The killers inside

Antibiotics are becoming less effective against drug-resistant bacteria. So what are the alternatives, asks **Mark White**.

Zane Archer found a cure by looking online. That's usually a recipe for disaster, but he was ready to try anything in 2008 after close to a decade of serious infections by seven superbugs. He had picked up one – the virulent MRSA – after one of many surgeries on his sinuses, the root of his problems. "From there it got worse and worse," he says.

He suffered chronic sinusitis, swallowed endless cocktails of antibiotics that never cured him but gave him a blistered oesophagus, went through countless hospitalisations for powerful IV antibiotics, picked up fungal infections and developed a bowel disorder. "I was very sick," he says.

The former competitive bodybuilder from Queensland's Sunshine Coast is an extreme example of a growing problem – bacterial resistance to antibiotics, the "magic bullets" used to vanquish disease since their introduction in the 1940s.

A 2013 report by the Office of Australia's Chief Scientist warns there is a "genuine threat of humanity returning to an era where mortality due to common infections is rife … Some bacteria are now so resistant that they are virtually untreatable with any of the currently available drugs."

But what Archer stumbled across was a treatment that predates the likes of penicillin – phages, viruses designed to "eat" bacteria, administered in liquid or pills. Every 48 hours, phages destroy about half the world's bacteria, each constantly mutating, one forever hungrily chasing the other.

Phages were in widespread medical use in Soviet Russia, based around Georgia where research began in 1923. And it was in that country's capital, Tbilisi, where he found the Phage Therapy Centre (PTC), claiming a 95 per cent success rate – as reported by the Polish Academy of Sciences – in tackling chronic conditions that "don't respond to conventional antibiotic therapies". Phages are still moving to human trial stage in the United States and Australia.

Archer is one of 16 Australians to be treated at the centre for conditions such as chronic lung infections, chronic urinary tract infections and intestinal infections. He paid $5000 – the going rate is $4000-$6000 – for the therapy, which didn't include travel or board. Doctors mixed a phage, which was squirted daily into his sinuses and swallowed, also giving him antibiotic and Camelyn injections (a honey extract). Up to 90 days' worth of phage treatment can be imported into Australia for personal use under government regulations, says the centre's chief executive Christopher Smith.

"After the first week I could feel something was changing," Archer says. After three weeks' treatment he returned home. It would be another two years before his body fully recovered, but the infections had gone. "It definitely works," he says, flatly. His doctor hadn't heard of phages, and thought he was wasting his time.

Professor Tom Riley, of the University of Western Australia, nominates phages, probiotics ("friendly bacteria") and phytomedicines (plant drugs) as three nonconventional sources of antibiotics. So, are they credible replacements for conventional drugs that don't always work the way they're supposed to?

Data shows deaths from bacterial causes are growing. Professor Matt Cooper, head of the Institute for Molecular Bioscience at the University of Queensland, says 170 Australians a week die of untreatable sepsis and blood infections; that's 9000 a year. The figure is set to double by 2030. The Australian Commission on Safety and Quality in Health Care puts the annual cost of antimicrobial resistance at $250 million to the health system and $500 million to the community. Imminent dangers include a gene called NDM-1, which can transfer from one bacterium to another bestowing resistance to almost all conventional antibiotics, with a handful of cases already seen at Westmead and Prince of Wales hospitals in Sydney. There's also *Clostridium difficile*, which can cause severe diarrhoea, colon infection and a fever, and is at near epidemic levels in the US (500,000 infections a year including 14,000 deaths). The first few cases were seen in Australia in 2012.

"There's worse to come here," Professor Riley says, nominating the latter as his biggest worry.

Just before the last election, then innovation minister Kim Carr announced $45 million would be spent on establishing a research facility aimed at fighting antibiotic-resistant bacteria. A Coalition government spokesman would not comment on whether it will still be established.

Experts estimate we have decades before we run out of options, though problems are slowly mounting. Antibiotics that used to be given in a pill to take at home are already being replaced by injections of more powerful ones in hospital. Hip replacements, for example, will become more dangerous, as bugs evolve out of reach of drugs packed into wounds to stop infection.

