ORIGINAL ARTICLE

The Extended Stability of Cervical Swabs in *care*HPV™ Collection Medium

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ABSTRACT

Introduction: The *care*HPV™ Test is a US FDA approved, CE mark, and WHO prequalified *in vitro* diagnostic test designed to screen for 14 high-risk human papillomavirus (HRHPV) genotypes. The *care*HPV™ Test is one of the commercial HPV test validated to be used in low resource settings, boasting the economy of processing a maximum of 90 samples per batch and a near point-of-care turnaround time of 3 hours. According to the manufacturer, cervical swabs stored in *care*HPV™ Collection Medium are stable for 30 days when stored between 2-8°C. However, we often had difficulty consolidating enough samples for a full batch-test within 30 days, especially when screening women living in the low-density villages in rural Sarawak, Malaysian Borneo. This study aimed to evaluate the stability and repeatability of cervical swabs preserved in *care*HPV™ Collection Medium stored at 4°C exceeding the recommended 30 days using the *care*HPV™ Test. **Methods:** Two groups of confirmed HRHPV-positive and HRHPV-negative cervical swab samples in *care*HPV™ Collection Medium consisting of 4 samples each were maintained at 4°C and tested using the *care*HPV™ Test at Day -38, -123, -131, -223, and -395. **Results:** All cervical swabs in the *care*HPV™ Collection Medium stored at 4°C remained stable for testing and demonstrated 100% repeatability for at least 395 days from the day of collection. **Conclusion:** The *care*HPV™ Test can be successfully performed on cervical swabs preserved in *care*HPV™ Collection Medium, which were stored at 4°C for at least 395 days.

Keywords: *care*HPVTM, Human papillomavirus, Cervical swabs, Extended stability, Cervical cancer

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INTRODUCTION

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women worldwide. Cervical cancer is responsible for approximately 570,000 cases and 311,000 deaths annually (1). It was estimated that more than 80% of cervical cancer incidences were from low and medium-income countries (LMICs) that lack organised screening and human papillomavirus (HPV) vaccination programmes(2). There is also a significant disparity between the urban and rural populations(3,4), mainly due to the inequitable access to proper healthcare facilities, poverty, and other cofactors (5).

Human papillomavirus (HPV) is the primary factor in the development of cervical cancer (6). Currently, more than 200 HPV genotypes have been identified with approximately 40 genotypes are sexually transmitted, and 14 of them are oncogenic and referred to as high-risk HPV (HR-HPV) (7). Since oncogenesis from infection to the development of precancerous lesions and cancer is a long and complicated process, this opens up a window of opportunity for prevention, diagnosis, and treatment (8). Early cervical cancer screening combined with HPV vaccination will effectively reduce cervical cancer incidence, as demonstrated in many developed countries (1). Cervical cancer screening using the conventional Papanicolaou (Pap) smear was initiated in Malaysia in 1969, with an annual cost of approximately RM3.55 million (approximately USD800,000) in 2003 (9). Despite the investment, the national Pap smear coverage was only 23% in 2002 and 22% in 2012, far from the recommended coverage of 80% by the World Health Organisation (WHO)(10). Pap smears have a very high specificity of 98-99%, but their sensitivity is generally accepted as 50% (11). A successful Pap smear programme with trained healthcare professionals, including smear takers, cytotechnologists, cytopathologists, colposcopists, and programme managers, could achieve a sensitivity of 75% (11). Nonetheless, a cross-sectional study in 2013 involving 316 eligible women in West Malaysia

showed a very high non-adherence rate to the Pap-free program, revealing other problems with the Pap smear programme (12).

