

## Spotlight

### Keeping talent at home

*Programs aim to stem brain drain of researchers from developing countries*

Several years ago, Dr. Veronica Mulenga, a Zambian physician, was offered a two-year research training fellowship in the US at Miami University. She learned her research skills there in state-of-the-art facilities. But the situation when she returned home was markedly different. Mulenga, now a consultant pediatrician at the University Teaching Hospital in Lusaka, conducts clinical research on treatment for HIV-infected children. While she made the decision to put up with the less-than-ideal laboratory and research conditions, many of her colleagues haven't. Instead they have left the country to work elsewhere. "They become frustrated with the systems they come back to," she says. "Quite a lot of people return and then leave again."

This phenomenon of specialized workers leaving their posts in resource-poor countries is often referred to as brain drain, and it is attracting increasing international attention. There are now conferences, declarations, and programs dedicated to limiting brain drain. Most of these efforts have focused on healthcare workers, including clinicians and nurses, because of shortages that became apparent after the recent massive scale-up of AIDS treatment programs in developing countries. However, relatively little attention is being paid to what many view as a similar and related phenomenon that is occurring in the research sector. Evidence suggests that a significant proportion of

biomedical and clinical researchers from developing nations leave their countries of origin or never return after receiving their training abroad. The result is a shortage of qualified scientists needed to investigate health problems of national importance, track illnesses, evaluate clinical programs, collaborate with international researchers, improve health systems, inform public policy, and train succeeding generations of researchers and technicians.

#### Large-scale problem

The US has the largest number of working scientists and engineers of any country, but over half of those who hold advanced degrees are foreign-born. According to US census figures, many of these individuals come largely from low- and middle-income countries. The situation is similar in other developed countries. More than two thirds of the world's researchers live in developed countries, while staggeringly few researchers live in the least-developed countries—only 4.5 researchers per million inhabitants, compared with 374 researchers per million inhabitants in other developing countries and 3272 per million in developed countries.

Clearly, brain drain is one of the reasons that developing nations are home to relatively few highly-trained researchers, but some have argued that the migration of researchers from developing to developed countries can have positive implications. Well-paid professionals send money home and they can also help set research agendas in powerful nations and within development agencies. In fact, experts suggest that the movement of researchers between countries might lead to more sharing of knowledge,

which could actually benefit poor countries. Some commentators have even questioned the need for qualified researchers to be well represented across the globe, arguing that building research infrastructure requires significant investments and specialized research programs cannot exist everywhere.

However, a strong research and development capacity in science and technology is closely linked with economic development. Leaders of highly-industrialized nations have become increasingly concerned about the loss of their own trained researchers. In recent years the European Union has undertaken several major efforts to plug the brain drain of European biomedical researchers flowing to the US. In some countries, including China and India, political leaders are endeavoring to build the research workforce with the understanding that it will contribute to sustained development.

#### Home-grown talent

When it comes to developing countries, there are many reasons why home-grown researchers are needed. "We're in a better position to know conditions that are very common here and that matter to us and therefore need to be researched," says Mulenga. The capacity to set national research priorities—and devote funds to them—can be critical for developing countries because many of the major medical problems affecting their populations have traditionally escaped the interest of northern

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research institutions. This problem has been termed the '10/90' gap, reflecting studies showing that less than 10% of global health research money was being used in the 1980s and 1990s to investigate 90% of the world's health problems.

The scales may now be shifting as support grows for AIDS, tuberculosis, and malaria programs, but they are still far from balanced. According to experts at the Council on Health Research for Development (COHRED), a Switzerland-based international organization devoted to building health research capacity in resource-poor countries, under-investment persists in health research relevant to problems common in low- and middle-income countries.

Sometimes developed and developing country medical research interests coincide, such as with HIV/AIDS and tuberculosis. But here again, the existence of highly trained researchers in developing countries offers distinct advantages. As collaborators they can facilitate the conduct of research in their home countries, settings with a high prevalence of infection and where new drugs, diagnostics, or vaccines could one day prove most useful. "When it comes to the people you're studying, you're in a better position to know them, know their culture and the ways they understand things," says Mulenga. That helps indigenous researchers ensure that prospective volunteers receive the information they need to provide truly informed consent (see *VAX* June 2005 *Primer on Understanding Informed Consent*).

