluation systems (Chirenje et al. 2001; Sankaranarayanan, Budukh & Rajkumar 2001; World Health Organization 2002; Murillo et al. 2008; Othman, Rebolj 2009). Cognisant of the resource and organisational constraints in developing countries, experts have suggested prioritising high coverage among older women, ensuring that those with detected abnormalities return for follow-up and treatment and reducing screening frequency (World Health Organization 2002; IARC 2005). Models developed by IARC suggest that screening women of an appropriate age once in a lifetime may reduce the incidence of cervical cancer by 30% and screening women once every 10 years from age 30 on can theoretically reduce disease rates by 64% (IARC Working Group on Cervical Cancer Screening 1986). There has been some criticism of these IARC models as they are based on high coverage and optimal follow-up and treatment, conditions not very likely in developing countries. However a re-evaluation of the models to include the effect of lower coverage still indicate that when resources are limited, the

highest priority group for screening are those aged 35 or over, and that screening every 5 years will achieve a major impact (World Health Organization 2002).

Research on ways to improve programme efficiency is recognised as a high priority (World Health Organization 2002). It has been recommended that middle-income countries with inefficient cytology-based screening programmes should reorganise their programmes based on experiences and lessons learnt elsewhere, whilst those without any cervical screening programmes should consider implementation in a limited geographical regions before expanding nationally (Sankaranarayanan, Budukh & Rajkumar 2001; Murillo et al. 2008). Experience from other middle-income countries suggests that the following elements of a cytology based-screening programme need particular attention: consistent cytology reporting systems, standardised management guidelines, referral and feedback systems for clients with abnormalities and staff training to improve competency (Lazcano-Ponce et al. 1999; IARC 2005).

2.4 Primary prevention through HPV vaccination

2.4.1 Features of current vaccines

The recognition that HR-HPV is a necessary cause of cervical cancer paved the way for the development of HPV vaccines against cervical cancer. Currently two vaccines are available: a quadrivalent vaccine, containing virus-like particles (VLP) related to HPV types 6,11, 16 and 18 and a bivalent vaccine containing VLPs related to HPV types 16 and 18 (Harper et al. 2006; FUTURE II Study Group 2007). Both vaccines offer protection against the two HPV types responsible for the majority of cervical cancer lesions, with the quadrivalent vaccine offering additional protection against two types associated with genital warts. The vaccines are prepared from empty protein shells and produced by recombinant technology (Schiller et al. 2008). They do not contain any live biological material and so are non-infectious. Both vaccines are designed to be prophylactic, not therapeutic. The vaccines must be refrigerated and are given as a series of three 0.5 ml intramuscular injections. The key characteristics of both vaccines are described in Table 2.6.

Table 2.6: Key characteristics of HPV vaccines

	Quadrivalent vaccine	Bivalent vaccine
Manufacturer and trade name	Merck (Gardasil®)	GlaxoSmithKline (Cervarix™)
Virus-like particles (VLPs) of types	6, 11, 16, 18	16, 18
Substrate	Yeast (<i>S. Cerevisiae</i>)	Baculovirus expression system
Adjuvant	225µg aluminium hydroxyphosphate sulphate	500 µg aluminium hydroxide, 50 µg 3-deacylated monophosphoryl lipid A
Injection schedule	0, 2, 6 months	0, 1, 6 months

Source: (World Health Organization 2007)

The efficacy of the vaccines has been tested in randomized controlled trials that have been conducted in Europe, North America, Latin America and in the Asia-Pacific region (Harper et al. 2006; FUTURE II Study Group 2007). None of the trials have been conducted in Africa. Phase II efficacy trials have focused on HPV infection endpoint and the phase III studies on disease endpoints. These trials include a number of different types of analysis: the according-to- protocol (ATP) analysis includes only the ideal participants who adhere to all aspects of the protocol, the intention-to-treat (ITT) includes all participants who participate in the trial where participation is defined as receiving at least the first vaccine dose and the modified- intention- to-treat (MITT) analysis excludes participants who violate some aspects of the trial protocol.

The efficacy of the bivalent vaccine in preventing HPV infection was assessed in a randomised controlled trial that included 776 women with a median age of 23 years who were followed up for 4.5 years (Harper et al. 2006). In the ATP analysis the incidence rate of HPV16/18 was 0.2 per 100 person-years in the vaccinated group compared to 5.6 per 100 person years in the placebo group, with a vaccine efficacy of 96.9% (95% CI 81.3% - 99.9%) in preventing incident HPV 16/18 infections.

In an interim analysis of a phase III double-blind, randomised controlled trial of the bivalent vaccine, 18 644 women aged 15 - 25 years were followed up for a mean of 14.8 months since the first vaccine dose to determine vaccine efficacy in preventing CIN lesions (Paavonen et al. 2007). A modified- intention- to- treat (MITT) analysis showed that in total 23 women developed CIN 2 or worse lesions with HPV16 or 18 detected in the lesion; 2 in the vaccinated group and 21 in the placebo group (incidence rate of 0.02 and 0.22 per 100 person-years in the placebo and vaccinated group respectively). For the endpoint CIN2 or worse the vaccine efficacy was 90.4% (CI 53% - 99%).

The efficacy of the quadrivalent vaccine in preventing incident HPV infection was assessed in a randomised controlled trial where 277 women received the quadrivalent vaccine (median age 20.2 years) and 275 women received a placebo (median age 20.0 years). After 30 months the incidence rate of HPV infection with types 6, 11, 16 or 18 (types covered by the vaccine) was 0.7 per 100 women-years in the vaccine group and 6.5 per 100 women years in the placebo group (ATP analysis). Vaccine efficacy was 89% (95% CI 70% - 97%) (Villa et al. 2005).

A combined analysis of the four phase III randomized controlled trials of the quadrivalent vaccine included 20 583 women aged 16 -26 years who were followed up for a mean of 3 years after their first vaccine dose (FUTURE II Study Group 2007). A total of 86 CIN2 or worse lesions with HPV17 or 18 present in the lesion were detected; 1 in the vaccinated group (incidence rate < 0.1 per 100 person-years) and 85 in the placebo group (incidence rate 0.4 per 100 person-years. In women who were HPV16/18 naive ATP vaccine efficacy for the endpoint CIN 2/3 was 99% (95% CI 93% -100%). In the ITT analysis, which included women who were HPV16/18 naive or HPV16/18-infected at day 1, efficacy was 44% (95% CI 31% -55%).

Both vaccines induced high serum antibody levels in almost all vaccinated individuals at levels 10 to 104 times higher than those seen in natural infections (Harper et al. 2004; Harper et al. 2006; Villa et al. 2006). Younger individuals produced higher antibody levels than older participants.

The endpoint of CIN 2 or worse has been widely accepted as a proxy for cervical cancer that can be studied ethically. In children or young adolescents however, it is not practical to study this endpoint, since cervical specimens would be required, and the endpoint is rare in young people. Bridging studies are therefore conducted, in which the antibody responses of young people are compared with those of women for whom data on the clinical endpoint CIN2/3 is available. Bridging studies have shown that the antibody titres were approximately two-fold (Schiller et al. 2008) higher in boys and girls compared to women (Block et al. 2006; Pedersen et al. 2007; Schiller et al. 2008). The potential benefit of vaccinating males include direct protection against HPV-related warts and indirect protection for women from cervical cancer by reducing transmission of HPV.

Both vaccines have shown cross-protection against HPV types not specifically included in the vaccine. The bivalent vaccine has shown protection against incident HPV45 and 31 (Paavonen et al. 2007), types seen commonly in Africa (Clifford et al. 2006). Unpublished reports indicate that the quadrivalent vaccine is able to produce antibodies to HPV45 and 31 (Smith et al. 2006). Further studies are needed to assess whether administration of the vaccine will reduce CIN caused by HPV types not found in the vaccine.

In the HPV vaccine trials adverse events at the injection site (pain, erythema and oedema) occurred more frequently in vaccine recipients than controls, but the incidence of serious adverse events was not significantly higher among vaccine recipients in any of the trials (Cutts et al. 2007; World Health Organization 2007; Schiller et al. 2008).

In high income countries cohort models have been used to estimate cost-effectiveness of HPV vaccines and found that, in a setting of existing cervical cancer screening, the addition of an HPV vaccine has the potential to be a cost-effective use of health care resources, using cost per life year gained and cost per quality adjusted life year gained as effectiveness measures (Kulasingam, Myers 2003; Sanders, Taira 2003; Brisson et al. 2007; Jit, Choi & Edmunds 2008). A recent study in South Africa showed that adding the HPV vaccine to the current cervical cancer screening strategy in the country is cost-effective (Sinanovic et al. 2009). In low- and middle-income countries, however, whilst potentially cost-effective, HPV vaccines may be unaffordable

at the current market price of US \$120 per dose (Goldie et al. 2007; Goldie et al. 2008; Tangcharoensathien, Limwattananon & Chaugwon 2008; Sinanovic et al. 2009).

The magnitude of benefit from HPV vaccination in a country will depend on the burden of HPV disease attributable to the types contained in the vaccine, vaccine efficacy, duration of protection and vaccine coverage. Theoretical models have estimates of the likely impact given different scenarios. For example, with a vaccine efficacy of 95% and 80% coverage a vaccine containing HPV 16 and 18 will theoretically reduce cervical cancer incidence by 54% (Bosch 2003). Results of dynamic simulation models that considered the benefits of herd immunity, suggest that, if high coverage of females can be achieved, little additional reduction in cervical cancer is gained by vaccinating males (Garnett et al. 2006; Kim, Goldie 2009).

Although protection against HPV16/18 infection and CIN lesions has been demonstrated in the randomised controlled trials discussed above, the question of long term protection remains and will only be answered in years to come when results from ongoing long-term studies become available. Several other questions on the effectiveness of the vaccine remain. These include: questions on the need for a booster vaccine, cross-protection, the minimum number of doses needed, efficacy with different dosing schedules, the minimum age of vaccination, efficacy if combined with other vaccines, vaccine efficacy in males and efficacy in immune-compromised individuals. Studies either underway or in the preparatory stage include a trial of two versus three doses, studies in HIV positive individuals, efficacy studies in young men and older women and the development of polyvalent vaccines. At a population level HPV vaccines will reduce not eliminate cervical cancer and screening programmes will need to continue.

2.4.2 Experience in introducing HPV vaccine in developed countries

Over the past few years a number of studies have been conducted on HPV vaccine acceptability issues, focussing on knowledge and attitudes towards cervical cancer, HPV and HPV vaccination in relation to uptake and potential opposition to the vaccine (Pitts, Clarke 2002; Giles, Garland 2006; Moreira et al. 2006; Noakes, Yarwood & Salisbury 2006; Zimet et al. 2006; Mosavel, El-Shaarawi 2007; Ogilvie et al. 2007; Rosenthal et al. 2007; Vanslyke et al. 2008; Zimet, Shew & Kahn 2008). A number of studies conducted prior to the registration of the HPV vaccine and

primarily in developed countries, found that most parents and potential recipients had limited knowledge about cervical cancer, HPV and the importance of regular screening measures. However, despite poor levels of knowledge, health care providers were willing to recommend HPV vaccination and parents were interested in having their children vaccinated. Most studies concluded that information and knowledge about HPV, cervical cancer and the importance of regular screening need to be improved so as to promote informed decision making with regards to HPV vaccination (Mosavel, El-Shaarawi 2007; Vanslyke et al. 2008).

The vaccines are currently licensed for use in more than 100 countries. Some developed countries have introduced HPV vaccination programmes in the public sector. A national programme vaccinating schoolgirls aged 12- to 13 years began in the United Kingdom in September 2008. An evaluation of vaccine coverage and acceptability has shown encouraging results (Brabin et al. 2008). Vaccine uptake was 70.6% for the first dose and 68.5% for the second dose. Results for uptake of the 3rd dose have not been published as yet. Generally acceptability was good and no serious adverse events were reported. Eight percent of the parents refused vaccination with the main reason being insufficient information about the vaccine and its long term safety. Vaccine uptake was significantly lower in schools with a higher proportion of ethnic minority girls. Challenges in delivery included integrating the programme into the school academic calendar and arranging for alternate appointments for girls that missed their original scheduled appointments. A national school based vaccination programme was also introduced in Australia in April 2008 for girls aged 11 to 12 (Garland et al. 2008a; Shefer et al. 2008). After the first year of the school-based programme, compliance through dose 3 was estimated to be 80%. Some provinces in Canada have introduced publicly funded school-based HPV immunisation programmes (Shefer et al. 2008). The United States does not have a national programme, but the Advisory Committee on Immunization Practices advises that all adolescent females receive 3 doses of the HPV vaccine. Since 2006, CDC has conducted a population-based survey, the National Immunization Survey-Teen (NIS-Teen), to estimate vaccination coverage among adolescents aged 13 -17 years. In 2009 27% of adolescent girls had received 3 doses of the HPV vaccine (Centre for Disease Control 2010).

Experience from these countries indicate that important issues to address include establishing national guidelines and recommendations, providing information about the HPV vaccine to the public, identifying delivery options, establishing an infrastructure for vaccine delivery and a system to monitor vaccine implementation. Even in high-resource countries there are challenges to a school-based vaccine delivery such as synchronisation of vaccination schedule with the school calendar, obtaining parental consent and vaccinating those that have missed a dose.

2.4.3 Issues for introduction in developing countries

Developing countries bear the burden of cervical cancer and women in developing countries have the greatest need for primary prevention through HPV vaccination. Although the HPV vaccine has been licensed for use in many developing countries, no government sponsored HPV vaccination programmes exist in these countries. Experience with introduction of other vaccines such as the Hepatitis B vaccine indicate that people in developing countries wait decades before a new vaccine is available in the public sector (Kane, Brooks 2002). Currently HPV vaccines are available in the private sector and as part of research projects in developing countries. In 2006 projects were initiated in India, Peru, Vietnam and Uganda by PATH, an international non-profit organisation, to explore strategies for HPV vaccine delivery in middle and low income countries. Formative research showed that although knowledge of the HPV vaccine and of cervical cancer was low, the vaccine was acceptable to communities (PATH 2009). Project evaluation results are anticipated in 2010/2011 (PATH 2009). The sustainability of such pilot projects is likely to be a huge challenge once the research period or period of vaccination donations comes to an end.

A major barrier to introduction in developing countries is the high cost of the vaccine. Unless HPV vaccines are made available at a significantly reduced price, it is extremely unlikely that they will become available to women in middle and low income countries. The Global Alliance for Vaccines and Immunization (GAVI) was established in 1999 and provides financial assistance to the 75 poorest developing countries for development of infrastructure and introduction of new vaccines (Kaddar, Lydon & Levine 2004). GAVI has indicated that it will make HPV vaccine provision a priority. However middle-income countries, such as South Africa are not eligible for GAVI support and will need to find alternative ways to fund an HPV vaccination programme. In addition to the cost of the vaccine, delivery costs will also need to be

considered. In making the decision of whether to introduce the HPV vaccine countries also need to consider the issue of competing health priorities including introduction of other vaccines such as the rotavirus and pneumococcal vaccines (Andrus et al. 2008).

Rumours and myths have negatively impacted on delivery of other vaccines such as tetanus vaccine in Mexico, Philippines and Uganda, and the polio vaccines in Nigeria and India (Aylward, Heymann 2005; Kane et al. 2006). HPV vaccine is associated with a sexually transmitted infection and targets primarily females and could be seen as a conspiracy to sterilise young women (Kane et al. 2006). Acceptability may also be questioned by those who feel the HPV vaccine will promote sexual promiscuity (Zimet, Shew & Kahn 2008).

Delivery of vaccines to adolescents is a challenge (Biddlecom, Bankole & Patterson 2006; Kane et al. 2006). In developing countries vaccines are usually delivered through the Expanded Programme on Immunization (EPI) (World Health Organization 2005). It is estimated that EPI has high coverage and that 75% of children worldwide receive basic immunisation (Kane et al. 2006). However there is wide variation in coverage in developing countries, particularly in Africa. The EPI primarily targets infants and success with immunizing adolescents for example with tetanus vaccine has been mixed (Kane et al. 2006). There are few adolescent health programmes in developing countries, but where these exist they could potentially serve as another entry point for HPV vaccines (Pollack et al. 2007). Sexual and reproductive health programmes are responsible for cervical cancer screening and will need to be involved in HPV immunisation as part of comprehensive strategies to prevent cervical cancer. School-based delivery strategies have been used in developed countries. However in many developing countries poor school enrolment rates are likely to limit the success of this strategy (Hewett, Lloyd 2005; Biddlecom, Bankole & Patterson 2006). It has been suggested that in such countries annual door-to door immunisation campaigns may be more successful (Pollack et al. 2007). Several challenges exist to the introduction of the HPV vaccine and limited formative research is available to guide vaccine introduction in developing countries (Harries et al. 2009).

In summary, two prophylactic HPV vaccines are currently available and offer potential for primary prevention of cervical cancer. Questions on the long-term efficacy, vaccine efficacy in

HIV positive individuals and cross-protection against other HPV types are currently unanswered and are particularly relevant in the South African setting. The high cost of the vaccine is a major barrier to its introduction in developing countries. Formative research to guide introduction of the vaccine in developing countries is lacking.

2.5 HIV and cervical cancer

2.5.1 HIV and HPV infection

Women infected with HIV have a higher prevalence of HPV and are at a greater risk of developing cervical SILs compared to HIV negative women (Wright et al. 1994; Sun et al. 1997; La Ruche et al. 1998; Minkoff et al. 1998; Massad et al. 1999; Palefsky et al. 1999; Ellerbrock et al. 2000; Duerr et al. 2001; Jamieson et al. 2002; Hawes et al. 2003; Schuman et al. 2003; Harris et al. 2005; Rowhani-Rahbar et al. 2007; Massad et al. 2008). The increase in HPV prevalence could be due to reactivation of latent infection or new incident infections (Strickler et al. 2005). Several mechanisms may explain the association between HIV and HPV-related disease (Palefsky 2006). HIV decreases cell-mediated immunity which plays a critical role in the control of HPV infection. HIV diminishes local immune response at the tissue level and this might result in increased HPV infection. In addition there might be a direct interaction between the 2 viruses, with HIV interacting with HPV at a molecular level, leading to an increased expression of the HPV E6 and E7 oncogenes (Palefsky 2006).

A meta-analysis of 20 studies from North America, Europe, Africa, Asia and South/Central America found that the highest HPV prevalence was in HIV positive women from Africa (Clifford et al. 2006). The highest HPV prevalence worldwide has been reported in Zambia. Among 145 HIV-infected women attending HIV/AIDS treatment at a tertiary level care facility, the prevalence of HPV was 97.2% for any HPV and 90.3% for HR-HPV (Sahasrabuddhe et al. 2007). Women in this study were severely immunocompromised (median CD4 count 165/uL). HR-HPV was detected in 68% of HIV-infected women recruited from a tertiary colposcopy clinic and a primary health care clinic in Cape Town, South Africa (Denny et al. 2008). Factors

associated with a high HPV prevalence include a high HIV viral load and a low CD4 count (Minkoff et al. 1998; Palefsky et al. 1999; Jamieson et al. 2002; Hawes et al. 2003).

A number of studies in developed countries have shown an increase in the prevalence of HPV infection in HIV positive compared to HIV negative women. The Women's Interagency HIV study (WIHS) is a prospective cohort study of 2056 HIV-positive and 569 HIV-negative women at six sites around the United States that was set up to characterise the natural history and pathogenesis of HIV infection and its complications in HIV-positive women when compared with a group of age and risk-matched HIV-negative control subjects (Palefsky et al. 1999). The prevalence for any HPV infection was 63% among HIV positive women compared to 30% among HIV negative women, and that for HR-HPV 13.6% and 3.0% respectively. Another multisite prospective study in the United States, the HIV Epidemiology Research (HER) Study, was established to define the effects of HIV on the health of women and has reported similar results. HIV positive women participating in the HER study had a higher prevalence of any HPV compared to HIV negative women (63.7% vs. 27.4%), and a high prevalence of HR-HPV (19.1% vs. 7.7%) (Jamieson et al. 2002). In a study conducted among HIV positive and HIV negative women living in the New York City area HPV DNA was detected in 56% of HIV positive women and 31% of HIV-negative women (Sun et al. 1997). In Brooklyn the prevalence for any HPV was 73% among HIV positive women compared to 43% among HIV negative women (Minkoff et al. 1998). Ahdieh et al (2000) reported an HPV prevalence of 69.6% among HIV positive women and 26.2% among HIV negative women, with a HR-HPV prevalence of 23.4% and 8.3% respectively. As can be seen findings from the studies above are remarkably consistent. In HIV positive women the relative risk for high risk HPV is greater than that for all HPV.

Fewer studies comparing the HPV prevalence in HIV positive and HIV negative women have been conducted in developing countries, but results are similar to that seen in developed countries. La Ruche et al. (1998) reported an HPV prevalence of 59.5% among HIV positive women compared to 24.1% in HIV negative women in Abidjan. In a study in Dakar the prevalence for any HPV was 69.1% among women with HIV-1, 61.8% among women with

HIV-2 and 25.3% in HIV negative women, with a HR-HPV prevalence of 53.6%, 41.2% and 15% respectively (Hawes et al. 2003).

Similar to HIV negative women, considerable variation in regional HPV type distribution has been reported in HIV positive women (Clifford et al. 2005; Clifford et al. 2006). Among HIV positive women with normal cytology HPV16 is the most common HR-HPV type seen, with types 31 and 35 also high in Africa. HPV16 is the commonest type seen in all HIV positive women with HSIL, but HPV16 was proportionately less prevalent in HIV positive women with HSIL compared to HIV negative women with HSIL (Clifford et al. 2006). A shift towards HPV types other than HPV16 in HIV positive women with HSIL when compared to HPV negative women with HSIL has been documented. These types include the HR-HPV types 18, 51, 52 and 58 and low-risk types 11, 53 and 61. Studies have documented a higher rate of multiple concurrent HPV types in HIV positive compared to HIV negative women, not only with HR types but also with types with little potential to cause cytological abnormalities in immunocompetent women (Ellerbrock et al. 2000; Duerr et al. 2001; Clifford et al. 2006; Rowhani-Rahbar et al. 2007). It is not clear to what extent the low-risk types are benign infections in the presence of another type or whether they have the potential to induce HSIL in immunocompromised women. In a study in Cape Town the commonest HPV types seen in HIV positive women with HSIL were HPV 16 (26%), 52 (22%) and 53 (20%) (Denny et al. 2008), whereas in a study in Johannesburg the commonest HPV types in women with HSIL were HPV 16 (42%), 56 (22%) and 66 (17%) (Firnhaber et al. 2010). HPV16 and /or HPV18 were present in 44% of women with HSIL in the Cape Town study and 42% of women in the Johannesburg study. Limited information is available on HPV types in HIV positive women with ICC (Clifford et al. 2006). In Zambia among 28 women with cervical cancer the commonest HPV types seen in descending order were HPV52 (46.4%), HPV58 (35.7%), HPV16 (35.7%), HPV35 (28.6%) and HPV31 (25.0%) (Sahasrabudde et al. 2007).

Studies have shown that HPV viral load may predict the risk of cervical abnormalities in HIV positive women (Heard et al. 2000; Lillo et al. 2005; Lillo, Uberti-Foppa 2006). High HPV viral load has been associated with histological severity and lesions size (Lillo, Uberti-Foppa 2006). Information on HPV viral load among South African women is lacking.

Persistent HPV infection is a prerequisite for cervical abnormalities. HIV positive women have been shown to have a higher rate of persistent HPV infections compared to HIV negative women. Sun et al (1997) reported persistent HPV infections (defined in the study as the detection of the same type of HPV at two or more examinations during a period of 3 to 12 months) in 24% of HIV positive women compared to 4% of HIV negative women. Koshiol et al. (2006) also reported an association between HIV positivity and duration of HPV infection and found that the time to clearance was longest for HPV16

Further information on the prevalence of HPV in different stages of the HIV epidemic in South Africa will help in estimating the impact of the HIV epidemic on cervical cancer and its precursors.

2.5.2 HIV and cervical cancer precursor lesions

HIV positive women are at a significantly higher risk of cervical abnormalities compared to HIV negative women. In the WIH study the prevalence of cervical abnormalities was 38.3% among HIV positive women compared to 16.2% among HIV negative women (Massad et al. 1999). HIV positive women were at a significantly higher risk of LSIL (OR 8.9, 95% CI 4.8 -16.4) and for HSIL (OR 2.7, 95% CI 1.1 - 6.3) compared to HIV negative women. The prevalence of abnormalities among HIV positive women in this cohort has remained above 25% since the start of the study in 1994, with the majority of lesions being low-grade (Massad et al. 2008). In a European cohort study on the natural history of HIV infection 24.2% of HIV positive women had an abnormal Pap smear at baseline (Delmas et al. 2000). In the HER study SILs (both LSIL and HSIL) were detected in 18.8% of HIV positive women and 5.3% of HIV negative women (prevalence ratio 3.9, 95% CI 2.4 - 6.2) (Duerr et al. 2001).

A number of studies have reported on the prevalence of abnormalities in HIV positive women in Africa and have detected high rates of cervical abnormalities. The prevalence of cervical abnormalities among HIV positive sex workers in Zaire was 27% (Laga et al. 1992) and 26% among sex workers in Kenya (Kreiss et al. 1992). A cervical abnormality prevalence of 26 % was documented among HIV positive family planning attendants in Zimbabwe (Chirenje et al.

2002). One of the highest rates of cervical abnormalities recorded in any population was reported in severely immune-compromised women attending a tertiary hospital in Zambia (93.3%) (Parham et al. 2006). In South Africa the prevalence of cervical abnormality in HIV positive women was 55% in a study conducted in Cape Town and 50% in a study in Johannesburg (Denny et al. 2008; Firnhaber et al. 2010).

The only study in Africa comparing the prevalence of cervical abnormalities in HIV positive and HIV negative women was conducted in Senegal among women with HIV-1 infection attending an outpatient infectious-disease clinic (Hawes et al. 2003). The prevalence of cervical abnormalities was 37% in HIV positive women compared to a prevalence of 16% among HIV negative women. Women with HIV-1 were at a significantly higher risk of HSIL compared to HIV negative women with an adjusted odds ratio of 3.7 (95% CI 1.9 - 7.4).

A number of studies have shown that among women with HIV, higher HIV plasma RNA loads and lower CD4 counts are associated with increasing degree of cervical abnormality (Massad et al. 1999; Hawes et al. 2003; Harris et al. 2005; Denny et al. 2008). Rates of abnormality in women with CD4 cell counts > 500cells/uL are similar to rates seen in HIV negative women. HIV positive women have higher progression and lower regression rates of cervical lesions compared to HIV negative women (Strickler et al. 2005). These rates need to be considered in developing cervical cancer screening policies for HIV positive women.

2.5.3 HIV and invasive cervical cancer

Studies have produced inconsistent results on the association between HIV and ICC (Sitas et al. 1997; La Ruche et al. 1998; Sitas et al. 2000; Gichangi et al. 2003; Massad et al. 2004; Mbulaiteye et al. 2006; Massad et al. 2008; Stein et al. 2008; Adjorlolo-Johnson et al. 2010). In a cross-sectional study conducted in Abidjan 2 198 women attending outpatient gynaecology clinics were screened for cervical lesions and HIV infection (La Ruche et al. 1998). A significant association was seen between HIV infection and HSIL (OR 5.8, 95% CI 3.6 to 9.6) but no association was seen between invasive cervical cancer and HIV. Of the 18 women with invasive cervical cancer, 14 were HIV negative and 2 HIV-1 positive and 2 HIV-2 positive. A hospital based case-control study conducted in Johannesburg, South Africa between 1992 and

1995 found no association between invasive cervical cancer and HIV (OR 0.6, 95% CI 0.2 - 1.9 (Sitas et al. 1997)). However, data from an ongoing case-control study in a similar setting that commenced in 1995 showed an increased risk of cervical cancer, OR 1.6, 95% CI 1.1 - 2.3 among HIV positive women for the period 1992 to 1999 (Sitas et al. 2000). The most recently analysed data from this study, for the period 1995 to 2004, also reported an increased risk of cervical cancer in HIV positive women (OR of 1.6, 95% CI 1.3 - 2.0) (Stein et al. 2008). A similar increased risk of invasive cervical cancer among HIV positive women was reported in a case-control study conducted in Kenya (OR 2.0, 95% CI 1.1 - 3.5) (Gichangi et al. 2003) and in Uganda (OR 2.4 95% CI 1.1 - 4.4) (Mbulaiteye et al. 2006). In the WIH study, 462 HIV negative and 1661 HIV positive women were followed up between 1994 and 2001 and no association between HIV and ICC was documented (Massad et al. 2004). No cases of ICC were observed in HIV negative women and 1 case of ICC was observed among HIV positive women (IR 1.2 /10 000 women-years). The low ICC rates in the WIH study could be a result of the intensive screening programme in which all study participants are screened with Pap smears every 6 months. The disparate results on the association between HIV and invasive cervical cancer in the studies described above may be due to variations in the competing causes of mortality, stage of the HIV epidemic at the time the study was conducted and efficacy of cervical cancer screening programmes in different settings. A recent study conducted among HPV positive women in Côte d'Ivoire reported an association between HIV infection and cervical cancer (OR 3.4, 95% CI 1.1 - 10.8) (Adjorlolo-Johnson et al. 2010).

Two studies conducted in South Africa have shown that mean age of HIV positive women with ICC is 10 to 15 years lower than that of HIV negative women (Lomalisa, Smith & Guidozi 2000; Moodley, Moodley & Kleinschmidt 2001).

2.5.4 The impact of HAART on cervical lesions

HAART decreases HIV viral loads, increases CD4 cell counts and decreases most opportunistic infections (Hogg et al. 1998; Palella et al. 1998). Since the introduction of HAART there has been a decline in certain malignancies in HIV infected individuals (Jacobson et al. 1999; Ledergerber, Telenti & Egger 1999). HAART has the potential to influence the relationship between HIV and cervical cancer in contrasting ways. Firstly, by prolonging life HAART

lengthens exposure to HPV infection thereby increasing the likelihood of cervical SILs and cervical cancer. Conversely, because HAART restores immune-competence, it may reduce the risk of cervical SILs and cancer. However, it has also been suggested, that once a particular level of cervical disease is reached immune re-constitution may be of limited value (Palefsky 2003; Palefsky 2006). Non-immune factors such as chromosomal instability and genetic changes caused by HPV DNA integration with the host cell genome are thought to be important in progression of disease at this stage.

Studies on the impact of HAART of cervical SILS are complicated. It is unethical to randomize women to HAART. Most studies have compared women on HAART to those not on HAART or compared women before and after HAART initiation. However HAART is only initiated once the CD4 cell count falls below a certain level (usually < 350/uL in developed countries), so women on HAART usually have more advanced disease a priori. Studies on the impact of ARVs on the natural history of cervical SILs have produced mixed results, with some studies showing benefit (Heard et al. 1998; Minkoff et al. 2001; Heard et al. 2002; Ahdieh-Grant et al. 2004) and others no or limited effect (Orlando et al. 1999; Lillo et al. 2001; Moore et al. 2002; Heard, Palefsky & Kazatchkine 2004; Heard, Potard & Costagliola 2006). Recent results from a prospective cohort of HIV positive women in Soweto, South Africa, showed that HAART was associated with 28% decrease in risk of progression from a normal/ LSIL Pap to HSIL (adjusted hazards ratio 0.72, 95% CI 0.52 - 0.99). However HAART had no impact on regression (Omar et al. 2011). HAART has not resulted in the clearance of cervical HPV (Heard, Palefsky & Kazatchkine 2004). In studies showing increased regression rates or decreased progression rates among HAART users, the benefit has been modest and the majority of women initiating HAART did not regress to normal (Ahdieh-Grant et al. 2004; Heard, Palefsky & Kazatchkine 2004; Heard, Potard & Costagliola 2006; Omar et al. 2011). A review of cancer incidence data from 23 prospective studies in North America, Europe and Australia has shown that since the introduction of HAART there has been no reduction in the incidence of cervical cancer (International Collaboration on HIV and Cancer 2000). However, the attributable effect due to a reduction in those with HIV is likely to be small as the numbers of HIV positives are very small

in relation to the population of women at large. The implications of all of these findings are that women on HAART will still need rigorous screening and close-follow-up.

2.5.5 Prevention of cervical cancer in HIV positive women

The efficacy and safety of the current HPV vaccines in HIV infected individuals is as yet unknown. The current bivalent and quadrivalent vaccines are prophylactic, hence they are likely to have limited benefit in HIV positive women as many will already be infected with HPV. Both HIV and HPV are sexually transmitted and a successful HPV vaccination programme before sexual debut is likely to help in preventing cervical lesions in women infected with both HIV and HPV.

There are no data specifically on the efficacy of screening in HIV positive women. A number of studies have assessed the accuracy of cytology in HIV positive women. Some studies have found that the accuracy of cytology was no different in HIV positive and negative women (Boardman et al. 1994; Korn et al. 1994). Others have reported a higher false negative rate in HIV positive women compared to HIV negative women (Maiman et al. 1991; Fink et al. 1994; Goodman et al. 2000). For example Goodman, et al.(2000), in a cross-sectional study, reported a false negative rate of 37% in the HIV positive compared to a rate of 21% in the HIV negative group. Where colposcopy services are not readily available, more frequent cytology screening has been suggested for HIV positive women, although with little supporting evidence (IARC 2005). The CDC and US Public Health service recommended that HIV positive women be screened for SILs more frequently than HIV negative women (Centers for Disease Control (CDC) 1997).

Following the initial diagnosis of HIV infection, it is recommended that women have 2 Pap smears 6 months apart, if both these are negative then annual Pap smears are recommended. These recommendations are not feasible in developing countries, where both HIV and cervical cancer are common, and resources are limited.

A study in Zimbabwe evaluated accuracy of the HC2 test in detecting HSIL in a population at high risk for HIV. The sensitivity and specificity of the HPV test for HSIL were, respectively, 90.7% (95% CI 77.9% - 97.4%) and 41.3% (95% CI 34.5% - 48.3%) in HIV positive women and

61.5% (95% CI 31.6% -86.1%) and 74.5% (95% CI 68.0% - 80.3%), respectively, in HIV negative women (Womack et al. 2000). Denny, et al. evaluated the performance of VIA in detecting SILs lesions and reported no difference in sensitivity, but a lower specificity among HIV positive women compared with HIV negative women (Denny et al. 2002). The low specificity observed in the studies above limit the use of VIA and HC2 as a screening test for HSIL in HIV positive women.

In summary research has shown that HIV positive women have a higher incidence and prevalence of HPV and are infected with a broader range of HPV types than HIV negative women. Further studies are needed to better understand the impact of HAART on the natural history of cervical cancer. In South Africa there is limited information on HPV related cervical disease in HIV positive women. Data on the risk of HPV-related cervical disease, HPV prevalence, types and viral load will assist in planning comprehensive cervical cancer preventive strategies, by permitting estimation of the likely impact of current and future HPV vaccines and the expected burden of cervical precursors and cervical cancer among HIV positive women

2.6 Summary

This review shows that cervical cancer is an important public health problem in developing countries. In South Africa, it remains an important cause of morbidity and mortality, underscoring the need for a comprehensive prevention strategy. The natural history of cervical cancer is known and provides a scientific basis for decisions regarding preventive strategies. Epidemiological evidence suggests that in resource-constrained countries, such as South Africa, screening programs be directed at women in their thirties with the aim of identifying and treating women with HSILs. Secondary prevention through organised cytology-based screening programs has reduced cervical cancer incidence and mortality in developed countries. This success has not been replicated in developing countries. Research on ways to improve cytology-based screening programme efficiency in middle-income countries has been identified as a high

priority. Research is also lacking on how other screening tests, such as HPV testing and VIA, will perform as routine screening tests in real health service settings in developing countries.

