Self-sampling in Human Papillomavirus screening during and post-COVID-19 pandemic

Cheng Siang Tan, PhD1; Nadia Diyana Hamzah, MBBS1; Zul Hisyam Fikri Ismail, MD1; Abigail Rembui Jerip, MD1; and Mardiana Kipli, Dr ObsGyn1

1Centre for Tropical and Emerging Diseases, Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kota Samarahan, Sarawak, Malaysia; 2Bario Health Clinic #10, Ministry of Health Malaysia, Bario, Sarawak; 3Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kota Samarahan, Sarawak, Malaysia

ABSTRACT

Introduction: Cervical cancer is the third most common cancer among Malaysian women. Sarawak, the largest state in Malaysia has consistently recorded the highest cervical cancer rate in the country where nearly half of its population still live in the rural areas and is at increased risk of the disease due to inequitable access to healthcare. The nationwide lockdown due to the COVID-19 pandemic halted the accessibility to cervical cancer screening programme. The aim of the study is to determine the feasibility of providing primary HPV DNA test using the self-sampling method to the hard-to-reach population in the interior of Sarawak during the COVID-19 pandemic.

Materials and Methods: This is a cross-sectional study where women aged between 20-80 years were recruited via convenient sampling from villages in Long Banga, Sarawak over a five-day outreach programme. Cervicovaginal self-samples were obtained and screened for the presence of high-risk human papillomavirus DNA (HR-HPV) using the careHPVTM Test. A self-administered questionnaire was also administered to determine the sociodemographic and perception towards the self-sampling method.

Results: The 55 women recruited consist of ethnic backgrounds of Penan (58.18%), Kenyah (25.45%), Iban (5.45%), Saban (3.64%), Kelabit (3.64%), Malay (1.82%) and Chinese (1.82%). The prevalence of HR-HPV was 1.85% (n=1/55). Nearly 80% of the women were unemployed, and more than half have had primary education. Nine (16.4%) have heard about HPV, and seven (13%) knew HPV infection could cause cervical cancer. Three of them had HPV vaccination, and only one (1.85%) knew the brand of the HPV vaccine. Although 40% preferred self-sampling over clinician-collection, only ten (18.2%) women have completed the self-collection perception questionnaire.

Conclusion: Primary HPV DNA screening using the self-sampling method can be carried out in the remote areas during the COVID-19 pandemic without compromising mobility restriction.

KEYWORDS:
Self-sampling; Human papillomavirus; indigenous population; rural; COVID-19 pandemic

INTRODUCTION

Cervical cancer (CC) is the second cause of death among Malaysian women after breast cancer. It is ranked as the third most common female cancer in Malaysia. CC is linked to the persistent infection by one or more of the high-risk human papillomavirus (HR-HPV), although other cofactors such as multiple sex partners, early sexual debut, smoking, and co-infection with Chlamydia trachomatis, have catalytic effects on the oncogenic progression of HRHPV infection to precancer and cancer.1-2 Currently, more than 200 human papillomaviruses have been identified, with approximately 40 of them are sexually transmitted and 14 of them (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) are oncogenic and known as the HR-HPV.3-4

Cervical cancer is one of a few preventable cancers by early cervical cancer screening and effective vaccination. Cervical cancer screening through Pap smear was begun in Malaysia since 1969, and was gradually incorporated into the postnatal care programme. Three decades later, the national coverage is stagnant at around 22%, far below the recommended coverage of 80% by the World Health Organization (WHO).4-5

The strong association of HR-HPV infection with cervical cancer has triggered the paradigm shift in CC prevention strategies worldwide. For example, population-based HPV vaccination using the bivalent HPV vaccine in many countries has shown significant success in reducing the rate of CC.4 In addition to this, the more sensitive molecular assays detecting the HRHPV genomic DNA are gaining market share and is actively replacing Pap smear as the primary cervical cancer screening tool in many countries such as the Netherlands, Turkey, United Kingdom, Norway, Italy, Sweden, Germany, and Finland, while many more are in the transition state.4-5

Sarawak is the largest state in Malaysia with approximately 2.4 million people living on a 124,450 km² land, making it the least densely populated state. Nearly half of the population still lives in the rural areas and some in the remote villages with inequitable access to healthcare. It is not surprising that Sarawak has consistently recorded the highest rate of CC in the country, with the Age-Standardised Rate (ASR) of 12.1/100,000 compared to the national ASR of 6.2/100,000.6-7 Our study site was Long Banga (3.2015N, 115.4018E), a town
Within the district of Bario that lies in the deep interior of Sarawak, Long Banga is located south of Bario and consists of villages such as Long Lamei, Lio Mato, Long Spigen, Long Kerong, and Long Sait. All these villages will be referred to as Long Banga here. Due to its geographical location and economic development, Long Banga is still devoid of road access but is linked to Miri city via a 16-seat Twin Otter plane. Its surrounding villages are connected to the main towns (including Bario town) via logging trails and/or a network of rivers.

