Washington University researchers and international partners go to great lengths to help solve some of the world’s most pervasive health challenges.

BY TERRI NAPPIER
Gary Weil, MD, leads a large global network of researchers and organizations in the Death to Onchocerciasis and Lymphatic Filariasis (DOFL) Project, which is funded by the Bill & Melinda Gates Foundation. In Africa and Asia, researchers conduct population-based epidemiology studies and clinical trials. The group also develops and evaluates diagnostic tests for lymphatic filariasis (LF), onchocerciasis (oncho) and intestinal worm infections, which are major public health problems in the developing world.

At Washington University, Weil’s lab consists of 12 members, including Peter Fischer, PhD, associate professor of medicine, who calls the abundant resources available at the university a veritable “Disneyland for researchers.” Case in point: Weil’s lab collaborates with researchers from The Elizabeth H. and James S. McDonnell III Genome Institute’s Helmholtz Sequencing Project, which is led by Makedona Mitreva, PhD. Mitreva’s group is conducting both basic genomic research and working on projects with practical goals, such as the development of improved diagnostic tests, vaccines and new drugs for parasitic diseases.

Merck & Co.* Johnson & Johnson and GlaxoSmithKline donate the drugs for the mass drug administration programs, and the U.S. Agency for International Development and Britain’s Department for International Development support the funding to distribute them. Ministries of health and NGOs help with in-country planning and organization. And the Gates Foundation funds operational research to study the effects of these mass treatments and to find ways to improve the regimen. The foundation hopes this research will generate new knowledge that can be used to shorten the time required to eliminate LF and oncho.

***Thirty years ago, half the adults who lived near rivers in African countries, where oncho occurred, were blind,” Weil says. “After Dr. Roy Vagelos, a former chair of biochemistry, left Washington University to become CEO of Merck, he made the decision in the late ’80s to support a massive donation program for Merck’s anti-parasitic drug Ivermectin. His decision was revolutionary; nobody had done anything on this scale before. Despite dissent within the industry, Merck built a special factory to manufacture the donated medicine and established an NGO to distribute it. Today, the program provides more than 100 million treatments per year. So Dr. Vagelos represents another university connection in the long-term fight against these diseases.*"

One challenge is complications caused by loiasis, a third parasitic disease that is common in areas of central Africa. Medications for treating LF and oncho can cause serious adverse effects, including coma and death, in those who also have loiasis. Weil’s research team is investigating the effect of a novel treatment for LF that is safe to use in areas with loiasis.

An additional benefit of the MDA programs for LF and oncho, by contrast, is that the drugs used to treat those infections are also effective against intestinal roundworms, another public health problem in the tropics. Weil’s group is working to quantify this side benefit. Intestinal roundworms represent a formidable problem. Close to a billion people have giant roundworms, and 800 million and 700 million, respectively, have whipworms and hookworms. These soil-transmitted diseases cause severe anemia, and they impair growth and cognitive development in children, who are especially vulnerable to the effects of these worms.

The Séké Pembé study is part of a much larger global effort, the Death to Onchocerciasis and Lymphatic Filariasis (DOFL) Project, which is

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F rom Brazzaville, the Republic of the Congo’s capital city, Gary Weil, MD, travels inland by truck to Madingou. The distance is only 250 kilometers (155 miles), but the road conditions are poor. Deep ruts and churned-up dirt turn a trip of 2½ hours into seven. Weil says it is like “driving through chocolate powder.” He strains through the ubiquitous dust to see large trucks loaded with supplies, and often masses of men, careening in both directions. Such conditions cause vehicles to crash, overturn and, at times, plummet down cliffs. The drive is not for the faint of heart.

Weil, professor of medicine and of molecular microbiology at the Washington University School of Medicine, arrives safely in the small capital town of Madingou District. His research team’s base camp is located here in Congo’s Bouenza region. A tiny laboratory within a small, tin-roofed hospital serves as a training facility for his French counterparts and in-country partners.

