CERVICAL CANCER AND ITS CONTROL IN NIGERIA: CHALLENGES AND THE WAY FORWARD

Abimbola Omolara Kolawole
Nigeria

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CERVICAL CANCER AND ITS CONTROL IN NIGERIA: CHALLENGES AND THE WAY FORWARD

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Master of Public Health

By

Abimbola Omolara Kolawole

Nigeria

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ABSTRACT

Cervical cancer (CC) is a major public health problem. Globally 1.4 million women are living with the disease and 7 million people may have precancerous changes. Eighty percent of the 493,000 annual new cases and 80-85% of annual deaths from cervical cancer occur in Low Income Countries (LIC) having less than 5% of the global cancer resources. In Nigeria, the most populous African country 9,922 cases are diagnosed annually and 8,030 die. These figures are expected to increase by about 25% within 10years. The incidence rate ranging from 25 per 100,000 to 30 per 100,000 women is 5-6 times higher than incidence in High Income Countries. The affected women come with advanced disease which poses great challenge to the struggling health system.

Cervical cancer now considered a 'Sexually Transmitted disease' and Human Papillomavirus (HPV) is the necessary cause. Nigerian women of all ages have a high prevalence HPV of 26.3%. This is due to many determinants and co-factors like early sexual debut, multiple sex partners, low condom use, high parity, high incidence of other Sexually Transmitted Infections including HIV, poverty, illiteracy, micronutrient deficiency, poor hygiene and absence of a National prevention program. Underlying all these is the low status of Nigerian women which limits access to health.

Control of CC in Nigeria may contribute to achieving four out of the eight Millennium Development Goals. The disease is preventable through health promotion, sexual risk reduction and screening procedures followed by treatment of precancer using simple out-patient procedures. The cervical cytology-based population screening using Papanicolaous' smear proven to be effective in High Income Countries (HIC) is currently not effective or feasible in Nigeria due to insufficient human and material resources. Alternatives being proposed include Visual Inspection with Acetic acid (VIA), HPV DNA testing, less frequent smears and HPV vaccination. These options need to be explored for Nigeria, hence the need for a National policy and guidelines on CC control.

KEY WORDS: Cervical cancer, cervix, control, cancer, pre-cancer, SIL, CIN, HPV, Nigeria, Neoplasia, Low Income Countries (LIC), Low resource (LR), High Income Countries (HIC), dysplasia, prevention, Screening, Squamous cell Carcinoma, genital tract.

ABBREVIATIONS/ACRONYMS

ABUTH	Ahmadu Bello University Teaching Hospital
ACCP	Alliance for Cervical Cancer Prevention
AIDS	Acquired Immune Deficiency Syndrome
CC	Cervical Cancer
CDC	Centre for Disease Control
CHW	Community Health Workers
CIN	Cervical Intraepithelial Neoplasia
CN	Cervical Neoplasia
FGN	Federal Government of Nigeria
FMOH	Federal Ministry of Health
GDP	Gross Domestic Product
HCP	Health Care Provider
HCW	Health Care Worker
HDI	Human Development Index
HIC	High Income Countries
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR-HPV	High Risk Human Papilloma virus
HSIL	High grade Squamous Intraepithelial Neoplasia
IUD	Intra Uterine Device
LEEP	Loop Electrosurgical Excision Procedure
LIC	Low Income Countries
LMIC	Low and Middle Income Countries
LR-HPV	Low Risk Human Papilloma virus
LSIL	Low grade Squamous Intraepithelial Neoplasia
MCH	Maternal and Child Health
MIC	Middle Income Countries
NDHS	Nigerian Demographic and Health Survey
NGO	Non Governmental Organization
OR	Odds Ratio
PapSmear	Papanicolaou's Smear
PHC	Primary Health Centre
RCTs	Randomized Controlled Studies
RH	Reproductive Health
RR	Relative Risk
SSA	Sub Saharan Africa
SCJ	Squamo Columnar Junction
STD	Sexually Transmitted Disease
STIs	Sexually Transmitted Infections
SIL	Squamous Intraepithelial Neoplasia
VIA	Visual Inspection with Acetic Acid
VILI	Visual Inspection with Lugol's Iodine
WHO	World Health Organization

GLOSSARY

Acetowhite: Abnormal white area on cervix after application of 3-5% acetic acid indicating possible precancer stages

Cervix: Lowermost part of the uterus in contact with the vagina ('neck of the womb').
Cervical Epithelium: The cell layers covering the cervix (the 'cervical skin').

Squamo Columnar Junction: The part of the cervix where two different cell types meet, usually the place where abnormalities start.

Cervical Cancer, Cervical Neoplasia: Excessive, abnormal, uncontrollable new growth of cervical cells

Cervical Precancer: State when abnormal cellular changes have started but have not progressed to cancer.

Cervical Intraepithelial Neoplasia: Term for grading the abnormalities of the cervical epithelium based on the depth of tissue affected.

Chemotherapy: Drugs for treating cancer.

Colposcope: Instrument used to examine the cervix with (4 times) magnification.

Dysplasia: Abnormalities of cervical epithelium that may progress to cancer

Squamous Intraepithelial lesions: A newer terminology under the Bethesda System of reporting for cervical precancerous changes restricted to the epithelium.

Radiotherapy: Radiation treatment for cancer. It may be 'Brachytherapy' when the radiation source is applied close or within the body or 'Teletherapy' when radiation is beamed on the body from a distance.

Radical Surgery: Extensive surgery for cancer involving removing as much of the involved tissues as possible.

CHAPTER 1: INTRODUCTION AND BACKGROUND INFORMATION ON NIGERIA

1.1 Introduction

As in many Low income countries (LIC), Nigerian women face a lot of challenges; socially and health-wise. They bear the brunt of illiteracy and poverty in addition to consequences of their sexuality or childbearing. In the course of my work in Obstetrics and Gynaecology in Northern Nigeria, I realized that cervical cancer is an important problem affecting Nigerian women. It is the commonest malignancy of the female genital tract (Anorlu et al 2007) and is the commonest cancer of women in Northern Nigeria and the commonest cause of cancer death in the women (Rafindadi et al 1999). The only exception is Ibadan, in Southwest Nigeria where it has become second to cancer of breast since 1980s (Parkin et al 2003, Ohaeri et al1999). It affects the poor, uneducated women often living in underserved areas reflective of poor access to health-care as well as gender and economic inequity (Hammouda et al 2005, Drain et al 2002). It exposes the vulnerability of women who may be put at risk by their spouses' high sex risk, a situation common in patriarchal societies like Nigeria.

Cervical cancer (CC) develops from 4th to 6th decade of life but is preceded by precancerous changes about 10-20 years earlier (WHO 2006b). It affects women above 30years usually a period of economic productivity. The death of a woman from CC causes significant economic loss to the household, community and nation (ACCP 2004b) as Nigerian women are involved in agriculture and trading in addition to their domestic activities. The economic loss due to CC is difficult to quantify. Since it is a slow growing cancer, women are not diagnosed until they become symptomatic and the tumor is advanced causing very offensive vaginal discharge, bleeding (Emembolu & Ekwempu 1988, Adewuyi et al 2008) and great human suffering. Then management is difficult and cure usually impossible. Ultimately, a slow, painful death occurs.

Currently in terms of global and national priority and magnitude CC is surpassed by HIV/AIDS and Tuberculosis. It results in loss of 3.3 million DALYs compared to their 84 and 35 million DALYs (PRB 2008). However, there are proven feasible and cost-effective, preventive measures. CC prevention through screening cost $15-$50 per DALY and an estimated DALYs averted per million USD spent of 20,000-60,000 (DCPP 2007) which is comparable to cost-effectiveness of other public health interventions like childhood vaccination (Goldie et al 2001). Therefore, CC should be addressed as a public health priority in Nigeria.

The causal link between Human Papilloma Virus (HPV) and cervical cancer has been made and the virus is the 'necessary cause' (Vaccarella et al 2008). Therefore it is a 'sexually transmitted malignancy' which is

preventable. Some of the underlying determinants like poverty, and lifestyle choices including early coitus and multiple sexual partners (Kitchener & Symmond1999) are preventable at the community level through 'Behaviour Change and Communication (BCC)' to delay age of initiating sex and promote 'safe sex' (Shepherd at al 1999). In developed countries the incidence and mortality from CC has been falling yearly mostly due to well established prevention programs. It has moved from being the second common cancer cause of death to the sixth (Cox 2006) or even ninth position (Spitzer 1998). This prevention is based on cervical cytology using 'Papanicolaou's Smear (Pap smear)', with or without HPV-DNA testing to screen for pre-invasive or pre-cancerous changes which are then treated using simple outpatient procedures like Loop Electrosurgical Excision Procedure (LEEP).

Nigeria however, has no National Policy or program for cervical cancer prevention. Instead, the National Program for Sexually Transmitted Infections is expected to contribute to reduction in HPV infection. Preventive efforts are neither deliberate nor coordinated. However, control of CC will contribute to eradication of poverty, promotion of gender equity and indirectly to achievement of universal primary education, reduction of child mortality and improvement of maternal health. This study will review CC in Nigeria, its magnitude and the determinants. It will also analyze the preventive strategies within the global context with the aim of making recommendations that may guide Nigerian national policy on cervical cancer prevention. This is the motivation for carrying out this study.

1.2 Background information

1.2.1 Socio-demography

The Federal Republic of Nigeria is a West African country with six geopolitical zones; South West, South East, South-South, North West, North East, North Central, 36 states and a Federal Capital Territory. It has more than 250 ethnic groups, with the main ones being Hausa-Fulani in the North, Yoruba in the South West and Igbos in the South East. Christianity and Islam are the two main religions (WHO 2008a). Nigeria the most populous African and indeed "black" country has a population of about 140 million (FRN 2007). About 1 in every 5 negroid person and 1 in 4 Africans is a Nigerian. The burden of various diseases becomes substantial due to the large population. The fertility rate is 5.5 and growth rate is 3.2%, hence the population will double in 23years (FRN 2007).

It has one of the lowest levels of family planning use in the world (PRB 2008) with Contraceptive Prevalence rate of 12.6% (WHO 2006e). Nigerians have large families with 66% of women and 71% of men wanting more children. About 15% of married women use contraceptives but only 9% use a modern method (NDHS 2003, Oyedokun 2007). Oral contraceptives are used by 1.8% of reproductive age women

(WHO/ICO2007). There is a high rate of unsafe abortion, 80% of pregnancies in unmarried teenagers are unwanted since only 10% of them use contraceptives (AGI 2004). The mean age at first marriage for women is 17.5years and early pregnancy results in 16% of all births. The median age at first marriage is 19years for urban and 17years for rural female; it is higher for the more educated female. Age of marriage varies from 15years in northeastern and northwestern Nigeria to 20years in Southeastern and Southwestern regions (NDHS 2003). In some communities it is a taboo for a girl to attain menarche in her parents' home. She is expected to be married before (Kabir et al 2004, Advameg 2007).

1.2.2 Socio-economic indices

The country in spite of immense physical and human resources is classified among the world's poorest 20 countries (WHO strategy 2007). It has some of the world's worst health indices mostly because of poor planning and poor governance. The socio-economic indicators are lowest in north-west and north-east. The Mean literacy rate is 68% for people over 15years of age (male 75.7% and 60.6% females) (Leahy 2006, NDHS 2003). The country has GDP per capita of $456, a Gini index of 44 and about 70% live below one dollar per day. Most households spend 2/3 of their income on food (World Bank 2007). Women and children are more vulnerable to effects of poverty and are prone to diseases.

1.2.3 The health system

Nigeria operates a decentralized health system from federal to state and local government ministries of health. The Federal Ministry of Health (FMOH) is responsible for policy, planning, disease surveillance and supervision of the other levels. It provides tertiary care and oversees training of doctors and nurses in the sixteen Teaching Hospitals with medical schools and twenty-three Federal Medical Centres (Lambo n.d, Miller et al 2007). There are 50 schools of Nursing and 6 schools of public health (Miller et al 2007). Most of the 100 trained pathologists are based in these tertiary institutions where cancer is treated (WHO 2008a).These cytopathologists are responsible for reviewing slides and diagnosing cancers. It is estimated that 2/3rd of Nigeria's 3000 obstetricians and gynaecologists (including trainees) are working within the country (Ezechi 2007).

The states operate secondary care through General Hospitals and some Comprehensive Health Centres. They also train nurses, midwives and Community Health Extension workers (CHEWS). The Local government is responsible for Primary Health Care. This is delivered in Primary Health Centres which are the closest health units to the people in the community. However, there is poor access to facilities and lack of equipment and manpower. The total health expenditure as percentage of GDP is 4.6% to 5.0% (WHO 2008c) and most of this is spent on staff salary. The per capita total expenditure on health is 51 international dollars while the per capita government expenditure on health is 13 international dollars which is far

from the \$34 WHO recommended (WHO 2002a). Consequently, most people (90%) pay out-of-pocket for health since the National Health Insurance is not fully operational (WHO 2008c). (See Nigeria's health expenditure in annex 4). There are 12 hospital beds per 10,000 population, 28 physicians per 100,000 people and 103 Nurses per 100,000 people (WHOSIS 2008). In spite of a vigorous National Program on Immunization (NPI), the national immunization coverage rate for completed third dose of Diphtheria, Tetanus Pertusis (DTP) in 2005 was 25%. The immunization system performance assessed as percentage of districts with 80% or more DTP-3 coverage is 3% (WHO/ICO 2007). This has significant implications for future implementation of HPV vaccination.

Currently, the health priorities of the Nigerian government are HIV/AIDS, Malaria, Tuberculosis and childhood diseases (Lambo n.d). Infectious diseases like Malaria, dysentery, pneumonia, and occasional outbreaks of Cholera, meningitis are common. The HIV prevalence of 5.0% has led to a population of People Living with HIV/AIDS (PLWHA) of about 3.6 million (WHO 2006e), some of whom are women and may have higher incidence of precancerous changes of the cervix and require screening (Anorlu 2007b, Chama et al 2005). The HIV prevalence among 15-49 years old has reduced to 3.9% (WHO/ICO 2007). The common non-communicable diseases include hypertension, diabetes mellitus and cancers (WHO 2008). Cancers are responsible for 4.4 % of deaths. In women deaths occur from breast and cervical cancers mostly and Age standardized Mortality rate from cancer is 157 per 100,000 people (WHOSIS 2008).

CHAPTER 2: PROBLEM STATEMENT, STUDY OBJECTIVES, METHODOLOGY

2.1 Problem statement

Cervical cancer is considered a sexually transmitted disease and therefore preventable. It is a major public health problem of LICs including Nigeria. Globally, it is the second commonest cancer of women (breast cancer ranking first), and about 400-500,000 new cases occur per year, eighty percent of these in LICs (Ferlay 2002, ACCP 2004) having only 5% of global resource for cancer control (WHO 2005a). Most of the 300,000 annual deaths from the cancer occur in LICs, where advanced disease is common and facilities for care is limited (Reproline 1998, Ohaeri 1999). In Nigeria, it is the commonest genital tract cancer and is the commonest cancer of women (Gharoro et al 2006, Uzoigwe 2004) especially in Northern Nigeria (Rafindadi et al 1999). The age specific incidence rate is 28.5 per 100,000 (Ferlay 2002).

The commonest type the Squamous cell carcinoma of cervix occur in 85% of cases and about 99.7% of these are associated with one or more Human Papilloma Virus (HPV) strains (Kitchener & Symonds 1999, Munoz 2006), the commonest sexually transmitted viral infection usually acquired within 2-5 years of starting sexual activity (Creasman 2007). About 630 million people are infected worldwide and currently have no cure (Outlook 2007). Although there may be spontaneous regression, persistent infection with viral types like 16, 18, 31, 33 often result in high-grade precancerous lesions of the cervix that may progress to invasive cancer within 10-20 years (Anorlu et al 2000, Creasman 2007). The HPV infection prevalence in Nigeria was 26.3% (Thomas et al 2004). Although some of the HPV types found in Nigerians differ including 33, 58, 70, 81 (Thomas et al 2004, Tornesello 2007, Clifford 2005), this infection is still potentially preventable with the recently developed HPV vaccines. Cervical cancer screening program is to detect these HPV induced pre-cancerous changes.

The various determinants of cervical cancer can be studied using the Lalonde model; this includes lifestyle, biologic, environmental and health care/service factors. Lifestyle or behavioural factors or choices as well as environmental factors are important determinants. HPV is considered the "necessary cause (Vaccarella et al 2008)", while demographic factors like social class, marital status, ethnicity and religion play major roles. Sexual behaviour determinants include early onset of sexual activity, multiple sex partners, unprotected sex as well as high parity, early age at first parity (Trottier & Franco 2006, Outlook 2007) and poor genital hygiene (Shepherd et al 1999, Hammouda et al 2005). Co-factors for HPV include infection with HIV or other STIs like Chlamydia and Herpes. The initiation of sexual activity makes a woman regardless of age 'at risk' of developing Squamous Cell Carcinoma (SCC) of cervix. It is associated with poverty

and is common in south-East Asia, Sub-Saharan Africa and Latin America (Shepherd et al 1999).

There is a strong association with male partner factors like multiple sex partners, having same sex partners. Circumcision is protective against HPV infection (Munoz 1996, Outlook 2007). Other factors include smoking (Vaccarella et al 2008), alcohol use and probably dietary pattern (Rock 2000). Some case control and cohort studies from Africa found that Human immunodeficiency Virus (HIV) was associated with a higher incidence of pre-cancerous and cancerous lesions of cervix. The inclusion of CC as an 'AIDS defining illness' is however being challenged (Bower et al 2006). Prolonged use of steroid contraceptives was recently found to cause a slight increase in the incidence of cervical cancer (Vaccarella et al 2006, Trottier & Franco 2006).

The prevention of CC can either be primary through health promotion of healthy lifestyles and behaviors or secondary through early detection including screening or tertiary (Shepherd at al 1999, WHO 2002). In most developed countries, introduction of National screening programs resulted in reduction in incidence and mortality from CC (Chirenje 2005). However, the incidence remains high in LICs like Nigeria because of few skilled personnel, high cost of service, lack of national policy and 'political will' which precludes screening using Papanicolaou's smear (Pap's smear). In addition, absence of simple out-patient procedures for treating pre-cancerous lesions makes prevention programs ineffective. Consequently, other low-cost alternatives like visual inspection with acetic acid (VIA), speculoscopy, and reduced Pap smear screening intervals are being suggested (Denny et al 2005, Sankaranarayanan et al 2001). The HPV vaccine available for primary prevention in HIC remains unavailable in LICs countries like Nigeria due to the cost (Trottier & Franco 2006, Kane et al 2006).

