With the help of the Vermont community, Beth Kirkpatrick, M.D., and her colleagues are finding a more effective way to counter a disease that affects tens of millions of people across the globe every year.

**Stopping Typhoid in its tracks**

by EDWARD NEUERT

“It’s Dosing Day!” Clinical Research Associate Katrin Sadigh says in a stage whisper, as the hands of her wristwatch read 7:30 a.m. on a Wednesday morning in late July. Sadigh, along with Associate Professor Beth Kirkpatrick, M.D., and several other colleagues are clustered at one end of the hallway of the third-floor corridor of the Arnold Wing of the University Health Center in Burlington. There’s a pause of several seconds, and a few anxious glances, and then down the hallway comes the first of this morning’s 15 important guests — volunteers who today will swallow a dose of a new vaccine for typhoid fever that could help better the lives of millions of people half a world away.

“It’s important to keep in mind the 80 percent rule — the fact that more than eight out of ten prospective vaccines never make it past Phase I trials,” says Kirkpatrick, as she stands in the crowded doorway of her lab space in Stafford Hall. Next to her stands a stack of insulated shipping cartons that contain blood samples from Miami Research Associates in Florida, and from the Bloomberg School of Public Health at Johns Hopkins University. Lab personnel are busily pulling blood vials, arranging tests, and logging data. A few steps away, in a small office area, assistants are interviewing prospective participants for the next round of this Phase II vaccine dosing.

All the activity swirling around Kirkpatrick is focused toward one effort: proving the safety and dosing level of an oral typhoid vaccine developed by Emergent Technologies of Rockville, Maryland. If proven, this vaccine could be a vastly more versatile tool to prevent typhoid cases in the developing world, thanks to

Brian Kilonzo '11 works on typhoid vaccine analysis.

photography by RAJ CHAWLA
its single dose and powdered stored form, that makes it much easier to administer and transport than current vaccines, which are either delivered by injection or multiple doses, or need constant refrigeration before use.

Since coming to UVM in 1999, Kirkpatrick, who has a faculty appointment in both the Department of Medicine and the Department of Microbiology & Molecular Genetics, has built a unit with a reputation for tackling some of the most pressing needs in vaccine research. Through her efforts, last year UVM/Fletcher Allen was chosen as the single participating academic medical center in the nation to collaborate with the Navy Medical Research Center and a Denmark-based company in testing a new vaccine against one of the most common foodborne bacteria, Campylobacter jejuni.

Kirkpatrick has made infectious disease research her focus for years. After receiving her medical degree from Albany Medical College and completing a residency at Rochester, she pursued a fellowship in infectious diseases at Johns Hopkins and certification in Tropical Medicine and Travelers’ Health in Peru.

“My research in infectious disease and vaccines really stems from my interest in global health in general,” she says. That interest earned her a shared 2006 Frymoyer Scholarship at the College that funded work to enhance global health education for medical and nursing students.

Today in Vermont, and throughout the U.S., typhoid is a disease more read about than seen, thanks to improvements in sanitation and antibiotics. The disease is a bacterial illness, caused by Salmonella enterica, that commonly causes severe chills, sweating and pain, along with high fever, diarrhea, and internal bleeding that can lead to death. It was seen in large outbreaks in the U.S. during the Civil War, when 25 percent of soldiers who died of disease succumbed to typhoid. (Typhoid killed both Abraham Lincoln’s son, William, and the president’s famous debate partner, Senator Stephen Douglas.) In Vermont, as in many other states, mass outbreaks were fairly common in the 19th and early 20th centuries. An outbreak in Windsor in 1894 sickened more than 130 people, killing ten percent of those.

Typhoid continued to be a major problem in rapid-

ty-growing U.S. cities in the early 20th century. It was at this time that Mary Mallon, a cook in the New York area, became famous as “Typhoid Mary,” the first healthy carrier of the disease to be identified by public health authorities.

Nowadays, only an isolated case or two of typhoid occurs in Vermont every decade, but in parts of the world where sanitation and drinking water supply are still below standard, Salmonella enterica is a common and devastating visitor. An estimated 22 million people in the developing world had typhoid in the last year, and at least 200,000 died from it; most of them were children.

Though there are two approved vaccines for combating typhoid, both present problems for delivery. “In the many regions where lack of infrastructure means refrigeration is not possible, getting a vaccine to the people who need it most is a real problem,” says Kirkpatrick. “That’s the promise of this vaccine, that it will be highly effective, and much easier to use as a public health tool.”

The development of this new vaccine, as with all others, followed the carefully-mapped pathway set out by the U.S. Food and Drug Administration, which is set up to protect the safety of vaccine trial volunteers at every step. After a small first study confirmed safety in humans, two Phase I trials were conducted by Kirkpatrick in 2003 and 2005. Kirkpatrick’s lab developed a specialty in the complicated analysis of blood samples from volunteers to confirm the presence of anti-typhoid antibodies in their systems after vaccination, and this led naturally to their doing all the immunology for the latest Phase III trial.

For second-year medical student Brian Kilonzo, who worked in the Kirkpatrick lab this summer, typhoid is anything but a disease that happens “elsewhere.” A native of Kenya, Kilonzo grew up with the risk of typhoid as a regular part of daily life. “It’s personal, for me,” he says. “Being a part of helping test this vaccine is very meaningful.” Kilonzo originally met Kirkpatrick and heard about the vaccine trial through the College’s Global Health Group. Second-year student Erin Beardsworth also spent this past summer working on the project. The medical students helped hang posters seeking recruits, screened prospective volunteers over the phone, assisted in lab work, and helped run the three “dosing days” when volunteers received the vaccine. Beardsworth, who was a trained phlebotomist before medical school, helped draw blood samples from the volunteers on dosing day. A third current medical student is one of the study participants.

As Dosing Day proceeds, participant David Vuono seems calm and completely at peace with the fact that he’s about to swallow a few thousand inactive typhoid microbes. This is territory he’s covered before.

“I was a volunteer in the Campylobacter study last year,” the 25-year-old photographer and UVM graduate explains in the waiting area. “I survived that one just fine, and I’m sure I will this one too. For me this is a learning experience and a chance to help with something important.” Vuono and his fourteen fellow volunteers in the group have all been extensively briefed on the safety and possible side effects of the vaccine. They all keep a diary in which they log such information as twice-daily temperature readings. They come back to the clinic six times over the following month for evaluation. All trial participants receive a $550 payment.

Ultimately, all the preparation and careful planning comes down to the moment when Vuono and his group unscrew the caps on their liquid doses, and sip down the lemon-lime flavored concoction. If this trial is a success, in a year or so thousands of other people throughout the developing world will also be swallowing the vaccine as a part of a final stage of development, widespread Phase III field trials.

“That will be the ultimate test, but we wouldn’t get there without our volunteers,” says Kirkpatrick. “It’s really a tribute to our relationship with the community that people are willing to do this.”