



As half a dozen African countries roll-out national HPV vaccine programmes, these schoolgirls read why they need the vaccine.

## PUBLIC HEALTH

# Prevention comes of age

*Sub-Saharan countries lag behind in screening and treatment for human papillomavirus. But national efforts and the introduction of low-tech methods could change that.*

BY MICHAEL EISENSTEIN

It winds its way across bumpy terrain packed in coolers loaded in the back of trucks, lashed to bicycles or even carried by hand. But however it gets there, the human papillomavirus (HPV) vaccine, a key weapon in the fight against cervical cancer, is finally making its way to African communities that desperately need it.

In the developed world, access to diagnostic resources, highly trained physicians and modern medical technology has diminished the threat of cervical cancer. The UK death rate from this disease fell by 70% between 1970 and 2008<sup>1</sup>, and national vaccination programmes promise further decreases. But the picture remains bleak in the developing world, particularly in sub-Saharan Africa. In eastern Africa, for example, cervical cancer incidence and mortality rates are respectively 5-fold and 12-fold greater than in Western Europe.

In much of Africa, the problem is exacerbated by the equally high prevalence of HIV infection, which weakens women's immune defences and allows HPV to rapidly achieve the chronic infection state that is the prelude to cancer. "Because

of HIV/AIDS, we began to see cancer of the cervix appearing in very young women," says Mulindi Mwanahamuntu, a gynaecologist at the University Teaching Hospital in Lusaka, Zambia. "In some cases, we're finding it at the age of 20." Subsidized antiretroviral drugs have extended the lives of many HIV-infected patients, but the persistence of HPV means that many coinfecting women will instead succumb to cervical cancer. "We will see a huge spike in cervical cancer in the next 10 years or so, largely driven by HIV," says Lynette Denny, professor of obstetrics and gynaecology at the University of Cape Town in South Africa.

## CHEAP SHOTS HAVE BIG IMPACT

In the United States, a full course of Merck's Gardasil or GlaxoSmithKline's Cervarix vaccine costs more than US\$300 — far beyond the reach of low- and middle-income countries. However, both companies have made sizeable donations to support early-stage vaccination programmes in low-income countries, with promises of price subsidies in the future. A donation of two million doses of Gardasil over three years has allowed the government of Rwanda to embark on Africa's

first national HPV vaccination programme<sup>1</sup>, expected to reach 130,000 girls in 2012. Lesotho followed suit in January with a national vaccination programme of its own, and the Nigerian government recently announced its intention to launch nationwide HPV immunization by the end of this year.

Meanwhile, half-a-dozen other African countries are pushing towards full-scale national vaccination. European and Tanzanian physicians have joined forces to determine the efficacy and costs of school-based vaccination programmes, for example. According to Deborah Watson-Jones, an epidemiologist at the London School of Hygiene & Tropical Medicine, the programme was made possible by donations from Merck's Gardasil Access Program and the US non-profit organization Axios Healthcare Development. "After discussions with the Ministry of Health, it was agreed that we would apply for that donation for Tanzania and do a school-based vaccination programme in three districts around Mwanza city, including urban and rural areas," she says. The demonstration was a success, delivering the full course of three shots to about three-quarters of the targeted girls.





IMAGES COURTESY OF PATH

Schoolgirls at Ibanda Kyarukumba Primary School in Uganda wait their turn for the HPV jab. In Uganda, projects have reached up to 90% of target populations.

Funds from the Bill & Melinda Gates Foundation enabled the non-profit health organization PATH to conduct what many consider to be a seminal demonstration programme of HPV vaccination in Vietnam, Peru, India and Uganda. In each country, PATH ensured that national governments and local communities had a central role in designing vaccine delivery procedures to ensure maximum participation and to make it easy to rapidly expand the programmes. “We talked to parents and women’s groups and community leaders and advocates and district health officials, all the way up the chain to the national level, to get an understanding of what people knew and what information they needed to accept the vaccine,” says Scott LaMontagne, country research manager for PATH’s HPV vaccine project. The programmes proved a remarkable success, routinely vaccinating more than 80% of the target population, reaching more than 90% in some communities<sup>2</sup>.

