Dear Editor,

Please find enclosed a modified version of my Microreview manuscript “HPV to cervical cancer: prevention and screening in developing countries”. To address the concerns and comments raised by the 3 reviewers, I made the following changes to improve and clarify the manuscript. It is my hope that these changes make the manuscript acceptable for publication in Microreviews in Cell and Molecular Biology.

Sincerely,

Madeline Minnix

1. Expanded upon my information
2. Fixed grammatical errors
3. Added a new study to help with understanding

**HPV to cervical cancer: prevention and screening in developing countries**

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**Key Words:**

Cervical cancer, Human papillomavirus, HPV, Pap smear, screening, prevention

**The human papillomavirus, or HPV, is a cornerstone when it comes to cervical cancer. The virus can be detected in approximately 99.7% of all cervical cancers. In poorer countries, cervical cancer is a leading cause of cancer deaths among women. For this reason, it is critical to screen for the virus, as well as get vaccinated against HPV before it has the opportunity to infect and cause cancer. Cervical cancer is screened in women through a few different methods. The most common screening technique is annual pap smears, but these result in a high number of false positives and are especially difficult to screen for in developing countries due to lack of trained professionals and supplies availability. Because of this difficulty, large randomized control trials have looked at screening for HPV to detect and prevent cervical cancer. Three trials conducted in three south American countries compared the efficacy of HPV-based screening and cytology-based screening over a median six-year period. They evaluated the study based on participation in different screening methods and follow-up appointments by those diagnosed. Against cervical cancer, their findings showed that HPV-based screening beginning at age 30 provides 60-70% greater protection in comparison to cytology.**

**Introduction**

In 2012, cervical cancer was the fourth most common cancer among women and ranked seventh overall among all cancers [1]. The human papillomavirus (HPV) is vital in understanding cervical cancer as its DNA is found in 99-99.7% of invasive cervical cancers. HPV is considered a sexually transmitted disease (STD) because the virus can pass from person to person during sexual activity. The STD arises from someone infected with oncogenic HPV that can form precursor lesions of cervical cancer, high-grade squamous intraepithelial lesions (HSILs), also referred to as high-grade cervical intraepithelial neoplasia (CIN) [2]. The goal with screening for HPV is to hopefully detect and treat the virus before it has the chance to evolve into full-on cervical cancer. The earlier the virus is detected, the more likely women are to overcome the disease.

Worldwide, the prevalence of cervical cancer is not evenly distributed. In industrial countries, cervical cancer incidence has been on the decline due to primary and secondary prevention methods in addition to widespread information campaigns. Primary prevention of cervical cancer targets HPV directly through vaccination. Three different brands of vaccines are administered based on availability and cost, but some vaccines protect against more types of cervical cancer than others. The World Health Organization recommends females get vaccinated between 9-14 years old and before they are sexually active. Secondary prevention of cervical cancer seeks to detect the presence of cancer. One of the most common screening procedures is a Pap smear. This procedure is performed by collecting a tissue sample from the cervix and looking for the prevalence of precancerous lesions [3]. These prevention and detection methods are readily available to all women in developed countries with little to no hassle. Developing countries lack easy access to these prevention methods as well as education about the virus, leading to a much higher incidence rate in these countries. The more impoverished regions account for 87% of cervical cancer deaths worldwide. This is substantial when considering women face an initial cervical cancer incident risk increase at 20 years old, and they reach the peak risk anywhere from 40 to 50 years old. Screening helps to lower these risks by detection and treatment of cervical cancer precursors. To see the effects of providing increased access to screening and treatments, over a quarter million women were provided with access to varying screening procedures in Guatemala, Nicaragua, and Honduras.

**Recent Progress**

 With the prevalence of HPV vaccination and screening becoming more easily accessible to even the poorest communities, the World Health Organization (WHO) was prompted to declare that it is possible to eliminate cervical cancer as a public health problem. This comes as the Scale-Up project was introduced in parts of Central America. The Scale-Up project is the follow-up project to PATH’s 2011 project START-UP (Screening Technologies to Advance Rapid Testing for Cervical Cancer Prevention—Utility and Program Planning). The START-UP project found that cervical or vaginal HPV testing had more favorable results than a visual inspection with acetic acid (VIA) or the more common Pap smear testing in a resource-limited environment. The success of this study led to the continuation of Scale-Up.

