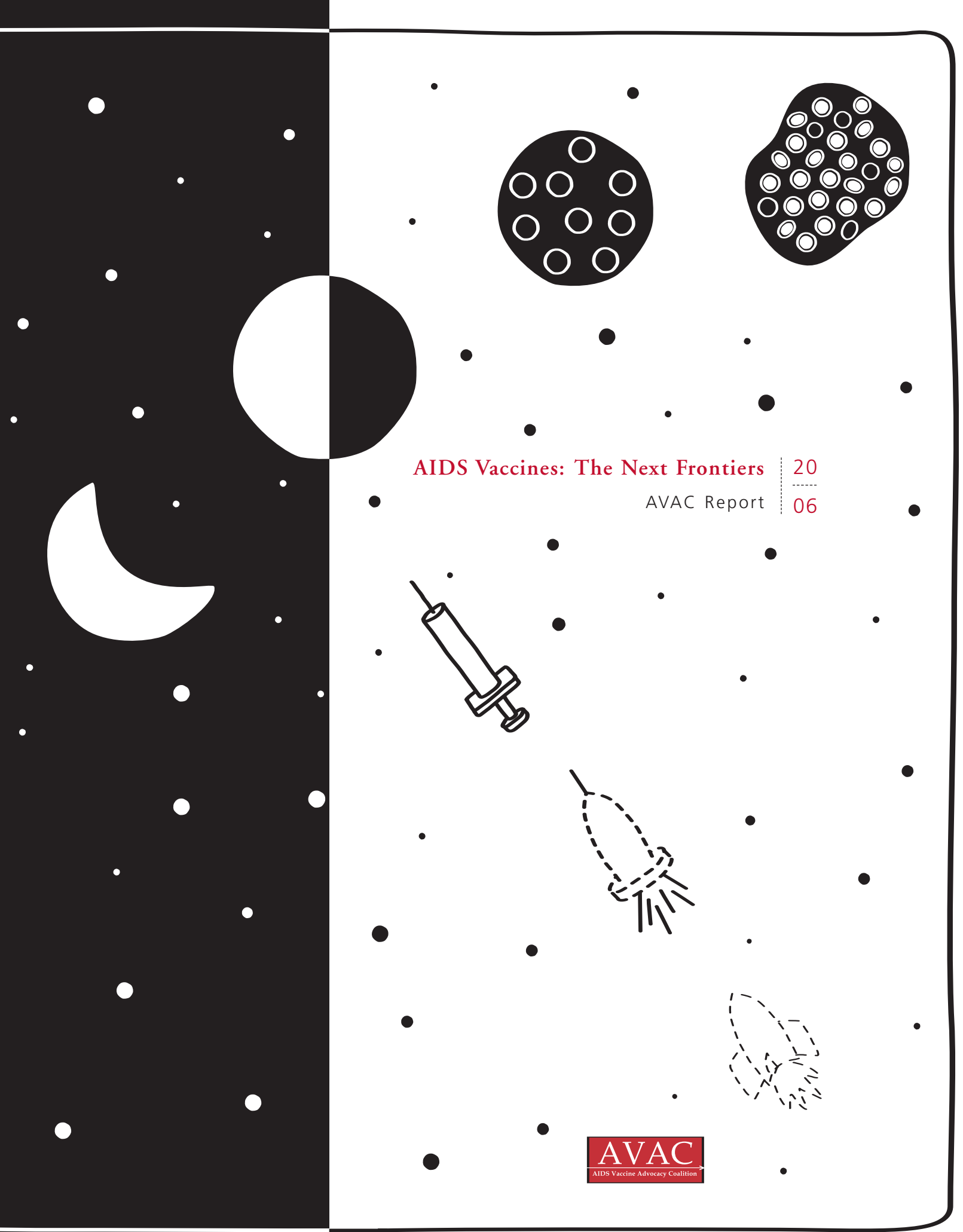

AIDS Vaccines: The Next Frontiers

AVAC Report

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AVAC
AIDS Vaccine Advocacy Coalition

03. The Emerging Adolescent Agenda: HPV Vaccine, AIDS Prevention Research, and the New Opportunities for Reaching the Young People of the World

Two years ago, in 2004, the AVAC Report examined the issue of adolescents and HIV vaccine research in its article, "The Missing Cohort." Then, we pointed out that there were compelling reasons to include adolescents in HIV/AIDS vaccine trials, and that their absence from most studies of new biomedical interventions for HIV/AIDS prevention was an obstacle to progress in the field.