From Madingou, Weil and the team venture north to their field-study site. Along the way, the group must cross the Niari River tributary on a small barge. The flat-bottomed boat has no motor, so the ferrymen use the river’s current to guide the vessel back and forth from shore to shore. It can take 30 to 45 minutes to cross the slim waterway. Once on the other bank, the team resumes its journey, stopping at the third village, Séké Pembé.

At this rural site, researchers are conducting a multiyear study to determine whether a novel mass drug administration (MDA) program can effectively treat and ultimately eradicate certain worm diseases. Such parasitic diseases affect nearly 2 billion people and cause major disability for millions around the globe.

Considered “neglected,” these tropical diseases do not garner the same level of international funding as HIV/AIDS, malaria and tuberculosis. “AIDS, malaria and TB are very serious global diseases, causing many deaths,” Weil says. “But in terms of numbers, many more people are infected with these helminth (worm) diseases, which cause chronic illnesses and disability — blindness and an inability to walk.”

Lymphatic filariasis (LF), for example, is a leading cause of disability worldwide and affects 120 million people, with more than 1.4 billion people who live and work near rivers in sub-Saharan Africa. Spread by small black flies, oncho causes blindness and severe skin disease.

Weil has been studying these afflictions for decades. The road to progress has been long, but current MDA programs offer reasons for optimism.

“In the case of LF, if 70 percent of the people take the free medicines once or twice a year for a period of five years, we can rid most areas of the disease,” Weil says. “About 500 million people take these medicines each year, and the program is making good progress in many areas. However, some countries have not started MDA programs yet, and some ongoing programs face significant challenges.”

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supported by the Bill & Melinda Gates Foundation. The DOLF Project is part of the foundation’s program “to reduce the burden of neglected infectious diseases on the world’s poorest people.”

Weil serves as the DOLF Project’s primary investigator. His lab caught the attention of the Gates Foundation because of its three decades of research and field studies. In an early effort, for example, Weil and his laboratory created a novel test for diagnosing heartworms in dogs, which is a cousin of the parasites that cause LF and oncho in humans. This work led to a new diagnostic test for LF in humans that is now used around the world to map the disease and measure improvements related to MDA. Field-testing of the new tool led Weil to Egypt, where he and his collaborators worked for 20 years to nearly eradicate the disease in 2007, until political upheaval brought the project to a halt. Weil subsequently moved that field study to Sri Lanka.

Today, with a five-year, $13 million grant from the Gates Foundation, Weil manages teams and partners at 12 study sites in eight countries: five in Africa (Democratic Republic of the Congo, Ghana, Ivory Coast, Liberia, Republic of the Congo) and in Indonesia, Papua New Guinea and Sri Lanka. (See sidebar on pg. 13 for more on the global team and study sites.)

“We started the DOLF Project in 2010,” Weil says. “It took us a long time to find the appropriate study sites and right collaborating scientists. Last fall, we requested supplemental time and funds for the project, and the Gates Foundation has agreed to an additional three years’ funding.”

The project’s objectives remain: 1. large-scale testing of alternative mass drug administration strategies with modeling and cost analysis; 2. randomized clinical trials with current drugs using combinations and schedules; 3. population-based studies to assess the impact of mass treatment programs for LF and oncho on intestinal worm infections.

Weil says progress is being made in all of the DOLF Project field-study sites, but the progress has been uneven. For example, one study in Liberia had to be halted for a year starting in early 2014 due to the Ebola outbreak.

“We regularly update stakeholders and share preliminary results with the World Health Organization, funding agencies, other technical experts and drug donors,” Weil says. “When we experience delays, they know why. And when positive results come in, we are able to help inform policy, and that’s what the Gates Foundation wants: to change the world through changing policy.”
NEW AVENUES OPEN FOR CHANGE

As director of Washington University’s Institute for Public Health, William Powderly, MD, aspires to change the world as well. By design, Powderly, the J. William Campbell Professor of Medicine, also serves as director of the institute’s Global Health Center, which was formed to enhance and strengthen existing university research, as well as to increase its potential to improve lives. Powderly says Weil’s path serves as a great model for the center.

