Melioidosis? Never heard of it…

Deadly tropical infections that kill within 48 hours don't usually go unnoticed. But one killer has been largely ignored for decades. Now, thanks to worries about bioterror, it is being taken more seriously. Peter Aldhous reports.

Mention melioidosis in most circles — even those with a passing interest in tropical medicine — and you'll be met with blank stares. The infection is often misdiagnosed because the bacterium that causes it, the soil-dwelling *Burkholderia pseudomallei*, triggers multiple symptoms that mimic those of other diseases. In parts of Asia where *B. pseudomallei* is endemic, this serial killer often commits its crimes without even being identified as a suspect.

Not so in Ubon Ratchathani, a bustling provincial capital in northeast Thailand. For Wipada Chaowagul, a specialist in internal medicine at the city's Sappasitprasong Hospital, melioidosis is public enemy number one. Each year, the hospital admits about 200 people who test positive for *B. pseudomallei*. Up to half of them die.

Chaowagul's patients are mostly rice farmers. When the rains come each year, between May and October, *B. pseudomallei* threatens anyone paddling in the flooded paddy fields that surround Ubon — especially those already weakened by other conditions such as diabetes. Some develop internal abscesses or inflamed joints; others have difficulty breathing. Many are overwhelmed by the infection, and die from septic shock within 48 hours.

Chaowagul wants to run clinical trials of new antibiotics, to see if they can reduce this toll. But for Thailand's overstretched healthcare system, such drugs are prohibitively expensive. No pharmaceutical company has volunteered to donate its products, so Chaowagul's plans remain stalled. "If we use our own money, we have a problem," she says.

In from the cold

This tale is echoed for 'orphan' diseases across the developing world — unless pathogens afflict rich Westerners, they tend to attract little research money. But *B. pseudomallei* may soon lose its orphan status, thanks to fears that it might be used as a biological weapon. Through its richly funded biodefence initiative, the US National Institute of Allergy and Infectious Diseases (NIAID) is now encouraging microbiologists to begin working on the bacterium. "We're looking at building a research base," says Michael Schaefer, an official at the NIAID's headquarters in Bethesda, Maryland.

There are many puzzles to solve. *Burkholderia pseudomallei* is a resilient organism, able to hunker down in the soil or inside the cells of its human victims for years on end, only emerging when conditions favour its growth. One US Vietnam veteran, probably infected after breathing in aerosols of *B. pseudomallei* whipped up by helicopters, first became sick 26 years later. Vanaporn Wuthiekanun, who works on *B. pseudomallei* in the Wellcome Trust unit at Mahidol University in Bangkok, has cultured the bacterium from a sample kept in distilled water for a decade. "It's very tough," she observes.

For the most part, *B. pseudomallei* is thought to get its nutrition from rotting organic matter, and when the opportunity arises, by parasitizing soil-dwelling amoebae. Its ability to infect human cells may simply be an unhappy consequence of the mechanisms that allow it to do the latter. But these mechanisms are poorly understood, as are the ecological factors that influence *B. pseudomallei*'s distribution across the tropics. One mystery is why it is absent in central Thailand — where it is replaced by its cousin, the harmless *B. thailandensis*.

"It's probably something to do with the soil, but we haven't worked it out yet," says Nick Day, who heads the Wellcome Trust's Bangkok unit. As if the scientific challenges weren't enough, researchers out in the field also face obstacles imposed by southeast Asia's history of conflict. "We're keen to do soil surveys in Cambodia, but we're afraid of the landmines," says Wirongrong Chierakul, who works in Day's unit.

From the limited information available, it is clear that *B. pseudomallei* is present in the

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soil in parts of Asia that record few cases of melioidosis. Almost certainly, this is because of inadequate medical diagnosis. "The distribution of cases tends to follow the distribution of decent microbiology labs, of which there are remarkably few," says Day.

In places where melioidosis has been recognized as an important public-health issue, the priority is finding more effective treatments. Having evolved to compete in the soil with organisms that secrete antibacterial compounds, *B. pseudomallei* is resistant to many drugs. Until the mid-1980s, melioidosis was treated in Thailand with a cocktail of four conventional antibiotics. Only about one in five patients pulled through.