Two years later, in 2006, adolescents, particularly girls and women, remain at great risk of HIV infection and other sexual and reproductive health problems. When compared with male counterparts, they are disproportionately more likely to be HIV-infected before they celebrate their sixteenth birthday. And in several countries, marriage is actually an HIV risk factor for young women, even those who practice fidelity—one of the pillars of the PEPFAR prevention policy.

Nor can we forget the needs of adolescent boys and young men. In the United States, for example, some of the highest rates of new HIV infections are found in young men of color who have sex with other men. This was true two years ago, and it is true today.

So why is AVAC re-visiting the issue of adolescents in this year's report? The answer is simple: even though the alarming statistical backdrop has remained the same, some important things have changed.

In June 2006, Merck received FDA approval for Gardasil™, its vaccine against human papillomavirus (HPV). This vaccine, which prevents infection with the HPV strains that cause cervical cancer, was found to have superb efficacy in trials of 20,000 young women around the world. The vaccine is currently licensed for use in young people up to age 26, and is likely to be most effective in pre-adolescents or adolescents before the age of sexual debut, when HPV exposure occurs. Also in June, the Bill & Melinda Gates Foundation announced a US$27.8 million grant to the Program for Appropriate Technology in Health (PATH), which will oversee pilot HPV vaccine introduction projects in India, Peru, Uganda and Vietnam.

There are also new developments on the AIDS prevention front. As South Africa gears up for HVTN 503, a study of the Merck adenovirus-based candidate, it is planning for a nested substudy of the vaccine in adolescents—the first AIDS vaccine trial of its kind. Meanwhile, there are illuminating findings coming from microbicide trials which have enrolled women as young as 16 years of age.

Taken together, these developments add up to increased momentum in the field. But the elements of a nascent immunization program for adolescent girls, and an expanding knowledge base about how to ethically enroll adolescents in HIV prevention trials, will

not automatically coalesce into an ongoing, coordinated effort to improve health and reduce disease among the world's young women and men.

There is still much work to be done on the advocacy front. And so AVAC is revisiting the adolescent issue in this year's report with the goal of identifying steps that we and others can take to ensure that the promise of current events is realized in concrete changes in the future.

Laying a foundation for the future: HPV vaccine delivery

AVAC believes that the licensure and plans for introduction of HPV vaccine are among the most important events to happen in the HIV/AIDS vaccine field this year. Of course there are important differences between HPV vaccines and potential AIDS vaccines (see Table 3), and HPV vaccines do not offer a perfect model for AIDS vaccine delivery—at this point, there is no such thing. However, taking an active interest in careful planning and implementation of delivery strategies for HPV vaccines—including honest, open analysis of what does and does not work—may be the single best step we can take to plan for access to an AIDS vaccine in the future.

Here are four important reasons why:

- **The same populations that need HPV vaccine the most also need HIV vaccines and other new prevention strategies.** Adolescent girls are at disproportionate risk for HIV infection in many parts of the developing world. In addition, adolescent boys and young men, particularly men who have sex with men, are also at high risk of HIV and must not be overlooked as a critical target population for enhanced, innovative adolescent health and wellness programs.

- **HPV vaccine presents a unique opportunity to develop a delivery infrastructure that reaches a population at grave risk for HIV/AIDS and other sexually-transmitted diseases.** An adolescent delivery platform for HPV vaccine could be enhanced or expanded to include HIV/AIDS vaccines, microbicides, male circumcision and other HIV/AIDS prevention interventions as they are identified.

- **Ensuring rapid access to HPV vaccine in high-need developing countries will upset the long-standing paradigm of delayed introduction of novel vaccines in developing countries.** It took twenty years from licensure to see widespread introduction of hepatitis B vaccine in the developing world. This is one of the many shameful examples of delays in distributing life-saving vaccines where they are needed most. AIDS prevention advocates can do more than make promises that AIDS vaccine access will not be business as usual. With HPV vaccine there is a concrete opportunity to make good on these commitments and, in the process, to build regulatory capacity at national and international levels.