HPV vaccines offer great potential for primary prevention of cervical cancer. However, several challenges exist to the introduction of the HPV vaccine and limited formative research is available to guide vaccine introduction in developing countries. The prevalence of HPV types in South Africa will be important in assessing the possible magnitude of benefit from vaccines.

Research, conducted mostly in developed countries, has shown that HIV positive women are at a higher risk of HPV infection and cervical cancer precursor lesions, but has produced inconsistent results on the association between HIV and ICC. In developing a comprehensive cervical cancer prevention strategy, it will be important to determine the role that HIV plays in the risk of cervical cancer precursor lesions and cervical cancer.

The following chapter provides information on the context of cervical cancer prevention in South Africa

Chapter 3: The South African context

Chapter 3 provides information on the context of cervical cancer prevention efforts in South Africa. The structure of the chapter is as follows:

3.1. Health and health care in South Africa

3.1.1. The health system during apartheid

3.1.2. Key changes in health care policy since 1994

3.1.3. Current health system challenges

3.2. History and experience of cervical cancer prevention efforts in South Africa

3.2.1. Access to cervical cancer screening services

3.2.2. Community knowledge, attitudes and practice

3.2.3. Development of the current national cervical cancer screening policy

3.2.4. HPV vaccines in South Africa

3.3. Summary

3.1 Health and health care in South Africa

South Africa is a middle income country spending 8.6% of its gross domestic product on health (World Bank 2009). This health expenditure is similar to high income countries and higher than most other middle and low income countries (Table 3.1). Compared to other African countries, SA has a relatively well developed health infrastructure. However there is a disconnect between the investments in health and the health status of its people (Table 3.1). South Africa's oppressive history has had a profound impact on health and health care delivery in the country. In addition South Africa has been severely affected by the HIV/AIDS epidemic - it has the world's largest population of people living with HIV (UNAIDS/WHO 2009). Since the advent of democracy in 1994 there have been a number of bold health policy initiatives and reforms, however these have not always been followed by successful implementation.

Table 3.1: Health expenditure and health status in South Africa and selected high, middle and low income countries (2007)

Country	% of total gross domestic product spent on health	Life expectancy at birth in years	Infant mortality rate per 1000 live-births
High income			
United Kingdom	8.4	80	5
Australia	8.9	81	5
The Netherlands	8.9	80	4
Upper middle income			
South Africa	8.6	51	47
Chile	6.2	79	7
Botswana	5.7	53	44
Lower middle income			
India	4.1	63	54
Nigeria	6.6	48	91
Vietnam	7.1	74	20
Low income			
Tanzania	5.3	55	73
Nepal	5.1	66	43
Haiti	5.3	61	67

Source: (The World Bank 2009)

3.1.1 The health system during apartheid

During apartheid Black South Africans were denied social, economic, political and health rights. Poverty, squatter settlements, the migrant labour system and the subordinate position of women created an environment favorable for the efficient transmission of sexually transmitted infections (STIs) (Kark 1949), including HPV. Apart from the favorable environment for HPV transmission, health services for Black South Africans were underdeveloped, including preventative services such as cervical screening. A notable feature of health services in South Africa has been fragmentation. Prior to the apartheid era health facilities were racially segregated and curative and preventative care were separated. In the 1940's there was a realization that these divisions needed to be addressed and that a broader perspective on health was needed. The Gluckman Commission was appointed, by order of the governor-general, to review health service provision in the country (Gluckman 1970). The Commission was influenced by local and international developments in the field of social and preventive medicine. In 1945 the commission recommended the establishment of a unitary health service (Gluckman 1970). However, when the National Party took over in 1948 these recommendations were ignored and instead fragmentation was further entrenched. Ten "homelands" were created for Black South Africans. By the mid-1980s the South African public sector health system consisted of 14 different authorities: 10 Bantustan health departments, 3 "own affairs" health departments for Whites, Coloureds and Indians and the National Department of Health. This resulted in duplication of services and wastage of resources. Each of these authorities also had different health policies and guidelines, with a general lack of overarching policy direction. Multiple incompatible health information systems were set up by the different health authorities and none provided health planning information (Bradshaw, Mbobo 1995). The emphasis in the health sector was on curative, tertiary urban health care. In 1992/93 only 11% of health expenditure was on primary health care, whilst 44% was spent on tertiary hospitals (McIntyre et al. 1995). Access to health services was significantly worse for those living in rural compared to urban areas.

During the apartheid years private health care expanded. Private sector health services were paid for largely through medical insurance schemes. Until the late 1970's membership to these schemes was restricted to White South Africans. The Medical Schemes Act 72 of 1967, served to

transfer the health care of White South Africans from the public to the private sector (Republic of South Africa 1967). By 1992/1993 the private health sector accounted for almost 58% of the total health expenditure, but served only 23% of the population (McIntyre et al. 1995). Although Pap smears were available in the private sector, in essence, only a minority of mostly White South African women had access to these services. While the country had state-of-the-art high technology health facilities in the private sector, by 1994 based on international standards the country had an estimated shortfall of 600 to 1000 health clinics (McIntyre et al. 1995).

During the apartheid years women's health services consisted mainly of maternal health services and there was an emphasis on contraceptive services aimed at limiting population growth amongst the Black population (Cooper et al. 2004). There was no comprehensive reproductive health or cervical screening policy. In the 1990's international conventions, such as the 1994 International Conference on Population and Development (ICPD) in Cairo and the 1995 Fourth World Conference on Women in Beijing, expounded on the links between women's reproductive health, women's rights and socio-economic development, and emphasised the need for a broadened definition of reproductive health (United Nations 1994; United Nations 1996). At the same time in South Africa civil society organisations active in gender and women's health began lobbying for the creation of locally appropriate reproductive health policies.

3.1.2 Key changes in health care policy since 1994

In 1994, the newly elected democratic government inherited a deeply fragmented inequitable health system. The vision of the new government was a unified national health system, integrating the public and private sectors. In 1994/1995 the fourteen health authorities were consolidated into one national and nine provincial departments of health. In the South African Constitution (Republic of South Africa 1996), health was enshrined as a right and the government was mandated to provide access to health care services, including reproductive health care. In response to the constitutional mandates the Department of Health (DOH) increased access to services by eliminating user fees for public primary health care and all fees for pregnant women and children under the age of six years. A clinic infrastructure development

programme was set up in 1994, and by 1998, 485 new clinics were built and 248 existing clinics were upgraded to improve access to primary health care (Pillay 2001).

In 1997 the DOH published a White Paper for the Transformation of the Health System in South Africa, which proposed a primary health care (PHC) approach, the development of a district health system (DHS) and the reduction of inequities (Department of Health 1997). Primary health care is seen as key in the plan to transform health services. A comprehensive integrated package of essential PHC services was developed in 2000 (Department of Health 2001). This package of services is meant to be provided to the entire population and to form the foundation of a unified health system. Lessons from other countries that have adopted a comprehensive primary health care approach suggest that key to success is a strong district health system (Rohde et al 2008). The development of the DHS, however, has been delayed by finalisation over local government boundaries and confusion over governance responsibilities.

The new government embarked on a number of policy initiatives to regulate practices in the private sector. A moratorium was placed on the building of private hospitals. The Medical Insurance Schemes Act of 1998 prescribes minimum benefits and prohibited risk rating (Republic of South Africa 1998). However, the resources located in the private sector have not been made available to the broader population (McIntyre, Gilson 2002). The new government had hoped to address this public-private inequity through implementing a National Health Insurance (NHI) scheme, but there have been intense debates about a NHI scheme. In 2009 a ministerial advisory committee was appointed to advise government on the development of policy and the implementation of a NHI scheme. Detailed proposals are expected in 2010/2011.

The National Health Act, finally passed in 2003, provides the overall legal framework for the health system in South Africa (Republic of South Africa 2003). According to the Act the national DOH has the responsibility of policy formulation, whilst the provincial departments of health are responsible for implementation of national health policy, norms and standards. The Act (61 of 2003) also formally established the DHS and District Health Councils (DHC). The DHS is meant to be the most decentralised structure of health governance and management. Both the district health system and primary health care are defined as provincial responsibilities. Local

government is responsible for preventative and promotive services. Provision is made for provincial government to delegate health services to local government if they wish. Three tiers of hospitals exist: tertiary, regional and district. The primary health care system includes the district hospitals, community health centres and nurse-driven clinics.

A concerted effort has been made to redress past neglect of the health needs of poor women. The essential PHC package includes reproductive services and states that these services are to be provided in an integrated comprehensive manner (Department of Health 2000). Since 1994 many laws and policies affecting women's health have been passed and show a concern for the health needs of women beyond their role as mothers (see Table 3.2). However there has been no strategy for implementing these policies and for the delivery of the PHC package of services.

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Table 3.2 Law and policies affecting women's health

Year	Policies and laws passed
1994	<ul style="list-style-type: none">• Free public health services for pregnant women and children under the age of 6 years introduced
1995	<ul style="list-style-type: none">• Government ratifies the United Nations Convention on the Elimination of all forms of Discrimination Against Women
1996	<ul style="list-style-type: none">• South African Constitution adopted• Choice on Termination of Pregnancy (CTOP) Act passed which provides the framework for legal abortion services
1997	<ul style="list-style-type: none">• Maternal deaths made a notifiable condition• Patients Rights Charter launched
1998	<ul style="list-style-type: none">• Population Policy introduced shifting focus away from population control• Domestic Violence Act passed prohibiting physical, sexual and emotional violence against women• Sterilisation Act passed. Only the consent of the woman requesting sterilisation is required
2000	<ul style="list-style-type: none">• National Cervical Cancer Screening Guidelines introduced, stating that every woman is entitled to three free Pap smears (in the public sector) in her lifetime at 10-year intervals, starting at age 30
2001	<ul style="list-style-type: none">• National Contraceptive Policy Guidelines introduced, providing guidance for the provision of contraception
2002	<ul style="list-style-type: none">• Government approves provision of HIV post-exposure prophylaxis for rape survivors• Prevention of mother to child transmission (PMTCT) programme introduced country-wide
2003	<ul style="list-style-type: none">• ART use in public sector approved
2007	<ul style="list-style-type: none">• Sexual Offences and Related Matters Act passed, establishing a broader definition of rape
2008	<ul style="list-style-type: none">• CTOP Amendment Act passed, further increasing access to abortion services

Sources: (Cooper et al. 2004; Mhlanga 2008)

3.1.3 Current health system challenges

The implementation of the policy and programme initiatives described above has been sub-optimal. The delays and difficulties in implementing the basic building block of the new health system viz. the DHS, have resulted in uncertainty in health service governance and in confusion regarding through which organisational structures to route programme implementation. Between 1995 and 2005 health expenditure in the public sector has remained relatively stagnant (McIntyre, van den Heever 2007), making implementation of new programmes and policies challenging. In addition the health sector faces a crisis in terms of declining numbers of health personnel, particularly in the most disadvantaged rural areas (Wadee, Khan 2007; Daviaud, Chopra 2008). There has been a decrease in staffing capacity including professional nurses, who form the backbone of the cervical cancer screening programme. Reasons for the decline in health personnel include: a decreased in the production of nurses which is related to the lack of a human resource plan and the closing of nursing colleges as part of a cost-containment drive, provision of early retrenchment packages to nurses, emigration of health care providers and AIDS related illness among health care providers. The professional nurse-to-population ratio has decreased from 149 per 100 000 in 1998 to 116 per 100 000 in 2008 (Day, Gray 1998; Day, Gray 2008). In facilities with shortages of lower cadre health workers professional nurses often have to perform tasks meant for lower skilled workers, resulting in inefficient use of human resources (Daviaud, Chopra 2008). Maldistribution of nurses, poor skills mix at clinic level, increasing demands on primary care nurses and inadequate attention to nurses' knowledge, skills and attitudes have all been identified as problems that hamper the implementation of health programmes (Kawonga, Fonn 2008; Coovadia et al. 2009). Leadership and management skills to successfully implement policies and programmes have been lacking (Coovadia et al. 2009).

South Africa faces a quadruple burden of HIV/AIDS, communicable diseases, non-communicable diseases and injury-related disorders (Bradshaw et al. 2003). Despite socio-economic development in South Africa, the distribution of wealth and income in South Africa remains unequal (May 2000). The Gini coefficient for South Africa has increased from 0.56 in 1995 to 0.73 in 2005 (a value of one reflects complete inequality while a value of zero reflects complete equality), making South Africa an extremely unequal society (World Bank 2009). Health problems that are rooted in poverty persist.

In the past 18 years the HIV epidemic has grown exponentially, with antenatal surveillance data showing an increase in HIV prevalence among women attending public sector antenatal care services from 0.7% in 1990 to 29.3 % in 2008 (Department of Health 2009). There are currently more than 5 million people with HIV/AIDS in South Africa, with women more severely affected than men. HIV/AIDS has increased the demand for medical care dramatically, with the public sector carrying the heaviest load. Between 1995 and 2000 HIV related hospital admissions increased 7-fold (Shisana et al. 2003). Apart from the increased resources needed to address the epidemic and the increased workload, health care workers are also infected by HIV. It is estimated that 17.5% of health workers in primary health care settings are infected with HIV, with younger workers (aged 18 to 35 years) more severely affected. HIV-related absenteeism, nurse attrition and burnout amongst non-infected staff all impact on health service delivery (Shisana et al. 2004).

3.2 History and experience of cervical cancer prevention efforts in South Africa

3.2.1 Access to cervical cancer screening services

Cytological screening has been available in South Africa for more than 40 years. However, in the public sector, screening was conducted for most of this time in an ad hoc manner and focussed on women attending family planning clinics. Women who did not attend family planning services had little or no access to Pap smear screening. The ad hoc cervical cancer screening resulted in over-intense frequent screening of a small proportion of the population, the exclusion of most women at high risk and very low population coverage. A study among rural women workers in the Western Cape showed that women attending family planning services were being 'overscreened' with annual Pap smears, while women not on contraceptives were being excluded from cervical cytological screening (London 1993).

Women attending family planning services tend to be younger women, who typically experience significantly lower rates of disease than do older women. A study conducted in the Free State

Province in 1989 showed that at that time almost one third of Pap smears were being done in women aged 15 to 24 years (Cronje et al. 1989). Similarly a review of Pap smears done between 1988 and 1992 at the Groote Schuur Hospital Cytopathology Laboratory in Cape Town showed that there was an overemphasis on screening young women, whilst those in the age groups at which precancerous lesions are more likely to occur were considerably less likely to be screened (Bailie 1994a; Bailie, Barron & Learmonth 1995). The peak incidence of screening was in women aged 20 to 29 years, however, the highest proportion of smears showing CIN3 were in women aged 30 to 39 years. A study conducted in one district in the Western Cape Province reported that only 37% of Pap smears taken in the public sector clinics in 1998 were in women older than 30 years (Smith, Moodley & Hoffman 2003). Although cervical screening is now meant to be available at all primary health care facilities, missed opportunities have been documented. For example only 2.3% of eligible patients attending a primary health care clinic in Worcester in the Western Cape Province were asked about a cervical smear (Mphatsoe, Pather 2008).

3.2.2 Community knowledge, attitudes and practice

Little has been done in South Africa to raise awareness of the need for cervical screening either in the health services or at a community level. The importance of public education was demonstrated in the “Project Screen Soweto” study (Leiman 1987). In the early 1980s, “Project Screen Soweto” failed to recruit the planned 90 000 clients per year and the project was terminated after five years. The study authors suggested that one of the reasons for the failure was that the project lacked an appropriate awareness campaign and no consumer demand for screening had been created.

A number of studies in South Africa have shown that women have limited knowledge of cervical cancer and Pap smears, and few have had Pap smears. A community-based survey in an urban area in Cape Town showed that only 37.2% of the participants had had a Pap smear (Bailie, Pick & Cooper 1996). The main reason for not having had a Pap smear was that the participant had not heard of it. Only 27.3% of women attending the gynaecological outpatient department at King Edward VIII, a tertiary hospital in KwaZulu Natal Province, had had a Pap smear. Further

the authors reported poor communication about Pap smears by health care providers (Wellensiek et al. 2002). A study conducted in the Eastern Cape Province showed that 63.6% of women had heard about a Pap smear and knowledge was associated with older age, higher education level and higher parity (Lartey, Joubert & Cronje 2003). However, only 35.3% of all respondents had ever had a Pap smear. Among those that had heard of a Pap smear, the main reasons for not having one was that it was not suggested by a health care provider and women feeling that it was unnecessary (40.4% and 37.8% of respondents respectively). More extreme findings were reported in a cross-sectional study conducted in a rural area in KwaZulu Natal in 2005 (Hoque, Hoque & Kader 2008). This study reported that 49% of women had heard of a Pap smear, however only 18% had ever had Pap smear. Among those who did not have a Pap smear, the majority said that it was because they were not ill, 12 % said it had not been suggested by a health care provider, and 6% cited bad attitudes of the health care provider as their reason for not asking for a Pap smear. Cervical screening is clearly not seen as a priority by health care providers, and there has been limited discussion on the importance of Pap smears with clinic attendees.

Fonn, et al. demonstrated a receptiveness and responsiveness among women to attend health services to have a Pap smear once they are informed of the importance of cervical screening (Fonn et al. 2002). As part of a multicentre survey to determine prevalence of cervical abnormalities among South African women, a call was made to women in ten geographically defined areas in all provinces to attend the local health service for a Pap smear. Encouragingly 70% of women attended health services specifically for a Pap smear, mostly as a result of information provided by clinic staff and the limited advertising that was part of the project. Of the 20 603 women who participated in the study 80% had never had a Pap smear previously (Fonn et al. 2002).

3.2.3 Development of the current national cervical cancer screening policy

Over the past four decades there have been a number of calls to introduce a cervical cancer screening programme in South Africa. In 1962 an editorial in the South African Medical Journal discussed the use of Pap smears and a plea was made to the government to “cut red tape” so that “this most important public health service” could be introduced (Editorial 1962). However in the

mid 1970's the Department of Health advocated that Pap smears only be done when the cervix appeared abnormal (Bloch 1979). Clinicians reacted strongly and called for this policy to be revoked (Bloch 1979; Grant 1982). Although Pap smears were theoretically available in the public sector, mostly at family planning and antenatal clinics, little screening occurred. In 1990 the South African Society of Obstetricians and Gynaecologists (SASOG), sent a proposal to the then Department of National Health and Population Development (DNHPD) recommending that a Pap smear screening programme be implemented in the country in which "every woman in South Africa should have three free Pap smears at the ages of 25, 35 and 45 years" (Bloch et al. 1994). Some academic debate on the ages at which the smears should take place followed, but the recommendation was ignored by the DNHPD (Bailie 1994b; Bloch et al. 1994; Fonn 1994). In 1991 the Women's Health Project (WHP) was established at the University of Witwatersrand with the aim of developing policy proposals, conducting policy related research and lobbying for improvements in women's health in South Africa. In preparation for a Women's Health Conference that was held in December 1994, the WHP hosted a workshop on cervical cancer screening earlier that year (Klugman, Stevens & Arends 1995). At the workshop, attended by health service managers and providers, non-governmental organisations, community-based organisations, clinicians, researchers and academics, recommendations for a cervical cancer screening strategy were developed. It was recommended that a cervical cancer screening programme that targets older women be set up in South Africa and that women be offered three free Pap smears, at ten year intervals (Klugman, Stevens & Arends 1995). These recommendations served as the basis for the development of the current national cervical cancer screening guidelines. Post-apartheid in the late 1990's, the NDOH identified cancer of the cervix as a national health priority. In 2000, the National Cancer Control Programme developed policy guidelines for the country stating that every woman is entitled to three free Pap smears (in the public sector) in her lifetime at 10-year intervals, starting at age 30 (Department of Health 2000). The policy aimed to screen 70% of women aged 30 years and older within 10 years. It was based on the best available epidemiological data of how to achieve the greatest reduction in cervical cancer, taking into account resource constraints and conforms to WHO recommendations for screening in resource-limited countries (World Health Organization 2002). The ultimate aim of the South African screening policy is to reduce cervical disease by detecting and treating pre-cancerous lesions in a timely manner.

The South African cervical cancer screening programme is based on cytological examination of cervical specimens. Women are screened with conventional Pap smears usually done by professional nurses in primary care centres. Estimates showed that there were sufficient professional nurses in the public sector to screen all eligible women (Fonn 2003). However these estimates did not take into account the impact of the HIV testing and treatment interventions on health services and attrition of nurses in the public sector (Kawonga, Fonn 2008) both of which have placed massive additional burdens on nursing staff.

Compared to other developing countries, South Africa has a relatively well developed cytology infrastructure. Pap smear slides are sent to the National Health Laboratory Service (NHLS), where they are read by cytotechnologists. The NHLS was established in 2001, amalgamating the various state laboratories and the South African Institute of Medical Research to form a single public health laboratory service in South Africa. It comprises approximately 260 laboratories countrywide. Local guidelines state that cytotechnologists can read a maximum of 48 Pap smears per day. Reviews of laboratory capacity indicate that there is a shortage of cytotechnologists (Fonn 2003; Michelow, Dubb 2003).

Pap smear results are sent from the laboratory back to the clinics, and clients are informed either by the laboratory or by clinic staff if further follow-up is required. Clients with HSILs or persistent LSILs are referred for a colposcopic assessment. Colposcopy services are based at secondary and tertiary level hospitals.

The DOH cervical cancer screening guidelines (DOH, 2000) does not make reference to HIV. Cervical cancer screening practices for HIV positive women vary widely in the public sector (Niederfahrenheit 2008; Batra, Kuhn & Denny 2010). A study conducted at three HIV clinics based at primary health care facilities in the Western Cape reported that only 13.2% of HIV positive women had ever had a Pap smear (Batra, Kuhn & Denny 2010), whilst another study

conducted at three ARV clinics in the same province reported that 59.1% of women had at least one Pap smear (Niederfahrenheit 2008). In 2010 the HIV/AIDS directorate of the National Department of Health released clinical guidelines for the management of HIV positive adults which advocates Pap smears every 3 years in HIV positive women (National Department of Health 2010). The extent to which health care providers are aware of, and implement, this policy is unknown.

3.2.3 HPV vaccines in South Africa

The recent development of two prophylactic HPV vaccines (Harper et al. 2006; FUTURE II Study Group 2007), a bivalent vaccine that targets HPV16 and HPV18 and a quadrivalent vaccine that targets HPV types 16, 18, 6 and 11, offers potential for primary prevention of cervical cancer in SA. Both vaccines have been licensed for use in South Africa since March 2008. However they are not yet available in the public health sector. Key opinions about the potential introduction of the HPV vaccine in the public sector in South Africa are not known.

3.3 Summary

The above sections have detailed the context of health care in South Africa. Compared to other middle-income countries, South Africa has a relatively well-developed infrastructure. Post-apartheid health sector transformation has been characterised by bold policy initiatives and a number of policies have been developed to address women's health needs. However there has been a gap between policy making and policy implementation. Moving from a fragmented, curative centred health system to a unified health system based on the comprehensive primary health care approach has proven to be challenging. The HIV/AIDS epidemic in South Africa has added another level of complexity. Cervical cancer has been recognized as a priority. The challenge now is to implement a comprehensive cervical cancer prevention strategy.

Chapter 4: Implementing a cytology-based cervical cancer screening programme in South Africa

This chapter presents the methods, results and discussion for the first study objective i.e. to design, implement and evaluate health system interventions for public sector cytology-based cervical screening services in South Africa. Specific objectives were to improve the organisation and functioning of cervical cancer screening services; improve staff knowledge, attitude and practice (KAP), improve client KAP, increase service utilisation and Pap smear coverage. The chapter is structured as follows:

4.1. Methods

4.1.1. Study setting

4.1.2. Study design

4.1.3. Data analysis

4.2. Description of interventions

4.2.1. Re-organisation of cervical screening services

4.2.2. Staff training

4.2.3. Cytology services

4.2.4. Referral process for clients with cervical abnormalities

4.2.5. Record keeping and data collation

4.2.6. Community awareness

4.2.7. Study products

4.3. Results

4.3.1. Organisation of services

4.3.2. Staff knowledge, attitudes and practices

4.3.3. Cytology services

4.3.4. Referral and feedback

4.3.5. Record keeping and data collation

4.3.6. Client knowledge, attitudes and practices

4.3.7. Number of Pap smears and Pap smear coverage

4.3.8. Referral of clients with HSILs

4.4. Discussion

4.1 Methods

4.1.1 Study setting

This study was conducted between January 2001 and May 2003. Three of the nine provinces in South Africa were included in a study to design, develop and evaluate health system interventions for public sector cytology-based cervical screening services. In consultation with respective provincial health authorities, one sub-district site per province was purposively selected to represent different socio-economic, geographical and health system contexts in the country. The sites represented the different range of challenges that are likely to be experienced in various contexts within the country viz. urban vs. rural, varying levels of unemployment and varying levels of health system infrastructure. Table 4.1 summarises the socio-demographic and geographic characteristics of the three study sites.

The clinics in Site 1 had been performing Pap smears for many years. Pap smears were and still are sent to public cytology laboratory (Laboratory A). Colposcopy services are provided by a tertiary hospital in Cape Town. Appointments for clients with an abnormal Pap smear that need to be seen at the colposcopy clinic are made by the cytology laboratory. The laboratory mails a letter with the colposcopy date directly to the client. A study conducted in 1998 showed that the majority of smears were being done on younger women (Smith, Moodley & Hoffman 2003).

Clinics in Site 2 had also been performing Pap smears for many years. Pap smears were sent to a public sector laboratory (Laboratory B) until April 2002, thereafter, as part of the provincial restructuring plan, Pap smears were sent to another public sector laboratory (Laboratory C). Cytology results are sent back to the clinics. Clinic staff refer clients with abnormal Pap smears to a secondary level hospital, where, during the pre-intervention phase of this study, clients had a non-colposcopy-guided punch biopsy and those with a positive histology result were referred to the colposcopy clinic at a tertiary hospital in Johannesburg.

None of the clinics in Site 3 were performing Pap smears prior to this study.

Table 4.1: Socio-demographic characteristics and locations of study sites

	Site 1	Site 2	Site 3
Geographical location	A sub-district located in the City of Cape Town Metropolitan Municipality (CCTMM), Western Cape Province Urban area 30 kilometers from Cape Town	A sub-district located in the Ehurkhuleni Municipality (EM) in Gauteng Province Urban area 45 kilometres from Johannesburg	A rural area in Waterberg district in Limpopo Province Situated 250 kilometres north of Johannesburg
Socio-demographic characteristics	Mostly Coloured population (84%) with a minority Black population (15%) 72% of population have attained some high school education (i.e. grade 8 or higher) Unemployment rate of 30% Housing: 94% formal, 6% informal 2001 per capita expenditure on primary health care for CCTMM: R500	Mostly Black (75%) population, with a minority Coloured and White population 74% of population have attained some high school education Unemployment rate of 40% Housing: 78% formal, 22% informal 2001 per capita expenditure on primary health care for EM: R550	Mostly Black population (97%) 48% of population have attained some high school education Unemployment rate of 30% Housing: 80.5 formal, 6.6% informal, 12.9% traditional 2001 per capita expenditure on primary health care for Waterberg: R190
Catchment population	280 000	230 000	202 000*
No. of clinics included in study	All 9 primary care clinics in the sub-district were included	All 7 primary care clinics in the sub-district were included	5 of 10 clinics in the district were included

* In this Site, 5 clinics serving a population of 202 000 were included in the study. Distances between the clinics are far greater in Site 3 than in the other study sites.

Data source: (Statistics South Africa (SSA) 2003; Day, Gray 2008)

4.1.2 Study design

A pre-and post-intervention cross-sectional study design was used. A number of health system and community awareness interventions were developed and implemented. Pre-and post-intervention surveys were conducted and included: facility audits; staff KAP surveys, client KAP surveys and a review of laboratory and clinic records. The dates of the pre-and post-intervention surveys and of the implementation activities are outlined in Table 4.2 below. Activities in Site 3 started approximately 6 months after those in Sites 1 and 2.

Table 4.2: Study timeline

Activity	Date
Pre-intervention assessments	
Health facility audit	April - May 2001
Staff KAP survey	April - May 2001
Clinic and laboratory record review	May - July 2001
Client KAP survey	April 2002 - July 2002
Intervention implementation	
Staff training	August 2001 – April 2002
Re-organisation of services	December 2001
Introduction of Pap register	May 2002
Introduction of data collation sheets	May 2002
Introduction of referral and feedback forms	July 2002
Implementation of cytology request and report forms	July 2002
Community launches	May 2002 - September 2002
Post-intervention assessment	
Health facility audit	November 2002 - March 2003
Staff KAP survey	November 2002 - January 2003
Client KAP survey	November 2002 - March 2003
Clinic and laboratory record review	March 2003
Follow-up of clients with HSIL	April 2003

Trained interviewers conducted both pre- and post- intervention facility audits to obtain information on the organisation of cervical cancer screening services. Interviews were conducted with facility managers at the 21 clinics included in the study, using a structured questionnaire. Interviewers also conducted a walk-through inspection and completed a facility check-list (Appendix A). Data were obtained on the organisation of Pap smear services, staffing, management and referral of clients with abnormal Pap smears, cytology reporting and turnaround times (refers to the time from taking a Pap smear to the time the Pap smear result is received at the clinic), record keeping, availability of Pap smear equipment and the availability of information, education and communication (IEC) materials.

A pre- and post-intervention cross-sectional KAP survey was conducted among professional nurses to determine their knowledge and attitude to the screening policy, knowledge of cervical cancer, cervical cancer screening practices and management of clients with cervical abnormalities. The number of staff interviewed is shown in Table 4.3 below. The main reasons for staff not participating in the survey was that they were either ill, on leave or were on night duty. In Site 1 a trained interviewer administered a structured questionnaire (Appendix B). In Sites 2 and 3, due to staff time constraint, questionnaires were self-administered. The pre-intervention survey took place in the first year of the study (April- May 2001) and the post-intervention survey 6 months after the interventions had been implemented (November 2002 - January 2003). In Site 3 the post-intervention survey took place over the end- of-year vacation period and more staff were on leave in the post- compared to the pre-intervention survey.

Table 4.3: Number and percentage of staff interviewed

	Site 1	Site 2	Site 3	Total
Pre-intervention	51/62 (82.3%)	29/34 (85.3%)	31/32 (96.9%)	111/128 (87.5%)
Post-intervention	40/49 (81.6%)	28/32 (87.5%)	22/33 (66.7%)	90/114 (78.9%)

Data are number of staff interviewed/total staff complement (%)

A pre- and post- intervention cross-sectional survey was conducted among clinic attendees to assess client knowledge and attitudes concerning Pap smears and cervical cancer, and to determine Pap smear screening history. Sample size calculations were based on an expected increase of at least 6% in the proportion of women attending the health services who ever had a Pap smear after the interventions had been implemented. The required sample size with a significance level of $\alpha = 0.05$ and power of 80% was 1024 for the three sites in both the pre- and post-intervention survey groups. Women were recruited from the general waiting area of the clinic. All women 25 years and older attending the clinic for any reason were eligible for enrollment. Systematic sampling was used and every 5th woman in the waiting area of the clinic was selected to participate in the study. Trained interviewers collected data using a structured questionnaire (Appendix C). The pre-intervention survey took place between April and July 2002 and the post-intervention survey 6 months after the interventions had been implemented. A total of 1 121 and 1 118 women were interviewed before and after the intervention, respectively (Table 4.4)

Table 4.4: Number of clients interviewed per site

	Site 1	Site 2	Site 3	Total
Pre-intervention	445	341	335	1 121
Post-intervention	449	341	328	1 118

To evaluate screening and treatment services clinic records and cytology laboratory data were reviewed. Laboratory data were examined for the period January 2001 to December 2002, yielding information by clinic on the number of clients screened, their ages, the endocervical component of the Pap smears, and the occurrence of abnormalities. Pap smear coverage was calculated by dividing the number of new (not repeat) Pap smears performed on women in the target age by the total number of women of that age in the catchment area. Catchment population data was obtained from the relevant health authorities.

Clinic Pap smear registers, which were one of the interventions introduced at each clinic, were examined for the period July to December 2002 (post-intervention), to provide information on

the numbers of new or repeat smears done, the age of women screened, turnaround times and action taken for abnormal Pap smears. To answer questions about timely treatment for women with HSIL, Pap smear register data for women screened between July 1 and October 31, 2002 (post-intervention period), were reviewed. It was expected that clients with HSIL would be seen at the colposcopy clinic within 6 months. Client attendance at colposcopy clinics and hospitals through to the end of April 2003 (i.e. up to six months after being diagnosed with HSIL) was checked using colposcopy clinic records. Colposcopy and biopsy findings and treatment were recorded. No information on treatment and follow-up of client with HSILs was available from clinic records prior to the study.

Research staff kept notes on service functioning during site visits and at meetings with providers and managers throughout the course of the study. Information on the extent to which intervention tools were being utilised was collected.

Ethical approval was granted by the University of Cape Town, Faculty of Health Sciences Research Ethics Committee and the University of Witwatersrand Human Research Ethics Committee. Written informed consent was obtained from all study participants.

4.1.3 Data analysis

A health systems approach was used to assess the performance of the cervical cancer screening programme pre-and post-intervention. A performance evaluation typically involves measurement of indicators of provision (are the services available, accessible and of adequate quality), utilisation and coverage (Habicht, Victora & Vaughan 1999). Indicators that were used to assess the cervical cancer screening programme are shown in Table 4.5. The indicators selected were adapted from the list of performance indicators recommended by IARC (IARC 2005). This list was limited by data available from cytology laboratories, hospital registries.

Data analysis was conducted using the statistical programme STATA 10.1 (STATA Corporation, College Station, Texas). Descriptive statistics (medians and proportions) were used to characterise the variables. Pre-and post-intervention proportions were compared using the chi-

squared and Fisher's Exact test in the case of small numbers and, medians were compared using the Wilcoxon rank-sum test.

Table 4.5: Indicators used to assess the cervical cancer screening programme

<p>Service provision</p> <p><i>Screening services</i></p> <ul style="list-style-type: none"> • Number of clinics providing cervical screening services • Number of clinics adequately equipped • Number of clinics with client information (posters, pamphlets etc.) • Number of clinics using a Pap register • Number of clinics using appropriate referral, recall, and feedback systems <p><i>Staff knowledge, attitudes, and practices</i></p> <ul style="list-style-type: none"> • Knowledge of cervical cancer and screening policy • Attitudes to cervical cancer screening policy • Proportion of staff trained and able to perform Pap smears • Proportion of staff performing Pap smears • Proportion of Pap smears that have adequate endocervical component • Proportion of women with abnormal smears that are appropriately managed <p><i>Cytology services</i></p> <ul style="list-style-type: none"> • Number of laboratories using consistent and appropriate management recommendations • Average turnaround times for results <p><i>Client knowledge, attitudes, and practices</i></p> <ul style="list-style-type: none"> • Knowledge of cervical cancer and Pap smears • Sources of information • Attitudes toward screening • Proportion of clients that ever had a Pap smear
<p>Utilisation of services</p> <ul style="list-style-type: none"> • Number of women attending health services that ever had a Pap smear • Number of women with HSILs treated within 6 months
<p>Coverage</p> <ul style="list-style-type: none"> • Pap smear coverage calculated as total number of new smears done in a year /number of women 30 years and older in catchment area

4.2 Description of interventions

Intervention development was informed by the results of the pre-intervention surveys. Common problems identified pre-intervention are outlined in Table 4.6.