HPV DNA tests can only be performed using molecular techniques, as the virus is not readily culturable nor elicits any meaningful immune response to the infecting virus(13). Numerous commercial molecular tests have been developed based on either the template amplification or signal amplification techniques. Digene® Hybrid Capture 2 (Digene HC2) (QIAGEN) is one of the commercial HPV DNA tests that employ the signal amplification technique. Digene® HC2 is currently the most widely used HPV test in the United States and remains the gold standard in HPV diagnostics(14), although newer methods are gaining market share worldwide. A simplified version of Digene® HC2 known as the careHPV™ Test has been developed for use in low-resource settings, with portability, economy, and a turnaround time of approximately 3 hours, ideal for use in the rural areas, as long as reliable power is available (15). The *care*HPV™ Test screens for 14 known HRHPV genotypes (HPV16,18,31,33,35,39,45,51,52,56,58,59,66 and 68) with the semiquantitative positive cutoff value that correlates with cervical intraepithelial neoplasia 2(CIN2) or worse(16,17). The *care*HPV™ Test is a closed-batch system running on a 96-well plate format and handling up to 90 samples per batch(18). Cervical swabs obtained using the careBrush (QIAGEN) and stored in the corresponding *care*HPV™ Collection Medium (QIAGEN) are stated to be stable at 15-30°C and 2-8°C for 14 days and 30 days, respectively(19,20), a property that is crucial for the transportation and consolidation of specimens for batching purposes.

Sarawak, Malaysian Borneo, has a population of >2.47 million based on the 2010 census (21) with a low population density of 23/km2. Approximately half of the population lives in rural areas, many of which are still inaccessible by road(22). The rate of cervical cancer in Sarawak is currently the highest in Malaysia, with an age-standardised rate (ASR) of 12.1/100,000 compared to 3.8/100,000 in Kelantan, West Malaysia (National mean ASR=6.5, 2011)(21). This is not surprising, as women living in low-resource settings are often at higher risk of developing cervical cancer and have poorer prognosis due to the inaccessibility to a proper healthcare facility, poverty, lack of awareness, and the presence of other cofactors(5,23).

Our team conducts monthly cervical cancer screening in rural Sarawak using the *care*HPV™ Test and visual inspection using acetic acid (VIA) as part of the capacity building effort towards the Screen and Treat Strategy as recommended by the WHO(24). As much as the same day *care*HPV™ result is desired to triage high-risk human papillomavirus (HRHPV) positive women for VIA and treatment, we found it to be a challenge to achieve the maximum batch capacity of the *care*HPV™ Test. It would be sensible to consolidate samples collected from a few outreach programmes to achieve the maximum economy of the batch capacity, but this is limited by the recommendation that samples can only be stored for no more than 30 days if stored at 2-8°C. The purpose of this paper is to study the stability and repeatability of clinician-sampled cervical swabs stored under refrigeration in *care*HPV™ Collection Medium over a period of 1 year (the recommended storage of 30 days).

MATERIALS AND METHODS

The clinician-collected cervical swabs preserved in *care*HPV™ Collection Medium were residual volumes from the *care*HPV™ test performed on 22nd April 2019 in Bario, Sarawak, Malaysian Borneo (15). The samples were transported back to the Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, at room temperature and then stored at 4°C until use. Four HRHPV-positive (Pos-1-4) and four HRHPV-negative (Neg-1-4) samples were randomly selected and consistently tested together with new batches of samples in the subsequent *care*HPV™ tests at Day-38, -123, -131, -223, and -395 using the protocol recommended by the manufacturer. Briefly, free HPV DNA is hybridized by complementary RNA, then captured by DNA/RNA hybrid-specific antibodies coated on the magnetic beads. The captured DNA/RNA hybrids are detected by alkaline phosphatase conjugate, that reacts with an added chemiluminescent substrate to produce light (expressed as relative light unit [RLU] which is proportional to the number of bound alkaline phosphatase molecules per target. The samples were recorded as positive if achieved or surpassed the threshold of 1.0 relative light unit coefficient (RLU/CO), which corresponds to 1.0pg/mL of HPV DNA(16). The *care*HPV™ test performed on 22nd April 2019 represents Day-0. Test days follow the batch test and are not scheduled as a separate study, filling the blank wells that would otherwise be wasted. The study was approved by Universiti Malaysia Sarawak Medical Ethics Committee UNIMAS/NC-21. 02/03-02 Jld. 3 (17).

RESULTS

All four previously tested positive samples (Pos1-4) yielded positive results, while all four previously negative samples (Neg-1-4) yielded negative results when tested at Day-38, -123, -131, -223, and -395, demonstrating 100% stability and repeatability compared to their initial results from Day 0 (Table I).