2.2 Study questions
This thesis will answer the following research questions:
Is cervical cancer a significant problem of Nigerian women?
What is the trend of the disease, natural history and epidemiology of the disease?
What are the main determinants of CC in Nigeria?
What preventive strategies are available and how effective are they?
Which strategies can be recommended for a policy on National Prevention Program in Nigeria?

2.3 Aim and objectives
The **aim** of the study is to review cervical cancer in Nigeria; analyze the main determinants, the available prevention strategies and to make recommendations towards development of a national screening policy/ program.

The specific objectives include:
1. To review the epidemiology and natural history of cervical cancer including the HPV viral types.
2. To analyze the burden and trend of cervical cancer in Nigeria.
3. To discuss the many determinants contributing to cervical cancer in Nigeria.
4. To analyze the current primary, secondary and tertiary preventive strategies and their effectiveness.
5. To make recommendations or guidelines for national prevention policy/program

Target population: The Nigerian women, Ministry of Health, ABUTH and Society of Obstetricians and Gynaecology (SOGON) are the beneficiaries of this thesis as it will hopefully contribute to CC policy and implementation of a National prevention program**.**

2.4 Methodology

The study is a review of published literature and 'grey literature' (theses and dissertations). These were mostly databases from the internet like PUBMED, SCOPUS Cochrane Library. Google Scholar search engine was used. Other sources included hand searched journals, WHO RHL, Globocan, DHSS and websites of WHO, World Bank, UNDP.

Limitations: The study is a review of publications and grey literature published in English language, any error inherent in these secondary data can affect this analysis. Nigerian publications were more difficult to get. There was no opportunity for primary data collection and analysis. Most of the ongoing cervical cancer screening projects in Nigeria are new and detailed information is not available yet for proper analysis.

CHAPTER 3: MAGNITUDE, TREND AND EPIDEMIOLOGY OF CERVICAL CANCER

3.1 Global picture of cancer of cervix

Worldwide, women suffer most commonly from cancers of the breast and of the cervix. Cervical cancer is often the commonest cancer and leading cancer cause of death of women in LICs (PRB 2004). Globally about 1.4 million are living with CC while up to 7 million may have precancerous changes (WHO 2006c). It affects women in the 4-6th decade from 35years onward, when they have small children and are critical to economic and social life of their families and communities (Ferlay 2000, ACCP 2004c). It is preceded by precancerous HPV induced changes 10-20 years before malignancy result.

Yearly, 493,000 new cases arise; about 80% in LICs. Also 80-85% of the 274,000 annual deaths occur in LICs where screening programs are absent (Outlook 2007). Cervical cancer is 6 times commoner and the mortality rates are 4 times more in LIC (Kitchener & Symonds 1999). The highest incidence rates of over 30 per 100,000 women is found in Central and South America, the Caribbean, Sub-Saharan Africa (SSA), and parts of Oceania and Asia. Five out of the 7 countries with the highest incidence rates are in Sub-Saharan Africa and India alone has 134,000 annual new cases (Drain et al 2002).

However, North America and Europe have incidence rates less than 10 per 100,000 (Ferlay 2002). The rates in developed countries are low mostly due to National screening programs in existence for about 50 years. This has reduced CC deaths by 80% in Iceland and 70% in the USA (PRB 2004). A half of CC cases have never been screened before (Outlook 2007). Cervical cancer leads to loss of 471,000 DALYs (Lewis 2004). It causes 2.4 million weighted Years of Life Lost (YLL) in LIC compared to 0.3 million in HIC and is the leading cancer cause of YLL in SSA. The burden of CC is expected to increase with ageing population which tends to be earlier in LICs due to harsh health and living conditions (ACCP 2004c).

3.2 Magnitude of cervical cancer in Nigeria

There are 36.59 million Nigerians aged 15 years and older who are at risk of CC (Adewole et al 2005). Annually 9,922 women are diagnosed with CC and 8,030 die (WHO/ICO 2007). Moreover these figures are hospital based and are grossly underestimated. The high HPV prevalence of 26.3% in women and 24.8% in women with normal cervical cytology correlate with the high CC incidence of 16.7 per 100,000 women and Age Standardized incidence rate of 28.5% (Ferlay 2002). Some studies gave incidence rates of 25-30 per 100,000 women (Adewole et al 2005, Gharoro 2006). This is similar to incidence in other West African countries but lower than some East African countries like Tanzania (Ferlay 2002). It constitutes 4.4% of gynaecology admissions and 74.6% of all gynaecological malignancies in Benin University Teaching Hospital and 4.2% and 66.2% respectively in

ABUTH, Zaria (Emembolu & Ekwempu 1988). It accounted for 60% of histologically confirmed tumors in women in Ilorin and 19.9% of all cancers of women in Ibadan (Babarinsa et al 1998). More recently in Zaria the figures have increased to 77% of all female genital tract tumors (Mohammed 2006) and 15.5% of total cancers seen between January 2001 and December 2005 (Samaila et al 2007). In ABUTH since radiotherapy services began in 1996, four thousand out of 5708 gynaecologic cancers treated were CC (Gharoro 2006) and there is often a long waiting time.

The epidemiology and natural history of Human Papillomavirus, pre-cancer and cervical cancer
Cervical cancer develops from uncontrollable growth of the epithelial lining of the cervix. The main stimulus or primary cause is persistent infection by the oncogenic (High Risk) HPV variants. HPV are simple, non-enveloped double-stranded DNA-viruses. HPV is the commonest viral sexually transmitted disease and affects 660 million people (WHO 2005b, CDC 2007). It is acquired soon after onset of sexual activity and about 50-80% of sexually active women will get infected with the virus at least once in their lifetime (ACCP 2004a, WHO 2005b). HPV infection can occur at any age and has been reported in healthy young children (Cutts et al 2007). Genital HPV infection is transmitted by genital skin-to-skin contact and not only penetrative sexual intercourse. It is asymptomatic and has no cure (PRB 2004). The infection is mostly self-limiting and clears within two years in 90% of cases. Only 50-60% of women develop serum antibodies to HPV after natural infection (Cutts et al 2007).

However six out of about 50 viral types affecting the genital areas may cause persistent infection and abnormal precancerous changes called 'dysplasia' or Squamous intraepithelial lesions (SIL) or Cervical Intraepithelial Neoplasia (CIN) changes in the cervix. The persistence of HPV infection cause high grade lesions or severe dysplasia over a latent period of about 10-20 years and leads to CC in about 5% of the initially infected women (Ferlay 2002). The commonest histologic type of CC is the Squamous cell carcinoma occurring in 85% of cases. It behaves differently from adenocarcinoma type (Babarinsa et al 1998, Rafindadi et al 1999) which is less preventable by cytology screening programs. The other factors which may influence progression of pre-cancer to cancer include lifestyle factors like age of first intercourse, multiple sex partners, early age at first birth, high parity, tobacco use (Shepherd et al 1999, Sitas 2006) as well as, reduced immunity like in HIV (Nappi 2005, Anorlu 2007b), male circumcision and use of hormonal contraceptives (Vaccarella et al 2006). Condoms use may reduce prevalence of HPV (Winer et al 2006).

3.4 HPV and cervical cancer

HPV virus is proven as the necessary cause for CC (Walboomers et al 1999). It is the missing link and the previously unknown coital factor (Creasman 2007). Cervical cancer does not develop without persistence of 'High Risk HPV' (HR-HPV) in the cervix which is the first identified

necessary cause for human cancer. However it is not a sufficient cause as some cofactors are contributory (Bosch et al 2002). The relative risk for CC in the presence of HR-HPV is higher than association between smoking and lung cancer. The pooled odds ratio (OR) from a study of 1918 women was 158.2 (95% CI, 113.4-220.6) (Denny et al 2005). It causes almost all CC and accounts for loss of 3.3 million DALYs annually (Low et al 2006, Schiffman et al 2007). There are more than 100 genotypes identified with about 50 causing genital infection. The distribution varies in different countries. They are subdivided into either 'High Risk' (HR-HPV) or 'Low Risk' (LR-HPV) genotypes based on whether they cause cancers or benign diseases. The HR-HPV include 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and the common LR-HPV causing genital warts and low grade cervical lesions include 6,11. About 99.7% of CC is associated with HR-HPV and types 16 and 18 accounts for 70% of cases globally (Koshiol et al 2008, Walboomers et al 1999). Other HPV-associated cancers are vulva, vaginal, anal, oropharyngeal, mouth, penis and scrotum (Cutts et al 2007).

Transmission
The primary mode of transmission of genital HPV is 'skin to skin' or 'skin to mucosal surface' and not only by penetrative sexual intercourse (Paavonem 2007, Koshiol 2008). It can also be transmitted in same-sex union between men or between women; also through sharing sex toys and possibly formites (CDC 2007).

Natural History, Biological mechanism of HPV and CC: Annex 5

Risk Factors for HPV
The strongest determinant of HPV infection is sexual activity (Koshiol 2008, Kjaer 2001). The number of sex partners a woman has or that her partner has over a lifetime is associated with likelihood of HPV infection often with many HPV types (Cutts et al 2007, Winer et al 2006, Outlook 2007). Circumcision of the male partner has been found to be protective against HPV (Bosch et al 2002, Rivet 2003). Condoms give partial protection (CDC 1988) and although disputed by some, a longitudinal study found reduced incidence and protection against new infections (Winer et al 2006). The infection is commoner in younger ages below 25 years depending on the age of sexual debut (Cutts et al 2007), whereas in Nigeria and some rural areas in India the prevalence of HPV is high in women of all ages due to inability to clear HPV, nutritional deficiencies or reduced immunity (Thomas et al 2004, WHO 2005b). The host genetic factors and immune response determines clearance of the virus, thus HPV is commoner in HIV positive women and multiple infections are common (Cutts et al 2007). Other factors like cigarette smoking, micronutrient deficiencies, increasing parity, long term hormonal contraceptives use, and presence of other STIs tend to facilitate HPV acquisition or reduce clearance (Rock et al 2000, Shepherd et al 1999).

3.5 HPV pattern in Nigeria

HPV is widely spread in Nigeria. The overall prevalence of HPV in the Ibadan, Nigeria arm of IARC study was 26.3%; and 24.8% in women without cervical lesions (Thomas et al 2004). The HR-HPV was predominant (19.7%) and was mostly types 16, 31, 35, 58. LR-HPV were found in 6.6% and mixed infections with more than one HPV type occurred in 33.5% of HPV positive cases. Although there was a small peak in women below 25 years, HPV prevalence remains persistently high in all age groups See figure 3.1 (Thomas et al 2004, Vaccarella et al 2006). HPV 16 appeared to a play a smaller role in CC in Nigeria than in Europe (Clifford et al 2005, Munoz et al 2006). Okene, northcentral Nigeria had a similar incidence of 21.6% with HR-HPV prevalence of 16.6% and 3.5% having mixed infections (Schnatz et al 2008). The slight difference in figures may be due to the different assays used-PCR versus serology. The main risk factors contributory to HPV in Nigeria; table 4.1 (Thomas et al 2004) were being unmarried, illiterate, being positive for anti-Herpes Simplex virus antibodies; also tobacco use (OR of 1.6), parity, multiple sex partners of women (OR of 1.35) and their spouses' extramarital affairs (OR 1.83 if with sex worker).

Figure 3.1

Age-specific prevalence of HPV and anti-HSV antibodies in Nigeria
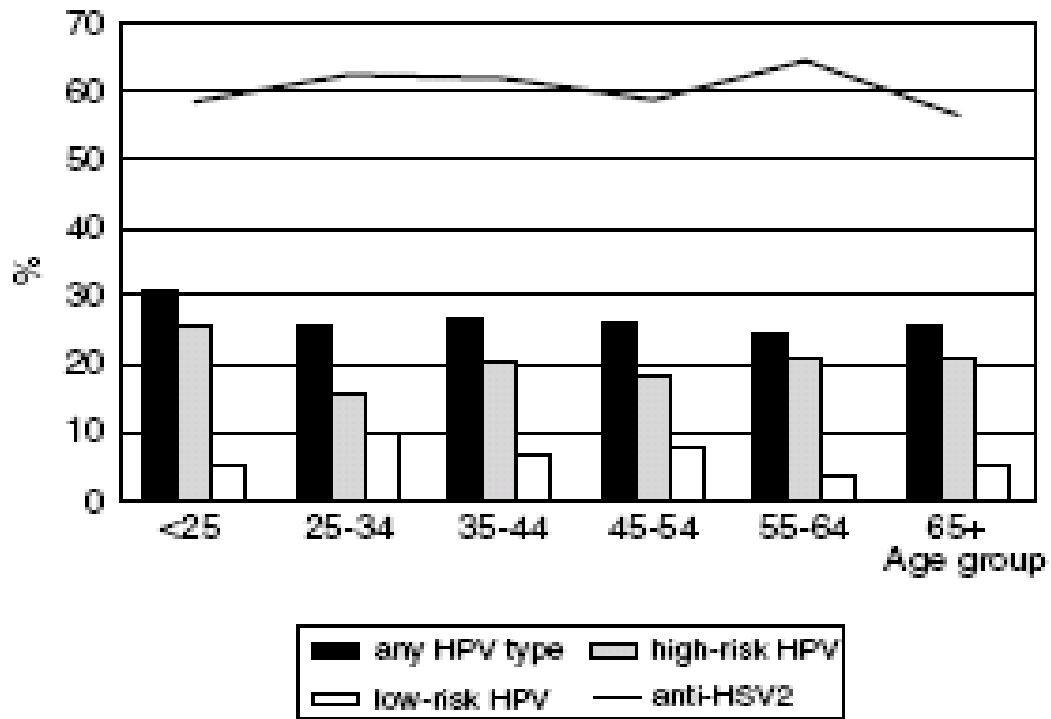

Figure I   Age-specific prevalence of HPV and anti-HSV-2 antibodies

Source Thomas et al 2004

CHAPTER 4: DETERMINANTS/CO-FACTORS OF CERVICAL CANCER

The various factors or determinants associated with cervical cancer can be viewed using the Lalonde model (1974). These include biologic, lifestyle, environmental and health service factors. Gender and political determinants often influence lifestyle and environment. The HPV a biologic agent is the major determinant and proven necessary cause of cervical cancer and has been discussed earlier.

4.1 Biological determinants

Female sex: Cervical cancer is a malignancy of women. The female anatomy and the various changes occurring in a lifetime make CC a possibility. The cervix as the lowermost part of the uterus is covered with an epithelium which undergoes different changes as the woman grows. It is the part of the uterus is in contact with vaginal fluid and semen. The squamo-columnar junction (SCJ) of the cervix undergoes metaplasia during adolescence and is the target of HPV (Creasman 2007). Thus cervical HPV infection occurs in many women soon after commencing sexual intercourse (Kjaer et al 2001) hence the association between CC and early coitus.

Male factors: It has also been suggested that frequent exposure of the cervix to prostaglandin-rich semen may contribute to malignant transformation of HPV-infected cells. CC is commoner in spouses of uncircumcised men (Rivet 2003) probably because smegma under the foreskin is favourable for HPV and other STIs. Husbands of women with CC were also more likely to have penile cancer (Creasman 2007) which is also associated with HPV infection (Parkin et al 2003). The association between male circumcision and CC in Nigeria is yet to be explored.

Heredity/genetic factors: There seems to be some genetic factor in the causation of CC as the disease may run in families. There may be 2-3 times higher risk if a mother or sister has the disease (ACS 2008, Omigbodun et al 1992). This may be due to an inherited inability to clear HPV or similarity in lifestyles and environmental factors.

Age: Increasing age is a determinant of CC. The disease is commoner in women between 4th and 5th decade (Juneja et al 2003, Outlook 2007). Studies from Zaria-Nigeria, found mean age of women diagnosed with CC to be 43 years (Abdul et al 2006) and median of 48years (Adewuyi et al 2008). This allows a latent period of 10-15 years between exposure to HPV after sexual debut and development of CC. The incidence of pre-malignant disease and invasive CC rises after 30years of age (Obafunwa 1991). In Ibadan, Nigeria, although HPV prevalence peaked at 25 years of age, it persisted in older ages (Thomas, 2004) which may explain high incidence of CC in much older women.

Parity: There has been a consistent association of high parity with CC in HPV positive women (Munoz et al 2002, Vaccarella et al 2006). This association appears stronger as parity increases. While para 1 or 2 HPV positive women had OR of CC of 2.3, para 7 or more had OR of 3.8 compared with nullipara. The probable explanation may be that number of pregnancy reflects frequency of unprotected sexual exposure (including risk of HPV), each pregnancy exposes the women to high levels of endogenous oetrogens-progestrones. Also the cervix undergoes squamous metaplasia in pregnancy, and ectopy which is commoner in pregnancy exposes the SCJ to vaginal fluid which may contain HPV (Munoz et al 2002). In vitro studies suggest that hormones may affect regulation of viral promoters and malignant transformations of HPV-infected cells into cancer (Vacarella et al 2006a). High parity is common in Nigeria with a TFR of 5.7 per woman (NDHS 2003) and CC was commoner in Nigerian women of higher parity (Emembolu & Ekwempu 1988) however only a modest association (OR 1.7) was found in prevalence of HPV in para 1 or 2 compared with nullipara (Thomas et al 2004).

Other biological agents:
Sexually Transmitted Infections (STIs): Presence of other STIs especially ulcerative ones like chancroid and viral ones like Herpes Simplex Virus (HSV), HIV are considered co-factors in aetiogenesis of cancer and there is an associated increase in SILs (ACS 2008, Shepherd et al 1999, CDC 1988). This may be due to sexual behavior being the confounder (Vacarella 2006b) or limited ability to clear HPV (Mandeblatt 1999). There is higher prevalence of HPV in HSV positive women. The prevalence of anti-HSV antibodies was 61.3% in Ibadan, Nigeria, and having anti-HSV antibodies had OR of 1.6 for HPV (Thomas et al 2004).

HIV: The exact nature of interaction between HIV, cervical dysplasia and CC is yet undetermined (Walraven 2003, Mayaud 2001). However, HIV positive women have higher incidence of Pap smear abnormalities including pre-malignant changes (Nappi 2005, Ellerbrock 2000, Chirenje 2005, Chama 2005). Although invasive CC was added as an AIDS-defining illness by CDC Atlanta in 1993 (Castro 1992), this is currently being challenged for lack of strong evidence (Bower et al 2006). However a meta-analysis (Mandelblatt 1999) found OR for Cervical Neoplasia (CN) of 8.8 in HIV positive women compared to 5.0 in HIV negative women. There was an apparent interaction which was dose dependent when those with CD4 count less than 200 were studied. The suggested mechanisms for a possible co-factor role for HIV in cervical neoplasia included HIV promoting oncogenic effect of HPV thus leading to persistence of HPV infection, higher replication and increased progression. A molecular interaction between HIV-1 'tat protein' and HPV oncoproteins may also lead to progression (Mandelblatt et al 1999, Chirenje 2005).