Table 4.6: Common problems identified in the pre-intervention surveys

Area of service	Issues
Programme organisation	<ul style="list-style-type: none"> • No Pap smear targets • Inadequate record keeping and client follow-up • Inadequate communication between clinics, laboratories and treatment facilities • Lack of equipment and client education materials
Client recruitment	<ul style="list-style-type: none"> • Low levels of community knowledge about Pap smears • Low Pap smear coverage • Missed opportunities for screening in clinics • Lack of information, education and communication materials
Providers	<ul style="list-style-type: none"> • Providers' resistance to the national policy • Providers' knowledge gaps (e.g. policy, natural history of cervical cancer, screening objectives, and management of clients)
Cytology	<ul style="list-style-type: none"> • Long turnaround times • No standardised terminology for cytology results • No standardised recommendations for client management, and use of outdated protocols, resulting in inappropriate management and/or staff confusion
Colposcopy	<ul style="list-style-type: none"> • Poor referral and feedback systems
Health information	<ul style="list-style-type: none"> • No data to assess client management • No data collection or collation

In developing and implementing the interventions the research team adopted a participatory, capacity building approach. This approach seeks to empower providers through active participation in research and development activities, in problem identification and in developing solutions in relation to particular questions (Macaulay et al. 1999). At the start of the study a steering committee, consisting of key role-players, was set up nationally and in each study district to provide support and advice and to ensure sustainability of the interventions. Smaller

task groups were also set up to guide the development of specific interventions. The interventions consisted of: re-organisation of cervical screening services; staff training; re-design of cytology request and report forms; improving the referral process for clients with cervical abnormalities; improving record keeping and data collation and a community awareness programme. Facility and programme managers were encouraged to coordinate the following components:

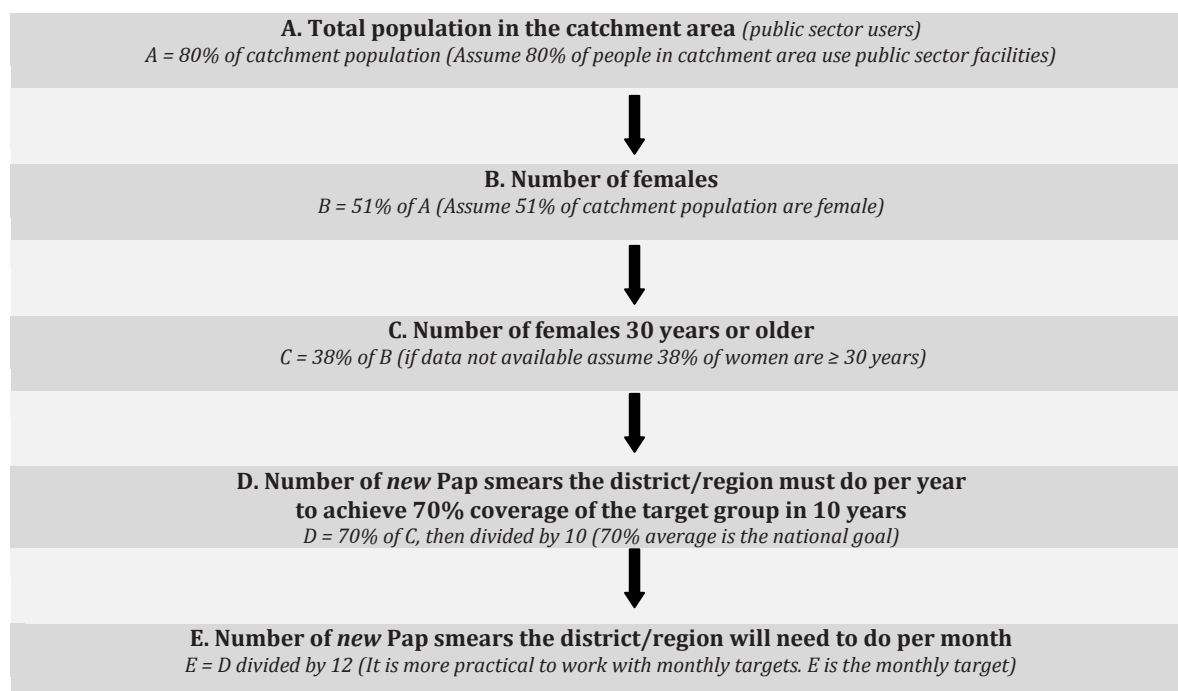
- Screening services—prepare health facilities for screening services, ensure that appropriate equipment is available, and ensure that staff are trained to perform Pap smears
- Cytology services—monitor and address turnaround times
- Client management at the primary care level—implement standardised management guidelines for clients with abnormal Pap smears and establish mechanisms for informing clients of results and for tracking clients who need re-screening or referral for further management
- Colposcopy and treatment services—ensure women’s access to colposcopy and treatment services where necessary, and establish mechanisms for referral to and feedback from these services
- Client recruitment— establish an IEC programme to inform and educate men and women in the community about cervical cancer, as well as women utilising health facilities for other health concerns
- Monitoring and evaluation—ensure that mechanisms are in place to collect and analyse key cervical screening data and to use indicators to further strengthen and inform the screening programme

4.2.1 Re-organisation of cervical screening services

A key element in planning is setting goals for the programme, specifically in terms of the target group, the proportion of the target group that should be screened (the coverage goal), and the screening interval. The goal for the national cervical screening programme is to achieve 70% coverage of women 30 years or older within the first 10 years of implementation. At the start of a cervical screening programme, managers need to estimate the number of women 30 years or older in their area of jurisdiction, and develop a plan to screen 70% of these women over the

subsequent 10 years. During the 10 years, managers will need to regularly monitor progress towards achieving this goal of 70% coverage of the target population. An annual screening goal is required to monitor progress. A tool was developed that enabled managers and providers to determine annual and monthly screening targets for each sub-district and clinic (Figure 4. 1).

Figure 4.1: Estimating screening goals for a cervical screening programme



In order to reach a cervical screening coverage of 70% in 10 years in women 30 years and older (step D in Figure 1 above), managers in all three study sites decided to screen 7% of the target population per year. This translated into a coverage goal of 7% of women aged 30 years and older per annum for the next 10 years.

Research staff assisted facility managers in organizing services to meet these targets. Changes included increasing the number of rooms that could be used for screening, as well as increasing the number of days and hours on which screening would be provided and, where possible, establishing fast-track queues for clients returning for results. The latter is a separate queue for clients returning to the health service for their Pap smear results.

An equipment and supplies audit form was drawn up to assist in determining equipment needs for the increased workload. The audit form compared the quantities of equipment available against the quantities required to cater for the anticipated workload. Where there was a shortfall, the manager took action to acquire additional equipment.

4.2.2 Staff training

The research team provided training for all clinic staff. Training for doctors and nurses was conducted in two phases. The first phase was directed at all doctors and nurses working in the clinics and focused on the epidemiology and natural history of cervical cancer, the rationale for the South African national screening policy and on the health system interventions that had been developed. In the first phase of training a total of 152 staff were trained in Site one; 29 in Site two and 31 in Site three. The second phase of training was directed at staff responsible for taking Pap smears and/or managing cervical screening services. This phase focused on Pap smear technique (theory and practical) and management of clients with abnormalities. The training approach differed slightly in each site, because of differences in staff availability, numbers to be trained, and local preferences for direct or “training of trainers”-type training. In the second phase of training 40 nurses were trained in Site one; in Site two 7 master trainers trained 21 nurses and; in Site three 8 master trainers, trained 15 nurses. Staff training took longer than expected, not because large numbers of staff were to be trained but because training had to be phased so as not to disrupt services.

Research staff also provided an orientation session for all other clinic support staff (receptionists, administrators, radiographers etc.), so they would be better able to support cervical cancer screening services. This two-hour training focused on what the cervical screening policy was trying to achieve as well as on how the support staff could become advocates for the women being screened e.g. by informing clients that Pap smear services were available at the clinic. A total of 93 support staff were trained: 64 in Site one; 16 in Site two and 13 in Site three.

Materials developed for all training sessions were made available to the local, provincial and national departments of health, both electronically and in hard copy format.

4.2.3 Cytology services

The pre-intervention surveys identified the need for uniform cytology reporting and appropriate standardised guidelines for the management of abnormal cervical cytology within the South African context. To address this, a national consultative meeting was held with representatives from: the National, Provincial and Local Departments of Health, the South African Society of Clinical Cytology, the South African Institute for Medical Research, the National Health Laboratory Services and pathologists, clinicians and nurses. Based on this meeting and various discussions, the research team designed new cytology request and report forms. The forms clearly state the cytology results and have standard recommendations for client management, based on the New Bethesda System (NBS) (Solomon 2002), and adapted for the South African screening policy. Laboratory B and C began to use these forms to report cytology results. Staff at Laboratory A were reluctant to change the reporting format and management guidelines, but agreed to use the request and reporting forms for a six-week trial period in 2002 while simultaneously using their existing format.

Research staff worked closely with staff at the three laboratories to encourage improved communication between the laboratories and primary care facilities and colposcopy services. The study did not have any specific intervention, such as increasing cytology staffing, which would have shortened the turnaround times for results. Laminated posters were developed for clinic staff, depicting the standard client management guidelines to be followed based on the cytology result.

4.2.4 Referral process for clients with cervical abnormalities

Interventions that were directed at improving the referral of clients with cervical abnormalities included: a module on management and referral of clients with cervical abnormalities which was a part of staff training, standardised recommendations on the cytology report form and a laminated poster for clinic staff describing standard client management and referral guidelines as an easy-to-use algorithm. In an attempt to improve communication between referral centres and primary care services, the research team facilitated discussions between staff at both levels, and standard referral and feedback letters were designed.

4.2.5 Record keeping and data collation

The pre-intervention survey indicated that none of the sites had a system for collecting, analysing and collating data to monitor and evaluate a cervical screening programme. A health information task team was set up at each site to identify information needed by managers to monitor and evaluate the cervical cancer screening programme and mechanisms to collect the information. A paper-based clinic Pap register was developed to record data about each Pap smear performed. The register collects information on client contact details, the date the smear was taken, the Pap smear results and actions taken. Data collation sheets were also developed to assist with production of monthly, quarterly and annual summary statistics that allowed for monitoring of services. These sheets summarize Pap register data and provide information on: the number of Pap smears per month, proportion of Pap smears in the target age group, proportion of Pap smears with an endocervical component, proportion of repeat Pap smears, and management of abnormal Pap smears. Programme and facility managers, as part of their managerial duties were responsible for data collation. Facility managers were also tasked to check on various aspects of the cervical cancer screening programme during facility supervisory visits. These included: the management of abnormal Pap smears, cytology turn-around times, feedback from colposcopy clinics and turnaround times for cytology results.

4.2.6 Community awareness

In each study site a task team was set up to develop and implement an IEC campaign to provide information and education in cervical cancer screening to potential clients in clinics as well as in the community. The teams included representatives from the health services, community organisations and non-governmental organisations. A cervical cancer awareness campaign was launched in the three sites once the screening services at the health services had been established or strengthened (community launch in Site 1 in May 2002; Site 2 in June 2002; Site 3 in September 2002). The launch took place at a community venue in each site and consisted of talks by experts as well as opportunities for community members to ask questions. The purpose of the campaign was to raise awareness about the screening services, publicise the availability of screening services in the sites and encourage screening according to the South African policy.

The Site 1 IEC task team spearheaded development of a pamphlet and a series of three posters; these were then translated into local languages appropriate for Sites 1 and 3 (Afrikaans, English, Xhosa, SiPedi and SeTswana). The pamphlets and posters included information on: what cervical cancer and Pap smears are; who is at risk of acquiring cervical cancer, how cervical cancer can be prevented (through Pap smears), recommended age and frequency of cervical cancer screening and the need to return for results and further management if necessary. Site 2 did not utilise these materials because IEC materials had already been developed by the local provincial health department. The posters and pamphlets were distributed via health facilities, non-governmental organisations, and community-based organisations and were displayed at health facilities, shops, taxi ranks, and other public places in the study sites.

Local newspapers published articles and press releases developed by the IEC task team about cervical cancer and screening during, and soon after the launch. In each site one or more radio spots discussed cervical cancer and screening during and soon after the launch. Additionally, in Site 2, recorded messages were broadcast throughout the community a few days before the launch, using a public address system and a roving banner publicising cervical cancer prevention.

In all three sites community health committees and community-based organisations identified possible peer educators. These included existing health motivators, community leaders, and church elders. The research team trained a total of 50 peer educators: 20 in Site 1, 11 in Site 2 and 19 in Site 3. Once trained, the peer educators distributed pamphlets and gave talks on cervical cancer within their communities.

During the staff training health providers were encouraged to recruit eligible clients who were attending the health services for other health matters, to avoid missed opportunities for cervical cancer screening.

4.2.7 Study products

Based on lessons learned in training staff and in managing the implementation and evaluation process, a two-volume manual was produced: Volume I is a guide for programme managers

(Cervical Health Implementation Project (CHIP) 2004b) and Volume II is a guide for trainers (CHIP 2004a). Besides providing overall guidance for programme managers, Volume I contains suggested client management protocols, client referral and feed-back letters, client tracking systems, tools for estimating target populations, audit forms for equipment and supplies, monitoring and evaluation tools, and client IEC materials.

4.3 Results

4.3.1 Organisation of services

The tools to calculate Pap smear targets and assess equipment had been used by all clinics. Following the interventions there was an improvement in the availability of services (Table 4.7). There was an increase in the number of clinics offering Pap screening services (from 16 to 21 clinics) and offering Pap smear services on demand i.e. without an appointment (from 7 to 16). Prior to the interventions none of the clinics offered a fast track system for clients to receive results and post-intervention 19 clinics offered this service. Overall the percentage of staff trained to do Pap smears increased significantly from 58.5% to 85.8% ($p < 0.001$), with the greatest increase occurring in Site 3 (13.8% to 77.4%). There was a significant increase in the number of staff doing Pap smears at all three sites, with an overall increase from 38.5% to 61.1% ($p < 0.001$)

Pre-intervention data showed that equipment availability varied between sites and clinics. In Sites 1 and 2, district health authorities helped to equip the clinics. In Site 1, the Provincial Department of Health designated special funds in 2002 for cervical screening equipment. In Site 3, however, the situation improved only marginally during the study, despite clinic requests to district and provincial health authorities for equipment. At the post-intervention evaluation, in Site 3 one clinic still had only one speculum, most clinics only had one lamp for the whole facility.

The availability of IEC materials improved post-intervention, with the majority of clinics having a poster announcing the availability of Pap smears. Pre-intervention only one of the 21 clinics displayed a poster showing the availability of Pap smears, and no other IEC materials were

available in any of the clinics. Post-intervention in Site 1 Pap smear posters were displayed in seven of the nine clinics, other posters announcing the general availability of Pap smears in five clinics, and smaller signs indicating screening times were present in eight of the nine clinics. Site 2 had decided to use existing materials developed by the provincial health department. However the post-intervention assessment found posters in only two of the seven clinics and pamphlets in only four clinics. Staff reported that they had run out of stock and that further supplies were not available from the Department of Health. Six of the seven clinics in Site 2, however, had a notice informing clients that Pap smears were available. In Site 3 all five clinics displayed the cervical cancer posters and four of the five clinics had pamphlets; staff at the other clinic had run out of pamphlets and these had not been reordered.

Peer educators reported concerted recruitment efforts after training. In the six months after training, peer educators, with little external support, reported providing information about cervical cancer, mostly in clinic waiting rooms and at community gatherings. Over a 6-month period peer educators reported making contact with 1 363 people in Site 1; 1 560 people in site 2 and 1 757 people in Site 3.

Table 4.7: Service availability

Service element	Site 1 9 clinics		Site 2 7 clinics		Site 3 5 clinics		Total 21 clinics		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	p-value*
No. of clinics offering services	9 (100.0)	9 (100.0)	7 (100.0)	7 (100.0)	0 (0.0)	5 (100.0)	16 (76.2)	21 (100.0)	0.048
No. of clinics offering Pap smear screening on demand i.e. without an appointment	4 (44.4)	4 (44.4)	3 (42.9)	7 (100.0)	0 (0.0)	5 (100.0)	7 (33.3)	16 (76.2)	0.012
No. of clinics with fast track for Pap results	0 (0.0)	8 (88.9)	0 (100.0)	6 (85.7)	0 (0.0)	5 (100.0)	0 (0.0)	19 (90.5)	<0.001
No. of staff trained to do Pap smears (compared with all professional staff)	48/68 (70.6)	44/48 (91.7)	24/33 (72.7)	29/34 (85.3)	4/29 (13.8)	24/31 (77.4)	76/130 (58.5)	97/113 (85.8)	< 0.001
No. of staff doing Pap smears (compared with all professional staff)	28/68 (38.2)	28/48 (58.3)	22/33 (66.7)	27/34 (79.4)	0/29 (0.0)	14/31 (45.2)	50/130 (38.5)	69/113 (61.1)	< 0.001

Data are n (%) * Pre- and post-proportions were compared across all sites, p-values are from χ^2 and Fisher's exact tests

4.3.2 Staff knowledge attitude and practices

In total 111 and 90 professional nurses took part in the pre- and post-interventions staff KAP surveys, respectively. For the most part these were the same, though fewer staff during the follow-up. Across the three sites, in both pre-and post-surveys the majority of staff interviewed were female professional nurses older than 35 years. In Sites 1 and 2, more than 90% of respondents had been qualified as a nurse for more than five years, which contrasted sharply with the comparatively less experienced staff in Site 3, where only 45% reported that they had qualified more than five years before.

Table 4.8 shows an increase in staff knowledge of and improved attitudes toward the cervical screening policy after the interventions. Pre-intervention, the number of staff who knew there was a national cervical screening policy differed significantly by site. Staff at Site 1 were significantly more likely to be aware of the national screening policy compared to staff at Site 2 (90% vs. 66%, $p = 0.007$) and compared to staff at Site 3 (90% vs. 55%, $p < 0.001$). Pre-intervention there were no significant differences in terms of policy awareness between staff in Sites 2 and 3 ($p = 0.399$). In the post-intervention survey there were no significant differences in the proportion of staff aware of the policy between the three sites. Staff at all three study sites showed greater awareness of the policy in the follow-up survey and there was a significant overall increase between the two surveys in the proportion of staff who agreed with the policy (from 23% to 68%, $p < 0.001$). Of those who disagreed with the policy, the main reason offered at both surveys was that the interval between smears was too wide.

Table 4.8: Staff knowledge of and attitudes toward screening policy and Pap smear practices

Knowledge/attitude	Site 1		Site 2		Site 3		Total		
	Pre N=51	Post N=40	Pre N=29	Post N=28	Pre N=31	Post N=22	Pre N=111	Post N=90	p value*
Aware of policy	46 (90.2)	39 (97.5)	19 (65.5)	25 (89.3)	17 (54.8)	18 (81.8)	82 (73.8)	82 (91.1)	0.002
Correctly stated policy	29 (56.9)	38 (95.0)	7 (24.1)	24 (85.7)	12 (38.7)	12 (54.5)	48 (43.2)	74 (82.2)	<0.001
Agreed with policy	7 (13.7)	25 (62.5)	6 (20.7)	21 (75.0)	12 (38.7)	15 (68.2)	25 (22.5)	61 (67.7)	<0.001
Ever performed a Pap smear	43 (84.3)	39 (97.5)	15 (51.7)	25 (89.3)	4 (12.9)	13 (59.1)	62 (55.8)	77 (85.6)	<0.001

Data are n (%)

* Pre- and post-proportions were compared across all sites, p-values are from χ^2 and Fisher's exact tests

In the pre-intervention survey, overall, just over half of the participants had ever performed a Pap smear with significantly more staff in Site 1 performing Pap smears compared to staff in Site 2 (84% vs. 52%, $p < 0.001$) and staff in Site 3 (84% vs. 13%, $p < 0.001$). Staff at all three sites felt that more Pap smears could be done at the facilities. Pre-intervention in Sites 1 and 2 participants cited that the main obstacle to performing Pap smears was insufficient staff, whereas in Site 3 the main obstacle was a lack of equipment. Overall the proportion of staff who ever performed a Pap smear increased significantly in the post-intervention survey (56% to 86%, $p < 0.001$). Although the proportion of staff that ever performed a Pap smear in Site 3 increased post-intervention, this was still significantly lower compared to the post-intervention proportion of staff that ever performed a Pap smear in Site 1 ($p < 0.001$) and Site 2 ($p = 0.016$). In the post-intervention survey participants in all 3 sites mentioned staff shortages as the main obstacle for not performing more Pap smears.

Nurses' lack of understanding of how to manage clients with abnormal cytology results was recognised as a problem in the pre-intervention survey and in discussions with nurses during training. At pre-intervention 35% of the participants in Site 1, 10% in Site 2 and none in Site 3 were aware of the correct management for a HSIL. As part of the intervention the recommended management approach for a client with a HSIL result was a clear "refer for colposcopy." In the post-intervention survey, nurses who had done Pap smears in the previous three months were asked to describe the management of clients with HSIL. Of the 58 nurses who responded, only 40 (69%) correctly stated the appropriate management for HSIL (63% in Site 1, 87% in Site 2, and 45% in Site 3).

4.3.3 Cytology services

Clinic staff at all three sites and laboratory staff at Laboratories B and C reported being satisfied with the new cytology request and report forms. Staff in Laboratory A used the request and report forms during a six week trial period and reported that the forms were easy to use. However the laboratory management indicated that it would not be possible to adopt the new forms until further discussions were held with the newly-formed NHLS, and discontinued using the forms after the six-week trial period ended.

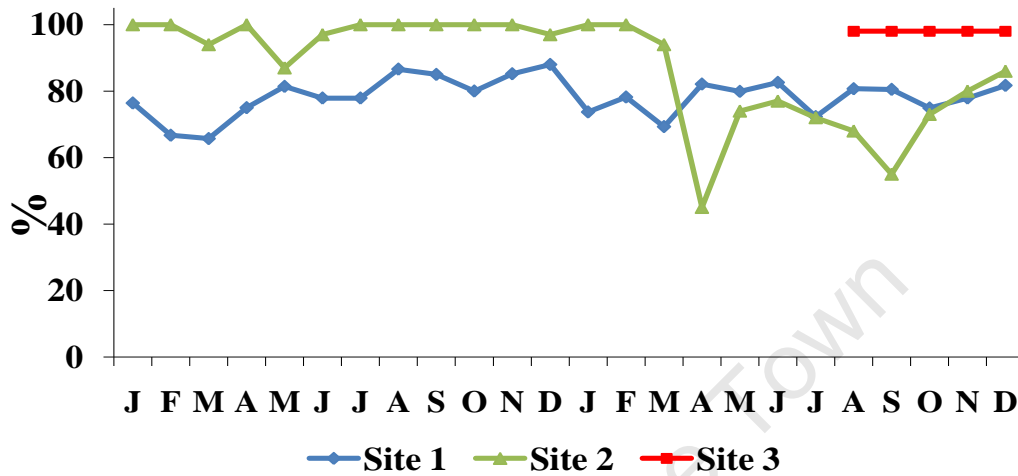
Despite discussions with laboratory staff and encouragement of clinic staff to follow up with laboratories when results were not returned quickly enough, problems with long turnaround times persisted. In Site 1 in the pre-intervention survey, health managers reported that they waited 3.1 weeks, on average, to receive laboratory results. At the time of the post-intervention assessment this had increased to 5.6 weeks. Examination of Pap register data in Site 1 revealed that 5% of laboratory reports had not been received after four months, and that for those received, the average turnaround time was five weeks. Severe laboratory staff shortages were given as the reason for these increased delays.

In Site 2 in the pre-intervention survey health managers estimated that smear results were available at the clinic in six weeks. When Site 2 began sending slides to Laboratory C, turnaround times were reduced to an estimated two weeks, primarily because Laboratory C had an established transport courier system that collected specimens from and delivered results to facilities. A review of the Pap registers in Site 2 clinics, however, revealed that the turnaround time in late 2002 was nine days, however, 9% of results had still not been received by clinics after four months.

Health managers in Site 3 reported that turnaround times remained long, and that results were returned to the clinics in eight weeks. A review of Pap register data showed that almost one-fifth of results had had not been received by Site 3 clinics up to four months later, and of those received, the mean turnaround time was 6.3 weeks.

Over the study period three different laboratories read cytology smears. The proportion of smears read in Laboratory A serving Site 1, that had endocervical cells varied each month between 65% and 88% (Figure 4.2). In Laboratory B which served Site 2 until March 2002, 99% of smears (range per month, 96 -100% per month) had endocervical cells present. When Site 2 clinics began sending slides to Laboratory C (from April 2002), the percentage of smears with sufficient endocervical cells decreased to between 45% and 86% per month. Laboratory B also served Site 3 and the percentage of smears with an endocervical component were almost 100% for Site 3.

Figure 4.2: Percentage of Pap smears with endocervical component, 2001- 2002



Note: Site 2 switched from Laboratory B to Laboratory C in April 2002. Site 3 used Laboratory B throughout

4.3.4 Referral and feedback

The system for referring Site 1 clients to the colposcopy clinic at the tertiary hospital did not change over the course of the study, with the laboratory continuing to contact clients by letter about colposcopy appointments. The only change made was that laboratory staff recorded the date of the colposcopy appointment on the cytology report that was returned to the clinic. At one clinic, one of the professional nurses reported phoning colposcopy clients to reassure them, and at another, the staff reported sending an additional letter to clients to provide more information. Staff at other clinics in Site 1 reported that clients often came to them seeking clarification about the colposcopy appointment letter they had received from the laboratory.

During the post-intervention assessment, none of the health facility managers or staff providing screening services in Site 1 reported ever having seen the feedback letters. However research staff did find feedback letters in client folders. The clinic administrator had filed them without communicating their contents to any of the nursing staff.

In Site 2 staff reported using the standard referral letters for clients that needed further assessments at secondary and tertiary levels. To reduce unnecessary visits, research staff tried to persuade the provincial authorities to modify the referral pattern, so that clients would go straight to the provincial tertiary level hospital for a colposcopy assessment as the secondary level hospitals did not have colposcopy machines. However, this did not happen as provincial authorities felt they needed to address referral patterns for the province as a whole. Non-colposcopy-directed biopsies were discontinued at the secondary level hospital. Clients with abnormal Pap smears were assessed by a gynaecologist at the secondary level hospital and referred to a tertiary hospital. By the end of the study the originating clinics still did not receive feedback from the secondary or tertiary level hospitals.

Although an agreement was reached during the study in Site 3 about referring cancer patients or those with HSIL directly to the regional hospital, staff mostly continued to refer clients to the district hospital, from where they were again referred to the regional hospital, causing a needless intermediary visit. Staff reported that they never received feedback from the referral hospitals.

4.3.5 Record keeping and data collation

Pre-intervention there was a lack of tools for data collection and collation. Post-intervention there was a positive response to the introduction of the Pap registers. Pap smear registers were filled in correctly in all three sites and were being used by staff to track clients with abnormal Pap smears. However the data collation sheets were not being consistently used by all facility managers. Facility managers reported discussing cervical screening statistics at clinic meetings, however there were no reports or minutes of meetings available to verify this.

4.3.6 Client knowledge, attitudes and practices

The women interviewed in both surveys were most commonly in the health centre that day for general medical consultations or to accompany someone. Only 16 (1.4%) of the pre-intervention group and 22 (2.0%) of the post-intervention group were at the health service specifically for a Pap smear. The overall socio-demographic profile of women in the pre- and post-intervention surveys were similar (Table 4.9). The overall median age for women in the pre- and post-intervention group was 36 years (interquartile range 30 - 45) and 35 years (interquartile range 29 - 44) respectively. In the pre-intervention group women in Site 2 were slightly older (median age 38 years, interquartile range 32 - 47) compared to women in Site 1 (median age 36 years interquartile range 30 - 46) (Wilcoxon p-value = 0.015) and women in Site 3 (median age 34 years interquartile range 29 - 41) (Wilcoxon p-value < 0.001). In the post-intervention survey there was no significant difference in the mean age between sites ($p = 0.063$). The overall education levels of women in the pre- and post-intervention surveys were similar. The majority of women in the pre- and post-interventions surveys were unemployed. The highest employment level was in Site 1 and the lowest in Site 3 in both the pre- and post-intervention surveys.

Table 4.9: Socio-demographic profile of clients

	Site 1		Site 2		Site 3		Total		
	Pre N=445	Post N=449	Pre N=341	Post N=341	Pre N=335	Post N=328	Pre N = 1121	Post N = 1118	p value*
Married	302 (67.8)	268 (59.6)	123 (36.0)	117 (34.3)	140 (41.8)	147 (44.8)	565 (50.4)	532 (47.6)	0.183
Employed	141 (31.7)	123 (27.4)	92 (27.0)	74 (21.7)	48 (14.3)	60 (17.6)	281 (25.1)	258 (23.0)	0.250
Attended high school	296 (66.5)	325 (72.4)	229 (67.1)	225 (66.2)	220 (65.7)	224 (68.3)	745 (66.5)	774 (69.3)	0.160

Data are n (%)

* Pre- and post-proportions were compared across all sites, p-values are from χ^2 and Fisher's exact tests

Changes in clients' knowledge about cervical cancer are provided in Table 4.10. Overall although the proportion of women that had had heard of cervical cancer had increased post-intervention (50% to 54 %), this difference was not statistically significant ($p = 0.079$). Similarly the proportion of women that had heard of Pap smears increased from 52 to 56%, but this increase was not statistically significant ($p = 0.065$). Significantly more women in the post-intervention survey had knowledge about the cervical cancer screening policy. In both the pre- and post-intervention surveys clients in Site 1 had significantly higher knowledge of cervical cancer, Pap smears and the policy compared to clients in Sites 2 and 3. In Site 1 knowledge levels increased significantly across all knowledge measures post-intervention, except for the proportion of clients that had ever heard of a Pap smear which was already high in the pre-intervention survey. In Site 2 the proportion of women who had ever heard of cervical cancer and the proportion that knew that cervical cancer can be prevented decreased significantly post-intervention ($p < 0.001$ for both measures). There was no significant increase in any of the knowledge measures in the post- compared to pre--intervention survey in Site 2. Women in Site 3 had very low levels of knowledge of Pap smears, cervical cancer and the cervical cancer screening policy in the pre-intervention survey and although there were significant increases in knowledge levels post-intervention, levels were still low.

The proportion of women that ever had a Pap smear remained constant at 38% during the pre-and post-intervention surveys. Pre- and post-intervention, reported use of Pap smears was 78% vs. 74% in Site 1 ($p = 0.134$), 18% vs. 20% in Site 2 ($p = 0.433$), and 5% vs. 8% in Site 3 ($p = 0.141$). Among women that had not previously had a Pap smear, two-thirds of the women in Sites 2 and 3 and one-third of the women in Site 3, in both the pre- and post-intervention surveys said the reason for not having had a Pap smear was that they had never heard of a Pap smear. Once the interviewers had described and explained the reasons for a Pap smear, more than 85% of respondents expressed interest in having one.

Table 4.10: Clients' knowledge about cervical cancer prevention

	Site 1		Site 2		Site 3		Total		
	Pre N=445	Post N=449	Pre N=341	Post N=341	Pre N=335	Post N=328	Pre N=1121	Post N=1118	p- value*
Ever heard of Pap smear	424 (95.2)	423 (94.2)	107 (31.4)	107 (31.4)	32 (9.6)	73 (22.3)	563 (50.2)	603 (53.9)	0.079
Knows part of body examined for by Pap smear	379 (85.2)	404 (90.0)	94 (27.6)	103 (30.2)	29 (8.7)	68 (20.7)	502 (44.8)	575 (51.4)	0.002
Knows that national policy calls for first Pap smear after age 30	81 (18.2)	250 (55.7)	39 (11.4)	46 (13.5)	8 (2.4)	54 (16.5)	128 (11.4)	350 (31.3)	0.000
Knows that national policy states calls for Pap smear every 10 years	120 (26.9)	167 (37.2)	8 (2.3)	7 (2.1)	0 (0.0)	4 (1.2)	128 (11.4)	178 (15.9)	0.002
Ever heard of cancer of the cervix	324 (72.8)	372 (82.9)	176 (51.6)	111 (32.6)	81 (24.2)	140 (42.7)	580 (51.7)	623 (55.7)	0.065
Knows cervical cancer can be prevented	263 (59.1)	297 (66.0)	121 (36.0)	80 (23.5)	54 (16.1)	100 (30.5)	438 (39.1)	477 (42.7)	0.084

Data are n (%) * Pre- and post-proportions were compared across all sites, p-values are from χ^2 and Fisher's exact tests

In both surveys women were asked if they had received information on Pap smears or cervical cancer in the preceding six months, from a variety of sources. Results are shown in Table 4.11. In the post-intervention survey a higher proportion of women reported having heard or seen cervical cancer information from all sources of information.

Although these differences were significant, the majority of women interviewed in both the pre- and post-intervention surveys had not seen a poster or pamphlet; heard or read; or had discussions about cervical cancer and Pap smears. In the post-intervention survey posters, pamphlets and the radio were the most common source of information in Site 1, whereas the radio and health worker group talks were the most common in Sites 2 and 3. Although the proportion of individual discussions with health workers increased post-intervention this remained very low.

