PREVALENCE AND DETERMINANTS OF HIGH RISK HUMAN PAPILLOMAVIRUS (HPV) AMONG WIVES OF MIGRANT WORKERS – A STUDY IN FAR-WEST NEPAL

by

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A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham, in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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This dissertation research focuses on the risk factors associated with high-risk HPV infection (HR-HPV) and abnormal cervical cytology in Nepali women residing in Nepal’s Far-West district of Achham. The first part of this dissertation assesses the HR-HPV test concordance of self-collected vs. clinician-collected cervico-vaginal specimens. Of 261 women with both clinician- and self-collected cervical samples, 25 tested positive for HR-HPV, resulting in an overall HR-HPV prevalence of 9.6% (95% Confidence Interval [CI]: 6.3 – 13.8). The overall Kappa value for clinician- and self-collected tests was 0.64 (95% CI: 0.48 – 0.84), indicating a “good” level of agreement. The second part of this dissertation investigates the association between 251 women whose husband’s migrate for work and their high-risk HPV (HR-HPV) infection status and their abnormal cervical cytology status. Half of study participants (50.8%) had husbands who reported migrating for work at least once. Women 34 years and younger were significantly less likely to test positive for HR-HPV than women older than 34 years (OR 0.22, 95% CI 0.07 – 0.71). HR-HPV infection and abnormal cervical cytology status were not directly associated with a husband’s migration. The last part of this dissertation investigates the link between rates of sexually transmitted disease (STD) symptoms and geospatial differences among migrant workers using the Nepal Demographic Health Survey.
(NDHS). Data was restricted to 9,607 married women in the 2011 NDHS. Multivariate logistic regression models assessing the odds of reporting STD symptoms in the 2011 NDHS found that women whose husbands migrated for a year or more were more likely to report STD symptoms than women whose husbands were not currently migrating for work if they lived in Nepal’s Mid-West region (OR 1.93 95%CI 1.02 – 3.67) or Nepal’s Far-West region (OR 2.89 95%CI 1.24 – 6.73). The burden of increased risk factors for HR-HPV infection and abnormal cervical cytology could result in increases in HPV prevalence in the wives of Nepali migrant workers.

Key words: HPV, Nepal, Cervical Cytology
DEDICATION

To my mother Linda Johnson and my sister Meredith Johnson
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There are many people without whom this dissertation would never have been written. My professor and mentor Dr. Shrestha. Without his patience and dedication my time at UAB would not have been the same. His mentorship made this dissertation possible.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>v</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF TABLES AND FIGURES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xi</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
</tbody>
</table>

## CHAPTERS

**ASSESSMENT OF HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTIONS USING CLINICIAN- AND SELF-COLLECTED CERVICAL SAMPLING METHODS IN RURAL WOMEN FROM FAR WESTERN NEPAL** ................................................. 14

**THE RELATIONSHIP BETWEEN SPOUSAL MIGRATION AND HIGH-RISK HUMAN PAPILLOMAVIRUS VIRUS INFECTION AMONG WOMEN RESIDING IN THE FAR-WEST REGION OF ACHHAM NEPAL** ............................................. 40
THE ASSOCIATION BETWEEN GEOSPATIAL FACTORS AND A HUSBAND’S MIGRATORY STATUS AMONG NEPALI WOMEN REPORTING REPRODUCTIVE TRACT INFECTIONS IN THE 2011 NEPAL DEMOGRAPHIC AND HEALTH SURVEY ..................................................................................................................66

DISCUSSION .................................................................................................................................93

APPENDIX:

A ORGANIZATIONAL DEFINITIONS OF THE TERM MIGRANT ...........112

B VILLAGE DEVELOPMENT REGIONS OF ACHHAM, NEPAL ..........114

C DEMOGRAPHIC AND HEALTH SURVEY FOR WOMEN PARTICIPATING IN A ONE DAY HEALTH CAMP IN ACHHAM, NEPAL .........................116

D UAB IRB STUDY APPROVAL .................................................................124

E NEPAL HEALTH RESEARCH COUNCIL IRB STUDY APPROVAL .....128
LIST OF TABLES AND FIGURES

Figure/Table Page

INTRODUCTION

1 Figure 1. Achham District in the Far-West Development Region of Nepal in Relation to Nepal’s Capital, Kathmandu .................................................................7

ASSESSMENT OF HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTIONS USING CLINICIAN- AND SELF-COLLECTED CERVICAL SAMPLING METHODS IN RURAL WOMEN FROM FAR WESTERN NEPAL

1 Table 1.1. Socio-demographic and Behavioral Characteristics, and Human Papillomavirus (HPV) mRNA Results in Women Participating in a Health Camp in Achham District of the Far western Nepal .................................................................30

2 Table 1.2. Prevalence and Concordance of High Risk-Human Papillomavirus (HR-HPV) Test Results Between Clinician-collected and Self-collected Cervico-vaginal Samples at a Health Camp in Achham District, Nepal in 261 women ......................31

3 Table 1.3. High-risk Human Papillomavirus (HR-HPV) Test Results on Clinician-collected or Self-collected Cervico-vaginal Specimens Stratified by Liquid-based Cytology, Achham District, Nepal (N=278) .................................................................32

4 Figure 1.1 Study Sample Size Algorithm according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines .........................33

THE RELATIONSHIP BETWEEN SPOUSAL MIGRATION AND HIGH-RISK HUMAN PAPILLOMAVIRUS VIRUS INFECTION AMONG WOMEN RESIDING IN THE FAR-WEST REGION OF ACHHAM NEPAL

ix
THE ASSOCIATION BETWEEN GEOSPATIAL FACTORS AND A HUSBAND’S MIGRATORY STATUS AMONG NEPALI WOMEN REPORTING REPRODUCTIVE TRACT INFECTIONS IN THE 2011 NEPAL DEMOGRAPHIC AND HEALTH SURVEY

1 Table 3.1: Percent of married women reporting RTI symptoms by descriptive characteristics in the 2011 Nepal Demographic and Health Survey (NDHS) ..........81

2 Table 3.2: Descriptive Characteristics of Women in the 2011 Nepal Demographic and Health Survey (NDHS) by Developmental Region.....................................................84

3 Table 3.3: Multivariate logistic regression models determining the odds of reporting RTI symptoms stratified by a husband’s migration time in the 2011 Nepal Demographic and Health Survey (NDHS) .........................................................................................................................87

4 Figure 3.1: Percentage of married women reporting RTI symptoms in the 2011 Nepal Demographic and Health Survey .................................................................88

5 Figure 3.2: Difference in the percentage of RTI symptoms reported by women whose husbands are living at home and women whose husbands are living away from home in 2011 Nepal Demographic and Health Survey (NDHS) ........................................89
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTINO</td>
<td>Actinomycosis</td>
</tr>
<tr>
<td>AGUS</td>
<td>Atypical Glandular Cells of Undetermined Significance</td>
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<tr>
<td>ANM</td>
<td>Auxiliary Nurse Midwife</td>
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<td>ASC-H</td>
<td>Atypical Squamous Cell-cannot exclude HSIL</td>
</tr>
<tr>
<td>ASCUS</td>
<td>Atypical Squamous Cells of Undetermined Significance</td>
</tr>
<tr>
<td>BCC</td>
<td>Benign Cellular Changes</td>
</tr>
<tr>
<td>DHS</td>
<td>Demographic and Health Survey</td>
</tr>
<tr>
<td>EA</td>
<td>Enumerated Area</td>
</tr>
<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
</tr>
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<td>GIS</td>
<td>Geographic Information System</td>
</tr>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
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<td>HPV</td>
<td>Human Papillomavirus</td>
</tr>
<tr>
<td>HR-HPV</td>
<td>High Risk Human Papillomavirus</td>
</tr>
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<td>HSIL</td>
<td>High-grade Squamous Intraepithelial Lesion</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<tr>
<td>LMIC</td>
<td>Low and Middle Income Country</td>
</tr>
<tr>
<td>LSIL</td>
<td>Low-grade Squamous Intraepithelial Lesion</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger Ribonucleic Acid</td>
</tr>
<tr>
<td>NFCC</td>
<td>Nepal Fertility Care Center</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>NDHS</td>
<td>Nepal Demographic and Health Survey</td>
</tr>
<tr>
<td>NLSS</td>
<td>Nepal Living Standards Survey</td>
</tr>
<tr>
<td>RH</td>
<td>Reproductive Health</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous Cell Carcinoma</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic Status</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually Transmitted Infection</td>
</tr>
<tr>
<td>STD</td>
<td>Sexually Transmitted Disease</td>
</tr>
<tr>
<td>UNSAT</td>
<td>Unsatisfactory</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
<tr>
<td>VDC</td>
<td>Village Development Committee</td>
</tr>
<tr>
<td>WNL</td>
<td>Within Normal Limits</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION

Human Papillomavirus (HPV) is a common sexually transmitted infection (STI) that is a necessary component for the development of cervical cancer. Researchers currently agree on at least 150 known genotypes of HPV, of which 18 genotypes are considered to be either high risk or probable high risk (HR-HPV) (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) [1]. It is expected that over 80% of the female population will be exposed to HPV at some point during their lifetime. However, upwards of 90% of women infected with HPV “clear” (HPV DNA undetectable through testing) within 1-2 years [2]. Women who do not clear their HPV infection are at risk for developing cervical malignancies that could develop into cervical cancer within 5-15 years. Invasive cervical cancer is the 4th most common cancer among women worldwide, with an estimated 527,624 new cases and 265,653 deaths annually [3] with the majority of cervical cancer cases being squamous cell carcinoma followed by adenocarcinomas [4]. Worldwide, mortality rates of cervical cancer are substantially lower than cervical cancer incidence with a ratio of mortality to incidence of 50.3%.

The World Health Organization (WHO) Information Centre on HPV and Cervical Cancer states the incidence of cervical cancer in Nepal is 14.9 per 100,000 people, making Nepal a country with one of the highest rates of cervical cancer in the world [5].
Approximately 2,150 cases of cervical cancer occur in Nepal each year, resulting in over 1,100 deaths for a mortality rate of over 50% [5]. Despite Nepal’s epidemic of cervical cancer, there is very little information in Nepal on the social determinants of HPV infections nor is there a national cancer registry. Previous studies estimate the prevalence of high-risk HPV types in other South Asian countries to be as high as 14% in the general adult population [6, 7]. Rates of cervical cancer in South Asia range from 5.3 per 100,000 people in Afghanistan to 20.2 per 100,000 people in India [8]. More info on HPV and cervical cancer is needed in order to better address Nepal’s cervical cancer epidemic.

It is unknown if international and domestic migration is associated with HPV infection in Nepal. The pool of Nepal’s international and domestic migrant workers is quite large. In Nepal, a country of 29 million people, over 2.2 million individuals are engaged in migrant work [9, 10]. These workers annually send approximately 3 billion dollars in remittance to Nepal, comprising 15% of Nepal’s GDP [11]. Half of Nepali migrant workers come from Nepal’s Far-West developmental region where less than 20% of Nepal’s population resides [12]. Because of India’s and Nepal’s open border policy and the proximity of the Far-West region of Nepal to India, 70% of Nepali migrant workers from the Far-West region travel to India for work. Over 75% of the remaining 30% of migrant workers travel to Qatar, Saudi Arabia, or Malaysia [13, 14]. Migratory work is a cyclical phenomenon in Far-West Nepal. The majority of Nepali migrant workers from the Far-West region return to Nepal after several months, however almost 15% of the migrant working population returns home after 5 years [15].

In order to determine if labor migration in Nepal is associated with HPV and abnormal cervical cytology, it is necessary to properly define migration for employment.
Migrant work can be highly diverse and the vernacular used to describe it so abstruse that it can be difficult to precisely describe what effect migratory work has on a population’s health. For this reason it is important to use a satisfactory definition of migratory work for research purposes. Nepal has been abiding by the treaties, regulations, and terminology of the International Organization for Migration (IOM) since joining the organization in 2006. The IOM recognizes that there is no universally accepted definition for "migrant" on an international level [16] and defers to the United Nations definition of “migrant” as “an individual who has resided in a foreign country for more than one year irrespective of the causes, voluntary or involuntary, and the means, regular or irregular, used to migrate” [17]. However, the IOM acknowledges that common usage of the term “migrant” includes certain kinds of shorter-term migration, such as seasonal farm-workers who travel for short periods to work planting or harvesting farm products. The lack of clear terminology regarding migration has compelled the IOM to create a “Glossary on Migration” [16] where subdivisions of the term “migrant” are defined in greater detail. Because Nepal has been abiding by the IOM’s rules and regulations for migrant workers, this dissertation will use IOM’s definition of “migrant” stated above as, “an individual who has resided in a foreign country for more than one year irrespective of the causes, voluntary or involuntary, and the means, regular or irregular, used to migrate”, in this study. However, we will also consider working outside of Nepal for less than one year to be migrant work because of the possibility that working away from home for less than one year could be associated with HPV infection and developing an abnormal cervical cytology (Appendix A).
Circular migration, where an individual leaves their partner for work and returns periodically [18] is correlated with an increased risk of sexually transmitted infections (STIs) [19]. By engaging in STI risk behavior, such as using commercial sex workers, migrant men have the potential to become infected with an STI while working abroad and transmit their infection to their primary partner when they return home [20].

Complicating the cycle of migration and acquiring STIs, migratory men sometimes establish parallel partnerships between work and home, forming long-term bridges which could facilitate the spread of STIs [21]. It is not only migratory men who facilitate the transmission of STIs; the partners left at home have the potential to also engage in risky sexually behavior [22]. Previous studies have shown the longer wives are away from their migrant husbands, the more likely they are to engage in STI risk behaviors [23]. Rural women whose husbands lived overseas were at an elevated risk to have any HPV infection compared to women whose husbands lived with them [24].

Only a handful of studies have investigated the association of cyclical migration and STIs in Nepal, most of which focus on HIV. Labor migrants make up 41% of total known HIV infections in Nepal [25], while 8% and 22% of returning migrant workers from the Nepali district of Doti were found to be infected with HIV and syphilis respectively [26]. Other studies drawing samples from the Far-Western communities of Achham, Doti, and Kailali reported that about 6–10% of men returning from Mumbai compared to up to 4% men working in other parts of India and up to 3% of those working in Nepal were HIV-positive [26, 27]. Similar to other parts of the world, cyclical migration of married Nepali men could increase the risk of STI for the wives of migrant workers.
Previous research on labor migration in other countries found different levels of SES to be highly associated with varying rates of STIs in migrant workers [28, 29]. Latino day laborers in California who reported frequent exposure to racism were more likely to engage in high risk sexual behavior when compared to day laborers who did not report frequent exposure to racism [30]. Over half of migrant workers residing in the urban Chinese areas of Shenzhen, Guangzhou and Wuhan have received education on STIs, suggesting that a lack of education in migrants is associated with contracting STIs during migration [31].

In Nepal, risk factors for contracting STIs differ between the wives of migrant workers and their migrant husbands. Literacy, education, and age at first marriage were consistently found in multiple studies to be risk factors associated with STIs in the wives of Nepali migrant workers [32, 33]. Nepali women who are knowledgeable about the risks for contracting HPV are more likely to have a university degree, never have been married, and are more likely to be young [34]. Conversely, alcohol consumption, amount of time away from home, country of migration, the use of commercial sex workers, age, and education were found to be significantly associated with STIs in married male Nepali migrant workers [25, 32, 33, 35]. Knowing the STI risk factor differences between males and females when investigating the association between STIs and Nepali labor migration is important. Important risk factors that are not considered during a study could potentially introduce gender biases into analyses of migration and STIs.

The use of commercial sex workers is one of the most common ways Nepali migrant workers are exposed to STI while away from home. Lack of family restraint, alcohol consumption, and low HIV/STI knowledge are known to create conditions where
it is socially acceptable among migrant workers and their peers to use commercial sex workers [35, 36]. A 2010 cross sectional study conducted in 110 migrant workers who have returned home within the last 2 years found that 31% of returning migrants used commercial sex services at least once while away from home [37]. Poor socio-economic status, caste-related discrimination, and lack of employment opportunities push large groups of young Dalits to migrate to India for employment, where they engage in sex with female sex workers at high rates [25]. It is possible that through the use of commercial sex workers while working abroad, Nepali migrant workers are contracting HPV and transmitting it to their wives when they return home.