That was when Chaowagul teamed up with Nick White, who now directs the Wellcome Trust's southeast Asia programme, but was then heading up its Bangkok unit. The trust, Britain's largest biomedical research charity, has a long-standing interest in tropical diseases, and so agreed to launch a clinical trial to test a newer antibiotic, called ceftazidime. It halved the death rate[1]. The drug's high cost posed a problem, but has since been lowered. "If you have the results of a trial, you can create a political snowball," says Day. "Very often the prices will come down."

Drug shortage

But Chaowagul still loses more than 40% of her patients. So she and White next turned to a class of antibiotics called the carbapenems, which in lab tests seemed to be effective against *B. pseudomallei*[2]. But carbapenems are even more expensive than ceftazidime, and manufacturers were reluctant to donate them for trials. It wasn't until 1994 that White won a supply of a drug called imipenem from the US-based giant Merck, after writing a personal letter to Roy Vagelos, the company's chief executive.

The initial trial yielded encouraging but inconclusive results. Although there were fewer treatment failures than for ceftazidime, the sample size was too small to confirm whether the death rate was reduced[3]. The researchers wanted to press ahead with a larger study. But by then Vagelos had left Merck, and White's requests for further donations of imipenem fell on deaf ears. With the drug costing about US$100 per patient, per day, the trial was doomed. "We just couldn't afford it," says White.

Allen Cheng, a clinician at the Menzies School of Health Research in Darwin, Australia, recounts similar difficulties. He is running a trial in Ubon to see whether Thai melioidosis patients are helped by granulocyte colony-stimulating factor (GCSF), a signalling molecule that can boost the production of white blood cells. "This is virtually a self-funded project," says Cheng. The firms he approached showed little interest.

Melioidosis is also a local problem in northern Australia. There, GCSF is used routinely, and the death rate has been reduced to less than 20%. But it's unclear whether similar results could be achieved in Thailand. Australian melioidosis patients are rushed into intensive care. But in Ubon, those infected with *B. pseudomallei* must take their chances on overcrowded general wards. At least the melioidosis patients get beds near to the nursing stations. Those with less serious conditions are jammed into corridors, on balconies and outside the elevators.

P. ALDHOUS

Vanaporn Wuthiekanun visits a Thai rice field — the favourite haunt of a bacterial killer.

Against this gloomy background, the NIAID's biodefence initiative has provided a beacon of hope. *Burkholderia pseudomallei* has not yet been used as a biological weapon, but its close relative, *B. mallei*, was used as a biological agent in the First World War. It causes glanders, a disease that kills horses and, more rarely, people. The bacterium was spread by German troops in an attempt to disable the Russian army's horses and mules.

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Tough opponent: *Burkholderia pseudomallei* is a particularly resilient soil bacterium.

DENNIS KUNKEL MICROSCOPY

Potent weapon

Given the potential for *B. pseudomallei* and *B. mallei* to be deployed by bioterrorists, the NIAID is keen to promote research on both, and last August held a meeting in Bethesda to kick-start interest. Those who have for years ploughed a lonely furrow in melioidosis research can scarcely believe the shift in gear. "Two or three years ago, no one else was working on this disease in North America," says Donald Woods, a microbiologist at the University of Calgary in Alberta, Canada. "Now there are ten labs."

The time is right for an influx of money and personnel. Last year saw the publication of the complete genome sequence of *B. pseudomallei*[4], a product of the Wellcome Trust's enthusiasm for tropical medicine and genomics. It appeared next to another paper[5] describing the genome of *B. mallei* — a project backed by the NIAID. The two sequences should provide clues for researchers trying to understand the organisms' virulence, and suggest targets for drug development.

The genome projects have also revealed that *B. mallei* evolved directly from *B. pseudomallei*, losing parts of its genome along the way[6]. For clinicians, this close relationship is encouraging. With funding from the US military and the Canadian government, Woods has developed a vaccine against glanders. In December, he began tests to see whether it can prevent horses from becoming infected with *B. mallei*. If the results are positive, Woods has high hopes that the vaccine will also protect people against melioidosis.

Maybe so, but those who have struggled to launch clinical studies in Thailand are unsure about the extent to which the biodefence bonanza will yield tangible benefits for them and their patients. For Cheng, one question overrides all others: "How do we stop people dying?"

NIAID officials say that the initial focus will be on basic research. But their goal is to use this knowledge to develop improved diagnostic tools, treatments and vaccines. And Schaefer says that the agency will consider funding clinical trials, if a strong case can be made. "The scope of the biodefence effort is very broad," he says. ■

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