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Table 4.11: Source of information and discussions about Pap smears or cervical cancer in preceding six months

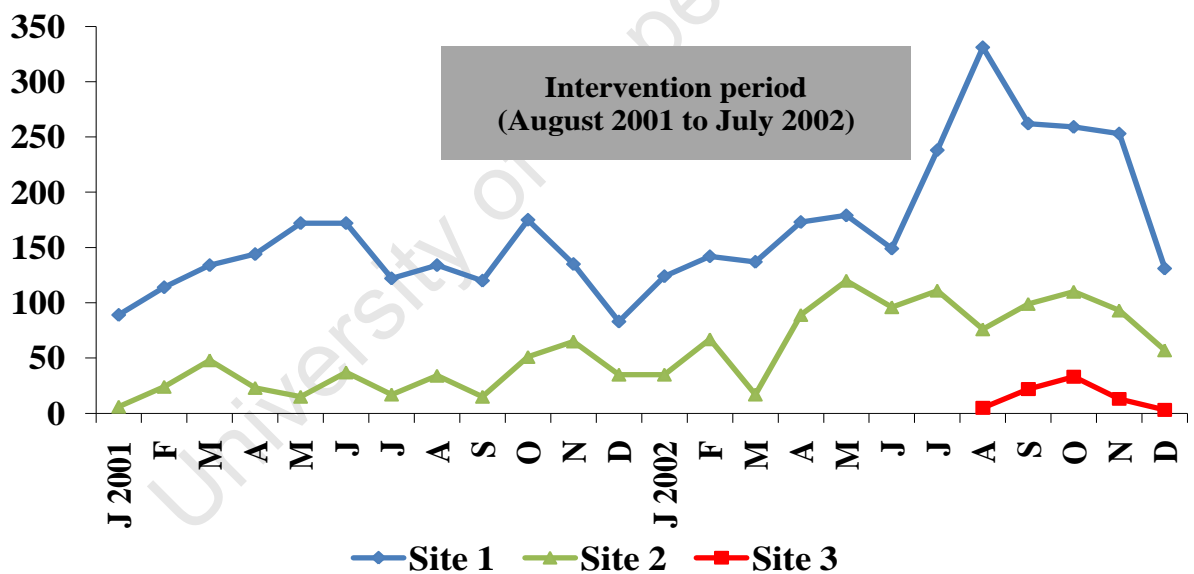
	Site 1		Site 2		Site 3		Total		p- value*
	Pre N=445	Post N=449	Pre N=341	Post N=341	Pre N=335	Post N=328	Pre N=1121	Post N=1118	
Poster	76 (17.1)	238 (53.0)	23 (6.7)	17 (5.0)	4 (1.2)	39 (11.9)	103 (9.2)	294 (26.3)	<0.001
Pamphlet	26 (5.8)	215 (47.9)	14 (4.1)	20 (5.9)	7 (2.1)	23 (7.0)	47 (4.2)	258 (23.1)	< 0.001
Group talk with health worker	44 (9.9)	130 (30.0)	14 (4.1)	116 (34.0)	17 (5.0)	69 (21.0)	35 (3.1)	315 (28.2)	< 0.0010
Discussion with health worker	17 (3.8)	58 (12.9)	14 (4.1)	17 (5.0)	7 (2.1)	6 (1.8)	38 (3.4)	81 (7.2)	< 0.001
Organised talk in community	4 (0.9)	40 (8.9)	14 (4.1)	14 (4.1)	7 (2.1)	6 (1.8)	25 (2.2)	60 (5.4)	< 0.001
Radio	71 (16.0)	180 (40.1)	82 (24.0)	170 (49.9)	40 (11.7)	148 (45.1)	193 (17.2)	498 (44.5)	< 0.001
Newspaper	26 (5.8)	143 (31.8)	23 (6.7)	14 (4.1)	7 (2.1)	3 (0.9)	56 (5.0)	160 (14.3)	< 0.001

Data are n (%) * Pre- and post-proportions were compared across all sites, p-values are from χ^2 and Fisher's exact tests

4.3.7 Number of Pap smears performed and Pap smear coverage

In the three sites overall, the total number of Pap smears (new and repeat) performed increased from 1 964 in 2001 to 3 466 in 2002, with the majority of the increase occurring in the post-intervention period (from July 2002). In the pre-intervention phase 84% of Pap smears in Site 1 and 70% of the Pap smears in Site 2 were in the appropriate target age. In the post- intervention phase this increased to 94% in Site 1 and 84% in Site 2. In Site 3 no Pap smears were being done in the pre-intervention phase and 88% of Pap smears in the post-intervention phase were in the appropriate target age. The number of Pap smears done per month for each site for 2001 and 2002 is shown in Figure 4.3.

Figure 4.3: Number of Pap smears per month



In 2001, staff in the nine clinics in Site 1 performed 1 594 Pap smears, an average of 132 per month. In the post-intervention period (July to December 2002) the average number of Pap smears performed per month increased to 246 per month, an 86% increase. Of these 76% were new (not repeat) smears. Clinics in Site 2 did 370 Pap smears in 2001, an average of 31 per month. In the post-intervention period this increased to an average of 91 per month, a 194% increase. Of these smears 90% consisted of Pap smears done on new clients. No Pap smears were being done in the

clinics of Site 3 prior to this study. For the period August to December 2002 staff performed 133 Pap smears, 96% of which were new (not repeat) smears.

All three sites had set a target of screening 7% of the eligible women in their catchment populations per annum. Pre-intervention Pap smear coverage for the period January to December 2001 was calculated by dividing the number of new Pap smears done in that period by the target catchment population. In Sites 1 and 2 all interventions were only implemented by June 2002 and in Site 3 by July 2002. To calculate an annual post- intervention Pap smear coverage for a 1-year period, we assumed that sites would continue to perform the same average number of Paps performed per month as they did in the period July to December 2002 for Sites 1 and 2 and August to December for Site 3, for a 1-year period. Pap smear coverage per site is shown in Table 4.12.

Table 4.12: Pap smear coverage

	Site 1		Site 2		Site 3	
	No. of new Paps	Coverage	No. of new Paps	Coverage	No. of new Paps	Coverage
Pre-intervention	1 211	2.3%	333	0.9%	0	0%
Post-intervention*	2 240	4.2%	962	2.1%	256	0.8%

*post-intervention data are annualised

4.3.8 Referral of clients with HSILs

Across the three sites, 28 women had a result of HSIL in the post-intervention period between July and October 2002 and all were referred for colposcopy (Table 4.13).

Only 14 women with HSIL had a colposcopy assessment and/or biopsy within 6 months of the Pap smear and six (43%) had their diagnosis confirmed.

Table 4.13: Referral and management of clients with HSILs

	Site 1	Site 2	Site 3	Total
Number of smears done in a 4-month period	1 090	396	60	1 546
Number of HSILs identified (%)	19 (1.7%)	6 (1.5%)	3 (5.0%)	28 (1.8)
Number of clients referred for further management	19	6	3	28
Number that attended colposcopy services within 6 months of Pap smear	12	0	2	14
Number in which the diagnosis of HSIL was confirmed by histology	4	-	2	6

4.4 Discussion

This study identified a number of challenges to public sector cytology-based cervical cancer screening in South Africa. It also demonstrated that significant improvements can be made through a multifaceted intervention. The three sites in this study were purposively selected. The infrastructural and socio-demographic situations differed between the sites but are likely to be representative of the main types of health settings in South Africa.

The pre- and post- intervention study design is common in health system research as it corresponds to program evaluation activities. A limitation of the design is that without a control group it is difficult to be certain that changes can be attributed to the interventions. Due to research resource constraints in this study, it was not possible to include a control group. However, as there were no other cervical cancer screening activities in the research sites, it is likely that changes observed in this study can be

attributed to the research interventions. A limitation of the study is that the interventions took place over a fairly short period and evaluations took place soon after the interventions were introduced, results need to be viewed with this in mind. Although the study officially lasted two years, initial progress was slow, especially in Site 3, where services were being established for the first time. Training staff and developing IEC materials took longer than expected, so there was not enough time remaining in the study to support the services for as long as expected or desired. Funding constraints meant that follow-up staff and client surveys took place less than six months after all the interventions were implemented. Providers' knowledge, attitudes, and practices were assessed a very short time after training and intensive support; this might have yielded more positive results than if the survey had been conducted later. The relatively lower response rate among providers in Site 3 was due to the post-intervention interviews being conducted during the end-of-year vacation period. This could have introduced bias if leave allocation was related to level of experience and knowledge of staff.

Measures of community knowledge were based on surveys of clinic attendees. It is unlikely that the systematic sampling of clinic attendees could have introduced any bias, as queues in the waiting area were not ordered according to any pattern. However the women interviewed are likely to represent a sample of the population who are more likely to attend modern health facilities and possibly more likely to avail themselves to cervical screening. A more representative community-based sample might in fact show even poorer results in terms of improved cervical cancer KAP.

Rather than setting up distinct data-gathering systems specifically for this research study, systems based in the health services were used. Although this made the data more visible to clinic staff, and offered the potential for data to be used for health service quality improvement, it also meant there was less control on data quality. The use of routine data systems illustrates the difference between efficacy (results under ideal conditions) and effectiveness (real conditions) of health system interventions.

In managing a health systems research study, there is always a fine balance between intervening too much and establishing a non-replicable scenario or intervening too

little and achieving negligible results. In this case, the intervention and the site support did not last very long and health service managers and providers were instrumental in developing the interventions. However the services were supported fairly intensively by the research staff over this short period, probably much more than would be expected in reality.

As a result of the interventions cervical screening services became more available and many more women were screened. However, clinic staff were not proactive in recruiting clients for Pap smears. This was shown by the client survey which found that most women, once they were informed of Pap smears, were interested in having one, suggesting further potential for increasing coverage among general clinic attendees.

As a result of the training more staff were able to perform Pap smears, and knowledge of and attitudes toward the cervical screening policy improved. The post-intervention assessments showed an increase in the proportion of women screened in the national screening policy recommended target age group. However, knowledge gaps remained, especially with regard to the management of clients with abnormal Pap smears and post- intervention only 69% of staff who had performed Pap smears in the preceding 3 months correctly stated the appropriate management for HSIL. Although, in the short 4-month follow-up of clients with HSILs, we noted that all HSIL clients were appropriately referred by clinic staff for colposcopy, staff did not confirm client attendance at the colposcopy clinic.

The presence of endocervical cells in the Pap smear indicates that the specimen has been collected from the transformation zone of the cervix (Solomon et al. 2002). It is often used to assess staff competence in taking good Pap smears and it is generally accepted that 80% of Pap smears taken should have an endocervical component present (Herbert, Johnson & Patnick 1995). However, detection of endocervical cells is also dependent of the skill of the by cyto-technician in reading Pap smear slides (Roberson et al. 2002). In our study we noted a dramatic change in reported endocervical component when Site 2 changed the laboratory used in April 2002. This together with the considerable difference in the presence of endocervical cells reported at the various laboratories was disturbing and has important resource and

individual client implications. In this study we were unable to disentangle whether the lack of endocervical cells reported was due to a poorly taken Pap smear or from a poorly interpreted Pap smear. Further research into the accuracy of endocervical reporting is required so that appropriate corrective action can be taken.

Also of concern was that only 44% of women referred for colposcopy after a cytology HSIL result were found to have high-grade disease. This was a very small sample and further research is needed on laboratory quality assurance and diagnostic thresholds.

The turnaround time for clinics to receive Pap smear results from the laboratories continued to be long. To a large extent, this is a function of continued cytology staff shortages and limited recruitment to the field (Michelow, Dubb 2003). Poorly functioning administrative and transportation systems also contribute to this problem. The NHLS and respective provincial authorities need to examine these issues as a matter of urgency. Without investment in the training of new cytology laboratory staff and attention to strengthening systems for sorting and transporting specimens, an accelerated client recruitment drive would cause serious problems for the laboratories.

Clients' awareness of Pap smears and cervical cancer was very low pre-intervention, especially in Sites 2 and 3. Reasons for the decrease in client knowledge in Site 2 (i.e. the proportion of clients that had ever heard of cervical cancer and the proportion of clients that knew cervical cancer could be prevented) are not clear, but could be related to the fact that Site 2 had decided to use pre-existing IEC materials, rather than those developed by the study. Further, Site 2 also reported a shortfall in supply of provincial IEC materials. Overall the time and resources needed for the IEC campaign were high and the results were minimal. Although more women reported receiving information via the radio, posters and pamphlets post-intervention, this did not translate into an increase in the number of Pap smears among women interviewed, which remained constant at 38%. The proportion of women who had a Pap smear differed across the three sites both at baseline and post-intervention, with the highest proportion reported in Site 1 and the lowest in Site 3. These differences could be related to differences in the health care infrastructure and per capita expenditure between the sites (see Table 4.1) and highlight the importance of health care context

in implementing a cervical cancer screening program. The addition of an intervention to an already under-resourced area with poorly functioning health systems may not lead to the desired improvement in screening coverage unless pre-existing infrastructure weaknesses are addressed.

The proportion of clients who reported receiving Pap smear information from discussions with the health provider during the post-intervention survey was very low (7%). Perhaps it was unrealistic to expect a larger change as the post-intervention survey was conducted after a relatively short intervention period. However, this does represent a considerable missed opportunity. Studies elsewhere have shown the importance of provider interactions in affecting health behaviour (Mandelblatt, Yabroff 2000; Miedema, Tatemichi 2003; Ogedegbe et al. 2005). Coverage could have been significantly increased if clinic staff approached women attending health facilities for any reason, discussed cervical cancer screening and offered them a Pap smear.

Post-intervention staff at all three sites cited staff shortages as one of the barriers to doing more Pap smears. During the study period the number of professional nurses decreased from 130 to 113, and increasing demands were being placed on a shrinking workforce. The shortage of primary care nurses in the public sector health services has been recognised nationally (Day, Gray 1998; Day, Gray 2008; Kawonga, Fonn 2008; Coovadia et al. 2009). Unless this crisis is addressed the successful implementation of a national cervical screening programme will be severely hampered.

It is critical that women with HSILs are identified, referred and treated, as the majority of these lesions progress to invasive cervical cancer (Kinlen, Spriggs 1978; Chang 1990). Programmes need to focus every effort on ensuring that the women identified with HSILs attend colposcopy appointments. Although all women with HSIL seen over a four-month period were informed of the need to attend a referral facility, there still was considerable loss to follow-up in this population. Despite efforts to improve inter-facility linkages and establish feedback systems so that clinics know which of their clients fail to attend referral visits, these continued to malfunction. Clinic staff did not follow-up the relatively small number of clients with

HSIL that were referred to colposcopy to confirm attendance. Poorly managed clinic administrative systems also meant that feedback letters from the colposcopy centre were being filed without staff having reviewed the contents. At the district and provincial levels, it was difficult to affect changes to referral and feed-back letters, reporting systems, and forms.

Establishing well-functioning information systems are essential for successful programme monitoring and evaluation. At the clinic level the Pap smear registers were being used by staff to collect data on clients. However the data were not being optimally used to track clients with abnormal Pap smears. Data collation and use of data for programme monitoring by facility and programme managers also continued to be sub-optimal. This reflects a wider problem of limited information management capacity within the health system and is not restricted to cervical cancer prevention services (Coovadia et al. 2009). Managers had not detected or acted upon: the failure of clinics to meet monthly Pap smear targets, problems with follow-up of clients with abnormalities and poor feedback from colposcopy services.

The South African cervical cancer screening policy requires that women with normal cytology results return for a repeat smear in 10 year intervals. Loss to follow-up will compromise the potential benefit of the cervical cancer screening strategy. Systems to track women and ensure they return for repeat Pap smears will need to be developed.

A positive outcome of the study was that the interventions and manuals developed are being used by the National Department of Health to set-up and provide cervical screening services. The cytology request and reporting forms have subsequently been adapted and adopted by the NHLS. However cervical cancer screening programmes will not be effective in reducing cervical cancer mortality unless there is a high coverage of the target population (World Health Organization 1986; IARC 2005). Although the number of women screened post-intervention increased, none of the sites was able to meet their annual target coverage (7%). Perhaps the target was unreasonably high within the short time period that interventions were being implemented. The annualised coverage in the first year post- intervention was 4.2% at best. In future years the three sites will need to significantly increase the number of

women screened to reach an average coverage of more than 7% each year; in order to meet the national goal of 70% coverage within 10 years.

Evidence suggests that implementing and re-organizing health programs is complex and requires multifaceted interventions and ongoing support (Grol & Grimshaw 2003 2003; Grol & Wensing 2004). Developing systems to ensure access to high quality cytology-based services is a known challenge (Lazcano-Ponce et al. 1999; Sankaranarayanan, Budukh & Rajkumar 2001; IARC 2005). Our end results show that with health system interventions, cervical cancer screening service related outputs can be substantially improved. However cervical cancer screening coverage and follow-up of clients with HSIL was sub-optimal and, despite an IEC campaign, client KAP did not improve. In our experience co-ordinating and linking the different service facilities, embracing shared goals, developing common protocols, defining areas of responsibility, and defining management goals and activities proved to be challenging tasks. This was due in part to competing health demands, but it was also due to bureaucratic inertia that impede all efforts to change the way things have always been done and to poor stewardship, leadership and management. These problems have been described elsewhere (Coovadia et al. 2009) and are not unique to the cervical cancer prevention programme. Although it has been suggested that alternate screening technologies, such as visual inspection with acetic acid or HPV testing be explored particularly in low-income countries, for any cervical cancer strategy to be successful in South Africa the more fundamental challenge is one of political will and improved stewardship and management in the health system.

Chapter 5: Preparing for HPV vaccination in South Africa

This chapter presents the methods, results and discussion for the study objective: To understand key opinions about, challenges to, and opportunities for the introduction of the HPV vaccine in the public sector in South Africa. The chapter is structured as follows:

5.1. Methods

- 5.1.1. Study design
- 5.1.2. Study setting
- 5.1.3. Data collection
- 5.1.4. Data analysis

5.2. Results

5.2.1. Community level

- 5.2.1.1. Knowledge and perceptions of cervical cancer
- 5.2.1.2. Views on vaccination as a means of primary prevention of cervical cancer
- 5.2.1.3. Possible opposition to the HPV vaccine
- 5.2.1.4. HPV vaccine delivery

5.2.2. Provider level

- 5.2.2.1. Views on current cervical cancer screening policy and programme
- 5.2.2.2. HPV vaccine as a method of cervical cancer prevention
- 5.2.2.3. Possible opposition to the HPV vaccine
- 5.2.2.4. HPV vaccine delivery

5.2.3. Policy level

- 5.2.3.1. Views on current cervical cancer screening policy and programme
- 5.2.3.2. HPV vaccine as a method of cervical cancer prevention
- 5.2.3.3. Possible opposition to the HPV vaccine
- 5.2.3.4. HPV vaccine delivery

5.3. Discussion

5.1 Methods

5.1.1 Study design

A qualitative study was conducted in the Western Cape Province between February 2007 and March 2008, to explore key opinions about, potential challenges to and opportunities for, HPV vaccination introduction in South Africa. Qualitative research has its origins in the social sciences but is increasingly being used in health service research (Mays, Pope 1995). It focuses on understanding how beliefs and perceptions influence behaviour, and is particularly useful in exploring a topic about which little is known (Pope, Mays 1995). In conducting this study an ecological conceptual perspective was utilised. This perspective recognises that individual health behaviors are influenced at different levels within a complex environment (Green, Kreuter 2005; McLaren, Hawe 2005). The ecological model provides a framework to collect both content-specific and contextual information. It allows for the integration of multiple levels and contexts in understanding complex health issues. Our enquiry was directed at three levels of influence: community, health service provider (institutional level) and policy (Table 5.1).

The community level of enquiry included discussions with women who had children eligible for the HPV vaccine as they would be key in making decisions as to whether their child would or would not receive the vaccine. In addition these women would be aware of organisations and individuals likely to influence health making decisions in the community. At the provider level individuals who were involved in the following services were interviewed: reproductive, maternal, child or school health. The policy level of enquiry included policymakers as well as individuals likely to influence the policy-making process: managers and directors working in sexual and reproductive health, and women's and child health at the provincial and national level; managers in the education directorates at provincial and national level; and academics and researchers in the fields of sexual and reproductive health, virology, infectious diseases and cervical cancer.

Table 5.1: Levels of enquiry, study respondents and data collection methods

Level of enquiry	Respondents	Data collection method
Community level	Women with children aged 8 to 18 years	Focus group discussions
Institutional/Provider level	Primary care nurses School health nurses Doctors working at primary health care clinics Clinic managers	In-depth interviews
Policy level	Provincial policy makers - Departments of Health and Education National policy makers - Departments of Health and Education Researchers Academics	In-depth interviews

5.1.2 Study setting

Three sites in the Western Cape Province were selected for the community and health service provider level of enquiry. The sites were selected to represent different urban and rural settings in the Province. Site A is a rural area located in the Breede Valley, a wine and fruit growing area 120 kilometers from Cape Town, and has a population of 143 520 (67% Coloured, 20% Black and 13% White). Site A has an unemployment rate of 20% and 59% of the population have attained a Grade 8 or higher level of education (Statistics South Africa 2003). Site B, an urban area formally designated for Coloured South Africans, is located approximately 30 kilometers from Cape Town and has a population of 305 343 (84% Coloured, 15% Black). It has an unemployment rate of 30% and 72% of the population have attained Grade 8 or higher level of education (Statistics South Africa 2003). Site C, is an urban area in a coastal suburb of Cape Town. It has a population of 21 843 (38% Black, 35% White and 27% Coloured). Seventy-two percent of the adult population have attained Grade 8 or higher level of education and the area has an unemployment rate of 21%

(Statistics South Africa 2003). Cervical cancer screening services are provided at the primary care clinics in all three sites. Only Site B has school health nurses.

For the policy level of enquiry policy makers as well as individuals likely to have an effect on the policy making process were from the Western Cape Province or based at a national level.

5.1.3 Data collection

For the community level of enquiry six focus group discussions were held; 2 in each of the three study sites. Providers in the six health care facilities assisted in purposively identifying and recruiting focus group participants (women with children aged 8 to 18 years). In total 43 female community members participated in the focus group discussion. On average, there were seven members per focus group (range 5 to 10). The median age of the participants was 32.7 years (interquartile range 27-35 years), 33 (77%) had completed some secondary school education, 26 (60.5%) were unemployed, and all had children eligible for HPV vaccination. Focus group discussions were conducted at either the health care facility or at a community venue (the church hall or public library).

In-depth interviews with health care providers were undertaken in six public sector health care facilities (two in each of the three study sites) providing reproductive, maternal and child health and cervical screening services. Twenty four in-depth interviews were conducted with: 2 doctors, 17 primary care nurses (2 of whom were also clinic managers) and 5 school health nurses.

A total of 26 in-depth interviews were held with policy makers and key policy informants. Study participants for the provider and policy level in-depth interviews were selected through purposive and snowball sampling (Bernard 1994). This enabled inclusion of individuals who had insights into the range of topics explored in the study.

Interview guides for the focus-group discussions (Appendix D) and in-depth interviews (Appendix E and F) and were semi-structured, open-ended and probing. Key issues explored included: understandings and perceptions of cervical cancer;

views and experiences on current cervical screening policy and programmes; experience with vaccination programmes in general; views about primary prevention of cervical cancer through vaccination; knowledge of the HPV vaccine; issues related to HPV vaccine safety, efficacy and cost, target populations, possible opposition and optimal age for vaccination; service delivery issues and the role of the private sector.

Interview guides and consent forms were piloted to check for language appropriateness and understanding. Experienced fieldworkers trained in qualitative research methods conducted the in-depth interviews and focus group discussions. Focus group discussions were conducted in the local language of participants. Interviews and focus group discussions were digitally-recorded and transcribed verbatim.

All participants provided written informed consent. Participants were assured that individual data would be confidential and anonymity maintained. Ethical approval was granted by the University of Cape Town, Faculty of Health Sciences Research Ethics Committee and the Western Cape Province and City of Cape Town Health Departments granted permission to conduct the study at the selected research sites.

5.1.4 Data analysis

Data were analysed using a thematic analysis approach in which main themes and categories were identified and analysed within and across data (Boyatzis 1998; Braun, Clarke 2006). Initial categories for analysing data were drawn from the interview guides. The transcripts were manually coded individually by members of the research team and then cross checked by another member of the research team for coder variation. Any coding discrepancies encountered were discussed and resolved by consensus. Over several meetings the research team identified key themes.

5.2 Results

Themes emerging from perceptions and insights expressed by respondents illustrate potential barriers to and facilitators for HPV vaccine introduction, and are highlighted below.

5.2.1 Community level

5.2.1.1 Knowledge and perceptions of cervical cancer

All focus group participants had heard of cancer and the general view was that perceptions of cancer within communities had changed over time, making it easier to discuss cancer and to access help.

Those years cancer was a sin. One couldn't just speak about their cancer then the other people gossiped. It was almost like they had a big virus but today you can speak about it if there is a chance for you to be helped.

(Focus group participant, Site C)

The majority of focus group participants had heard of cervical cancer and some knew of relatives or friends that had cervical cancer. In discussions on the cause of cervical cancer some participants alluded to the association between sexual activity and cervical cancer, others suggested injectable contraceptives and sexual trauma as possible causes.

Those people that have cervical cancer at a late age are sometimes people that where sexually active from a very early age and also if they have had many sexual partners and you don't go for the pap smears it can happen that you at a later stage develop cancer and cancer is ... and it can happen that the womb has to be removed.

(Focus group participant, Site A)

Although some women had prior experience with having a Pap smear, in general the purpose and preventive nature of Pap smears was poorly understood. For some, Pap smears were associated with “cleansing or scraping the womb”, after exposure to a sexually transmitted infection or after being raped. Others viewed Pap smears as a means of ensuring fertility.

5.2.1.2 Views on vaccination as a means of primary prevention of cervical cancer

All respondents were aware of the childhood immunisation programmes and had positive attitudes toward vaccination as a prevention tool. None of the focus group participants had heard of HPV or the HPV vaccine. Once basic information about both the link between HPV and cervical cancer and the HPV vaccine was provided by the interviewer, a positive attitude emerged from the groups towards this new product. Focus group participants reflected on the vaccine's potential for a future generation of women and girls.

If it can improve the future for all our daughters then it is a good thing. In the past we never knew about things like this and a lot of women's reproductive organs were removed because they contracted cancer. So I think it is a good thing.

(Focus group participant, Site B)

I have one daughter and I have to go and tell her what I heard here and I must tell her the reason why she should have that injection. It's for her health and her own good. If she is not going to do it now and at a later stage when she becomes sexually active and she gets the germ from another person or she transfers it then it is for their own health if they have it... (Focus group participant, Site A)

Some participants did not understand that the currently available HPV vaccines are prophylactic, not therapeutic, and enquired about the vaccine as a means to protect themselves against cervical cancer. When it was explained by the interviewer that the current vaccines need to be given prior to the onset of sexual activity, respondents suggested vaccinating children from the age of 9 years. This was related to perceptions of early onset of sexual activity in the community.

I will actually insist on it – the vaccine that you are speaking about especially for the children of the age 9 because I, as a mother, if I look at our community... the children in our community are very sexually active because they are already starting at the age of 10 and 11, they start with boyfriends and things like that. Prevention is better than cure. (Focus group participant, Site A)

Most community respondents' felt that boys and girls should be vaccinated as this would have a greater mutual benefit.

Because men today have lots of women and maybe the girl is not as active as the man and now he comes from a lot of women and maybe he comes and gives that to his steady girlfriend. I think it is something good to be given to them both for their protection. (Focus group participant, Site C)

A few community respondents had questions around the quality of the vaccine that would be used and concerns were raised that a cheaper, inferior vaccine could have a negative impact on fertility as this interchange suggests:

Many a time we use vaccines that are not on the same standard as first world countries even private vaccines and government vaccines in South Africa are totally different. Are they going to give us a cheaper vaccine with more side effects which we only see in 30 years and anything to do with the womb? Is it going to affect fertility later on in the child's life? That is something I would be a bit conscious about, a bit scared. (Focus group participant, Site B)

Yes, maybe the women can become sterilised because of that injection and they can perhaps never have children again. These are things that will be discovered. (Focus group participant, Site B)

Many community participants wanted the vaccine to be free like other childhood immunisations or available at low cost.

It should be free. Even if the government thinks about it - it is easier to give the three injections than to treat cancer later on because to treat cancer it is very expensive in the hospitals....The private hospitals are very expensive but it should be free. It would be cheaper for the whole country if it was given for free. (Focus group participant, Site C)

5.2.1.3 Possible opposition to the HPV vaccine

Focus group participants did not feel that having the HPV vaccine would be perceived by adolescents as permission to engage in sexual activity. In discussion on possible opposition to the HPV vaccine, participants commented that some parents and church groups may object to HPV vaccination if it were associated with sexual activity and STIs. Community respondents suggested marketing the vaccine as a prevention method against cancer rather than against a STI. Respondents pointed to the role of women's organisations and non-governmental organisations in preparing the way for the HPV vaccine.

5.2.1.4 HPV vaccine delivery

Community respondents mentioned both clinics and schools as possible routes for HPV vaccine delivery. Health care clinics were often named as the most suitable location for the distribution of the vaccine as "most people come to the clinic with their children to receive other immunisations." Other participants expressed support for delivery through schools to ensure coverage for all and to dovetail with the life skills school curriculum.

5.2.2 Provider level

5.2.2.1 Views on current cervical screening policy and programme

Most health care providers interviewed were aware of the national cervical screening policy. However a number of providers did not understand the rationale for the current policy and commented that starting cervical screening at the age of 30 years and at 10 yearly intervals, as the national guidelines suggest, was not optimal to ensure cervical health.

I'm concerned about the women younger than 30 years, that's a concern for me, because sometimes you do, if they fall pregnant or some, some reason, maybe they have a VD, a vaginal discharge or some other reason and then the doctors investigate and then it ends up being cervical cancer. We had one case like that a couple of years ago. (Primary health care nurse)

Providers felt that the current cervical cancer screening policy had not taken the HIV/AIDS epidemic into consideration and suggested that HIV positive women should be screened at a younger age and more frequently. A few providers were misinformed about the national policy, for example:

What I heard of the original policy was that women had to be screened every 10 years, and then they reduced it to every 5 years, and now I've heard that women are to be screened every year... in their reproductive years that would be between the ages of 14 and 45. (School nurse)

Providers were asked about challenges to implementing the current cervical cancer screening policy. Clinic managers mentioned low staff morale and heavy workloads as barriers to implementation.

You get a lot of resistance from the clinic staff, because they see it as extra work, so you had to work relatively hard on motivation, to motivate sisters as well about the policy... (Clinic manager)

Some providers mentioned that more needs to be done to educate women about Pap smears. A comment by one provider confirmed the views expressed in the focus group discussions that many women consider Pap smears a means of preventing infection. Providers also mentioned difficulties with getting clients to return for management of abnormal Pap smears.

A lot of women aren't aware, and there's an incorrect perception, women come here asking for a Pap smear because they have got an infection. They don't look at Pap smears as a cancer screening tool, they look at it as I've got a problem and I need a Pap smear, so I think a lot more needs to be done as far as educating people. (Primary health care nurse)

5.2.2.2 HPV vaccine as a method of cervical cancer prevention

A few providers working in reproductive health services had limited knowledge of the HPV vaccine, however the majority of providers interviewed had not heard of the vaccine. Once basic information on HPV vaccine as a means of primary prevention of

cervical cancer had been given by the interviewer, health service providers were in general supportive of the vaccine.

A few health service providers raised questions about the HPV types in South Africa, and the likely impact of the vaccine on cervical cancer rates.

Is it protecting against the strains that we have here... because you say it's two and here are, I know that there are more than two, that are carcinogenic strains. So I'm not so sure whether, I mean we've got the same strains, so whether it will be worth our while, you know, to give it (Family medicine doctor)

Providers felt that the age at which to initiate vaccine should be determined by the median age of sexual activity, which was considered to be between 9 and 15 years. Providers had mixed views on whether boys should be included in a vaccination programme. Some felt that saw vaccinating boys as a means of complete eradication of the virus. Others pointed to difficulties with attracting males to the health services

I don't know how receptive they're[boys] going to be to you know – reproductive health has always been focused on females more, then we have to have a whole mind set about, and reasons why, education as to why it is necessary, because it[HPV vaccine] can protect, you know, them. So I think it would be very difficult... (Clinic manager)

Providers raised questions about side-effects, how the vaccine would have to be administered and efficacy of the vaccine. A few providers specifically mentioned that parents would want to know about the effect of the vaccine on fertility.

The side-effects, nothing is 100%, the community they would worry that the vaccine will make their children barren.... will it? (Primary health care nurse)

5.2.2.3 Possible opposition to the HPV vaccine

The majority of the health care providers did not anticipate opposition to the introduction of the HPV vaccine from parents. Some providers thought that religious organisations may object to the vaccine on the grounds of promoting sexual

promiscuity, but felt that this could be countered by providing information about the long term health benefits of the vaccine in preventing cervical cancer.

5.2.2.4 HPV vaccine delivery

Delivery through schools was considered by many providers to be appropriate in terms of accessing the target population. Respondents also pointed to the role of the school curricula (particularly life skills) in assisting with educating children about protection from HPV and other sexually transmitted infections. However, a lack of human resource capacity was considered a potential barrier to delivery through schools. Some respondents recommended that a programme be created through a joint effort of schools and clinics to ensure effective vaccine roll out.

The school nurses are at the moment, to my knowledge, they've got a high case load and I don't think that they're going to be very happy accepting an extra project like this and so human resources is going to be a very big issue (Clinic manager)

Health service providers recounted the difficulties they had in reaching adolescents and most had reservations about HPV vaccine delivery through adolescent clinics. Providers also mentioned that in their experience adolescents who attended youth clinics were already sexually active, therefore youth clinics would not be suitable in reaching the appropriate target group.

Teenagers don't want to come to the clinic for those things. We are having a problem with family planning, we even tried another project to try to attract them, that we are having a special clinic for them you know, on Fridays, anything for family planning and voluntary counseling and testing services but, I'm telling you, that they don't want to come (Primary health care nurse).

5.2.3 Policy level

5.2.3.1 Views on current cervical screening policy and programme

Policy key informants expressed concern that the current cervical cancer screening policy had not considered the effect of HIV on cervical cancer. Many respondents suggested a revision of the national cervical screening policy by reducing the 10 year

time interval. However, respondents were also mindful of the impact more frequent screening would have on the health system.

But now with HIV and AIDS the compromised immune system can speed the progression of HIV and AIDS ...what would the effect of cervical cancer also have on a patient who's already immune compromised. So in that instance, it might necessitate reducing the period, the 10 year interval between the patients... (National Department of Health: Women's Health Programme)

Discussion on the current cervical screening policy and programmes led many policy makers to speak more generally about the structural constraints endemic to the healthcare system. Human resource shortages, patient education and lack of referral centers were mentioned as key barriers to implementation of the current cervical cancer screening programme.

But practically it's impossible, looking at the resources that you have, go to one clinic where you have only one nurse, automatically that nurse wouldn't be able to do it and they would give priority to the acutely ill patients as opposed to doing the screening, you know, and then you book the patient, they don't turn, they don't come back and you must understand, there's a lot of education that it still needs to go into that, making people aware how important that is, because they do the bookings, but people don't turn up. So can you see, so there are many lost opportunities, we would be doing better than we do now.

(Provincial sexual and reproductive health programme manager)

Half the screening programme is extremely flawed, it's a policy, which if it were properly implemented and had 80% coverage of the target age group, would have an impact on cervical cancer prevention, but we're nowhere near there, we haven't got anywhere near the correct coverage, we're using cytology as a screening test which is okay, but it's got lots of problems and particularly in low resource settings...

(Academic/Clinician)

When you find an abnormal smear, there's nowhere to send the lady, I mean there is no-one who sees them, there's no colposcopy at all in our area – so that's a big

problem you see. So if you can prevent it by vaccination, to me it's much, much better than having a system where you have a health system that's not working properly
(Researcher)

5.2.3.2 HPV vaccine as a method of cervical cancer prevention

Policy key informants had heard of the HPV vaccine and expressed strong support, viewing it as an important adjunct to existing cervical cancer prevention strategies as shown below.

I think it's excellent, really, because we have an opportunity to prevent the majority, the majority of cervical cancer. I think there's great opportunity in this vaccine. The only draw-back is that South Africa has such a backlog of women who have already been exposed to human papillomavirus and the only way we can prevent it in those women, and I'm sure there're loads of them out there is by doing Pap smears or screening and so that still needs to happen and so, if South Africa introduces the vaccine, we'll have to have Pap smear programmes or screening programmes on-going for quite a long time (Public health specialist)

Similar to providers, many policy makers felt that the age at which to initiate vaccine should be determined by the median age of sexual activity. Researchers and academics highlighted that an additional consideration in deciding on the optimal target age group is immunological response. It was mentioned that pre-adolescents had a stronger immune response than adolescents and for this reason a vaccination programme should focus on pre-adolescents.

