

# SECTION 12: COUNTRY EXPERIENCES WITH INTEGRATING HPV TESTING IN NATIONAL CERVICAL CANCER SCREENING PROGRAMS

## UNITED STATES OF AMERICA

Through the first half of the 20th century, the United States (U.S.) had a high burden of cervical cancer, similar to the current situation in many low- and middle-income countries. The introduction of Pap smears in the 1950s was the starting point for screening in the U.S. (Benard VB *et al.* 2014). Although clinical trials to evaluate its potential effectiveness were not carried out before its implementation (Cuzick J *et al.* 2008), opportunistic Pap tests resulted in the first successes in early detection of cervical cancer. The drastic reduction in cervical cancer cases and deaths in the ensuing decades (Benard VB *et al.* 2014) demonstrated the effectiveness of Pap tests and led to the preparation of clinical guidelines. Although the cervical cancer incidence rate continues to decline, over 12,000 women develop the disease every year (Benard VB *et al.* 2014). In 2011, over 4,000 women died from this very preventable disease. In 2012, while 88.8% of women in the U.S. had been screened in the preceding five years, approximately 8,000,000 women had still not been screened for cervical cancer.

To date, the U.S. does not have an organized national cervical cancer screening program. There is, however, the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) which provides screening services to women living at, or below, 25% of the federal poverty line and who do not have health insurance or sufficient coverage (Lee NC *et al.* 2014).

### Introduction of HPV testing

In 1999, the U.S. Food and Drug Administration (FDA) approved the use of an HPV test (Digene Hybrid Capture 2) as a triage method, for follow-up of women screened by cytology and with atypical squamous cells of undetermined significance (ASCUS) (Saraiya M *et al.* 2013). Its use grew after a large study confirmed its effectiveness for triage (Solomon D *et al.* 2001). NBCCEDP began to authorize HPV test triage as part of its program in 2002 (Saraiya M *et al.* 2007). In 2003, the FDA approved dual testing with HPV and Pap tests in women aged 30 years and older. Immediately afterwards, the American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society (ACS) changed their screening guidelines to recommend screening with dual testing or the Pap test alone, both at an interval of three years (Saraiya M *et al.* 2013).

In 2012, the U.S. Preventive Services Task Force (USPSTF), ACOG, and ACS consolidated their cervical cancer guidelines (Saraiya M *et al.* 2013) While the new guidelines maintained the option of Pap tests at a three-year interval, they gave preference to co-testing with HPV tests and Pap test in women aged 30 and older and increased the screening interval to every five years due to the high negative predictive value of the HPV tests (Bulkman NW *et al.* 2007; Dillner J *et al.* 2008; Naucler P *et al.* 2007). That same year, NBCCEDP included co-testing in its program (Benard VB *et al.* 2014). In 2014, the FDA approved the first HPV test for primary cervical cancer screening in women aged 25 years and older, after a large study confirmed effectiveness similar to the Pap test. Immediately, the Society of Gynecologic Oncology (SGO) and the American Society for Colposcopy and Cervical Pathology (ASCCP) recommended HPV testing as primary screening for women starting at age 25 years, with three-year intervals after a negative result (Huh WK *et al.* 2015).

## Lessons learned

The following lessons, based on the experience of the United States with opportunistic screening, can be important for other countries in their first steps to integrate HPV testing into a screening program.

Over the years, groups of experts made changes to U.S. cervical cancer screening recommendations to keep them updated with scientific advances and better understanding of the disease. Unfortunately, these continuous changes resulted in major confusion among health care providers about the screening methods they should use, which intervals are appropriate, and the target age groups. Many providers hurried up to adopt HPV testing in their practice, but without following the recommended increase in screening interval. Some even started doing yearly co-testing instead of adhering to the three and now five-year interval. Cervical cancer screening recommendations need to be clear and consistent since their implementation time tends to be long, and years can go by before physicians and other health care providers begin to use the guidelines in their practice.

There are disparities in cervical cancer screening in the U.S. The screening coverage is generally high, but it is notably lower in areas of the country with less infrastructure and economic resources. The southern region reports more cases and more deaths from cervical cancer and a greater percentage of women who have not been screened in previous years in comparison with other regions of the country (Benard VB *et al.* 2014). The United States Affiliated Pacific Island Jurisdictions (USAPI) are another example where health care providers recognize the lack of resources and the high cost of Pap tests as important barriers to cervical cancer screening (Townsend JS *et al.* 2014). HPV testing can be a feasible screening option in low resource environments since testing can be done by self-sampling, and it usually requires fewer financial, technical, and human resources to obtain results.

## MEXICO: Introducing HPV testing and lessons learned

National and international scientific evidence shows that the human papillomavirus (HPV) test offers several advantages, among them:

- Greater sensitivity and specificity for detection of precursor lesions.
- Greater ease in sample collection.
- Greater screening coverage, especially in marginalized areas.

Furthermore, in a study in rural Mexico, comparing the effectiveness of HPV self-sampling with Pap tests, the HPV test was found to detect 4.2 times more women with invasive cancer than when using the Pap test (Lazcano-Ponce E *et al.* 2011).

For these reasons, Mexico first introduced HPV testing into the cervical cancer screening program in 2008, when Hybrid Capture 2 (HC2) was introduced in a pilot program in Morelos. HPV testing was expanded in 2009 to 21 states with 12 regional laboratories, prioritizing municipalities with a lower Human Development Index. In 2010, 32 states integrated HPV testing with HC2 for primary screening into their cervical cancer screening programs.