- **HPV vaccine introduction requires careful messaging around scope and duration of vaccine-related prevention, screening and care for women who are already infected, and the need for continued condom use, irrespective of receipt of the vaccine.** Sound familiar? These are some of the key messages that will need to be conveyed to multiple audiences and in multiple contexts as part of the introduction of any partially effective HIV prevention intervention (see chapter 4). Getting them right in the context of HPV vaccine is critical for the program and, arguably, for multiple inter-related fields that will be speaking to the same target populations for many years to come.

There are several steps that the AIDS vaccine field can take to optimize the potential benefits of HPV—both as a stand-alone intervention and in relation to HIV prevention:

- **Advocate for international and national financing commitments to ensure widespread access to the vaccine in resource-poor settings.** The Global Alliance for Vaccines and Immunization (GAVI) has yet to determine whether or not it will finance developing countries' purchase of HPV vaccines. The HIV/AIDS prevention field can and should contribute to a strong "investment case" for this vaccine to be presented to the GAVI board, and should also lend support to groups lobbying for tiered-pricing and other strategies to make this high-priced vaccine (in the US, Gardasil™ will

TABLE 3 HPV VACCINE AND HIV VACCINES: HOW DO THEY COMPARE?

KEY SIMILARITIES	KEY DIFFERENCES
New vaccine designed to prevent a sexually transmitted infection.	HPV vaccine can be—and is being—positioned as an "anti-cancer" vaccine, which can potentially distance it from the more sensitive world of sexually transmitted infections and sexuality, especially for girls and young women.
HPV vaccine requires three immunizations; AIDS vaccines currently in development also require a series of patient visits.	Burden of disease is very different—HPV is a significant public health problem for women and accounts for substantial morbidity and mortality with some 500,000 new cases diagnosed and 250,000 deaths each year. However, no where near the scale of the HIV/AIDS epidemic.
For maximum individual and public health impact, both vaccines are ideally delivered to young people before sexual debut (i.e., 10-13 years of age). This group is not currently reached effectively by health or social services.	Low levels of awareness of cervical cancer in many settings, even among health professionals and policy makers. Even in settings where there is some overall awareness, little knowledge of association between HPV and cervical cancer.
Both vaccines have the potential to raise complex social and familial concerns about behavioral disinhibition, "promiscuity" and so forth.	For AIDS, especially in high prevalence and incidence settings, pervasiveness of educational messages—and impact on families and people—mean people will likely be more aware and willing to consider being vaccinated against HIV than against HPV which is relatively unknown on its own or in connection with cervical cancer.
A young woman's ability to access an HPV—or AIDS—vaccine will be influenced by many interlocutors— policymakers, providers, parents, and peers. In some settings, the actual people—in research, regulatory agencies, or ministries—may be the same.	AIDS has very vocal constituency and commitment and leadership at the highest levels; HPV will need to build constituency and political will.
Partial efficacy—although the HPV vaccine has been hailed as "nearly 100% effective" that is only against the four targeted strains of HPV. In effect this means that even with perfect coverage, it will potentially be able to prevent around 70% of cervical cancers.	
HPV vaccine was developed in the absence of a validated animal model or correlates of protection. Industry acted on a breakthrough (generation of virus-like particles).	

cost approximately US$360 for three injections) widely available.

HPV vaccine was also one of the products mentioned as a candidate for the G8's proposed vaccine financing initiative. At the G8 meeting in July, the world leaders failed to reach consensus on this initiative; at subsequent meetings and in other forums, the AIDS vaccine field should lend its voice and its expertise to strong calls for public financing, which would make this vaccine available and affordable from Appalachia (the region with one of the highest rates of cervical cancer in the United States) to Tanzania (one of the highest rates of cervical cancer in the world, according to the World Health Organization), and all points in between.

- **Document and learn from HPV experiences with clinical trials and pilot introduction programs.** The four pilot projects being undertaken by PATH will provide critical lessons about HPV vaccine delivery. These projects will examine a range of operational and political questions with the aim of informing and promoting favorable HPV vaccine policy at the global level. Each country involved (India, Uganda, Peru and Vietnam) is using a different model, and the PATH project includes a research and documentation effort to learn from these models, which will explore issues such as school- versus community-based delivery programs, feasible and acceptable target populations, community information needs, and prospects for financing of vaccine purchases and delivery. The Ugandan project has a stated objective of learning lessons in preparation for an HIV/AIDS vaccine. This is an objective that should be embraced by the AIDS prevention field as a whole.