Once you become sexually active, HPV enters the picture, is pretty much the take home message. So you've got to do it before then for it to be effective, so probably younger than 15, towards 12 and that's also probably where it's going to have, from an immunological perspective, a more robust response. That's going to be required to sustain the population level impact and the individual benefit
(Physician/Researcher)

Respondents had mixed views on including boys in a vaccination programme. Some felt that because of the high cost of the vaccine, males should not be included at this

stage Others pointed to the benefit of protection against anogenital warts if the quadrivalent vaccine is used, and the added benefit of herd immunity.

So, yes it can protect boys against types 6 and 11, but they count probably for less than 75% I would guess, of the warts in men, so it's not going to protect against all. You also have the second benefit you get, is that you reduce the transmittance to the women, of 18 and 16 as well, the men obviously if they were vaccinated, would not get those two common oncogenic ones, therefore if they have sex with someone who's not been vaccinated, the woman hasn't yet received her vaccine, then she may be protected through the vaccination of the man (Researcher/STI clinician)

Some policy makers felt that they required more information on the vaccine efficacy and side-effects. Questions on the safety of the vaccine in HIV positive individuals were spontaneously raised.

What we needed to know is their safety amongst HIV infected patients given the high prevalence of HIV in our country and we thought of, giving it okay from 9 it would be safe, but we could be having 9 year olds who are already HIV infected, maybe from mother to child transmission ((National Department of Health: Women's Health Programme)

When discussing the HPV vaccine as a method of cervical cancer prevention, most policy makers spontaneously raised concerns about cost. Policy makers mentioned that the government was considering rolling out the pneumococcal and rota-virus vaccines in the public sector, both expensive vaccines, and felt that introducing the HPV vaccine in the public sector would be unaffordable. Researchers and academics suggested that a reduced price be negotiated with the vaccine manufacturers.

5.2.2.3 Possible opposition to the HPV vaccine

Many policy informants anticipated some opposition from religious groups that generally oppose vaccines was to be expected. Some mentioned that the “negative reaction of the Christian right in the USA to the HPV vaccine” could influence religious groups in South Africa. However, most respondents felt that parental and public opposition would not be a major problem. A number of policy informants

suggested marketing the vaccine as a “cancer vaccine” rather than a “STI vaccine” as a means of minimizing opposition and referred to past experiences with the Hepatitis B and the introduction of the HPV vaccine elsewhere.

Hepatitis B is also sexually transmitted, nobody ever talks about that side of it at all, they never talk about well let's vaccinate our kids because they might get Hepatitis B when they become sexually active, but it's a reality, especially in South Africa with the high carrier rates, so I think that's a good thing to look at... (Researcher)

To my understanding there's been a lot of outreach by the various pharmaceutical companies to those groups to kind of alleviate any concerns and I think they've been relatively successful in saying this is a cancer vaccine. It's not about STI's, but protecting young girls from cervical malignancy that's highly prevalent, it's preventable now with this vaccine and I think that's a tactic that can be successful (Clinician)

The media and organisations such as LoveLife and Soul City were mentioned as potential sources of facilitating introduction of the HPV vaccine.

5.2.3.4 HPV vaccine delivery

Respondents had differing views in terms of who should manage the HPV vaccine programme. The Expanded Program on Immunization (EPI) was considered by some policy informants as a suitable location due to extensive experience with procuring, managing and monitoring vaccine delivery.

I strongly feel it should be under the EPI where all vaccines are stored and looked after. Because if you're going to start, get a new lot of people looking after vaccines again, then it's going to be another disaster, so rather with people who should be knowing about that – vaccine management and vaccine, the cold chain management is crucial (Provincial child health programme manager)

However, some respondents were concerned that the EPI traditionally was targeted at younger children and might not be able to reach optimum coverage in an older cohort of children.

I would be concerned about just labeling it EPI, because I think EPI is, traditionally is a sort of baby, under 5' , and I'd be worried that if we kick it to EPI and then wipe our hands and you know, feel like the job's done, it won't get done (Academic)

A maternal and child health manager referred to the planned introduction of the combined diphtheria and tetanus vaccine at age 12 by the EPI and suggested that the HPV vaccine could be administered in tandem with this vaccine.

For the most part policy informants felt that adolescent health had been neglected in South Africa, and that distributing the HPV vaccine at youth and adolescent clinics, which were few in number and located only in urban areas, would result in limited coverage. However some policy informants felt that a HPV vaccine would help prioritise adolescent health in the country and argued for distribution via strengthened youth clinics.

Most policy makers felt that the target population would be best accessed through a school delivery system. However many also pointed out that the school health system would need considerable strengthening to achieve adequate coverage. Department of Education respondents felt that the vaccine could be delivered through schools, but that this would require an increase in human resources, specifically school health nurses. Further it was suggested that the vaccine be accompanied by educational messages which could be delivered through the life-skills orientation curriculum.

Respondents were asked to comment on the possible role of the private sector with regard to uptake of the HPV vaccine. Many policy informants mentioned that general practitioners (GPs) see a broad range of patients throughout the life cycle and could be an important source of access to the HPV vaccine. In addition it was mentioned that private health care providers generally form a rapport with their patients and this would be valuable in promoting a new product like the HPV vaccine. Others felt that the private sector would play a minimal role in promoting the vaccine as most medical insurances do not cover vaccines and that vaccination is traditionally the domain of the public sector.

Some respondents pointed to the possible role of pharmacies in increasing access to the HPV vaccine, mentioning the increasing role pharmacies are playing in childhood immunisations and delivery of contraceptives. A policy informant reflected on the role of HPV manufacturing companies in driving the process and cautioned against being “seduced” by drug companies at the expense of continued secondary prevention measures such as Pap smears.

5.3 Discussion

This is the first study undertaken in South Africa exploring key opinions about HPV vaccination and provides important insights into introduction and acceptability issues. Cervical cancer was perceived as a priority health condition and there was general support for the HPV vaccine at all three levels of enquiry. For many policy informants and providers an overriding concern was the overextended health care system with limited capacity to provide adequate public sector cervical screening services. The need for an adjunct product to prevent cervical cancer resonated strongly with all respondent categories.

This study was conducted just prior to the licensing of the HPV vaccine in South Africa, and not surprisingly knowledge about the vaccine was limited, particularly at the provider and community level. Studies in developed countries have also reported poor levels of knowledge of HPV and the HPV vaccine among health providers, community members and policy makers (Sherris et al. 2006; Zimet et al. 2006). For the HPV vaccine to be effectively introduced in South Africa, a comprehensive education and training strategy will be required. Health service providers will need to understand: the natural history of HPV, how the vaccine works, the vaccine schedule, the vaccine’s limitations and the safety and side-effect profile. Providers will also need communication tools to facilitate effective discussions with clients, such as pamphlets and visual aids. This study also highlights the need for continued training and education of health service providers regarding the rationale for the current national cervical screening policy.

An education and communication strategy will also need to provide clear information about the vaccine to the public, including information on the vaccine's efficacy, side-effects and recommended vaccine schedule. Rumors and misconceptions have done significant damage and have impeded the delivery of other vaccines elsewhere (Aylward, Heymann 2005; Kane et al. 2006). As was seen in our community level focus group discussions and in interviews with providers, a vaccine that targets adolescent females could be seen as a plot to sterilise females. A communication strategy with clear concise messaging that addresses this concern will be an important part of an HPV vaccine programme.

In common with studies from other settings, our findings suggest that considerable health promotion efforts are also needed to improve community knowledge about cervical cancer and the need for regular cervical screening (Moreira et al. 2006; Zimet et al. 2006; Mosavel, El-Shaarawi 2007). The perception that Pap smears are important to clean the womb, treat STIs and ensure fertility, rather than to prevention cancer has been described previously in studies conducted in South Africa (Abrahams, Wood & Jewkes 1997; Wood, Jewkes & Abrahams 1997). This perception could have been fostered by the previous availability of Pap smears mostly at family planning clinics. Health education efforts need to emphasize the importance of Pap smears in preventing cervical cancer through early detection of pre-cancerous lesions.

The ways in which a vaccine against genital HPV is promoted will be critical to its acceptance amongst young girls and parents. Community respondents advised on highlighting the vaccine's cancer preventive properties, rather than focusing on the fact that the vaccine protects against an STI. The notion that vaccinating against an STI might encourage risky sexual behaviour has received media attention and interest in other settings (Zimet et al. 2006; Waller, Wardle 2008; Zimet, Shew & Kahn 2008). Research on parental attitudes suggests that most parents in developed countries have positive attitudes toward HPV vaccination of adolescents (Constantine, Jerman 2007; Rosenthal et al. 2008). However the minority of parents who were not accepting of the HPV vaccine indicated concern about sexual disinhibition. An increase in risky sexual behaviour through use of vaccination, however, has yet to be scientifically proven (Brewer et al. 2007; Herzog et al. 2008). In our study,

respondents did not feel that opposition to the vaccine would be a major obstacle, but felt that some religious groups might object to the vaccine because of a fear of increased risky sexual behaviour. As HPV vaccines are approved and become available it will be important to monitor community attitudes and beliefs, and provide accurate science-based information so that parents are able to make informed decisions.

The target population for HPV vaccination is likely to vary from country to country because of differences in available resources. Most respondents felt that the age of immunisation should be at the lower end of the current recommended age range for the HPV vaccine (9 to 26 years), with an underlying concern by many that the high levels of sexual abuse and violence in South Africa had significantly decreased the age of sexual exposure. This is not surprising given the high levels of gender-based violence in South Africa and has been reported in other studies in similar settings (Dunkle et al. 2004; Orner et al. 2006).

Although some countries have licensed the HPV vaccine for use in males, there is still debate as to whether males should be included in an HPV vaccination programme (Kane et al. 2006; Castle, Scarinci 2009; Cuschieri 2009; Hibbitts 2009). Some argue that vaccinating boys offers additional protection for females through herd immunity whilst also offering protection against anogenital warts and anal cancer for men and promotes equality between the sexes (Hibbitts 2009; Hull, Caplan 2009). Others argue that vaccinating boys is not cost-effective (Cuschieri 2009; Kim, Goldie 2009). A recent study that assessed the cost-effectiveness of including males in a HPV vaccination programme concluded that good coverage in females obviates the need to vaccinate males (Kim, Goldie 2009). Data on genital warts in South African men is lacking and would assist in assessing the potential benefit that could be derived by vaccinating boys. Further research on whether this benefit is likely to make HPV vaccination more appealing to young men is needed. However, current infrastructure limitations make inclusion of males in an HPV vaccination program in South Africa unlikely. In our study focus group participants felt that boys should be included suggesting that there should be equal social responsibility and mutual benefit. Most policy informants felt that although there were benefits vaccinating boys, cost would preclude inclusion of males in an HPV vaccination programme in South Africa.

Vaccinating pre-adolescents and adolescents is a relatively new phenomenon and one that poses challenges in both developed and developing countries (Brabin et al. 2008; Zimet, Shew & Kahn 2008). Immunisation service delivery through the EPI has been fairly successful in South Africa, and as stated by some respondents the country has a good infrastructure of trained staff, systems to maintain the cold chain and an information system. However although immunisation coverage nationally is high there are districts in the country with immunisation coverage rates of only 60% (Mhlanga 2008). Further in South Africa, a regular health care visit for immunisation at age 12 is currently not well established. This may well change with the planned introduction of the combined diphtheria and tetanus vaccine at age 12 and could be an ideal time for the HPV vaccine to be administered as part of the EPI.

In South Africa 86% of school aged girls are enrolled in primary schools (UNICEF 2010) and thus delivery of the vaccine through schools would be a good way to reach a large number of girls in the target age group. However South-Africa does not have a well established school-based health system and few districts have school health nurses. Experience with school-based delivery of the HPV vaccines in the UK and Australia have been promising, with high coverage rates and good vaccine acceptability (Brabin et al. 2008; Garland et al. 2008a; Shefer et al. 2008). Even in these countries with well established school-health systems there were challenges in integrating the 3-dose HPV vaccine schedule into the school academic calendar and arranging for alternate appointments for girls that missed their original scheduled appointments. Cognizant of these challenges, should South Africa decide on a school-based delivery system, it would be advisable to pilot a school-based HPV vaccine delivery programme in advance of national roll-out. Strategies to reach the approximately 14 % of school girls that are out of school will also need to be explored.

Young adolescents do not routinely interact with health systems in most countries including South Africa. An attempt has been made in South Africa to develop adolescent health programmes at primary care level through the National Adolescent Friendly Clinic Initiative (NAFCI) (Ashton, Dickson & Pleaner 2009). These clinics could serve as a delivery point for the HPV vaccine, however there are few such

clinics across the country and, unless the adolescent-friendly clinic initiative is expanded, HPV vaccine coverage will be low.

While not likely to play a major role in achieving coverage goals in South Africa, the private sector could play an important role in generating knowledge and experience with the vaccine amongst health professionals and the community at large.

Price is likely to be one of the most challenging obstacles to HPV vaccine introduction in the developing world. In our study, policy informants spontaneously raised concerns about the cost of the vaccine. Although a recent study in South Africa showed that adding the HPV vaccine to the current cervical cancer screening strategy in the country was cost-effective, the vaccine is unlikely to be affordable in the public sector at the current market price of US \$120 per dose (Sinanovic et al. 2009). South Africa is not eligible for GAVI support for vaccine introduction and should a decision be made to introduce the HPV vaccine into the public sector, the South African government will need to negotiate a substantially reduced price with pharmaceutical companies manufacturing the vaccine. Competition between the two pharmaceutical companies producing the vaccines (GSK and Merck) could drive down the price of HPV vaccines, although the firms may prefer to compete on the basis of product characteristics. Other financing options such as international donor support for the vaccine might need to be explored.

Our study was conducted in one province in South Africa for the community and service delivery levels of inquiry, and with provincial and national respondents for the policy level. As the focus groups were conducted during the day, it is not surprising that the unemployment rate among focus group participants was much higher than the demographics of the study population. Opinions expressed by focus group participants might not be generalisable to the study population. The results are therefore not necessarily representative of South Africa or beyond, but instead are meant to assist in framing the issues for HPV vaccine introduction strategies. Some issues will require further investigation and consideration in other socio-cultural settings, whilst others might be broadly applicable. Health-related decisions are often negotiated in broader social networks including religious and local community leaders (Kane et al. 2006). Due to resource constraints we were unable to include important community

gatekeepers (e.g. religious leaders), whose counsel is likely to be sought before important decisions are taken. Future studies should explore the perceptions of community gatekeepers and explore the possibility of using community leaders in building acceptance and disseminating information.

The HPV vaccine offers a new primary preventive strategy for cervical cancer and our formative research indicated broad support for the introduction of the vaccine. Important challenges that need to be addressed include: procurement of the HPV vaccine at a reduced price, implementation of a comprehensive IEC strategy and considerable development of school health services.

University of Cape Town

Chapter 6: HIV, cervical cancer precursor lesions and cervical cancer among South African women

In the previous two chapters results of research on the challenges in implementing a cytology-based program in South Africa (secondary prevention) and the potential challenges to and opportunities for implementing a HPV vaccination program in South Africa (primary prevention) were presented. South Africa has been severely affected by the HIV/AIDS epidemic - it has the world's largest population of people living with HIV (UNAIDS/WHO 2009). In developing a comprehensive cervical cancer preventive strategy for South Africa, the implications of the HIV/AIDS epidemic will need to be considered. Two studies were undertaken to determine the role that HIV plays in the risk of cervical cancer and cervical precursor lesions. The first study was conducted to determine the association between HIV, cervical cancer precursor lesions and cervical cancer among South African women. Chapter 6 presents the methods, results and discussion for this study and is structured as follows:

6.1. Methods

6.1.1. Study site and study population

6.1.2. Data collection

6.1.3. Data analysis

6.2. Results

6.2.1 Socio-demographic and reproductive characteristics

6.2.1 HIV and invasive cervical cancer

6.2.1 HIV and cervical cancer precursor lesions

6.2.1 High-risk HPV, HIV and SILs

6.3. Discussion

6.1 Methods

6.1.1 Study site and study population

Data for this study were derived from a case-control study that examined the association between hormonal contraceptives and invasive cervical cancer (ICC). The case-control study was conducted in the Western Cape Province from January 1998 to December 2001 (Shapiro et al. 2003). In 2004 anonymous HIV testing was done on stored serum samples and the relationship between HIV, cervical cancer precursor lesions and cervical cancer was then explored.

Women who utilised the public sector health services, were less than 60 years of age and lived within 150 kilometres of Cape Town were eligible for the case-control study. Cases were Coloured and Black women with first occurrences of histologically confirmed ICC, stages Ib to IV, diagnosed less than 6 months previously at two tertiary public sector gynaecologic oncology clinics in the Province. Women with stage Ia cervical cancer (non-invasive), a previous history of any cancer and those that had not resided in the study region for the preceding six months were excluded. Early Stage Ia cervical cancer cannot be clinically detected. Women with Stage Ia cervical cancer were excluded (in the original case-control) study to avoid selection bias due to more intensive screening in women using hormonal contraceptives. In total 526 cases of cervical cancer were identified, two of whom refused to be interviewed. The median age of the cases was 46 years. The stage of the cancer, based on clinical and pathological findings, was abstracted from oncology clinic records (Shapiro et al. 2003).

The controls were identified either at the two tertiary level hospitals, local public sector hospitals or the community health care centres and were frequency-matched to the cases in a ratio of approximately 3:1 for decade of age, ethnic group and area of residence. The women had a primary diagnosis of trauma or acute infections that were judged to be independent of contraceptive use or risk of cervical cancer. Women with a history of any cancer or those who had not resided in the study region for the preceding six months were excluded. In total 1654 controls were identified, 107 (6%) of whom refused to participate, and 6 women who were found to have stage Ia

cervical cancer and were excluded from the study. The median age of the remaining 1541 controls was 44 years (Shapiro et al. 2003).

6.1.2 Data collection

Trained nurse interviewers collected data from the cases and controls using a structured questionnaire that was administered in the subjects' preferred language (English, Afrikaans or Xhosa). Data was collected on socio-demographic status, sexual behaviour, contraceptive use, Pap smear history, obstetric and gynaecology history and risk factors for cervical cancer. The nurse interviewers performed Pap smears using a cytobrush and took endocervical samples for HPV testing. Pap smears were interpreted at the South African National Health Laboratory Service and were classified according to the Bethesda system (Solomon et al. 2002). Endocervical scrapings were taken from the controls only and were assayed for HPV infections using the Digene Hybrid Capture 2 HPV test (Digene Corporation, Gaithersburg, MD) which detects 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). The assay denaturing protocol was modified in that instead of denaturing the entire specimen, 70µl of specimen material was removed and mixed with 35µl of denaturing agent. Test results were classified as positive according to the manufacturer's instructions.

As part of the study protocol, and with a view to testing future hypotheses, blood samples were obtained and stored at -70°C. In 2004 anonymous HIV testing was done on stored serum samples, using the ELISA AXSYM screening (Abbott) followed by confirmatory ELISA (Vironastica) and latex agglutination (Capillus) if necessary. HIV data were available for 486 (93%) of the 524 cases of cervical cancer, and HIV and Pap results for 1365 (89%) of the controls.

Serum samples were also screened for Herpes Simplex Virus type 2 (HSV2) and syphilis. Aliquots of sera were tested for HSV2 using ELISA screening and for syphilis by rapid plasma reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) tests.

6.1.3 Data analysis

Data analysis was conducted using the statistical programme STATA 10.1 (STATA Corporation, College Station, Texas). Socio-demographic and reproductive characteristics were compared between cases (n=486) and controls (n= 1365). Odds ratios and 95% confidence intervals were estimated for categorical variables using one of the levels of the variable as the referent category. The median ages of HIV positive and HIV negative cases were compared using the Wilcoxon rank-sum test. Adjusted HIV ORs and 95% CIs were calculated using multiple logistic regression. Variables entered in the model included those of a priori interest and were: age, number of sexual partners, *herpes simplex virus type 2* (HSV2) infection, prior Pap smears, use of hormonal contraceptives and ethnicity. Cut-off values were guided by the literature and the distribution of the factor in the data. To avoid over adjustment age at sexual debut was excluded from the model.

For the association between HIV and cervical cancer precursors the analysis was restricted to the control group which consisted of 103 women with ASC-US, 53 with LSIL, 50 with HSIL and 1159 with normal cytology. Prevalence ratios and 95% CIs were estimated for categorical variables across each grade of cervical cytology abnormality, using women with normal cytology as the reference group. Prevalence ratios were preferred to odds ratios as the latter would tend to overestimate the associations when the prevalence of variables are high (Thompson, Myers & Kriebel 1998). The risk of SILs was compared for women infected with both HR-HPV and HIV, or neither HR-HPV and HIV. For this analysis women with SILs (both HSIL and LSIL) were compared to women without SILs (normal cytology and ASC-US). The outcome selected was the more clinically significant SIL. The clinical significance of ASC-US is not clear. ASC-US is an equivalent cytological diagnosis that was introduced by the Bethesda classification system and denotes cellular changes that are more marked than reactive inflammatory changes but are not diagnostic of neoplastic or pre-neoplastic conditions (Solomon et al. 2002). The majority of ASC-US lesions regress within 24 months (Melnikow et al. 1998; Schlecht et al. 2003). Adjusted PRs and 95% CIs were calculated for SILs in women with both HIV and HR-HPV (or either of these viruses) using log-binomial regression (Barros, Hirakata 2003). Variables entered into the log-binomial regression model

included those of a priori interest and were: prior Pap smear, smoking, number of sexual partners, HSV2 infection, age, ethnicity and use of hormonal contraceptives. Cut-off values were guided by the literature and the distribution of the factor in the data. To avoid over adjustment age at sexual debut was excluded from the model.

Ethical approval for the overall study and, later, for the anonymous HIV testing was granted by the University of Cape Town Faculty of Health Sciences Research Ethics Committee and the Boston University Ethics Review Board. Written informed consent for the overall study was obtained from all study participants.

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6.2 Results

6.2.1 Socio-demographic and reproductive characteristics

Table 6.1 provides socio-demographic and reproductive characteristics for the cases and controls. The cases and controls were similar with regard to age, ethnic group, educational level, residence and marital status. On univariate analysis there was a significant association between cervical cancer and sexual behaviour. Cases were more likely to have had four or more sexual partners (OR 1.57, 95% CI 1.23 - 2.01) and had their sexual debut before the age of 16 years (OR 0.65, 95% CI 0.52 - 0.82). Cigarette smoking was significantly associated with cervical cancer (OR 1.34, 95% CI 1.11 - 1.71). Controls were significantly more likely to have used any hormonal contraceptive (OR 0.53 95% CI 0.41 - 0.69). There was no significant difference in oral or injectable contraceptive use among cases and controls. Cases were significantly less likely than controls to have had a prior Pap smear (OR 0.38, 95% CI 0.30 - 0.46). There was no significant difference in STIs, including HIV, between the cases and controls.

Table 6.1: Socio-demographic and reproductive characteristics

Characteristic	Cases N = 486	Controls N = 1 365	p-value	Odds ratio	95% Confidence interval
Age					
< 35 years	61 (12.5)	219 (16.0)		1	
≥ 35 years	425 (87.5)	1 146 (84.0)	0.061	1.33	0.98 - 1.81
Education level					
< grade 8	397 (81.7)	1090 (80.0)		1	
≥ grade 8	89 (18.3)	275 (20.0)	0.3830	0.89	0.68 - 1.16
Ethnic group					
Coloured	367 (75.5)	1 030 (75.5)		1	
Black	119 (24.5)	335 (24.4)	0.980	0.99	0.78 - 1.3
Residence					
Rural	208 (42.8)	632 (46.3)		1	
Urban	278 (57.2)	733 (53.7)	0.182	1.15	0.93 - 1.42
Marital status					
Single	116 (23.9)	297 (21.8)		1	
Married	223 (45.9)	704 (51.6)	0.117	0.81	0.62 - 1.06
Widowed	70 (14.4)	158 (11.6)	0.485	1.13	0.78 - 1.63
Divorced/separated	76 (15.6)	205 (15.0)	0.742	0.94	0.66 - 1.34
Sexual partners					
< 4	355 (73.1)	1 109 (81.2)		1	
≥ 4	127 (26.1)	252 (18.4)	< 0.001	1.57	1.23- 2.01
Sexual debut					
< 16 years	156 (32.1)	323 (23.7)		1	
≥ 16 years	318 (67.1)	1 008 (75.7)	< 0.001	0.65	0.52 - 0.82
Parity					
< 5	381 (78.6)	1 106 (81.5)		1	
≥ 5	104 (21.4)	251 (18.5)	0.162	1.20	0.93 - 1.55
Hormonal contraceptive use					
Never	117 (24.1)	197 (14.4)		1	
Ever	369 (75.9)	1 168 (85.6)	< 0.001	0.53	0.41-0.69
Tobacco use					
Never	159 (32.9)	550 (40.3)		1	
Ever	326 (67.1)	815 (59.7)	0.004	1.34	1.11- 1.71
Prior Pap smear					
No	242 (49.8)	370 (27.1)		1	
Yes	244 (50.2)	994 (72.8)	< 0.001	0.38	0.30 - 0.46
Syphilis infection					
No	464 (95.5)	1295 (94.9)		1	
Yes	22 (4.5)	70 (5.1)	0.545	0.86	0.53 - 1.41
Herpes simplex 2 infection					
No	165 (34.0)	459 (34.3)		1	
Yes	321 (66.0)	878 (65.7)	0.416	1.1	0.88 - 1.34
HIV infection					
Negative	457 (94.0)	1287 (94.3)		1	
Positive	29 (6.0)	78 (5.7)	0.838	1.05	0.67 - 1.62

Data are n (%)

6.2.2 HIV and invasive cervical cancer

Overall 6.0% (29) of the cases (486) and 5.7% (78) of the controls (1365) were HIV positive. The adjusted odds ratios for variables of interest and cervical cancer are displayed in Table 6.2. There was no significant association between HIV and ICC (adjusted OR 1.05, 95% CI 0.65 - 1.70). On multivariate analysis history of a Pap smear was a strong protective factor for ICC (adjusted OR 0.36, 95% CI 0.29 - 0.46). Other factors associated with ICC were: number of sexual partners (adjusted OR 1.70, 95% CI 1.30 - 2.23) and smoking (adjusted OR 1.33, 95% CI 1.02 - 1.74).

Table 6.2: Multivariate association of demographic factors, reproductive factors and HIV with invasive cervical cancer

Variable	Adjusted odds ratio ¹ (95% confidence interval)	Adjusted odds ratio ² (95% confidence interval)
HIV infection	1.18 (0.76 - 1.85)	1.05 (0.65 - 1.70)
Prior Pap smear	0.38 (0.31 - 0.47)	0.36 (0.29 - 0.46)
Sexual partners \geq 4	1.63 (1.23 - 2.10)	1.70 (1.30- 2.23)
Smoking	1.32 (1.06 - 1.65)	1.33 (1.02 -1.74)
Parity \geq 5	1.07 (0.82 - 1.40)	1.18 (0.89 - 1.57)
Age *	1.02 (1.01 - 1.03)	1.01 (0.99 - 1.02)
Black	1.03 (0.81 - 1.31)	0.77 (0.55 - 1.06)
Hormonal contraceptive use	0.57 (0.44 - 0.76)	0.74 (0.55 - 1.00)
HSV2 infection	1.07 (0.86 - 1.34)	0.92 (0.72 - 1.19)

Adjusted odds ratio¹ adjusted for age only

Adjusted odds ratio² adjusted for all other variables in the table

* For an increment of 1 year

HIV, human immunodeficiency virus; HSV2, herpes simplex virus type 2

Among women with cervical cancer, those that were HIV positive were 6 years younger than those that were HIV negative [HIV positive cases median age 40 years (interquartile range 28 - 49 years), HIV negative case median age 46 years (interquartile range 40 - 52 years) (Wilcoxon p-value = 0.004).

Overall the majority (71.4%) of women with cervical cancer presented with late stage disease (stages III and IV). Analysis of HIV exposure by stage of cervical cancer at presentation showed that 4.9% of women with late stage cervical cancer were HIV positive compared to 8.6% of women with early stage cervical cancer (stages 1b and II). These differences were not significant (OR 0.54, 95% CI 0.24 - 1.29).

6.2.3 HIV and cervical cancer precursor lesions

Among the controls the prevalence of ASC-US, LSIL and HSIL was 7.5%, 3.9% and 3.7% respectively. The socio-demographic and reproductive characteristics for the controls across Pap smear category are presented in Table 6.3. Women with a history of a Pap smear had a significantly lower prevalence of ASC-US, LSIL and HSILs. Black women compared to Coloured women had a significantly higher prevalence of ASC-US and HSIL. A history of four or more sexual partners was significantly associated with a higher prevalence of ASC-US, LSIL, but not HSIL. Parity was associated with a slightly elevated risk of HSIL, but not of ASC-US or LSIL. Early sexual debut and smoking were not associated with an abnormal Pap smear.

The prevalence of HSV2 infection was significantly higher among women with all categories of abnormal Pap smear compared to women with normal cytology. HSV2 infection was significantly associated with HIV infection (prevalence ratio 5.2 95% CI 2.4 – 11.1)

Among the controls, 50% (39/78) of HIV positive women had an abnormal Pap smear (20.5% ASC-US, 17.9% LSIL and 11.5% HSIL), compared to 13% (167/1287) of the HIV negative women (6.8% ASC-US, 3.0% LSIL and 3.2% HSIL). Using women with normal cytology as the reference category, the prevalence ratios associated with HIV infection were: ASC-US 4.0 (95% CI 2.6 - 6.4), LSIL 7.9 (95% CI 4.6 - 13.5) and HSIL 5.3 (95% CI 2.7 - 10.3) (Table 6.3).

Table 6.3: Socio-demographic and reproductive characteristics according to cytology result

Characteristic	Normal	ASC-US			LSIL			HSIL		
	n = 1159	n= 103			n = 53			n = 50		
	%	%	PR*	95% CI	%	PR*	95% CI	%	PR*	95% CI
Age										
< 35 years	15.4	14.6	1		30.2	1		18.0	1	
≥ 35 years	84.6	85.4	1.07	0.63-1.80	69.8	0.44	0.25-0.78	82.0	0.84	0.41-1.67
Education attainment										
< grade 8	79.6	80.6	1		81.1	1		82.0	1	
≥ grade 8	20.4	19.4	0.95	0.59-1.51	18.9	0.91	0.47-1.79	18.0	0.86	0.43-1.75
Ethnic group										
Coloured	77.8	60.2	1		66.0	1		62.0	1	
Black	22.2	39.8	2.14	1.47-3.10	34.0	1.8	1.00-3.04	38.0	2.07	1.19-3.61
Residence										
Rural	46.2	45.6	1		49.1	1		48.0	1	
Urban	53.8	54.4	1.02	0.70- 1.48	50.9	0.89	0.53-1.51	52.0	0.93	0.54-1.60
Smoked tobacco										
Never	39.7	46.6	1		45.3	1		36.0	1	
Ever	60.3	53.4	0.77	0.53-1.12	54.7	0.80	0.47-1.36	64.0	1.16	0.66-2.05
Ever married										
No	20.8	31.1	1		20.8	1		26.0	1	
Yes	79.2	68.9	0.61	0.41-0.91	79.3	1.00	0.52-1.91	74.0	0.76	0.41-1.40
Hormonal contraceptive use										
Never	14.5	13.6	1		7.6	1		22.0	1	
Ever	85.5	86.4	1.07	0.62-1.84	92.5	2.02	0.74-5.54	78.0	0.62	0.32-1.18

Table: 6.3 continued

Characteristic	Normal n = 1159	ASC-US n= 103			LSIL n = 53			HSIL n = 50		
	%	%	PR*	95% CI	%	PR*	95% CI	%	PR*	95% CI
Sexual partners										
< 4	83.7	66.0	1		64.2	1		81.6	1	
≥ 4	16.4	34.0	2.38	1.62-3.48	35.9	2.68	1.57-4.62	18.4	1.14	0.56-2.32
Sexual debut										
< 16 years	24.1	26.3	1		18.0	1		30.0	1	
≥ 16 years	75.6	73.7	0.90	0.59-1.38	82.0	1.43	0.70-2.90	70.0	0.75	0.42-1.36
Parity										
< 5	81.7	83.3	1		84.6	1		70.0	1	
≥ 5	18.3	16.7	0.90	0.55-1.49	15.4	0.81	0.39-1.71	30.0	1.85	1.03-3.33
Prior Pap smear										
No	25.3	35.9	1		37.7	1		40.0	1	
Yes	74.7	64.1	0.63	0.43-0.93	62.3	0.58	0.34-0.99	60.0	0.52	0.30-0.91
Syphilis infection										
No	95.2	94.2	1		88.5	1		91.7	1	
Yes	4.8	5.8	1.2	0.55-2.62	11.5	2.42	1.08-5.44	8.3	1.74	0.64-4.68
HSV2 infection										
No	36.7	21.6	1		19.2	1		21.3	1	
Yes	63.3	78.4	2.00	1.26-3.16	80.8	2.35	1.12-4.64	78.7	2.09	1.05-4.16
HIV infection										
HIV negative	96.6	84.5	1		75.6	1		82.0	1	
HIV positive	3.4	15.5	4.04	2.55-6.39	26.4	7.85	4.55-13.54	18.0	5.31	2.74-10.29
HR-HPV status										
Negative	89.0	68.9	1		35.6	1		16.0	1	
Positive	11.0	31.1	3.13	2.13-4.58	64.2	11.68	6.83-19.99	84.0	32.31	15.44-67.61

* PR, unadjusted prevalence ratio reference category women with normal Pap smear.

Among women with abnormal Pap smears, HIV positive women tended to be younger, with the age differences only statistically significant for LSIL (see Table 6.4)

Table 6.4: Median age of HIV positive and HIV negative women with abnormal Pap smears

Cervical cytology	HIV positive		HIV negative		Z statistic	p - value
	Median age	Interquartile range	Median age	Interquartile range		
ASC-US	44	37 - 48	44	39 - 51	1.025	0.305
LSIL	32	28 - 38	41	37 - 44	2.412	0.016
HSIL	42	32 - 45	49	40 - 55	1.820	0.069

HIV, human immunodeficiency virus; ASC-US, atypical squamous cells of undetermined significance; LSIL, low grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions
Z statistic and p-value from Wilcoxon rank-sum

6.2.4 High-risk HPV, HIV and SILs

Overall 17.2% of controls were positive for HR-HPV. The prevalence of HR-HPV increased significantly with increasing severity in cytological abnormality. With women with normal cytology as the reference group the prevalence ratios associated with HR-HPV were: ASC-US 3.1 (95% CI 2.1-4.6), LSIL 11.7 (95% CI 6.8-20.0) and HSIL 32.3 (95% CI 15.4-67.6).