Countries in SSA with high HIV prevalence also have high incidence of CC especially in East and South Africa countries like Zambia (Parham et al

2006) and Zimbabwe. The OR/risk of CC in HIV positive women was 1.6 and 2.4 in South Africa and Uganda respectively (Newton et al 2001, Sitas et al 2006, Chirenje 2005). In Kenya, women younger than 35 years having CC were 2.6 times more likely to be HIV positive (Gichangi et al 2003). A similar association was reported from Nigeria where HIV positive women are younger and present with more advanced and aggressive CC (Adewuyi et al 2007, 2008, Anorlu 2007a). Nevertheless, registry data from Nigeria has not shown the expected rise in the incidence of CC over the past four decades (Parkin et al 2003).This requires further research.

4.2 Lifestyle Determinants

CC as a sexually transmitted disease is influenced by lifestyle, habits and sexual behaviour.

Sexual debut: Early commencement of sexual activity especially in adolescence is associated with greater risk of CC because of vulnerability to HPV infection (Shepherd at al 1999, Ogunbode et al 2005, Rafindadi et al 1999). Sexual debut before 18 or 20years is a strong determinant of CC in later life (Kjaer et al 2005, Vaccarella et al 2006). This is very important in Nigeria where more than 80% adolescents are sexually active by 20years of age (NDHS 2003) and legal age of consent is 13 or 16 years in different regions (Odili 2002). This regional variation may contribute to the pattern of CC in Nigeria. In southern Nigeria with higher female literacy, sexual debut occur around 19years and outside marriage (NDHS 2003) unlike in Northern Nigeria where early sexual activity occur in the context of early marriage (AGI 2004) which is part of the culture. Girls may be married usually to older, sexually-experienced men before menarche in some places (Kabir et al 2004, Advameg 2007).

Number of sex partners: Women having multiple sex partners are prone to HPV and CC. This is because of more frequent exposure to different variants of the virus (Appleby et al 2007). Spouses of men who have had multiple partners either before or during the current marriage are also at increased risk (Hammouda et al 2005, Bayo et al 2002, Drain et al 2002). This pattern is important in Nigeria where mean number of sex partners of women (self-reported) was 1.7 (Thomas et al 2004, Vacarrella 2006b). This may explain the higher incidence of CC in polygamous marriages (Emembolu & Ekwempu 1988, Adewuyi et al 2008, Bayo 2002) or in women whose husbands admitted visiting prostitutes. The OR of number of sex partners and CC was marginal in Nigeria being 1.4 (Thomas et al 2004).

Unsafe sex: Unsafe sex is a determinant of HPV infection and CC (Sherris 2000, Grimes 1995), condom use offers partial protection against transmission of genital HPV (CDC). The protection is partial because virus can be shed from the areas not covered by the condom. However, some women with CIN had more spontaneous regression when their partners used condoms (Winer et al 2006). Also correct and consistent use of condoms has been associated with 70% protection against HPV and a lower incidence of CC (CDC 2007, Sherris 2000, Outlook 2007). The effect

of condoms and spermicides on CC increased with duration of use (Grimes 1995). However, in spite of campaigns on condom use in Nigeria, only 47% of men and 23% of women reported condom use during 'high-risk sex' in a past year (NDHS 2003); and reasons for non-use include diminished pleasure, inconvenience and cost (NDHS 2003). This low usage may contribute to higher incidence of HIV and other STIs which may facilitate HPV infection (CDC 2001).

Contraceptives: The use of hormonal contraceptives; injectables and pills has been associated with a slight risk of CC both Squamous cell cancer and adenocarcinoma (Moreno et al 2002; Castellsaque et al 2006). This link was stronger for pills than injections. It was higher when women started pills earlier than 25years of age or use it longer than 10years and are HPV positive, the OR for CC was 4.48 (Bosch et al 2002, Moreno et al 2002). However on stopping them the CC rate 10 years after was similar to the rate in 'never users' (Appleby et al 2007). Therefore WHO recommends that the risk is small and there is no need to restrict usage (WHO 2006c). The probable mechanism may be via the role of oestrogens and progesterones in facilitating acquisition of HPV or in causing reduced clearance (Vaccarella et al 2006, 2008,). Using Intra Uterine Devices (IUD) has not been associated with development of CC and OR for HPV infection in Nigeria users was 1.3 (Thomas et al 2004). However women using IUDs and other contraceptives may be diagnosed more because of more frequent contact with health facilities. They may also report more frequent sexual activity or may be more educated, thus more aware of symptoms of CC. In spite of these, contraceptive prevalence in Nigeria ranges from 8-13% (Oyedokun 2007, NDHS 2003) and fear of cancer is a common reason for non-utilization of contraceptives.

Smoking: An association between smoking HPV infection, CIN-3 and CC has been reported (McIntyre-Seltman et al 2005). Current smokers have a higher risk of being HPV positive and this risk increases with number of cigarettes smoked per day and the duration of smoking, OR for CC among smokers was 2.6 (Vaccarella et al 2008). Although the exact mechanism is unknown this effect may be due to impairment of immune response in smokers, leading to delayed clearing of virus and persistence of HPV infection (Vacarella et al 2008). Nicotine induced carcinogens have been found in cervical mucus of smokers (Shepherd at al 1999). Also smokers may have a higher number of sex partners and may not participate in CC screening programs (McIntyre-Seltman 2005). Nigerians have a relatively low incidence of smoking and tobacco use of about 20% (Obot 1990), varying in different study populations. The prevalence of smoking in Nigerian women ranges from 1.8% (Thomas et al 2004, Vaccarella et al 2008) to 10% (Chollat-Traquet 1992). The OR of being HPV- positive in Nigerian woman smoker was 1.6 (Thomas et al 2004). This risk is modifiable and cessation of smoking reduces the risk of CC (Shepherd at al 1999).

Alcohol: Alcoholic women have a higher risk for SIL and some cancers including CC. However this has not been significantly demonstrated in Nigerian women (Rafindadi et al 1999, Thomas et al 2004). Standardized incidence rate for CC of 2.9 was found in Sweden (Weiderpass et al 2001). The probable mechanism may be due to higher risk of HPV infection and progression. Also alcoholics may have associated confounding lifestyle factors like smoking, higher number of partners or dietary deficiencies. They may also not utilize cervical cancer screening facilities (Weiderpass et al 2001).

4.3 Environmental determinants

Cervical cancer is affected by social, economic, culture and physical environment. It is commoner in SSA, Latin America and Asia than Europe and America. This may be due to socio-economic factors and the availability of screening programs rather than the physical climate. The HIC had similarly higher prevalence figures about a century ago prior to onset of cervical cancer screening programs (ACCP 2004). Notwithstanding, there is a difference in HPV distribution across the continents, the variants of HPV 16 found in SSA and Asia are considered more virulent leading to a more aggressive disease over a shorter incubation period (Schnatz et al, 2008, Drain et al 2002). Also living in rural areas for most of one's life was surprisingly associated with OR of 4.9 in Algiers (Hammouda et al 2005) probably due to poverty, malnutrition or hygiene.

Hygiene: Environmental and personal hygiene have been associated with CC in LICs countries. This may be confounded by poverty and low socio-economic status. In Mali, poor living conditions and re-using sanitary towels ('menstrual clothes') carried a higher risk of CC (Bayo 2002). Poor water supply and lack of soap may contribute to spread trough transmission of HPV from dirty skin or fomites (CDC 2007). The relationship between vaginal douching for personal hygiene and CC is controversial; it was protective in North Africa (Bayo et al 2002, Hammouda et al 2005, Chaouki et al 1998) but had no effect in Jos, Nigeria (Sagay 2007). Childbirth in unhygienic condition and commencing coitus less than 40 days post-delivery may be associated with CC (Juneja et al 2003).

Nutrition: It has been suggested that deficiencies of some micronutrients may increase risk of CC, probably through their influence on immune system (Sitas et al 2006, Gulliano & Gapstur 1998). Many population-based studies have suggested that eating a diet rich in folate (vitamin B9), vitamin A, beta-carotene, selenium, vitamin E and vitamin C from fruits and vegetables may protect against CC and low levels in red blood cells and tissues may be associated with CC (Rock et al 2000, Gulliano & Gapstur 1998, Juneja et al 2003). The evidence is however inconclusive and may be related to smoking or contraceptive use. There is need to explore this link in Nigeria.

Drugs and toxins

Diethylstilbestrol (DES): Exposure to this (Oestrogenic) drug given to some women to prevent miscarriage between 1940 and 1971 is associated with development of a clear-cell adenocarcinoma a variant of CC. This occurred in 1 out of every 1,000 women whose mothers took DES during pregnancy. They are at risk of CIN and SCC if they get HPV infected (ACS 2008).

Socio-cultural environment: The social-cultural environment influences lifestyle and sexual behaviour globally and in Nigeria. There is some variation in the prevalence of CC probably due to the prevailing customs in the different regions. Generally, CC has been the commonest cancer of women in Nigeria (Emembolu & Ekwempu 1988, Rafindadi et al 1999, Galadanci et al 2003, Adewuyi et al 2008, Mohammed 2006). However in the southern part, it is often second to breast cancer (Thomas et al 2004, Parkin 2003). The age of sexual debut is low in Nigeria and depends on the culture. The literacy level is higher in southern Nigeria where girls also tend to copy western lifestyle including sexual practices. In the North, there is a predominant Islamic culture which is arguably associated with lower status of women, low female literacy rate and early marriage in North (Advameg 2007, Wall 1998). The girls are married off before or just after menarche around 12-13years (Kabir et al 2004), and usually to older men. Therefore the women have a longer sexual lifespan and are at risk of contacting HPV and other STIs from the older more experienced partners in the marriage (NDHS 2003).

Polygamy automatically equates with multiple sex partners which is a significant determinant of CC (Bayo et al 2002, Hammouda et al 2005). In Nigeria, polygamy is common especially among muslims (NDHS 2003). The incidence of extramarital affairs may also be as high as 11% (Mitsunaga et al 2005). Only 15.6% of women in Ibadan believed their husbands had never had extramarital affairs (Thomas et al 2004). This increases risk of STIs and CC, as some of these affairs are with female sex workers (Hammouda et al 2005, Bayo et al 2002). The culture encourages unlimited sexual freedom for men, while expecting women to be faithful to a partner at a time (Mitsunaga et al 2005). Increase frequency of divorce and re-marriage which is also common in Nigeria may facilitate CC (Wall 1998). Specific customs like widow inheritance; when a widow is married off to her late husband's relation also facilitates CC (Odili 2002, Ezekwem 2002). The practice of 'spouse sharing'-when a wife is allowed to sleep with close visitors of her husband, though rapidly disappearing (Osagbemi & Adepetu 2005) increases risk of STIs.

Socio-economic determinants: There has been a consistent association between low socio-economic status (SES); poverty, low literacy and CC. Cervical Cancer is a disease of the poor, uneducated, underserved woman (Juneja et al 2003, ACS 2008). This association was reported in many cancer studies probably since higher prevalence of HPV is associated with

poverty (Thomas et al 2004, Shepherd at al 1999). Countries with low HDI have higher prevalence of CC. This may be because of interaction of CC with illiteracy, poor genital hygiene, nutritional deficiencies and gender inequity. These countries lack national programs of cancer screening and have 2-6 times higher CC rates than HICs (Drain et al 2002). Nigerian women of low SES have higher risk of CC (Thomas et al 2004, Rafindadi 1999).

Figure 4.1

Global distribution of adult female population and cervical cancer by Human development Category (source Drain et al 2002)
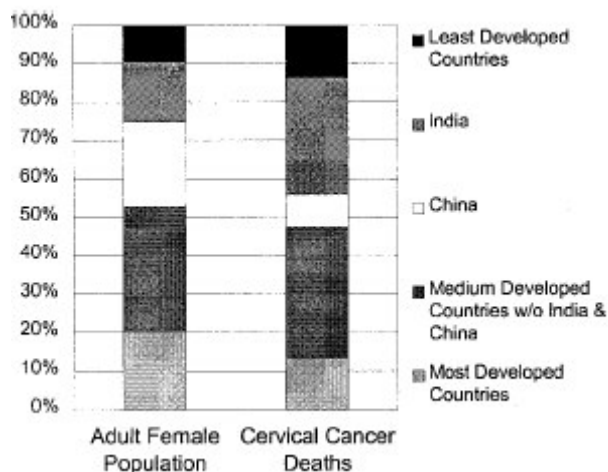
Illiteracy: Worldwide, illiteracy is closely associated with higher prevalence of HPV infection and CC (Drain et al 2002, Shepherd et al 1999). This is likely due to the association between illiteracy and low SES and poor access to health facilities. It may also be due to ignorance about CC (Anorlu et al 2000, Sitas et al 2006) and its prevention, or poor hygiene and nutritional deficiencies as confounders. In Algeria the OR of having HPV infection was 2.7 among illiterates compared to women who had more than secondary education (Hammouda et al 2005). Nigeria women have literacy rate of 60.6 % (NDHS 2003) and is lower in the North. In the Ibadan study 45.7% women were illiterates and OR for HPV was 1.7 compared with educated women (Thomas et al 2004). This is the trend nationwide for CC (Emembolu & Ekwempu 1988, Adewuyi et al 2008).

Ethnicity: Cervical cancer is believed to be commoner in some ethnic groups like Africans, Latinas and rare in Jews, Amish (ACS 2008, Juneja et al 2003). This may be a reflection of access to health, sexual behaviors and poverty.

Religion: Cervical cancer is rare in nuns and a lower incidence of CC is found in the predominantly Muslim countries of North Africa and Middle East compared with SSA (Chaouki et al 1998, Hammouda et al 2005). This may be associated with a more conservative sexual behavior or the practice of circumcision (Drain et al 2002).The effect of religion on cancer

in Nigeria is inconclusive (Ekanem 1987, Emembolu & Ekwempu 1988 1999).

Political environment: The political environment influences health policy and financing, thus in Nigeria other pressing issues of governance, corruption, economy, has prevented health attaining priority status. In the health sector, the global priorities of HIV/AIDS, Tuberculosis, Malaria, Maternal Mortality ultimately tops the National agenda. Hence there is currently no separate policy for cancer control, and there is yet no National screening program. However recently, cancer control is attracting some attention (Lambo n.d).

4.4 Health system determinants

Cervical cancer is commoner in countries with weak health system and low health spending and there seems to be a relationship between distribution of health workers and the incidence of CC globally (Drain et al 2002). Nigeria's health system like other African countries has problems of organization, stewardship, financing and provision of services. Since 10 years ago availability, accessibility, utilization and quality of service has been poor (WHO 2008a). There are fewer health workers than required and these stay mostly in urban areas. Health financing is poor; the government spends only$5- $8 per capita, per year on health compared to $34 recommended by WHO for LIC (WHO 2008a). Health insurance is new and 90% of private funding is 'out-of-pocket' payment. (See annex 4). There was no definite budget line for cancer which explains the lack of CC control program. Consequently, the level of awareness of CC is low, the health seeking behaviour is poor and the health facilities are often inaccessible, hence women come to hospitals with advanced stages of cancer (Gharoro et al 1999, Briggs & Katchy 1990).

Meanwhile, improving access to RH services and presence of STI control led to a low and declining rate for CC of 5.2/100,000 in China compared to 30.7 per 100.000 in India (ACCP 2004c). The presence of a National cervical cancer screening program accounts for the low and declining incidence of CC in developed countries. USA had a 75% decline in cervical cancer within 40years of starting CC screening and reports annual reduction of about 3% (Katz & Wright 2006, Cox 2006). Netherlands reported 5.1% annual reduction in incidence among 60-74year olds (Bulk et al 2005). No country has reported a decrease in CC rate without an organized screening program. The presence of a National cancer control policy and a population-based cancer prevention program determine the rate of CC, both are currently lacking in Nigeria.

4.5 Gender

CC is a disease of women and reflects the gender inequality especially in LICs like Nigeria. It is influenced by low status of women, female subjugation which are very prevalent in patriarchal societies like Nigeria. Illiteracy is higher in women as a higher premium is placed on boys'

education. Also girls are likely to get married to older men who may have had other partners (NDHS 2003). Nigeria women are expected to have many children and prove their reproductive capacity (Oyedokun 2007). Women in some parts of Nigeria are easily divorced and remarried and are exposed to greater risk of CC.

Table 4.1   Summary of results from the Ibadan study

Odds ratios (OR) for HPV positivity and corresponding 95% confidence intervals (Cls) according to sociodemographic and reproductive characteristics 932 women in Ibadan, Nigeria.

		HPV positive			
		N	(%)	OR[b]	95% CI
Number of women					
Age (years)					
<25	120	37	(30.8)	1	
25-34	189	48	(25.4)	0.8	(0.5-1.3)
35-44	134	36	(26.9)	0.8	(0.5-1.4)
45-54	196	51	(26.0)	0.8	(0.5-1.3)
55-64	172	42	(24.4)	0.7	(0.4-1.2)
≥65	121	31	(25.6)	0.8	(0.4-1.4)
X^2 for trend				0.74	ρ = 0.39
Education					
Primary or better	495	121	(24.4)	1	
Illiterate	417	117	(28.1)	1.7	(1.1-2.5)
Chewing habit					
No	600	147	(24.5)	1	
Yes	331	98	(29.6)	1.4	1.0-1.9
Marital status	687	178	(25.9)	1	
Married	62	25	(40.3)	2.1	(1.1-3.9)
Single	183	42	(23.0)	0.8	(0.5-1.3)
Divorced/widowed					
Number of pregnancies					
0	57	22	(38.6)	1.7	(0.8-3.4)
1-2	134	39	(29.1)	1	
3-4	164	45	(27.4)	0.8	(0.5-1.4)
5-6	230	49	(21.3)	0.6	(0.3-1.0)
≥7	326	87	(26.7)	0.7	.(04-1.3)
X^2 for trend				1.96	ρ = 0.16
Age at first pregnancy (years)					
≥25	253	69	(27.3)	1	
20-24	479	115	(24.0)	0.8	(0.6-1.2)
≤19	132	38	(28.8)	1.0	(0.6-1.7)
X^2 for trend				0.02	ρ=0.90

HPV= Human papillomavirus [a]Some figures do not add up to the total because a few are missing [b]Adjusted for age. Source Thomas et al 2004

CHAPTER 5: PREVENTION STRATEGIES FOR CERVICAL CANCER

Generally 43% of all cancers are preventable (WHO 2002b) usually by primary, secondary or tertiary means. Primary measures include increasing physical fitness, control of obesity/over weight, tobacco and alcohol as well as promotion of healthy diet rich in vegetables and fruits. CC is now considered a sexually transmitted disease and thus preventable (Reproline 1998, Grimes 1995). HPV is the primary aetiological factor which interacts with other risk factors like high risk sexual behaviour, (multiple sex partners, early sexual debut), smoking, poverty and others. Prevention of HPV infection will prevent CC. Primary prevention aims at preventing incidence or onset of disease (Sloan & Gelband 2007, WHO 2002b). It targets the entire population at risk usually in the absence of signs and symptoms. Primary prevention of CC involves risk reduction; preventive vaccination, and probably diet modification or supplementation (Rock et al 2000).