During the current COVID-19 pandemic, China has taken a controversial measure to contain the spread of SARS-CoV-2 by locking down the entire 19 million population in Wuhan city at the end of January 2020. Malaysia followed suit and enforced a nationwide lockdown termed the Movement Control Order (MCO) on the 18th March, 2020. The National Cervical Cancer Screening Programme came to a halt. If this situation remains, the delay in accessing essential healthcare will likely see an increase in women presenting with late-stage cervical cancer, a situation which will contribute to both direct and indirect mortality from this preventable and treatable disease. Even before the pandemic, as high as 76% of cervical cancer patients were only diagnosed at Stage 2 or worse.20

During the current MCO due to the COVID-19 pandemic, the whole small district of Bario, including its surrounding villages were cut off. Malaysia had eased the lockdown restriction on the 4th May, 2020 under the Conditional Movement Control Order (CMCO), restoring the courier service to Bario. With this, we took the opportunity to study the feasibility of providing primary HPV screening using the self-sampling method to the hard-to-reach population in the interior of Sarawak during the COVID-19 pandemic.

The HPV genotyping, follow-up testing, and the cytological screening results are beyond the scope of this manuscript.

MATERIALS AND METHODS

Reaching the hard-to-reach communities

A convenient sampling method was employed in this population-based HRHPV prevalence study, and we envisaged to recruit as many participants as possible over the 5-day outreach programme during the CMCO period in May 2020. Recruitment in Long Banga includes non-virgin females living in villages such as Long Banga itself, Long Lamei, Lio Mato, Long Spigen, Long Kerong, and Long Sait (see Figure 1).

Self-sampling kit

The self-collection kits were sent from Kota Samarahan to Bario town using the national courier service. Every self-collection kit consisted of a reusable ziplock bag containing a careBrush (Qiagen, Shenzhen, China), one vial of careMedium (Qiagen, Shenzhen, China), self-sampling instruction, a patient information sheet with a questionnaire and consent form.

The pictorial self-sampling instruction was adapted from the Guidelines for Primary HPV Testing in Cervical Cancer Screening in Malaysia 2019 (http://ogsm.org.my).

A questionnaire was included that consisted of questions grouped in three parts: (1) sociodemographic and socioeconomic factors like name, age, race, the highest level of education, employment status - 5 questions; (2) awareness and knowledge of about HPV infection - 4 questions; and post-sampling - 4 questions. The questionnaire was pretested on 90 women before being used.

Self-sampling

Participants were given time to go through the patient information sheet, self-collection instruction, and complete the questionnaire. Verbal instruction was given whenever necessary. Women were allowed to perform self-collection in their privacy. The instructions were the person was to take off her undergarments and place one leg on a support such as a chair or a toilet bowl. She then was to hold the free end of the careBrush’s handle and gently push the other end with the brush to the top of the vagina. When the careBrush was inserted in her vagina, the woman was to turn the handle two or three turns, remove the careBrush completely from her vagina, and put it back into the careHPV™ Collection Medium, snap the careBrush handle to break it, cap the tube, and seal it with parafilm. Finally, she was to put the specimen and other documents into the ziplock bag and return it to the health volunteers. The specimens were then consolidated and brought back to Bario town, air-flown to Miri and couriered back to the Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak at room temperature.

HPV DNA Test and reporting

Samples were screened for HR-HPV DNA using the careHPV™ Test (Qiagen, Shenzhen, China) on 20th May, 2020. Results were reported back to the health volunteers in Bario via email, and the results are communicated to the participants in-person. The HRHPV positive woman was triaged for further screening according to the National Cervical Cancer Screening Guideline, and those negative for HRHPV infection were advised rescreening in 3-5 years later.

This study was approved by the Universiti Malaysia Sarawak Medical Ethics Committee (UNIMAS/NC-21.02/03-02 Jld.3(17). All participation was voluntary, and the participants were briefed about the study, and they all provided written informed consent before their participation.

RESULTS

The mean and median age of the participants was 40.5 and 39.5 years, respectively. The cohorts from 20-29, 30-39, and 40-49 years old represented 83.6% (n=46/55) of the sample size. There was only one HRHPV positive woman detected, which gives the prevalence of 1.85% in the population. The sole HRHPV positive case was an unemployed Penan woman in the 30-39 age cohort and had only attended primary education (Table 1). Only 5.5% (n=3/55) had attained tertiary education; while 40% (n=22/55) and 54.5% (n=30/55) had attended secondary and primary education (Table 1).

Unemployment was high at 76.4% (n=42/55) as most of them are housewives. Some 16.4% (n=9/55) are self-employed or engaged in agricultural activities, and only 7.3% (n=4/55) were employed and having a stable payroll (Table 1).
All participants had completed the HPV literacy survey, with most of them (83.6%; n=46/55) stated that they had never heard about HPV. Only 16.4% (n=9/55) had heard about HPV, with seven of them knew that HPV infection could lead to cervical cancer. Of the 7 women who knew the oncogenic nature of HPV, three had received HPV vaccination, but only one knew the brand of the vaccine (Figure 2).