Scale-Up was implemented from 2015 to 2018 in selected regions of 3 different Central American countries—Guatemala, Honduras, and Nicaragua—in coordination with the Central American ministries of health (MOHs). El Salvador was also included, but they followed a different timeline, so their findings are likely to be reported soon, and they were not included in this particular review. There were three phases included in the Scale-Up project: preparation, pilot testing, and expansion. The goal of this project was 1.) raising community awareness about HPV and cervical cancer, 2.) facilitating adoption and encouraging HPV testing, 3.) vaginal self-sampling for test specimens to facilitate rapid screening uptake, and 4.) developing indicators to be monitored throughout. Each country selected its target population for the treatment [4].

In this study, a total of 231,741 women were screened using HPV tests. Three different tests were used in this phase (Pap, VIA, and HPV), but the HPV test was the most popular method used with 59.7% overall. In Guatemala, 52.0% of screenings were conducted using the HPV tests (N=85,226), 76.3% in Honduras (N= 72,873), and 52.3% in Nicaragua (N = 73,642), as displayed in figure 1. HPV screening of self-collected samples was above 90% in both Nicaragua (97.1%) and Guatemala (90.2%). In Tegucigalpa, Honduras, 74.0% were reached via self-collecting samples, which considerably increased the number of overall tests in the area. The test results showed that 13.6% of women tested were found to have HPV detected. Guatemala had the lowest percentage of HPV (12.4%) followed by Nicaragua (14.2%) and Honduras with the most (14.5%) as noted in figure 1 below.

***Figure 1.******Comparison of the percentages tested for HPV and the percentage of those diagnosed.***

After the screening phase, the participants whose screens detected HPV were triaged and further treated. There was some difficulty, however, in getting women to return for follow up treatment. Overall, 73.7% of the women who tested positive for HPV showed up for triage. The highest follow-up percentage was in Nicaragua, with 85.5% of women following up. This was followed closely by Guatemala, with 84.2% women returning. Lastly was Honduras, with only 50.1% women returning.

This experiment was successful in providing nearly half a million women with HPV/cervical cancer screening. Many participants in this trial reported that it was their first time receiving HPV or cervical cancer screening of any kind. This is a huge accomplishment because it is likely that cancers and precursors that would have gone undetected were able to be caught and treated. It also provided data about the efficacy of different types of testing work in poorer regions. It provided insight into who was likely to return for triage and treatment based on the test type and makeup of the population. One of the biggest challenges in these underserved areas is the availability of screening resources, but by offering access through this process, many women were able to receive a diagnosis and treatment.

**Discussion**

 Because of the uneven distribution of cervical cancer infections and the even harsher reality of death percentage in poorer countries, tools to close the HPV infection gap are necessary. Low burden solutions and education seem to be providing a way to lower this discrimination. When self-collected samples were introduced in this project in the third year of screening, the number of women tested increased. The self-collection of samples allows women to bypass the uncomfortable pelvic exam that might deter some women from visiting a doctor. In addition, it decreases the need for a larger number of trained professionals required for pelvic examinations, Pap smears, and VIA that might be difficult to come by in some areas. Education of the population is also essential. Knowing that this cancer is caused by a virus that is transmitted sexually and can be prevented through safe techniques can lead to more women protecting themselves.

 This model of promoting screening procedures in more impoverished regions and countries would go a long way in helping decrease the number of deaths caused by cervical cancer. If this model were replicated in rural African areas where information and screening for HPV and cervical cancers are low, countless lives could be helped. The first thing women need to know is their risk factor. The presence of HPV in the body does not necessarily mean that you will get cervical cancer, but the chances are astronomically increased. In the studies conducted in Central America, several women were screened for the first time. Without this screening, they would have never known to seek treatment at this early stage. Like most cancers, early detection of the virus or cancer results in the best outcomes.

 One of the questions that I feel this research failed to address was the prevalence of HPV vaccines in countries with a poorer demographic. Would the population see fewer HPV and cervical cancer precursors incidences if there was widespread administration of HPV vaccines to the younger population? And, would there be any benefit to male vaccination as a way to prevent transmission to females during intercourse? In the United States, a study was conducted that evaluated the cost effectiveness of vaccinating 12-year-old boys in addition to 12-year-old girls. Their findings showed that it was potentially cost effective to administer HPV vaccines to males in areas where female vaccination was low [5]. However, when considering all of the other side effects associated with HPV, vaccination does become more cost effective for the male population. In countries with poorer demographics, like the ones that participated in the Scale-Up study, could likely prevent illness and save the country money in the long run.

 Ideally, women all over the world would receive the HPV vaccine at a young age to prevent some of the most common types of cervical cancer and then turn to secondary prevention from age 20 on via annual screening procedures. However, that is not always feasible for women all around the world. So, until access to lower burden screening solutions are available, we will be unable to reach the WHO’s ultimate goal: elimination of cervical cancer as a public health problem.

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