Secondary prevention should reduce the prevalence of disease by early detection in asymptomatic people. It aims at the pre-clinical phase of the disease (ACS 2008). Measures for secondary prevention of cervical cancer include screening using Papanicoloau's smear, HPV-DNA testing, visual inspection with acetic acid (VIA), Visual inspection with Lugol's Iodine (VILI), cervicography and speculoscopy. Tertiary prevention is targeted at people with proven disease. The aim is early and appropriate treatment to prevent recurrence or complications. It includes palliative care for incurable disease (WHO 2002c, ACCP 20004a). The most effective prevention approach when resources are available is combination of HPV vaccination of pre-adolescents, sex education and screening of women above 30 years of age (Agosti & Goldie 2007,Outlook 2007).

5.1 Primary prevention
This involves health promotion, risk reduction and control of STIs. Health promotion messages will include cessation of smoking, promoting a healthy diet rich in vitamins. The other determinants like illiteracy, socio-cultural, gender, poverty; hygiene, political and health system are currently not addressed for CC control but as part of broader National issues beyond health. Promoting a diet rich in carotenoids (Vitamin A), Ascorbic acid (C) and Folates (Vitamin B) may reduce CC incidence. Many on-going trials suggest that carotenoids reduce risk and progression of CC (Rocket al 2000). This is probably due to the direct effect on regulation of cell growth or via improvement in immune system. Vitamin C, due to its antioxidant properties, inhibits oncogenesis, stimulate immune system and enhance stability and utilization of folates. However recent RCTs have not proven that folate-rich diet protect against CC (Gulliano 1998). Also, ongoing trials show Vitamin E (an antioxidant) to be protective through enhancing Cell mediated immunity.

5.1.1 Sexual risk reduction

Risk reduction is done through promotion of healthy sexual lifestyle, reducing or eliminating risky sexual behavior that increases exposure to HPV (Rock 2000, Shepherd at al 1999). This is often part of the measures for STI and HIV control in many countries including Nigeria (Shepherd at al 1999, FGN 2003, NACA 2004) and may reduce CC incidence by 50% (Grimes 1995). It is to reduce risk of getting HPV and other STIs by delaying onset of sexual activity, reducing number of partners, promoting safe-sex and reducing parity (DCPP 2007, Shepherd et al 1999, WHO 2002a). Legislation to increase age of consent for sex and marriage suggested by Juneja (2003) though useful will be difficult to implement in Nigeria. These should focus on pre-adolescents before sexual debut since lifelong sexuality patterns get established during adolescence (Shepherd at al 1999). Those already sexually active should be advised on partner reduction and condom use.

These messages are delivered either using the strategy of school based sex education (Kirby 2005) or community based programs (Rock et al 2002) often using peer educators. This was effective as part of general STI and HIV control program (Shepherd at al 1999). Adolescents were taught communication and negotiation skills which are useful in negotiating condom use and avoiding STIs (Shepherd at al 1999, Kirby 2005). Condoms give partial protection against HPV (CDC 2007) but protects against other STIs like chancroid, gonorrhea, which may be co-factors for CC (CDC 2004). Health promotion should also include messages to discourage initiation of smoking and to encourage cessation (Shepherd at al 1999, WHO 2002b). This is especially important as smoking often starts in adolescence. The message should promote personal hygiene, encourage female education and possibly delay use of oral contraceptive pills (through delaying sexual debut), as these are other co-factors for development of CC.

5.1.2 HPV vaccination

The casual link between HPV and CC has been proven (Walboomers et al 1999, Bosch 1995) and HPV vaccines are the most promising approach to CC control in developed countries. The developed vaccines: the quadrivalent Gardasil[R] by Merck and the bivalent vaccine Cervarix[R] (Glaxo-SmithKline) have undergone clinical trials and are approved for vaccination since 2006 by about 45 countries. The target age ranges from 9-26years or 9-15 years old girls in some countries (Okonofua 2007). They were approved in USA for pre-adolescent girls from June 8th 2006 (WHO 2006b). Similarly the Netherlands will commence vaccination of 12 year-old girls from September 2009 (EUVAC.NET 2008). These vaccines will reduce the burden of HPV-associated diseases (Cutts et al 2007, WHO 2006b) but the impact can only be evaluated after some years. The HPV vaccines are made from virus-like particles (VLP) which are products of recombinant technology. The Gardasil[R] vaccine was developed against the HR-HPV types

16, 18 and LR types 6 and 11 which cause genital warts. The bivalent vaccine is against HPV 16 and 18. They are licensed for prevention of HPV infection and not currently for treatment (WHO 2006b, Brooke & Sherris 2006). See annex 5 for schedule.

Challenges of HPV Vaccination: The major challenge facing HPV vaccination is the high cost. The full course costs between $300 and $500 and is inaccessible to the people who need it most (Agosti & Goldie 2007, Katz 2006, Cutts et al 2007, Okonofua 2007). Also, it has generated some controversy as some believe it will encourage promiscuity. It has also raised ethical issues as to the role of parents in giving consent (WHO 2006a, 2006b, Charo 2007). Since the vaccination age neither fit into the childhood immunization schedule nor school entry immunizations, achieving high coverage is a challenge (WHO 2006b, WHO 2005b). Furthermore, some fear that HPV vaccination will lead to reduced utilization of cervical cytology screening (Katz 2006). However, cytology will still be necessary for older women already infected with HPV. Also the vaccines are to prevent CC attributable to the specific HPV types they were licensed for, although cross-protection against other types like 31 and 41 may be possible (Outlook 2007, Cutts et al 2007). Few may still develop CC from other HR-HPV (ACCP 2004).

5.2 Secondary prevention of cervical cancer

It is amenable to screening because the cervix is accessible for examination. Moreover HPV induced pre-malignant changes precede invasive CC by about 10 to 15 years (ACCP 2004, Bosch et al 2002, ACCP 2004) thus giving an incubation period during which simple interventions can be used for treatment and prevention of progression to invasive CC (WHO 2006c) thus fulfilling the classic Wilson & Jungner (1968) criteria for screening (Andermann 2008).

The preferred screening method is the Papanicolaou's Smear (Pap smear) introduced by George Papanicolaou in 1943. It is the oldest, widely used tool of CC prevention and was responsible for the 50-70% reduction in CC incidence and mortality in developed countries (Cox 2006). Other methods of secondary prevention include visual inspection with acetic acid (VIA) , visual inspection with Lugol's Iodine (VILI), speculoscopy, cervicography, Laser induced fluorescence, polar probe and photodynamic therapy; see annex 6 (Rock et al 2000). However, most cervical screening tests involve pelvic examination which is culturally unacceptable to many women especially in LICs (Denny 2005a).

Box 1. Wilson and Jungner's screening criteria.

1. Condition sought should be an important health problem*: CC is common and is treatable*.
2. *There should be accepted treatment for patients with recognized disease:* There are standard treatment protocols for CC
3. Facilities for diagnosis and treatment should be available: *CC can be diagnosed and treated in many centres globally.*
4. There should be recognizable latent or early symptomatic stage: *CC has latent precancer phase of 10-15years.*
5. There should be a suitable test or examination: *Cytology, VIA tests have sensitivity, specificity for detecting precancer*
6. Test should be acceptable to population: *The test is acceptable mostly in the HICs. In LIC acceptability is fair because pelvic examination may be unacceptable*
7. Adequate understanding of natural history of condition including development from latent to declared disease: *the cause of CC and progression is known*.
8. There should be agreed policy on whom to treat as patients: *Policy and reporting guidelines exist on abnormal cytology; and there is FIGO staging*
9. Cost of case finding (and diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole: *CC screening is more cost-effective than treatment*
10. Case finding should be continuing process not a "once and for all" project: *Organized CC screening programs are continuous.*

5.2.1 Cervical cancer screening using cytology

It is based on early detection of pre-malignant HPV-induced abnormalities in the cells exfoliated from the cervix. Invariably countries reporting reduction in cervical cancer incidence and mortality have instituted a cervical cancer screening program based on the Pap smear (ACCP 2004, WHO 2002c). Nordic countries like Norway, Finland have reported significant reduction in cervical cancer. United Kingdom with a recently introduced 'organized screening program' in 1988, and the USA with 'opportunistic screening program' are reporting reduction in CC (WHO 2006d). Screening programs and target populations vary in different countries; there may be an organized population-based program where target women are called for periodic tests as in Netherlands (Holland et al 2006) or opportunistic where women are screened whenever they are in contact with health services or when there is an indication (Cox 2006). ACOG (2003) recommends annual smears for all sexually active women (or all women older than 18years), after three or more negative smears, Pap smears are performed less frequently at the discretion of the physician. This is difficult to implement in LICs hence a different recommendation for low resource countries (ACOG 2004).

Generally, cytology is simple, highly specific and affordable in many MICs and HICs. It requires expertise, a good laboratory and repeat smears may be necessary (ACCP 2004a, WHO 2002c). In LICs it is often unaffordable; requires quality control and the expertise for subsequent colposcopic

examination may be absent (Cronje 2004, 2005). It has not been cost-effective in these settings (Goldie 2001, Cronje 2003) and a similar reduction in CC incidence and mortality was not seen in LICs except Chile (WHO 2002c). Although it has a specificity of 95-99%, the sensitivity may be less than 50% (Sankaranarayanan, Denny et al 2005). Finally, its effectiveness is lower in older women since the SCJ migrates into the endocervical canal (Creasman 2007, WHO 2002c). Although impact of cytology on CC has not been evaluated by randomized controlled trials (RCT), cohort and case control studies showed marked reduction in mortality and incidence of cervical cancer following introduction of Pap smear (Denny et al 2005). It is thus, recommended for large scale CC screening programs where resources are available (WHO 2006c). *Annex 6 for technique for pap smear and follow-up management.*

5.2.2 Visual screening test

VIA: Visual Inspection with Acetic acid (also called Direct Visual Inspection) involves the inspection of the cervix in a bright light following application of 3–5% acetic acid with a swab to the cervix. The abnormal cervical epithelium appears white with sharply demarcated edges after one-minute (Sankaranarayanan 2005, Cronje 2005, WHO 2006c). The abnormal area is biopsied immediately or after colposcopy. The test gives immediate result and the patient may have further investigations for diagnosis (ACCP 2004) or simple out-patient treatment with cryotherapy or LEEP at the same visit (Denny 2005, ACCP 2004a). VIA has sensitivity similar to or even greater than cytology ranging from 66 to 96% (WHO 2002c, ACCP 2004) but specificity is lower at 64-98%. It has positive predictive value of 92-97% in detecting HSIL (ACCP 2004, Tsu 2005, Belinson 2001).

The test is cheap, simple and easily taught to middle cadre health workers often within 2 weeks. The result is known immediately, thus making single visit strategy for screening and treatment possible (Denny 2005, Cronje 2005). It can be used as a second test after cytology or HPV testing to select cases unsuitable for cryotherapy (Outlook 2007). It was found to be cost-effective for screening programs in Kenya, South Africa, Zimbabwe, India (Goldie 2005, Mandelblatt 2002, Denny 2000a). However, the limitations of VIA include low specificity which may lead to over-treatment (ACCP 2004, Cronje 2005). It is also a subjective test and inter/intra-observer variation may occur. There is a learning curve with higher positive test rates reported by least experienced workers and quality assurance is difficult (WHO 2002c, ACCP 2004). It is however being promoted as an alternative to cytology in LICs like Nigeria where cytology is unavailable.

VIAM: Visual inspection with acetic acid and magnification has been evaluated. The magnification is up to 2 to 4 times. It had slightly higher sensitivity than VIA (Roblyer et al 2007) which was not statistically significant (Sankaranarayanan 2005, Denny 2005).

VILI: Visual inspection with iodine (VILI). It is similar to VIA and is based on the fact that abnormal epithelial cells lack glycogen and cannot take-up Lugol's iodine stain. The abnormal areas appear pale yellow (mustard-colour), while the normal tissue appears mahogany brown (ACCP 2004a manual). It has higher reproducibility and higher sensitivity than cytology (WHO 2006c), but similar specificity to VIA (Sankaranarayanan 2005, Tsu 2005). Sensitivity is 77.8–98.0% and specificity of 73 to 91.3%. Combining VILI with VIA improves specificity (Cronje 2004). The advantages and limitations are similar to those of VIA but it needs further evaluation.

HPV-DNA TESTING: This newer technology is based on the detection of high risk HPV DNA in cervical or vaginal smears (Outlook 2007, WHO-constitution 2002, and ACCP 2004). The sample is collected by a health worker or the woman (Wright et al 2000) using swab or a small brush. It is inserted into a special container having preservative and transported to the laboratory (WHO 2006c). The specimen is evaluated using hybrid capture or polymerase chain reaction (PCR) technologies which are molecular based tests (Sankaranarayanan 2005). It can serve as adjunct test to cytology to improve sensitivity (WHO 2006c, Cronje 2005) and is very useful in triage of 'Abnormal Squamous Cells of Undetermined significance (ASCUS)'. It may prevent unnecessary colposcopy or frequent repeat smears (ACCP 2004C, Cox 2006) thus saving cost (Goldie & Kim 2004, Mandelblatt 2002). It has been evaluated as a viable primary screening test and an alternative to cytology in Low Resource (LR) setting (Kuhn et al 2000, WHO 2002c). As a primary screening test, the sensitivity for precancer and CC ranges from 50-95%. Most studies report 85% or more which surpasses cytology (WHO 2006c, Kuhn et al 2000, Cronje 2005). The specificity also ranges from 50%-95% (mean 80%). The negative predictive value of 99.5% and PPV of 12.8% (Sankaranarayanan 2005).The sensitivity is however lower with self-collected vaginal samples (Kuhn 2000 et al), in women younger than 30 years and in populations with high HIV prevalence (WHO 2000c).

It is an objective test which identifies women with HR-HPV and those at risk of developing CC and precancer within the next 2 to 3 years (WHO 2002c). Combining it with cytology improves the predictive value. When both are negative, the risk of CIN 3 developing within 45 months of follow up is 0.24% and 0.8% after 10 years. A single positive test predicts a 4.4% risk of CIN 2/3 within 45 months and 7% risk by 10 years. Screening interval may be increased to 3 years after a negative HPV test (Cox 2006). Since the required expertise is not as high as for cytology and it can be automated (Computerized processing), it is suitable for large population based screening (WHO 2002c, ACCP 2004c) and has in-built quality control. It may be useful in countries with few personnel to take samples or where women dislike pelvic examination (Wright et al 2000, Lewis 2004). However it is expensive and the technology may be scarce (WHO 2002c). It also requires about 6-8 hours processing time so it may be necessary to

return for results (Cronje 2005). Currently there is an attempt to develop the fast HPV test which will make results available in about two hours and thus applicable to LR settings (Outlook 2007).

Table 5.1 Accuracy of screening tests in LICs

Test	Sensitivity	Specificity
Cytology	31-78%	91-99%
HPV testing	61-90%	62-94%
VIA	50-96%	44-97%
VILI	44-93%	75-85%

Source: *Sankaranarayanan R (2006) ACCP Evidence base: Implications for policy and practice*

5.2.3 Subsequent management of screened women

Screening should not be done unless there is facility to manage the positive cases (Andermann et al 2008) and CC can only be controlled by linking screening with adequate treatment and follow-up (WHO 2006c, ACCP 2004b). Definitive diagnosis may be done after screening test using the gold standard of colposcopy and biopsy during the same visit or at another visit. This is the traditional approach (ACCP 2004). After visual tests, confirmation may be done by cytology, colposcopy or others. The intermediate approach involves treatment after a positive screening test and retrospective confirmation after treatment by biopsy result (ACCP 2004, ACCP manual (3). The 'screen and treat' approach is treatment based on the result of the screening done (WHO 2006c, ACCP 2004a, Blumenthal 2007, Denny 2005). Treatment and diagnosis may require referral to higher levels of care following counseling on importance of compliance (ACCP 2004c, WHO2006c).

5.2.4 Treatment modalities for precancer

These range from the use of in-patient modalities like cold knife cone biopsy and simple hysterectomy (usually under anaesthesia) to simple out-patient procedures which are either ablative (destroying all abnormal tissue); cryotherapy, laser vaporization, or excisional like LEEP which leaves tissue for histology (ACCP 2004, WHO 2006c).

Cryotherapy: This involves destruction of the abnormal tissue by freezing using either nitrous oxide or carbon dioxide (WHO2006c, ACCP 2004) from a cryoprobe which produces an ice-ball. The double freeze technique is preferred. The cryoprobe is applied twice to the cervix for about 3 minutes during an interval of 5 minutes for thawing (WHO 2006c). It is done without anesthesia, electricity and by non-physicians on out-patients

(ACCP 2004a). However when the lesion is large, extending to vagina or the endocervical canal, effectiveness is less (ACCP 2004d, WHO 2006c). Side effects include profuse watery discharge up to four weeks during which patient abstain from sex. Mild Pain, bleeding and cramping may occur and a temporary increase in virus shedding in HIV positive women (ACCP 2004a). It is the most practical treatment approach for LIC since it is simple cheap and can be done as part of "see and treat" (Single visit) approach (Denny 2005, Tsu 2005, Sankaranarayanan 2005). The cure rate for small lesions is 86 to 95% (WHO 2006c).

Loop electrosurgical excision procedure (LEEP): This is also called "Large Loop Excision of the transformation zone" (LLETZ). A thin electric wire loop driven by low-voltage electricity is used to excise the lesion and the transformation zone, while coagulating blood vessels (WHO 2006c). Thus tissue is available for histology. The procedure is done under colposcopic guidance and usually requires local anaesthesia. Cure rate is often more than 90% (91-98%) but severe bleeding may occur in 1-4% of patients (Sankaranarayanan 2002). Also it is not used when lesions extend more than 1cm into the endocervical canal (ACCP 2004a). It requires expertise, so it is done by physicians in secondary or tertiary health facilities.