“Gary Weil’s work started as very basic science — researching worms — and then it turned into discovering better diagnostics,” Powderly says. “Now he has taken a major lead worldwide in the treatment and eradication of filariasis, managing a global program funded by the Bill & Melinda Gates Foundation.”

In hopes of replicating Weil’s model, Powderly — himself a specialist in HIV/AIDS and co-director of the Division of Infectious Diseases at the School of Medicine — works with others at the Center for Global Health & Infectious Disease, a subunit of the Global Health Center. He says that infectious disease research is a Washington University strength. Besides worm diseases, exceptional research programs focus on other parasitic diseases (leishmaniasis and schistosomiasis), malaria and tuberculosis, to name a few.

Regarding malaria, the World Health Organization (WHO) reports that 3.2 billion people live in areas at risk of transmission. In 2013, an estimated 198 million cases occurred with approximately 600,000 people dying, mostly children under the age of 5 in Africa. University scientist Daniel Goldberg, MD, PhD, professor of medicine and of biomedical systems engineering, is working to build new diagnostics to detect the parasite secretes various proteins to affect red blood cells and reproduce. Novel findings are leading to new targets for drug development and new university and global partnerships.

Q: How should we as a society approach emerging infectious diseases?
WP: What has tended to happen over the past 30 to 40 years is that a crisis happens, money is invested into it; things settle down; funding is reduced. When the next crisis happens, we are not as prepared as we should be, and we have to start the process over again.

The fundamental lesson is that we need to have sustained investment in a public health infrastructure, not only in the United States, but across the world, to be able to get an early indication of a disease when it is emerging and ideally start to plan to control it before it becomes an epidemic.

It’s a combination of preparing our local and state health departments, strengthening our Centers for Disease Control and Prevention (CDC), and building out from there globally — working with relevant ministries of health through the World Health Organization and strengthening WHO, because the Ebola crisis showed it has some issues as well.

I think the Europeans have a very similar view. They’ve gone from each country having its own to having a European CDC equivalent based in Sweden. I think they too, would see the value of partnering to strengthen preparedness on a worldwide level.

It’s a lot like insurance. If you take the view not to have homeowner’s insurance and to just pay every time a tornado hits and hope that it doesn’t, that’s one approach. And that’s what we’ve been doing with public health regarding preparedness for epidemics.

Many of us think there is a better approach, which is actually to build a baseline insurance system to give infectious disease experts an early warning, so that we are able to see what’s coming and be more prepared. This is not fanciful; an epidemic is going to happen. We’ve already had examples: Ebola was one. In many ways, we were fortunate with Ebola, even though people were understandably scared, because quarantine works.

If you were to ask most infectious disease specialists, “What virus worries you most?” they would say a viral influenza. People dismissed the pandemic we had in 2009 — the H1N1 strain — yet many people died, particularly younger people and pregnant women. And it spread all over the world very rapidly.

Q: Why do you think the response to influenza is so laissez-faire?
WP: We in the medical field in 2009 saw young people and pregnant women die, but for most people in the community, it was still a flu. They’ve recovered.

We get complacent. The whole measles vaccination situation is an example of people becoming complacent about an illness that they think has gone away — one that doesn’t affect them on a day-to-day basis. If you go back a couple of generations, people remember enough about polio. But that memory will recede, and maybe a generation from now, people will ask, “Who needs a polio vaccine?” Then you’ll see kids with polio. Unfortunately, that’s human nature — not to worry about something because it’s not part of your folk memory.

Q: Could you speak about the need to improve predictive models?
WP: It is certainly an area that needs to be developed. If you were to create an infrastructure to identify disease patterns earlier, then you would need to develop models that actually work. Just as weather predictions have become so much better than, say, 20 years ago, we need similar predictive model — one that could identify whether a small outbreak of a viral infection in country X or country Y could become a worldwide epidemic.