- **Collaborate on advocacy and communication campaigns at every level.** From a public health perspective, new vaccines are often embraced as a "silver bullet"—the complete solution to stopping a given disease. For HPV vaccines and, in all likelihood, for AIDS vaccines, this description does not apply. Cervical cancer develops years after infection with HPV (just as symptomatic AIDS often develops years after infection with HIV). This means that the public health impact of these vaccines in terms of reduction of deaths or cancer incidence will not be seen for several years. Nor will the vaccine protect women who have already been exposed or who live in places where there are cancer-causing HPV strains in circulation that are not targeted by the vaccine. Here, too, there are key similarities with HIV/AIDS vaccines and other potentially partially effective interventions. In any country where there is an HPV program, there is the potential—if not the imperative—for AIDS prevention research advocates to collaborate, ensuring that there are harmonized messages that manage expectations about HPV vaccines today, and lay the foundation for the introduction of future partially effective interventions.

Next Steps: AIDS Prevention Research Reaches Out to Adolescents

The AIDS prevention field can learn from HPV. It can also learn from its own experiences. After several years of discussing whether it would be possible to enroll adolescents into trials, there are fresh examples of innovative work with adolescents coming from within the field.

One exciting example comes from the Phase III trial of Carraguard, a microbicide candidate developed by the US-based Population Council. Trial sponsors recruited young women 16 years and older for its three trial sites in South Africa. The trial protocol was approved by the South African Medicines Control Council as well as the ethics review boards at the University of Cape Town, University of Limpopo/Medunsa Campus, the Medical Research Council, South Africa, and the Population Council.

In order to inform young women about the trial, the study staff members who conduct community outreach, first requested permission to speak at local schools. After receiving permission from schools' administrations, the study staff held meetings at schools to disseminate information about the HIV pandemic and different prevention methods individuals can employ to protect themselves from infection. The trial was also discussed, and interested students were invited to visit the study clinic to receive more information. Clinic hours were expanded to accommodate student schedules should they choose to volunteer and so that formal information sessions and regular appointments could be scheduled when school is not in session.

One of the key issues for adolescent enrollment in prevention trials is whether or not parental consent should be a pre-requisite. In the Carraguard trial, two of the three ethics review boards initially approved the enrollment of young women (16-17 years old) with or without parental consent letting the participant decide whether or not she wanted to inform her parents. Ultimately, during the trial, the third ethics committee changed its stance and approved enrollment without parental permission. Young women who attend

information sessions are encouraged by study staff to bring their parents or guardians if possible. Women who are abstinent are encouraged to remain abstinent. However based on data collected in the trial to date, it is clear that 16-17 year-olds in the trial population are sexually active and at risk for HIV, thereby underscoring the need for their participation in this and future trials.

More insights could come from the planned proof-of-concept South African trial of the Merck adenovirus vaccine candidate that will include a sub-study of adolescents. The study, HVTN 503, proposes to enroll adolescents at sites around the country.

The study is designed to determine safety and immunogenicity in the adolescent population; however, there is a potential that the data from this sub-study may also be included in the final analysis of the larger Phase IIb trial. In preparation for the study, investigators in Cape Town and Soweto surveyed South African mothers and found that almost 90% were willing, or probably willing, to have their children participate.

AVAC welcomes these developments and encourages the field to take the following steps to ensure that we continue moving in the right direction.

To do this we must gather, discuss and disseminate information on some of the critical issues related to adolescent participation in research. These include:

- Parental informed consent: when is it mandatory; when is it optional; who decides?
- Social harm, stigma and subsequent access to care for adolescents identified as HIV-infected during the screening process
- Ongoing information/counseling needs for adolescent participants to address potential misconceptions about the protection/benefit that might come from experimental product
- Assessing the impact of trial participation on school or work attendance, sexual activity and other risk behaviors

The AIDS vaccine field, along with other partners in AIDS prevention research, should also continue to call for, participate in and learn from country-level activities designed to clarify the regulatory environment around enrolling adolescents in clinical trials and delivering licensed products to adolescents. In May 2006, the US Food and Drug Administration (FDA) issued *Development of Preventive HIV Vaccines for Use in Pediatric Populations,* a guidance document designed to help trial sponsors and product developers understand FDA expectations and requirements. This document is a vital step forward, and AVAC is proud to have worked with the Elizabeth Glaser Pediatric AIDS Foundation and other groups to advocate for its publication.