Cold knife conization: Cold knife conization is done as an in-patient procedure using regional or general anesthesia. It is done when outpatient techniques are not feasible or available. Also when there is suspicion of micro-invasion or involvement of endocervical canal (WHO 2006c). A surgical blade is used to excise a cone of cervical tissue with the base containing the lesion and transformation zone and the apex in the endocervical canal. The tissue is available for histology and cure rate can be as high as 90-94% (WHO-40 2006). However, it requires highly skilled personnel; hospitalization and complications include bleeding infection, decreased future fertility as well as complications of anesthesia (WHO-40 2006). It is often feasible only in secondary or tertiary health facilities.

5.2.5 Follow up of precancer
Women treated for precancer require follow-up visits at 6weeks, 6months and 12months. This is to exclude complications and recurrence. Those with LSIL can return to screening program if no abnormality is seen. However, those with HSIL require closer surveillance which often includes annual screening for 5years (WHO 2006c). Recurrence may require further treatment and is commoner in HIV positive women (ACCP 2004a, Nappi et al 2005).

5.3 Tertiary prevention: current approach to CC management
This includes treatment and palliative care given to diagnosed cancer cases with the aim of avoiding complications and improving quality of life (DCPP

2007). About 80% of CC arise from existing SIL (Waggoner 2003) and during screening some prevalent CC cases are identified (Cox 2006). Cervical cancer is potentially curable if detected early and adequately treated (WHO 2002b). This requires specialized cancer treatment centres or tertiary hospitals and standard National guidelines or protocols (WHO 2006c). Annex 10 shows a conceptual framework 'Quality in the Continuum of Cancer Care (QCCC)' that summarize different aspects of cancer prevention and care.

5.3.1 Treatment options

The treatment options depend on the stage of CC and the woman's choice. It usually involves people from various disciplines. During each stage of the management, counseling is done and informed consent taken. Currently these options include surgery, radiotherapy and chemotherapy singly or as a combination. The outcome of treatment and the quality of patient's life depends on the stage of CC, quality of treatment and compliance with follow-up (ACCP 2002(2), ACCP-2002). Surgery is done for early stages especially in younger women while radiotherapy is used in all stages. Chemotherapy has limited role in treating recurrent or very bulky CC. See details annex…..

Palliative management: This is essential for the women presenting with advanced, incurable CC. It is also recommended in areas with no facilities for CC treatment, a common finding in many LICs (WHO 2002b, ACCP 2002c). It is the 'active total care given to a person with terminal illness who is near the end of his/her life'. It involves support of those with advanced, incurable disease (ACCP 2002, WHO 2002b, Sloan 2007). The goal is to avoid unnecessary suffering and improve quality of life of women with advanced CC and their families (WHO 2006c). Preferably palliative care should be community-based either in the patient's home or in hospices. This allows the patient to spend time with family and relieves burden on the health system. Occasionally, it may be necessary to manage complications in the hospital (ACCP 2002, WHO 2006c). The components include:
-Medical care of symptoms and complications of disease like bleeding, infection, vaginal discharge (ACCP-2002)
-Psychosocial support which includes counseling emotional support and management of depression
-Spiritual support (Ohaeri 1999a,1999b)
-Pain relief: This should involve liberal use of strong analgesics using the "step ladder approach" It should be timed and not on demand (WHO 2006c)
-End of life care.

5.4 Cervical cancer prevention in low resource (LR) settings

In low resource countries including LIC and MIC, the screening model of the high income countries may be unrealistic. This is mostly due to

insufficient finance to organize a cytology-based CC prevention program. Also in many LR countries there are insufficient human resources like cytopathologists, colposcopists and other specialists. The available laboratories may lack the capacity to handle the number of slides (WHO 2006c). Furthermore women in LR countries are less likely to comply with follow-up appointments which may be necessary in a cytology-based program (Sankaranarayanan 2001, Santos et al 1996). Some MICs and LICs like Nigeria already have some form of screening though neither organized nor efficient. These are mostly opportunistic screening offered to younger women utilizing maternal and child health facilities (PATH 2000) often excluding older and poorer women. Thus in Latin American countries like Mexico, Colombia, with screening programs dating from 1970s, a reduction of cancer incidence and mortality has not been achieved except in Chile where the existing program was reorganized in the 1990s.(PATH 2000). A prior attempt in South Africa-the 'Soweto program' also failed due to poor participation of target population (PRB 2004). In SSA only few countries have opportunistic screening. Currently there are few on-going cross-sectional/randomized screening intervention studies in Burkina Faso, Congo, Ghana, Guinea, Kenya, Mali, Niger and even Nigeria (Sankaranarayanan 2001, ACCP 2004c).

5.5 Effective programmes in low resource countries

Planning effective cancer screening programs in LR countries requires an initial situation analysis to identify the magnitude of cancer problem, the available resources and strategies for cancer control. There is the need to advocate, develop or influence policy makers and ultimately train the needed manpower (PRB 2004, ACCP 2004, PATH 2000). The issues to be addressed include:

Target group: unlike in HICs, where all sexually active women constitute target population and screening commences soon after sexual debut (ACOG 2003, Cronje 2005), LICs lack resource. Since the natural history of CC show that the peak age for SIL is around 35years with a range of 30-50years (PRB 2004, ACS 2008) these women should constitute the target population in LR countries (PATH 2000, ACCP 2004).

Screening test: LR countries without existing cytology programs are advised to use cost-effective screening tests alternative to cytology (Sankaranarayanan et al 2001, WHO 2006). Cost-effectiveness studies based on modeling (Goldie et al 2001,2005, Mandelblatt 2002) found that compared with 'no screening', single life-time screen at 35years of age; HPV-testing followed by treatment at second visit cost 39 USD per YLS and led to 27% reduction in cancer incidence. Meanwhile, VIA with immediate treatment of positive women at same visit was next effective. It saved cost and reduced CC incidence by 26% and increased life expectancy by factor of 0.84. Cytology with treatment at second visit was least effective-causing 19% of $81/YLS. It was concluded that HPV-DNA was more effective than

visual test but less costly than cytology. Therefore, for richer countries with laboratory infrastructure (Denny et al 2000a, Kuhn et al 2000) HPV-DNA testing may be the test of choice. Since these are absent in many LR countries, single-visit approach using VIA followed by immediate cryotherapy is a safe, acceptable and cost-effective strategy (ACOG 2004, WHO 2006c, ACCP 2002).

Table 5.2 Comparing screening strategies with 'no screening' in South Africa

Type and Frequency of Screening	Reduction in CC incidence %	Cost per year of Life saved ($ US)
One visit VIA + Cryotherapy HPV test + Cryotherapy	26 32	Cost saving* 14
Two visits HPV test Pap smear	27 19	39 81
Three Visits Pap smear	17	147

* Costs were more than recouped by savings from not managing invasive CC
Source: Goldie et al 2001

The screening approach: An integrated approach is considered to be better than vertical programs (Bradley et al 2005, deKoning 2005, ACCP manual-2004). A cancer screening program can be integrated into the different levels of health facilities and can use existing staff, and facilities. It may however increase in staff workload.

The screening frequency: the traditional cytology program involves multiple visits for screening, collection of result, further diagnostic tests before treatment is given. It increased costs and compliance with follow-up was poor (Denny et al 2000b). However, even in HICS, the trend now is to increase screening interval from annual to 3 to 5 yearly for women with negative smears (ACOG 2003). In LR settings once-per-lifetime screening of 35-40 year-olds is recommended, if there is more resource 2-3 tests per lifetime can be done at 5yearly or 10yearly intervals (WHO 2006c, ACCP 2004). This can be changed to 3yearly interval and the target age increased to 20-65 years when resources increase. Annual screening is not feasible or necessary in LR settings (Sankaranarayanan 2001).

Screening coverage: An effective CC screening program should have coverage of 80% or more (PRB 2004). Poor coverage is a major cause of failure of programs. Most cases of cancer occur in previously unscreened women and increasing program coverage is considered more beneficial than increasing frequency of screening (ACCP 2004).

Treatment Approach: This vary from the 'traditional approach' that involves multiple visits, intermediate approach or the single visit 'see and treat' approach. The treatment location can also be 'static' in fixed clinic facilities or 'mobile or outreach' types to distant communities (ACCP 2004).

The traditional approach involves screening with cytology, VIA or HPV test followed by colposcopy and biopsy at the second visit. In the intermediate approach; screening is done at first visit and during second visit colposcopy and biopsy are done, however treatment is offered during the second visit even in absence of biopsy result. In the single-visit approach which was evaluated in South Africa (Denny et al 2005b) and Thailand (RTOG 2003), following screening usually with VIA or HPV-DNA, the woman is treated at same visit if suitable. This is the preferred option in LR settings. However there are criticisms that it represents a lower standard of care and may cause over-treatment (Suba 2005, 2006).

Follow-up management of cancer and precancer in LR is challenging. Preferably cancer care should be centralized in order to build capacity of staff and save costs for the health system (Adebamowo 2007). Also a strong referral network with good information management is important so that screened women with disease are appropriately managed and followed up. Those without disease should be monitored and recalled in future and should not be lost from the program (ACCP 2004, WHO 2006c). The Global Satellite Mobile (GSM) phones can be used for this in countries where they are present.

WHO (2002b) and IARC (Sankaranarayanan 2001) suggested that since many LIC and SSA countries lacked both human and financial resource to organize and sustain a screening program whether opportunistic or organized they should emphasize primary prevention of cancers in general (WHO 2002c), and focus on early diagnosis and treatment of cancer including palliative care. Moreover, they should concentrate on improving health service capacity to diagnose and treat cervical precancer and early invasive cancer before considering even limited screening program. VIA is recommended as a good tool for early clinical diagnosis where cytology is absent However, MIC with some form of screening program are advised to reorganized and concentrate on higher coverage, less frequent screening and to focus on high risk group of 30-50years or 35-49years.Those without any existing program are advised to start with pilot programmes in limited regions before scaling up.

In contrast for Nigeria, Adewole (2005) proposed an integrated model linking CC screening with existing HIV counseling and testing programs. He suggested screening all women 15-64years old (about 32milion) at least once in their lifetime using Pap smear read within 2 hours using 'cytovant' and VIA, HPV testing and spectroscopy as additional tests. Those with positive results could benefit from cryotherapy or LEEP. The LEEP specimen can be subjected to fast histology and the diagnosed CC cases treated accordingly. He believes that Nigeria has resources to treat about 8000 CC cases within a year. Nevertheless, the program should be phased starting with pilot project in a small locality. In my view this requires significant financial and political commitment.

5.6 Selected case studies

Some projects on CC screening done by ACCP in Ghana, South Africa, Kenya, Thailand and India and by the American-Vietnam association in Vietnam illustrate strategies used in LR settings. See box 2. The projects used different approaches and demonstrated that population based screening programs (ACCP 2004, PATH 2000) could be successful and that visual techniques were viable, cost effective alternatives to Pap Smear (Goldie 2001, Denny 2005, Mandelblatt 2002).

Box 2. Selected case studies

Ghana: CC screening was not common, people were unaware (Adanu 2002) and Pap smears were available in only few locations (PRB 2004). Two centres- Ridge Hospital and Amasaman Health centres in the Greater Accra Region were chosen. Project was done between 2001-2002 at Ridge Hospital and 2002-2003 in Amasaman Health Centre. Following Sensitization through a TV program, the attendance for screening increased from 5 per day to 300 a day. The Nurses used VIA, followed by cryotherapy. The 'single visit approach' was tested so women with positive results were treated on same day. About 13% had positive results in Ridge Hospital and 6% in the Health Centre and most were treated on same day. Counseling and male involvement were done and the project was acceptable (Corneli 2004, Blumenthal 2007).

South Africa: In 1970s health department recommended screening only for women with abnormal looking cervices and by 1980s screening was not considered a National priority. A recent policy of 3 free Pap smears to women over 30years every 10 years was unsuccessful due to poor uptake and variable services in the country (PRB 2004, Denny 2005). In 1990s, ACCP started a three-year project, running in 3 districts in Cape Town to develop, test and evaluate cervical screening in primary care settings. This led to improved staff knowledge, attitude and practice. Persistent problems included constant migration of women in search of work, and where services were available 60-80% of screen-positive women did not return for treatment (Denny 2005, Megevand 1996). Thus, a mobile clinic approach was used offering free Pap smear screening and on-site treatment during same visit. Health education improved compliance. The drop-out rate was 3% compared to 34% when women were referred to nearby clinic for treatment (PATH 2000).

Thailand: An initial program in Mae Sot District of Northern Tak province offering free Pap smear found that only 20% of women 18-65years in 1991either knew about pap smears or were screened. Strategy was changed in 1993-1996, to increase awareness by providing information through personal contact using Village Health Workers and Health Centre staff in 54 villages (PATH 2000). Women aged 25-60years were given free Pap smear by public health nurses supervised by a physician in mobile clinics. Evaluation in 1997 showed uptake rate increased from 20% to 70%. Another project using Visual techniques in Roi Et province found that mobile clinics reached 3 times more people than clinic-based service; 4 years after one-fourth of eligible women had been screened (Kleine & Gaffikin 2004).

Vietnam: The American-Vietnam project group following studies on the epidemiology of CC and the different patterns in incidence between North and South Vietnam based on history of husband's military service (Huynh 2004), were able to establish a cost effective population based CC screening program based on cytology (Suba 2005, 2006). They argue that Pap smear is feasible and sustainable in LICs and they were able to demonstrate 60-90 % reduction in CC within 3 years of introduction to a previously unscreened population (Suba 2005). Also that 'Screen and treat' may be second-rated service and failure of Pap smear in some LICs was due to socio-political issues and not the test itself (Suba 2006).

CHAPTER 6: CURRENT STATE OF CERVICAL CANCER CONTROL IN NIGERIA

The Control of CC is impossible without prevention of HPV infection, identification of precancer stages through screening and subsequent management of identified invasive diseases. There is currently no national policy on cancer control (FMOH 2004) and no organized program for cancer prevention in Nigeria. However control of reproductive cancers is mentioned in the National Policy on Reproductive Health and Strategic Framework (Lambo n.d) and HPV infection prevention may occur within the National program for STI and HIV control (FGN 2003,WHO 2006e).

6.1 Primary prevention in Nigeria

Primary prevention using health promotion to reduce risk factors for CC includes delaying sexual debut, education on reducing number of sex partners, mutual monogamy with uninfected partner and promoting condom use are not deliberate programs in Nigeria, rather they are within the program for HIV Control of National Action Committee on AIDS (NACA 2004) and the FMOH guidelines for prevention of STIs (2003). Moreover, HPV vaccination as primary prevention is not feasible for now.

6.1.1 HPV vaccination in Nigeria

It has been suggested that HPV vaccination will extend to LICs by around 2010 (ACCP 2004). It is considered the most promising strategy for cervical prevention in LICs currently lacking organized cervical cancer screening programs (Walraven 2003, ACCP 2004, Cutts et al 2007, Sloan 2007). However, before HPV vaccination become reality in Nigeria some issues should be addressed:
-Will the current vaccines offer sufficient protection against cervical since some other HPV variants like HPV 31 also contribute significantly?
-How will be vaccine be made affordable to the teeming Nigeria population, 70% of who live below poverty level.
-How do we ensure sufficient vaccination coverage in view of the currently poor national vaccination coverage levels?
-How do we ensure acceptability of the vaccine in some parts of Nigeria (especially Northern Nigeria) where vaccines are viewed with suspicions of either being dangerous to health or as having ante-fertility effects?
-How do we strengthen the health system to allow integration of HPV vaccination into the SRH, immunization and adolescent Reproductive Health programs?
-How soon can policy on CC prevention be formulated and how will HPV vaccination be integrated into it?
-How will the high HIV prevalence affect HPV vaccination program?

Currently vaccine coverage for 3rd dose of DTP (Diphteria, Tetanus, Pertusis) in 2005 was 25% and the percentage of districts with 80% or more coverage using this indicator of immunization system performance

was 3%. Measles vaccination coverage was 35% and 3rd dose of polio vaccine was 35% in 2005(WHO/ICO 2007). These low figures imply that before HPV vaccination is introduced there is need for strategies and measures of increasing uptake. Also financing mechanism for vaccine procurement and delivery is needed. Subsidies, and tiered pricing through GAVI and other international organizations may be necessary (WHO 2006b, Agosti 2007, Kane et al 2006).

6.2 Secondary prevention in Nigeria

Secondary prevention of CC is haphazardly done due to absence of national guideline; until recently when VIA began, Pap smear was mostly used. There is currently no national population/community based program (Amotsuka 2007, WHO/ICO 2007, Adewole 2005) rather opportunistic screening is done in tertiary hospitals by specialists, few General hospitals and hardly by private practitioners (Anorlu 2007a). Screening is often done in evaluating women presenting with symptoms of vaginal discharge, bleeding or cervical lesion; hence it is more for diagnosis than screening (Anorlu 2003, Kolawole 2001). However, unlike population screening, opportunistic screening is less cost-effective as only few young women utilizing health facilities are screened repeatedly (ACCP 2004).

Annex 9 show summaries of selected studies done on awareness and utilization of CC screening in Nigeria. They either focused on target population in the community or female health workers (FHW) who are uniquely positioned as providers/client to recommend the test or screen women. They are expected to know more about the test and possibly utilize it. Surprisingly the rate of CC screening among female health workers is as low as in the general population. Less than 10% of female doctors have undergone Pap smear (Babarinsa et al 1998).

Generally, more than 50% of respondents knew or had heard of CC except in Ibadan where awareness of cervical screening using Pap smear was 3.5% among low socio-economic status women (Ajayi 1998).Utilization of Pap smear ranged from 0.5% in Enugu (Chukwuali 2003) to 20.8% in Kano (Kabir 2005), however mostly less than 10%. Some barriers to uptake of Pap smear include ambivalent attitude of Nigerian doctors towards screening (Anorlu 2000), high cost, ignorance, fatalistic attitude of Nigerians to cancer (Babarinsa & Adewole 1998, Ezem 2007, Kolawole 2001) as well as lack of privacy (Ogunbode & Ayinde 2005). However in Enugu, price subsidy did not increase test uptake probably because of ignorance and lack of consciousness about preventive health (Chukwuali 2003). It has been suggested that making a pap-smear part of the pre-employment medical examination may improve utilization (Babarinsa 1998). Although most women had a positive attitude to the test and will recommend or use it in future, some female health workers still disapproved of the test (Audu 1999, Ezem 2007).

