Citation: C. Aldous, E. Gkioulekas, P. Oldfield, "Ivermectin", In: "Controversies in the Pandemic" (editors: J. Varon, P.E. Marik, M. Rendell, J. Iglesias, C. de Souza, P. Prabhudesai), Jaypee Brothers Medical Publishers, New Delhi, India, 2024
(author's preprint)

Ivermectin

Colleen Aldous [1], Eleftherios Gkioulekas [2], Philip Oldfield [3]

[1] Nelson R. Mandela School of Clinical Medicine of the University of KwaZulu-Natal, Durban, South Africa
[2] School of Mathematical and Statistical Sciences, University of Texas Rio Grande Valley
[3] Scientific and Regulatory Consultant, Rigaud, Quebec, Canada

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I. Introduction

A brief history of the discovery of ivermectin

Microbiologist Satoshi Ōmura, the 2015 Nobel Prize for Medicine winner with William Campbell, carries a picture of his wife and daughter and a small plastic specimen bag wherever he goes [1]. In 1970 he used this small specimen bag to collect NRRL 8165, the mould later named *Streptomyces avermectinius*, from the woods close to a golf course along the ocean at Kawana in Ito City in the Shizuoka region of Japan.

Ōmura worked at the Kitasato Institute (KI), a research institution in Japan recognised as a world-leading centre for discovering drugs and vaccines, primarily those derived from natural sources. Founded in 1914 by Shibasaburo Kitasato, the father of serotherapy and nominated for the first Nobel Prize in 1901, the institute has a long history of investigative research and developing chemotherapeutic drugs for practical use [1].

Researchers at the KI turned to nature to find specimens because they believed in the almost unlimited abilities of microorganisms to produce novel compounds. They deliberately selected unusual microorganisms to maximise the chances of finding new compounds [2]. They attempted to isolate microbes from every kind of natural environment, primarily from soil and later from seaweed, plant leaves, and plant roots. They believed that the source could significantly impact the type of microbe found. They also believed that nature's microbes produce metabolites offering therapeutic promise. The KI isolated extraordinary microorganisms, cultured them, and evaluated the bioactivity of potential compounds.

In 1971 Ōmura, encouraged by Professor Yukimasa Yagisawa, General Manager of the Japan Antibiotics Research Association (JARA), to exploit the possibilities for research work overseas, went to the US on a sabbatical. Professor Max Tishler had invited him to work as a Visiting Research Professor in the newly-formed Chemistry Department at Wesleyan University in the US. Tishler had recently retired as President of the Merck Sharp & Dohme Research Laboratory (MSDRL). While on sabbatical, Ōmura sought research collaborations in the US to secure funds to support research work in Tokyo after his return. He visited many major U.S. pharmaceutical companies, presenting a proposal for a collaborative research project. Tishler approached his successor at MSDRL, Dr L.H. Sarett, with Ōmura's collaboration ideas. This discussion expedited the research collaboration between Ōmura and MSDRL, which began in April 1973 [2].

Ōmura and William Campbell from MSDRL collaborated to find growth-promoting antibiotics suitable for animals, enzyme inhibitors, and general-purpose antibiotics produced by microorganisms. As part of this initiative, the KI isolated extraordinary microorganisms, cultured them, and then undertook preliminary in vitro evaluation of the bioactivity of any compounds they deemed potentially interesting. The most promising specimens were then sent to MSDRL for in vivo testing in the laboratory run by his co-Nobel Prize winner, William C. Campbell; among them were extracts from NRRL 8165 and thousands of other microbes collected by Ōmura and his colleagues [2].

In Campbell's laboratory, the ivermectin precursor, avermectin, which had been extracted from NRRL 8165, was discovered as a result of an antihelminthic screening test conducted on mice infected with the nematode *Nematospiroides dubius*. The test involved using an extract that was later fractionated to reveal macrocyclic lactones as the active components responsible for eliminating the nematode infection. Among these lactones, Avermectin B1a was found to have the leading activity [1].

Ivermectin for veterinary use

Further research by Campbell's group revealed that Avermectin B1 had superior potency and safety compared to all known antihelminthic therapies at the time. It could resolve various animal nematode (roundworm) infections [1].

MSDRL chemists later made a minor chemical modification to Avermectin B1 to create ivermectin, marketed in 1981 for animal use. Ivermectin was effective not only against nematode infections, such as heartworm in dogs and various worm species in commercial livestock, but also against ectoparasitic insects like fleas, ticks, and botflies, which cause significant economic losses in the livestock industry [1,2]. It quickly became a "blockbuster drug" in veterinary medicine due to its efficacy, potency, and safety in treating various parasitic infections. Resistance to ivermectin began to appear, initially in small ruminants and more significantly in cattle parasites, especially Cooperia spp. However, there have been no reports of resistance in canine heartworms or among equine Strongyloides parasites. Ivermectin continues to be an essential drug for livestock and other domestic animals globally.