Fifty-one percent (40/78) of the HIV positive women were positive for HR-HPV, compared to 15% (195/1287) of the HIV negative women. HIV positive women were almost five times more likely to have HR-HPV present compared to HIV negative women (prevalence ratio 5.1 95% CI 3.3-7.7). Women infected with both HIV and HR-HPV were at a higher risk of SILs than women infected with neither of these viruses (adjusted prevalence ratio 19.8, 95% CI 11.0 – 35.7) (Table 6.5). On the linear scale the increased risk of SILs when both viruses are

present is approximately equal to the sum of the increased risk when each virus is present on its own i.e. there is no additive interaction.

Table 6.5: HIV, HR-HPV and risk of SIL

	SIL absent N =1 262	SIL present N = 103	Adjusted PR*	p-value	95% CI
HIV negative HR-HPV negative	1 069 (96.9%)	23 (2.1 %))	Reference	-	-
HIV positive HR-HPV negative	34 (87.5%)	4 (12.5 %)	4.68	0.003	1.67 - 13.12
HIV negative HR-HPV positive	138 (70.5%)	57 (29.5 %)	14.06	<0.001	8.74 - 22.61
HIV positive HR-HPV positive	21 (52.6%)	19 (47.4 %)	19.82	<0.001	10.99- 35.73

SIL, squamous intraepithelial lesions PR, prevalence ratio; CI, confidence interval; HC2, Hybrid Capture 2; HR-HPV, high-risk human papillomavirus; HIV, human immunodeficiency virus;

* PR prevalence ratio adjusted for prior Pap, smoking, number of sexual partners, smoking, parity, HSV2 infection, age and ethnicity

6.3 Discussion

This study provides data on the risk of cervical SILs and ICC for HIV positive women in the Western Cape Province in South Africa. The extent to which HIV increases the risk for cervical cancer is especially important in South Africa given the size of the HIV epidemic.

In our study HIV positive women did not have an excess risk of invasive cervical cancer (adjusted OR 1.05 95% CI 0.65 - 1.70). However our study was conducted at an early stage of the HIV epidemic in the Western Cape Province. During the period of our study the estimated HIV prevalence in women attending public sector antenatal clinics in the Western Cape was 7.1% in 1999, 8.7% in 2000 and 8.6% in 2001 (Department of Health 2009). Our study was also conducted at a time when antiretroviral therapy was not available. The lack of association between HIV and ICC could be due to the competing risk of mortality from other

conditions associated with HIV. A case-control study conducted in Johannesburg, South Africa between 1992 and 1995 found no association between invasive cervical cancer and HIV (OR 0.6, 95% CI 0.2 - 1.9 (Sitas et al. 1997)). However, the most recent data from another case-control study in the same setting reported an increased risk of cervical cancer (OR 1.6, 95% CI 1.3 – 2.0) among HIV positive women (Stein et al. 2008). The estimated HIV prevalence in women attending antenatal clinics in Johannesburg for the period of the latter study ranged from 12.0% in 1995 to 33.1% in 2004 (Department of Health 2009), which was much higher than the antenatal HIV prevalence in the Western Cape during our study. Studies elsewhere have produced inconsistent results on the association between HIV and invasive cervical cancer (La Ruche et al. 1998; Gichangi et al. 2003; Massad et al. 2004; Mbulaiteye et al. 2006; Adjorlolo-Johnson et al. 2010). These inconsistencies across studies are likely to be due to variations in the competing causes of mortality, stage of the HIV epidemic at the time a study is conducted and the efficacy of cervical cancer screening programmes in different settings.

Studies have reported that HIV positive women are more likely to present with advanced ICC compared to HIV negative women and that lesions progress more rapidly and recur more frequently in HIV positive women (Fruchter et al. 1996; Gichangi et al. 2003). In our study a very high proportion of women presented with advanced invasive cervical cancer and we observed no association between HIV and the stage of presentation of cervical cancer. Our findings are similar to other studies conducted in South Africa where the majority of women irrespective of HIV status present with late stage disease (Lomalisa, Smith & Guidozi 2000; Moodley, Moodley & Kleinschmidt 2001). The high proportion of women presenting with advanced ICC is of particular concern as stage at diagnosis is an important determinant of prognosis (Sankaranarayanan et al. 1998; Wabinga et al. 2003).

In the Gauteng Province HIV positive women with ICC were nine years younger than HIV negative women (Lomalisa, Smith & Guidozi 2000). A study in KwaZulu –Natal Province reported that on average HIV positive women with ICC cancer were 15 years younger than HIV negative women with ICC (Moodley, Moodley & Kleinschmidt 2001). In our study the difference in median age between HIV positive and negative women with ICC was smaller than either of these studies (six years) and probably reflects the earlier stage of the HIV epidemic in the Western Cape at the time of our study, compared to study sites elsewhere in the country.

A number of studies have reported on the high prevalence of cervical abnormalities in HIV positive women in Africa. Fifty percent of the HIV positive women in our study had a cytological abnormality, which is similar to that observed in 397 HIV-positive women from Cape Town (prevalence of abnormal cytology 55%) and a cross-sectional study of 1010 HIV positive women in Johannesburg where 50% of women had cervical abnormalities (Denny et al. 2008; Firnhaber et al. 2010). Apart from a study in Zambia that reported a cervical abnormality prevalence of 93% in severely immunocompromised women attending a tertiary hospital (Parham et al. 2006), other studies in Africa have reported a lower prevalence of abnormal cytology among HIV positive women than has been reported in South Africa. Hawes et al. (2003) reported a cytological abnormality prevalence of 37% among women with HIV-1 infection attending an outpatient infectious-disease clinic in Senegal, Chirenje et al. (2002) reported a cervical abnormality prevalence of 26 % among family planning attendants in Zimbabwe, Laga et al. (1992) 27% in sex workers in Zaire, and Kreiss et al. (1992) 26% among sex workers in Kenya.

Our study is the only study in South Africa that has reported on the association between HIV status and SILs, as other South African studies did not include a comparative HIV negative group. Our finding, that HIV infected women were at a significantly higher risk of LSIL and HSIL compared to HIV negative women confirm the findings of studies from both developed and developing countries (Massad et al. 1999; Duerr et al. 2001; Hawes et al. 2003). In our study HIV positive women were 7.9 times likely to have a LSIL than HIV negative women which is similar to that reported by the WIH study in the US (Massad et al. 1999). We observed a significantly increased risk of HSIL (PR 5.3 95% CI 2.7 – 10.3) among HIV positive women, which was in keeping with findings from other studies: the HER study based in the US, the WIHS, and a study in Senegal found that HIV positive women were at a significantly higher risk of HSILs compared to HIV negative women (ORs 4.0, 2.7 and 3.7 respectively) (Massad et al. 1999; Duerr et al. 2001; Hawes et al. 2003).

Internationally it has been shown that screening for cervical cancer precursors by means of Pap smears, reduces the incidence of cervical cancer (Sankaranarayanan, Budukh & Rajkumar 2001; IARC 2005). This was confirmed in our study where significantly more controls (73%) than cases (50%) reported having a previous Pap smear (adjusted OR 0.36 95% CI 0.29 - 0.46). An important consideration in developing a cervical cancer screening policy for the public sector, where one aims to maximise the benefit of limited resources, is

the age at which to initiate screening. This is influenced by the peak age at which SILs, particularly HSIL the immediate precursor to ICC, are observed. In our study we observed a tendency for HIV positive women with SILs to be younger than HIV negative women with SILs (median age 32 vs.41 for LSIL, and 42 vs. 49 for HSIL respectively). This age difference between HIV positive and HIV negative women was significant for women with LSIL but not for those with HSIL. These findings suggest that the current South African national cervical screening policy needs to be revised taking into account the impact of the HIV/AIDS epidemic on SILs.

The high prevalence and risk of cervical abnormalities documented in our study underscores the importance of developing screening and management guidelines for HIV positive women. The HIV prevalence among adult women in the Western Cape in 2002 was 7.6% (Dorrington, Bradshaw & Budlender 2002). Based on our study results 50% of these women i.e. 49 076 HIV positive women in the province, had cervical lesions in 2002. As anti-retroviral therapy becomes increasingly available in the public sector in South Africa, the life expectancy of HIV positive women will increase. It is important that this benefit is not offset by an excess risk in cervical cancer. In developed countries it is recommended that HIV positive women have two cytological assessments within the first year after HIV diagnosis and annually thereafter, with referral for colposcopy for any smear showing an ASC-US or more severe lesion (Centers for Disease Control 1997). These guidelines are not feasible in resource-poor settings. It is critical that a cervical cancer screening programme, informed by local research on the natural history of cervical abnormalities, is put in place for HIV positive women.

South Africa has introduced a national cervical screening policy stating that all women 30 years and older are entitled to three free Pap smears in their lifetime, at 10 year intervals (Department of Health 2000). If the policy is adequately implemented, over the next few years many women in South Africa will be screened for the first time and many abnormal cervical lesions will be detected. Based on our study findings that 1 in 4 women with LSIL, and 1 in 5 women with HSIL, were HIV positive, every effort should be made to ensure that women who are screened and found to have SILs should also be offered HIV voluntary counselling and testing.

The HR-HPV prevalence was 17.2% among the controls in our study, with prevalence rising significantly with increasing severity of cytological abnormality. This prevalence is likely to be representative of the study population as controls were selected from the same neighbourhood as the cases. Our finding that HIV positive women were almost 5 times more likely to have HR-HPV present compared to HIV negative women, are in agreement with others that have shown an association between HIV, high-risk HPV and cervical abnormalities (Sun et al. 1997; La Ruche et al. 1998; Minkoff et al. 1998; Palefsky et al. 1999; Ahdieh et al. 2001; Massad et al. 2001; Jamieson et al. 2002; Hawes et al. 2003). Mechanisms that explain the increased prevalence of HPV in HIV infected individuals include decreased immunity associated with HIV, chromosomal instability, as well as a possible direct interaction between the 2 viruses, with HIV interacting with HPV at a molecular level, leading to an increased expression of the HPV E6 and E7 oncogenes (Palefsky 2006). The latter two mechanisms are not fully understood. For the combination of HIV and HR-HPV infection, we estimated a 20-fold increase in the risk of SILs, which was almost equal to the sum of the increased risk when each virus was present on its own suggesting no biological synergism between the viruses.

In our study incident cases were used and controls were sampled at the time of the occurrence of a case i.e. we used incidence density sampling. In this design the incidence rate ratio can be directly estimated by the odds ratio (Pearce 1993; Knol et al. 2008). An advantage of this method is that it reduces bias from secular changes in the prevalence of exposure during the course of the study.

A potential limitation of our study is that cytological abnormalities were not histologically confirmed. However, some studies have shown that the Pap smear sensitivity and specificity are similar among HIV negative and HIV positive women (Wright et al. 1994; Branca et al. 2001). Further, the cytologists were blinded to HIV status and there is no reason to suspect differential misclassification according to HIV status. Non-differential misclassification would, if anything, dilute the estimated effect of HIV. An additional limitation of our study was that immune status was not recorded. A strong association between immune status (CD4 counts and HIV viral load) and cervical abnormalities has been demonstrated in other studies (Delmas et al. 2000; Massad et al. 2001; Schuman et al. 2003).

In summary South African HIV positive women are at a significantly increased risk of cervical HR-HPV infection and SILs. As the population of HIV-infected South African women survive longer through increased access to ARVs, invasive cervical cancer is likely increase and become an increasing public health burden, unless a functional cervical cancer screening programme is implemented.

Chapter 7: HPV infection and cervical cancer precursor lesions among women initiating HAART

This is the second study examining the role of HIV in cervical cancer among women in South Africa. The study was undertaken a later stage of the HIV epidemic in the Western Cape Province to determine the HPV prevalence, HPV types, HPV viral load and prevalence of cervical precursor lesions among women initiating HAART. Chapter 7 presents the methods, results and discussion for this study and is structured as follows:

7.1. Methods

7.1.1. Study design

7.1.2. Study site and study population

7.1.3. Data collection

7.1.4. Data analysis

7.2. Results

7.2.1. Socio-demographic and reproductive characteristics

7.2.2. HR-HPV prevalence

7.2.3. HPV types

7.2.4. HPV viral load

7.2.5. Risk factors for SILs

7.3. Discussion

7.1 Methods

7.1.1 Study design

A cross sectional survey was conducted at a public sector ART clinic in Cape Town, South Africa, between January and May 2007.

7.1.2 Study site and study population

The ART clinic is based at a Community Health Centre in the Nyanga Health District of the Metro Region in Cape Town. Nyanga is a predominantly African township situated 26 kilometres from Cape Town. It has a population of 58 723 and 48% of the population live in informal dwellings (City of Cape Town 2003). In 2005 the estimated antenatal HIV

seroprevalence was 29.1% (Department of Health, Western Cape 2006). The ART clinic was started in 2004 by a non-governmental organisation, Absolute Return for Kids (ARK), and taken over by the Provincial Government of the Western Cape (PGWC) in 2006/ 2007. Patients are eligible for HAART if they have stage IV disease or a CD4 cell count below 200 cells/ μ L. Patients undergo clinical and psycho-social assessment and three group treatment-readiness sessions to ensure that they are ready to initiate and remain on long-term therapy.

Women, eighteen years and older, who were being considered for initiation of HAART were eligible for inclusion in the study. Every second female client on the HAART eligible patient register was informed of the study by clinic staff and referred to the research nurse, who explained the details of the study and obtained informed consent. Women who had a hysterectomy, were menstruating or pregnant at the time of the study were excluded. A total of 120 women were referred by clinic staff to participate in the study. Nine women were excluded because they were menstruating and two declined to participate because of time constraints.

7.1.3 Data collection

A structured questionnaire (Appendix G) was used to collect data on socio-demographic status, sexual behavior, history of a STI, obstetric and gynaecology history and risk factors for cervical cancer. The questionnaire was piloted prior to the study and the final questionnaire was administered by the research nurse in the client's preferred language (Xhosa or English). The research nurse also conducted a pelvic examination; took a Pap smear using a cytobrush and collected cervical samples for HPV testing with Digene cervical samplers. The samples for HPV testing were stored in Digene transport medium at -80°C until required.

Pap smears were interpreted at the South African National Health Laboratory Service and classified according to the Bethesda classification system (Solomon et al. 2002). Women with HSILs were referred to the regional colposcopy clinic and those with other cervical abnormalities asked to return for repeat Pap smears according to the clinic protocol.

Cervical samples were assayed for HPV infection using the Digene Hybrid Capture 2 (HC2) assay (Digene Corporation, Gaithersburg, MD) which detects 13 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). For each specimen a relative light unit (RLU) ratio,

which is the ratio of light emitted by the specimen to the light emitted from the mean RLU of triplicate positive control specimens containing 1 pg/ml of HPV DNA (5000 copies of HPV genome), was calculated. Specimens with a ratio of < 1.00 were considered negative, and those with a ratio of ≥ 1.00 were considered positive. Low, but positive RLU values were not retested and were considered positive for the purposes of the analysis. The RLU ratio reflects a semi-quantitative measure of the HPV viral load for one or more of the 13 HR-HPV types. The HC2 test does not provide type-specific HPV data.

HPV types were determined using the Roche Linear Array HPV Genotyping test (Roche Molecular Systems Inc. California USA), and the results were validated utilizing the betaglobin according to the manufacturer's instructions. The Linear Array assay detects a total of 37 HPV types. Individual HPV types were divided into 14 oncogenic (high risk) types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 73 non-oncogenic types (low risk): HPV 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39 and CP6108.

All clients have blood taken for CD4 counts by the health service authority as part of their assessment for HAART eligibility. CD4 count data were extracted from clinical records. The cyto-technician and laboratory technician were blinded to the clinical profile of the clients.

7.1.4 Data analysis

Data analysis was conducted using the statistical programme STATA 10.1 (STATA Corporation, College Station, Texas). Descriptive statistics analyses were based on percentages for categorical variables and medians and interquartile (IQR) ranges for continuous variables.

Continuous and categorical variables were compared between women with and without squamous intraepithelial lesions (SILs). Women with SILs included those with either HSIL or LSIL. Women without SILs included those with ASC-US or a normal Pap smear. ASC-US is an equivalent cytological diagnosis that was introduced by the Bethesda classification system and denotes cellular changes that are more marked than reactive inflammatory changes but are not diagnostic of neoplastic or pre-neoplastic conditions (Solomon et al. 2002). The clinical significance of ASC-US is not clear and the majority of lesions regress within 24 months (Melnikow et al. 1998; Schlecht et al. 2003).

Continuous variables were assessed for skew and as all showed non-normality they were compared using the Wilcoxon rank-sum test. Proportions were compared using Chi-squared and, Fischer's Exact test in the case of small numbers. Prevalence ratios and 95% confidence intervals were estimated using one of the levels of the variable as the reference category. Prevalence ratios were preferred to odds ratios which would tend to overestimate the associations when the prevalence of variables is high (Thompson, Myers & Kriebel 1998). Adjusted prevalence ratios and 95% confidence intervals for predictors of SILs were determined using Poisson regression with robust variance (Barros, Hirakata 2003). Log-binomial regression was not used as the analysis could not converge (Barros, Hirakata 2003). Variables entered into the model were based on a priori considerations and were: HR-HPV infection, age, number of sexual partners, smoking, prior Pap smear, hormonal contraceptive use and CD4 cell count. HR-HPV infection was categorized as: HR-HPV negative as the referent group and HR-HPV positive in categories according to the median HPV viral load.

Ethical approval was granted by the University of Cape Town, Faculty of Health Sciences Research Ethics Committee. The PGWC health department granted permission to conduct the study at the ART clinic. Written informed consent for the study was obtained from all study participants.

7.2 Results

7.2.1 Socio-demographic and reproductive characteristics

A total of 109 women were included in the study. The socio-demographic and reproductive characteristics for the overall study population and according to cervical cytology results are presented in Table 7.1. Overall the median age of the participants was 31 years (interquartile range 27-36 years), the majority of women were unemployed (80.7%), just under half (47.7%) were either married or in a stable relationship and most participants had attended high school (55.1%). Fifty-five percent of the participants were currently on contraception (data not shown). Of these, 40% were using condoms only, 28% condoms and another contraceptive method, 23% injectable contraception, 2% oral contraception and 6% another

method. Most women reported having had an STI (84.4%). Of these 27.1% gave a history of having an STI in the preceding week.

A total of 98 out of 109 women had an adequate Pap smear and of these 65 (66.3%) had an abnormal Pap smear. ASC-US was reported in 15 (15.3%), LSIL in 39 (40.0%), HSIL in 10 (10.2%) and atypical squamous cells- cannot exclude HSIL (ASC-H) in 1 (1.0%) of women. None of the women had cervical cancer. The median age of women with SILs was 30 years (interquartile range 26 - 36 years) and that of women without SILs was 32 years (interquartile range 28 - 39). This difference was not significant (Wilcoxon test, p-value = 0.377). A smaller proportion of women with SILs were employed compared to women without SILs, but this difference was not significant (PR 1.04, 95% CI 0.71-1.54). Significantly more women with SILs compared to women without SILs had ever smoked (PR 1.73, 95% CI 1.22-2.44). There were no other significant socio-demographic differences between women with and without SILs.

Overall 42% of women had had a previous Pap smear. Although a greater proportion of women without SILs (48.9%) had had a Pap smear compared to women with SILs (34.0%) this difference was not significant (PR 0.73, 95% CI 0.48-1.12). There was no significant difference in hormonal contraceptive use between women with and without SILs. The median CD4 count among women with SILs [124 cells/ μ L (interquartile range 62 - 168)] was not significantly different to that of women without SILs [126 cells/ μ L (interquartile range 64 - 179)] (Wilcoxon p-value = 0.893).

Table 7.1: Socio-demographic and reproductive characteristics for the overall study population and according to cervical cytology results

Characteristic	Overall N = 109	SILs absent N = 48	SILs present N = 50	PR	p- value*	95 % CI
Attended high school	60 (55.1)	28 (58.3)	25 (50)	0.85	0.408	0.58-1.25
Married or in stable relationship	52 (47.7)	22 (45.8)	24 (48.0)	1.04	0.830	0.71-1.54
Employed	21 (19.3)	12 (25.0)	7 (14.0)	0.68	0.169	0.36-1.26
Ever smoked	21 (19.3)	5.0 (10.4)	16 (32.0)	1.73	0.009	1.22-2.44
Sexual debut \geq 17 years	61 (55.6)	30 (62.5)	24 (48.0)	0.75	0.149	0.51-1.11
Sexual partners \geq 4	63 (57.8)	26(54.2)	30 (60.0)	1.13	0.560	0.75-1.67
Ever pregnant	89 (81.7)	40 (83.3)	40 (80.0)	0.90	0.670	0.56-1.43
Ever used injectable contraception	97 (89.0)	43 (89.6)	43 (86.0)	0.86	0.589	0.51-1.45
Ever used oral contraception	29 (26.6)	11 (22.9)	13 (26.0)	1.08	0.723	0.70-1.67
Ever used condoms	55 (50.5)	21 (43.8)	30 (60.0)	1.38	0.107	0.92-2.07
Ever had an STI	92 (84.4)	41 (85.4)	43 (86.0)	1.02	0.934	0.58-1.80
Past Pap smear	46 (42.2)	23 (48.9)	17 (34.0)	0.73	0.135	0.48-1.12

Data are N (%) * p-values are from chi-squared tests for proportions or Fisher's exact tests where numbers in the cells were < 5.

PR, prevalence ratio; CI, confidence interval; STI, sexually transmitted infection; SILs squamous intraepithelial lesions

7.2.2 HR-HPV prevalence

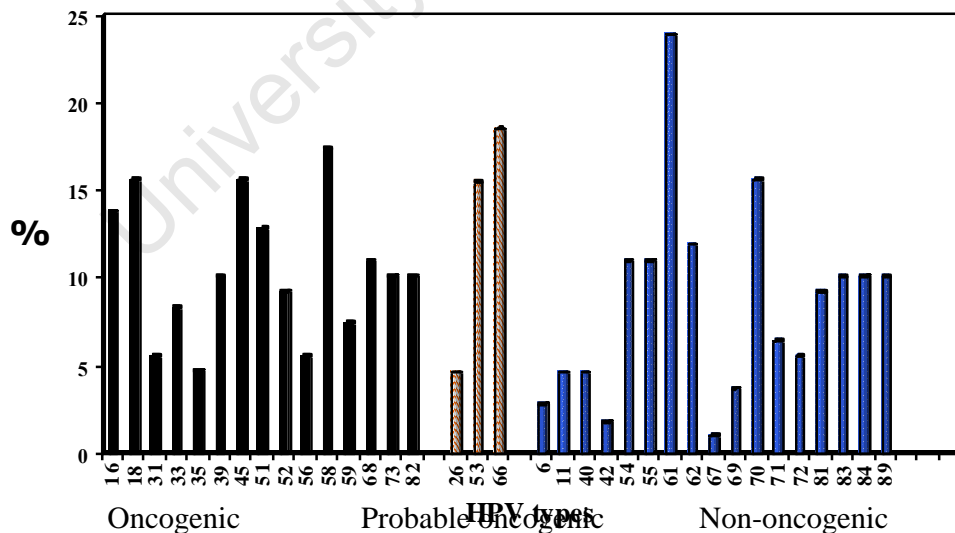
The overall prevalence of HR-HPV using the Digene test was 78.9 % (95% CI 69.8% - 85.9%). Women with SILs had a significantly higher prevalence of HR-HPV compared to those without SILs [96.0% vs. 58.3%, PR 6.95 (95% CI 1.93-26.33)]. Although the median CD4 count among women with HR-HPV [119.5 cells/ μ L (interquartile range 62 - 168)] was lower than that of women without HR-HPV [154 cells/ μ L (interquartile range 66 - 183)], this difference was not significant (Wilcoxon p-value = 0.146).

7.2.3 HPV types

Overall 89% (95% CI 81.20 - 93.93) of women had a positive Roche Linear Array HPV Genotyping test. A total of 35 HPV types were detected in the 109 women. The median number of HPV types per woman was 3 (interquartile range 1 - 5), with multiple types (≥ 2 types) detected in 70.4% of all participants and in 78.4 % of participants with a positive Roche Linear Array HPV Genotyping test. Women with SILs were significantly more likely than women without SILs to have multiple HPV types [92.0% vs. 47.9%, PR 4.83 (95% CI 1.91 - 12.19)]. Sixty three percent of women with a CD4 count < 100 cells/ μ L had multiple HPV types present compared to 73% of women with a CD4 count ≥ 100 cells. This difference was not significant (PR 1.16 95% CI 0.88 -1.54)

The prevalence of the different HPV types detected is shown in Figure 7.1. Overall HPV types 61 and 66 were most commonly detected, with a prevalence of 23.9% and 18.5% respectively. The prevalence of HPV 16 and 18 was 13.8% and 15.6% respectively and the prevalence of types 6 and 11 was 2.75% and 4.6%, respectively.

Figure 7.1: Prevalence of HPV types detected in 109 women initiating antiretroviral treatment



Among women with SILs the most prevalent HR-HPV/oncogenic types were HPV types 18 (24.0%), 35 (22.0%) and types 16, 45 and 58 all with a prevalence of 20.0%. Among the 10 women with HSIL the most common HR-HPV type was HPV 45 (prevalence 40.0%),

followed by HPV types 16, 35, 39, 58 and 51 all with a prevalence of 30.0% and HPV types 18, 31, 33 and 66 all with a prevalence of 20.0%.

7.2.4 HPV viral load

The estimated median HPV viral load was 181.1 RLU among women that were HC2 positive. The median HPV viral load in women with SILs (404.8 RLU interquartile range 89.4 - 1394.8) was significantly higher than women without SILS (60.3 RLU interquartile range 8.6 - 199.5) (Wilcoxon p-value = 0.0002). Table 7.2 provides information on the median HC2 viral load and inter-quartile range by each category of cervical abnormality. The analysis showed an overlap in the range of viral loads for the cytology categories. There was a significant trend of increasing HPV viral load with increasing severity of cytological abnormality ($p_{\text{trend}} < 0.0001$).

Table 7.2 HPV viral load and cervical cytology

Cervical cytology	N	Median HPV viral load in RLU	Interquartile range
Normal	17	14.30	3.28 - 190.06
ASC-US	11	90.27	33.59 - 232.08
LSIL	37	365.49	82.06 - 1259.64
HSIL	10	594.55	177.50 - 1504.88

$p_{\text{trend}} < 0.0001$

ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; HPV, human papillomavirus; RLU, relative light units

The median HPV viral load among women with a CD4 count < 100 cells/ μL (81.3 RLU interquartile range 11.0 - 464.9) was lower, but not significantly different compared to women with CD4 count ≥ 100 cells/ μL (189.8 RLU interquartile range 49.1 - 915.9) (Wilcoxon p-value = 0.07).

7.2.5 Risk factors for SILs

Multivariate regression was carried out to determine independent risk factors for SILs. The model showed that HPV viral load and smoking were associated with an increased risk of SILs (Table 7.3). The risk of SILs was five times higher for those that were HC2 positive and had a viral load of ≤ 181.1 RLU (the median HPV viral load) compared to those that were HC2 negative (PR 4.95, 95% CI 1.19 - 20.63). For women that were HC2 positive with a

HPV viral load > 181.1 RLU the risk of SILs was 8.4 times higher compared to those that were HC2 negative (PR 7.61, 95% CI 1.88- 30.75). Smokers were 1.5 times more likely to have SILs compared to non-smokers (PR 1.55, 95% CI 1.13 - 2.14). None of the other variables examined were significant risk factors for SILs.

Table 7.3: Multivariate association of demographic factors, reproductive factors and HPV with SILs among HIV positive women on HAART

Variable	Adjusted PR ¹ (95% confidence interval)	Adjusted PR ² (95% confidence interval)
HC2 positive and low HPV viral load	5.53 (1.36 - 20.78)	4.95 (1.19 - 20.63)
HC2 positive and high HPV viral load	8.39 (2.16 - 32.65)	7.61 (1.88 - 30.75)
Smoking	1.73 (1.22 - 2.45)	1.55 (1.13 - 2.14)
Sexual partners \geq 4	1.10 (0.73 - 1.66)	0.98 (0.69 - 1.41)
Prior Pap smear	0.73 (0.48 - 1.12)	1.05 (0.71 - 1.56)
Hormonal contraceptive use	0.81 (0.47 - 1.40)	0.95 (0.61 - 1.50)
Age	0.99 (0.97 - 1.02)	1.00 (0.98 - 1.02)
CD4 cell count	1.00 (0.99 - 1.01)	1.00 (0.99 - 1.01)

PR¹ adjusted for age only; PR² adjusted for all other variables in the table
 PR, Prevalence ratio; HC2, Hybrid Capture 2; HPV human papillomavirus
 Low HPV viral load < 181.1 RLU (median), compared to HC2 negative
 High HPV viral load \geq 181.1 RLU (median), compared to HC2 negative

7.3 Discussion

Our study of women initiating HAART recorded an exceptionally high prevalence of cervical abnormalities (66%). This is much higher than that recorded in studies conducted among HIV positive women in developed countries, where the prevalence of abnormal cytology reported ranged between 19% to 39% (Wright et al. 1994; Massad et al. 1999; Ahdieh et al. 2000; Delmas et al. 2000; Duerr et al. 2001; Schuman et al. 2003; Massad et al. 2008), and is one of the highest recorded in Africa (Hawes et al. 2003; Moodley et al. 2006; Parham et al. 2006; Anorlu et al. 2007; Firnhaber et al. 2010). The only study to report a higher prevalence of

cytological abnormalities than our study, was that conducted by Parham et al among women attending an HIV-care clinic at a tertiary centre in Zambia (abnormal Pap smear prevalence of 94%) (Parham et al. 2006). The latter study was conducted among women with a median CD4 count of $< 200\mu\text{L}$ and of a similar age to our study population. Previous studies conducted among HIV positive women in South Africa have recorded abnormal Pap smear prevalence of between 50 and 55% (Moodley et al. 2006; Denny et al. 2008; Firnhaber et al. 2010). These studies were conducted in women with either an unknown CD4 status (Moodley et al. 2006) or a higher median CD4 status (Denny et al. 2008; Firnhaber et al. 2010) than was observed in our study. The associations between low CD4 counts, HPV and cervical dysplasia have been previously documented (Delmas et al. 2000; Heard et al. 2000; Hawes et al. 2003; Schuman et al. 2003; Parham et al. 2006; Denny et al. 2008; Firnhaber et al. 2010). Hawes et al. (2003) found that among 433 HIV positive women, the presence of LSIL or worse was strongly correlated with decreased CD4 cell counts. HSIL was not present among women with $\text{CD4} > 500/\text{mm}^3$, however among women with CD4 cell counts of < 500 cells/ μL , each 100 cells/ μL decrease in CD4 count was associated with a 1.7 fold increased risk of HSIL diagnosis (Hawes et al. 2003). Similarly a study in Cape Town found that HIV-infected women with a baseline CD4 count > 500 cells/ μL had a lower risk of developing SILs over a 36 month period, compared to women with a baseline CD4 cell count < 200 cells/ μL (hazard ratio =0.43, 95% CI 0.20 – 0.93) (Denny et al. 2008). It has been suggested that severe immune-suppression might be associated with irreversible cellular damage (Palefsky 2006). Possibly because of the severe immune-suppression among women in our study population (median CD4 125 cells/ μL), we found no association between CD4 count and the prevalence of cervical abnormalities.

Women infected with HIV have a higher prevalence of HPV and are at a greater risk of developing cervical SILs (Wright et al. 1994; Sun et al. 1997; La Ruche et al. 1998; Minkoff et al. 1998; Massad et al. 1999; Palefsky et al. 1999; Ellerbrock et al. 2000; Duerr et al. 2001; Jamieson et al. 2002; Hawes et al. 2003; Schuman et al. 2003; Harris et al. 2005; Rowhani-Rahbar et al. 2007; Massad et al. 2008). Effective screening and early treatment of precancerous cervical lesions are key in preventing the progression to invasive cervical cancer in both HIV positive and negative women (IARC 2005). The majority of women in our study had not had a previous Pap smear (58%). Two other studies in South Africa have recorded even lower rates of Pap smear screening among HIV positive women attending HIV clinics. A study among HIV positive women in Johannesburg observed that 73% of HIV

positive women attending a HIV clinic had not had a previous Pap smear, whilst a study among three HIV clinics in the Western Cape found that 87% of women had not had a previous Pap smear (Batra, Kuhn & Denny 2010; Firnhaber et al. 2010). The low Pap smear screening rates are of concern and highlight the urgent need for clear national guidelines for cervical screening for HIV positive women in South Africa.

Studies have shown that HIV positive women have a high prevalence of HR-HPV, and this is associated with high HIV viral loads and low CD4 counts (Palefsky et al. 1999; Ahdieh et al. 2000; Jamieson et al. 2002; Hawes et al. 2003; Sahasrabuddhe et al. 2007; Denny et al. 2008; Firnhaber et al. 2010). The prevalence of HR-HPV (79%) in our study is amongst the highest recorded in the literature. HR-HPV was significantly associated with SILs (PR 6.95 95% CI 1.93 - 26.33). Although women in our study with HR-HPV tended to have a lower CD4 count than those without HR-HPV, these differences were not significant, but could be a result of our small sample size.

The majority of our participants (70%) had multiple HPV types present. Studies elsewhere have also shown that a high proportion of HIV positive women are infected with multiple HPV types (31% - 87%) (Jamieson et al. 2002; Levi et al. 2004; Luque et al. 2006; Rowhani-Rahbar et al. 2007; Sahasrabuddhe et al. 2007; Denny et al. 2008). The high prevalence of multiple HPV types is most likely a result of the decreased immunity in HIV positive women, which allows for more efficient replication of HPV and a greater likelihood of HPV persistence (Palefsky, Holly 2003). Most studies have reported an inverse association between the number of HPV types seen and CD4 levels (Palefsky 2006; Sahasrabuddhe et al. 2007; Denny et al. 2008; Firnhaber et al. 2010). The women in our study were severely immune-compromised and we found no association between immune-suppression (CD4 levels) and the number of HPV types detected. We did however find that the median number of HPV types and the proportion of women with multiple HPV types present, increased as the severity of the cervical abnormality increased.

Information on HPV types present in HIV positive women is important as HPV type is a strong determinant of progression from persistent HPV infection to cancer (Khan et al. 2005; Schiffman, Castle 2005). Clifford et al have shown that there is considerable variation in regional HPV type distribution in HIV- positive women, with HPV types 31 and 35 being particularly high in Africa (Clifford et al. 2006). In our study the most prevalent HPV types

among all women were HPV61 (23.9%), 66 (18.5%), 58 (17.4%), 18 (15.6%), 45 (15.6%) and 70 (15.6%); and the most common HR-HPV types among women with SILs were HPV types 18 (24.0%), 35 (22.0%) and types 16, 45 and 58 all with a prevalence of 20.0%. Among the ten women with HSIL in our study, HPV45 (40%) was the commonest HR-HPV type followed by types 16, 35, 39, 58 and 51 all with a prevalence of 30%. Two other studies have reported on HPV types among HIV positive women in South Africa, and although both also observed a high HPV16 prevalence, other HPV types reported were different from those in our study (Denny et al. 2008; Firnhaber et al. 2010). In a study in Cape Town the commonest HR-HPV types seen in HIV positive women with HSIL were HPV 16 (26%), 52 (22%), 35 (18%) and 18 (35%) (Denny et al. 2008), whereas in a study in Johannesburg the commonest HR-HPV types in women with HSIL were HPV16 (42%), 56 (22%), 33(14%) and 59 (11%) (Firnhaber et al. 2010). Among 77 women with HSIL or cervical cancer in Zambia, HPV 52 (42%) was the most common, followed by HPV 58 (32%), 16(22%), 45 (22%) and 63 (22%) (Sahasrabuddhe et al. 2007). As has been shown in other studies, we found that although HPV 16 was common among women with SILs it did not predominate over other types to the same extent as is usually seen in HIV negative women (Clifford et al. 2006; Luque et al. 2006; Sahasrabuddhe et al. 2007; Denny et al. 2008; Firnhaber et al. 2010). Forty-four percent of the women with SILs in our study had HPV16 and/or HPV 18 present, thus a significant proportion of cervical abnormalities could potentially have been prevented by HPV vaccination before the onset of sexual activity. However a relatively high prevalence of HPV types not covered by the HPV vaccine was also seen. This has been documented by others (Clifford et al. 2006; Sahasrabuddhe et al. 2007; Denny et al. 2008; Firnhaber et al. 2010) and has important implications for the potential impact of HPV vaccines currently available. It also highlights the fact that screening for cervical cancer remains essential for optimal cervical cancer prevention. In our setting maximum benefit would be obtained from a polyvalent HPV vaccine.

