

Table of Contents

1 Introduction	1
1.1 Cervical cancer	1
1.1.1. Cervical cancer epidemiology in the world	1
1.1.2. Cervical cancer epidemiology in Bolivia	3
1.2. Human papillomavirus	4
1.2.1. Brief history	4
1.2.2. Structural and functional characteristics of HPV	5
1.2.3. Phylogenetic and epidemiological classification of HPV	7
1.2.4. HPV infection epidemiology	9
1.2.5. HPV Vertical transmission mode	11
1.2.6. HPV Horizontal transmission mode	12
1. 2.6.1 Sexual	12
1. 2.6.2 Non sexual	12
1.3. HPV infection	13
1.3.1. Productive infection.	13
1.3.2. Abortive infection as a precursor of cervical cancer	15
1.3.3. Latency phase or asymptomatic infection and regression	19
1.3.4. HPV immune escape mechanisms	19
1.3.4.1. Immune escape mechanism through HPV infectious cycle	20
1.3.4.2. Immune escape mechanisms by host alteration gene expression	20
1.3.4.3. Immune escape mechanisms by alteration of protein functions	21
1.3.4.4. Immune escape by altered cytoplasmic trafficking of host proteins	21
1.3.4.5. Immune escape due to inappropriate innate leukocyte activity in HPV-associated cancers	22
1.4. Risk factors for the development of cervical cancer	22
1.4.1. Viral factor	23
1.4.2. Cofactors	23
1.4.2.1. Age of first sexual intercourse	23
1.4.2.2. Number of sexual partners	23
1.4.2.3. Multiparity	24
1.4.2.4. Hormonal contraception	24

1.4.2.5. Tobacco	25
1.4.2.6. Coinfections and immunosuppression	25
1.4.2.7. Medical care access	27
1.5. Evolution of preneoplastic lesions to cervical cancer	27
1.5.1. Changes in the terminology and correlation of the cytological and histological classification of preneoplastic cervical lesions	27
1.5.2. Progression and regression of preneoplastic lesions	29
1.6. HR-HPV associated diseases	30
1.7. Prevention of cervical cancer	31
1.7.1. Primary prevention	31
1.7.1.1. HPV Vaccines	31
1.7.1.2. Modification of sexual behavior	33
1.7.2. Secondary prevention	34
1.7.2.1. Screening at the cervical transformation zone in the secondary prevention	34
1.7.2.2. Screening methods	36
1.7.2.2.1. Cytology.	36
a) Conventional cytology	36
b) Cytology on liquid basis	37
c) Cytology nomenclature	37
1.7.2.2.2. Visual Inspection	39
a) Visual inspection under acetic acid	39
b) Inspection with Lugol's iodine (VILI)	40
1.7.2.2.3. HPV infection detection	40
a) Nucleic acid amplification assays	42
b) Signal amplification assays	45
c) HPV self-sampling	47
1.7.2.3. Clinical assessment	48
a) Colposcopy	48
b) Biopsy	49
c) Endocervical curettage	49
1.7.2.4. Treatment methods of precancerous lesions.	49
a) Cryotherapy	50
b) Loop electrosurgical excision procedure	51

c) Cold knife conization	52
1.7.2.5. Management according to histology results	52
a) Low-grade intraepithelial lesions	52
b) High-grade intraepithelial lesions	52
1.7.3 Tertiary prevention	53
1.8. Current status of the cervix cancer prevention program in Bolivia	54
2. Objectives	55
3. Materials and Methods	56
3.1. Organization of the intervention team	56
3.1.1. General coordinator	56
3.1.2. Responsible for the information system	57
3.1.3. Laboratory analysis of HPV	57
3.1.4. Cytology analysis	57
3.1.5. Responsible for VIA	57
3.1.6. Responsible for the area of gynecology and colposcopy	57
3.1.7. Responsible for the area of recruitment, education and monitoring of patients	58
3.1.8. Responsible for the histopathology laboratory	58
3.1.9 Responsible for hospital infrastructure and medical support	58
3.2. Study population	59
3.2.1. Phase 1: cervical cancer knowledge assessment	62
3.2.2. Phase 2: assessment of acceptance and confidence in self-sampling	62
3.2.3. Phase 3: Evaluation of the agreement in the HR- HPV detection between the self-sampling and the physician-sampling	62
3.2.4. Phase 4: Evaluation of HPV self-sampling on screening coverage	62
3.2.5. Phase 5: Sensitivity, specificity and predictive values of HR-HPV performed on self-samples, to detect CIN 2+ or worse lesions in a primary screened population	63
3.2.6. Phase 6: Sensitivity and positive predictive values of Pap smear and VIA to detect CIN 2+ or worse lesion in a HR-HPV DNA positive population	64
3.2.7. Phase 7: Analysis of the lost samples in the study population	64
3.2.8. Phase 8: Quality control on biopsy analysis	65