Box 3. Kaduna Study

A study carried out in ABUTH, Kaduna-State among 257 female health workers (Kolawole 2001). Showed that though 96.5% had heard of CC only 50% knew it was preventable by Pap smear. Among those surveyed, 66.7% had correct knowledge about the test and 65.2% knew the test was available in their hospital. Many did not believe they were at risk of CC; only 26% knew that Pap smear screening test should be done for sexually active women. About 45.1% had a definite positive attitude to the test, 3.9% were equivocal saying 'it was a necessary evil'18% had an outright negative attitude. Consequently, although 22.7% considered going for the test only 9.3% had ever done the test. In about a half of these (54.2%) the test was voluntary or self-referred, 25% had test as part of a compulsory medical check-up. In 20.8% it was because they had symptoms referable to the cervix. Majority (80.5% will recommend the test, 16.3% were unsure and 3.1% will definitely not! The reasons for not recommending or promoting the test were:

1. Lack of (sufficient) knowledge   -23.9%
2. 'Not in position to do so'   -8.3%
3. 'No opportunity to do so'   -7.3%
4. 'Not Interested'   -5.8%
5. Ignorance about those needing it   -7.4%
6. 'Test not available'   -4.9%
7. 'Test will cause anxiety and sadness'   -1.5%

This pattern of results from Kaduna state is a reflection of what many Nigerian female health workers feel about CC screening generally and the use of Pap smear.

6.2.1 Pilot projects for CC screening in Nigeria

There are few small-sized pilot projects in Nigeria; mostly in Lagos-State, Ibadan (Oyo-State), Abuja-federal capital territory and Enugu-State. They are mostly vertical projects organized by NGOs like Rotary (Olaniyan 2006) and 'Save our future foundation' (Amotsuka 2007) and Medical Women Association Nigeria (MWAN) in Enugu (Chukwuali 2003). These involve hospitals located in urban areas. Some collaborate with foreign universities and other international organizations like the UK-based University College London- Elizabeth Garrett Anderson Institute for Women's health collaboration in Lagos led by Dr Olaitan Adeola (Diagbare 2008). The operation 'Stop Cervical Cancer Nigeria (SCCAN)' coordinated by Prof. Adewole of UCH Ibadan, in collaboration with MD-Anderson Cancer Centre, British Colombia Cancer Agency, Rice University department of Bioengineering. (SCCAN 2008, Lambo n.d).

Most of these projects use Pap smear and are based in tertiary hospitals, but Abuja Rotary project, the Ibadan 'Save our future foundation' (Olaniyan 2006, Amotsuka 2007) and Lagos projects involved the communities. Recently VIA approach is being promoted and used including IARC-Sagamu project. The projects' details are in annex 8. However, most tertiary hospitals with pathology departments have capacity for cytology; specialists report on slides including the few taken by private practitioners and general hospitals. The direct cost of the test range between ₦1,500 and ₦5,000 (about $12.5-$43)(Roblyer 2007). However indirect cost of

transporting slides or patients is high thus restricting access to few educated, wealthy women usually residing in urban areas (Adewole 2005).

6.2.2 Challenges of managing precancer in Nigeria

Although worldwide the current trend is to use simple, minimally-invasive, out-patient procedures for treatment of precancer (SIL) in Nigeria these procedures are often unavailable (Omigbodun 2005, Adewole 1998). Colposcopy was introduced in the premier Teaching Hospital – University College Hospital, Ibadan in 1994 but is still absent in many teaching hospitals; where available there may be no trained personnel to do the procedure. ABUTH where I work is only recently building capacity for colposcopy following acquisition of colposcope in 2006 as part of the 'VAMED project' (Lambo n.d). In the absence of this facility many women are subjected to more extensive and expensive in-patient surgical procedures like cold-knife cone biopsy (Conization) and Hysterectomy (Adewole 1998). It is therefore not surprising that some women refuse screening tests since they believe they cannot be managed even when precancer is diagnosed. These women are often young and desirous of fertility and hysterectomy or cone biopsy are bad options for them.

Cryotherapy is used in Ibadan, Lagos and Sagamu (Adewole 1998, Anorlu 2000) it has not started in Zaria. However with the commencement of pilot projects especially on VIA, the situation may improve. LEEP is functional at National Hospital, Abuja (Olaniyan 2006) and may be present in UCH as part of project 'SSCAN'. Laser vaporization is currently unavailable. Therefore physicians often have no option than observation of LSIL with follow-up which is difficult in LICs (Santos et al 1996); or to manage HSIL with cone biopsy and 'simple total hysterectomy'. Occasionally diathermy fulguration is done especially when there's associated cervicitis. The main problems of managing CIN given by gynaecologists were as follows (Omigbodun 2005):

1. Lack of awareness (sufficient knowledge) -   88.1%
2. Lack of equipments especially colposcopes   66.4%
3. High cost of treatment   -   53%
4. Inadequate follow-up   -   49.3%

Lack of knowledge because many Nigeria gynecologists are not trained to use these equipments which are absent in many Teaching hospitals due to poor funding of cancer service in Nigeria (Briggs 1990). The tables 6.1 & 6.2 below show how Nigerian Gynecologists manage abnormal smears.

Table 6.1 Usual Procedures for Investigation of patients with different grades of Cervical Intraepithelial Neoplasia (CIN) by Nigerian Gynaecologists

Usual approach to investigation	CIN I	CIN II/III
	Number (%) of responding Gynaecologists	Number (%)of responding Gynaecologists
Colposcopy and biopsy	13 (9.7)	32 (23.9)
Cone biopsy	4 (3.0)	19 (14.2)
Follow-up smears	92 (68.7)	12 (9.0)
UVI and biopsy	13 (9.7)	31 (23.1)
VIA or VILI and biopsy	6 (4.5)	30 (22.4)
Referral	6 (4.5)	10 (7.5)
Total	134 (100.0)	134 (100.0)

Omigbodun AO and Ayinde 2005

Table 6.2 Usual approach for Treatment of different CIN grades by Nigerian Gynaecologists

Usual approach to treatment	CIN I	CIN II/III
	Number(%) of responding Gynaecologists	Number (%) of responding Gynaecologists
Ablative therapy (diathermy etc)	8 (6.0)	10 (7.5)
Cone Biopsy	33 (24.6)	69 (51.5)
LEEP	0 (0.0)	1 (0.7)
Observation and follow-up	85 (63.4)	7 (5.2)
Referral	2 (1.5)	2 (1.5)
Hysterectomy	6 (4.5)	45 (33.6)
Total	134 (100.0)	134 (100.0)

Omigbodun AO and Ayinde 2005

6.3 Challenges and prospects of managing CC in Nigeria

Annually almost 10,0000 cases of CC are diagnosed in Nigeria (WHO/ICO 2007). It is estimated that from the 32 million women between 15 and 64 years old (and CC incidence of 25 per 100, 000 women) at least 8,000 new CC cases will be detected annually if women were to have one-time screen (Adewole et al 2005). Most of these will present with advanced disease; about 80% with stage III disease (Miller 2007, Ekanem 1987). This is because of lack of awareness about CC in the community, illiteracy, poor health seeking behavior, poverty, fatalistic attitude and lack of confidence in heath services (Gharoro & Ikeanyi, Ayinde 2004). The common belief in

Nigeria is that cancer is a 'death sentence'; since it is incurable by western medicine (Durosinmi 2008) many will seek traditional or spiritual care until they also fail (Briggs 1990, Ohaeri 1999a).

6.3.1 Resources for cancer care

Human resources for cancer care are limited in Nigeria, See annex 3. There is currently no sub-specialist training in gynecologic oncology and most general gynecologists gain experience 'on the job'. There are no national protocols or guidelines for cancer care although recently a National Consultative Committee on Cancer was mandated to produce one. There are also no centralized or specialized centres for cancer care (Lambo n.d, Durosinmi 2008). There were probably less than 20 doctors and radiotherapists with special interest in cancer (Ohaeri 1999) and very few oncology nurses (Lambo n.d). Surgical skills for cancer management are becoming scarce. Only a few teaching hospitals with more experienced, older gynecologists have the capacity to offer radical surgery. In many places patients are referred for radiotherapy instead (Briggs 1990, Gharoro 1999). Palliative care is new in Nigeria and a multi-disciplinary approach is not used. Patients are rather managed according to their individual conditions. However interest in palliative care is emerging, as evident by formation of a National Association on Palliative care and designation of some teaching hospitals including ABUTH as 'centres of excellence' in palliative care. The Nigeria Society for the study of Pain has put Pain management on the national agenda (Lambo n.d, Adebamowo 2007).

Material resources and services
In tertiary hospitals where cancer is managed, there is long waiting time and long interval between diagnosis and definitive management (Briggs 1990, Gharoro 1999). This contributes to poor patient survival. There is poor financial access to management as cancer patients like other patients are expected to pay user fees and mostly out-of-pocket. Initially there was a policy that cancer and tuberculosis patients were exempted from paying hospital bills until the Structural Adjustment Program of the World Bank was introduced in 1987 (Ransome-Kuti 1998). Health insurance is currently in early phase of development and is currently restricted to public servants. Moreover, not all aspects of cancer care are covered and most of these patients are poor, living in rural areas in unpaid employment. Geographical access is poor as the very few cancer treatment centres are located in tertiary hospitals within urban areas and patients travel long distances to get there (NDHS 2003).

Radiotherapy: Only 15% of the 4 million Nigerians needing radiotherapy for cancer have access to it (Lambo n.d). Ideally the recommended ratio is one radiotherapy machine to 250,000 people (Parkin et al 2006, Sitas et al 2006). Radiotherapy is available in 6 sites (5 government owned) and only 4 functional now (Lambo n.d, Durosinmi 2008). Ancilliary investigation like CT-Scans, MRI are fewer than 10 in Nigeria and mostly too expensive for

the patients. Below is an estimate of cancer resources available in Nigeria (Lambo n.d, Ohaeri 1999):

Manpower

Specialists with Oncology interest   -<20
Radiation Oncologists   -17
Therapy Radiographers   - 6
Medical Physicists   - 8
Oncology Nurses   -Very few

Services

Radiotherapy:-
Teletherapy   - 4 Cobalt machines, 2 Linacs
Brachytherapy   - 3 (Functional)

Investigations   - CT scans <10 in Nigeria

Chemotherapy: Although this has limited place in CC, very few cancer drugs are readily available. Most are imported and are unaffordable (Durosinmi 2008). The poor nations have 50% of cancer patients and consume only 5% of cytotoxic drugs unlike developed countries with 39% of cancer cases (WHO 2008).

6.3.2 Policy/Financing

The poor state of cancer care in Nigeria should not be surprising as there is no policy on cancer control to guide CC management. There was no budget line in the FMOH for cancer until recently (Lambo n.d).   The Nigerian government has not shown enough commitment to cancer prevention. This is because non-communicable diseases like cancers are considered of low priority in LICs (WHO 2005, Durosinmi 2008). However CC is caused by a virus and behaves as an STI and is cheaper prevented than cured. Having a policy is the first step in CC control. A control program is achievable through partnerships between government, private sector, International organizations and NGOs. It requires better quality cancer data for planning so population-based cancer registries with computerized records are urgently needed. Technical assistance for this may be received from International Agency for Research on Cancer (IARC) (Parkin 2003). Meanwhile, CC control should start from the community and primary prevention is important. These efforts should be linked to each level of health facilities where capacity should be built to enable them play roles in CC prevention program. It is necessary to generate demand for CC service by improving access, availability and affordability of prevention service while improving the quality of cancer management (ACCP 2004, Zapka 2003). Finally, effective monitoring and evaluation mechanism should be built into the program.

CHAPTER 7: DISCUSSION AND CONCLUSIONS

7.1 Summary of principal findings

This review of both global and Nigerian data showed that cervical cancer is a major Public Health problem in Nigeria. A consistently high incidence between 25/100,000 to 30/100,000 women coupled with the high population increases magnitude of CC. Although, unlike the situation in South and East Africa where HIV has increased incidence of precancer and CC, in Nigeria, very few studies have explored this link in a convincing manner (Adewuyi et al 2008,2007, Anorlu 2007b). In Maiduguri (Chama 2005) and Ilorin a higher incidence of precancer was reported in HIV positive women. There is need to explore whether the HIV prevalence of 5% (WHO 2006e) or the likelihood of increasing aging population in Nigeria will increase the burden of cancer (ACCP 2004).

The natural history of cancer in Nigeria is not very different from the picture from other countries. The main aetiologic factor which is considered the necessary cause is the HR-HPV. These variants which may persist and induce cervical precancer changes are common in Nigeria. The sero-prevalence of HPV in Nigeria is high and this persist even in older women unlike in other countries with a single peak in HPV below 25years or a bimodal picture as in many Latin American Countries (WHO/ICO 2007). This high prevalence may be due to presence of many determinants of HPV in the country and the likelihood of super-infection by newer variants in older women (Thomas et al 2004). It might also be associated with poor nutrition, hygiene or poor immune status in the studied populace. Mixed infection was commoner and HPV-16 appeared to play a smaller role in Nigeria. However, this HPV picture is similar enough to the global trend and the licensed vaccines will be useful in the future.

Apart from HPV, there are many other determinants or co-factors for CC in Nigeria. Biologic determinants like heredity/genetics have not been strongly observed in Nigeria although there were occasional reports of familial cancer (Omigbodun 1992). Cervical cancer is still commoner between 4th and 5th decades and precancer peaks about 10 years earlier in Nigeria (Obafunwa 1991). The high prevalence of STIs like Herpes simplex, Chancroid, Gonorrhea in Nigeria was found to be associated with HPV infection. This may be due to underlying high risk sexual behavior of having multiple sex partners, low prevalence of condom use and visits to female sex workers (Thomas et al 2004, Tornsello 2007).

Some social-cultural factors possibly contribute to high prevalence of CC in Nigeria. Commonly sexual activity commences early and often in the context of early marriage. The legal 'age of consent' arguably varies between 13 and 16 (Odili 2002). Polygamy is common and no tribe or religion appears exempted from the practice (Mitsunaga 2005). However it is commoner among Muslims and in Northern Nigeria where CC has

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consistently been the commonest cancer of women (Adewuyi et al 2008, Madong 2003). The low status of Nigerian women and female subjugation causes poor access to information about health and health services, hence the low level of awareness about CC and late presentation to the hospital with advanced disease. The custom of male circumcision did not appear to have been protective against CC in Nigeria this needs further research because of recent reports of protective effect of circumcision on STIs including HIV (Rivet 2003). Illiteracy and poverty are rife in Nigeria and women and children are worst affected, both are associated with CC which is a disease that reflects inequity. Nigeria has a low HDI and a higher proportion of her illiterates are women (NDHS 2003). These women have poor health seeking behaviour and poor access to health. CC may also be commoner in them due to poor nutrition (Thomas et al 2004) or poor level of hygiene.

Lifestyle determinants of CC which contribute to HPV infection in Nigeria include early sexual debut, multiple sex partners and non-use of barrier contraceptives like condoms. Although smoking and alcohol are considered globally as co-factors of HPV and CC, the strength of association in Nigerian studies was small probably due to small number of smokers in the sample (Thomas et al 2004). Also the observed association with combined contraceptives was not reported in Nigeria women. Parity is a consistent, strong co-factor for CC and was reported in Nigerian studies though association was weak (Thomas et al 2004). Typically, Nigerians have a high Total Fertility Rate of 5.7, and frequent trauma to cervix and the hormonal changes of pregnancy are suggested explanations for increased risk.

Cancer is common in Nigeria because of absence of political will, policy and a weak health system. Cancer has not been a National public health priority and the absence of a definite policy and program for cancer attests to this. No country globally has reported a fall in their CC rate in the absence of a screening program.

7.2 Prevention strategies

The control of cancer is based on institution of primary, secondary and tertiary measures (including palliative care). Worldwide, primary measures for cancer including risk reduction and health promotion are generally subsumed to the secondary measures although there is evidence that they are effective (Shepherd at al 1999, Grimes 1995). However their implementation requires a broad program of STI control, promoting good diet and healthy lifestyle and smoking cessation. Achieving sexual risk reduction through delaying sexual debut, reducing number of sex partners and promoting message of condom use, require advocacy and may be legislation (Juneja et al 2003) although behavioral issues are difficult to change (Shepherd at al 1999). Nigeria needs a definite strategy of primary prevention for CC in addition to its role in HIV and STI control.

Secondary prevention of cancer in Nigeria is limited to opportunistic screening of women seen in health facilities, or during family planning or MCH programs. Thus, the few services for CC screening are based in tertiary hospitals in urban areas. They are mostly cytology-based and are unaffordable to the rural poor. There is yet no organized National program and no policy on cervical cancer screening (Kolawole 2001, Babarinsa 1998). However, there are ongoing pilot studies in about six locations in the country as shown in table 8 and few programs are exploring use of VIA as alternative to cytology. These are on small scale and are not well distributed over the geopolitical zones. Nigeria has some human resource that can be mobilized for a screening programme (Adewole 2005). There are about 100 pathologists and 2000 gynaecologists (Ezechi 2007) and some technologists and Nursing staff. While these numbers may be inadequate to cover the large population they can be utilized profitably to provide screening and precancer treatment. However integrating CC screening with HIV- PMTCT and VCT programs as suggested by Adewole (2005) while reducing program cost may target mostly younger women of low risk and may further stigmatize both HIV and CC.

Tertiary prevention in Nigeria is similar to the situation in the rest of SSA. The many challenges have been discussed especially shortage of human and material resources to treat many women presenting with advanced disease. Cervical cancer management is not standardized or guided by a national treatment protocol yet and it is not always available, accessible, affordable or even acceptable to the patient.

7.3 Strengths and weaknesses of the study

The strengths of this study include the approach to the problem of cancer from a global perspective before coming down to the Nigerian situation. It reviewed global studies and related them to the situation in low resources settings and Nigeria. Comparisons were made with other countries. Also data were included from grey literature and no age-restriction was placed on the studies used. However, being a desk review, there might have been some publication bias as usually positive studies are reported and published. Moreover locally published papers were more difficult to access and they were fewer unlike data from developed countries.

7.4 Conclusion:

Cervical cancer should be a public health priority in Nigeria. It affects many women and no region of the country is excluded. It affects women in their prime when they are very vital to their families, communities and the nation. It is a reflection of gender and economic equity. CC is cheaper to prevent than cured and there are cost-effective prevention strategies that can be adapted to the Nigerian situation. Controlling CC will contribute to achieving some MDGs in Nigeria. There is need to draw a national policy to

guide CC screening and management in Nigeria. Appropriate and feasible technologies like VIA are available and should be used in the proposed national program pending when resources improve. Control of cancer in Nigeria is not only a public health issue but it is a human right and ethical issue.