But there are still unanswered questions, particularly for adolescents. The FDA guidance does not address how Institutional Review Boards (IRBs) should approach potential approval of trials enrolling adolescents. Here, one critical issue is identifying or clarifying the circumstances under which research on HIV vaccines in adolescents or infants could be approved as "presenting the prospect of direct benefit" to those adolescents and infants under DHHS §46.405 or FDA §50.52.

There is also a need to understand the risks that the IRBs will consider, including effects such as behavioral disinhibition and stigma.

The FDA does not have the monopoly on regulatory decisions around the world. It is vital to support country-level processes, such as the ones that have taken place in South Africa and Botswana, where legal precedents on age of consent for everything from marriage to HIV testing have been researched as part of an effort to clarify the environment for clinical trials.

The broader AIDS prevention research field should incorporate plans for gathering data on adolescents and children into product development plans. The field is seeking to coordinate its activities more than ever before (see chapter 4). Questions about safety and efficacy in adolescents should be identified and prioritized as part of the product development pathway for all candidates. This does not mean that all vaccine candidates should be tested in adolescents to start off

BOX 6 TELLING THE TRUTH TO SAVE LIVES: THE ONGOING FIGHT FOR EVIDENCE-BASED PREVENTION

In the United States, the past year's discussions over HPV vaccine have underscored the current climate of discomfort, and political disincentive, for talking openly about sex. HPV is transmitted by skin-to-skin contact, primarily during sexual intimacy. Yet the desire to distance the vaccine from sex—and to focus solely on the less-stigmatized disease of cervical cancer—has led to some high-flying verbal gymnastics. One prominent researcher speaking on Capitol Hill suggested to a packed room of staffers that skin-to-skin HPV transmission didn't necessarily mean sexual transmission. It could also be sports related: "Think of wrestling," she said.

When we talk about HPV vaccine or HIV vaccines or any other intervention that has to do with young women's and men's lives and bodies, we should not be thinking of wrestling. Every country will make its own decisions about how to position and describe HPV vaccines. But no country or community should lose sight of the need to ensure that young women receive accurate and age-appropriate information about their lives and their bodies. This means discussing their right to education, employment opportunities, family planning and yes, sexual pleasure. It means telling the truth about the effectiveness of condoms in preventing the spread of HIV and ensuring that interventions that can prevent diseases are provided when they should be, with appropriate information and follow-up to ensure that the public health impact is maximized and personal risk of stigma and discrimination are minimized, if not eliminated.

with, but it does mean that all product developers should have a plan for when and how they will gather information about this critical population.

Continuing the fight

It is far too soon to claim any victory at all when it comes to the fight to safeguard the health and well-being of the world's young people. But we at AVAC are heartened by signs that more and different stakeholders are entering the fight with the understanding that it is essential to any long-term progress in public health worldwide. We will hold ourselves accountable to doing our part to maintain this momentum, both by working towards implementation of recommendations made throughout this chapter and by taking on the following activities ourselves.

AVAC Commits

- At AVAC, we have been working to articulate a pathway for IRB approval and to promote research to identify and mitigate risks to adolescents arising from trial participation. We will continue to do this through ongoing consultations with key stakeholders, and by publishing a background paper.
- We will actively participate in collaborative efforts to build a constituency for HPV vaccines. We are one of the co-conveners of the "Stop Cervical Cancer: Accelerating Global Access to HPV Vaccines" conference to be held in December 2006. There, we will work with policy makers, funders, and experts from adolescent health, sexual and reproductive health, cancer prevention and other arenas to develop a joint platform for action.
- We will lead and support efforts to solidify and systematize documentation of experiences with enrolling adolescents in clinical trials and reaching them with services, including HPV vaccine. We will seek out and act on opportunities to feed this information into policy frameworks, impact-modeling exercises, and country-level discussions.