Ivermectin for human use

Ivermectin has been used extensively in human health, improving billions of people's general health and well-being worldwide since it was first used in 1988 to treat onchocerciasis (river blindness), a disease caused by a parasitic worm (*Onchocerca volvulus*) and transmitted through the bites of infected blackflies. It is multipurpose, highly effective, broad-spectrum, safe, well-tolerated, and can be easily administered. Satoshi Omura and William Campbell were awarded the Nobel Prize in Physiology or Medicine in 2015 because their work has had a significant impact on global health, particularly in the treatment and control of debilitating diseases like onchocerciasis and lymphatic filariasis (elephantiasis), a disease caused by filarial worms (*Wuchereria bancrofti, Brugia malayi, and Brugia timori*) [3], which is transmitted to humans through mosquito bites.

Ivermectin for onchocerciasis and lymphatic filariasis and the Mectizan program

In the mid-1970s, the global community mobilised to address the major problems of neglected tropical diseases. The UN-based Special Programme for Research & Training in Tropical Diseases (TDR) was established in 1975, with onchocerciasis and lymphatic filariasis among its target diseases.

Ivermectin's role in human medicine began in 1978 at the MSDRL, with William Campbell being the driving force behind investigating its potential for human use. After receiving positive results from testing ivermectin on large livestock, Campbell suggested to the MSDRL management that an avermectin could prevent the blindness associated with onchocerciasis. This hypothesis was confirmed through clinical trials led by Mohammed Aziz of Merck, which showed that a single dose of ivermectin dramatically reduced the microfilaria burden in humans, ameliorating the disease.

Ivermectin causes almost complete clearance of dermal microfilariae, the immature form of the parasite that causes onchocerciasis, within two days after the start of treatment, reducing the load to virtually zero within eight days [2]. It produces long-term suppression of circulating microfilariae, making it an ideal treatment for patients with severe itching that may occur in people with onchocerciasis.

In addition to its direct effects on the disease, ivermectin has also been associated with various secondary benefits. For example, in a survey of 3,125 community members in Nigeria who had been receiving ivermectin, there was an 18.5% reduction in body itching, reduced skin rash (17.3%), and reports of 11.7% better vision [2]. The World Health Organization has certified Colombia, Ecuador, and Mexico free of onchocerciasis. Transmission has also been halted in Guatemala.

Currently, transmission has been restricted to the Amazonas region of Brazil and Venezuela. In Africa, where the disease was much more prevalent, infection rates are down fivefold. In 2014, most African countries with endemic infection moved from onchocerciasis control with annual doses of ivermectin to elimination campaigns with twice-annual dosing.

Ivermectin has also been used in elimination campaigns for lymphatic filariasis, greatly reducing the number of human cases. Ivermectin's use in treating lymphatic filariasis has a significant history. In the mid-1980s, even before ivermectin was approved for human use to treat onchocerciasis, Merck was conducting trials of ivermectin to measure its impact against lymphatic filariasis and to find optimal treatment dosages. The drug showed promise in interrupting the transmission of infection, opening up the prospect of eliminating the disease. This was made possible thanks to GSK agreeing to donate albendazole, another anti-parasitic drug [2].

In 1997, following advances in both diagnosis and treatment, the World Health Organization classified lymphatic filariasis as one of six "eradicable" or "potentially eradicable" infectious diseases and requested Member States to initiate steps to eliminate lymphatic filariasis as a public health problem [2]. In late-1998, following the registration of the drug for lymphatic filariasis, Merck extended its ivermectin donation programme to cover lymphatic filariasis in areas where it co-existed with Onchocerciasis [2]. Subsequently, in 1999/2000, the WHO launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF) [4]. Ivermectin has since been used extensively to treat lymphatic filariasis, a disease that threatens over 1 billion people in over 80 countries.

The Mectizan Program

The Special Programme for Research & Training in Tropical Diseases (TDR) and the Onchocerciasis Control Programme (OCP) made ivermectin affordable and accessible for those most in need. Initially, Merck had indicated a price of $3 per tablet for ivermectin, which would cost a treatment dose of $6, a price beyond the reach of those most affected by the disease. TDR and OCP, recognising the potential of ivermectin as a community-level tool to interrupt parasite transmission, campaigned to reduce the treatment cost [5].