As for the self-sampling perception survey, only 10 (18.2%) of the participants provided their responses. Only 40% (n=4/10) stated that they preferred self-sampling, and half of them stated that self-sampling was easy to perform while the other half found it difficult. The two participants who found self-sampling easy provided self-collected vaginal samples without expressing any concern. One of the other two
participants who found self-sampling to be difficult and was concerned if she had done it right, but the other did not express any concern. Majority of the participants (60%; n=6) who have responded mentioned that they preferred clinician-collection over self-sampling, and all of them found self-sampling to be difficult and expressed concern whether they have done the procedure correctly (Figure 3).

**DISCUSSION**

This is an active population-based HRHPV prevalence study where sampling was carried out at the remote villages in Long Banga rather than hospital-based as done by other researchers. The prevalence of HRHPV in Long Banga was determined to be 1.85% (n=1/55), which is much lower than the prevalence of 8% (n=6/75) in Bario town, using the same assay in 2019. Considering both studies, the updated prevalence of HRHPV in the small district of Bario would be 5.38% (n=7/130), similar to the population-based HRHPV prevalence in other states in Malaysia such as Sabah (4.6%) and Selangor (6.5%). However, other researchers have reported a much higher prevalence in Peninsular Malaysia, ranging between 25.6-46.7%.

The sole HRHPV positive woman was a Penan in the age-cohort 30-39, which is consistent with the national cervical cancer incidence trend, which increases at age >35 years and peaks between 50-74 years old. However, we are not able to determine if the positivity correlates with cervical intraepithelial neoplasia as we did not follow-up with cytological test in this study.

All participants had attended some level of formal education. More than half of the women had reported attending at least primary education, which was not surprising as primary education is mandatory in Malaysia. Public-funded schools are being offered to citizens for free, even in the deep interior of Sarawak. Furthermore, the retention of females in school is relatively high, at least true for primary education, and we see that only 40% of the women have attended secondary education. The three participants who had attended tertiary education were government officials serving in the area, and their higher level of awareness about HPV may have distorted the actual HPV and cervical cancer awareness in the study population.

The awareness of HPV was found to be inferior among the women in Long Banga, which may be attributed to the lower education level of the participants. Most other HPV awareness studies had been carried out among the university students and consistently found that higher education level correlates with higher awareness on HPV and cervical cancer, but even so, gaps exist such as the methods for prevention, symptoms, and consequences of HPV infection. Thus, intentional and targeted campaigns are required to bring HPV and cervical cancer education to the hard-to-reach populations to improve their awareness level.

The majority of the participants who have responded to the questionnaire prefer clinician-collection over self-sampling. This is an expected response from rural women who have never been offered such a new method before. Their possible unfamiliarity with their reproductive anatomy may increase their fear of inflicting self-injury due to performing the sampling technique incorrectly. However, they were still willing to undergo self-sampling, indicating that self-sampling can be an acceptable new norm and outweigh the women’s potential shyness to be inspected by medical personnel. This is not surprising as a longitudinal study conducted by Hood et al., have revealed that 47% of women have initially indicated their unwillingness to perform self-sampling. However, when given an opportunity, they would seize the opportunity, meaning that offering an opportunity is more important than the acceptability of self-sampling method. Furthermore, population-based randomised trials have also shown that self-sampling has resulted in a four-fold increase in cervical cancer screening uptake, and HPV education on the safety of self-collection can improve the acceptance rate of the self-collection method.

Self-sampling has provided the women in Long Banga with accessibility to cervical cancer screening. It allows them to have their cervicovaginal samples collected in their privacy and at the time of COVID-19 pandemic without compromising the strict standard operating procedures imposed by the government. This study may not have accomplished the screen and treat strategy recommended by WHO, but the 55 women were successfully screened using a more sensitive method than the traditional cytology offered under the National Cervical Cancer Screening Programme. At the time of writing, the small district of Bario and the rest of the villages remained free from SARS-CoV-2 infection.
This study has several limitations. The sample size represents approximately 8.73% (n=55/630) of the female population in Long Banga, and larger sample size is desired to improve the significance of the data. We must highlight that postal service is not available to the villagers and postal delivery of self-sampling kit to individual addresses as described by Kobetz et al., is impossible. We cannot discount the possibility of improper sampling technique as it was carried out in privacy of participants but other studies have shown high-concordance between clinician-collection and self-sampling. The careHPVTM Test lacks a housekeeping gene such as beta-globin for internal control and, therefore, is not possible to validate the adequacy of the starting material. However, we must bear in mind that vaginal swab differs from cervical swab as it targets free virions secreted into the cervicovaginal fluid rather than cell-bound or genome-integrated HPV DNA. Lastly, self-administered questionnaire is open to self-report bias which could have been minimised by having a full-time interviewer.

**FUNDING**

The study was funded via the “Sigek kamek, Sigek kitak” (One for you and One for me) Campaign organised by Pink and Teal Empower and SDG Research @ Borneo Grant GL/F05/MCUN/08/2020.

**REFERENCES**


