

Russian Experts Help Ethiopia Establish Cell-based Rabies Vaccine Production

Scientists Provide Technical Assistance to Help Ethiopia Tackle Rabies Prevention and Treatment through the USAID-supported Strategic Health Partnership Initiative

Rabies is preventable, yet it remains a significant cause of both human and animal deaths in many parts of the world. The Alliance for Rabies Control reports that an estimated 55,000 people die each year from the virus — most in Africa and Asia — although they are quick to point out that this number is greatly underestimated because “reliable data indicating the true incidence of human rabies are scarce or non-existent.” This lack of data translates to rabies being relatively low on the agendas of many policymakers, particularly in cash-strapped developing nations. As a result, effective control and surveillance programs are not implemented.

Rabies has been present in Ethiopia for centuries, with various traditional treatments referenced in local medical books since the early 1800s, according to research conducted by the Ethiopian Health and Nutrition Research Institute (EHNRI) in Addis Ababa.

“Our retrospective data for the last four decades indicate that canine rabies is well established with no decline in the annual number of confirmed cases,” says Mr. Kelbesa Urga, Senior Researcher, Assistant Professor, and Director of the Vaccine and Diagnostics Production Directorate at EHNRI. “Some 80 percent of brain samples diagnosed at our laboratory are confirmed positive for rabies each year and an average of 1,500 people come to us annually for post-exposure treatment from Addis Ababa and nearby areas,” he reports.

As is true in much of the world, dogs are the primary vector for human infection with the rabies virus. “Dogs were responsible for 92 percent of the cases in which humans received post-exposure treatment for rabies at EHNRI and, of the 20 or 30 animals we quarantine here each week, 90 percent are dogs,” Mr. Urga explains.

There are a number of reasons rabies represents a significant public health concern in Ethiopia, many of them related to the fact that there is no framework for effective surveillance, data monitoring, and guidance. According to Mr. Urga, there is no census to ascertain the dynamics of the canine population, nor any household survey data to determine the ratio of owned versus stray dogs in the country. Animal control is also an issue.

“We have no legislation to certify dogs are vaccinated, which is needed to control animal movement in case of an outbreak and there is no mechanism for monitoring rabies among wildlife or strays ... in fact, there is no established surveillance system, so rabies cases are underestimated and underreported,” he points out. On the prevention side, there is no regular



In Ethiopia, where rabies is a serious public health concern, Dr. Artem Metlin (left) and Dr. Denis Bankovskiy have helped produce a rabies vaccine using cell cultures.

mass vaccination of dogs to maintain an 80 percent herd immunity, which is the standard for controlling rabies. “So far, we do not have a rabies control program in place and EHNRI is the sole institute in the country to provide rabies diagnosis, post-exposure treatment, consultation, and distribution of vaccine to the regions,” Mr. Urga says.

Russian Experts Help Usher in New Era of Rabies Prevention and Treatment

Ethiopia has long been one of only a handful of countries around the world that are still using the old Fermi-type phenolized sheep brain tissue vaccine. “This outdated vaccine is very dangerous and, according to the World Health Organization, should not be used on humans,” says Dr. Artem Metlin of Russia’s Federal Centre for Animal Health. “Known side effects include severe allergic reactions, encephalitis, partial paralysis, and even death,” he explains. It is also very painful. The course of treatment is 17 5-mililiter injections administered in the stomach area.

In June 2009, Dr. Metlin began a four-month technical assistance assignment at EHNRI at the request of the Ethiopian Ministry of Health. His mentorship there was sponsored through the Strategic Health Partnership Initiative, a unique multilateral project of the Russian Ministry of Health and Social Development, the US Agency for International Development (USAID), and the American International Health Alliance (AIHA).

“The Ethiopian Government recognizes that rabies is a serious problem and it is one of the strategic focus areas that emerged from the recent business process reengineering undertaken by the Ministry of Health,” explains Dr. Medhin Zewdu Tsehau, Director General at the Office of the Minister of Health. “Our goal is to build the capacity to manufacture 10 vaccines and we’re starting with rabies,” she says. That’s where Dr. Metlin comes in.



In August 2009, Dr. Metlin displays the Fermi-type rabies vaccine derived from phenolized sheep brains. According to WHO, this type of vaccine is not recommended for human use, but it is the standard of care available in Ethiopia.