Given the dearth of information regarding HPV infections in Nepal, this study proposes an assessment of risk factors and determinants of high-risk HPV in Nepali women residing in Achham district of Far-West Nepal (Figure 1), focusing on women whose husbands have or are currently migrating for work. We hypothesize that women whose husbands engage in migrant work will be at a greater risk for HPV infection than women whose husbands do not engage in migrant work. The burden of increased risk factors for HPV infection could result in increases in HPV prevalence in the wives of Nepali migrant workers.
Figure 1: Achham District in the Far-West Development Region of Nepal in Relation to Nepal’s Capital, Kathmandu.

This dissertation is significant because the increasing amount of Nepalese who participate in both international and domestic migratory work represents a potentially new mechanism for the introduction of HPV infections in Nepal. Chapter 2 of this dissertation assesses the distribution of HR-HPV and the type-specific prevalence of HR-HPV16/18/45 among women in rural Far Western Nepal while also comparing the self-collection of cervico-vaginal specimens with clinician-collected specimens as a method of sample collection for HPV screening. Chapter 3 of this dissertation investigates the association between a husbands’ migration for employment and HR-HPV infection and abnormal cervical cytology among their spouses in Nepal’s Far West Achham District. Lastly, Chapter 4 of this dissertation investigates the link between rates of STD symptoms and regional differences among migrant workers using the nationally representative Nepal Demographic and Health Survey.
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CHAPTER 2

ASSESSMENT OF HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTIONS USING CLINICIAN- AND SELF-COLLECTED CERVICAL SAMPLING METHODS IN RURAL WOMEN FROM FAR WESTERN NEPAL

by

DEREK C. JOHNSON, MADHAV P. BHATTA, JENNIFER S. SMITH, MIRJAM-COLETTE KEMPF, THOMAS BROKER, STEN H VERMUND, ERIC CHAMOT, SHILU ARYAL, PEMA LHAKI, SADEEP SHRESTHA

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14
Abstract

Nepal has one of the highest cervical cancer rates in South Asia. Only a few studies in populations from urban areas have investigated type specific distribution of human papillomavirus (HPV) in Nepali women. Data on high-risk HPV (HR-HPV) types are not currently available for rural populations in Nepal. We aimed to assess the distribution of HR-HPV among rural Nepali women while assessing self-collected and clinician-collected cervico-vaginal specimens as sample collection methods for HPV screening. Study participants were recruited during a health camp conducted by Nepal Fertility Care Center in Achham District of rural far western Nepal. Women of reproductive age completed a socio-demographic and clinical questionnaire, and provided two specimens; one cervical-vaginal specimen using a self-collection method and another cervical specimen collected by health camp auxiliary nurse midwives during a pelvic examination. All samples were tested for 14 different HR-HPV mRNA and also specific for HPV16/18/45 mRNA. Of 261 women with both clinician- and self-collected cervical samples, 25 tested positive for HR-HPV, resulting in an overall HR-HPV prevalence of 9.6% (95% confidence Interval [CI]: 6.3 – 13.8). The overall Kappa value assessing agreement between clinician- and self-collected tests was 0.64 (95% CI: 0.48 – 0.84), indicating a “good” level of agreement. Abnormal cytology was reported for 8 women. One woman identified with squamous cell carcinoma (SCC), and 7 women with high grade squamous intraepithelial lesions (HSIL). Seven of the 8 women tested positive for
HR-HPV (87.5%) in clinician-collected samples and 6 in self-collected samples (75.0%).

This is the first study to assess HR-HPV among rural Nepali women. Self-collected sampling methods should be the subject of additional research in Nepal for screening HR-HPV, associated with pre-cancer lesions and cancer, in women in rural areas with limited access to health services.
Introduction

The World Health Organization (WHO) Information Centre on Human Papillomavirus (HPV) and Cervical Cancer states that the incidence of cervical cancer in Nepal is 24.2 per 100,000, making Nepal a country with one of the highest cervical cancer rates in South Asia[1]. Over 2100 cases of cervical cancer are reported in Nepal each year, with a case-fatality rate of over 50%. However, this estimate is most likely an underestimation of the actual cases due to lack of national cancer registry as well as screening and follow-up [1,2]. Epidemiologic and virologic data indicate that oncogenic HPVs are the primary (and necessary) causal agents of cervical cancer [2,3]. Worldwide HPV16 and HPV18/45 account for over 70% of the high risk HPV strains (HR-HPV) associated with cervical cancer. While it is assumed HR-HPV types follow similar distributional patterns in invasive cervical cancer across the globe, the actual distribution of HPV is not known for several resource-limited countries, including Nepal [4].

Previous studies estimate the prevalence of HR-HPV types in other South Asian countries to be between 8-14% in the general female population [5,6]. However, currently, there are no official WHO estimates of the prevalence or type-specific distribution of HPV in representative population-based samples of women in Nepal.

To date, information on HPV in Nepal has been limited to study samples drawn from populations in selected urban areas in the central region of the country, with an emphasis on women with invasive cervical cancer[7,8]. An International Agency for Research on Cancer (IARC) study reported a prevalence of 8.6%, 6.1%, and 1.9% for any HPV, HR-HPV types, and HPV16, respectively among 932 married women aged 15-59 years from a general population in Bharatpur, a city in the south-central part of Nepal [7].
Among a smaller subset of women diagnosed with invasive cervical cancer, Bhusal and colleagues found that HPV16 was the most common HR-HPV (50% of HR-HPV) detected followed by HPV18 (18% of HR-HPV) [8]; however, this result from 44 cancer patients cannot be generalizable. The distribution of HPV in the general population including cervical cancer patients in various parts of the country is still unknown.

There is considerable variation in the limited number of cervico-vaginal and cervical cancer reports across Nepal, with most reports originating from hospital-based registries because there is no national cancer registry [9-12]. The far western region of Nepal is very rural with limited access to health services made worse by extreme topography, economic, socio-cultural, and ethno-linguistics regional differences. This area is known to have a higher prevalence of risk factors for poor reproductive health compared to the general Nepali population, which may exacerbate the rates of HPV infections and cervical cancer in the region[5,13]. Only 52% of women in far western Nepal give birth in the presence of a skilled birth attendant compared to the national average of 82% [14,15]. The infant mortality rate in Achham is 61 per 1,000 and the maternal mortality rate is 950 per 100,000, both of which are higher than the national average of 42 per 1,000 and 170 per 100,000, respectively [14]. A significant proportion of the adult male population in far western Nepal seasonally migrate to cities in India to work as migrant laborers, which could put them at an increased risk for sexually transmitted infections (STIs) including HPV [16].

The introduction of self-sampling for HPV detection in Nepal could help mitigate the problems of insufficient access to cervical screening. HPV self sampling has been shown to have high rates of agreement with physician collected HPV samples [17,18] and
in most settings self collection has demonstrated a better ability to detect cervical abnormalities of CIN2+ or greater than Pap smear testing in women with low socioeconomic status[19]. Providing a self sampling option for women living in less developed countries could also bolster screening participation by making screening more convenient and private for women [20].

The regional differences in the risk profile for HPV infections and cervical cancer within Nepal necessitate the need for assessing the prevalence and type-specific distribution of HR-HPV infections in different regions of the country. Currently, there are no estimates of HPV prevalence or distribution in Nepal’s rural populations. This is the first study to assess the distribution of HR-HPV and the type-specific distribution of HR-HPV16/18/45 among women in rural far western Nepal. Our study also compares the self-collection of cervico-vaginal specimens with clinician-collected specimens as a method of sample collection for HPV screening in a resource-limited setting.

Materials and Methods

Ethics Statement

The Institutional Review Board at the University of Alabama at Birmingham and Ethics Review Board at the Nepal Health Research Council approved this study.

Study site and population

This study was conducted in the Sanphebagar Village Development Committee (VDC) within the Achham District. Achham is one of the most remote districts in far western Nepal. Due to poor and mountainous road conditions, it takes over 13 hours to
drive the 500 km from Kathmandu to Mangalsen, the Achham district headquarter. Achham district covers an area of 1,680 km$^2$ and only 36 of its 75 VDCs are connected by roads. According to the 2011 Nepal Demographic Health Survey, the population of females in Achham District was 141,643, which included 34,204 adolescent girls (aged 10-19), 60,937 women of reproductive age (aged 15-49) and 21,143 seniors (aged 60 years and above)[13]. The district’s population experiences a greater burden of risk factors for poor health outcomes, has higher rates of seasonal migration and access to a fewer health care facilities compared to the general Nepali population [21]. Currently, only two hospitals operate in Achham District; the government’s district hospital in Mangalsen and Bayalpata Hospital, operated by non-profit organization Nyaya Health in collaboration with the Nepali government [13]. Achham district is also served by 12 health posts and several temporary primary health care outreach clinics primarily conducted by various non-governmental organizations (NGOs).

Women of reproductive age were recruited from the Sanphebagar VDC, approximately 25 km from Mangalsen, during a one day health camp conducted on July 5$^{{\text{th}}}$, 2013 by Nepal Fertility Care Center (NFCC). Established in 1988, NFCC is a Nepali NGO with the primary objective of complementing and supplementing the Government of Nepal’s national reproductive health programs [22]. Health camps are regularly conducted by NFCC and advertised ahead of time through networking with government bodies at all levels of administration from the center to the VDC level. Women who attended the health camp received a wide array of routine free reproductive health services including family planning counseling and sexually transmitted infection (STI) testing. Trained Auxiliary Nurse Midwives (ANMs) with several years of clinical
experience performed pelvic examinations while volunteer health professionals experienced in conducting surveys assisted in recruitment coordination and data collection during the health camp. Women were included in the study if they were of reproductive age (at least 16 but no more than 60 years old) and had a cervix but not menstruating and not pregnant during the visit. Consent forms were distributed and read to each participant before they agreed to enroll in the study. Each form was signed and dated by the study participant, a witness, and the study coordinator. A woman who opted not to participate in the research study was provided the same clinical services during the health camp as those participating in the research study.

*Survey Instrument Development and Administration*

A questionnaire to assess socioeconomic, clinical, reproductive health, and migration related factors was developed for this study. The questionnaire was first developed in English, then translated into Nepali, and then translated back to English independently for quality control. NFCC staff assisted in the development of the questionnaire in order to insure that the survey questions were culturally sensitive and appropriate. In order to help assure the validity and comprehensiveness of the survey instrument, questions were based on English translations of the Demographic and Health Survey [23], and the National Living Standards Survey (NLSS) [24].

A dialect of the Nepali language known as “Dotyali” is spoken in far western Nepal. However, the term “Dotyali” is a macro-term used to describe a wide variety of local dialects in far western Nepal [25]. The local Dotyali/Nepali dialect spoken in Achham does not have a written form; thus, making it difficult to translate the questionnaire into
the local dialect. People living in Achham, however, speak and understand Nepali. In order to ensure that participants fully understood each question and were comfortable while completing the survey, female interviewers who spoke the local Achham dialect were recruited locally.

*Biospecimen Collection and Laboratory Analyses*

Each study participant was asked to provide two specimens during her health camp visit. One specimen was self-collected, using the APTIMA Cervical Specimen Collection and Transport (CSCT) kit (Hologic/Gen-Probe, San Diego, CA), and another specimen was collected by a health camp ANM during pelvic examination. While waiting for their pelvic examination, women were given instructions on self-collection of a cervico-vaginal sample. A health staff member, centrally trained to give instructions on self-sampling procedures, instructed the women to insert a cytobrush (Hologic/Gen-Probe, San Diego, CA) into the vagina as far as possible, rotate it 5 times in each direction, then swirl the cytobrush in the APTIMA specimen transport medium (Hologic/Gen-Probe, San Diego, CA). Health camp ANMs collected clinician cervical specimens by inserting a cytobrush into the cervical canal and rotating 3-5 times, withdrawing and then rotating firmly around the full circumference of the transformation zone. Cytobrushes were then swirled in ThinPrep (TP) PreservCyt medium (Hologic/Gen-Probe, San Diego, CA).

Both clinician- and self-collected cervico-vaginal samples were transported to the Hologic/Gen-Probe, Inc. laboratory in San Diego for HPV testing. Laboratory testing of HPV was performed using a generic APTIMA HR-HPV mRNA (APTIMA HPV)
(Hologic/Gen-Probe, San Diego, CA) and then specific genotyping using APTIMA HPV16 18/45 Genotype (Hologic/Gen-Probe, San Diego, CA) Assays [26]. Samples were first tested using the APTIMA HPV Assay to detect the presence of E6/E7 mRNA from at least one of 14 different types of HR-HPV (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Samples testing positive by APTIMA HPV Assays were retested with APTIMA HPV16 18/45 Genotype Assay to detect the presence of HPV16 or HPV18/45 genotypes. Cervical cytology was assessed for research purposes using clinician-collected ThinPrep PreservCyt medium (Hologic/Gen-Probe, San Diego, CA), with results classified according to the Bethesda criteria. Women with atypical squamous cells of undetermined significance (ASCUS) or worse were referred to either the government’s district hospital in Mangalsen or Bayalpata Hospital for additional testing and follow-up.

Statistical analysis

The mean, standard deviation, median, inter-quartile range, and percentages were calculated for self-reported demographic, socioeconomic, and behavioral characteristics. An exact version of McNemar chi-square test was used to test for differences in HPV prevalence in clinician vs. self-collected specimens. Positive and negative agreement percentages and Kappa statistics values were used to describe agreement in detecting HR-HPV between clinician- vs. self-collected samples. We report point estimates for prevalence, % concordance, and Kappa statistics and associated 95% confidence intervals (95% CI). SAS version 9.2 (SAS Institute, Cary, NC) was used to perform all statistical analyses.
Results

In total, 389 women registered for the health camp. Three hundred and sixty three women completed a survey; clinician-collected specimens were available from 278 women while self-collected specimens were available from 300 women (Figure 1.1). Eight of the 300 self-collected samples were excluded due to invalid HPV test results. Thirty one women with a self-collected specimen did not have a clinician-collected specimen; 17 women with a clinician-collected specimen did not have a self-collected specimen. In all, 261 women had both self- and clinician-collected valid samples, with self-reported questionnaires being available for 248 of these women (Figure 1.1).

The median age of the participants was 33 years (IQR: [26 – 40]) and the median age at first marriage was 17.5 years (IQR 15 - 19). The median number of children per woman was 3.0 (IQR: [2.0 – 4.0]) and 56% of women currently used some form of contraception. Over half of the study participants reported having heard of cervical cancer (58.1%), while only 16% reported having heard of HPV (Table 1.1).

Twenty women tested positive for HPV in clinician-collected samples while 17 women tested positive for HPV in self-collected samples and 25 out of 261 individuals tested positive for HR-HPV in either sampling method, resulting in an over-all HR-HPV prevalence of 9.6% (95% CI 6.3 – 13.8). Five individuals who tested positive for HR-HPV tested positive for HPV16, resulting in an overall prevalence of 1.9% (5 HPV16+/261 individuals with both a clinician- and self-collected test) for HPV16. Only one individual tested positive for HPV18/45. Thus, among those with HR-HPV, only 24% (6/25) were either type HPV16 or HPV18/45. Five individuals tested positive for HR-
HPV in the self-collected specimens, but did not test positive for HR-HPV in the clinician-collected samples. Eight individuals tested positive in clinician-collected samples tests but not in the self-collected samples.

The non-stratified Kappa value assessing agreement between the HR-HPV test results using clinician- and self-collected specimens was 0.62 (95% CI 0.43 – 0.81), indicating a “good” level of agreement (Table 1.2). The overall negative agreement was 94.7% (95% CI 93.3 – 96.2) and overall positive agreement was 48.0% (95% CI 30.1 – 65.9) (Table 1.2). There was 100% agreement between self-collected and clinician-collected sample test results for women who tested positive for HPV16. The Kappa value for women who tested positive for HR-HPV other than HPV16 or HPV 18/45 was 0.49 (95% CI 0.26 – 0.73). The negative agreement for women who tested positive for HR-HPV other than HPV16 or HPV 18/45 was 94.9% (95% CI 93.5 – 96.3) and the positive agreement 35.0% (95% CI 12.1 – 57.9) (Table 1.3).

ThinPrep (TP) (Hologic/Gen-Probe, San Diego, CA) cervical cytology readings based on clinician-collected samples were available for 278 women. High grade cytological abnormality was reported for 8 women, with one woman identified with squamous cell carcinoma (SCC), and 7 women with high grade squamous intraepithelial lesions (HSIL). Of the 8 women with either SCC or HSIL, 7 of them tested positive for HR-HPV (87.5%) in clinician-collected samples and 6 in self-collected samples (75%). However, 4 of the 7 women who tested positive for HR-HPV tested positive for HPV16 or HPV 18/45 in clinician-collected samples versus 3 in the self-collected samples (Table 1.3). Sixteen ThinPrep (TP) (Hologic/Gen-Probe, San Diego, CA) samples were unable to
be tested for cytology due to inadequate amount of specimen from spillage or evaporation during shipment or other sampling issues.