Involving these researchers also increases potential volunteers' trust in the research program, says Pat Fast, director of medical affairs at IAVI. "We want populations and governments to trust that research is conducted appropriately, both from an ethical and a scientific standpoint," she says. "That's best done by having researchers from the country or region conduct the research."

### **The leak**

Brain drain often occurs because of factors that drive researchers out of their jobs or native countries. Many young researchers leave their countries to pursue advanced studies and fail to return home. Others leave for the prospect of career advancement, which is often limited in home countries. Poor working

conditions in some developing countries also motivates researchers to relocate to wealthier countries.

According to the African Health Researcher Forum (AfHRF), African countries on average spend less than 0.5% of their national health budgets on research. Shortages in supplies and equipment, poor management, and an insufficient number of technicians take a toll on researcher productivity, says Professor Job Bwayo, principal investigator at the Kenya AIDS Vaccine Initiative (KAVI) in Nairobi.

Another complaint among scientists is that policymakers tend to ignore or dispute their findings. This, too, contributes to brain drain. "If you do research and don't see action taken, you want to go somewhere else," says Carel IJsselmuiden, director of COHRED.

Salary differentials also play a major role in brain drain. Researcher salaries are notoriously low in some developing countries. The need to earn a living wage drives some trained scientists to give up research and take other jobs in their countries, sometimes called 'internal brain drain.' This term is also sometimes used to describe researchers who give up government research in favor of positions with international research initiatives or non-governmental organizations (NGOs) that are working in the country and can offer higher salaries, a controversial subject.

### **Brain gain**

Numerous studies have found that the majority of expatriate professionals wish to return to their own countries and contribute to them in some way. But they often report that they do not know how, and that their native countries have failed to reach out to them. "Those scientists should be supported and encouraged to come back and participate in the research of their own countries," says Bwayo. He says scientists working abroad can also mentor and teach the next generation. A number of programs have been established to help expatriates share their skills in their home countries and some governments are now promising top salaries to lure their scientists back home.

Steps to counter brain drain are also being taken much earlier, beginning with the initial education of a scientist.

Training programs, which used to involve several years abroad in Europe or the US, are increasingly offered by developing countries such as Brazil, Nigeria, Kenya, Mali, Thailand, Malaysia, and the Philippines. And researchers who receive financial support from their governments or international donors to train outside their home countries often must agree in advance to return home and work for an allotted time.

Several groups, including the World Health Organization, the US National Institutes of Health, and the US Centers for Disease Control and Prevention, are also helping to train and support local scientists. The AfHRF and other developing-country institutions are similarly engaged in building capacity, improving the quality of collaborations, and giving developing country researchers a voice in setting and implementing the global health research agenda.

Some developing country scientists say that collaborating with well-funded teams of foreign researchers has made it much easier for them to stay in their countries. KAVI's Bwayo says that international collaboration with IAVI has brought supplies, equipment, reagents, training, presentations at international meetings, and, just as importantly, salary support.

But international collaborations also have their share of problems and frustrations for national scientists. In some cases NGOs run the show from start to finish. "They have their own research agenda, and locals don't participate in deciding what that should be," says Bwayo. "They only use the locals as a front to allow them to conduct research in the country." Some national scientists also complain that international programs tend to collaborate with the same researchers, therefore limiting the potential to build capacity in younger generations of scientists.

### **Looking to the future**

Northern and southern researchers have learned from these experiences, and many now recognize that mutual respect and capacity-building are critical features of successful collaborations. "The most important thing that we all need to help with is to provide a career path for researchers who want to stay in their countries," says Fast. That involves supporting both researchers and their

institutions. "This is not something one research organization can completely achieve."

Ijsselmuiden agrees. He points out that some developing countries maintain dozens of research contracts with a range of funding agencies and the various efforts are uncoordinated. A more efficient and sustainable approach would be for donors to work together to support research infrastructure, including universities and perhaps

regional centers of excellence. That way an epidemiologist trained in the context of an AIDS vaccine trial could transfer her skills to another research program once the original trial is completed.