Studies conducted in both HIV positive and negative women have documented an increase in HPV viral load with increasing severity of cervical lesions (Heard et al. 2000; Sun et al. 2001; Sun et al. 2002; Dalstein et al. 2003; Levi et al. 2004; Wu et al. 2006). HPV viral load might therefore be useful in differentiating women at a higher risk of SIL, which would increase the specificity of HPV testing as a screening assay. This could be particularly useful in HIV positive women as a large proportion of HIV positive women have HPV present. In our study we assessed HPV viral load using the HC2 test. HC2 provides a semi-quantitative

assessment of viral load. It does not distinguish between single and multiple HPV infections, nor does it adjust for differences in the number of cells collected for viral quantification (specimen cellularity). Some studies have shown that HC2 results can be considered as reflective of HPV viral load (Pretet et al. 2004) while others have not (Gravitt et al. 2003). Gravitt et al (2003) found that although HPV viral load as measured by real time PCR increased linearly with increasing grade of SIL, HPV viral load measured by HC2 did not. In contrast Pretet et al. (2004) found that real time PCR and HC2 viral load measurements were significantly correlated and that adjustment for specimen cellularity was not necessary. Most HIV negative women will be infected with only one HPV type and therefore the RLU measured by HC2 will reflect the viral load of that HPV type. HIV positive women are more likely to be infected with multiple HPV types compared to HIV negative women (Jamieson et al. 2002; Rowhani-Rahbar et al. 2007), but it is not known how many HPV types, in HIV positive women infected with multiple HPV types, contribute to cervical disease. It remains controversial if the HC2 test will give meaningful results in HIV positive women. In this study we investigated whether an increased HPV viral load, as measured by HC2, reflects increased risk of cervical disease if the result includes a combination of many HPV types and found an association between HPV viral load and SILs. The risk of SIL was 5 times higher (adjusted PR 4.95, 95% CI 1.19 - 20.63) for those that were HC2 positive and had a viral load of ≤ 181.1 RLU (the median HPV viral load), and 8 times higher for those that were HC2 positive with a HPV viral load > 181.1 RLU (adjusted PR 7.61, 95% CI 1.88 - 30.75), compared to women with a negative HC2 test. We speculate that HPV viral load might be clinically useful in predicting SILs in HIV positive women if a higher cut-off point is used, but further studies are needed to test this hypothesis.

In our study women who smoked were at a higher risk of SILs compared to women that had never smoked (adjusted PR 1.55, 95% CI 1.13 - 2.14). This finding is consistent with other studies that have reported an increased risk of developing HSIL and or cervical cancer, with odds ratios in the range of 2 to 5 among HPV-positive women (IARC 2005). Nicotine and tobacco-specific carcinogens have been detected in the cervical mucus of smokers (Prokopczyk et al. 1997) and it has been shown that cigarette smoke condensate can cause malignant transformation of HPV16 immortalized human endocervical cells (Yang et al. 1996). Both of these findings strengthen the plausible role of cigarette smoking in cervical cancer. Strategies to decrease cigarette smoking among South African women could assist in decreasing the prevalence of cervical abnormalities.

A strong association between HIV viral load and cervical abnormalities has been demonstrated in other studies (Delmas et al. 2000; Massad et al. 2001; Schuman et al. 2003). However, due to resource constraints we were unable to collect data on HIV viral load. Another limitation in our study was that cytological abnormalities could not be histologically confirmed in all women.

In the past few years there has been a significant increase in access to HAART in the public sector health services in South Africa, with an estimated 40 fold increase in HAART coverage between 2001 and 2008 (Adam, Johnson 2009). Internationally since the introduction of HAART there has been a decline in certain malignancies in HIV infected individuals (Jacobson et al. 1999; Ledergerber, Telenti & Egger 1999). However the impact of HAART on SILs and cervical cancer remains modest at best (Heard et al. 1998; Orlando et al. 1999; Lillo et al. 2001; Minkoff et al. 2001; Heard et al. 2002; Moore et al. 2002; Ahdieh-Grant et al. 2004; Heard, Palefsky & Kazatchkine 2004; Heard, Potard & Costagliola 2006). Recent results from a prospective cohort of HIV positive women in Soweto, South Africa, showed that HAART was associated with a decrease of 28% in risk of progression from a normal or LSIL to HSIL (adjusted hazards ratio 0.72, 95% CI 0.52 - 0.99). However HAART had no impact on regression (Omar et al. 2011). Thus HIV-infected women on HAART continue to have a substantial risk for cervical cancer. As HAART becomes increasingly available in the public sector in SA, the life expectancy of HIV positive women will increase. Women receiving HAART are assessed regularly, and the opportunity to prevent cervical cancer in these women through regular screening, should not be missed. In providing services for HIV positive individuals initiating HAART, health service managers need to include resources for cervical cancer screening and to be cognizant of the fact that more than 60% of the women initiating HAART are likely to have an abnormal Pap smear and will require further treatment.

In summary, women initiating HAART in SA have an extremely high prevalence of HR-HPV and SILs. This has major health planning and resource implications. Long-term longitudinal studies of the natural history of cervical lesions in women initiating HAART will be critical to inform the development of locally relevant, rigorous screening protocols.

Chapter 8: Concluding discussion and recommendations

Chapter 8 reflects on the main findings and discusses opportunities for and challenges to comprehensive prevention of cervical cancer in SA. The chapter is structured as follows:

8.1 Implications of main findings

8.1.1. Policy environment

8.1.2. Leadership

8.1.3. Managerial capacity

8.1.4. Human resource issues

8.1.5. Public awareness

8.1.6. The challenge of HIV

8.1.7. Health system development and support

8.2. Recommendations

8.1 Implications of main findings

As a result of considerable scientific advances in the past decade strategies for both primary and secondary prevention of cervical cancer are available. Regrettably, despite these advances, the disease continues to cause significant morbidity and mortality particularly in low and middle-income countries. No comprehensive cervical cancer prevention programme exists in sub-Saharan Africa. This thesis set out to examine the challenges to and opportunities for preventing cervical cancer in South Africa, a middle-income country with a relatively well-developed health infrastructure compared to most sub-Saharan countries. Four main questions were explored: a) can a cytology-based based screening programme be effectively implemented in South Africa? ; b) what are the potential challenges to and opportunities for implementing an HPV vaccination programme in South Africa? ; c) what is the association between HIV, HPV, cervical cancer precursors and cervical cancer in South Africa and d) what is the prevalence of HPV and cervical cancer precursors, and the HPV types and HPV viral load in women initiating ART? These questions have local relevance in that the findings will help to shape public health efforts to prevent cervical cancer in South

Africa. In addition findings are of relevance to other middle-income countries contemplating implementing a cervical cancer prevention programme. Findings related to each of the study questions were discussed critically in the relevant chapter, and are briefly re-visited below before the more general issues that arise from the work as a whole are discussed.

a) Can a cytology-based based screening programme be effectively implemented in South Africa?

To determine whether a cytology-based screening programme could be implemented in South Africa a study was conducted to design, implement and evaluate health system interventions for public sector cytology-based cervical screening services in South Africa (chapter 4). As a result of the health system interventions service related outputs increased. Health workers gained knowledge and changed their attitudes and practices. The number of Pap smears performed increased by 76%, with 90% of these smears done on women in the appropriate target age group. However the overall Pap smear coverage targets were not met and timely treatment for women with HSIL was a problem. Efforts to improve referral, feedback and health information systems proved challenging. Although there were some improvements in client's knowledge of cervical cancer and Pap smears, this did not translate into an increase in the number of Pap smears among women interviewed post-intervention.

b) What are the potential challenges to and opportunities for implementing an HPV vaccination programme in South Africa?

A qualitative study was conducted to explore key challenges to and opinions about HPV vaccination introduction in South Africa. Policy makers, providers and community members all indicated support for the introduction of the HPV vaccine. Respondents had limited knowledge of the HPV vaccine and requested more information about the vaccine side-effects and efficacy. The high cost of the vaccine was perceived as a barrier by policy makers. Providers and policymakers noted that the DOH had sufficient experience with managing vaccines, but at the same time recognised that the HPV vaccine would need to reach a different target age group compared to that usually served by the EPI programme. The school based health system was suggested as the most appropriate form of delivery by many respondents, but concern was expressed about the capacity of the current school health

system to deliver the vaccine. Introduction of the HPV vaccine will need to be accompanied by a strong information, education and communication strategy that addresses issues of HPV vaccine safety, side-effects and efficacy as well as provides ongoing education on cervical cancer screening and cervical cancer.

c) What is the association between HIV, HPV, cervical cancer precursors and cervical cancer in South Africa?

A case-control study was conducted to determine the association between HIV and cervical cancer. The study was conducted at an early stage in the HIV epidemic and prior to the introduction of ART. At this early stage of the HIV epidemic HIV positive women did not demonstrate an excess risk of invasive cervical cancer (adjusted OR 1.05, 95% CI 0.65 - 1.70). A separate analysis of the controls was undertaken to determine the association between HIV and cervical cancer precursors and HPV. Among HIV positive women 50% had an abnormal Pap smear and 51% had HR-HPV present. HIV positive women were nearly five times more likely to have HR-HPV present compared to HIV negative women (prevalence ratio 5.1 95% CI 3.3 - 7.7). Women infected with both HIV and HR-HPV were at a higher risk of SILs (LSIL and HSIL) than women infected with neither of these viruses (adjusted prevalence ratio 19.8, 95% CI 11.0 - 35.7).

d) What is the prevalence of HPV and cervical cancer precursors, and the HPV types and HPV viral load in women initiating HAART?

A cross-sectional survey was conducted at a public sector ART clinic in Cape Town, to determine the HPV prevalence, HPV types, HPV viral load and prevalence of cervical precursor lesions among women initiating HAART. Sixty six percent of women had an abnormal Pap smear, the HR-HPV prevalence was 78.9 % and the median HPV viral load was 181.1 RLU. Among women with SILs (LSIL and HSIL) the most prevalent HR-HPV types were HPV types 18 (24.0%), 35 (22.0%) and types 16, 45 and 58 all with a prevalence of 20.0%. Multivariate regression was carried out to determine independent risk factors for SILs (LSIL and HSIL). HPV viral load and smoking were associated with an increased risk of SILs. The adjusted PR was 4.95 (95% CI 1.19 - 20.63) for those that were HC2 positive and a viral load of \leq 181.1 RLU (the median HPV viral load) compared to those that were

HC2 negative. For those that were HC2 positive with a HPV viral load > 181.1 RLU the adjusted PR was 7.61 (95% CI 1.88- 30.75), compared to those that were HC2 negative. Smokers were 1.5 times more likely to have SILs compared to non-smokers (PR 1.55, 95% CI 1.13 - 2.14).

The latter two studies (c and d) show that it is crucial to strengthen and expand cervical cancer prevention programmes in settings where HIV prevalence is high.

8.1.1 Policy environment

The advent of democracy in South Africa created an opportunity for hitherto neglected health conditions in the country to be addressed. The new government has demonstrated a commitment to reproductive rights and women's health. Nationally, cervical cancer was finally recognised as a priority health condition in the country. In 2000 the South African NDOH signalled its commitment to addressing cervical cancer by formulating the national cervical screening policy (Department of Health 2000). This policy adopts a public health approach, focussing on the age group most at risk of developing HSILs, and if properly implemented has the potential to decrease the incidence of cervical cancer by more than sixty percent (IARC Working Group on Cervical Cancer Screening 1986; World Health Organization 2002). In our interviews with policymakers in 2007 (chapter 5), all indicated that cervical cancer was still a priority condition. Policymakers were supportive of the HPV vaccine as an important primary preventive strategy whilst still recognising the importance of an ongoing secondary preventive strategy viz. screening with Pap smears. The enabling policy environment and the supportive views toward comprehensive prevention are a constructive starting point; however there are many challenges that need to be addressed before the benefits of reduced cervical cancer morbidity and mortality will be seen.

8.1.2 Leadership

An important function of the National Department of Health is to provide effective leadership. It is important that leaders not only determine the content of policy, but also the mechanisms and resources to implement the policy. Leaders should bring together relevant partners to discuss these mechanisms and assist in identifying ways to mobilise resources for

health programmes. Although the National Department of Health set up a Cervical Cancer Task Team, consisting of researchers, academics, clinicians and managers to discuss and advise on cervical cancer prevention efforts, the team has had few meetings, and no plan of action has been developed. Further, sectors other than health for example the Department of Education that are critical to a comprehensive cervical cancer prevention programme are not part of this Task Team. The NDOH has failed to harness the considerable academic and research resource available in the country. Although policy makers indicated their support for the HPV vaccine in interviews conducted in our research in 2007, and in a statement issued at the 3rd Stop Cervical Cancer in Africa conference held in 2009 (Stop Cervical Cancer in Africa 2009), there has been little progress toward HPV vaccine introduction in South Africa. Policy makers have stated that the high price of the vaccine is a barrier to introduction. However the DOH has not negotiated a reduced public sector price with the HPV vaccine manufacturers nor has it identified alternate funding sources. Strong dynamic leadership that has oversight of the cervical cancer prevention programme and facilitates policy implementation is needed.

8.1.3 Managerial capacity

Managing a comprehensive cervical cancer prevention programme is complex and demanding. Secondary prevention using Pap smears as the screening test requires adequately trained staff to perform and interpret the smears, a good laboratory infrastructure with quality assurance mechanisms, transport systems to get smears to the laboratory, mechanisms for communicating the results to women and ensuring all women with abnormal smears are followed-up and treated, referral and feedback systems and a system to monitor and evaluate the performance of the programme. Primary prevention involves: reaching and vaccinating pre-adolescents with three doses of the HPV vaccine, mechanisms to educate and inform the public of the vaccine, trained personnel to deliver the vaccine, systems to maintain the cold chain and to monitor coverage and side-effects. Should a school-based delivery system be used to implement the HPV vaccine, the vaccine schedule will need to be integrated into the school's academic calendar. Managing a comprehensive cervical cancer prevention entails synchronisation of various government and non-governmental departments; coordination of activities in communities and in health facilities (primary, secondary and tertiary), management of health personnel and establishing a functional monitoring and evaluation

system. In short skilled managers are needed to drive and co-ordinate a cervical cancer prevention programme.

In our experience of setting up secondary cervical cancer screening services in three areas in South Africa (chapter 4), it was clear that the capacity of managers was variable and often limited. Although most managers were able to make facility level changes such as instituting fast-track queues for clients returning for Pap smear results, or increasing the times that cervical cancer screening was offered, most were unable to effect changes outside the facility level. This was either due to a lack of authority, a lack of skills or to bureaucratic inertia. For example in one of the study sites we found counter-intuitive referral patterns which meant that clients requiring a colposcopy assessment were making unnecessary visits to the regional hospital before being referred to the tertiary hospital. However the health manager did not have sufficient authority to change the existing referral pattern. We found that the health manager's ability to secure equipment for Pap smears was variable across the three project sites with one site where the manager was able to secure provincial funds for equipment, yet in another site the manager was unable to acquire funds for basic equipment.

Other programmes such as the ART and the tuberculosis control programme have found that lay counsellors can play an important role in stimulating demand for a service among the community, allaying fears and providing support for people once they are diagnosed with a particular illness (Schneider et al. 2006; Abdool Karim et al. 2009). As part of our research in setting up secondary screening services, community members were trained as peer-educators. Although these community members reported that they had delivered talks to various groups in the community, none of the managers actively engaged with the peer educators or included them in a cervical cancer preventative strategy.

An important aspect of managing a programme is collecting, collating and using data to inform decision-making. Although data collation tools were developed as part of the research study on implementing cytology-based screening (chapter 4), managers did not use the tools or the available information to identify and correct problems. This failure to recognise the importance of using data to monitor and evaluate a programme is also seen at provincial and

national levels. It is now ten years since the DOH cervical screening policy was launched, however it is still not possible to get reliable cervical screening statistics. Some provinces are able to provide coverage data, but no information is available at a national or provincial level on the proportion of women with HSIL that are appropriately managed, a key aspect of a cervical screening programme. If clients with precursor lesions fail to be treated, screening efforts have been wasted. Further it is unethical to offer screening without ensuring follow-up and treatment services (Sackett 1975). To monitor the impact of a comprehensive cervical cancer prevention programme, a national population-based cancer registry is needed, yet this has still not been set-up in South Africa. The current national cancer registry provides data on the incidence of cervical cancer, however as a pathology-based registry it is prone to underreporting. Further there are serious backlogs with the registry reports on cancer incidence, with data currently only available for up to 2001. The lack of a culture of utilising data for planning, monitoring and evaluating services is not unique to cervical cancer programmes and has been recognised in other programmes in South Africa (Schneider, Barron & Fonn 2007; Harrison 2009). Strengthening of managerial capacity and systems is critical to the success of a comprehensive cervical cancer prevention programme.

8.1.4 Human resource issues

Attaining high coverage of either primary or secondary cervical cancer prevention efforts requires an adequate supply of trained, motivated health providers. In South Africa professional nurses, the backbone of the primary health care system, perform most of the Pap smears. Should the HPV vaccine be introduced in South Africa, professional nurses will most likely be responsible for administering the vaccine as currently they perform most of the childhood vaccinations. A number of studies have demonstrated the key role providers play in affecting health behaviour (Mandelblatt, Yabroff 2000; Miedema, Tatemichi 2003; Ogedegbe et al. 2005). In our research on implementing a cytology-based screening programme (chapter 4) we found that prior to the health care provider training intervention 73% of professional nurses were aware of the national cervical cancer screening policy, however only 43% could correctly state the policy and only 23% agreed with the policy. When we interviewed health care providers in the HPV vaccine study in 2007 (chapter 5), it was apparent that some health providers were misinformed about the national cervical screening policy and that many did not understand the rationale for the policy. Poor health worker knowledge is a barrier to successful implementation of a comprehensive cervical

cancer preventive strategy. Research has shown that barriers to change can be overcome with tailored interventions (Fox & Kahn 2010). Encouragingly we demonstrated that health worker knowledge and attitudes could be changed with a health worker training intervention. The government has articulated a commitment and orientation towards a PHC approach, however skills development and reorientation of curricula toward primary health care has lagged behind (Lehmann 2008). Training curricula for primary health care nurses and in-service training programmes across the country need to include training on the rationale for the cervical cancer screening policy and ensure that staff have the technical skills to perform their tasks. Manuals based on our experience of implementing a health worker intervention programme for cervical cancer screening are available to guide the content and process of health worker training (Cervical Health Implementation Project (CHIP) 2004a; Cervical Health Implementation Project (CHIP) 2004b).

Linked to training are issues of ongoing supervision, feedback and support. Research has shown that supervision and feedback by senior staff is important in improving professional practice and health-care outcomes (Pattinson 2006). Despite an improvement in staff knowledge and attitudes, we found considerable missed opportunities for cervical cancer screening post-intervention (chapter 4). This highlights the important role health managers need to play in monitoring missed opportunities and supervising and motivating staff to be proactive in their screening efforts.

An inadequate supply of health workers has been identified as a key constraint to implementing health programmes in South Africa (Schneider et al. 2006; Kawonga & Fonn 2008; Coovadia et al. 2009). Issues of staff shortages and increased workload were raised by providers, during interviews regarding HPV vaccine introduction. In our research on implementing cytology-based screening in three sites in South Africa, we observed a 13 % staff attrition rate over an 18 month period, and staff shortages were cited as a barrier to performing Pap smears. In order to meet the national goal of screening 70% of women over the age of 30 years within 10 years, 550 000 new Pap smears will need to be done per year in the country (Fonn 2003). Although earlier estimates indicated that the country had sufficient nurses available to carry out this task, these require revision as the estimates failed to take into account the increasing demands of the HIV epidemic and exodus of nurses from the

health services (Fonn 2003; Kawonga, Fonn 2008). Further the production of nurses has not kept up with population growth (Kawonga, Fonn 2008). Unless strategies to increase nurse production and retain existing staff are implemented, fewer nurses will be available for cervical cancer prevention efforts and motivation of the remaining staff is likely to become an increasing problem. The delegation of tasks to less specialized cadres, also referred to as task shifting, is increasingly being discussed as an option to address the human resource crisis facing many African countries hard hit by the HIV epidemic (Lehmann et al. 2009). Evidence suggests that task shifting can lead to improvements in health service access and coverage (Lehmann et al. 2009). Lower cadre nurses have been successfully used to perform Pap smears in a research study in South Africa and in a rural district in India (Fonn et al. 2002; Rao et al. 2007). Expanding the roles of other cadres could increase the number of staff that can provide Pap smears and should be explored. However for task shifting to be successful, lower cadre of staff must be properly trained, supervised and supported.

A study conducted in South Africa in 2003 showed that should the cervical screening policy be implemented, more cyto-technicians will be required to process the increased number of Pap smears (Fonn 2003). In our research on implementing a secondary cervical screening programme in three sites, we noted that turnaround times for clinics to receive Pap smears were long and to a large extent this was a result of laboratory staff shortages. If the three study sites had actually reached their proposed coverage targets, many more Pap smears would have had to be processed and even longer delays could have been expected. The shortage of cyto-technicians must be addressed if Pap smears are to remain the secondary screening method for cervical cancer prevention in South Africa.

8.1.5 Public awareness

Our research showed that women's awareness of cervical cancer, Pap smears and the HPV vaccine was low. We found, however that once women were informed about Pap smears by the research field workers, the vast majority indicated interest in being screened. Similarly once women were informed of HPV vaccines, they were supportive of its introduction in the public sector. These results suggest that once women are informed they are keen to be part of primary and secondary cervical cancer preventive strategies. Efforts to improve client knowledge and practice are clearly required. In our experience, mounting a community IEC

campaign proved to be expensive and time-consuming, and unless a district or province undertakes a long and sustained community IEC campaign, the results are likely to be dismal. It is probably better to spend those limited resources to create opportunities in health services to inform women about prevention of cervical cancer.

8.1.6 The challenge of HIV

We demonstrated that HIV positive women in South Africa are at a significantly increased risk of cervical HR-HPV infection and SILs compared to HIV negative women (chapter 6). These results are consistent with findings elsewhere (Sun et al. 1997; La Ruche et al. 1998; Minkoff et al. 1998; Massad et al. 1999; Palefsky et al. 1999; Ahdieh et al. 2001; Duerr et al. 2001; Massad et al. 2001; Hawes et al. 2003). In our study HIV positive women were not at an increased risk of ICC, however this study was undertaken at an early stage of the HIV epidemic. Data from a case-control study conducted at a later period and in an area with a higher HIV prevalence than our study, have shown that HIV positive women in South Africa are at an increased risk of ICC (Stein et al. 2008). The only way to prevent development of ICC in these women is through screening and early treatment of precursor lesions. There is an urgent need for HIV positive women to be screened for cervical cancer, in particular the increasing numbers of women accessing HAART so that the benefits of HAART are not partially offset by an excess risk in cervical cancer. The NDOH cervical cancer screening guidelines (Department of Health 2000) does not make reference to screening HIV positive women. We found that in the absence of specific policy and guidelines the majority of HIV positive women in our studies had not had a previous Pap smear.

In our study (chapter 6) we observed that HIV positive women with SILs had a tendency to be younger than HIV negative women with SILs, suggesting that HIV positive women should be screened at a younger age in South Africa. In 2010 the HIV/AIDS directorate of the National Department of Health released clinical guidelines for the management of HIV positive adults which advocate a Pap smear on HIV diagnosis and then a repeat Pap smear every 3 years if the cytology results are normal (National Department of Health 2010). Women with LSIL or ASCUS are to have a repeat Pap smear in one year and women with HSIL, a second LSIL or a second ASCUS lesion are to be referred for colposcopy. This differs from the annual screening recommended for HIV positive women in better resourced

countries. Two studies in South Africa have also suggested screening intervals of two to three years in HIV positive women (Denny 2008, Omar 2010), however further longer-term studies are needed to assess whether this screening interval can be extended in resource constrained countries such as South Africa.

The National Department of Health clinical guidelines for the management of HIV positive adults has major resource implications as it is estimated that there are 3 000 000 women living with HIV in South Africa (UNAIDS/WHO 2008). If all HIV positive women are screened according to the new policy, approximately 1 000 000 Pap smears will need to be performed among HIV positive women per year over the next 3 years. Extrapolating from our study findings annually between 38.4% and 55.3% (based on results from chapters 6 and 7 respectively) of the women screened will have a lesion that will require a repeat Pap smear (ASC-US/LSIL) i.e. annually between 384 000 and 553 000 women will need a repeat Pap smear. Between 10.2% (based on results from chapter 7) and 11.5% (based on results from chapter 6) will have HSIL and will require referral for colposcopy i.e. annually 10 200 to 11 500 HSILs will be detected. There are limitations to these estimates: they do not include the women with an inadequate Pap smear that will require a repeat smear and do not take into account women who will be entering and leaving the cohort of HIV positive women. However, they provide some idea of the likely impact of the HIV epidemic on the cervical cancer screening workload and can assist in planning appropriate screening and treatment services.

The extent to which health managers and health care providers are aware of or are implementing the National Department of Health clinical guidelines for the management of HIV positive adults is unknown. Given that implementation of the 10-year screening policy has proved challenging in South Africa, the feasibility of screening HIV positive women more frequently in the current South African health care context is questionable. To implement the screening policy for HIV positive women, Pap smear screening will need to be integrated into HIV and ART clinics and staff at these clinics will need to be trained to perform Pap smears and manage women with abnormalities. Colposcopy and cytology services will need to be expanded to meet the anticipated increase in workload, additional financial resources will be required to implement the policy and systems set-up to monitor and evaluate the implementation of the policy. The extent of this challenge is huge and strong

leadership, management and commitment is required. However the scale-up of ART in South Africa could provide an opportunity to develop cervical cancer screening services for all women, provided that HIV care is integrated into existing service delivery, rather than delivered as a separate vertical programme.

8.1.7 Health system development and support

Given the complexity in implementing cytology-based screening, other technologies are being explored for secondary prevention of cervical cancer in low and middle-income countries (IARC 2005; Sankaranarayanan et al. 2005). These methods do offer some advantages over cytology-based screening, but also have constraints. VIA is less costly than Pap smears, reduces demands on laboratory facilities, and can be used in a one visit screen-and-treat approach (Sankaranarayanan et al. 2005). However VIA has a low specificity and is associated with over-treatment. Similar to cytology-based screening, VIA is prone to subjectivity and provider training and ongoing quality assurance are important to support VIA based screening services (IARC 2005). Although VIA has been used to screen women in research settings in South Africa (Denny et al. 2002; Denny et al. 2005), no information is available on how VIA will perform as a routine screening test in real health service settings in the country. A rapid HPV test, *careHPV*, has been tested in a research setting in China with encouraging results (sensitivity (90%) and specificity (84%) to detect HSIL) (Qiao et al. 2008). However this test is not yet commercially available.

HPV triage followed by a Pap smear for HPV test positives has been suggested elsewhere as a rational approach because of the higher sensitivity of the HPV test and the higher specificity of cytology (Cuzick 2006). An alternative screening option for South Africa would be a screening algorithm with an initial rapid HPV test, followed by Pap smear screening of HPV test positive women. As rapid HPV test results are available within a few hours, clients with positive test could immediately go on to have a Pap smear. Further the rapid HPV test could be performed by technical staff. Using this as the primary screening test would have the advantage of decreasing the number of women that require a Pap smear - an advantage given the current shortage of professional nurses to perform Pap smears. Further research is required to determine the efficacy, feasibility and cost-effectiveness of this proposed approach.

Replacing the Pap smear with an alternate test will however, not overcome the need for a functional health system. While research into new technologies has progressed, strengthening of the health system, which is required for any of these technologies to impact on morbidity and mortality rates, has received considerably less attention.

Investment in overall health system strengthening is critical to prevention of cervical cancer in South Africa. The example of Chile, a middle-income country like South Africa, is worth considering, as it has faced similar challenges to South Africa in terms of re-organizing the cervical cancer screening program. Until 1985 Chile had an opportunistic screening programme in which women attending family planning services were screened on an ad hoc basis, with poor supervision of screening activities and little monitoring and evaluation of services (Sepulveda, Prado 2005; Salas 2006). In 1986 Chile re-oriented its cervical screening programme using a health systems development approach. The Chilean programme focussed on improving technical skills, managerial capacity and strengthening the health system. The result has been an improvement in organisation of the cervical cancer screening services with a 39% reduction in age-adjusted cervical cancer mortality rates between 1986 and 2001 (11.1 per 100 000 women to 6.8 per 100 000 women) (Sepulveda, Prado 2005; Salas 2006).

Without strong leadership, improved management capacity and a strengthened health system, implementation of a comprehensive cervical cancer prevention programme is unlikely to succeed.

8.2 Recommendations

The following recommendations are made for a comprehensive cervical cancer prevention programme in South Africa:

- To reduce the high incidence of cervical cancer in South Africa, a secondary prevention programme needs to focus on recruiting large numbers of women, providing good-quality-screening services and ensuring that those with precursor lesions are treated. Locally relevant health system interventions have been developed. However for these interventions to have a beneficial effect, a functional health system

must be developed. The following recommendations are made for strengthening the health system:

- Ensure that a system to monitor and evaluate the cervical cancer screening programme is set up and that managers at all levels are able to utilise health information in decision making
 - Develop the capacity of health managers to plan, implement, monitor and evaluate health programmes through management training programmes
 - Explore mechanisms to improve the supervision skills of health managers
 - Incorporate supervisory duties into staff contracts and performance appraisals of staff at various levels
 - Allocate resources so that all primary health care clinics are equipped to perform Pap smears
 - Investigate the use of lower nursing cadres to conduct Pap smears
 - Integrate skills required to implement the cervical screening into the nursing curriculum and continuing professional development programme
 - Ensure that cytology quality assurance programmes are in place
 - Increase the production of cyto-technicians
 - Ensure that an efficient referral system is in place for clients with cervical abnormalities
- Local research should be conducted to explore the efficacy, cost-effectiveness and feasibility of a screening algorithm with an initial rapid HPV test, followed by Pap smear screening of HPV test positive women.
 - The HPV vaccine offers potential for primary prevention of cervical cancer in South Africa. However the high price of the vaccine is a major barrier. The National Department of Health must negotiate a price reduction with the pharmaceutical industry. In addition accessing international funding mechanisms, such as the United Nations Children's Fund (UNICEF) should be explored.

- Recognizing that introducing the HPV vaccine will present some unique challenges (pre-adolescent target age, dose schedule, delivery mechanism through schools etc.) a pilot demonstration project should be set-up. This will provide an opportunity to test field logistics, develop appropriate training programme and materials for providers, develop appropriate educational materials for the community, monitor potential opposition and evaluate factors that may impact on coverage and uptake.
- There is worldwide variation in HPV prevalence and types. Further studies on the HPV types present among women in South Africa are needed to evaluate the potential impact of HPV vaccines.
- A national population-based cancer registry should be set up to assess the impact of primary and secondary cervical cancer preventive strategies.
- Current knowledge on the impact of HIV on cervical disease is limited. South Africa has a high prevalence of both HIV and cervical cancer and is well placed to conduct a cohort study that would increase our understanding of cervical disease in HIV positive women. A long term cohort study will also inform screening policies for HIV positive women in resource constrained studies as it will provide information on regression and progression rates of cervical cancer precursor lesions.
- Our current understanding of the impact of HAART on the natural history of cervical lesions is limited. As HAART programmes are scaled up in South Africa, an ideal opportunity exists to conduct a longitudinal study of the natural history of cervical lesions in women initiating HAART. This research will inform cervical screening practices for HIV positive women on HAART.

Ultimately successful prevention of cervical cancer in South Africa requires renewed political commitment, adequate resource allocation and an investment in health systems development.

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Appendix A: Health facility audit

PART A: KEY INFORMANT INTERVIEW

Clinic name:

District: **Province:**

Job title: **DATE: (DD/MM/YY)**

1. ACCESSIBILITY

ORGANISATION OF SERVICES

1. Does this health facility provide Pap smear services?

1. Yes
2. No

2. What is the total number of consulting rooms at your clinic? _____

3. In how many rooms are Pap smears performed? _____

4. Do women require an appointment to have a Pap smear?

1. No
2. Yes: (describe how the appointment system works) _____

5. Do women have to wait in a separate queue for a Pap smear?

1. Yes
2. No

6. Does this health facility have mobile services?

1. Yes
2. No

7. Do the mobile services provide Pap smears?

1. Yes
2. No
3. Not applicable

STAFF

8. How many staff are assigned to work at this facility, and how many of these are trained to take Pap smears?

	Number working at facility.	Number trained in taking Paps
1. Staff nurses	<input type="text"/>	<input type="text"/>
2. Professional nurses	<input type="text"/>	<input type="text"/>
3. Doctors	<input type="text"/>	<input type="text"/>

9. How many staff actually perform Pap smears (i.e. those doing at least one Pap smear per month)?

1. Staff nurses
2. Professional nurses
3. Doctors

2. CYTOLOGY REPORTING

10. To which cytology lab(s) do you send your Pap smear specimens?

Lab 1 _____

Lab 2 _____

Lab 3 _____

11. On average, how long does it take for cytology results to return to your clinic from the cytology lab?

(indicate turnaround time for each lab they utilise)

Lab 1 _____

Lab 2 _____

Lab 3 _____

3. FOLLOW-UP

12. If a client has an abnormal Pap smear, who notifies her of the results?

- (i) The person who receives the result
- (ii) The person who did the smear
- (iii) One person is in charge of the follow-up
- (iv) The lab notifies her
- (v) Other (please specify) _____

13. How are clients with abnormal Pap smear results contacted and followed-up *(ask for description of follow-up system)* _____

14. Is there a system in place by which records are kept and reviewed to ensure that results were received and the clients that need follow-up are followed up?