Phages can't replace antibiotics – they're not as useful for systemic infections – but they show promise for treating wounds and throat problems. AmpliPhi, one of the major phage research facilities in the world, has a lab in a factory unit on the northern beaches. They're working with the US Army on a phage for MRSA to treat wound-related infections, which is about to be sent to Walter Reed Hospital in the US for trials. Dr Tony Smithyman, who founded the company in 2000, hands a clear fat-bottomed 30ml bottle of it over, the first batch from the production line.

AmpliPhi has all the fittings familiar to TV viewers – vast ovens, devices jiggling liquid in test tubes, and then rows of 1000-odd phages in one side of a glass-fronted fridge with yellow caps, with containers wrapped in foil to their right, like leftover food. Many are still being developed; one to alleviate cystic fibrosis begins British trials this year.

Smithyman tells of treating a patient in Westmead in 2007 who had a pseudonoma infection resistant to all antibiotics, and faced radical surgery. Given no alternative, the hospital approved the use of phages, and one was ordered from Georgia.

The patient had been unable to urinate. The day after the first treatment Smithyman received a call from the hospital, with clinicians yelling, "This is working!" After six days, they reintroduced an antibiotic with the phages, and by day 10 the infection had cleared.

"The game we're in is in trying to put together mixes that pre-empt the chances of bacteria developing resistance," explains Sandra Morales, AmpliPhi's head of research. Phages can plan ahead for resistance. "They're incredible organisms," adds Smithyman, reverently.

Antibiotics are increasingly ineffective against *C. diff*, but a probiotic treatment is 95 per cent effective in one dose, and close to 100 per cent in two. That treatment is faecal matter transplant (FMT) – literally, transplanting healthy poo into the sufferer's gut.

Riley says he'd choose it over conventional treatment: "It's got the best cure rate of everything."

The medical establishment agrees: Dr Katie Ellard from the Australian Society of Gastroenterologists calls it the "appropriate way" to treat C. diff.

Professor Thomas Borody, of the Centre for Digestive Diseases in Five Dock, which offers novel treatment and research for gastrointestinal conditions, estimates he has performed FMT 4000 times – including nine times in one day last November.

"It's so dramatic," he says. "Someone might have 25 diarrhoea episodes one day, the next they're constipated." He says patients have been brought in from intensive care units at the Royal North Shore Hospital, given the transplant and taken back by ambulance.

His unit was the only one offering the treatment for decades. "It takes a long time for people to remove old bullshit beliefs like stress causes ulcers," he says.

Now there are a handful of other clinics opening up in capital cities and regional centres. "It's just beginning," he says.

The third alternative – phytomedicines – are plant-based remedies including garlic, honey (for wound infections), artusenate (malaria), cranberries (urinary tract infections) and tea tree oil. Riley's team has been studying the effects of tea tree oil on MRSA. It was one of the seven superbugs Archer had.

"Some of those phytomedicines work pretty well," he says. "A lot of them are used topically [on the skin], they're green and clean and environmentally friendly."

Alternatives can only help so far.

"They're part of the solution," Cooper says. "They're not going to replace antibiotics."

Big Pharma has cut research into new antibiotics to the bone, focusing on so-called "lifestyle drugs" such as statins, which are taken for years, rather than the few weeks needed to treat an infection.

Ending the overprescribing of antibiotics would be a healthy start. But as Professor Tom Gottlieb, head of infectious diseases at Sydney's Concord Hospital, says: "That's like looking at a solution asking for how people can create world peace. You can't avoid hoping it will happen and you don't know how one does it."

UNDER THE MICROSCOPE

Many small research projects are under way across Australia. Dr Kathryn Holt, of the University of Melbourne, is using DNA sequencing to examine how bacterial infections are transmitted in hospitals and the wider community, and how they become resistant.

Dr Sarah Dunstan, at the University of Melbourne, is working with a Singaporean academic on tackling multidrug-resistant tuberculosis. And the CSIRO is working on projects that include investigating the secretion made by soldier beetles to ward off predators, which has known anti-microbial qualities.

Monash University academic Sheena McGowan describes the PlyC phage she's studying as like a "flying saucer carrying a pair of warheads". She is examining its effects on illnesses like scarlet fever and strep throat.

"That's what I've always called it. The flying saucer does dock on to the bacteria and warheads chew through the wall."

But she cautions that it takes 15 years and $1.5 billion to bring a new drug to market. "We're doing the grassroots research. We need someone else to kick in the money going into clinical trials."

Drafted: Soldier beetle secretions are being studied for their anti-microbial properties.