In other words, we would have both the satellite images and warning signals — ways of tracking and saying that this is behaving in a way that is worrying. For example, if tracking found three cases in country X last week and 10 cases this week, we’d be able to infer, if there are 20 cases next week, we need to do something.

Q: Who would be responsible for looking at patterns?
WP: It’s a combination of infectious disease epidemiologists, statisticians and data analysts — people who are able to examine the data, pick out the needle in the haystack and see different patterns. It’s people who know how to use data, and they often don’t come from medical backgrounds. The people with the necessary skills might come out of Google, but it would need to be in combination with an infectious disease epidemiologist who understands the dynamics of infection.

A conversation with William Powderly, MD, on global preparedness for emerging infectious diseases
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William Powderly, MD, wants the Global Health Center to build on another university strength: research in human nutrition. Mark Manary, MD ’82, the Helene B. Roberson Professor of Pediatrics and one of the world’s foremost experts in childhood malnutrition, works in sub-Saharan Africa, developing and introducing enriched peanut-butter foods to treat malnutrition in children; developing novel complementary foods for infants; and treating children 6 months to 5 years of age with uncomplicated severe acute malnutrition with therapeutic food plus antibiotics. On the antibiotics study, Manary worked closely with Indi Trehan, MD, assistant professor of pediatrics, and their results — which showed that the combination treatment cut death rates from childhood malnutrition compared with therapeutic food alone — helped establish new WHO guidelines in 2013 for treating severe malnutrition. Manary has also collaborated with Jeffrey Gordon, MD, the Dr. Robert J. Glaser Distinguished University Professor and director of the Center for Gut Microbiome and Nutrition Research, to determine whether gut microbes and their genes undergo changes as a result of treatment with therapeutic foods. And if alterations occur, does the “new state” persist after treatment ends, or are children again at risk of malnutrition? Gordon’s long-term genetic work on the gut microbiome has the potential to improve human nutrition across the globe.

Researchers tackle malnutrition on many fronts

“The conditions in which people are born, grow, live, work and age are at the root of ... inequalities in health.”

Powderly stresses that the latter objective allows partners to frame the discussion, “stating what their problems, priorities and needs are.” Washington University could then determine if it has the capabilities and resources to assist in those areas.

“We typically come and go depending on the interests of our researchers, funding opportunities and other factors,” Powderly says. “If we help other global institutions build their own infrastructure — and ideally create an environment for ongoing collaboration — even as different investigators move on, we will have made a more sustained impact.”

With the university’s newest McDonnell Academy partner, the University of Ghana, Powderly hopes to build such a model from the beginning.

“In Ghana, for example, I may think that TB is very important because of its prevalence in Africa. They may decide that too,” Powderly says. “Or they may decide that a key priority is maternal mortality and safer labor. Another big, challenging issue, maternal mortality has many implications for families.” Therefore, fostering a partnership with Washington University’s obstetrics and gynecology department might be viewed by partners at the University of Ghana as more important than working with the infectious diseases division.

When university researchers go into other countries, Powderly says, they cannot assume persons in those countries haven’t been thinking about their own problems, and for a long time. “We cannot adopt a neo-Colonialist attitude that we know best. We don’t,” Powderly says. “It’s about listening and developing partnerships. And we want them to be sustained, and to have long-lasting impact.”

Issouf Sanogo

Mark Manary, MD ’82, has worked in Malawi for decades on projects to prevent and treat malnutrition.

Mark Manary, MD ’82, has worked in Malawi for decades on projects to prevent and treat malnutrition.
Lora Iannotti, PhD, assistant professor at the Brown School, knows firsthand how important it is to identify partners for sustained impact. Having worked in Haiti for 25 years, she also understands what happens when short-term aid trumps long-term strategy.

“Many outside groups conduct their business without finding out if what they are doing is what the community wants or needs; then they leave,” Iannotti says. “This has wreaked havoc on the country.”