During the trials to test the drug's efficacy in field settings (Phase II trials starting in 1983), Merck continued to fund much of the work, with additional financial support from OCP and TDR. TDR's existing international network facilitated Merck's ability to develop workable relationships with researchers and institutions to conduct activities in Africa and South America. Thirteen community-level (Phase IV) trials were conducted between 1987-1989, with over 120,000 individual doses of ivermectin administered. Of the 13 community trials, TDR funded five in Liberia, Cameroon, Malawi, Guatemala, and Nigeria, and spent US$2.35 million in total. Over the period, TDR spent 25-35% of its total annual budget for all filariasis work on ivermectin.

Following the registration of ivermectin for human use in 1987, Merck & Co. Inc., in an unprecedented move, donated the drug (produced under the brand name Mectizan) to treat onchocerciasis in all endemic countries for as long as it was needed. The resultant drug donation program, organised through the independent Mectizan Donation Program (MDP) established and funded by Merck, was the first, largest, longest running and most successful of all, and proved a model for all others that have followed. This decision still stands today, with Merck providing approximately 300 million doses annually of ivermectin to control and eventually eradicate onchocerciasis and lymphatic filariasis.

Despite the large-scale campaigns undertaken, human helminthic resistance to ivermectin has not yet emerged, and it remains effective for onchocerciasis and lymphatic filariasis. Today, ivermectin is being increasingly used worldwide to combat other diseases, such as strongyloidiasis (which infects some 35 million each year), scabies (mite infestation which causes 300 million cases annually), pediculosis (lice infestation), gnathostomiasis, trichuriasis, myiasis, ascariasis, cutaneous larva migrans and filariases. New and promising properties and uses for ivermectin and other avermectin derivatives continue to be found.

Ivermectin for other pathologies

In addition to being used as an anti-parasitic, ivermectin has also been considered to treat several viral and other medical conditions, including asthma, Mycobacterium infections, and cancer. Some preclinical studies and research articles have explored the potential anti-cancer properties of ivermectin [3]. These studies are typically in vitro or in animal models, and more research is needed before any definitive conclusions can be drawn about the efficacy of ivermectin in treating cancer. Studies have examined the potential effects of ivermectin on Mycobacterium tuberculosis, generally in preclinical settings such as in vitro experiments or animal models. These studies are exploratory. The therapeutic potential of ivermectin for tuberculosis would need to be confirmed through rigorous clinical trials to assess its efficacy and safety, specifically in treating TB.

In mid-2020, at the Long-Term Care Facility (LTCF) in France, a 66-year-old female resident with scabies was treated with IVERMECTIN. Subsequently, other residents also came down with scabies. It was decided that everyone at the facility would be treated with ivermectin. During this time, the COVID-19 outbreak was rampant in the area. None of the ivermectin-treated residents or staff developed severe COVID-19 or died, while residents and staff from the other LTCF's in the area showed higher COVID-19 severity and death rates [6].

II. Mechanism of Action

It has become clear over time that ivermectin has different therapeutic uses, and many of them show different mechanisms of action of ivermectin. The mechanism of action as an antiparasite was the first to be elucidated.

Mechanism of action as an anti-parasitic

Ivermectin works by targeting glutamate-gated chloride ion channels (GUCl) in the invertebrates it is designed to affect [7]. These channels play fundamental roles in nematodes and insects but are not accessible in vertebrates, which is why ivermectin is safe for human and animal use [2].

When ivermectin binds to these channels, it disrupts neurotransmission in nematodes. This disruption is believed to interfere with the ability of microfilariae (immature worms) to evade the human immune system, resulting in the host's own immune response being able to overcome and kill them [7].

The drug has little direct effect on microfilariae when administered at pharmacologically relevant concentrations. Instead, it disrupts the fundamental host-parasite equilibrium [8]. The half-life of ivermectin in humans is 12-36 hours, while metabolites may persist for up to three days. As the lowest levels of dermal microfilariae occur well after this timeframe, it suggests that not all microfilariae affected by ivermectin are killed in the first few days [8]. Repeat dosing if this appropriate.

Ivermectin is now used to treat a variety of parasitic infections including scabies and intestinal worm infestations. While it is theoretically possible for a large die-off of parasites to lead to symptoms similar to a Herxheimer reaction, this is not commonly reported in the medical literature in the context of ivermectin use given the low doses prescribed for parasitic infections. The Jarisch-Herxheimer reaction is most commonly associated with the treatment of bacterial infections rather than parasitic infections.

Mechanisms of action for indications other than anti-parasitic

Before the COVID-19 pandemic, in addition to being used as an anti-parasitic, ivermectin had also been considered to treat several viral and other medical conditions, including asthma, Mycobacterium infections, and cancer. Table 1 lists some of these indications and the intended mechanism or action. The mechanism of action, if known, is described in detail in the appropriate references cited in the Table.