“When I first arrived at EHNRI, I knew nothing of local conditions and it was a really challenging situation,” Dr. Metlin acknowledges. “A lot of equipment had been ordered, but no one could properly install and service it. There were no manuals or standard operating procedures (SOPs) and the literature that was available was outdated. The building itself would have to be torn down and rebuilt from scratch to truly qualify as biosafety level two. And, because the rabies lab was a new department, most of the staff — though experienced — needed basic training in rabies-specific diagnostics,” he says.

Another challenge was the lack of legislative framework for both rabies policy and practice. “Rabies is truly a neglected disease ... even a small fraction of the funding international groups provide for HIV/AIDS could eradicate it in Ethiopia,” Dr. Metlin maintains. Instead, he says, “EHNRI is the only place in the country where rabies can be diagnosed. For proper surveillance, there should be a lab in each region. There is no reporting system and no lab diagnosis for people who are suspected to have died from rabies, so data cannot be accurately tracked.”



Dogs brought to EHNRI for rabies testing are quarantined in a small compound near the rabies lab to see if they develop clinical signs of infection.

Even worse is the lack of care available for people who may have contracted rabies. “If someone is bitten, they bring the dog here for observation and are referred to a nearby hospital,” he explains. Without an effective vaccine, though, these people must endure the risky, painful prophylaxis therapy currently available. If they develop clinical signs of rabies, no cure is available.

From the scientists and lab professionals at EHNRI to the highest levels of the Ethiopian Government, there is a commitment to change this.

Explaining that EHNRI has heavily invested in upgrading the facilities required to produce a rabies vaccine in keeping with modern standards, Mr. Urga says that the renovation is nearly complete. “The Government’s commitment to rabies control is visible and serious. The Ministry of Health has allocated several million Birr each year to produce a sufficient amount of vaccine for both humans and dogs. Our goal is to be self-sufficient.”

In his role of technical advisor, Dr. Metlin’s key priorities during the summer of 2009 were to set the process in motion for onsite vaccine production, build capacity at the rabies lab by training staff and developing SOPs and other resource materials, and develop a process for rabies control and surveillance.

“We prepared draft legislation for a rabies control program and submitted them to the Ministry of Health for approval and developed several SOPs related to rabies virus concentration and the adaptation of the virus to cell cultures — a process that can take up to six months,” he explains, noting that ongoing renovations to the lab impeded his progress in the actual production of the vaccine itself during his first four months at EHNRI.

Once the EHNRI lab acquired seed rabies virus from the US Centers for Disease Control and Prevention in Atlanta, the vaccine production process entailed preparing cell cultures, infecting them with the virus and allowing the cultures to grow for two to three days before testing the procedure to determine the exact length of time required. At that point, the resulting virus is



Conditions in the EHNRI Rabies Lab in August 2009. Sheep brains were ground using a mortar and pestle before being processed in the Fermi-type phenolized vaccine. Severe allergic reactions, encephalitis, and partial paralysis were common side effects.

inactivated and purified from the cells using a centrifuge. The purified virus is mixed, analyzed for quality, and bottled or freeze dried for longer storage, according to Dr. Metlin.

Having Laid the Foundation, Russian Mentors Succeed in Introducing Cell-Culture Vaccine Production at EHNRI Lab

When Dr. Metlin left Ethiopia in October 2009, he had helped lay a strong foundation at the rabies lab, but there was still much work to be done. With the support of USAID, he returned to EHNRI in mid-January 2010 accompanied by Dr. Denis Bankovskiy, a vaccine expert from the JSC Pokrov Biologics Plant in Volginskiy, Russia. Together, the two Russian experts hit the ground running. By the middle of February, the transformation in the rabies lab was nothing less than stunning.

“I expected it to be in worse condition when I arrived, but Dr. Metlin provided a significant amount of technical support and the Ethiopians had done a great deal of work during the previous months,” Dr. Bankovskiy admits.

“I was really surprised at the high quality, modern equipment, even if some of it is not yet up and running. Also, the lab staff have experience working with cells and are young and not set in their ways. They learn quickly and are eager to make changes here... there has been a lot of progress in the past month,” he continues, explaining that the two mentors have conducted a series of trainings on topics such as cell concentration, infecting cells with vaccine rabies virus strains, inoculating mice for vaccine trials, titration, and dissection of mice for brain sampling to perform rabies diagnostics tests — all designed to prepare their counterparts to work independently once they return to Russia.