CHAPTER 8: RECOMMENDATIONS FOR CERVICAL CANCER CONTROL IN NIGERIA

The following recommendations for further research, policy and intervention are made towards a cervical cancer control program for Nigeria. This involves the different levels of government and the health care system.

8.1 Research
- There is need for further studies on the distribution of cervical cancer and the incidence in Nigeria. This should be population-based and not estimated from hospital based data which are generally underestimates.
- There is need to establish computerized population-based registries at least one in each of the geopolitical zones.
- A meta-analysis should be done using data from the ongoing pilot studies to decide on cost-effective strategies and resource needs for Nigeria.
- More research is needed on the capacity of the health system to organize a national CC control program.
- Baseline studies should be done in the communities exploring the level of awareness about cervical cancer and their perceptions about current prevention strategies including cytology, visual techniques and HPV vaccination; as well as resources that can be mobilized from the community.

8.2 Policy
The government should show greater commitment for cervical cancer control by expediting policy making process and increasing funding for cervical cancer control.
- The central body for control: The recently constituted 'National Consultative Committee on Cancer Control' should be mandated to publicize its activities till date and be evaluated.
- Stake holders for cervical cancer control including women, politicians, heads of medical institutions, MOH officers, NGOs, professional groups including Society for Gyneacologists and Obstetricians of Nigeria (SOGON), Nigeria Cancer Society, Society of Oncology and Cancer Research in Nigeria should meet and decide on policy thrust.

Policy content:
- There should be sensitization on need for policy for National CC screening program.
- A policy on appropriate financing mechanism possibly based on public-private mix.
- It should establish protocols for screening preferably using VIA as primary and cytology as secondary method; and protocols for treatment

of pre-cancer and CC in Nigeria in view of current evidence and WHO recommendations.
- To determine target age for screening in Nigeria, preferably based on age specific incidence of cervical cancer. Initial target age may be 30 to 40years and later adjusted based on available resources.
- To determine population coverage rate of screening. These may be scale-up gradually over next 10 years until the recommended coverage rate of over 80%. The pilot projects should aim at 80% coverage in their site before they are scaled-up.
- To determine adequate screening frequency. Current evidence shows value of starting with 'once a life time' screening of women 35-50 years. This may be increased initially to ten-yearly screening (about 2 to 3 times per lifetime) and later five-yearly as resources increase.
- Policy to address task-shifting of screening to mid-level health workers like nurses and laboratory technicians.
- Policy on choice of program approach, although an integrated approach with program integrated into existing health facilities is recommended.
- Need to include more liberal access to opiates analgesics in the community to aid palliative care of cervical cancer patients.

8.3 Program/Intervention

The National program on CC control should be integrated into the existing health system. It should be community or population based.
- Existing personnel and facilities should be utilized optimally; there will be need for some re-training on screening techniques.
- There is need to train new personnel especially on alternatives to cytology. Mid-level health workers should be trained on screening techniques and counseling skills.
- A system of managing client records and National data should be developed.

Specific activities
Specifically at the different levels the following intervention should be implemented.
- The ongoing pilot projects should continue but may need to be modified or redefined. They should form the nuclei around which subsequent scale-up is done.
- In the next 3years, the remaining geopolitical zones without an on-going cervical cancer pilot project; South-South, North-East and North Central should commence small projects. Funding should be sourced from FGN, local NGOs and international bodies
- At the **project zones** (based on six geo-political zones) activities should involve communities, Primary Health Care, Secondary and Tertiary levels:
Community level:

- Level of awareness about CC and its prevention should be increased using community based peer educators and Community Health Workers (CHWs). These should mobilize targeted women for screening.
- Project should select at least 2 communities located more than 5km from the nearest Primary Health Centre (PHC) and should periodically organize cervical cancer screening outreach programs there until coverage of 80% is reached. CHWs should offer community-based palliative care.

Primary Health Centre:

- Two primary health centres should be chosen in each geopolitical zone and should be centres for 'static' or clinical-based screening. This may utilize visual techniques with 'see and treat' approach. The possibility of using trained doctors and nurses for cryotherapy should be explored. If treatment is unfeasible positive women should be referred to the nearest General hospital or tertiary hospital. An alternative is for trained health workers to go to these health centres on specified days to do the screening and treatment
- Training and supervision of CHW.

Secondary level:

- Initially program should involve at least two general hospitals per zone. They should have capacity and screen target population using visual techniques and cytology as secondary test if present.
- Positive women should be treated with cryotherapy as LEEP is unlikely to be available in General hospitals in the next 5years.
- They should organize outreaches to supervise the project PHCs and should act as referral centres to them.
- They should be involved in training mid-level personnel.

Tertiary level:

At least one Teaching Hospital or Federal Medical Centre (FMC) should be involved in each project zone.
- They should screen women using either visual or cytology techniques.
- They should maintain laboratories for cytology and CC investigations.
- They should take referral for management of pre-cancer using LEEP and cryotherapy should manage all cervical cancer patients including palliative care.
- They should organize and co-ordinate training of medical personnel needed in the program.
- They should oversee the population based cervical cancer registries.

Scale-up:

After establishing pilots in each geopolitical zone, as resources increase, more communities, PHC, General hospitals and tertiary hospitals should be involved. At the end of 10years each of the 36 States of Nigeria should have on-going cervical cancer screening program.

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ANNEX 1

Map of Nigeria Showing the Six (6) Geo-Political Zones
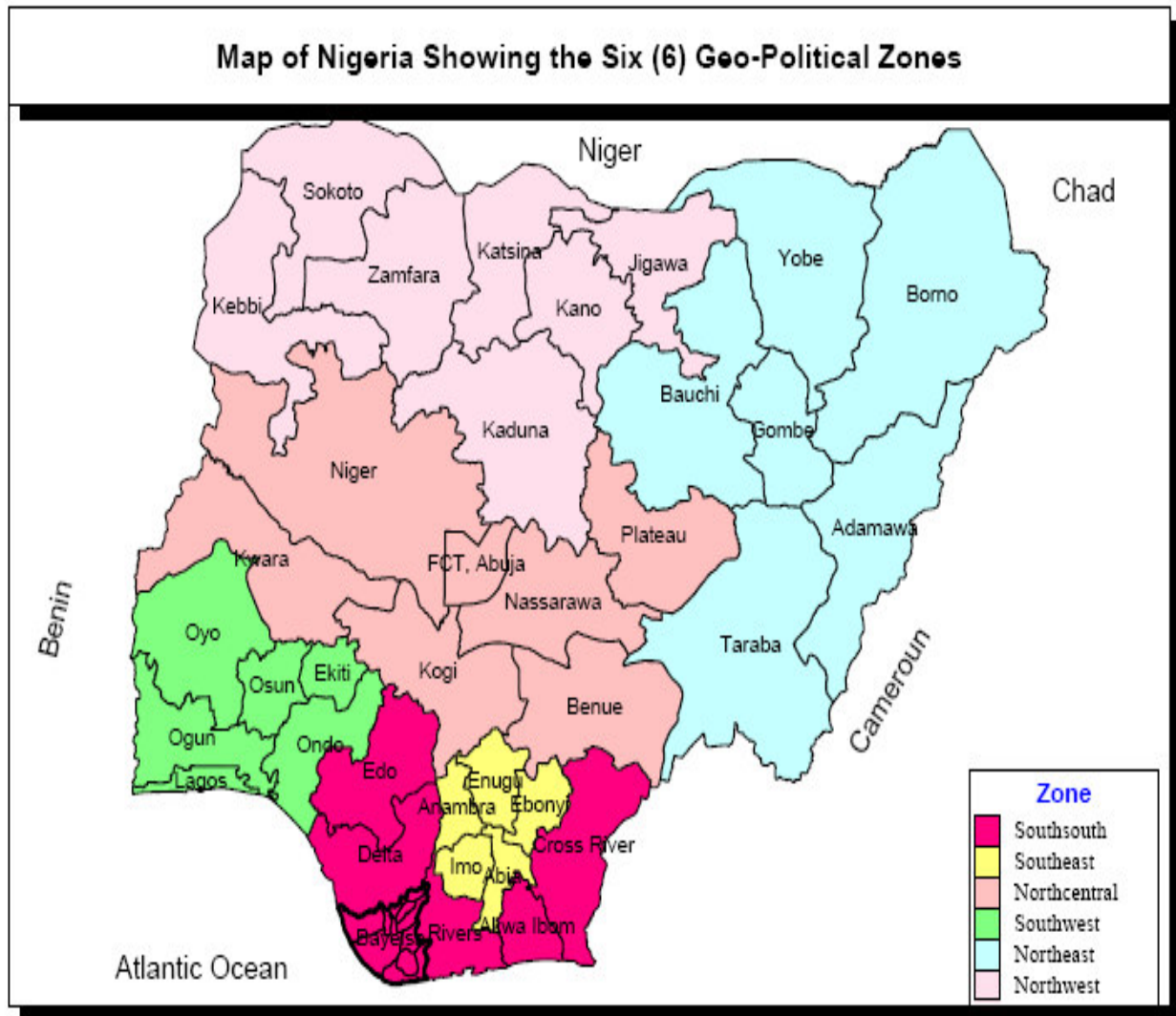
ANNEX 2
MAPS SHOWING PATTERN OF POVERTY & CERVICAL CANCER GLOBALLY

Estimate of world poverty

increasing burden of poverty
Source: RBM data/J. Sachs 1999
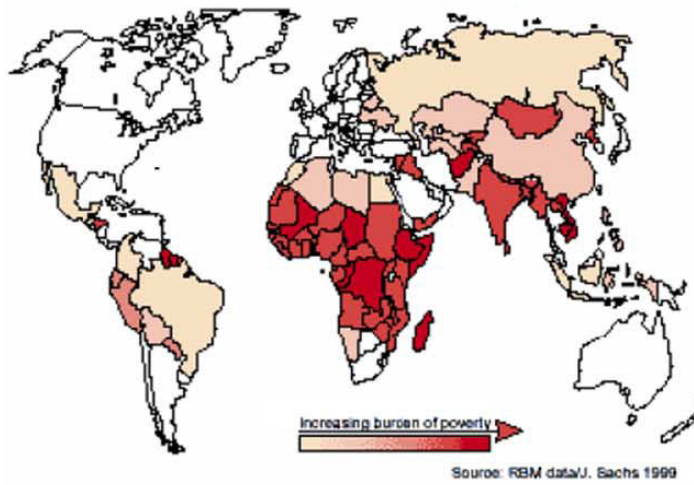
Cervix uteri
Age-Standardized incidence rate per 100,000

< 9.4   < 16.8   < 25.8   < 33.4   < 87.3
GLOBOCAN 2002, IARC

Cervix uteri
Age-Standardized mortality rate per 100,000

< 3.9   < 7.9   < 14.0   < 23.8   < 55.6
GLOBOCAN 2002, IARC

65
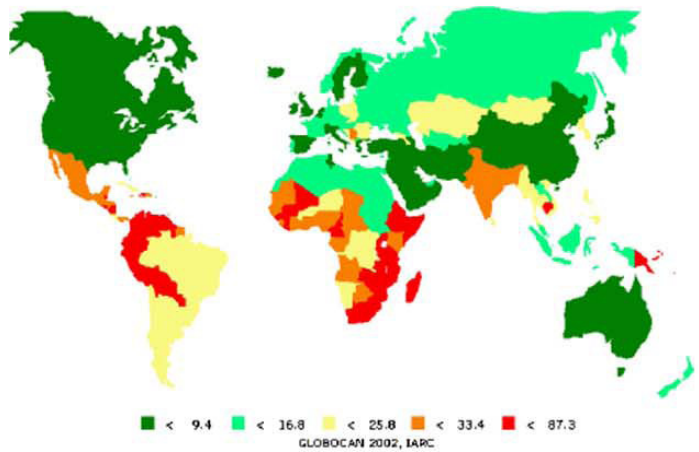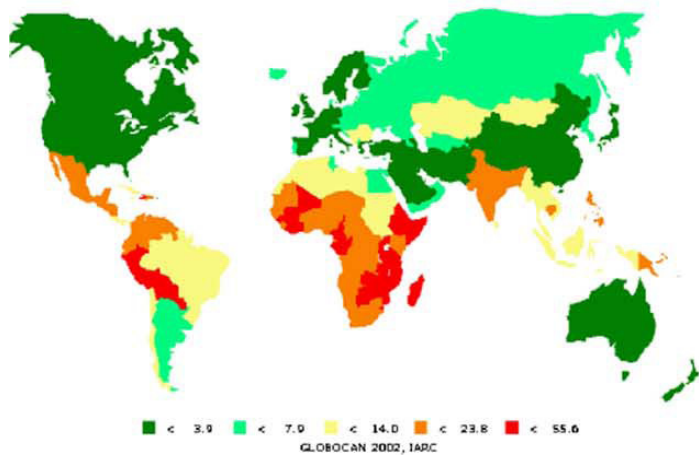
ANNEX 3

NIGERIAN SOCIO- DEMOGRAPHIC AND EPIDEMIOLOGIC INDICES

INDICATORS	VALUE
Total Population (NPC 2007)	140,003,542
Land Area (Sq km)	923,768
States	36 + 1 FCT
Number of Local Government Areas	774
Population Growth rates (NPC 2007)	3.2
Total Fertility Rate (year 2006)	5.5
Crude Birth Rate per 1000 (2005)	41
Crude Death Rate per 1000 (2005)	19
Life Expectancy at birth (years) -Male -Female	47 48
Adult Literacy Rate % (2004) -Male -Female	69.1 68.0 60.6
UNDP HDI ranking (2006)	159/177
Population Living below the poverty line, % <$1 per day (year)	70
Unemployment rate (2000) %	5.8
GNI per capita (2005) PPP International $	1040
Urban Population %	48
Infant Mortality Rate per 1000 (2006)	99
Under- Five Mortality rate per 1000 (2006)	191
Maternal Mortality Ratio per 100,000 (2000)	1100
HIV Prevalence %	5.0
Total Health Expenditure/capita (2004) (International $)	53
Total Health Expenditure as % of GDP (2004)	4.6
Estimated Number of Ethnic groups	250

Source: WHO and World Bank

Selected Human Resource in Health in Nigeria

Indicators	Value	
Physicians (number)	34,923	(2003)
Physicians (density per 1000 population)	0.28	(2003)
Nurses (number)	127,580	(2003)
Nurses (density per 1000 population)	1.03	(2003)
Pharmacists (number)	6,344	(2004)
Pharmacists (density per 1000 population)	0.05	(2004)
Community Health Workers (number)	115,761	(2004)
Community Health Workers (density per 1000)	0.91	(2004)
Laboratory Health Worker (number)	1,220	(2004)
Laboratory Health Worker (density per 1000)	0.01	(2004)

Source WHOSIS 2008

ANNEX 5

HUMAN PAPILLOMAVIRUS (HPV)
Natural History and Biological mechanism of HPV and CC
HPV infection occurs soon after sexual debut; within 3 months in a study (Kjaer 2001, Winer 2003). In 90% of times the infections is cleared by the immune system usually within 2 years and some antibodies may be produced in response (Paavonem 2007, Kjaer 2001, CDC 2002). In the remaining 5-10% cases the virus may persist in the cells and the integration of virus into the host cell leads to prolonged infection which in case of HR-HPV carries a higher risk of cancer (Bosch 2002). The HPV virions enter into the basal and parabasal cell though a breach in the epithelium of cervix especially during or after cervical trauma and viral DNA is introduced into host DNA in cell nuclei and immortalization may occur (Munoz 2006). Attempts to repair these cells cause proliferation and dissemination of the virus (Bosch 2002). Persistent infection and integration of HPV DNA into the Squamo-Columnar Junction (SCJ) of the cervix induces pre-cancer changes in the cervical epithelium which are either low grade (LSIL) or high grade (HSIL) based on severity and thickness of epithelium affected (Schiffman 2005, ACCP 2004a). The LSIL often resolves spontaneously or progress to HSIL and later invasive CC. Most untreated HSIL proceed to CC (Cox 2001, ACCP). The interval between the precancerous changes and invasive cancer ranges from 10-20 years occurring in ages 40-50years depending on other host and environmental factors (Parkin 2003, WHO 2006c).

Natural History of HPV & Cervical Cancer

Courtesy of M. Schiffman, National Cancer Institute.
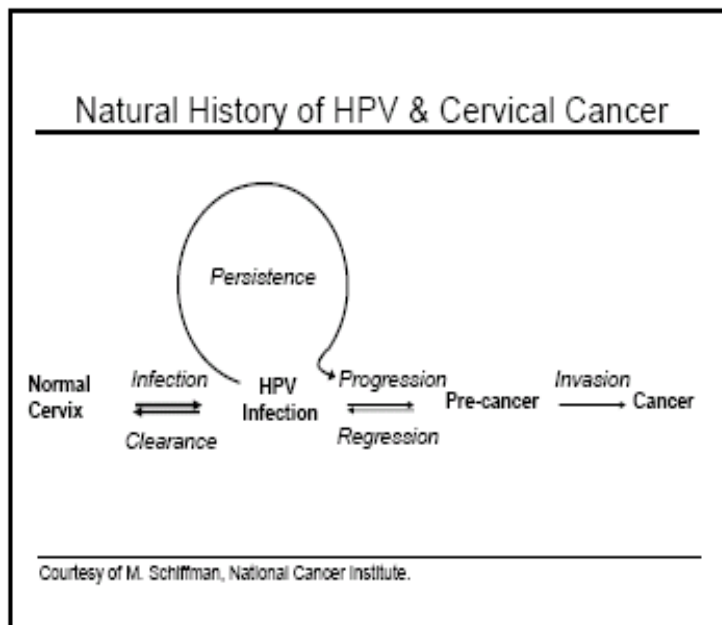
HPV VACCINATION SCHEDULE: They are not biologic products, non-infectious and contain no DNA (WHO 2006b). Gardasil is given in three doses of 0.5ml of intra-muscular injections with 2nd dose 3 months after the first and 3rd dose 6months after initial dose (Bass 2006). Cervarix[R] is given also in 3 doses of 0.5ml; a month after an initial dose 2nd dose is given and the last dose 6 months after

the 1st dose. Within one month the vaccine stimulates strong immune response 10-104 times higher than after natural infection (Cutts 2007). In previously uninfected women it gives more than 90% -100% protection against persistent HPV infection (WHO 2006b) , and current trials suggest that it remain efficacious against persistent HPV and CIN for 4-5years (WHO 2006b, Brooke & Sherris 2006). It is expected that if all adolescent girls are vaccinated, the incidence of cervical cancer will be reduced by 51% within 40-50years. There were no major adverse effects apart from swelling, erythema and pain in injection site (Cutts 2007). However in those already infected vaccine has lower efficacy

HPV Necessary for Cervical Cancer

Transmission: genital skin to skin contact

Transient HPV infection → Persistent infection with oncogenic HPV types

Low grade lesions: CIN 1/LSIL
(Episomal HPV, koilocytotic atypia, mild dysplasia, lesion extends to less than 1/3 of the epithelium, most lesions regress)

High grade lesions: CIN 2-3/HSIL
(HPV integrates into the genome, genomic instability, moderate or severe dysplasia, extension to full thickness of the epithelium, regression less frequent than for CIN 1)

Invasive cervical carcinoma
(Disease extends beyond basement membrane and invades connective tissue, metastatic spread to lymph nodes and distant sites)

Cofactors:
- Oral contraceptive use, other hormonal influences
- Parity
- Other STIs
- Smoking
- Nutrition
- Host genetics: Polymorphisms in HLA and other genes
- Viral genetics: Genotype, molecular variants

Trottier H. Vaccine. 2006; Ley C. J Natl Cancer Inst. 1991.