Table 1. Therapeutic indications of ivermectin along with purposeful mechanisms before the COVID-19 pandemic

Indications	Actions/Mechanisms	References
Viruses	By preventing the virus cargo protein from entering the nucleus, preventing viral replication.	Dengue virus [9] [10] Hendra virus [11] Human immunodeficiency virus [9] Venezuelan equine encephalitis virus [12] [13] Pseudorabies [14] human cytomegalovirus [9]
Mycobacterium infections	Not known	Tuberculosis [15]
Immunomodulatory	Reduced the production of pro inflammatory cytokines	Asthma [16] Anti-inflammatory [17]
Cancer	Induces cell death in cancer cells	Different mechanisms cause cell death in a variety of different cancers. [18] [19]
Neurological disorders	Treatment of motor neuron disease by silencing excessive neuronal activity using IVERMECTIN	A variety of different motor neuron diseases [20] [21] [22] [23]

In 2012 the discovery of inhibition of RNA helicase DDX23 [24] in flaviviruses established ivermectin's potential as a drug, not just for parasites but for viruses. Consistent with this, ivermectin inhibits viral replication of several flaviviruses by blocking a viral helicase. Susceptible flaviviruses include those causing yellow fever, dengue, West Nile virus and tick-borne encephalitis. Encouragingly, serial passage of yellow fever virus with increasing concentrations of ivermectin did not appear to select for viral resistance.

In May 2020, in a comprehensive systemic review by Heidary [25] the antiviral effects of ivermectin were summarised including in vitro and in vivo studies over the past 50 years. Several studies reported antiviral effects of ivermectin on RNA viruses such as Zika, dengue, yellow fever, West Nile, Hendra, Newcastle, Venezuelan equine encephalitis, chikungunya, Semliki Forest, Sindbis, Avian influenza A, Porcine Reproductive and Respiratory Syndrome, Human immunodeficiency virus type 1, and severe acute respiratory syndrome coronavirus 2. Furthermore, there are some studies showing antiviral effects of ivermectin against DNA viruses such as equine herpes type 1, BK polyomavirus, pseudorabies, porcine circovirus 2, and bovine herpesvirus 1.

In 2017, Laing et all [24] commented that intriguingly, ivermectin has a diverse range of effects in many different organisms, far beyond the endoparasites and ectoparasites it was developed to control. For example, ivermectin has been shown to regulate glucose and cholesterol levels in diabetic mice to suppress malignant cell proliferation in various cancers [26], to inhibit viral replication in several flaviviruses [27], and to reduce survival in major insect vectors of malaria and trypanosomiasis [27,28].

The use of ivermectin in vector control in malaria has been considered for over a decade. In 2013 Chaccour et al suggested further research into the use of endectocides, such as ivermectin, as an important potential addition to anti-malarial measures. In 2018, the Lancet published an article entitled "Ivermectin: repurposing an old drug to complement malaria

vector control" by Rabinovich as one approach to solving the problem of residual transmission of malaria. Ivermectin has been shown to reduce Malaria transmission by a further 44% when added to malaria prophylaxis [29]

Possible mechanisms of action against SARS-CoV-2

In the early stages of the COVID-19 pandemic, the mechanisms of action of ivermectin against SARS-CoV-2 were not widely known. A point to consider is that although ivermectin was licenced as an anti-parasitic, the additional indications shown in Table 1 were published before the COVID-19 pandemic. Therefore, these proposed mechanisms were already known during the COVID-19 pandemic.

By May 2020, a few months into the pandemic, a laboratory study from Australia drew attention to ivermectin as a possible therapeutic. It demonstrated that ivermectin effectively inhibited replication of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus by preventing it from entering the nucleus. This provided the first understanding that ivermectin could possibly be helpful in treating Covid-19. In a report by Caly *et al.* [30], it was demonstrated using TaqMan RT-PCR that ivermectin effectively inhibited replication of the SARS-CoV-2 *in vitro* by blocking the ability of the host cell IMPα/β1 protein complex to bind to the SARS-CoV-2 cargo protein in the cytoplasm, thereby preventing it from going through the nuclear pore complex (NPC) and entering the nucleus. The RNA genome of SARS-CoV-2 is replicated within the nucleus of cells. The authors noted a 93–99.8% decrease in viral RNA levels for ivermectin versus control treatments at 24 hours, both in the released and cell-associated viral RNA. Likewise, they reported that by 48 hours, there was a >5000-fold decrease of viral RNA, indicating that ivermectin treatment resulted in the effective loss of essentially all viral material by 48 hours. Consistent with this, no further reduction in viral RNA was observed at 72 hours. However, under the conditions tested [30], the ivermectin concentration that inhibited viral replication by 50% (IC50) was determined to be approximately 2 μM. Although this concentration is greater than expected in vivo, it demonstrated that, at least theoretically, ivermectin can neutralise the SARS-CoV-2 virus [31]. This experiment was a proof-of-concept exercise and never designed to determine dosages.