**Discussion**

To the best of our knowledge, this is the first HR-HPV prevalence study conducted among rural women from far western Nepal. Of 261 women with both clinician- and self-collected cervico-vaginal specimens who were tested for 14 HR-HPV types, 25 women tested positive with an overall HR-HPV prevalence of 9.6% (95% CI 6.3 – 13.8). A non-stratified Kappa value of 0.62 indicated “good” agreement between self- and clinician-collected HPV samples. The cytology of 8 women indicated either SCC or HSIL, of which 7 women who had clinician-collected samples tested positive for HR-HPV and 6 women who had self-collected samples tested positive for HR-HPV. Our study’s prevalence of HR-HPV (9.6%) is higher than the prevalence of HR-HPV (6.1%) found in Bharatpur, Nepal [7] and is similar to the prevalence of HR-HPV (9.9%) in India’s northern state of Uttar Pradesh, which borders central and western Nepal [27]. In each of these studies, HPV16 was the most common type of HR-HPV, while HPV18/45 was less common. While our study was limited to testing only HPV16 18 and/or 45 genotypes, it could still detect the presence of 14 different HR-HPV, without specific genotypes. Our findings suggest the distribution of HR-HPV follows the general HPV distribution patterns found throughout South Asia [28] and is similar to the distribution of HR-HPV in most regions of the world [28,29].

Only one woman tested positive for HPV18/45 (the APTIMA HPV 16 18/45 genotype assay can differentiate HPV 16 from HPV 18 and/or HPV 45, but does not
differentiate between HPV 18 and HPV 45), yet HPV genotypes 18 and 45 represented approximately 20% of HPV strains linked to cervical abnormalities in studies conducted by IARC and Bhusal [7,8]. While the proportion of women testing positive for HPV18/45 in our study is slightly lower than the world-wide distribution of HPV18/45 [28,29], it is likely that our study’s lower prevalence rates of HPV16 and HPV18/45 are due to small sample size and not attributable to a different distribution of HPV16 or HPV18/45.

The number of women with an abnormal cytology reading was low. However, these abnormalities pose a significant health risk to women given the dearth of reproductive health care access in rural Nepal. Despite the official Nepali government protocol of cervical screening using visual inspection with acetic acid (VIA), a paltry number of women actually undergo cervical screening each year [30]. Without proper access to reproductive health care, minor complications could result in bigger complications over time due to a lack of access to health care. Therefore, it is important to advise women with even minor cervical abnormalities on the importance of proper follow-up.

Non-stratified kappa values assessing the testing agreement between clinician- and self-collected specimens was 0.62 (95% CI 0.43 – 0.81), indicating a good level of agreement between the two sampling methods. Several studies conducted in rural areas of developing countries which have limited access to cervical screening have also found the results of HPV testing using self-collected samples comparable to the results of HPV testing using clinician-collected samples [18,31,32]. Other studies have suggested that HPV DNA tests in self-collected samples as a primary screening method for cervical cancer is superior to the IARC recommended visual inspection with acetic acid method of cervical screening [18,33].
Only a few studies have assessed the utility of testing for HPV using self-collected samples in less-developed countries [34-36]. The majority of these studies detect the presence of HR-HPV DNA, the HPV virus genome [34], while only a few studies have utilized HR-HPV messenger RNA (mRNA) tests, which detect the expression of genes related to E6/E7 [36]. Previous clinical studies suggest that testing for HR-HPV E6/E7 mRNA using the APTIMA HPV assay results in similar sensitivity and higher specificity for detecting high-grade lesions compared to DNA based tests [37,38]. However, the HPV prevalence as measured by the APTIMA HPV assay may be lower as compared to prevalence determined by a DNA based test without impacting clinical sensitivity for detection of cervical disease. This could result in underestimation of the actual prevalence of HPV in the population.

This cross-sectional study could not assess lifetime exposure to HPV, nor could it measure HPV persistence, which precedes and predicts the development of cervical precancerous lesions. However, while our study was not longitudinal, HPV prevalence is correlated with the risk of developing cervical cancer [39] and can still remain a good surrogate, specifically in a resource-limited setting like Nepal with limited data on HPV infection and cervical cancer. Our study’s small sample size hinders the precision of our prevalence and concordance estimates, which is indicated by the size of the confidence intervals. However, we were able to collect a wide array of data in this remote region in Nepal, which included both clinician- and self-collected samples in addition to a survey on demographic, socioeconomic, and behavioral characteristics. Our study sample may not be representative of the far western region of Nepal and may not be generalizable to the entire district of Achham. There are 9 districts in the far western Development Region.
of Nepal, covering the three major ecological zones (Mountains, Hills, and Terai). Achham District lies in the ecological “Hills” zone which is geographically and ethnically different from the other districts/ecological zones in the far western region. Therefore, it is difficult to assess any selection bias during recruitment of participants.

In summary, our study assessed the prevalence of HR-HPV among women in a rural region of far western Nepal. Furthermore, our study demonstrated that the self-collected cervical sample for HPV testing is a viable method with a high level of concordance with clinician-collected cervical samples. Self-sampling, while not as sensitive as clinician-collected specimens for detecting prevalent HR-HPV, associated with cervical pre-cancer or cancer [18], should be the subject of additional research as a method for screening women in rural areas with limited access to health services.
### Table 1.1. Socio-demographic and Behavioral Characteristics, and Human Papillomavirus (HPV) mRNA Results in Women Participating in a Health Camp in Achham District of the Far western Nepal

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Positive for HR-HPV(^{\ast}) (n=261)</th>
<th>Mean (SD), median (IQR) or Frequency (%)(^{\dagger})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Self- Collected Sample</td>
<td>20 (7.7)</td>
</tr>
<tr>
<td></td>
<td>Clinician- Collected Sample</td>
<td>17 (6.5)</td>
</tr>
<tr>
<td></td>
<td>Either Sample**</td>
<td>25 (9.6)</td>
</tr>
<tr>
<td>Age in years</td>
<td>Mean (SD)</td>
<td>33.8 (8.8)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>33 (26 – 40)</td>
</tr>
<tr>
<td>Age at first marriage (n=240)</td>
<td>Mean (SD)</td>
<td>17.3 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>17.5 (15 – 19)</td>
</tr>
<tr>
<td>Number of Children (n=248)</td>
<td>Mean (SD)</td>
<td>3.2 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>3.0 (2.0 – 4.0)</td>
</tr>
<tr>
<td>Husband ever migrated for work (n=240)</td>
<td>Yes</td>
<td>121 (50.4)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>119 (49.6)</td>
</tr>
<tr>
<td>Heard of cervical cancer (n=246)</td>
<td>Yes</td>
<td>143 (58.1)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>103 (41.9)</td>
</tr>
<tr>
<td>Heard of HPV (n=223)</td>
<td>Yes</td>
<td>36 (16.1)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>187 (83.9)</td>
</tr>
<tr>
<td>Currently use contraception (n=234)</td>
<td>Yes</td>
<td>132 (56.4)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>102 (43.6)</td>
</tr>
</tbody>
</table>

\(^{\dagger}\) SD= Standard Deviation; IQR=Inter-quartile range

\(^{\ast}\) High Risk HPV (HR-HPV) defined as testing positive for one of the following genotypes: (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

\(^{\dagger}\) Tested positive for HR-HPV in either clinician- or self-collected biospecimen.
Table 1.2. Prevalence and Concordance of High Risk-Human Papillomavirus (HR-HPV) Test Results Between Clinician-collected and Self-collected Cervico-vaginal Samples at a Health Camp in Achham District, Nepal in 261 women.

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinician-collected sample (95% CI)§</td>
<td>Self-collected sample (95% CI)§</td>
</tr>
<tr>
<td>HR-HPV* (n=25)</td>
<td>7.7 (4.4 – 10.9)</td>
<td>6.5 (4.1 – 10.2)</td>
</tr>
<tr>
<td>HPV16 Only (n=5)</td>
<td>1.9 (0.9 – 3.5)</td>
<td>1.9 (0.9 – 3.5)</td>
</tr>
<tr>
<td>HR-HPV not including HPV16</td>
<td>5.8 (3.0 – 9.1)</td>
<td>4.6 (2.7 – 7.9)</td>
</tr>
<tr>
<td>(n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-HPV in women testing</td>
<td>87.5 (46.7 – 99.3)</td>
<td>75.0 (35.6 – 95.5)</td>
</tr>
<tr>
<td>positive for HSIL or SCC**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

§95% CI = 95% Confidence Interval;  
*High-Risk HPV (HR-HPV) defined as testing positive for one of the following genotypes: (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68);  
**HSIL = High-grade Squamous Intraepithelial Lesion; SCC = Squamous Cell Carcinoma
Table 1.3. High-risk Human Papillomavirus (HR-HPV) Test* Results on Clinician-collected or Self-collected Cervico-vaginal Specimens Stratified by Liquid-based Cytology, Achham District, Nepal (N=278)

<table>
<thead>
<tr>
<th></th>
<th>SCC</th>
<th>HSIL</th>
<th>ASC-H</th>
<th>LSIL</th>
<th>AGUS</th>
<th>ASCUS</th>
<th>UNSAT</th>
<th>WNL/BCC/ACTINO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cytology Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-HPV (Clinician-collected Specimen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 16/18/45</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Other HR-HPV</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>HR-HPV (Self-collected Specimen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 16/18/45</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Other HR-HPV</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>12</td>
</tr>
</tbody>
</table>

*APTIMA HR-HPV mRNA Assay (Hologic/Gen-Probe, San Diego, CA)
**ThinPrep PreservCyt medium ((Hologic/Gen-Probe, San Diego, CA)

**SCC = Squamous Cell Carcinoma; HSIL = High-grade Squamous Intraepithelial Lesion; ASC-H = Atypical Squamous Cell-cannot exclude HSIL; AGUS = Atypical Glandular Cells of Undetermined Significance; LSIL = Low-grade Squamous Intraepithelial Lesion; ASCUS = Atypical Squamous Cells of Undetermined Significance; UNSAT = Unsatisfactory; WNL = Within Normal Limits; BCC = benign cellular changes; ACTINO = Actinomycosis
Figure 1.1 Study Sample Size Algorithm according to strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines
References


CHAPTER 3

THE RELATIONSHIP BETWEEN SPOUSAL MIGRATION AND HIGH-RISK HUMAN PAPILLOMAVIRUS VIRUS INFECTION AMONG WOMEN RESIDING IN THE FAR-WEST REGION OF ACHHAM NEPAL

by

DEREK C JOHNSON, PEMA LHAKI, MADHAV P BHATTA, MIRJAM-COLETTE KEMPF, PANKAJ BHATTARAI, ERIC CHAMOT, SHILU ARYAL, JENNIFER S SMITH, STEN H VERMUND, SADEEP SHRESTHA

Submitted to Gynecologic Oncology
Format adapted for dissertation
Abstract

To date, information on human papilloma virus (HPV) infection and cervical cancer morbidity in Nepal has been limited. Our study aims to investigate the association between the labor migration of a woman’s husband and the distribution of high-risk HPV (HR-HPV) infections as well as the association between the labor migration of a woman’s husband and the abnormal cervical cytology in women living in the rural Far-West Nepal district of Achham. Women were surveyed during a Nepal Fertility Care Center reproductive health camp. Trained health staff with several years of clinical experience collected cervical specimens for cervical cytology and HPV testing. Volunteer nurses and health professionals assisted in collecting survey data. Univariate and multivariable statistical tests were used to determine the association of covariates with a positive HR-HPV test, abnormal cervical cytology status, and a husband’s migration status. Our study sample consisted of 265 women. HR-HPV prevalence was 7.5% and the prevalence of abnormal cervical cytology, defined as atypical glandular cells of undetermined significance or worse using the Bethesda system, was 18%. The mean age for participating women was 33.9 (SD 8.8) years. Half of study participants had husbands who migrated for work at one time (50.8%). Women under the age of 35 were significantly less likely to test positive for HR-HPV than women who were older than 35 years of age (OR 0.21, 95% CI 0.07 – 0.63). Women whose husbands migrated outside of Nepal for work were less likely to have an abnormal cervical cytology test result than women whose husbands have never migrated for work after adjusting for additional
covariates (OR 0.38, 95% CI 0.17 – 0.83). Our study assessed risk factors associated with women whose husbands migrate for employment and testing positive for HR-HPV and abnormal cervical cytology in Far-West Nepal. Older age was associated with testing positive for HR-HPV, while having a husband who has migrated for work was protective against abnormal cytology outcomes. Our results suggest that a husband’s migration for work at a younger age could be delaying HR-HPV infections and abnormal cervical cytology in married women.
Background

In 2012, 528,000 new cases of cervical cancer were diagnosed, and 266,000 women died of the disease, nearly 90% of them in low- to middle-income countries [1]. Barriers to cervical cancer screening, such as access to health care, low levels of screening knowledge, and a lack of perceived benefits from screening impede early cervical cancer diagnosis in low and middle income countries (LMICs) [2, 3]. In Nepal, where routine cervical screening is not widely available, cervical cancer is usually only detected when it is at an advanced stage which results in high mortality.

Due to a current scarcity of cervical screening and treatment programs, it is important to identify sub-populations of Nepali women who are at a greater risk for cervical cancer. In addition to risky sexual behaviors, social factors such as education, wealth, and marital status are associated with abnormal cervical cytology outcomes [4-7]. A lack of work during the agricultural off-season has motivated a large proportion of men to migrate to urban areas within Nepal, India, or other countries for employment, potentially making migrant workers vulnerable to sexually transmitted infections (STIs) including high-risk human papillomavirus (HR-HPV). It is possible that male labor migration is also associated with the risk of developing cervical cancer in Nepal.

Over 2.2 million Nepalese are engaged in international and domestic labor migration; the Nepal Central Bureau of Statistics estimates that over half of Nepali households in the Far-Western development region of Nepal have at least one family member who participates in some form of migratory work [8]. This large group of highly
mobile Nepali migrant workers poses unique health challenges for Nepal [9]. Male Nepali migrant labor has been associated with increased risk of STIs including human immunodeficiency virus (HIV). In far western Nepal [10, 11] approximately 41% of HIV cases in Nepal occur in seasonal migrant laborers [12]. By analogy, it is therefore possible that male migrant work in Nepal could be a factor contributing to cervical cancer among Nepali women.

To date, studies of factors associated with HPV infection and cervical cancer morbidity in Nepal have been limited to a few studies in urban populations and one study in rural Nepal [2, 13]. This study aimed to investigate the association between husbands’ migration for employment and HR-HPV infection and abnormal cervical cytology among their spouses in Far-West Achham District.

**Methods**

*Nepali District of Achham*

This study was conducted within Sanfebagar Village Development Committee (VDC), a local Nepali governmental administrative division, in Achham District. The population of Achham has poor indicators of health compared to the general Nepali population. The life expectancy for both men and women in Achham during 2011 was 55 years and the maternal mortality rate was 950 per 100,000 live births, both of which are worse than the national life expectancy of 67 years and maternal mortality rate 170 per 100,000 live births [14]. Currently, there are only two hospitals in Achham. The government’s hospital in the district capital of Mangalsen and Bayalpata Hospital, a
collaboration between the Nepali government and the non-profit organization Possible Health (formerly Nyaya Health).

*Study Subjects*

Women were recruited from a Nepal Fertility Care Center (NFCC) reproductive health (RH) camp [15]. The RH camp was advertised through local newspapers and female support groups two weeks prior to conducting the camp. Women who attended the RH camp received a wide array of free reproductive health services, including testing for STIs, family planning counseling, and liquid cytology testing. Women were eligible for the study if they were between the ages of 16 and 60, had a cervix, were not menstruating, and were not pregnant. Consent forms were distributed and read to each participant before they agreed to enroll in the study. Each form was signed and dated by the study participant, a witness, and the study coordinator. A woman who opted not to participate in the research study was provided the same clinical services during the RH camp as those participating in the research study. Trained health staff with several years of clinical experience performed pelvic exams. Institutional review boards from the University of Alabama at Birmingham and the Nepal Health Research Council approved this study.