Ultimately, though, the balance of brain drain to brain gain will depend on the individual decisions of researchers themselves. Job Bwayo, like Veronica Mulenga, has decided to focus his efforts at home. "I can make my maximum contribution to this country by working in

this country," he says. "I don't ever want to leave." With AIDS taking an ever larger toll on the continent's talent, hopefully an increasing number of researchers will feel the same.

*This article was originally researched and written for IAVI Report in December 2006. Tragically, Professor Job Bwayo was murdered in Kenya on February 4, 2007. For his obituary see [www.iavireport.org/Issues/Issue11-1/Bwayo.asp](http://www.iavireport.org/Issues/Issue11-1/Bwayo.asp).*

## Global News

### Guidelines for male circumcision issued

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recently issued recommendations saying that adult male circumcision should be recognized internationally as an important intervention to reduce HIV transmission. The recommendations also advise countries with high HIV prevalence and low rates of male circumcision to consider rapidly and dramatically increasing access to this surgical procedure to men at risk of heterosexual transmission of HIV. The organizations released these guidelines following an international consultation with various governments, researchers, human rights advocates, funding agencies, and civil society members that was held from March 6-8 in Switzerland. According to the guidelines, circumcision should now be included broadly as part of a comprehensive strategy to prevent HIV transmission, along with the use of condoms, voluntary counseling and testing services, and the treatment of other sexually transmitted diseases. Many individual countries are also in the process of establishing national guidelines on the introduction of male circumcision programs.

The decision to recommend male circumcision as an HIV prevention tool comes on the heels of the results from three randomized, controlled clinical trials that have shown circumcision can reduce the risk of heterosexual transmission of HIV infection by as much as 60% in men. These trials were conducted in Kisumu, Kenya; Rakai District, Uganda; and Orange Farm, South Africa. Studies to predict the impact of different preven-

tion technologies on the course of the epidemic suggest that implementation of circumcision programs in sub-Saharan Africa could prevent 5.7 million new HIV infections over the next 20 years.

The WHO/UNAIDS guidelines recommend that more research be conducted on how male circumcision may impact HIV transmission to women, as well as the risks and benefits of performing circumcision in men who are already HIV infected. An ongoing study sponsored by the Bill & Melinda Gates Foundation is looking at how male circumcision affects HIV transmission to female partners. Limited data from studies already conducted suggests that HIV transmission between recently circumcised HIV-infected men and their female partners may be increased if they engage in sexual activity before their surgical wound is completely healed, and this process may take longer in HIV-infected men.

One concern shared by WHO/UNAIDS and organizations that will be implementing circumcision programs in developing countries is ensuring access to safe services, which requires training providers to conduct the procedure, providing sanitary settings and properly sanitized instruments, and then closely monitoring and evaluating circumcision programs once they begin to ensure that the circumcisions are being performed properly. The recommendations also suggest that men seeking circumcision be offered counseling services to prevent them from having the false perception that they are completely protected against HIV infection and therefore able to engage in high-risk behaviors, an idea known as behavioral disinhibition.

In Uganda, researchers are planning to establish a limited number of sites to serve as centers of excellence for adult male circumcision. The site in Kisumu

where the clinical trial of male circumcision was conducted has received funding from the US President's Emergency Plan for AIDS Relief (PEPFAR) to serve as a center of excellence in the region.



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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 24 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it. For more information, go to [www.iavi.org](http://www.iavi.org).

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## What are the major scientific obstacles to the development of an effective AIDS vaccine?

Over the past several years there has been significant scientific progress in understanding HIV infection and how the virus interacts with the human immune system. There has also been renewed political and financial commitment to the global effort to combat HIV/AIDS and there are now more than 30 ongoing clinical trials evaluating different AIDS vaccine candidates. Despite these advances, HIV is a difficult virus to target and developing a safe and effective vaccine that protects people against infection will involve overcoming several of the remaining scientific obstacles.

### Genetic diversity

One reason AIDS vaccine development is so complex is because HIV replicates, or makes copies of itself, extremely rapidly within an infected individual. Once HIV infects a CD4<sup>+</sup> T cell it quickly produces more viruses that can subsequently infect more immune cells, setting off a cycle of destruction that allows HIV to overwhelm and eventually destroy the immune system. But this replication process is imperfect and each time HIV copies its genetic material it makes mistakes. This results in a huge number of viruses, each having a slightly different genetic makeup, circulating within a single individual, as well as within the overall population.

