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 SWEDISH MEATBALLS GARLICKY SCHNITZEL HEARTY BAMEN PARMESAN-CRUMBED CHOPS The antiparasitic drug ivermectin, widely used in SA to treat animals (and elsewhere people too), recently hit the news when it was touted as both a prophylactic and a treatment for Covid-19. Here's what we know.

January this year, KwaZulu-Natal GP Dr Naseeba Kathrada and more than 500 other medical practitioners penned an impassioned plea to President Cyril Ramaphosa to allow doctors t

BY SAMEENA AMIEN

Cyril Ramaphosa to allow doctors to prescribe ivermectin for Covid-19. Under pressure from various quarters, the South African Health Products Regulatory Authority (SAHPRA) eventually cleared it for 'controlled compassionate use', meaning versions of the drug for human use may be imported and prescribed. However, doctors have to make a Section 21 application on behalf of every patient, at a fee of R300 each.

# **1** WHAT IS IVERMECTIN?

It's an antiparasitic drug that has been used by livestock farmers since 1981. In South Africa it's been registered for veterinary use only, but in some countries, mainly in the tropics, it's also used to treat people for infestations of head lice, the mite that causes scabies, and the parasitic worm that causes river blindness.

More than 40 years ago, a Japanese team under biochemist Satoshi Omura discovered a soil bacterium that produced an active class of compounds named avermectins, which exhibited excellent antiparasitic activity. A team headed by parasitologist William Campbell developed a mixture of two avermectin derivatives, which they called ivermectin. Omura and Campbell were awarded the Nobel Prize in Physiology or Medicine 2015 for their work.

# **2HOW DID AN ANTI-PARASITIC BECOME** A POTENTIAL CURE FOR A VIRAL DISEASE?

About eight years ago, researchers at Monash University in Melbourne, Australia, noticed that patients suffering from tropical and other RNA viral diseases like Dengue fever, West Nile fever and Zika did better when they were also taking ivermectin for a parasitic infection. They discovered it also had antiviral (or rather, virostatic, which means it doesn't kill the virus but just inhibits replication) and anti-inflammatory properties. In 2020, these researchers, in collaboration with the Peter Doherty Institute for Infection and Immunity, looked into ivermectin's therapeutic potential for Covid-19, and published their findings on 3 April. 'We found that even a single dose could essentially remove all viral RNA by 48 hours, and that even at 24 hours there was a really significant reduction in it,' said Dr Kylie Wagstaff, a lead researcher involved in the study.

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# **3**SO WHAT'S THE PROBLEM?

The test done was in vitro (that is, in a Petri dish) and not in vivo (using human subjects). So, while Dr Wagstaff and her team found the results very encouraging, since

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ivermectin was 'widely used and seen as a safe drug', she added that the use of ivermectin to combat Covid-19 would depend on the results of further pre-clinical testing and ultimately clinical trials, 'with funding urgently required to keep progressing the work'.

This was back in April 2020 and these were respected researchers. You'd have expected the World Health Organization (WHO), the National Institutes of Health (NIH) and other 'protectors' of our health to fund this research to save lives, even while they were funding vaccine research.

#### **HOW DOES** IT WORK?

Researchers say ivermectin binds to, and destabilises, the receptor that transmits the viral proteins into the human host's cell nuclei.

Also, in an in-silico (computersimulated) study, ivermectin has been shown to insert itself between the spike protein and our own cells' receptors, effectively blocking its entry into the cell in the first place, and preventing the virus from hacking the nuclear machinery to replicate itself. This seems to be its function when used as prophylaxis and in the early stages of the disease.

Ivermectin has anti-inflammatory properties too, which doctors say might be effective in dampening the cytokine storm that is such a marked feature of the later stages of the disease – the result of the body's immune system overcompensating to the point where it turns on itself.

All in all, it's no wonder the Front Line Covid-19 Critical Care (FLCCC) Alliance, a think-tank of renowned intensive-care specialists and scholars, is calling it a 'wonder drug'. In his testimony before the US Senate, the FLCCC Alliance's Dr Pierre Kory cited a clinical trial done in Argentina by the lead investigator of ivermectin there, Dr Hector Cavallo: 800 health-care

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workers were given ivermectin as a prophylactic, and a control group of 400 workers got nothing. Not one of the 800 fell ill, whereas 237 of the 400 in the control group (58%) contracted the disease.

#### **5** SO WHY HAS **5** IT BEEN SUCH A TOUGH SELL WITH THE AUTHORITIES?

Not all clinical trials are equal. Randomised controlled trials (RCTs) are the gold standard in scientific research. They're designed to show a clear correlation between cause and effect by eliminating most of the variables that could potentially cloud the findings.

As US pulmonologist Dr Negin Hajizadeh says, Covid-19 presents in so many different ways, and now in different variants, that it makes it difficult to control all the variables for a specific outcome in RTCs.

Dr Kory says we are basically at war with the virus – we simply don't have the time for RCTs now. Well-designed observational studies and meta-analyses can match and even supersede RCTs, he points out. Johannesburg nephrologist Dr Shoyab Wadee, a member of the Ivermectin Interest Group here, agrees that 'time is life', although he suggests proceeding with caution.

Other critics of the global regulatory bodies' reluctance to give the go-ahead to ivermectin are less diplomatic. Dr Hector Cavallo puts it down to the fact that there's no money for Big Pharma in ivermectin.

Yet others claim a Western bias: ivermectin is mainly used in developing countries. As Dr Paul Sax points out in *The New England Journal of Medicine Journal Watch*, 'We have to guard against two important biases here. First, that because we were burned by hydroxychloroquine means that all other repurposed antiparasitic drugs will fail too. Second, that studies done in low- and middleincome countries must be discounted because, well, they weren't done in the right places. That's not just bias, it's also snobbery.'

# **6**IT'S SAFE... WITH CAVEATS

Ivermectin has been around for 40 years, during which time about 3.7 billion doses have been administered to people. Most would consider this an excellent safety record – and it is, Dr Wadee says, but he acknowledges that recordkeeping and reporting of side-effects might not be rigorous enough in the countries where it's most often used.

The dosage has been cited as a problem too: a course for a parasitic infestation would probably run to one to three days max, so the effects in the case of longer-term treatment are not known.

Dr Wadee highlights another risk: resistance to the drug over time. It's already a problem in farming, and it leads to another serious side-effect: ecotoxicity. Studies have shown that ivermectin may be stored in soil for long periods and affects dung decomposition, which in turn affects dung beetles, earthworms and other invertebrates.

What's more, some veterinary ivermectin formulations contain ethylene glycol, or antifreeze, which can cause renal failure in humans.

# **7**WEIGHING UP THE OPTIONS

Most in the pro-ivermectin camp would say it's not a choice between ivermectin and the vaccine – there is room for both. But perhaps Dr Cavallo should have the final word: 'You can get herd immunity the hard way, by losing tens of thousands of lives, or you can do it the easier way, by helping patients recover.' �