*Laboratory Outcomes*

Study protocols on sample collection and testing have been previously described [13]. Briefly, health camp Auxiliary Nurse Midwives (ANMs) collected cervical specimens using ThinPrep® PreservCyt® medium (Hologic/Gen-Probe, San Diego, CA).
Cervical specimens were transported to the Hologic/Gen-Probe, Inc. laboratory in San Diego for HPV testing. Laboratory testing of HPV was performed using APTIMA® HR-HPV mRNA (APTIMA® HPV) (Hologic/Gen-Probe, San Diego, CA), which detects the presence of E6/E7 mRNA for 14 types of HR-HPV (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and APTIMA® HPV16 18/45 Genotype (Hologic/Gen-Probe, San Diego, CA) Assays [16]. Cervical cytology was assessed for research purposes using clinician-collected ThinPrep® PreservCyt® medium (Hologic/Gen-Probe, San Diego, CA), with results classified according to the Bethesda criteria [17]. Women with an abnormal cervical cytology were referred to local medical centers for additional testing and follow-up.

Demographic and Health Risk Survey

Women consenting to participate in the study completed a demographic and health risk survey, the details of which have been previously described [13]. Briefly, survey questions were translated from English into Nepali, and then back-translated to English for quality control. The Far-Western Nepali dialect known as “Dotyali” is sometimes spoken in this region; however, the term “Dotyali” is a macro-term used to describe a wide variety of local languages in Far West Nepal [18]. While Achham is not considered to be a major area where “Dotyali” is spoken, some villages bordering these areas use the language [19]. The local Nepali dialect spoken in the district of Achham does not have a written form, and thus the survey could not be translated into the local Achham dialect. However, our interviewers were from Achham and were able to speak
the local Achham dialect as well as “Dotyali”, a language in use in several villages bordering Achham.

Independent and Dependent Variables

We analyzed two separate outcomes of interest: HR-HPV infection (positive for at least one of the following types - HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and abnormal cervical cytology classified according to the Bethesda criteria. Cervical cytology was categorized as being either “Normal” (benign cellular changes, results within normal limits, atypical squamous cells of undetermined significance (ASCUS), or actinomycosis) or “Abnormal” (atypical glandular cells of undetermined significance, or low-grade squamous intraepithelial lesion (SIL), high-grade SIL, squamous cell carcinoma, or atypical squamous cell-cannot exclude high-grade SIL).

Demographic and socioeconomic variables included age, average number of children per woman, if a husband had ever migrated for work, if a migrating husband had returned home within the last 3 months, and the geographic location visited by a migrant husband. Age was categorized as being either 34 or younger or older than 34 in order to better represent the average age of women whose husbands had migrated for work. The geographic location of the husband’s migration was categorized as “Migrated within Nepal for work”, “Migrated outside of Nepal for work”, or “Has never migrated for work”. Additional variables included, STI awareness (“Have you heard of STIs?”), cervical cancer awareness (“Have you heard of cervical cancer?”), and type of current contraception use (“What type of contraception do you currently use?”). Type of contraception currently used was categorized in descriptive tables as hormonal, condom
use, other, and none. In multivariate models, type of contraception currently used was categorized as hormonal, condom use / other, and none due to a small number of women reporting condom use. Hormonal contraception was kept as a separate category because past studies have reported an association between abnormal cervical cytology and hormonal contraception use [20, 21]. Hormonal contraception use included the use of birth control pills, hormonal implants, and Depo-Provera™ injections. Self-reported health was categorized as “Excellent”, “Very Good”, “Good”, and “Fair/Poor”.

Statistical analysis

All statistical analyses were limited to married women. Cross-tabulations were used to describe the frequencies of potential risk factors associated with HR-HPV infection and the potential risk factors associated with an abnormal cytology outcome. Analysis of variance and Chi-square statistical tests were used to determine the univariate associations of continuous and categorical variables with a positive HR-HPV test and an abnormal cervical cytology result.

Variables included in the multivariable models were selected based on: a) a review of HPV risk factor literature from developing countries; b) a p-value of less 0.1 in the univariate analyses; or c) if they were of primary interest for the study. Cervical cancer awareness was included in the final models because it has been found to be associated with abnormal pap smears in previous studies [22]. The type of contraception used was included in the final models because it has been associated with abnormal cervical cytology in previous studies [23, 24].
Final models where HR-HPV and cervical cytology were dependent variables included the covariates: Age, cervical cancer awareness, type of current contraception used, and a husband’s migratory status. Multivariable logistic regression models generated odds ratios describing factors associated with HR-HPV positivity. Multivariable logistic regression models were also used to determine odds ratios associated with an abnormal cervical cytology test.

**Results**

Out of 386 women who registered for the RH camp, 363 women completed a demographic health survey. Of these 363 women, 265 were married and had a HR-HPV test, while 251 married women had a valid liquid-based cervical cytology reading (Figure 2.1). Twenty women (7.5%) tested positive for HR-HPV and 7.6% of women had abnormal liquid-based cervical cytology results. The mean age of study participants was 33.9 (SD 8.8) years and the average number of children per woman was 3.2 (SD 1.6). The percentage of women who reported their health to be “Excellent” was 26.2%, 31.6% of women reported their health to be “Very good”, 32.7% of women reported their health to be “Good”, and 9.5% of women reported their health to be “Fair/poor”.

Slightly over half of all women surveyed had husbands who migrated for work at one time (50.8%), of whom 59% migrated for two years or less. Of the 130 women whose husbands migrated for employment, 15.4% had husbands who migrated within Nepal and 84.6% had husbands who migrated outside of Nepal. The majority of migrant men returned home within the past three months (77.1%). India was the most frequent destination for a husband’s migration (81%). Women whose husbands had migrated
within Nepal were significantly younger than both women whose husbands migrated outside of Nepal for employment and women whose husbands had never migrated for work (Average age (SD): Migrated within Nepal, 28.8 (7.25), Migrated outside Nepal, 33.7 (9.3), Never migrated, 34.9 (8.5), p ≤ 0.01). Unadjusted odds ratios assessing the association between age and the migration status of a woman’s husband indicated that women whose husbands migrated within Nepal for work were over three times more likely to be 34 or younger than women whose husbands never migrated for work (Unadjusted OR (95% CI): 3.68 (1.15 – 11.78)). Women whose husbands migrated for work outside of Nepal were significantly less likely to be aware of STIs compared to women whose husbands migrated within Nepal for work or women whose husbands had never migrated for work (Awareness of STIs (N, %): 14 (70%) migrated within Nepal, 47 (44.3%) migrated outside Nepal, and 76 (63.3%) never migrated, p ≤ 0.02)

*High Risk HPV (HR-HPV)*

HR-HPV infected women were significantly older than non-infected women (mean 37.1, (SD 7.6) vs. mean 33.6, (SD 8.9), p ≤ 0.01). HR-HPV infected women were more likely to have an abnormal cervical cytology than women who were HR-HPV negative (HR-HPV infected 63.2% vs. uninfected 3.4%) (Table 2.1).

Multivariable logistic regression models using HR-HPV infection as the outcome determined that women 34 and younger were significantly less likely to be HR-HPV infected than women who were older than 34, after adjustment for current type of contraception used, awareness of cervical cancer, and husband’s migration status (OR 0.22, 95%CI 0.07 – 0.71, p ≤ 0.03) (Table 2.1). A husband’s migratory status was not
directly associated with HR-HPV infection (Migrated within Nepal OR 1.05, 95%CI 0.11 – 10.09; Migrated outside of Nepal OR 1.81 95%CI 0.64 – 5.07; Never migrated was reference).

To investigate the possibility that age could be a potential mediating factor in the relationship between a husband’s migration and testing positive for HPV we conducted a sensitivity analysis where we age from our models in order to investigate its effect on the point estimate of migration. After removing migration from the models the point estimate of age decreased by 10%, suggesting that age could be a mediating factor in the relationship between a husband’s migration and testing positive for HPV (OR 0.20 95%CI 0.06 – 0.67).

Cervical Cytology

We found 92.4% of women to have a normal cervical cytology, while 7.6% of women had high-risk cervical cytology results. Sixty percent of HR-HPV infected women were categorized as having an abnormal cervical cytology, while 87.5% of women with squamous cell carcinoma or high-grade SIL also tested positive for HR-HPV (Table 2.2).

Multivariable logistic regression models using abnormal cervical cytology status as the outcome with normal cervical cytology as the reference category determined that women 34 and younger were less likely to have an abnormal cervical cytology than women older than 34 (OR 0.31, 95%CI 0.11– 0.93, p ≤ 0.01), after adjusting for current type of contraception used, awareness of cervical cancer, and husband’s migration status (Table 2.3). Abnormal cervical cytology was not directly associated with a husband’s
migratory status (Migrated within Nepal OR 1.24, 95%CI 0.22 – 6.99; Migrated outside of Nepal OR 0.49 95%CI 0.16 – 1.53; Never migrated was reference).

**Discussion**

Younger age was protective against HR-HPV infection and having an abnormal cervical cytology. Additionally, a husband’s migration was associated with women being 34 and younger. Our results could suggest a possible association between the migration of a woman’s husband for employment and HR-HPV infection and abnormal cervical cytology in rural western Nepal. It is possible that married Nepali women are less likely to contract HPV when they are younger because their husbands are working away from home for extended periods of time during their younger years.

Our study’s inverse associations between younger age and HR-HPV infection contrasts with most reports that suggest younger women are more likely to test positive for HR-HPV than older women [25, 26]. Young women between the ages of 25 and 34 had the highest prevalence of HPV of any age group in a study of 2501 women living in Kolkata, India [25]. Women in younger age groups of the ATHENA study, a multi-center clinical trial of over 46,000 women had higher percentages of HPV infection than women in older age groups [26]. It is possible that the results from our study could indicate that age related cofactors, such as having a husband who has previously migrated for employment, could potentially delay HPV transmission among women.

HPV studies conducted in Indian provinces bordering Nepal have study populations with characteristics similar to our study population and show a similar prevalence of HPV infection to our study [27, 28]. Although it is almost impossible to
know the exact numbers of Nepalese who migrate to India for work due to the open border policies between the two countries, the Indian provinces bordering Nepal are known to have high rates of employed Nepali migrant workers, [29, 30]. Since the characteristics of our study sample are similar to the characteristics of HPV studies conducted in North India and the most popular destination for migration in our study sample was India, it is possible that the migration of workers from Achham traveling to India for employment plays a role in the HPV infection rates in Nepal, particularly for seasonal migrant workers who regularly return home.

It is possible the results of our study are due to cohort effects which were unable to be measured using our data. Political strife originating from Nepal’s 10 year long civil war caused an increase in the number of labor migrants between 1996 and 2007 [31]. With migratory work proving to be profitable for many Nepali citizens, the increase in migration which began during the civil war period has continued to this day. It is possible that older women who were married before the civil war period had husbands who were more financially secure during the warring period and therefore did not have to migrate for work. In contrast, it is possible younger women who were married either during or after the conflict might be more likely to have husbands who migrated for work. This phenomenon could help explain why women who were 34 and younger were less likely to test positive for HR-HPV than older individuals.

It is possible there is self-selection bias in our study sample. While we are interpreting the results of our study as suggesting it is the husband who is transmitting HPV to the women, this may not always be the case. It is possible that women are forming sexual relationships with other men while their husbands are away and are
choosing not to participate in our study because of social stigma. This could explain why younger women, who are normally at a greater risk for testing positive for HR-HPV then older women, are less likely to test positive for HR-HPV in our study sample.

Our study was a cross-sectional survey conducted in one area of Achham district and it is possible our study did not adequately represent the factors associated with HR-HPV infection in all of far west Nepal. However, our study was conducted in Sanfebagar VDC, which is 25 km from the district capital of Mangalsen. The proximity of our health camp to the district capital helped insure that a diverse population of women had access to the reproductive services we provided. The small sample size of our study reduces the generalizability of our findings. While our study sample consisted of 265 women, only 20 women tested positive for HR-HPV and only 19 women had an abnormal cytology result. The small number of women with outcomes in our study restricted the number of covariates we could include in our multivariate models. However, while our sample size is small, we were able to include several covariates in our models that are considered to be HR-HPV risk factors in other studies. It is possible some questions from our survey were misrepresented when translated into the local dialect spoken in Achham. Given that the Nepali dialect spoken in the district of Achham does not have a written form, we had to rely on our interviewers to translate our survey into the local Achham dialect when needed. Despite this, our survey should not have suffered from difficulties in communication because the majority of people living in Achham are able to speak and understand Nepali and our interviewers were able to speak the local Achham dialect.
Conclusions

Contrary to similar reports on HPV infection, there seems to be an increasing prevalence of HR-HPV with age in our study population. Further studies in a larger population are warranted to validate our findings and assess whether our observations are generalizable to spouses of migrant workers from other parts of Nepal.
Table 2.1: Descriptive characteristics and multivariable logistic regression model assessing risk factors associated with HR-HPV* infection in women attending a Nepal Fertility Care Center health camp in the Far-West region of Nepal.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=262)</th>
<th>HR-HPV negative* (N=245)</th>
<th>HR-HPV positive* (N=20)</th>
<th>P-value</th>
<th>Adjusted Odd Ratios (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤34 years</td>
<td>137 (52.3)</td>
<td>131 (54.1)</td>
<td>6 (30.0)</td>
<td>0.02</td>
<td>0.22 (0.07 – 0.71)</td>
</tr>
<tr>
<td>&gt;34 years</td>
<td>125 (47.7)</td>
<td>111 (45.9)</td>
<td>14 (70.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of children</td>
<td></td>
<td></td>
<td></td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.2 (1.6)</td>
<td>3.2 (1.6)</td>
<td>3.5 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.0 (2.0 – 4.0)</td>
<td>3.0 (2.0 – 4.0)</td>
<td>3.5 (2.5 – 4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical cytology§</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Normal (WNL/BCC/ACTINO/ASCUS)</td>
<td>205 (81.7)</td>
<td>224 (96.9)</td>
<td>8 (40.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-Risk (HSIL/SCC/ASC-H/AGUS/LSIL)</td>
<td>32 (12.8)</td>
<td>7 (3.0)</td>
<td>12 (60.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-Reported Health</td>
<td></td>
<td></td>
<td></td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>69 (26.2)</td>
<td>64 (26.3)</td>
<td>5 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>83 (31.6)</td>
<td>74 (30.5)</td>
<td>9 (45.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>86 (32.7)</td>
<td>81 (33.3)</td>
<td>5 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair/Poor</td>
<td>25 (9.5)</td>
<td>24 (9.8)</td>
<td>1 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Husband's migration status</td>
<td></td>
<td></td>
<td></td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Migrated within Nepal</td>
<td>20 (7.8)</td>
<td>19 (8.0)</td>
<td>1 (5.3)</td>
<td>1.05 (0.11 – 0.09)</td>
<td></td>
</tr>
<tr>
<td>Migrated outside of Nepal</td>
<td>110 (42.9)</td>
<td>100 (42.2)</td>
<td>10 (52.6)</td>
<td>1.81 (0.64 – 5.07)</td>
<td></td>
</tr>
<tr>
<td>Husband never migrated</td>
<td>126 (49.2)</td>
<td>118 (49.8)</td>
<td>8 (42.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has your husband returned working away from home in the past 3 months</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>98 (77.8)</td>
<td>88 (75.9)</td>
<td>10 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28 (22.2)</td>
<td>28 (24.1)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awareness of cervical cancer</td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (7.9)</td>
<td>131 (56.2)</td>
<td>11 (55.0)</td>
<td>1.15 (0.41 – 3.19)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>233 (92.1)</td>
<td>102 (43.8)</td>
<td>9 (45.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of current contraception use</td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Hormonal</td>
<td>69 (27.1)</td>
<td>62 (26.4)</td>
<td>7 (35.0)</td>
<td>2.14 (0.65 – 7.12)</td>
<td></td>
</tr>
</tbody>
</table>

*HR-HPV* indicates high-risk human papilloma virus.
<table>
<thead>
<tr>
<th>Condom Use</th>
<th>Other</th>
<th>Does not use contraception</th>
<th>Awareness of STIs** (n=255)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (25.9)</td>
<td>15 (5.9)</td>
<td>105 (41.2)</td>
<td>144 (56.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>62 (26.4)</td>
<td>13 (5.5)</td>
<td>98 (41.7)</td>
<td>134 (56.8)</td>
<td></td>
</tr>
<tr>
<td>4 (20.0)</td>
<td>2 (10.0)</td>
<td>7 (35.0)</td>
<td>10 (52.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. APTIMA® HR-HPV mRNA Assay (Hologic/Gen-Probe, San Diego, CA)
2. **STI=Sexually Transmitted Infection
3. *Hormonal contraception was defined as the use of birth control pills, hormonal implants, and Depo-Provera injections.
4. SCC = Squamous Cell Carcinoma; HSIL = High-grade Squamous Intraepithelial Lesion; ASC-H = Atypical Squamous Cell-cannot exclude HSIL; AGUS = Atypical Glandular Cells of Undetermined Significance; LSIL = Low-grade Squamous Intraepithelial Lesion; ASCUS = Atypical Squamous Cells of Undetermined Significance; UNSAT = Unsatisfactory; WNL = Within Normal Limits; BCC = benign cellular changes; ACTINO = Actinomycosis
5. %Models adjusted for: Age, Awareness of cervical cancer, Type of current contraception use, Husband’s migration status
6. The category “Other” was collapsed with “Condom use” in the multivariate analysis
Table 2.2. High-risk Human Papillomavirus (HR-HPV) Test* Results and a Woman’s Husband’s Migration Status Stratified by Liquid-based Cytology** (N=251).