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ANNEX 6

SECONDARY PREVENTION
Technique of pap smear and follow-up management:
The patient is placed in a lithotomy position and a sterile Cusco's speculum is inserted. A wooden spatula or a brush is then used to slightly scrape off some cells from the transformation zone of the ectocervix. The collected sample is smeared into a glass slide and is immediately fixed with a preservative (WHO 2006c, Rock 2000). The slide is transported to the laboratory where it is stained and examined under the microscope for abnormalities. These abnormalities are classified based on Bethesda system. More recently liquid-based cytology was introduced in mid 1990s (WHO 2006c, Denny2005, ACCP-Manual 2004). In this case a cytobrush is used to collect cells, the tip is broken into the special specimen bottle containing preservative and is transferred to the cytology laboratory where a slide is prepared and read. It has the advantage of shorter processing time and better quality of smears made from more representative samples of cells (WHO 2006c).

Following an abnormal pap smear a repeat test may be necessary and the woman subsequently referred for colposcopy and biopsy of the abnormal area. Colposcopy involves the use of a special instrument which magnifies the cervical cells (up to 4 times) and show areas of abnormal epithelium or blood vessels under a bright light. The abnormal area is then sampled using biopsy forceps (WHO 2006c, Disaia 1993, Olaniyan 2002). This requires skilled personnel usually gynaecologists. The biopsy specimen is examined by pathologists in the laboratory and the abnormality is graded. Pre-cancerous or dysplastic changes are managed usually with simple out patient excision procedures like LEEP or with the cheaper ablation procedure of cryotherapy (WHO 2006c) or laser vaporization. In the past in-patients procedures like cold-knife biopsy, simple hysterectomy or diathermy were used (Reproline 1998, Adewole 1998, Omigbodun 1991).

NEW SCREENING TECHNOLOGIES
These include speculoscopy, cervicography, computer imaging and experimental ones like laser-induced fluorescence, polar probe, photo dynamic therapy and multi spectral digital colposcope (Rock 2000, Roblyer 2007).
Speculoscopy: This is inspection of the cervix and vagina after application of 5% acetic acid, using chemiluminent light and low power magnification of 4 -6 power (Rock 2000). Examination is done with dimmed room lights and presence of aceto-white lesion is considered positive. It has been suggested that it may improve sensitivity pf Pap smear, however this is still unproven (Rock 2000).
Cervicography: This involves using a special camera to take two pictures of the cervix after applying 5% acetic acid, usually after Pap smear has been taken. The pictures are read by a colposcopic expert who gives standardized result. The sensitivity ranges from (Rock 2000, Ref 122). It may be useful for triage of mild cytological anomalies or as an alternative where cytology is unavailable (Rock 2000).
Laser induced fluorescence: - This is based on fluorescence induced by low-powered laser. The abnormal tissue shows a different endogenous fluorescence. It is still experimental (Rock 2000).
Photodynamic therapy is based on using a photosensitive drug which is selectively absorbed by abnormal tissue (Rock 2000). It is expensive and still experimental.

Computer imaging uses a computer to analyze colposcopic pictures or can be done during colposcopy itself. It has potential to be objective and save time (Rock 2000). However it is costly as it requires a colposcope.

Polar probe is based on difference in electrical properties between normal and cancerous tissues. It is still experimental and expensive (Rock 2000).

Multispectral Digital Colposcope (MDC) with ability to measure fluorescence and polarized reflectance. The trial was however suspended because of power outages and lack of technical back-up.

FIGO STAGING SYSTEM FOR CERVICAL CANCER

STAGE	DESCRIPTON
0	Carcinoma in situ (no evidence of invasion)
IA	Cancer diagnosed only by microscopy
IA1	Invasion 3 mm or less in depth and 7 mm or less in horizontal spread
IA2	Invasion more than 3 mm and not more than 5 mm with a horizontal spread 7 mm or less
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2
IB1	Clinically visible lesion 4 cm or less in greatest dimension
IB2	Clinically visible lesion more than 4 cm
II	Cervical cancer invades beyond uterus but not to pelvic wall or to the lower third of vagina
IIA	Tumor without parametrial invasion
IIB	Tumor with parametrial invasion
III	Tumor extends to the pelvic wall, and/or involves the lower third of the vagina, and/or causes hydronephrosis or nonfunctioning kidney
IIIA	Tumor involves lower third of the vagina, no extension to pelvic wall
IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
IV	Cervical cancer has extended beyond the pelvis or has involved (biopsy proven) the bladder or rectum
IVA	Spread to adjacent organs (bladder, rectum, or both)
IVB	Distant metastasis

TERTIARY PREVENTION OPTIONS
The management starts with investigations to confirm the diagnosis, evaluate the health status, and staging to determine extent of disease and the best treatment option. The main confirmatory test is tissue biopsy. This is either done as simple out-patient procedure which is usually adequate (WHO 2006c, Samaila et al 2007, Buekers 2007) or as part of an elaborate "Examination under anesthesia (EUA), staging and biopsy" procedure. Staging is done based on size of cancer growth and the involvement of surrounding tissues (Waggoner 2003). Special investigations like cystoscopy, proctoscopy are done during the procedure to assess the spread of tumor. Basic tests like Haemogram, urinalysis, electrolytes are done to evaluate the woman's health status while additional tests like Chest X-ray, Computerized Tomographic Scan (CT-Scan), Intravenous Pyelogram, Magnetic-Resonance Imaging (MRI) (Waggoner 2003, Buekers 2007) may be unavailable in LIC.

SURGERY: Early CC is can be treated with "radical surgery" and is done for disease including stages I up to stage II A. It is preferred for younger women where preservation of the ovaries is advised. Radical Hysterectomy usually involves removal of uterus, cervix, surrounding parametria and upper 2cm of vagina (Buekers 2007). There have been calls recently for simple hysterectomy for early stages like IA1 and possibly IA2 (WHO 2006c) and also fertility-sparing procedures like radical tracheletomy with pelvic lymphadenectomy (Waggoner 2003). This is used in micro-invasive (stage IA1) in women desiring children in future so the cervix parametria, upper vagina is removed in addition to pelvic lymph nodes (Buekers 2007). Surgery may also be needed in patients with complications like pyometria or urinary obstruction.

RADIOTHERAPY: This can be used for all stages of CC especially those above IB. It can also be used for palliation in advanced cases. There may be need to combine chemotherapy with radiotherapy in advanced cases in order to improve cure (WHO 2006c). Radiotherapy is either given as brachytherapy or teletherapy. In brachytherapy radioactive sources are inserted into the uterus and vagina so that the cancer tissues are killed. This is done at intervals in order to prevent damage to normal tissues like bladder and rectum. It is suited to less advanced CC when the cervical os is still open and may be curative (ACCP 2004). Teletherapy involves using external beam with the radiation delivered from a source outside the patient's body (like an X-ray machine) and is given in doses over weeks. It is usually done for advanced disease and palliation is the goal (WHO 2006c, ACCP).

CHEMOTHERAPY: Occasionally cancer drugs are used in addition to radiation or surgery especially for big growths. These drugs are cis-platinum based which also serve as radio-sensitizers that enhance the effect of radiation. They are also used for recurrent CC (Waggoner 2003).

ANNEX 8

Table Showing summary of sites of cervical cancer screening projects in Nigeria

Project Site	Organizers	Objectives	Activities	Results
1. Abuja, FCT. (Olaniyan 2006) Target population- Previously unscreened rural women	Rotary Club, Focal person; Dr. Olaniyan OB	-Create awareness about CC -Train PHC workers in Pap smear Screening -Encourage uptake of CC Screening in previously unscreened women	-Training workshop for Health workers in Abuja & environs -Awareness symposium for Stakeholders -On-site training of PH workers on pelvic exams and Pap smears -Pap smear Screening -LEEP Rx at National Hospital Abuja.	-65 workshop participants trained -862 women screened from 8 centres: 6.3% had CIN, 4.2% of CIN cases had colposcopy & LEEP, 2 patients diagnosed with CC had radiotherapy.
2. SouthWest Zone Ibadan, Oyo State, (Amotsuka 2007, UMC 2008) Since 2002 Target-Women in Community	'Save our future foundation' -O& G dept UCH, Catholic Hospital, Oluyoro, Family Medicine Dept, University of Mississippi, USA Focal person: Dr. C. Amotsuka	- Create awareness in women & men in market, churches, and mosques. -Capacity building of HW including client-friendly services -Equip project centres with needed tools	-Workshop on CC prevention in Sept 2003 for physicians & Nurses from 3 states in Southwest Zone ---Awareness campaigns in markets, churches, mosques. -Screening outreach services at hospitals and project sites -Collaboration with project Hospitals to continue screening, colposcopy & cryotherapy after community programs -Research assistance to UCH residents & MPH students, UI	-Training on VIA and Pap Smear, Colposcopy and cryotherapy demonstrated -Over 50 doctors & nurses on screening tests & client friendly services -Screening done according to protocol
3. SCCAN ' Stop Cervical Cancer Nigeria' Project Hqtrs- UCH, Ibadan Since 2006 (SCCAN 2008, Miller 2007, Roblyer 2007) Target-Women nationwide in multiple sites	University of Ibadan college of medicine, MD Anderson Cancer Centre, Texas, USA, British Colombia Cancer Agency, Rice University department of Bioengineering, Funding: Exxon Mobil Foundation Focal Person;	- To improve screening and treatment of cervical cancer in Nigeria. -Start from project headquarters and scale-up to 6 geopolitical zones of Nigeria	-Two-day workshop (Feb 2-3, 2006) for medical workers from the 6 geo political zones of Nigeria -Training conference on 'Effective National cervical cancer screening program in Low Resource Settings' -Clinical research on ' Multi-spectral digital colposcope' organized in University College Hospital, Ibadan	-70 participants trained -Pilot trial completed but larger trial suspended due to technical reasons; power- supply and lack of local technical support

| Project Site	Organizers	Objectives	Activities	Results
	Prof IF Adewole			
4. Lagos Cervical cancer Screening project, SouthWest Zone (cancercare, vanguard, Guardian) Since 2005. Target: Lagos- all women 30-65 years screened at least once in lifetime. Specific target- 10,000 women screened over next 2 years	University College London, (UCL) Elizabeth Garrett Anderson Institute for women's Health, St Kizito's Clinic, **Focal Persons**; Dr Olaitan A, UCL; Dr Anorlu RI, LUTH, Nigeria.	-To determine feasibility & acceptability of screening in sexually active women up to 70 years using Visual inspection techniques to detect signs of precancer & cancer. -Manage precancer with cryotherapy. -Screening project to continue in St. Kizito for 2 more years - Scale-up to 2 more clinics in next 2 years	-Sensitization campaign 2005 -Training and supervision -Screening program based on 'see and treat approach' in St. Kizito clinic in Lekki, Lagos. -Mobilization & sensitization in Surulere & Ikate, 2006. -Outreach Screening to Queen's College, Yaba, Ancilla Hospital, Iju, Airforce Hospital, Ikeja in 2007	> 3200 women educated about CC screening. > 1,500 women screened average 50 per week. -40 staff including 2 nurses trained in VIA technique -Equipments bought for 2 clinics -Evaluated by sponsors in 2007; adjudged satisfactory, hence decision to scale-up.
5. Sagamu, SouthWest, IARC study	Dr Peter Adefuye	Not available yet	Not available yet	Not available yet
6. Enugu, South East Zone. Medical Women Association of Nigeria (MWAN) centre. (Chukwuali 2003, Obi) Since 1990	Medical Women Association of Nigeria, Enugu Zone.	-To improve coverage of cervical cancer screening	-'Well-woman clinic'/Cervical cancer screening centre set up - Media campaign done	-815 had Pap smears between 1991 and 2000: only 0.5% had previous smear, 12.2% had abnormal smears: 85.9% SIL & 14.1% suspicious of invasion.

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Summary of Results from some Nigerian studies on cervical cancer screening

STUDY	STUDY POPULATION	RESULTS		
		Knowledge/Awareness	Utilization	Other results
Abuja Olaniyan 2000	Female Healthcare Providers	72.9%	9.6% of Pap	
Onah 2001	Nigerian Gynaecologists	--	--	Only 15% offered Pap smear to patients
Enugu Chukwuali 2003	Women	--	0.5% had previous pap smears	12.2% had dyskaryosis. Price subsidy did not increase uptake
Obi et al 2007	Women seen over 10 years	--	<1% of target population utilized screening	52.3% were referred cases
Owerri Ezem 2007	846 women	52.8% aware	7.1% had done test	Lack of awareness was commonest reason for non-use of test
Umuahia Anya et al 2005	144 Female Health providers	91.7% knew about cervical cancer	9 % utilisation	30.3% did not consider they were at risk. Main reason for non-utilisation was non availability of test
Benin Gharoro & Ikeanyi 2006	195 Female Health Workers in tertiary Hospital	65.2% knew about CC and 64.7% knew about Pap Smear	14.1% utilization	89.2% did not think they were at risk. Awareness of CC and FP correlated with utilization
Lagos				

STUDY	STUDY POPULATION	RESULTS		
		Knowledge/Awareness	Utilization	Other results
Anorlu 2007	General Practitioners		Only 5.4% screen patients though 17.8% had facilities for screening	Screening tests was selective-done mostly for symptomatic patients
Ibadan Ogunbode & Ayinde 2005	Market women in Ibadan	40.8% aware of CC (knowledge above average in 23.4%); 19.7% aware of Pap smear	5.2% utilization	33.3% will still not have the test even if it's free
Ayinde et al 2004	421 Female undergraduates	71% aware of CC; 33.5% aware of pap smear	8.3% utilization	--
Ayinde 2003	205 Female Health workers	----	6.8% utilization rate	--
Ajayi & Adewole 2002		96.8% aware of CC screening	55.6% offered screening	--
Ajayi & Adewole 1998	Family physicians		1.2% utilization	Cost was a major deterrent
Ayinde et al 1998	254 low socio economic status women attending General Outpatient Clinic	3.5% aware of CC screening	7.6% utilization rate	--
	---	70% aware		
Kaduna Kolawole 2001	257 Female Health workers	96.5% aware of CC 66.7% aware of Pap smear	9.3% utilization rate	See text
Maiduguri Audu et al 1999	500 women	< 10% aware of CC or Pap smear	Very Low	--

ANNEX 10 MODEL TO IMPROVE QUALITY: CANCER CARE CONTINUUM (Zapka JG et al 2003)

TYPES of CARE → **OUTCOMES**

Risk Assessment	Primary Prevention	Detection	Diagnosis	Cancer or Precursor Treatment	Recurrence Surveillance	End-of-Life Care	Risk Status
Age Family Hx Exposure Hx Genetics Lifestyle Screening Hx	Lifestyle counseling Chemo pre-vention	Screening (Asympto-matic) Appropriate Testing (Sympto-matic)	Imaging Biopsy Repeat Exams Laboratory Tests Other Appropriate Procedures	Excision Surgery Radiation Adjuvant Chemo Palliation	Testing Follow-up Care Palliation Survivorship Care	Palliative Care Advanced Care Planning Bereavement Support	Clinical Status Functional Status Quality of Life Satisfaction Mortality Quality of Death

Failure to Identify Need to Screen or Counsel

Failure in Access to Care

Primary Prevention Failure

Failure in Detection

Failure to Screen

Failure During Diagnostic Evaluation

Failure During Follow-up of Abnormal Result

Failure of Treatment

Failure During Follow-up of Diagnostic or treatment plan

Failure in Surveillance

Failure to Follow-up Surveillance Plan

Failure in Care

Failure to Access Care

POTENTIAL FAILURES DURING the PROCESSES of CARE

Nigerian National Expenditure on Health

Selected Indicators Ratio for Expenditures on Health	Years											
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Total Health Expenditure (THE) as % of GDP	5.2	4.3	4.9	5.5	5.4	4.3	5.3	5.0	4.7	4.0	3.9	4.1
External resources on Health as % THE	0.4	0.2	0.3	13.1	13.8	16.2	5.57	6.14	3.2	4.0	4.8	5.9
General Government Expenditure on Health (GGHE) as % of THE	21.7	21.8	21.9	26.1	29.1	33.5	31.4	25.6	27.4	30.8	30.9	30.1
Private sector Expenditure on Health (PvtHE) as % of THE	78.3	78.2	78.1	73.9	70.9	66.5	68.6	74.4	72.6	69.2	69.1	69.9
GGHE as % of General Government Expenditure (GGE)	7.1	7.1	7.1	7.1	5.4	4.2	3.2	3.1	3.2	3.5	3.5	3.5
Social Security Funds as % of GGHE	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pre-paid & Risk pooling as % PvtHE	2.4	2.9	2.5	2.4	3.4	5.1	6.5	6.7	6.7	6.7	6.7	6.7
Private households' out-of- pocket payment as % of PvtHE	95.0	94.5	94.9	95.0	94.8	92.7	91.4	90.4	90.4	90.4	90.4	90.4
General Government Expenditure on Health per capita Exchange rate	2	3	3	4	5	6	6	5	5	7	8	10
General Government Expenditure on Health per capita Int $ rate	9	8	9	12	13	13	15	12	13	13	14	15
International dollar rate (NCU per International $)	22.53	30.26	30.18	28.70	32.26	44.93	41.58	46.36	52.62	64.36	79.18	83.14

Source from WHO NHA series 2008-05-14