DISCUSSION

The *care*HPV™ Test is US FDA approved, CE mark, and WHO prequalified in vitro diagnostic test that has been extensively evaluated in numerous countries (18,25–28), Most literature on the use of *care*HPV™ has described the permanent installation of *care*HPV™

Table I: The Detection of HRHPV DNA from the confirmed positive and negative specimens stored in *care*HPV™ Collection Medium at 4°C at Day-0, -38, -123, -131, -223, -395 using the *care*HPV™ Test.

Specimens	Day-0	Day-38	Day-123	Day-131	Day-223	Day-395
Pos-1	+	+	+	+	+	+
Pos-2	+	+	+	+	+	+
Pos-3	+	+	+	+	+	+
Pos-4	+	+	+	+	+	+
Neg-1	-	-	-	-	-	-
Neg-2	-	-	-	-	-	-
Neg-3	-	-	-	-	-	-
Neg-4	-	-	-	-	-	-

instruments in established public healthcare facilities serving a high-density population, such as Drum Tower Hospital, Nanjing, China (29), within the second largest city in China, Moi Teaching and Referral Hospital, Eldoret, Kenya (30), the largest referral hospital in West Kenya, Barretos Cancer Hospital (BCH), Barretos, Sao Paulo, Brazil (31), Maternal and Child Health Hospital in Bachu County, Xinjiang, China (32), and the Institute of Cytology and Preventive Oncology, Uttar Pradesh, India (27), in the outskirt of New Delhi. They used the opportunistic sampling method, recruiting patients attending their facilities for consultation that may not be related to cervical cancer. Therefore, collecting a sufficient number of specimens for a complete batch-test during the recommended storage period may not be a matter of concern. However, our targeted population in rural Sarawak is of low density and may not readily have access to proper healthcare facilities, whereby bringing healthcare to them through medical outreach programmes may be the best option.

The *care*HPV™ Test protocol involves seven manual stages offering a realistic turnaround time of 3 hours. Despite its robust design, the *care*HPV™ Test System cannot tolerate power interruption. It will reboot itself back to the first stage, a default response that effectively voids the batch and wastes the *care*HPV™ Test Kit(18). Nevertheless, the high repeatability of samples in the *care*HPV™ Collection Medium allows storage, further consolidation, and retest at a future date to be carried out with confidence. Furthermore, samples with confirmed results can be used as positive and negative in-house controls.

Researchers in Denmark have reported the stability of self-collected vaginal swabs stored between 4-30 °C for up to 32 weeks without any significant increase in the Ct value (33). Other researchers have reported the stability of cervical swabs for up to 28 days when stored at fluctuating ambient temperature (34) and 4 °C (34,35). The shortest stability reported was one week when the self-collected vaginal swabs were stored at -20 °C prior to rehydration and testing (36). The prolonged stability of HPV DNA in various brushes and storage medium is not surprising as HPV virions are non-enveloped, icosahedral capsids, and double-stranded circular genome(37), all the ideal characteristics that confer stability to both the virion and its genomic materials.

This manuscript mainly discusses the extended stability of samples in storage for the benefit of consolidation to achieve the economy of a full batch test. However, the *care*HPV™ Test Kit with a lower capacity of 18 samples per batch in 24-well format is available (19) and would be ideal to be used as the primary cervical cancer screening method in the low-density population, such as in Sarawak. However, the 24-well format is not available in Malaysia at the time of writing.

Although the repeatability of the results shown using a small number of verified samples is high, we do not recommend prolonged storage of untested samples beyond the manufacturer's recommendation, as delayed results may not have significant clinical benefit for women. However, in an unforeseen event where stored samples are tested outside the recommended storage duration, such as during laboratory shut down due to the coronavirus disease-19 pandemic may still be valid if resampling is not feasible.

CONCLUSION

The *care*HPV™ Test can be successfully performed on cervical swabs preserved in *care*HPV™ Collection Medium, which are stored at 4°C for at least 395 days.

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