<table>
<thead>
<tr>
<th>Liquid-based Cytology** Results§ on Clinician-collected Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCHSILASC-HLSILAGUSASCUSWNL/BCC/ACTINO</td>
</tr>
<tr>
<td>SCC</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Total Cytology Results</td>
</tr>
<tr>
<td>HR-HPV* Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Husband’s migration status</td>
</tr>
<tr>
<td>Migrated within Nepal</td>
</tr>
<tr>
<td>Migrated outside of Nepal</td>
</tr>
<tr>
<td>Never migrated for work</td>
</tr>
</tbody>
</table>

*APTIMA® HR-HPV mRNA Assay (Hologic/Gen-Probe, San Diego, CA)
**ThinPrep® PreservCyt® medium ((Hologic/Gen-Probe, San Diego, CA)
§SCC = Squamous Cell Carcinoma; HSIL = High-grade Squamous Intraepithelial Lesion; ASC-H = Atypical Squamous Cell-cannot exclude HSIL; AGUS = Atypical Glandular Cells of Undetermined Significance; LSIL = Low-grade Squamous Intraepithelial Lesion; ASCUS = Atypical Squamous Cells of Undetermined Significance; UNSAT = Unsatisfactory; WNL = Within Normal Limits; BCC = benign cellular changes; ACTINO = Actinomycosis
Table 2.3: Descriptive characteristics and multivariable logistic regression model of cervical cytology in women attending a Nepal Fertility Care Center health camp in the Far-West region of Nepal

<table>
<thead>
<tr>
<th>Age (years) (n=248)</th>
<th>Overall</th>
<th>Normal (WNL, BCC/ACTINO / ASCUS) (N=232)</th>
<th>Abnormal (HSIL/SCC/ASC-H / AGUS/LSIL) (N=19)</th>
<th>P-value</th>
<th>Adjusted Odd Ratios (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤34 years</td>
<td>132 (53.2)</td>
<td>125 (54.6)</td>
<td>7 (36.8)</td>
<td>0.15</td>
<td>0.31 (0.11 – 0.93)</td>
</tr>
<tr>
<td>&gt;34 years</td>
<td>116 (46.8)</td>
<td>104 (45.4)</td>
<td>12 (63.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of children (n=244)</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>P-value</th>
<th>Adjusted Odd Ratios (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>3.2 (1.6)</td>
<td>3.0 (2.0 – 4.0)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.0 (1.6)</td>
<td>3.0 (2.0 – 4.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HR-HPV Status* (n=251)</th>
<th>P-value</th>
<th>Adjusted Odd Ratios (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>20 (7.9)</td>
<td>8 (3.5)</td>
</tr>
<tr>
<td>Negative</td>
<td>231 (92.0)</td>
<td>224 (96.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Self-Reported Health (n=235)</th>
<th>P-value</th>
<th>Adjusted Odd Ratios (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>64 (25.6)</td>
<td>57 (24.7)</td>
</tr>
<tr>
<td>Very good</td>
<td>82 (32.8)</td>
<td>75 (32.5)</td>
</tr>
<tr>
<td>Good</td>
<td>83 (33.2)</td>
<td>80 (34.6)</td>
</tr>
<tr>
<td>Fair/Poor</td>
<td>21 (8.4)</td>
<td>19 (8.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Husband’s migration status (n=243)</th>
<th>P-value</th>
<th>Adjusted Odd Ratios (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migrated within Nepal</td>
<td>19 (7.8)</td>
<td>17 (7.6)</td>
</tr>
<tr>
<td>Migrated outside of Nepal</td>
<td>107 (44.0)</td>
<td>102 (45.5)</td>
</tr>
<tr>
<td>Husband never migrated</td>
<td>117 (48.2)</td>
<td>105 (46.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Has your husband returned from working away from home in the past 3 months (n=122)</th>
<th>P-value</th>
<th>Adjusted Odd Ratios (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>94 (77.1)</td>
<td>88 (75.9)</td>
</tr>
<tr>
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**STIs** (n=251)  

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<td>108 (46.6)</td>
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<td><strong>STIs</strong></td>
<td>13 (68.4)</td>
<td>6 (31.6)</td>
<td></td>
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*APTIMA® HR-HPV mRNA Assay (Hologic/Gen-Probe, San Diego, CA)  
**STI=Sexually Transmitted Infection  
1Hormonal contraception was defined as the use of birth control pills, hormonal implants, and Depo-Provera injections.  
2SCC = Squamous Cell Carcinoma; HSIL = High-grade Squamous Intraepithelial Lesion; ASC-H = Atypical Squamous Cell-cannot exclude HSIL; AGUS = Atypical Glandular Cells of Undetermined Significance; LSIL = Low-grade Squamous Intraepithelial Lesion; ASCUS = Atypical Squamous Cells of Undetermined Significance; UNSAT = Unsatisfactory; WNL = Within Normal Limits; BCC = benign cellular changes; ACTINO = Actinomycosis  
%Models adjusted for: Age, Awareness of cervical cancer, Type of current contraception use, Husband’s migration status  
4The category “Other” was collapsed with “Condom use” in the multivariate analysis
Figure 2.1. Study design flow chart illustrating sample size of women attending a one day reproductive health camp in Achham, Nepal.
References


CHAPTER 4

THE ASSOCIATION BETWEEN GEOSPATIAL FACTORS AND A HUSBAND’S MIGRATORY STATUS AMONG NEPALI WOMEN REPORTING REPRODUCTIVE TRACT INFECTIONS IN THE 2011 NEPAL DEMOGRAPHIC AND HEALTH SURVEY

by

DEREK C JOHNSON, PEMA LHAKI, CHARLOTTE P. BUEHLER, MIRJAM-COLETTE KEMPF, ERIC CHAMOT, STEN H VERMUND, SADEEP SHRESTHA

In preparation for BMC Infectious Diseases
Format adapted for dissertation
Abstract

Geographic, economic, and social factors could be associated with the symptoms of reproductive tract infections (RTI) and if a husband is currently migrating for work among Nepali women. Our study investigates the geospatial factors associated with a husband’s migration status and RTI symptoms in married women using the Nepal Demographic and Health Survey (NDHS). Our study population was restricted to 9,607 married women in the 2011 NDHS. Male migration is defined as a non-resident husband who is currently migrating internationally or within the country. Geographic variables used in this analysis included NDHS sub-zone, development region, and urban/rural status. A woman was considered to have an RTI like symptom if she answered yes to either of the following questions: “Had abnormal genital discharge in last 12 months”, or “Had a genital sore or ulcer in last 12 months”. Multivariate logistic regression models stratified by year and husband migration status were used to investigate the association between the migration status of a woman’s husband and women reporting RTI symptoms while accounting for the complex survey design of the NDHS. Choropleth maps of the percentage of women reporting RTI symptoms by NDHS year were created to highlight areas with high percentages of RTIs. Overall, 31.9% of husbands were currently migrating work. The percentage of married women who reported a RTI symptom by development region was: Eastern 13.9%, Central 11.5%, Western 13.0%, Mid-Western 14.8%, Far-Western 9.0%. For women living in Nepal’s Mid-West region or Far-West region, multivariate logistic regression models assessing the odds of reporting RTI
symptoms stratified by development region found that women whose husbands were migrating for a year or more were more likely to report RTI like symptoms than women whose husbands were not currently migrating for work (Mid-West: OR 1.93 95% CI 1.02-3.67; Far-West: OR 2.89 95% CI 1.24-6.73). The results of this study suggest potential regional differences in Nepali women reporting RTI symptoms and the migration status of a woman’s husband could affect this association. It is possible a husband’s current migratory work could be associated with married women reporting RTI symptoms. Additional studies are needed to assess the role of labor migration on the percentage of women reporting RTI symptoms in Nepal.
Introduction

With a quarter of Nepal’s 29 million citizens living below the poverty line (1), Nepal is facing health and socioeconomic disparities which have compelled millions of Nepalese to look for work away from home. Currently, over 2.2 million Nepalese individuals are engaged in migrant work (2, 3). These workers annually send approximately 3 billion dollars in remittance to Nepal, comprising 15% of Nepal’s GDP (4). Having at least one household resident migrate for employment has become common in Nepal. Fifty seven percent of households report at least one member leaving home for work within the last 5 years. However, 66% of households in Far-West Nepal report at least one household member leaving home for work within the last 5 years (5). With such economic disparities in migrant labor and health issues, it is possible reproductive tract infections (RTI) are unequally distributed across Nepal.

Reproductive tract infections, which include sexually transmitted infections (STIs), could be linked to migrant work (6). At the time of this study no research has investigated RTIs in the wives of Nepali migrant workers. However, previous research has shown that men who engage in migrant work may engage in risky sexual behavior, and thus have the potential to contract STIs which could then be transmitted to their wives when they return home (7,8). Migrant workers represent less than 10% of Nepal’s population but represent 41% of the total known HIV infections in Nepal (9). A study in male migrant workers in the Nepali district of Doti found that 8% of migrant workers returning to Doti were reported to be infected with HIV and 22% were infected with syphilis (10). Low literacy rates among migrant workers are known to be associated with
increased rates of HIV and gonorrhea infection in Nepal (4,11). Indicators of socioeconomic status (SES) such as land ownership, education, and location of migratory work also affect STI transmission in migrant workers (12,13). Circular migration, where an individual leaves their partner for work and returns periodically, is one of the most common forms of migrant work in Nepal and it is correlated with an increased risk of sexually transmitted infections (14). Complicating the association between migration and acquiring STIs, migratory men sometimes establish parallel partnerships between work and home, forming long-term bridges which could facilitate the spread of STIs (15).

It is unlikely that STI rates among migrant workers are evenly distributed across the different regions of Nepal because migrant work is unevenly distributed across the different regions of Nepal. The geography of Nepal is divided into 5 developmental regions (Eastern, Central, Western, Mid-West, and Far-West) and 3 ecological zones (mountain, hill, and terai). The “mountain” and “hills” ecological regions represent over 77% of Nepali land mass but only 52% of the population. In contrast, the “terai” ecological region represents 23% of Nepal’s land mass and 48% of the population (16). The majority of migrant workers who travel to India for employment come from Nepal’s western developmental regions. However, of the migrant workers registered for labor permits in countries other than India, 64% of them come from the two non-western development regions of Nepal (Eastern Development Region, Central Development Region) (17). Approximately 19% of Nepal’s population lives in urban areas where 40% of urban adolescents have comprehensive knowledge of STIs (18). However, in rural areas of Nepal only about one-third of young men and one-fourth of young women have comprehensive knowledge of STIs (19). Residents of Nepal’s “Terai” ecological region,
representing 48% of the population, report some of the lowest rates of condom use in Nepal (3).

Regional and geospatial factors could potentially affect the sexual health of the wives of migrant workers in Nepal. Our study investigates the geospatial differences between the prevalence of RTI symptoms and a husband’s migration status among Nepali women using the Nepal Demographic and Health Survey.

Methods

Demographic and Health Survey Data

The Demographic and Health Survey program was established by the United States Agency for International Development (USAID) in 1984 (20). The goal of the DHS program was to provide decision makers and government officials with improved information and analyses useful for making health policy choices on marriage, fertility, family planning, reproductive health, child health, and HIV/AIDS. The standard version of the DHS is conducted every 5 years in Nepal and began in 1996. However, an in-depth assessment of fertility and family planning in Nepal was conducted by the DHS program in 1987 (21).

Of the 12,674 women of reproductive age (15-45) in the 2011 NDHS, our study sample was restricted to 9,607 married women. Data for the 2011 NDHS are based on a two-stage random sample design. During the first stage of sampling, a stratified sample of enumerated areas (EA) are selected with a probability of selection proportional to their size. An EA can be a city block or apartment building in urban areas, while in rural areas it is typically a village or group of villages. The population and size of sampled clusters
vary, but on average, clusters contain 100 to 300 households, of which 20 to 30 households are randomly selected for survey participation. During the second stage of sampling, a number of households are selected for surveying by equal probability systematic sampling in the EAs. In each selected household, a household questionnaire is completed to identify women age 15-49, men age 15-59 (15-54 or 15-49 in some surveys) and children under age five. Every eligible woman is interviewed with an individual questionnaire (22).

**NDHS Geographic Information Systems Data**

The NDHS has been collecting geographic information systems (GIS) data since 2001 and the methodology is described in detail elsewhere (22). Briefly, GIS coordinates in the NDHS represent the population center of a sampling cluster. Global positioning system coordinate locations are assessed at the lowest administrative unit that exists in both the sample frame and the most accurate geographic boundary GIS file. Rural coordinates that fall less than 10 kilometers (kms) from the border of their correct administrative unit are accepted and are manually placed into the proper administrative unit. Urban coordinates that fall less than two kilometers from the border of their correct administrative unit are also manually placed into the proper administrative unit. In an effort to ensure respondent confidentiality, both the latitude and longitude positions of all surveys contain random error according to the following criteria: a) urban clusters contain between 0 and 2 kms of error b) rural clusters contain 0 and 10 kms of error. The error is restricted so that coordinates stay within the country and within the NDHS survey region. (23).
GIS data for the 2011 NDHS is represented at 3 levels: 1) Nepal’s 5 development regions (Central, Eastern, Far-Western, Mid-Western, and Western); 2) Nepal’s 3 ecological zones (Hill, Mountain, Terai); and 3) across Nepal’s 13 sub-regions as combinations of the development and eco regions (Central Hill, Central Mountain, Central Terai, Eastern Hill, Eastern Mountain, Eastern Terai, Far-Western Hill, Far-Western Terai, Far/Mid/Western Mountain, Mid-Western Hill, Mid-Western Terai, Western Hill, Western Terai) (22).

RTI outcome and variables of interest

This study uses the definition of male migration found in the NDHS report, “Impact of Male Migration on Contraceptive Use, Unmet Need, and Fertility in Nepal” (19). The report defines male migration as a non-resident husband who has migrated internationally or within the country. This definition of a migrant husband does not specify a length of migration time nor does it differentiate between reasons for migration. However, given the high rate of male labor migration in Nepal, the report assumes the vast majority of non-resident husbands are away for work. The NDHS survey question “Is your husband/partner living with you now or is he staying elsewhere” is asked to assess male migration. If a woman states that her husband/partner is living elsewhere, then the amount of time her husband/partner is away from home is determined by the survey question “For how long have you and your husband not been living together”. We categorize the time a husband has been away from home as either away for one year or less, or away for more than one year.
A woman was considered to have a RTI like symptom if she answered yes to either of the following NDHS questions: “Had abnormal genital discharge in last 12 months” or “Had a genital sore or ulcer in last 12 months” (20). Covariates of interest were classified as demographic, SES, sexual behavioral, and geographic variables. Demographic variables included: age, used as a continuous and categorical variable for descriptive tables, and survey year. SES variables included: Asset based wealth index quintiles categorized as poorest, poorer, middle, richer, richest; woman’s educational level categorized as no education, primary, secondary, and higher education; and husband’s education level categorized as no education, primary, secondary, and higher education. Sexual behavioral variables included: contraception currently used categorized as condoms, other, and no contraception; ever heard of a STI; and age at first marriage. Geographic variables included development region categorized as Eastern, Central, Western, Mid-Western, and Far-Western; and Urban/rural residence. Ecological zone was categorized as mountain, hill, and terai. Our study includes the NDHS sub-zone, which is an amalgamation of development region and ecological zone and is categorized into 13 groups: Eastern mountain, Central mountain, Western mountain, Eastern hill, Central hill, Western hill, Mid-western hill, Far-western hill, Eastern terai, Central terai, Western terai, Mid-western terai, Far-western terai.