The systematic approach adopted by PATH has guided many of the efforts that followed. According to Emmanuel Mugisha, PATH’s vaccination project manager in Uganda, education and good communication were critical. “Even among health professionals, knowledge is limited — especially about the link between HPV and cervical cancer,” says Mugisha. Health workers also confronted the association of HPV infection with poor hygiene or prostitution, and removing this stigma was critical to boosting participation. Mugisha describes a lengthy, multipronged outreach process, combining poster and leaflet campaigns, radio phone-ins, and town-hall meetings led by PATH-trained health workers from the local community. Most parents also sought additional advice. “There was a process of talking with the neighbours or aunts or other family members, or seeking further information from health workers, or even going online,” says LaMontagne.

Schools offered an ideal venue for reaching

most adolescent girls in a given community, but there were many problems. For example, most HPV vaccination programmes target girls within a specific age range, but this can be problematic in regions where birth records are patchy or non-existent and where families do not closely track calendar age. “Both Uganda and Tanzania have experienced similar challenges with age-based delivery,” says Watson-Jones. “Age literacy is quite poor in some parts of Africa, and people may guess or lie about age to get their children into school.” Furthermore, the wide scatter of ages within a given primary school could send health workers scrambling to find 10-to-12-year-old girls, disrupting teachers’ work and making tracking a challenge. “Targeting a specific class or grade is much more feasible,” says Mugisha. “If every girl in [a particular year at school] is supposed to be vaccinated, then follow-up becomes very easy even if they change schools.”

Although fewer doses may confer some protection, full vaccine efficacy requires a full course of three doses — a regimen that makes scheduling a complicated chore. Absenteeism was a primary factor in reducing overall vaccine coverage, and planners also had to contend with individual school schedules for holidays and exams, and, in some cases, differences in term structure. With insufficient resources to hire additional personnel just for HPV vaccination, health workers’ time must be planned and managed carefully before dispatching them, sometimes across considerable distances, to deliver the vaccine. This effort requires close coordination with schools, and teachers and administrators were often an important ally. “They were instrumental to the success of the programme,” says Mugisha.

**HANDLING HIDDEN COSTS**

Both Tanzania and Uganda are looking to scale up vaccination by adapting lessons learned during their demonstration programmes.

“In Tanzania, they’re going for a class-based approach with health-centre back-up for girls who miss a dose,” says Watson-Jones, “and the programme will vaccinate a younger class because we’re slightly worried about primary-school dropouts.” Thanks to donations from GlaxoSmithKline and Merck, Mugisha estimates that Uganda has vaccinated more than 30,000 girls since launching its demonstration programme in 2008, and the government is now discussing how to vaccinate on a national scale.

Efforts to scale up vaccination will benefit from the support of the GAVI Alliance, based in Geneva, Switzerland. This organization, which underwrites vaccine access for many of the world’s poorest nations, including 38 countries in Africa, announced in April 2012 that it will add the HPV vaccine to its portfolio. “All in all, almost 60 countries will have national introduction in the next few years,” says LaMontagne, “and these numbers will only increase with the commitment by GAVI to support this vaccine.”

But many programme costs will not be covered by GAVI funding. Some of these are start-up costs and will subside over time. For example, the initially high investment in education and outreach will become less prominent as vaccine messaging takes hold in communities. On the other hand, the cost of basic supplies such as syringes will remain steady. Furthermore, HPV vaccination is logistically challenging, as it cannot be bundled with existing health interventions, which are typically targeted at infants or young children. “There are generally no platforms in place for the administration of vaccine to pubescent or adolescent girls,” says Denny. In Uganda, PATH attempted to piggyback on an existing programme called Child Days Plus, which provides nutritional and anti-parasitic interventions to schoolchildren. Vaccine coverage was limited by the use of an age-based approach, but Mugisha believes this programme still offers the best opportunity. “Health workers are already going

COURTESY OF JHPIEGO

to the schools,” he says. “You’re basically just adding the HPV vaccine to their package, and that eliminates additional transport costs.”

The GAVI Alliance is helping governments get started by implementing a separate funding programme to support the launch of vaccine demonstration schemes. PATH, meanwhile, is sharing its experiences and the training materials it has developed to date. Rwanda consulted PATH while designing its national programme, for example, and LaMontagne hopes that other nations with leaner budgets could avoid some expense by drawing on lessons learned by PATH. “There’s experience to be used,” he says, “and no need for countries to think they have to start their planning from scratch.”