HIV's extraordinary genetic diversity makes development of an effective AIDS vaccine much more difficult because it will have to protect against so many different virus strains. The vaccine against influenza provides a sobering example. Although the influenza virus varies substantially less than HIV, the vaccine still must be reformulated each year to be effective against the predominant strain of virus in circulation.

### Natural infection

Most licensed vaccines against other diseases are thought to work because they induce virus-specific neutralizing antibodies (see VAX February 2007 *Primer on Understanding Neutralizing Antibodies*). But even though several HIV-specific neutralizing antibodies have already been

discovered in infected individuals, it is still not known how much of a role they play in controlling HIV infection. The antibody responses generated against HIV naturally by the immune system are insufficient to clear an infection because there has never been a documented case of a person who was able to clear an established HIV infection.

In many long-term nonprogressors whose immune systems can control HIV infection for much longer than the typical decade, researchers do not often observe significant neutralizing antibody responses directed against HIV (see VAX September 2006 *Primer on Understanding Long-term Nonprogressors*). And even when neutralizing antibodies are generated against HIV, they are sometimes incapable of protecting against other closely-related strains of the virus. There are several confirmed cases of superinfection, where HIV-infected individuals are infected with a second strain of HIV despite having antibodies toward the strain they were already infected with.

Even though antibodies may not play a critical role in controlling HIV in infected individuals, researchers speculate that vaccine-induced HIV-specific antibodies would still be important, even necessary, in protecting someone against infection. This presents a significant challenge to AIDS vaccine researchers who have to discover new ways to induce immune responses—both antibodies and cellular immune responses (CD4<sup>+</sup> and CD8<sup>+</sup> T cells)—that are even more effective than those produced during natural infection.

### Immune system under attack

Part of the reason that it is more difficult to clear an HIV infection is that the virus's primary target is the immune system itself. This is one of the main challenges to developing a vaccine that could control HIV infection, rather than completely prevent it. HIV preferentially attacks CD4<sup>+</sup> T cells, a particular subset of immune cells that help orchestrate all of the other types of immune responses against pathogens. During HIV infection, many of these cells are damaged and can't function properly. As more and more of the CD4<sup>+</sup> T cells are eventually killed, the immune system becomes incapable of fighting off HIV, as

well as other viral and bacterial infections, and AIDS onset occurs. A partially-effective AIDS vaccine that could help bolster the immune response against HIV before too many CD4<sup>+</sup> T cells are damaged might help preserve some of the critical immune cells early in the course of infection and significantly slow disease progression. Such a vaccine may also reduce the likelihood of an infected individual transmitting HIV to others.

### Imperfect animal model

Another way to gather useful information about the types of immune responses that protect against infection is to study the virus in an animal model. But HIV does not infect any other animals so AIDS vaccine researchers must instead study a related virus, simian immunodeficiency virus (SIV). This virus infects some species of non-human primates, including rhesus macaques (see VAX October 2006 *Primer on Understanding AIDS Vaccine Pre-clinical Development*). This is not a perfect model for human infection since it is a different virus and any vaccine candidates that are tested in non-human primates must be based on SIV and not HIV.

### Immunogen design

The key to inducing strong antibody and cellular immune responses with a vaccine is selecting the right immunogen or antigen—either whole HIV proteins or pieces of protein—that will stimulate the immune system to induce the desired type and amount of responses. Designing immunogens to include in AIDS vaccines is very difficult and only incremental progress has been made in this area. Currently several different immunogens are being evaluated in both pre-clinical and clinical trials. These immunogens are being tested in combination with several different viral vectors (see VAX September 2004 *Primer on Understanding Viral Vectors*) and adjuvants (see VAX October 2004 *Primer on Understanding Vaccine Adjuvants*) to try to increase the level of immune responses that are generated. Other approaches to improve the immunogenicity of vaccine candidates can also be tried, including alternative delivery methods—such as intravenous, oral, or intra-nasal administration.