**Statistical Analysis:**

All statistical analyses were limited to married women. Cross-tabulations were stratified by survey year and were used to describe the frequencies of potential risk factors associated with a woman reporting RTI symptoms. Analysis of variance and Chi-
square statistical tests were used to determine the univariate associations of continuous
and categorical variables with a woman’s STI status for both within a single survey year
and across survey years. Multivariate logistic regression models stratified by year and
development region investigated the association of husband migration status and
reporting RTI symptoms while adjusting for asset based wealth index, contraception use,
age at first marriage, urban/rural status, and husband’s education. All variables included
in the multivariable models were selected based on: a) a review of the RTI risk factor
literature from developing countries or b) a p-value of less 0.1 in the univariate analyses.

Due to the complex survey design of the NDHS, specific statistical procedures
were used to correctly estimate variance. Variance estimation for univariate and
multivariate statistical methods contained in the SAS PROC SURVEY procedures in
SAS version 9.4 (SAS Institute, Cary, NC) were used to perform all statistical analyses
and account for the NDHS survey design.

ArcGIS version 10.1 (ESRI, Redlands, CA, USA, 2011) was used to produce
choropleth maps of the percentage and change in percentage of women reporting RTI
symptoms according to survey year and a husband’s migration status.

Results

Symptoms of RTIs were reported by 12.6% of married women. Of the 12.6% of
women who answered yes to at least one or more questions about RTI symptoms, 19.9%
said they had a genital sore or ulcer in the last 12 months, and 92.7% said they had a
genital discharge in the last 12 months. The average age of women surveyed was 31.28
(SD 0.13) years. Almost one third of married women were the wives of migrant workers,
Husband migration status: Not currently migrating 67.9%, One year or less 25.7%, More than one year 6.3%). Of the women whose husbands have migrated for work, 13.3% of them reported RTI symptoms.

Univariate analysis indicated that only age was significantly associated with married women reporting RTI symptoms (RTI symptoms by age: 15 to 25 11.3%, >25 to 35 14.0%, >35 12.2%, p-value 0.02) (Table 1). Developmental region was significantly associated with a husband’s migration status (Husband migration status: Eastern 32.4%, Central 26.9%, Western 39.7%, Mid-Western 29.6%, Far Western 34.6%, p-value 0.001). Almost twice as many women reported no formal education in the Far West region than they did in the Eastern region (Women reporting no formal education: Eastern 37.1%, Far West 61.2%, p-value 0.001) (Table 2). Women who reported RTI symptoms were more likely to reside in a rural area if their husband was a migrant worker (Rural residence: Migrant husband 91.7%, Non-migrant husband 84.2% p=0.001). Women who reported RTI symptoms and whose husbands were migrant workers were more likely to reside in the terai ecological zone than women who reported RTI symptoms and whose husbands were not migrant workers (terai ecological zone: Migrant husband 57.3%, Non-migrant husband 45.4% p=0.008). Multivariate logistic regression models, stratified by a husband’s time migrating for work, determined that women whose husbands migrated for a year or more were more likely to report RTI symptoms than women whose husbands were currently not migrating for work if they lived in Nepal’s Mid-West region (OR 1.93 95%CI 1.02 – 3.67) or if they lived in Nepal’s Far-West region (OR 2.89 95%CI 1.24 – 6.73) (Table 3). The prevalence of migrant wives reporting RTI symptoms was under
10% in two NDHS sub-zones (RTI symptoms: Central terai 9.4% and Far Western terai 9.0%) (Figure 1).

Married women whose husbands migrated for work were more likely to report RTI symptoms than married women whose husbands were not migrating for work in 7 of the 13 NDHS Sub-regions (Central Mountain, Far Western Hill, Eastern terai, Central terai, Western terai, Mid Western terai, and Far Western terai). Married women whose husbands were not migrating for work were more likely to report RTI symptoms than married women whose husbands migrated for work in 6 of the 13 NDHS Sub-regions (Eastern Mountain, Far/Mid/Western Mountain, Eastern Hill, Central Hill, Western Hill, and Mid Western Hill). Married women from the Central mountain Sub-region were the most likely to report RTI symptoms regardless of whether their husbands were migrating or not (Central mountain: Migrant husband 21.9% Non-migrant husband 17.3%) (Figure 2).

Discussion

The percentage of women with migrant husbands in the 2011 NDHS was 32.0%. The percentage of women reporting any RTI symptoms was 12.6%. While the migration status of a woman’s husband was not associated with reporting RTI symptoms in the univariate analysis, multivariate logistic regression models indicated increased odds of a woman reporting RTI symptoms if they resided in the Mid-Western or Far-Western development regions and their husbands were working away from home for more than one year. Our results suggest that geospatial factors are associated with married women
reporting RTI symptoms and that geospatial factors could cause a husband’s migration status to be a risk factor for RTI symptoms for women living in specific regions of Nepal.

Geospatial factors are known to affect STI rates in other South Asian countries (24-26). HIV prevalence among sex workers in South India ranges from less than one percent in some districts of Kerala and Tamil Nadu to more than 30% in districts of Maharashtra and Karnataka (27). Urban/rural status was a bigger predictor of demonstrating knowledge of STIs and HIV/AIDS transmission than other socioeconomic factors in the Bangladesh Adolescents Survey (28). Often it is not the physical characteristics of the geospatial area that are directly associated with STI rates, but risk factors specific to a group of people which are correlated with STIs. The Indian district of Kerala has some of the best quality health care and lowest rates of STIs in India. The health care delivery model is so effective it has been dubbed “The Kerala Model” by other Indian districts trying to mimic their results (29). It is most likely the health care infrastructure built by the people of Kerala that is associated Kerala’s low STI rates rather than the geospatial area of Kerala itself.

In Nepal, regions with high levels of STI risk factors are often associated with regions containing high levels of migration. The Eastern and Central development regions of Nepal have the largest number of men who have migrated for work and both regions have some of the worst indicators of STIs in Nepal (5). Reports from the 2011 NDHS found that men from the Central development region reported a higher percentage of sex worker usage than the national average. Women from the Central development region were the least likely to know where to obtain a condom while women from the Eastern development region were the least likely to report condom usage when having
sex (5). If both labor migration and STI rates are known to be associated with geospatial factors it is possible that STI rates among the wives of migrant workers could correlate with geospatial factors as well.

Results from our study indicate that married women whose husbands have migrated for work for more than one year and who reside in either the Mid-Western or Far-Western development region of Nepal are over twice as likely to report RTI symptoms then married women whose husbands are not migrating for work, after adjusting for wealth, contraception use, age at first marriage, urban/rural status, and a husbands education. Our results suggest that if a woman’s husband is engaged in migrant work, where she lives could affect the likelihood of her reporting RTI symptoms. The majority of male Nepali migrant workers who reside in the Mid-Western and Far-Western development region travel to India (30) to work in large Indian cities, such as Mumbai or New Delhi, where HIV prevalence among sex workers is high and the use of commercial sex workers is prevalent among Nepali migrant workers (10, 30). It is possible that diseases contracted by male migrant workers could be transmitted to their wives when they return to Mid-Western or Far-Western Nepal.

Development regions with high rates of migrant activity and RTI symptoms could represent entry points of STIs into Nepal. Previous studies have reported that although the percentage of individuals infected with HIV in Nepal is less than 1% of the population (31), over 40% of individuals who test positive for HIV have engaged in migratory work (10). Other studies have shown that approximately 22% of migrant workers returning to the Far West district of Doti test positive for syphilis (3). These studies in combination with our results could suggest that migratory work is a potential
mode of entry for STIs into Nepal. Truck stops and highway areas are well known for high STI rates in Nepal (32), suggesting that transient work is already known to be associated with the spread of STIs in Nepal. It is possible that migratory work, being a form of transient work, could represent a potential way in which new STI infections are entering Nepal. This phenomenon could explain why even though the overall rates of STIs in migrant workers is similar to the rates in non-migrant workers, infections which are relatively new to Nepal, like HIV or syphilis, are found in high concentrations within the migrant population.

There were limitations to this analysis. Our study was an ecological study and it may not be accurate to assume that characteristics at the group level can be applied to characteristics at the individual level. However data from the NDHS is nationally representative and provides a good population estimate of the data captured in the survey. Our outcome relies on the self-reporting of RTI symptoms. Syndromic identification of STIs is known to have low sensitivity (33). However, the World Health Organization considers syndromic identification of STIs as an acceptable form of screening in South Asia (34).

**Conclusions**

Our study suggests possible regional differences in RTI symptoms reported by married women in the NDHS. It is possible a husband’s migratory work could be associated with the rates of RTI symptoms reported by married women in specific regions of Nepal. Additional studies are needed to assess the role of labor migration on the rates of RTI symptoms in Nepal.
Table 3.1: Percent of married women reporting RTI symptoms by descriptive characteristics in the 2011 Nepal Demographic and Health Survey (NDHS)*.

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<th>Percent reporting RTI Symptom</th>
<th>P-value*</th>
</tr>
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<tr>
<td><strong>Husband’s Migration</strong></td>
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</tr>
<tr>
<td>Migrated for more than 1 year (N=540)</td>
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</tr>
<tr>
<td>Migrated for 1 year or less (N=2337)</td>
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<td></td>
</tr>
<tr>
<td>Not currently migrating (N=6575)</td>
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</tr>
<tr>
<td><strong>Age</strong></td>
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</tr>
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<tr>
<td>&gt;25 to 35 (N=3536)</td>
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<td>&gt;35 (N=3086)</td>
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<td><strong>Ever heard of a Sexually Transmitted Infection (STI)</strong></td>
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<td>Western hill (N=838)</td>
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*P-value for univariate analysis within the 2011 NDHS*
Table 3.2: Descriptive Characteristics of Women in the 2011 Nepal Demographic and Health Survey (NDHS) by Developmental Region*.

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</tr>
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<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>RTI Symptoms</strong></td>
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<td>(23.9 –</td>
<td>(22.6 –</td>
<td>(23.2 –</td>
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<tr>
<td></td>
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<tr>
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<td>Poorer</td>
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<td>Richer</td>
<td>Richest</td>
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<td>(26.4)</td>
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**Contraception Currently Used**

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<td></td>
<td>(44.5)</td>
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**Woman's education level**

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<th>Higher</th>
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<td>(4.9)</td>
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**Husband’s education level**

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**Ever heard of a Sexually Transmitted**

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### Infection (STI)

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<tr>
<td></td>
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<td>(9.0)</td>
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</table>

*P-value for univariate analysis within the 2011 NDHS*
Table 3.3: Multivariate logistic regression models determining the odds of reporting RTI symptoms stratified by a husband’s migration time in the 2011 Nepal Demographic and Health Survey (NDHS) *

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<tr>
<th>Development Region</th>
<th>Migrate for one year or less$</th>
<th>Migrate for more than one year$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern</td>
<td>1.49 (0.93 - 2.39)</td>
<td>1.03 (0.57 - 1.86)</td>
</tr>
<tr>
<td>Central</td>
<td>1.06 (0.66 - 1.72)</td>
<td>1.17 (0.66 - 2.08)</td>
</tr>
<tr>
<td>Western</td>
<td>1.08 (0.69 - 1.70)</td>
<td>1.40 (0.80 - 2.46)</td>
</tr>
<tr>
<td>Mid-Western</td>
<td>1.09 (0.75 - 1.58)</td>
<td>1.93 (1.02 - 3.67)</td>
</tr>
<tr>
<td>Far-Western</td>
<td>0.95 (0.47 - 1.91)</td>
<td>2.89 (1.24 - 6.73)</td>
</tr>
</tbody>
</table>

*Adjusted for: Wealth Index, Contraception Use, Age at first Marriage, Urban/Rural, Husband's Education $ Reference category was a husband not currently migrating for work
Figure 3.1: Percentage of married women reporting RTI symptoms in the 2011 Nepal Demographic and Health Survey

A) Percentage of women reporting RTI symptoms in the 2011 Nepal Demographic and Health Survey by sub-zone
Figure 3.2: Difference in the percentage of RTI symptoms reported by women whose husbands are living at home and women whose husbands are living away from home in 2011 Nepal Demographic and Health Survey (NDHS)

B) Difference in the percentage of married women reporting RTI symptoms whose husbands are living at home vs. the percentage of married women reporting RTI symptoms whose husbands are living away from home stratified by sub-zone. Positive values indicate that a higher percentage of women whose husbands are living away from home reported a RTI symptoms, while negative values indicate that a higher percentage of women whose husbands are living at home reported RTI symptoms.
References


CHAPTER 5

DISCUSSION

I have discussed the following throughout this dissertation. In Chapter 2, I have described the concordance of self-collected vs. clinician collected HR-HPV samples in women who attended a one day reproductive health (RH) camp in Achham, Nepal. At the time of writing this dissertation, this chapter provided the only account of HR-HPV prevalence and concordance between clinician collected HR-HPV samples with self-collected HR-HPV samples in Far-West Nepal. In Chapter 3, I described how HR-HPV infections and abnormal cervical cytology in married Nepali women is associated with a husband’s migration for employment. Lastly, in Chapter 4, I described how STD symptoms are associated with migration using nationally representative data from the NDHS. Specifically, I describe how regional specific prevalence of STD symptoms in Nepali women whose husbands migrate for work compared to women whose husbands do not migrate for work.

Data for this dissertation was collected during a one day RH camp conducted on July 5th, 2014 in Nepal’s Achham district, a region within the Sanphebagar Village Development Committee (VDC), approximately 25km from the district capital of Mangalsen (Appendix B). Data collection began at 8am and ended at 6pm. In total, 389
women were registered at the RH camp, 300 women provided self-collected samples, of which 292 were valid. Additionally, of the 389 women registered for the RH camp, 278 women provided clinician collected liquid based cytology samples. Registered women were directed to a room where health staff administered a demographic and health survey while they waited for services. Wait times for services were their lowest during the beginning of the RH camp and peaked in the late afternoon with women saying they waited a maximum of 2 to 3 hours before they were seen. During the screening process, health staff instructed women to provide a self-collected cervico-vaginal sample. Samples were collected by inserting a cytobrush (Hologic/Gen-Probe, San Diego, CA) into the vagina as far as possible and rotating it 5 times in each direction, then swirled in the APTIMA® specimen transport medium (Hologic/Gen-Probe, San Diego, CA). After a woman provided a self-collected HR-HPV sample, health camp ANMs collected a liquid based cytology specimen by inserting a cytobrush into the cervical canal and rotating 3-5 times, withdrawing and then rotating firmly around the full circumference of the transformation zone. Cytobrushes were then swirled in ThinPrep® (TP) PreservCyt® medium (Hologic/Gen-Probe, San Diego, CA).

Nepal Fertility Care Center (NFCC) staff were involved in the development and translation of the survey instrument in order to ensure the survey was culturally sensitive and questions were culturally appropriate. The survey was designed to assess socioeconomic, clinical, reproductive health, and migration related factors associated with HR-HPV infection and abnormal cervical cytology in women attending the health camp. Questions were first written in English, and then they were translated in to Nepali, and then they were lastly translated back to English for quality control (Appendix C).
All completed surveys and biological samples were collected together at the end of the RH health camp and packaged for storage. Surveys and biological samples were temporarily stored at NFCC before processing. Both clinician- and self-collected cervico-vaginal samples were transported to the Hologic/Gen-Probe, Inc. laboratory in San Diego for HPV testing two weeks after the RH camp. Surveys were entered into an encrypted Microsoft Access database which included automatic safeguards to help mitigate nonsensical values from being entered. Data entry was completed 3 months after the RH camp. Laboratory test results were processed within 2 months of the RH camp. Data for the 2006 and 2011 NDHS was procured after health camp surveys were entered. I used the data from the survey, biological samples, and NDHS for my dissertation.

The first part of my dissertation found “good” HR-HPV test concordance between clinician collected samples and self-collected samples (Kappa 0.64 95%CI 0.45 – 0.84). These findings agree with other studies comparing HR-HPV testing using clinician collected vs. self-collected samples [1, 2]. A review of 25 different studies on the concordance between clinician collected vs. self-collected samples for HR-HPV testing found that agreement was associated with the type of HPV test and the method of sample collection [3]. It’s possible the key to our “good” Kappa value is because this study used the APTIMA® HR-HPV mRNA assay for HR-HPV testing. HPV testing using signal-based assays, such as Quiagen HC2 assay, are less sensitive and specific for testing self-collected samples compared to clinician collected samples, resulting in lower agreement between the two tests. However, PCR-based HPV tests, like the APTIMA® HR-HPV mRNA assay, generally show similar sensitivity and specificity for both for self-collected and clinician collected samples, resulting in better test agreement [1].
Demonstrating that self-collected HPV samples are equivocal to clinician-collected samples is important for increasing cervical screening rates in Nepal. Several studies have indicated most women prefer self-collection of HPV samples to clinician collection of samples [4, 5]. By providing Nepali women with the option for self-sampling it could be possible to increase in the number of women being screened for HPV, a pre-requisite for cervical cancer [6, 7].