**SPOTLIGHT ON A QUIET KILLER**

To defeat cervical cancer, vaccination programmes must be coupled with robust screening and treatment programmes (see ‘Screen and treat’). This in turn requires political will, as the cost of sustaining any large-scale effort to control cervical cancer will ultimately fall to national governments. However, with limited resources available for a seemingly endless roster of public-health problems, including malaria, tuberculosis and HIV/AIDS, advocates for preventing cervical cancer must shout to be heard. “We’re getting a lot of requests for information and for technical assistance,” says Ricky Lu, a cervical cancer specialist at Jhpiego, a non-profit public-health organization associated with Johns Hopkins University in Baltimore, Maryland. “But ministries of health have limited resources to address many competing priorities.”

An odd silence seems to surround this killer of women, which has tragically come to be associated in some settings with immorality or irresponsible sexual behaviour. “We have women who are champions about breast cancer because they are survivors and they are able to talk about it, but it’s very rare you hear somebody talking about being a cervical cancer survivor,” says Mwanahamuntu. “This stigma exists everywhere, and it needs to stop.”

Fortunately, some of Africa’s most powerful women have taken notice. The Forum of African First Ladies Against Breast & Cervical Cancer has become a forceful voice for raising awareness, organizing conferences and bringing together medical experts and policymakers to take action. As more nations pledge their commitment to fight cervical cancer, there may be cause for hope that this disease is finally getting the attention it deserves. “Women need to be empowered to control their own sexuality and reproductive health,” says Denny. ■

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2. LaMontagne, D. S. *et al. Bull World Health Org.* **89**, 821–830B (2011).
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**SCREEN AND TREAT**

*First responders*



In Côte d'Ivoire, Tsigue Pleah (right) demonstrates cryotherapy to a local health worker.

Vaccines are a vital tool in the prevention of cervical cancer, but they’re not enough. Even if every adolescent girl were vaccinated, women already exposed to HPV would remain at risk. “We’re mopping the floor,” says gynaecologist Mulindi Mwanahamuntu of the University Teaching Hospital in Lusaka, Zambia. “But the tap is still running.”

The lack of options makes it critical to diagnose cervical cancer quickly. However, most poor nations lack resources for routine Pap smear screening. As an alternative, organizations such as Jhpiego, a non-profit health organization affiliated with Johns Hopkins University in Baltimore, Maryland, are promoting a low-cost alternative: visual inspection with acetic acid (VIA). Swabbing the cervix with an acetic acid solution, such as vinegar, turns precancerous lesions white, allowing health workers to recognize and remove them in the same visit. Removal is typically achieved by cryotherapy, using compressed carbon dioxide to cool a probe to temperatures that kill and remove precancerous cells with minimal side effects. “The cure rate for lesions of the right size — meaning less than 75% of the surface of the cervix — is around 90%,” says Ricky Lu, a cervical cancer specialist at Jhpiego. Lu adds that this single-visit ‘screen and treat’ approach is particularly valuable in poor areas of Africa where it is difficult to persuade women to return for a follow-up.

Jhpiego is helping the governments of Kenya, Tanzania, Mozambique, Ivory Coast and Burkina Faso to develop and implement national cervical cancer prevention programmes. One of the biggest success stories unfolded under the auspices of the Cervical Cancer Prevention Program in Zambia (CCPPZ), which trains Zambian health workers to perform VIA and

cryotherapy. After the implementation of VIA, and the training of health workers to perform it, screening has blossomed. “Our core team has screened over 80,000 women within the last five years,” says Mwanahamuntu, a CCPPZ director. “Before that, we barely screened 5,000 people in about 40 years.”

When properly performed by well-trained staff, VIA achieves specificity — the percentage of negative test results that represent true negatives — that rivals or surpasses the Pap smear<sup>3</sup> (see ‘Testing times’, page S8). However, the test is prone to false-positives. “It would never pass an FDA audit,” says obstetrician and gynaecologist Lynette Denny of the University of Cape Town in South Africa. But as many women in poorer nations may be screened just once in a lifetime, a tendency towards over-detection is probably better than the reverse.

The infrastructure built for VIA-based programmes can be used for other technologies when they come along. Women in high-income nations have access to kits that detect DNA from tumorigenic HPV strains, but these are expensive. However, there are high hopes for careHPV, a highly accurate test to detect HPV DNA, developed at PATH and commercialized by Qiagen, based in Hilden, Germany. This test can provide far more accurate test results than VIA in about 90 minutes. Although careHPV is too expensive to replace VIA, Qiagen has made clear its intention to make it affordable. The company has already donated 250,000 careHPV kits to Rwanda’s national cervical cancer programme, and imminent commercial launches in India and China could fuel broader demand and lower future costs. As a result, state-of-the-art diagnostics could come within reach of far more people.

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