“Our work in the lab is done step by step, so we prepare SOPs accordingly to ensure vaccine production is in accordance with international standards,” Dr. Metlin says. “We developed four or

five the last time I was here and we've done two more this time, as well as completed a lab manual."

In February, they produced the first batch of rabies vaccine and conducted initial trials on mice before proceeding to trials using dogs and, finally, humans. "None of these mice should die of rabies, but if any do we will need to reevaluate the process and make the necessary adjustments... it is a painstaking process," according to Dr. Metlin.

"The goal is to eventually produce 20,000 doses or more per year, but they will need some additional equipment to do that and, even then they will require more vaccine. If they ramp up production they may be able to sell some to other countries... it's much better to produce it here and provide jobs to people who need them, as well as income from sales," he stresses.

Dr. Tsehau from the Ministry of Health agrees. "It is critical that we develop this vaccine; the impact will spread beyond rabies because the process can be applied to other vaccines. We've invested a huge amount of money and the knowledge and skills the Russian mentors have transferred to staff at the rabies lab is invaluable," she says.

In the lab, the researchers who have worked side by side with Drs. Metlin and Bankovskiy say they are proud to be part of the groundbreaking changes that are happening at EHNRI.

Assistant Researcher Mrs. Bethlehem Newayasselassie has worked at EHNRI for 11 years, but just joined the rabies lab in June 2009. "I have witnessed small children suffering terribly while getting the existing vaccine and the memories of that have pained me for years," she says, explaining why the work of the lab is so important for the people of Ethiopia.

"There have been drastic improvements here since I started," she continues. "From day to day, we witness new changes being implemented. It's not just the physical transformation of the lab, it's also the new skills we are learning and the hands-on experience we are gaining from working with Denis and Artem."

Echoing her comments, Mr. Birhanu Hurisa, also an Assistant Researcher, says, "At first, we didn't have the virus, the equipment, or even the knowledge how to put them to use, which is the biggest improvement. Now, our hopes for the



Dr. Denis Bankovskiy works side by side with EHNRI Research Assistant Birhanu Hurisa isolating cells at the newly renovated rabies lab.





On February 15, 2010, Dr. Metlin oversaw EHNRI staff as they conducted the first round of clinical tests on mice using the initial batch of rabies vaccine produced on site.

future are without limit. We do have challenges. Supplies are limited and everything takes a long time, but we can overcome these issues and reach our goal,” he says with conviction.

For their part, Dr. Metlin concluded his assignment in mid-March and Bankovskiy finished his one month later. Both say they are eager to see the rabies control project through to completion.

“The mice trials were successful, so it would be very useful for us to return when they start production to evaluate procedures and work on quality control,” Dr. Metlin says. “To me, it’s very promising that staff are so enthusiastic and

eager to learn. They understand exactly how things need to change and want to work hard to make sure that happens.”

More about the Strategic Health Partnership Initiative

Launched in late 2007, the Strategic Health Partnership Initiative is a direct result of the 2005 Bratislava Initiatives, a joint Russian-American presidential agreement designed to strengthen cooperation on a number of cross-cutting issues, including the global fight against HIV/AIDS. It represents a unique collaboration between Russia’s Ministry of Health and Social Development and the United States Government through USAID. Designed to bolster Russia’s capacity to provide technical assistance to developing nations around the globe, the project exemplifies successful Russian-American cooperation within the global public health arena.

AIHA’s HIV/AIDS Twinning Center program — which supports PEPFAR’s capacity building efforts in Africa — and the Regional Knowledge Hub for the Care and Treatment of HIV/AIDS in Eurasia play a important role in strengthening Russia’s international technical assistance strategy. Leveraging relationships established through Twinning Center partnerships in Africa and the AIDS Training and Education Centers established in Russia with support from the Regional Knowledge Hub, AIHA is helping deploy a cohort of highly qualified Russian experts who share their knowledge and technical skills with colleagues in other countries in the region and in Botswana, Ethiopia, Namibia, and Tanzania. These experts work closely with the ministries of health and CDC staff in targeted nations to help strengthen critical laboratory services.