The introduction of this new technology in Mexico offers several lessons. These lessons are primarily related to the actual conditions in the health system where the technology is implemented. In particular, it was necessary to ensure that testing can be sustained over time without interruption and that follow-up and treatment services were available in the health system networks. Furthermore, health workers and the public needed to learn about HPV testing and accept the new technology. The following is a summary of the lessons learned:

- The biggest challenge was health worker acceptance of HPV testing, and changing the paradigm from Pap testing to HPV testing.
- Funding for the purchase of HPV test equipment and supplies needs to be ensured.
- An operational “platform” that ensures follow-up and treatment needs to be ensured.
- It is important to disseminate information among both physicians and the public about HPV infection, its relevance and meaning and the burden of cervical cancer.
- An algorithm for care needs to be developed and followed by all providers. The choice of follow-up algorithm is fundamental to the strategy’s success.
- Planning services need to consider the increase in number of women who will need follow-up care.
- The HPV test results given to women need to be accompanied by appropriate counseling to decrease loss to follow-up care.

## ARGENTINA:

### Implementation of the demonstration project for the introduction of HPV testing in the province of Jujuy

In Argentina, the National Cervical Cancer Prevention Program was re-launched in 2008, with the view to increase screening coverage in the target population, assure laboratory quality, timely diagnosis and treatment for women with precancerous lesions, and to implement an information system for monitoring and evaluation (Arrossi S *et al.* 2015). This work was initiated in Jujuy, in Northwest Argentina, one of the provinces with the highest cervical cancer mortality. Initially, the cytology based screening program was strengthened by equipping pathology laboratories, providing them with computers and implementing a screening information system, a nationwide online database. By the end of 2011, Jujuy had successfully met the screening program goals for coverage, diagnosis, and treatment rates. All Pap tests and biopsies had been registered into the information system, enabling all stages of the screening process to be monitored, from determining the screening coverage, to actively searching women to provide results and assure follow-up care.

Based on this experience, the National Cervical Cancer Prevention Program began the Demonstration Project for the Introduction of HPV Testing in Jujuy Province in 2011. The project is part of a national strategy that also includes introduction of HPV vaccination for girls aged 11 years.

The four-year Jujuy Project (2011-2014) was a project to develop, implement, and evaluate the programming components of a screening strategy based on HPV testing. It involved the introduction of screening based on HPV testing for all women aged 30 years and older, along with cytology as a triage test in HPV positive women. Cytology is taken together with the HPV testing, but it is only processed in the laboratory if the HPV test result is positive. All women with abnormal cytology results are referred to colposcopy and biopsy if necessary.

The goals of the Jujuy Project were to introduce HPV testing in all of the 270 health facilities and to achieve 80% screening coverage of the target population -women aged 30 to 64 years- which corresponds to an annual screening goal of 18,700 women.

Project implementation included the following activities as key components:

1. Presentation of the proposal to the national authorities and to representatives of provincial health programs and healthcare providers.
2. Establishment of a scientific advisory council, with representatives from scientific societies, national universities, NGOs involved in cervical cancer prevention, and international organizations, such as PAHO and IARC.
3. Development of screening, diagnosis, treatment algorithms in consensus with the country's main scientific societies and design of the provincial referral and counter-referral network.
4. It was established that the HPV laboratory would be set up as a service of the cytopathology laboratory centralizing the reading of all cytologies for women aged 30 years and older.

5. Communications materials were designed, and trainings were held for all healthcare providers involved in cervical cancer prevention in the province, including health center directors, gynecologists, and more than 700 health agents who belong to the provincial health system.

An evaluation of the first year of implementation showed that by the end of 2012, all provincial health centers were offering the HPV test and that 22,834 women had been screened, of which 99% were aged 30 years and older. Of these women, 13% were HPV positive and in this subgroup, 807 women had an abnormal cytology. In total, 191 CIN2+ lesions were found, of which 68% had been treated by December 2013 (Arrossi S *et al.* 2015).

As part of the Jujuy Project, the EMA study was carried out to evaluate the acceptability and effectiveness of HPV self-sampling to increase screening coverage. This was a population-based cluster-randomized study, which compared the effectiveness of HPV self-sampling with HPV testing performed in health facilities by medical professionals. The EMA study found that 86% of women accepted HPV self-sampling, and four times more women were screened as a result of the self-sampling strategy as compared to facility based screening (86% versus 20%) (Arrossi S *et al.* 2015).

The Argentine Ministry of Health then decided to expand HPV testing to the rest of the country, phasing in implementation. In 2015, the provinces of Tucumán, Neuquén, Misiones, and Catamarca were added, and extension of the program to the province of Buenos Aires is expected in 2016.

## Main lessons

- The introduction of testing needs to be part of a public health decision and strategy to reduce cervical cancer. Political commitment from health authorities is essential. Political commitment should result in actions to ensure coverage: the HPV test has an expiration date and needs to be used!
- Introducing HPV testing strengthens the impact of prevention activities but does not solve organizational problems; certain organizational conditions are prerequisites to testing implementation.
- Inclusion of testing needs the greatest consensus, agreement, and support possible from stakeholders in cervical cancer prevention.
- Inclusion of HPV testing boosts will, it is a mobilizing agent, but it does not supplant organizational work, with services, healthcare providers, and the community, necessary for taking a qualitative leap in cervical cancer prevention.
- It is possible to achieve high adherence to screening ages by professionals, but this can only be achieved through the coordinated action of all healthcare providers.
- Training/information of health professionals is essential to ensure they are all familiar with the test, its scientific basis, and that it is used as part of an organized program with a public health approach.