Through her multifaceted work, Iannotti collaborates with the Ministry of Education, the Ministry of Health and community health workers, as well as other NGOs, and, generally, they do not focus their work on prevention.

Determined to help remedy the situation, Iannotti worked with Washington University and Haitian colleagues to form an agreement with the Public University of North Cap-Haitien (UPNCH). She found inspiration for the new program in U.S. history. “Looking at the Progressive Era in our country, the big changes in public health came from prevention: improving health by boosting living standards, cleaning up the streets, implementing vaccinations, etc.,” she says.

In July 2015, UPNCH and Washington University jointly offered a public health summer institute. Iannotti hopes the institute eventually leads to a full degree program. While raising funds, the collaborative team — including two School of Medicine faculty members and four representatives of the Brown School — is developing the curriculum and course work through that. Iannotti says she is grateful for the support she has been receiving from colleagues and administrators. In particular, Brown School Dean Edward Lawlor, PhD, the William E. Gordon Distinguished Professor, has been a champion for university efforts in Haiti; he traveled there in summer 2014 to participate in Iannotti’s summer course, “Transdisciplinary Problem-Solving in Haiti: Public Health Interventions in Developing Countries,” and to visit research sites in Cap-Haitien. At those sites, Iannotti investigates the relationship between poverty, micronutrient deficiencies and infectious disease, particularly in young children.

The biggest nutrition problem now, she says, is not a lack of calories, but a lack of particular nutrients. “Poor-quality diets, as in our country, lead to what’s referred to as ‘hidden hunger,’” Iannotti says. “A lack of certain nutrients — vitamin A, B12, choline, iron and zinc, for example — can increase the risk for morbidity, impaired cognition and mortality.”

These nutrients, not surprisingly, are found in eggs, fish, meat and milk, which are typically more expensive and less affordable in Haiti and other resource-poor countries.

“As a result, people are stunted or chronically undernourished. They become ill or die from diarrheal disease and respiratory infections because their immune systems don’t function as well without these nutrients,” Iannotti says. (Globally, lower-respiratory infections were the No. 1 cause of premature death in 2010, and diarrhea was the No. 4 cause.)

For one project, Iannotti partners with Patricia Wolff, MD, professor emerita of clinical pediatrics at the School of Medicine, to produce and distribute a fortified snack, called Vita Mamba, for impoverished school-age children. Wolff, another longtime devotee of the people of Haiti, is founder and executive director of Meds & Food for Kids, which produces ready-to-use therapeutic foods to treat malnourished children. Wolff’s factory in Haiti produces this new snack, which contains fortified peanut butter, soy powder and all the vitamins and minerals these children need for a day. The UNDA Foreign Agricultural Service’s McGovern- Dole International Food for Education and Child Nutrition Program supports the project.

The research has shown significant improvements in children’s body composition with long-term implications for their health and development. Results will be reported to the U.S. Senate, together with those of other grantees, to help determine the composition of food aid commodities moving forward.

“Haiti has dire public health problems, yet the country has limited higher education in this field,” Iannotti says. “Basically, you have a small proportion of people who pursue medical degrees. They invest years and become trained to be doctors. Some will leave the country or work for international NGOs, and, generally, they do not focus their work on prevention.”

Lora Iannotti (left), PhD, assistant professor at the Brown School, has worked in Haiti for 25 years. She collaborates with in-country partners, such as Dominican Joseph (center), on public health and prevention research projects at the nexus of poverty, micronutrient deficiency and infectious disease.

The Next Generation Prepares to Help

William Powderly, MD, finds encouragement in what he calls “the keen student interest in having global experiences, in addressing global health challenges and in thinking of themselves as global citizens.”

Lora Iannotti, PhD, is one of the Washington University faculty members helping train this next generation of global health professionals. As chair of the global health specialization for the Brown School’s Master of Public Health program, Iannotti develops curricula. She also teaches “Global Health,” “Global Hunger and Undernutrition,” and “Transdisciplinary Problem-Solving in Haiti: Public Health Interventions in Developing Countries,” which was offered for the first time in summer 2014.