The second part of my dissertation investigated the risk factors associated with HR-HPV infection and abnormal cervical cytology. Using the same data collected in the first part of my dissertation I investigated the risk factors associated with HR-HPV infection and abnormal cervical cytology status within the wives of Nepali migrant workers. Out of the 278 women who provided a liquid based cervical cytology sample, 251 married women were used in this study because they had both a valid liquid-based cervical cytology test and completed a health survey. The prevalence of HR-HPV for women providing a valid liquid cervical cytology sample was 7.5%, while the prevalence of abnormal cervical cytology, defined as atypical glandular cells of undetermined significance or worse using the Bethesda system, was 7.6%.

In order to maximize resources allotted to cervical cancer screening and treatment programs, it is important to identify women who are at a greater risk than the general population for developing cervical cancer. In Nepal, lack of work during the agricultural off-season has motivated a large portion of the male population to migrate to the Nepal tarai, India, or another country for employment. It is generally believed that over half of Nepali households in the Far-Western development region of Nepal have at least one male family member who participates in some form of migratory work [8]. Wives of
Nepali migrant workers are a sub-population at risk for contracting STIs, including HPV, and therefore at an increased risk of developing cervical cancer.

The wives of migrant workers are at an increased risk for contracting STIs, both because of their own risk factors, such as a lack of knowledge of sexually transmitted disease, and because their husband’s risk of contracting STIs while migrating [9, 10]. Compared to women whose husbands are not engaged in migrant work, the wives of migrant workers have lower education levels and lower levels of income, both of which are associated with increases in STIs [11-13]. Returning migrant workers, in particular seasonal migrant workers, could possibly transmit STIs they contracted while away to their wives when they return home.

Results from our analysis indicate that being 34 years old or younger was protective against both an abnormal cervical cytology and testing positive for HR-HPV after adjusting for awareness of cervical cancer, type of current contraception used, and a husband’s migration status. A husband’s migration status was not significantly associated with an abnormal cervical cytology or testing positive with HR-HPV.

Young age protecting against HPV infection is most likely a country specific phenomenon dependent on Nepali social norms. Research conducted in the USA and in several European countries suggest that women from these countries are at the highest risk for contracting HR-HPV during their teens and 20’s [14-16]. However, research from Chile, Colombia, China and Mongolia indicated that rates of HPV infection either peaked in women in their mid-30s and 40s or that age-specific prevalence of HPV exhibited a "U" shaped curve [17-19].
There are several possible explanations as to why the risk for HPV infection declines with age in some areas while other areas experience a shift in peak age or a “U” shaped curve. It is possible the sexual behavior of middle age women and their partners differ by country [19]. It is also possible the increase in HPV prevalence in middle age women is due to population-specific effects. It is well known that sexual attitudes are closely related to social changes and are likely to affect the transmission of HPV [20].

Over 50% of our study population was married to migrant workers and the average age of women in this study was 33 years old. It is possible that migrant husbands of younger women were not available to transmit HPV during our study participant’s younger years because they were away from home, but later transmitted HPV to their spouses when they returned. It is also possible that women who were married before Nepal’s civil war period had husbands who were more financially secure during the warring period and therefor did not have to migrate for work, there by not exposing non-migrating husbands to possibly contracting HPV [21].

Demonstrating the risk factors associated with HR-HPV infection and abnormal cervical cytology is important for bolstering Nepal’s cervical screening programs. By identifying the risk factors associated with HR-HPV infection and abnormal cervical cytology, resources can be better used to target women who are at the greatest risk for developing cervical cancer. While being 34 or younger is protective against HR-HPV infection and abnormal cervical cytology, it is an uncommon conclusion to our analysis. It is possible that regional and cohort specific effects are affecting the age-distribution of HR-HPV in this study. For example, the time period for seasonal migration in Far-West Nepal typically begins after the harvest season and can extend until April. Data for our
study was collected in July, which is when males who perform agricultural work and would normally engage in migrant work during the agricultural off-season would be home. It’s possible that young women chose to work with their husbands on the farm rather than come to the RH camp during the month of July. This could cause an overabundance of young women whose husbands have not returned from working abroad and could cause the rates of HPV in young women to seem artificially low if they have not had sexual contact over a long period of time.

The third part of my dissertation investigates the link between rates of STD symptoms and regional differences among migrant workers using the 2006 and 2011 Nepal Demographic and Health Survey (NDHS). Our study found there were several regions of Nepal which reported lower rates of STD symptoms among the wives of migrant workers than among women whose husbands never migrated for work. Most regions of Nepal experienced an increase in the prevalence of married women reporting STD symptoms from 2006 to 2011.

At the time of writing this dissertation there was no large scale or nationally representative data on HPV or cervical abnormalities in Nepal, nor was there a national cancer registry in Nepal. In lieu of this lack of data, I decided to investigate STD symptoms using the NDHS. HPV and other STIs share many of the same SES risk factors, and HPV itself is an STI. HPV is one of the most common STIs in the world and is often found to be a co-infection when an individual tests positive for other STIs. Given that there was no available national data on HPV at the time of this study, I used STD symptoms as an outcome for our models.
Geospatial risk factors for STIs are important determinants of disease in a population. Efforts to implement successful interventions are increasingly becoming more localized and have been described by Dr. De Cock and colleagues as being dependent on “knowing your epidemic, globally and locally” [22]. Within the context of exploring the determinants of HR-HPV infection and abnormal cervical cytology in Nepal, geospatial techniques can be used for a variety of purposes. Not only can geospatial analysis be used to assess the geographical distribution of HR-HPV infections and abnormal cervical cytology, but it can also be used to better plan and improve screening and vaccination services within allotted spaces and over time [23, 24].

Our results suggest that geospatial and SES factors that are associated with married women reporting STD symptoms have changed over time. Our results also suggest that potential risk factors for reporting STD symptoms could include both a husband’s migration for work and geospatial factors. While the migration status of a woman’s husband was not associated with reporting STD symptoms within the 2006 and 2011 NDHS overall, select regions did show an association between the two. The percentage of STD symptoms reported between 2006 and 2011 significantly increased (7.4% vs. 12.6%) as did the percentage of migrant husbands (26.3% vs. 32.0%). Rural residence, ecological zone, and DHS Sub-zone were associated with the wives of migrant workers reporting and STD symptom in 2011, but were not associated with reporting and STD symptom in 2006, suggesting the increases in reporting STD symptoms and the percentage of wives of migrant workers has changed for specific regions over time. After adjusting for wealth index, contraception use, age at first marriage, urban/rural status, and husband’s education, multivariate logistic regression models indicated the odds of a
woman reporting STD symptoms increased if they resided in the Mid-Western or Far-Western development regions and their husband migrated for work for more than one year.

Our results suggest that 4 of the 13 NDHS Sub-zone regions in 2011 accounted for the majority of the wives of migrant workers reporting STD symptoms. Of the wives of migrant workers who reported STD symptoms, 63.2% of them resided in either the Western hills, Eastern terai, Central terai, or Western terai. Our results correspond with data suggesting that the majority of the top ten districts with the most migrant worker activity are located within the terai ecological zone (Dhanusa, Mahottari, Jhapa, Morang, Siraha, Nawalparasi, Saptari, Sunsari, Sarlahi and Rupandehi) [25]. These regions of increased migrant activity and wives reporting STD symptoms could represent entry points of STIs into Nepal. Previous studies have reported that although the percentage of individuals infected with HIV in Nepal is less than 1% of the population [26], over 40% of individuals who test positive for HIV have engaged in migratory work [27]. Other studies have shown that approximately 22% of returning migrant workers from the Nepal district of Doti test positive for syphilis [28]. These studies in combination with our results could suggest that migratory work is a potential mode of entry for STIs into Nepal. Truck stops and highway areas are well known for high STI rates in Nepal [29], suggesting that transient work is already known to be associated with the spread of STI. It is possible that migratory work, being a form of transient work, could represent a potential way in which new STI infections are entering Nepal. This phenomenon could explain why even though the overall rates of STIs in migrant workers is similar to the
rates in non-migrant worker, infections which are relatively new to Nepal, like HIV or syphilis, are found in high concentrations within the migrant population.

Using geospatial data on STD symptoms as a possible proxy for assessing areas of high HR-HPV prevalence will help Nepali health officials better target screening services to areas where they are most needed. The results of this dissertation suggest that western regions along the Terai show both the highest prevalence of women reporting STD symptoms and the greatest increases in STD symptoms from 2006 to 2011. Increased efforts to improve sexual health services among these regions could possibly decrease the rates of STIs among married women.

As with most studies, there are several limitations in my dissertation. The data for both chapter 1 and chapter 2 is part of a cross-sectional study and could not assess lifetime exposure to HPV, nor could it measure HPV persistence, which precedes and predicts the development of cervical precancerous lesions [30]. Additionally, this study tests for the presence of HPV mRNA which measures the integration of HPV DNA into the cells and under-estimates the prevalence of HR-HPV by 10-15% which would reduce our HR-HPV prevalence estimates [31, 32]. However, while this study was not longitudinal, HPV prevalence is correlated with the risk of developing cervical cancer[33]. HPV prevalence is a good surrogate for abnormal cervical cytology risk, specifically in a resource-limited setting like Nepal with limited data on HPV infection and cervical cancer.

The small sample size in chapter 2 and 3 hinders the precision of our prevalence and concordance estimates, which is indicated by the size of the confidence intervals. However, we were able to collect a wide array of data in this remote region in Nepal,
which included both clinician- and self-collected samples in addition to a survey on
demographic, socioeconomic, and behavioral characteristics. The study sample in chapter
2 and chapter 3 may not be representative of the far western region of Nepal and may not
be generalizable to the entire district of Achham. There are 9 districts in the Far-Western
Development Region of Nepal, covering the three major ecological zones (Mountains,
Hills, and Terai). Achham District lies in the ecological “Hills” zone, which is
geographically and ethnically different from the other districts/ecological zones in the far
western region. Personal testimony from women attending the health camp suggests that
some women traveled several hours to receive services and take part in the study. It is
possible that the difficulty in reaching the health camp could have introduced a form of
selection bias where women who were either healthy enough to travel the necessary
distance or had the resources to access transportation were over represented in our data.
However, this study was conducted in Sanfebagar VDC, which is 25 km from the district
capital of Mangalsen. The proximity of our health camp to the district capital helped
ensure that a diverse population of women had access to the reproductive services we
provided. It is possible some questions from our survey were misrepresented when
translated into the local dialect spoken in Achham. Given that the Nepali dialect spoken
in the district of Achham does not have a written form, we had to rely on our interviewers
to translate our survey into the local Achham dialect when needed. Despite this, our
survey should not have suffered from difficulties in communication because the majority
of people living in Achham are able to speak and understand Nepali and our interviewers
were able to speak the local Achham dialect. In chapter 3, the small number of women
with outcomes in our study restricted the number of covariates we could include in our
multivariate models. However, while our sample size was small, we were able to include several covariates in our models that are considered to be HR-HPV risk factors in other studies. Chapter 4 was an ecological study and it may not be accurate to assume that statistics at the group level can be applied to the individual level. However, data from the NDHS is nationally representative and provides a good estimate of the data captured in the survey. Chapter 4’s outcome relies on the self-reporting of STI symptoms. Syndromic identification of STIs is known to have low sensitivity [34]. However, the World Health Organization does consider syndromic identification of STIs an acceptable form of STI management in South Asia [35].

The research presented in this dissertation has the potential to improve Nepal’s cervical cancer screening capabilities. I have demonstrated that self-collected HR-HPV samples provide good testing agreement when compared to clinician collected HR-HPV samples with in the Far-West district of Achham. This information could potentially help increase the amount of women participating in cervical screening by making it easier to access services. I have investigated the potential link between a married woman’s HR-HPV status and if their husband migrated for work. This information has the potential to help conserve cervical screening resources by enabling health care providers to better target people at the most risk for cervical cancer in Nepal. Lastly, I have demonstrated that while male labor migration might not be a risk factor for their wives reporting STD symptoms overall, it is very likely that a husband’s labor migration significantly affects reports of STD symptoms in the Mid-Western and Far-West regions of Nepal after controlling for SES factors. This information lends support for increasing funding for reproductive health programs in western Nepal. Together I believe that this research will
help bring awareness to the size and scope of HPV and cervical abnormalities in Nepal, particularly within Nepal’s large migrant community.
Reference


APPENDIX A

ORGANIZATIONAL DEFINITIONS OF THE TERM MIGRANT
<table>
<thead>
<tr>
<th>Origination</th>
<th>Definition of the term “Migrant”</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Organization for Migration, Glossary on Migration¹</td>
<td>An individual who has resided in a foreign country for more than one year irrespective of the causes, voluntary or involuntary, and the means, regular or irregular, used to migrate</td>
</tr>
<tr>
<td>United Nations Convention on the Protection of the Rights of All Migrant Workers and Members of Their Families²</td>
<td>Person who is engaged or has been engaged in a remunerated activity in a State of which he or she is not a national</td>
</tr>
<tr>
<td>International Labor Organization, Migrant Workers (Supplementary Provisions) Convention, 1975³</td>
<td>A person who migrates from one country to another with a view of being employed otherwise than on his or her own account. The scope of Convention No. 97 excludes frontier workers, the short-term entry of members of the liberal professions and artistes, and seafarers (Article 11(2)).</td>
</tr>
<tr>
<td>European Agency for Safety and Health at Work⁴</td>
<td>EU nationals staying in an EU-25 country of which they are not nationals (citizens). In this perspective, people coming outside the EU-25 (non-EU or third country) are immigrants.</td>
</tr>
</tbody>
</table>

¹ Glossary on Migration, International Organization for Migration 2011  
² International Convention on the Protection of the Rights of All Migrant Workers and Members of their Families, New York, 18 December 1990, United Nations Treaty Collection  
⁴ European Agency for Safety and Health at Work. Literature Study on Migrant Workers 2012
APPENDIX B

VILLAGE DEVELOPMENT REGIONS OF ACHHAM, NEPAL
APPENDIX C

DEMOGRAPHIC AND HEALTH SURVEY FOR WOMEN PARTICIPATING IN A
ONE DAY HEALTH CAMP IN ACHHAM, NEPAL
Participant Demographics

1. Age______

2. What ethnicity do you belong to?
   __________ □ Don’t know (do not read) □ Refused (do not read)

3. What is your height in meters?
   ______

4. What is your weight in kilograms?
   ______

5. What is the highest grade of school completed?
   ______

6. What is your approximate personal monthly income (NRs), separate from other household income?
   ______

7. In what country were you born?
   ______

8. In what district were you born in?
   ______

9. If you were born outside of Achham, what year did you move to Achham?
   ______

10. Do you currently drink alcohol?
    □ Yes □ No □ Occasionally □ Don’t know (do not read) □ Refused (do not read)

11. In the past 30 days, at any one time, how often did you drink more than 4 drinks at one time?
    ______ □ I do not drink

12. How long have you been using tobacco products?
    ______ □ I do not use tobacco products

13. How do you rate your overall health?
    □ Excellent □ Very Good □ Good □ Fair □ Poor □ Don’t know (do not read) □ Refused (do not read)

14. Where did you first learn about sex?
    □ From parents □ From brothers/sisters □ From friends □ From husband □ From school □ Other
    (please say: ______) □ Don’t know (do not read) □ Refused (do not read)

15. Are you able talk about sex with your friends?

117
16. What age do you think girls should first learn about sex?