1. Yes
2. No

15. If yes to Q 14, describe the system and how it works: _____

16. If yes to Q 15, In your opinion, does the current system for follow-up work?

1. Yes: (explain why you think it works)

2. No: (explain why you think it does not work)

4. *PATIENT MANAGEMENT AND REFERRAL*

17. Do you use guidelines or protocols for the management of patients with abnormal Pap smear results?

1. Yes
2. No

18. If yes to Q 17, what is the source of these guidelines (who developed them?) _____

19. Where do you refer patients who need colposcopy and treatment?

20. Do you get feedback on the outcome of the referral for clients you refer to hospital for further management?

1. Yes, frequently
2. Yes, rarely
3. Never

5. RECORD-KEEPING

21. Describe how records of Pap smears are kept in this facility: _____

22. Do you have any suggestions for how you feel the system for record keeping can be improved?

THANK YOU FOR YOUR TIME

PART B: FACILITY CHECKLIST

1. ACCESSIBILITY

ORGANISATION OF SERVICES

1. Official opening time for this health facility: _____

2. Official closing time for this health facility: _____

3. Days of the week that health facility offers Pap smears:

<u>Day</u>		<u>Time</u>	
Monday		To	
Tuesday		To	
Wednesday		To	
Thursday		To	
Friday		To	
Other (specify)		To	
Other (specify)		To	

IEC

4. Information for patients about Pap smear service availability

(i) Poster(s) displayed announcing Pap smears are available at this health facility?

(ii) Poster indicates clearly the times/days that Pap smear service is available?

Yes No

5. IEC methods used to educate and inform patients about Pap smears:

(i) Educational videos

(ii) Posters

(iii) Health talks

(iv) Pamphlets to take home

(v) Other (specify) _____

Yes No

CYTOLOGY REPORTING

6. Cytology **request forms** available for each lab they use? (obtain copy)

(i) Lab 1 _____

(ii) Lab 2 _____

(iii) Lab 3 _____

Yes No

7. Do cytology **report forms** have the following information (tick appropriate box)?

(request copy of cytology report for each lab they use)

	Lab 1	Lab2	Lab 3
(i) Clinic name	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(ii) Clinic code	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(iii) Patient name	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(iv) Patient number	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(v) Date of smear	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(vi) Date of smear report	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(vii) Result of smear - Bethesda	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(viii) Result of smear - other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(ix) Recommended management included	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. FOLLOW-UP

8. System for patient follow-up:

	Yes	No
(i) Use standard notes/letters for follow-up of clients	<input type="checkbox"/>	<input type="checkbox"/>
(ii) Records kept of clients that need follow-up	<input type="checkbox"/>	<input type="checkbox"/>
(iii) From records are able to determine those that did & did not come for follow-up?	<input type="checkbox"/>	<input type="checkbox"/>

4. PATIENT MANAGEMENT AND REFERRAL

9. Guidelines for management of patients with abnormal Pap smear results

	Yes	No
(i) Each consulting room has a copy of the guidelines	<input type="checkbox"/>	<input type="checkbox"/>
(ii) Guidelines available in one or some consulting rooms only (specify which room(s) _____)	<input type="checkbox"/>	<input type="checkbox"/>

5. RECORD-KEEPING

10. Method for maintaining Pap smears patient records

	Yes	No
(i) Pap smear log book	<input type="checkbox"/>	<input type="checkbox"/>
(ii) General clinic register	<input type="checkbox"/>	<input type="checkbox"/>
(iii) Use minimum Data Set format	<input type="checkbox"/>	<input type="checkbox"/>
(iv) Other (specify) _____	<input type="checkbox"/>	<input type="checkbox"/>

11. Pap smear patient records include the following information

(ask to see records and indicate which of the following data are recorded)

	Yes	No
(i) Patient name		
(ii) Patient age / date of birth		
(iii) Patient contact details (physical address, telephone etc)		
(iv) Date smear taken		
(v) Date result of smear received		
(vi) Any past history of abnormal smear		
(vii) Whether first time or repeat smear		
(viii) If follow-up is needed		
(ix) If follow-up has been done		
(x) If referral is needed		
(xi) If has been referred		
(xii) Outcome of referral		
(xiii) Log book / recording book could not be located		
(xiv) No records kept by facility		
(xv) Other (please specify) _____		

12. Monthly/quarterly statistics and data collation reports for screening service (observe walls, and ask to see reports)

	Yes	No
(i) Statistics displayed on the walls		
(ii) Appropriate statistics displayed		
(iii) No statistics displayed on walls		
(iv) Monthly/quarterly reports available		

Appendix B: Staff KAP survey

DATE: (DD/MM/YY)

/ /

GENERAL/ BACKGROUND

1. Gender
 1. Female
 2. Male
2. Age in years _____
3. What is your position at your clinic? (**circle one only**)
 1. Sister in Charge
 2. Professional Nurse- Clinical Nurse Practitioner (CNP)
 3. Professional nurse
 4. Other (specify)
4. How long have you been qualified? (**circle one only**)
 1. Less than 2 years
 2. 2 to 5 years
 3. More than 5 years

STAFF TRAINING

1. Have you had family planning training?
 1. Yes
 2. No
2. Have you had any training in taking Pap smears?
 1. Yes
 2. No
3. Was your training in taking Paps linked to other training (such as family planning training or training for STD treatment)?
 1. Yes (specify which) _____
 2. No
 3. Not applicable
- 4.1. When did your training in taking Pap smears occur?
 1. In the last month
 2. In the last year
 3. In the last five years
 4. More than five years ago
- 4.2. If more than five years ago, have you had an update or refresher course?
 1. Yes
 2. No
- 5.1. Have you performed a Pap smear since your training in taking Paps?
 1. Yes
 2. No
- 5.2. If yes, when was the last time you did a Pap smear?
 1. In the last one month
 2. In the last three months
 3. More than three months ago
6. If you've never had training in taking Pap smears, have you ever performed one?
 1. Yes
 2. No

STAFF PRACTICES AND POLICY

1. If women come in for non-gynaecologic problems, do you talk to them about having a Pap smear? (**please circle one only**)
 1. Yes
 2. No
 3. Sometimes (please specify when you talk to them) _____

2. What criteria do you use to decide if a woman should have a Pap smear? (**circle all the criteria that you use**)
 1. Time duration since her last Pap smear
 2. Her age
 3. If she has had a Pap smear before
 4. If she is sexually active
 5. If she has multiple sex partners
 6. If she is pregnant
 7. If she has a vaginal discharge
 8. If she has abnormal bleeding
 9. If her cervix appears abnormal
 10. If she has had an abnormal Pap smear in the past
 11. If she requests one
 12. Other (please specify) _____

3. If a woman comes to you and asks why Pap smears are important, what do you tell her? (**may circle more than one response if wish to**)
 1. Pap smears will protect her from getting cancer
 2. Paps will help diagnose infections
 3. Cervical cancer is very common
 4. Other (please specify) _____

- 4.1 Do you know the National Policy regarding when women should have Pap smears?
 1. Yes
 2. No
- 4.2. If yes, what is the policy? (**circle correct one only**)
 1. Every ten years if the first one is normal
 2. Starting at age 30
 3. 1 and 2 (Every ten years starting at age 30)
 4. At least every ten years but preferably every two or three
 5. Other (please specify) _____
 - a. _____

INPUT ON SCREENING PROGRAM

1. Do you think that more Pap smears could be done in your clinic?
 1. Yes
 2. No

2. If more Pap smears were to be done at your clinic, when do you think they should be done? (**circle one response only**)
 1. Every day (at any time)
 2. Every day (only at certain times)
 3. Only on certain days
 4. Other (please specify) _____

3. What are the obstacles to performing Pap smears / more Pap smears at your service? (**circle all those that you feel are obstacles at your clinic**)
 1. Lack of equipment (speculum, spatula, slide, fixative)
 2. Not enough adequate lighting
 3. No room/space in which to do the exam
 4. Not enough staff
 5. Staff are reluctant because Paps are time-consuming

6. Clients will be made to wait even longer to see staff
7. It is difficult to follow up with every woman after she has a Pap
8. Women are not interested in coming in for Pap smears
9. Women do not know that they should come in for a Pap smear
10. Language barriers
11. Staff do not like performing Paps
12. Often run out of equipment (speculum, slides, fixative, spatulas)
13. Not been able to access equipment
14. Other (please specify) _____

4. What would motivate you to provide Pap smear screening at your clinic?

5. The majority of Pap smears are currently done on younger women. How can older women be reached to come in for Pap smears? (**circle the method(s) you agree with**)

1. Media
2. Community discussions/education
3. Posters
4. Pamphlets
5. Other (please specify) _____

6. Currently many women do not request Pap smears. Why do you think this is so? (**circle those you think are the reasons**)

1. Lack of education
2. Fear
3. Lack of concern over their own health
4. Pap smears are uncomfortable
5. It is difficult for them to get to the clinic
6. Long wait to see staff
7. They are shy
8. They do not feel comfortable around the staff
9. Other (please specify) _____

FOR STAFF THAT HAVE PERFORMED PAP SMEARS WITHIN THE LAST 3 MONTHS:

1. Do you get the results for the Pap smears that you perform? (**circle one answer only**)

1. Yes, often
2. Yes, rarely
3. No

2. Indicate the action required for each of the following Pap smear results.

Result	Action required	Do not know
High grade SIL (high grade squamous intraepithelial lesion)		
Dysplasia		
CIN 3 (cervical intraepithelial neoplasia grade 3)		

3. In your opinion, how much time does performing a Pap smear add to a client visit?

1. Less than 10 minutes
2. 10 to 15 minutes
3. More than 15 minutes

4.. After a Pap smear is done, how does a woman learn of the results? (**circle response for what is practised at your clinic**)

1. She is informed of the results when she next comes to the clinic
2. She has a follow-up appointment
3. She receives a letter
4. She is visited at home
5. Other (please specify) _____

ATTITUDES TOWARD POLICY AND SCREENING

1. For each of the following statements, please indicate whether you strongly agree, agree, disagree, or strongly disagree (**please respond to all 6 statements 17.1. to 17.6.**).

(*Strongly agree=1, agree=2, disagree=3, strongly disagree=4*)

1. 17.1. Women over 60 should have Paps	
2. 17.2. Nurses should tell all women over 30 to have Paps	
3. 17.3. Women should be able to have Paps in public health facilities whenever they want	
4. 17.4. My other responsibilities are more important than performing Paps	
5. 17.5. Sharing information with women about Pap smears will encourage women to have a Pap	
6. 17.6. Nurses are too busy to share information with women about Pap smears	

2.1 The National Policy states that women should have a Pap smear every ten years starting at age 30. Do you agree with this policy?

1. Yes
2. No

2.2. If no, why not? (**circle all the reasons you don't agree with policy**)

1. Every ten years is not often enough - every three to five years is ideal
2. Every ten years is not often enough - should have a Pap smear annually
3. It is difficult for women to remember to come back after ten years
4. Should have a Pap smear when pregnant
5. Should start even when under 30 years old
6. Should start when over 30
7. Should start when they become sexually active
8. Other (please specify) _____

3.1. Have you ever had a Pap smear yourself?

1. Yes
2. No

3.2. If no, why not? (**you may circle all that apply to you**)

1. Forgot
2. Was too busy
3. Paps are uncomfortable
4. Was embarrassed
5. Was afraid something bad would be discovered
6. Did not think I needed one
7. Other (please specify) _____

4. Do you have any other comments or suggestions for providing cervical screening services in your district?

Thank you for your time

Appendix C: Client KAP survey

Introductory remarks

Hello, my name is I do not work at this health center, but I work at the We are doing a health survey and would really appreciate it if I could ask you a few questions about your health. It will take about 10-15 minutes. You will not lose your place in the queue.

I am not going to write your name on the form, therefore anything you tell me will remain anonymous and be treated confidentially. You may stop the interview at any time you wish to. Your answers will help us to improve services. You do not have to participate if you do not want to.

Thank you.

Personal information

1	Can you tell me how old you are?	(_____years)	
2	Why did you come here today?	Accompanied someone else Treatment (medicines) Family planning Antenatal care Pap Smear Other (specify.....)	1 2 3 4 5 8
3a	What standard did you complete in school? <i>Interviewer: note here and code later</i>	
3b	Specify any other institutions (technikon/university/courses attended)	
4	What is your marital status ?	Married (incl. common law) Widowed Divorced/Separated Single (never married)	1 2 3 4
5	Are you living with your husband or any male partner right now?	Yes No Not Applicable	1 2 Skip to q 8 8 Skip to q 8
6	If you are living with your husband/partner is he employed?	Yes No Don't know	1 2 Skip to q8 9 Skip to q8
7	If yes, what is his job?	
8a.	Are you employed?	Yes No	1 2 Skip to q 9
8b	If yes: What is your job?	Skip to q 10
9	If no, are you:	Unemployed – looking for work? Unemployed - not looking for work? Disabled (physically or mentally) A pensioner (government or private civil pension/ not working due to old age) Housewife	1 2 3 4 5

		Student	6
		Self Employed	7
10.	Do you listen to the radio?	Yes No DK	1 2 Skip to q12 9 skip to q12
11.	What radio stations do you listen to? (Interviewer, circle yes to all mentioned)	YFM Metro Lesedi FM Radio Bop UWFM (Umhlobo wenene) Kaya FM Other (specify.....)	Yes No 1 2 1 2 1 2 1 2 1 2 1 2
12a	Have you ever been pregnant?	Yes No	1 2
12b	If Yes, how many pregnancies have you had?	(.....)	
13a	Have you ever used contraception/birth control?	Yes No	1 2
13b	Are you using contraception/birth control at the moment?	Yes No	1 2

Knowledge of Pap Smears and cancer of the cervix

14	Have you ever heard of a Pap Smear test?	Yes No Unsure	1 2 skip to q27 9 skip to q27
15	If Yes, what part of the body is examined during a Pap smear test? <i>Interviewer do not prompt. Code yes if any of the following words are mentioned spontaneously: Cervix/womb/vagina/private parts (or local word meaning same) mentioned</i>	(Note here:.....)	Yes No 1 2
16	What do you think a Pap Smear test is testing for? (Note here.....) <i>Interviewer: open-ended, do not prompt). Code yes if the following words are mentioned</i>	Cancer Cancer of the cervix AIDS/HIV STDs Infertility Other (specify.....) DK	Yes No 1 2 1 2 1 2 1 2 1 2 9
17	At what age does the Department of Health (DOH) say that a woman should have her first Pap Smear test? Before the age of 30 or after the age of 30 years?	Less than 30 years old More than 30 years old DK	1 2 9
18 (a)	Actually, the DOH says a woman should have her first Pap smear at the age of 30 years or older. Do you agree with this?	Yes No DK	1 2 9 skip to q19
18 (b)	Why do you say this (agree/disagree)?	

19	How often or how many years apart, does the DOH say that a woman should have a Pap Smear test during her life? <i>(Interviewer: read list)</i>	Once a year Every 2-5 years Every 6-9 years Every 10 years With each pregnancy Other..... DK	1 2 3 4 5 8 9
20 (a)	Actually, the DOH says that a woman should have a Pap Smear every 10 years. Do you agree with this?	Yes No DK	1 2 9 skip to q 21
20 (b)	Why do you say this (agree/disagree)? <i>Interviewer: note here and code later</i>	
21a	Do you think women who have stopped having sex should have Pap Smears?	Yes No DK	1 2 9 skip to q 22
21b	Why do you say that (yes or no)? <i>Interviewer: note here and code later</i>	
22a	Do you think women who have stopped having children should have Pap Smears?	Yes No DK	1 2 9 skip to q 23
22b	Why do you say that? <i>Interviewer: note here and code later</i>	
23	What does it mean if the Pap test is abnormal/shows that there is a problem? <i>Interviewer: note here and code later</i>	
24	Have you ever discussed Pap Smears with your husband/partner?	Yes No Not applicable (not married/no partner)	1 2 8
25	Have you ever discussed Pap smears with a <i>Interviewer read list and code yes if any of these are mentioned</i>	Family member Health worker Friends Anybody else (specify.....	<i>Yes</i> <i>No</i> 1 2 1 2 1 2
26	Do you think Pap smears are painful?	Yes No DK	1 2 9
<i>INTERVIEWER say to ALL respondents: A Pap smear is a test for cancer of the cervix.</i>			
27	Have you ever heard of cancer of the cervix/cancer of the mouth of the womb?	Yes No DK	1 2 skip to q33 9 skip to q 33
28	Do you know anyone who has had cancer of the cervix?	Yes No	1 2
29	At what age are women most likely to get cancer of the cervix?	As teenagers 20 – 35 years	1 2

	<i>(Interviewer, read the list and ask respondent to select which age group)</i>	Women over 35 DK	3 9
30a	Do you think you could ever get cancer of the cervix?	Yes No DK	1 2 9
30b	Why do you say this?	
31	Do you think cancer of the cervix can be prevented?"	Yes No DK	1 2 9
32	Do you think cancer of the cervix can be cured?	Yes No DK	1 2 9
33a	Interviewer: ask all respondents In the last 6 months, have you ever seen or heard about Pap smears or cancer of the cervix such as on: Interviewer, read list one by one	a. a poster b. a leaflet/pamphlet c. a talk by health workers d. personal discussion with a health worker e. an organised talk in the community f. a radio programme g. an article in the newspaper h. anything else? (specify)	Yes No DK 1 2 9 1 2 9 1 2 9 1 2 9 1 2 9 1 2 9 1 2 9 1 2 9
33b	What did you learn from these about pap smears and/or cervical cancer? <i>Interviewer: note response here and code later</i>	

Pap Smear History

This section for ALL respondents

First, explain what a Pap smear is:

A Pap smear is a simple test done on women to check if the mouth of the womb (cervix) is healthy. The client lies on a couch, on her back with knees bent and apart, and feet apart. The nurse/doctor places an instrument into the vagina to see the mouth of the womb. The mouth of the womb is gently wiped; a sample is taken and sent to the laboratory for testing. The results of this test will be sent to your clinic so you have to remember to go back for your results.

34	Have you ever had a Pap smear?	Yes No DK	1 skip to q 36 2 9 skip to q 44
35	If No , is there any reason why you have not had a Pap smear?) <i>Interviewer: note response here and code later</i>	Now skip to Q 44
36	If yes , how many times have you had a Pap Smear (in your life time)? <i>Actual if able to estimate (... ..)</i>	Once 2-5 times > 5 times DK	1 2 3 9
37	Have you ever had a Pap smear without it being part of other services?	Yes No DK	1 2 9
38	How many years ago was your last Pap	Less than 1 year ago	1

	Smear? <i>Actual if able to estimate (.....) years</i>	1-5 years 6-10 years > 10 years ago DK	2 3 4 9
39	After the last Pap smear, did you get the results?	Yes No DK	1 2 skip to q 41 9 skip to q 41
40	How did you get the results?	Client contacted the clinic Clinic contacted client Had made a follow-up appointment & attended Other..... DK/can't remember	1 2 3 8 9
41	Are you planning to have another Pap smear ever?	Yes No DK / unsure	1 2 skip to 44 9 skip to 44
42	If yes, when will that be?	Years from now.....	Skip to q 46
43	<i>For those not planning another pap smear (or not sure), can you tell me why that is?</i>	Skip to q 46

Never heard of a Pap smear, or never had a Pap smear?

This section is for those women who have never heard of a Pap smear, or they have heard of them, but never had one (women who answered no or DK to question 34/35)

44.	Do you think you would be interested in having a Pap smear?	Yes No DK	1 Skip to 46 2 9 Skip to 46
45.	If no, can you tell me why not?	

End interview. Thank the client for her help and ask "do you have any questions"

Appendix D: Focus group interview guide

INTRODUCTION

We are going to be talking to you today about a way to prevent cervical cancer.

1. Could you discuss what you know or have heard about cancer?
2. Could you discuss what you know or have heard about cervical cancer?
If participants are not familiar with cervical cancer, what kind of sicknesses do you know of that can affect a woman's reproductive system?
2. How do you think a woman gets cervical cancer?
3. How can a woman prevent cervical cancer?
Have you heard about any tests that prevent women from getting cervical cancer?
If so, have you gone for these services or do you know anyone who has gone for these services?
What was your experience like or what did they tell you about their experiences?
Where could a woman get these cervical cancer prevention services in your area?
4. Could you describe anything you might have heard about the HPV virus and/or the HPV vaccine? If participants have, could you describe what you have heard?

Interviewer: Then explain

The HPV virus is a sexually transmitted virus and is the virus most responsible for cervical cancer. A small number of women who are infected with the HPV virus may develop cancer of the cervix. A new HPV vaccine is now available in some countries but not yet in South Africa. This vaccine can be given to prevent cervical cancer.

- Will prevent cervical cancer (approximately 70 % of cases).
 - Should be before one starts having sex that is before they are exposed to the HPV virus
 - Will be given in 3 injections over 6 months
5. What are your thoughts or feelings about vaccination in general?
 6. Do you think people in your community would be interested in receiving the HPV vaccine?
 - What would then decide to have the vaccine?
 - What would them decide **not** to have the vaccine?
 7. How would you feel about young girls or your child receiving the vaccine?
 8. Who do you think would NOT want to use this vaccine?
 - Why would they **not** want to use it?
 9. Would you have any concerns about your child receiving the HPV vaccine? If yes, what would they be? If no, why not?
- Probes:**
- Would you have any concerns around safety, if yes what would they be
 - Would you have any concerns around the effectiveness of the vaccine?
 - Concerns around side effects
 - Have you had any other experiences with vaccines – if yes, what were they?
10. Do you think you would be prepared to pay for the vaccine? If yes, how much would you be willing to pay for the vaccine? If no, why not?
 11. What kinds of information would you like to receive about the vaccine before making decisions whether to have the vaccine or not.

12. Where do you think people in your community would like to get information about the vaccine?

13. Where do you think the vaccine should be made available?

Probes:

- Should it be available at clinics such as youth clinics or public health care clinics? Why? Why not?
- Should it be available at schools? Why? Why not?
- What other places do you think it should be available? Why?

14. Are there any individuals or people who you think could influence who would influence decisions to use it or **not** to use the HPV vaccine?

Probes:

- Would family or parents influence the decision?
- Would friends or peers influence the decision?
- Would healthcare providers influence the decision?
- Are there other people or organisations that may influence the decision to use or not use the vaccine? If yes, who are they?

15. Do you have any other thoughts, concerns or questions?

I would like to thank you for your time and for participating in the discussion.

University of Cape Town

Appendix E: Health care provider interview guide

Introduction

I would like to discuss some issues related to prevention of cervical cancer.

1. Are you aware of the South African cervical cancer screening policy?

If yes, could you discuss what you know?

If no, explain below.

Note to interviewer: Even if responded yes explain below starting with “Just to re cap”.

In an effort to reduce cervical cancer the National Department of Health introduced a cervical screening policy in 2000. According to this policy all women over the age of 30 years attending public sector services are entitled to three free Pap smears in their lifetime at 10-year intervals.

2. What are your views on this policy?

3. What has your experience been with regards to cervical cancer screening programs and cervical cancer treatment?

Probe: If not mentioned, what have your experiences been with doing Pap smears, getting and interpreting results from the lab and with women returning for their Pap smear results?

We now know that cervical cancer is caused by the human papillomavirus (HPV). HPV is a common, asymptomatic sexually transmitted infection. There are many types of HPV and certain high risk types of HPV cause cervical cancer. However, not all women who have HPV infection go on to get cervical cancer.

4. Had you heard of the HPV vaccine?

If yes, could you describe what you had heard?

There is now an HPV vaccine which is available in some countries but not yet in South Africa. This vaccine provides protection against 2 strains of HPV which are responsible for most, not all, of cervical cancer cases. The HPV vaccine is effective if it is given before one is sexually active and thus before exposure to the HPV virus. The vaccine must be given as 3 injections over 6 months. As with any new product, there are many questions about how best to deliver the vaccine and how to integrate the HPV vaccine into existing cervical cancer prevention programs.

5. What are your views about preventing cervical cancer by using a vaccine?

6. Who do you think is likely to use the HPV vaccine? Are there certain clients or groups that you think it would be most appropriate to offer the vaccine to? If so, who?

7. Currently the HPV vaccine has been licensed for girls and women elsewhere, what do you think about boys and young men receiving the vaccine?

8. Who should manage and be responsible for this program?

9. What would be the most suitable places for distributing the HPV vaccine?

Probe: Expanded programme on immunization (EPI) and Child Health, Sexual and Reproductive Health
How would you feel about administering the vaccine at youth/adolescent clinics or within the school health services?

10. Information/counseling:

What information/resources do you think providers would need to have to effectively introduce the HPV vaccine?

What do you think would be the most suitable means for providing information and counseling on the HPV vaccine?

11. Assuming the HPV vaccine is approved for use in South Africa, how would you feel about introducing it at the facility that you work at? What issues do you think would facilitate or hinder offering the vaccine at your facility?

12. Do you have any concerns that the introduction of the HPV vaccine could impact on existing cervical cancer screening programs and strategies?
If yes, what would they be?
13. How do you think the HPV vaccine should be integrated into existing screening programs?
14. Do you foresee any problems or opposition from health care providers, parents, community or religious organizations that could oppose the introduction of HPV vaccines?
If yes, what would be the best approach to handle any opposition or concerns?
15. What has been your experience in the introduction of other similar methods or new technologies? How can these experiences be applied to the introduction of the HPV vaccine?
16. Do you have any other comments, suggestions or questions that you would like to ask?

Thank you for your time.

University of Cape Town

Appendix F: Policy-makers interview guide

Introduction

I would like to discuss some issues related to prevention of cervical cancer.

1. Are you aware of the South African cervical cancer screening policy?
If yes, could you discuss what you know?
If no, explain below.

Note to interviewer: Even if responded yes explain below starting with “Just to re-cap”.

In an effort to reduce cervical cancer the National Department of Health introduced a cervical screening policy in 2000. According to this policy all women over the age of 30 years attending public sector services are entitled to three free Pap smears in their lifetime at 10-year intervals.

2. What are your views on this policy?
3. What has your experience been with regards to cervical cancer screening programs and cervical cancer treatment?
4. What sorts of priorities do you think cervical cancer prevention programs have in relation to other health programs.
5. Had you heard of the HPV vaccine? If yes, could you describe what you had heard?

Note to interviewer: discuss below even if have heard of HPV vaccine

There is now an HPV vaccine which is available in some countries but not yet in South Africa. This vaccine provides protection against 2 strains of HPV which are responsible for most, not all, of cervical cancer cases. The HPV vaccine is effective if it is given before one is sexually active and thus before exposure to the HPV virus. The vaccine must be given as 3 injections over 6 months. As with any new product, there are many questions about how best to deliver the vaccine and how to integrate the HPV vaccine into existing cervical cancer prevention programs.

6. What are thoughts around the HPV vaccine as a particular method of cervical cancer prevention?

Probes: Ask these questions if not discussed

Issues related to safety and efficacy: How effective would it have to be for you to consider recommending it? Could you comment?

Cost: Do you have concerns about cost? If yes, what are they?

Training and service needs: Do you have concerns about training and other service related needs such as procuring the drugs and delivery of a vaccine.

Target age: What do you think the target age should be for the vaccine? Why do you think it should be targeted at this age?

Who would use: Elsewhere the HPV vaccine has only been licensed for girls and women what do you think about boys and young men receiving the vaccine?

Information/counseling What do you think would be the optimal channels for providing information and counseling?

Distribution channels What do you think would be the optimal channels for HPV vaccine delivery?

7. The HPV vaccine has the possibility of being positioned in various programs, where do you think management of the HPV vaccine program should be best positioned? Why?
8. How would you feel about placing the vaccine at youth/adolescent clinics or within the school health services?
9. Is there anything else that you would need to consider in recommending or not recommending the HPV vaccine as part of your cervical cancer prevention strategy?

10. Do you have any concerns that the introduction of the HPV vaccine could impact on existing cervical cancer screening programs and strategies? If yes, what would they be? If no, why not?
11. Do you foresee any problems or opposition from parents, community, health care providers, religious organizations or anyone else? Probe why, why not?
12. Are there any groups or individuals that you believe could facilitate or hinder the introduction of the HPV vaccine?
 - If yes, who are they?
 - If yes, how could or would they facilitate or hinder introduction?
13. What has been your experience in the introduction of other similar methods or new technologies? How can these experiences be applied to the introduction of the HPV vaccine?
14. What role do you think the private sector could play in the introduction or uptake of the HPV vaccine?
15. Do you have any other comments, suggestions or questions that you would like to ask?

Thank you for your time.

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Appendix G: Questionnaire cervical intraepithelial lesions in HIV positive women initiating highly active antiretroviral therapy

1. Date of Interview _____ dd/mm/yy

I would like to ask you a few questions to see if you are eligible to be in the study.

2. Age _____

3. Date of Birth _____ dd/mm/yy

If younger than 18 years thank the respondent and discontinue the interview

4. Are you currently pregnant? _____

5. Have you had your uterus/womb removed? _____

6. Are you menstruating at present (bleeding or spotting). _____

If YES to questions 4, 5 or 6 thank the respondent and discontinue

If NO to question 4 and 5 and 6 then explain to the client that she is eligible and proceed with the interview

A SOCIO-DEMOGRAPHIC CHARACTERISTICS

Interviewer to transcribe Age and Date of Birth from page 1

1. Age _____

2. Date of Birth _____ dd/mm/yy

I would like to ask you a few questions about your education, marital status etc.

3. What is the highest level of education that you have completed?

0. Did not attend school at all	7 Std 5 Grade 7
1. Sub A Grade 1	8 Std 6 Grade 8
2. Sub B Grade 2	9 Std 7 Grade 9
3. Std 1 Grade 3	10 Std 8 Grade 10
4. Std 2 Grade 4	11 Std 9 Grade 11
5 Std 3 Grade 5	12 Std 10 Grade 12
6 Std 4 Grade 6	13 Tertiary (University/technikon/college)

4. Do you do work that you are paid for? _____

If NO skip to Q 6

5. If Yes: What is your job? Specify: _____

1. Professional (teacher, nurse, doctor, researcher)
2. Skilled (saleswork, hairdresser etc)
3. un/semiskilled manual (labourer, domestic worker)
4. Other

6. If NO, are you: _____

1. Unemployed-looking for work
2. Unemployed-not looking for work
3. Home-maker (by choice)

- 4. Full-time student
- 5. Disabled (physically or mentally) or a pensioner (government or private civil pension/not working due to old age)

7. **What is your current relationship status?**

Are you now

- 1. Married (including common-law)
- 2. Single: in a stable relationship
- 3. Single: in a casual/short term relationship
- 4. Single: no relationship now

B. SMOKING HISTORY

1. **Do you now or have you ever smoked cigarettes?**

- 1. Never
- 2. Ex-smoker (*stopped more than one year previously*)
- 3. Current smoker (*smoking sometime during the past year*)

If never smoked go to next Section on Pregnancy History

If current smoker go to question 5

If Ex-smoker go to question 2

2. **How many cigarettes did you smoke a day?**

3. **For how long did you smoke?**

- 1. ≤ 1 year
- 2. 1-5 years
- 3. ≥ 5 years
- 4. Don't remember

4. **How long has it been since you stopped smoking?**

- 1. 1-5 years
- 2. ≥ 5 years
- 3. Not sure/don't remember

5. **How many cigarettes do you smoke a day?**

6. **For how long have you been smoking?**

- 1. ≤ 1 year
- 2. 1-5 years
- 3. ≥ 5 years
- 4. Not sure/don't remember

C. PREGNANCY HISTORY

I am now going to ask you about pregnancies.

1. **Have you ever been pregnant?**

If NO go to next section on Contraceptive History

2. **IF YES: How many live children do you have?** _____

3. **Have any of your children died** _____

IF YES:

a. **How many** _____

4. **Have you had any stillborn infants?** _____

IF YES:

a. How many _____

5. Were any of these babies born by Caesarian section? _____

IF YES:

a. How many _____

6. Have you had any miscarriages? _____

(abortions/ectopic pregnancies)

IF YES:

a. How many _____

D. CONTRACEPTIVE HISTORY

I am now going to ask you about contraceptive methods

Have you ever used any of the following methods (Past use):

Interviewer to read each option

1. Birth control Pills (Oral contraceptive/"The Pill") _____

2. Injectable contraception _____

3. Foam/Jelly/Cream _____

4. Condom Male _____

5. Condom Female _____

6. Sterilization (Tubes Tied) _____

7. Partner's vasectomy _____

8. Other (e.g. Withdrawal) Specify _____

9. Are you currently using any contraception? _____

a. If YES which method are you using? _____

1. Birth control Pills (Oral contraceptive/"The Pill")
2. Intrauterine Device (IUCD/ Loop/ Coil)
3. Injectable contraception
4. Condom Male
5. Condom Female
6. Other

E. Pap/CERVICAL SMEAR HISTORY

I am now going to talk about Pap smears

Do you know what a Pap smear is? Could you describe this for me. If the person fully understands don't give an explanation again, otherwise say, let me go over it again and then give explanation: It is a test to detect abnormal cells in the mouth of the womb that could lead to cancer. When performing this test the doctor or nurse places an instrument called a speculum (spoon) in the woman's vagina so that he/she can see the mouth of the womb and the test is done.

Then interviewer to ask:

1. **Did, you ever have this test done?** _____

If NO go to next section on STIs

If YES,

2. **How many times have you ever had a Pap smear?** _____

3. How long ago did you have your last Pap smear? _____

1. ≤ 1 year ago (within the last year)
2. > 1 year ago but ≤ 5 years ago
3. > 5 years ago

4. Did you ever get the result of any of your Pap smears/tests?

a. If yes what were you told: _____

5. Have you ever been told that there was something wrong with the mouth of your womb?

a. If yes what were you told: _____

F. SEXUALLY TRANSMITTED INFECTIONS (STI)

I would like to talk about diseases or conditions that women often complain about. These include: a discharge from the vagina - sometimes this discharge causes itching or may be foul smelling or may cause you some worry; a sore, warts or blisters on the women's private parts

1. Have you had a vaginal discharge that has caused you some worry. _____

If No go to Q 3

2. If YES, When was the last time it occurred: _____

1. In the last week
2. More than 1 week but less than a month ago
3. More than 1 month but less than 6 months

3. Have you ever had ulcers/blisters/warts on the genitals _____

If No go to next section on Sexual Activity

4. If YES, When was the last time it occurred: _____

1. In the last week
2. More than 1 week but less than a month ago
3. More than 1 month but less than 6 months

G. SEXUAL ACTIVITY

The following questions are about private aspects of your life. I understand that these are sensitive questions about your personal sexual history. Please let me know if there is any question you do not wish to answer.

1. If you think back to the past, how old were you when you first had sex with a partner (even if unwilling) _____ years

2. Up until now, how many sexual partners have you had? _____

3. How many sexual partners have you had in the past year? _____

4. How many times have you had sex in the past month? _____

H. TREATMENT

1. Are you taking ARVs at present? _____

If No go to question 4

2. If Yes how long have you been on treatment? _____

3. What treatment are you currently on _____

4. If No – when do you think you will start ARV treatment? _____

(code later)

I. PELVIC EXAMINATION

Pelvic Examination

If the lesion is a wart or ulcer please record the site of lesion (vulva, vagina or cervix)

Symptoms	Present/	Absent	Comment	Code
Warts				
Discharge				
Ulcer				
Other observations				

Specimens for TESTS - tick when completed

WOMEN Cytobrush for Pap smear <input type="checkbox"/> Cytobrush for HPV <input type="checkbox"/>
--

J. DATA TO BE EXTRACTED FROM CLINIC RECORDS

Clinic record number _____

MOST RECENT CD4 COUNT

Date done dd/mm/yy

□□/□□/□□

Count _____

□□□