Further, Iannotti works with Carolyn Lesoregol, PhD, associate professor and associate dean of global strategy and programs at the Brown School, to help place students in international practicum sites. Under Lesoregol’s leadership, the Brown School is working to build an inventory of deep-rooted, permanent international sites from which students may choose.

At the School of Medicine, other opportunities exist for global learning:

• The Forum for International Health and Tropical Medicine (FIHTM) student group provides funding for 25 medical students interested in spring-break opportunities, summer research, clinical experiences and fellowships, “to prepare students as creative and critical thinkers about the intricacies of global health.” One rotation offered is assisting pediatrician Mark Manary, MD ‘82, in feeding the severely malnourished in Malawi. (See sidebar, pg. 19, for more on Manary.) FIHTM, whose faculty adviser is Gary Welé, MD, also hosts an annual global health symposium together with global health faculty. In April 2015, for example, FIHTM hosted a symposium in conjunction with the Global Health & Infectious Diseases Conference.

• The Global Health Scholars’ Pathway in Internal Medicine is committed to training future clinical and research leaders in global health. The pathway increases residents’ awareness of global health systems, enhances understanding of the impact of culture and poverty on population health, and fosters skills for providing care in resource-poor environments.

• The Global Health Center began a new program in 2014 – Summer Research Program in Global Health – to offer students an eight-week opportunity to work with faculty members who focus on global health. In the School of Engineering & Applied Science’s Department of Energy, Environmental & Chemical Engineering, student researchers look at the role of the environment in global health problems, including the spread of infectious diseases. Sustainable water, in both quality and quantity, is crucial to protecting human health. Sustainable air quality illustrate the need for the development of effective technologies. Sustainable air quality/and technologies that provide for clean air are also paramount in a rapidly developing world. Adverse health effects in both urban and rural areas from poor water and air quality illustrate the need for the development of effective technologies.
“It is important for us to further disseminate these positive results from the school snack,” Iannotti continues, “so that demand grows for the product and Meds & Food for Kids can build a sustainable business model.” (See sidebar on pg. 19 for more on efforts around global malnutrition.)

Another effort involves Iannotti; Zorimar Rivera-Núñez, PhD, assistant professor of social work at the Brown School; and Daniel E. Giammar, PhD, PE, the Walter E. Browne Professor of Environmental Engineering in the School of Engineering & Applied Science. Through the lens of their various disciplines, the team is assessing water contamination — beginning with toxic heavy-metal contaminants — and then determining as a group the impact of this contamination on nutrition.

In Haiti, 64 percent of the people do not have access to a latrine, and poor sanitation leads to unsafe drinking water. Further, certain water contaminants affect the absorption and metabolism of important micronutrients. The team plans to test microbial contaminants in future projects.

The project builds on Iannotti’s studies on nutritional outcomes in five Cap-Haïtien neighborhoods. Last summer, Iannotti, Rivera-Núñez, their UPNCH co-principal investigator and local university students determined the sources of water in these neighborhoods (government-built pumps and wells, community-built wells or family wells) and collected samples from each source, which Giammar is helping test. Where contamination is found to be higher, they’ll be able to target community development resources better and, ultimately, improve nutritional trials and other interventions.

“In many academic venues, but especially at Washington University, people are starting to talk about the importance of being ‘transdisciplinary.’ This approach is clearly what’s needed to address complex global health challenges,” Iannotti says. “Malnutrition — or any other global health challenge — won’t be solved unless we work across disciplines.”

Terri Nappier, executive director of periodicals in the Office of Public Affairs, is editor of the magazine.

In Haiti, Brown School Assistant Professor Lora Iannotti, PhD, also partners with Patricia Wolff, MD, professor emerita of clinical pediatrics at the medical school, to develop and distribute Vita Mamba, a fortified snack for impoverished school-age children. Research shows significant improvements in the body composition of children receiving the supplemental snack.

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