17. What age do you think boys should first learn about sex?

18. Where do you think people should first learn about sex?

19. Is OK for individuals who are not married to engage in pre-marital sex

20. Should people learn about sex before they marry?

21. Is it OK for adolescent boy to engage in premarital sex?

22. Is it OK for adolescent girls to engage in premarital sex?

23. Have you ever had sexual intercourse?

24. How old were you when you had sexual intercourse for the first time?

25. Have you ever heard about sexually transmitted infections (STIs)?

26. If you have heard about STIs, where were you taught about sexually transmitted infections (STIs) ?

27. Could you talk with your friends about diseases you can get from having sexual intercourse?

28. Do you believe it is OK for a man to have sexual intercourse with someone who is not his wife?

29. Do you believe it is OK for a woman to have sexual intercourse with someone who is not her husband?
30. How worried are you that you might get a sexually transmitted infection (STIs) from having sex?  
☐ Not worried at all ☐ Somewhat worried ☐ Very worried ☐ Don’t know (do not read) ☐ Refused (do not read)

31. Have you ever been told by a health care provider that you had a sexually transmitted infection (STIs)?  
☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

32. What is your marital status?  
☐ Married ☐ Not married (single) ☐ Divorced/Separated ☐ Widowed/widower ☐ Don’t know (do not read) ☐ Refused (do not read)

33. How old were you when you first married?  
_______

34. If your husband is dead, how did he die?  
_______

35. Have you or your husband ever been married more before?  
☐ Both of us have not ☐ My husband has ☐ I have ☐ We both have ☐ Don’t know (do not read) ☐ Refused (do not read)

36. Did a health worker ever say your husband had a sexually transmitted infection (STIs)?  
☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

37. How many children do you have?  
_______

38. Are you currently pregnant?  
☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

39. Do you want to become pregnant in the future?  
☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

40. How worried are you that you will become pregnant when you don’t want to?  
☐ Not worried ☐ A little worried ☐ Worried ☐ Very worried ☐ Don’t know (do not read) ☐ Refused (do not read)

41. Do you currently use family planning (contraception) when you have sexual intercourse?  
☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

42. What type of family planning (contraception) do you usually use?  
☐ I do not use contraception ☐ Pills ☐ Injectable (ex: Depo-Provera) ☐ Implants (ex: Nortplant) ☐ IUD ☐ Condoms ☐ Withdrawal ☐ Other_______ ☐ Don’t know ☐ Refused (do not read)

43. Have you ever had an abortion?  
☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

If yes, how many times have you had an abortion?  
_______ ☐ Don’t know (do not read) ☐ Refused (do not read)
44. How many people have you had sexual intercourse with?

__________  □ I have never had sexual intercourse  □ Don’t know (do not read)  □ Refused (do not read)

45. Could you talk about sex with your husband without being embarrassed?

□ I definitely could □ I probably could □ Not sure □ I probably could not □ I definitely could not □ Don’t know (do not read) □ Refused (do not read)

46. Could you start a conversation about contraception (birth control) with your husband?

□ I definitely could □ I probably could □ Not sure □ I probably could not □ I definitely could not □ Don’t know (do not read) □ Refused (do not read)

47. Could you tell your husband that you don’t want to have sex with him?

□ I definitely could □ I probably could □ Not sure □ I probably could not □ I definitely could not □ Don’t know (do not read) □ Refused (do not read)

48. Have you ever heard about cervical cancer?

□ Yes  □ No  □ Don’t know (do not read) □ Refused (do not read)

49. Have you ever heard about Human Papillomavirus (HPV)?

□ Yes  □ No  □ Don’t know (do not read) □ Refused (do not read)

50. Where did you first hear about cervical cancer?

□ School □ Government health clinic □ NGO health clinic □ Friends □ Family □ Not taught about cervical cancer □Other ______ □ Don’t know (do not read) □ Refused (do not read)

51. Is Human Papillomavirus infection (HPV) is a necessary part of cervical cancer?

□ Yes  □ No  □ Don’t know (do not read) □ Refused (do not read)

52. Have you ever heard about a vaccine that prevents common forms of Human Papillomavirus (HPV)?

□ Yes  □ No  □ Don’t know (do not read) □ Refused (do not read)

53. If Human Papillomavirus is necessary to cause cervical cancer would you be willing to give the Human Papillomavirus (HPV) vaccine to your children if it was free?

□ Yes □ No □ I have to ask my husband □ I have to ask my family □ Don’t know (do not read) □ Refused (do not read)

54. If you are willing to pay for the Human Papillomavirus (HPV) vaccine for your children, how much would you be willing to pay for the Human Papillomavirus (HPV) vaccine for your children?

__________

55. Are you currently working?

□ Yes  □ No  □ Don’t know (do not read) □ Refused (do not read)

56. What best describes your current work?

□ I Do not work □ Agriculture □ Construction □ Housekeeper □ Commercial services/Sales clerk □ Health care □ Education □ Other (Please State) ______ □ Don’t know (do not read) □ Refused (do not read)

57. Have you ever traveled outside of Nepal for work?

□ Yes  □ No  □ Don’t know (do not read) □ Refused (do not read)
58. Have you recently returned from traveling outside of Nepal for work in the past 3 months?
☐ I have not traveled for work ☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

59. What dates were you away from home?

60. What country did you most recently travel to for work?

61. What city did you live in while traveling?

62. Have you ever traveled outside of your district but within Nepal for work?
☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

63. Have you recently returned from traveling outside of your district but within Nepal in the past 3 months?
☐ I have not traveled for work ☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

64. What was the name of the district/neighborhood where you stayed while traveling for work?

65. Please rate your overall experience with your most recent time away from home for work?
☐ I have not traveled for work ☐ Very good ☐ Good ☐ Average ☐ Poor ☐ Very Poor ☐ Don’t know (do not read) ☐ Refused (do not read)

66. What best describes your job during your most recent time away from home for work?
☐ I have not traveled for work ☐ Agriculture ☐ Construction ☐ Housekeeper ☐ Commercial services/Sales clerk ☐ Health care ☐ Education ☐ Other (Please State)_____. ☐ Don’t know (do not read) ☐ Refused (do not read)

67. How did you find your job away from home?
☐ I have not traveled for work ☐ Family ☐ Friends ☐ Agency ☐ Newspaper/Radio/Media ☐ Government program ☐ Other (Please State)_____. ☐ Don’t know (do not read) ☐ Refused (do not read)

68. During your most recent time traveling for work, how often did you send money home?
☐ I have not traveled for work ☐ Weekly ☐ Monthly ☐ Bi-monthly ☐ Quarterly ☐ Bi-annually ☐ Annually ☐ Irregular ☐ Never ☐ Don’t know (do not read) ☐ Refused (do not read)

69. During your most recent time traveling for work, how did you pay for the cost of traveling?
☐ I have not traveled for work ☐ Agency ☐ Loans ☐ Personal savings ☐ Family savings ☐ Property/Land sales ☐ Other ☐ Don’t know (do not read) ☐ Refused (do not read)

70. Has your husband traveled either outside of his district or outside of Nepal for work?
☐ Outside of district ☐ Outside of Nepal ☐ Both ☐ My husband has never traveled for work ☐ Don’t know (do not read) ☐ Refused (do not read)

71. How did your husband find his job away from home?

121
☐ He has not traveled for work ☐ Family ☐ Friends ☐ Agency ☐ Newspaper/Radio/Media ☐ Government program ☐ Other (Please State)______. ☐ Don't know (do not read) ☐ Refused (do not read)

72. What are the dates of your husband’s most recent trip?

________

73. During his most recent trip, how long was your husband away from home?

________

74. If your husband’s most recent time traveling for work was outside of Nepal, what country did he travel to?

________

75. What city did your husband live in while traveling?

________

76. Has your husband returned from traveling for work?
☐ He has not traveled for work ☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

77. What best describes your husband’s job while traveling for work?
☐ He has not traveled for work ☐ Agriculture ☐ Construction ☐ Housekeeper ☐ Commercial services/Sales clerk ☐ Health care ☐ Education ☐ Other (Please State)______. ☐ Don’t know (do not read) ☐ Refused (do not read)

78. During your husband’s most recent time traveling for work, how often did he send money home?
☐ He has not traveled for work ☐ Weekly ☐ Monthly ☐ Bi-monthly ☐ Quarterly ☐ Bi-annually ☐ Annually ☐ Irregular ☐ Never ☐ Don’t know (do not read) ☐ Refused (do not read)
79. What best describes the type of house you currently live in?
☐ Owned ☐ Rented ☐ Other ☐ Don’t know (do not read) ☐ Refused (do not read)

80. Is agricultural land possessed by your household?
☐ Yes ☐ No ☐ Don’t know (do not read) ☐ Refused (do not read)

81. Other than agriculture does your household engage in other economic activities?
_____________

82. What is the approximate monthly income for your household?
_______
APPENDIX D

UAB IRB STUDY APPROVAL
### Project Revision/Amendment Form

**Form version: June 26, 2012**

*In MS Word, click in the white boxes and type your text; double-click checkboxes to check/uncheck.*

- Federal regulations require IRB approval before implementing proposed changes. See Section 14 of the IRB Guidebook for investigators for additional information.
- Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the Investigator’s Brochure, questionnaires, surveys, advertisements, etc.). See item 4 for more examples.

#### 1. Today’s Date

2014-07-11

#### 2. Principal Investigator (PI)

<table>
<thead>
<tr>
<th>Name (with degree)</th>
<th>Sadeep Shrestha, PhD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department</td>
<td>Epidemiology</td>
</tr>
<tr>
<td>Office Address</td>
<td>RPHB 217L</td>
</tr>
<tr>
<td>E-mail</td>
<td><a href="mailto:sshrestha@uab.edu">sshrestha@uab.edu</a></td>
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<td>48665</td>
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**Contact person who should receive copies of IRB correspondence (Optional)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Kristie Williams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone</td>
<td>5-7633</td>
</tr>
<tr>
<td>Office Address (if different from PI)</td>
<td>RPHB 220D</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E-Mail</th>
<th><a href="mailto:kdisdock@uab.edu">kdisdock@uab.edu</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fax Number</td>
<td>48665</td>
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#### 3. UAB IRB Protocol Identification

<table>
<thead>
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<th>Protocol Number</th>
<th>X120805001</th>
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</table>

**3.b. Protocol Title**

Epidemiology of HPV, STI and Cervical Cancer in Multi-Sites in Nepal
(Epidemiology of HPV in Cervical Cancer in selected communities of Kathmandu and Achham districts, Nepal)

**3.c. Current Status of Protocol—Check ONE box at left; provide numbers and dates where applicable**

- [x] Study has not yet begun
- [ ] In progress, open to accrual
- [ ] Enrollment temporarily suspended by sponsor
- [ ] Closed to accrual, but procedures continue as defined in the protocol (therapy, intervention, follow-up visits, etc.)
- [ ] Closed to accrual, and only data analysis continues

**Number of participants: 400**

<table>
<thead>
<tr>
<th>Date closed</th>
<th>Number of participants receiving interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of participants in long-term follow-up only:</td>
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</tbody>
</table>

#### 4. Types of Change

Check all types of change that apply, and describe the changes in Item 5.c. or 5.d. as applicable. To help avoid delay in IRB review, please ensure that you provide the required materials and/or information for each type of change checked.

- [ ] Protocol revision (change in the IRB-approved protocol)
  - In Item 5.c., if applicable, provide sponsor’s protocol version number, amendment number, update number, etc.

- [ ] Protocol amendment (addition to the IRB-approved protocol)
  - In Item 5.c., if applicable, provide funding application document from sponsor, as well as sponsor’s protocol version number, amendment number, update number, etc.

- [ ] Add or remove personnel
  - In Item 5.c., include name, title/degree, department/division, institutional affiliation, and role(s) in research, and address whether new personnel have any conflict of interest. See “Change in Principal Investigator” in the IRB Guidebook if the principal investigator is being changed.

- [ ] Add graduate student(s) or postdoctoral fellow(s) working toward thesis, dissertation, or publication
  - In Item 5.c., (a) identify these individuals by name; (b) provide the working title of the thesis, dissertation, or publication; and (c) indicate whether or not the student’s analysis differs in any way from the purpose of the research described in the IRB-approved HSP (e.g., a secondary analysis of data obtained under this HSP).

- [ ] Change in source of funding; change or add funding
  - In Item 5.c., describe the change or addition in detail, include the applicable OSP proposal number(s), and provide a copy of the application as funded (or as submitted to the sponsor if pending). Note that some changes in funding may require a new IRB application.
Add or remove performance sites
In Item 5.c., identify the site and location, and describe the research-related procedures performed there. If adding site(s), attach notification of permission or IRB approval to perform research there. Also include copy of subcontract, if applicable. If this protocol includes acting as the Coordinating Center for a study, attach IRB approval from any non-UAB site added.

Add or change a genetic component or storage of samples and/or data component—this could include data submissions for Genome-Wide Association Studies (GWAS)
To assist you in revising or preparing your submission, please see the IRB Guidebook for Investigators or call the IRB office at 934-3789.

Suspend, re-open, or permanently close protocol to accrual of individuals, data, or samples (IRB approval to remain active)
In Item 5.c., indicate the action, provide applicable dates and reasons for action; attach supporting documentation.

Report being forwarded to IRB (e.g., DSMB, sponsor or other monitor)
In Item 5.c., include date and source of report, summarize findings, and indicate any recommendations.

Revise or amend consent, assent form(s)
Complete Item 5.d.

Addendum (new consent form)
Complete Item 5.d.

Add or revise recruitment materials
Complete Item 5.d.

Other (e.g., investigator brochure)
Indicate the type of change in the space below, and provide details in Item 5.c. or 5.d. as applicable.
Include a copy of all affected documents, with revisions highlighted as applicable.

5. Description and Rationale
In Item 5.a. and 5.b, check Yes or No and see Instructions for Yes responses. In Item 5.c. and 5.d, describe—and explain the reason for—the change(s) noted in Item 4.

Yes ☒ No 🔴
5.a. Are any of the participants enrolled as normal, healthy controls?
If yes, describe in detail in Item 5.c. how this change will affect those participants.

Yes ☒ No 🔴
5.b. Does the change affect subject participation, such as procedures, risks, costs, location of services, etc.?
If yes, FAP-designated units complete a FAP submission and send to fap@uab.edu. Identify the FAP-designated unit in Item 5.c.
For more details on the UAB FAP, see www.uab.edu/fap.

5.c. Protocol Changes: In the space below, briefly describe—and explain the reason for—all change(s) to the protocol.

Derek Johnson doctoral candidate with the Department of Epidemiology who is listed on the protocol will use findings from this study for his dissertation. The proposed title is "Prevalence and Determinants of High Risk Human Papillomavirus (HPV) Among Wives of Migrant Workers - A Study in Achham District". The dissertation does not differ from the approved proposed research.

5.d. Consent and Recruitment Changes: In the space below,
(a) describe all changes to IRB-approved forms or recruitment materials and the reasons for them;
(b) describe the reasons for the addition of any materials (e.g., addendum consent, recruitment); and
(c) indicate either how and when you will reconsent enrolled participants or why reconsenting is not necessary (not applicable for recruitment materials).
Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:
- a copy of the currently approved document (showing the IRB approval stamp, if applicable)
- a revised copy highlighting all proposed changes with "tracked" changes
- a revised copy for the IRB approval stamp.
Signature of Principal Investigator __________________________ Date 11/12/14

FOR IRB USE ONLY

☐ Received & Noted ☐ Approved Expedited* ☐ To Convened IRB

Signature (Chair, Vice-Chair, Designee) __________________________ Date 11/7/14

DOLA 10-1-14

Change to Expedited Category Y / N / NA

*No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 56.111
APPENDIX E

NEPAL HEALTH RESEARCH COUNCIL IRB STUDY APPROVAL
19 July 2012

Dr. Sudev Shrestha
Principal Investigator
University of Alabama at Birmingham
USA

Ref: Approval of Research Proposal entitled Epidemiology of HPV in Cervical Cancer in selected communities of Kathmandu and Achham districts, Nepal

Dear Dr. Shrestha,

It is my pleasure to inform you that the above-mentioned proposal submitted on 14 May 2012 (Reg. no. 52/2012) has been approved by NHRC Scientific Review Board on 20 July 2012 (2069-04-21).

As per NHRC rules and regulations, the investigator has to strictly follow the protocol stipulated in the proposal. Any change in objectives, problem statement, research questions or hypotheses, methodology, implementation procedure, data management and budget that may be necessary in course of the implementation of the research project can only be made after prior approval from this council. Thus, it is compulsory to submit the detail of such changes intended or desired with justification prior to actual change in the protocol. If the researcher requires transfer of the bio samples to other country, the investigator should apply to the NHRC for the permission.

Further, the researchers are directed to strictly abide by the National Ethical Guidelines published by NHRC during the implementation of their research proposal and submit progress report and full study summary report upon completion.

As per your research proposal, total research amount is US$ 51,000.00 and NHRC processing fee is US$ 1,000.00.

If you have any questions, please contact the research section of NHRC.

Thanking you,
Sincerely Yours,

Dr. Shanker Pratap Singh
Member Secretary

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