3.2.9. Phase 9: Determination of the of use of different behaviors and therapeutic treatments for CIN, CIN2, and CIN 3 lesions in 2 nd level hospitals	65
3. 3. Exclusion and inclusion factors	65
3.4. Procedures	66
3.4.1. HPV Self-sampling collection procedure	66
3.4.2. HPV physician- sampling collection procedure	69
3.4.3. Surveys	69
3.4.4 Screening strategies	73
3.4.4.1. Mobile strategy	73
3.4.4.2. Stationary strategy	76
3.4.5. HR-HPV DNA detection	78
3.4.6. Cytological analysis	82
3.4.7. Visual Inspection under Acetic Acid	82
3.4.8. Colposcopy	83
3.4.9. Biopsy Analysis	87
3.4.10. Refresher courses on the treatment of cervical preneoplastic lesions	88
3.5. Statistics	89
4. Results	92
4.1. Assessment of Bolivian women knowledge about cervical cancer and acceptance and confidence towards HPV test self-sampling	92
4.1.1. Age distribution and level of education of the population	92
4.1.2. Degree of knowledge about cervical cancer and HPV and their prevention	93
4.1.3. Women acceptability post self-sampling procedure	94
4.1.4. Women confidence post self-sampling procedure	96
4.1.5. Evaluation of the agreement in the HR- HPV DNA detection between the self-sampling and the physician-sampling	98
4.1.6. Impact of HPV awareness campaign and self-sampling testing on screening coverage in the District 9 of Cochabamba	100
4.2. Evaluation of the effectiveness of high-risk human papilloma virus self-sampling test for cervical cancer screening in Bolivia	103
4.2.1. Gynecological history of the population in the phases that evaluated the clinical efficacy of the cervical cancer screenings	103

4.2.2. Sensitivity, specificity and predictive values of HR-HPV detection test on self-samples, Pap smear and VIA to detect CIN 2+ or worse lesions in a primary screened population	104
4.2.3. Sensitivity, specificity and predictive values of Pap smear and VIA to detect CIN 2+ or worse lesion in a HR-HPV DNA positive population	105
4.2.4. Quality control on biopsy analysis	107
4.2.5. Screening samples lost in the study population	108
4.3. Determination of the use of different clinic behaviors and therapeutic treatment methods for CIN 1, CIN 2 and CIN3 lesion in 2nd level hospitals	108
5. Discussion	111
5.1. Is Bolivia ready to receive a new screening test?	111
5.2. Current knowledge on cervical cancer and HPV	113
5.3. Acceptability of self-sampling collection	113
5.4. Confidence in self-sampling collection	114
5.5. Evaluation of the agreement in the detection of the HR-HPV between the self-sampling and the physician-sampling	115
5.6. Impact of the community participation and self-sampling on screening coverage	116
5.7. Sensitivity, specificity and predictive values of HR- HPV, Pap smear and VIA to detect CIN 2+ or worse lesions in a primary screened population	118
5.8. Sensitivity specificity and predictive values of Pap smear and VIA to detect CIN 2+ or worse lesion in a HR-HPV DNA positive population	120
5.9. Screening samples lost in the study population	121
5.10 Quality control on biopsy analysis	123
5.11. Determination of the use of different clinic behaviors and therapeutic Treatments methods for CIN 1, CIN 2 and CIN3 lesion in 2nd level hospitals	124
6. Conclusions	127
7. References	129