As time went on, other mechanisms of action for ivermectin in treating patients with COVID-19 spanned all phases of the disease process. A 2022 review [32] documented that in addition to the effects of ivermectin on SARS-CoV-2 replication through interaction with host proteins, it can also interfere with the entry of the virus, modulate the inflammatory response, inhibit haemagglutination and allow cardiac mitochondria to produce ATP in the presence of hypoxia, thus providing benefit at all stages of the disease. In total, ivermectin has over 20 mechanisms of action including antiviral, anti-inflammatory, antithrombotic and cardioprotective effects [32].

<u>Possible mechanisms of ivermectin during the viral replication phase</u>

During the viral replication phase of the disease, ivermectin focuses on preventing SARS-CoV-2 from entering the host cells. Ivermectin can prevent the SARS-CoV-2 virus from entering the host cell by directly interacting with the viral spike protein and binding to the Angiotensin Converting Enzyme 2 (ACE2) receptor. It interacted with the viral spike protein in the leucine 91 and histidine 378 region, forming a complex between the SARS-CoV-2 spike protein and the ACE2 receptor [33]. Furthermore, ivermectin formed five H-bonds with the ACE2 receptor at Arg273, Glu398, Ser511, Arg514, and Tyr515 [34]. Secondly, it is also able to prevent viral replication. As previously mentioned, Caly et al. demonstrated the potential of ivermectin to block the host cell's IMPα/β1 protein complex to bind to the SARS-CoV-2 cargo protein, effectively preventing it from going through the NPC and into the nucleus [30] In this in vitro study, although the IC50 was determined to be 2 μM, there is a possibility that ivermectin could still have an effect since fat-soluble ivermectin would tend to accumulate in the tissue compartment. Another possible mechanism is the inhibition of SARS-CoV-2 RNA-dependent RNA polymerase (RdrP), which prevents gene translation. Studies have shown that ivermectin binds to RdrP, potentially halting virus replication and assembly within the host cell [34,35].

During the replication phase, should SARS-CoV-2 enter the systemic circulation, this may cause red blood cell (RBC) clumping, in which the viral spike protein binds to the glycans on the RBCs. ivermectin has been shown *in vitro* to disrupt the binding of SARS-CoV-2 to the RBCs, eliminating clumping [36]. However, the clinical relevance remains to be seen

since, in the same *in vitro* study, it was demonstrated that milder variants of the disease, *i.e*., Omicron, produced a stronger clumping effect when compared with the Wuhan variant. Although not the same, possibly a related finding was that, using flow cytometry, there was an increase in complement activation products C3b, iC3b, C3dg, and C4d on circulating RBCs from hospitalised COVID-19 patients when compared with healthy subjects [37] Furthermore, viral spike protein was also bound to the RBCs, linking the SARS-CoV-2 spike protein to the observed increase of complement activation products in hospitalised patients with severe COVID-19. IVERMECTIN prevents the binding of the viral spike protein to the RBCs [37].

The SARS-CoV-2 virus has been shown to directly activate platelets, initiating the coagulation cascade process and the release of inflammatory cytokines and leukocyte-platelet aggregates (LPAs) via the viral Spike protein's binding to ACE2, primed by TMPRSS2, resulting in microthrombi and blood clots [38]. Ivermectin acts by blocking the interactions of the viral spike protein with ACE2 and TMPRSS2 on the surface of the platelets.

Possible mechanisms of ivermectin during the hyperinflammatory response phase

SARS-CoV-2 directly activates the TLR4 receptors, initiating the lipopolysaccharide (LPS)-mediated activation of the NF-Kb pathway and MAP3 kinases, increasing proinflammatory cytokines and chemokines responsible for cytokine storms. Ivermectin inhibits TLR4 signalling directly, preventing activation of the NF-kappa pathway and MAP3 kinases, which block the production of these proinflammatory cytokines and chemokines [39,40].

The SARS-CoV-2 virus enhances the STAT-3 pathway. STAT-3 physically binds to PAK1 and increases IL-6 transcription, a major proinflammatory cytokine. Ivermectin inhibits both STAT-1 and PAK1, effectively blocking the production of IL-6 [41].

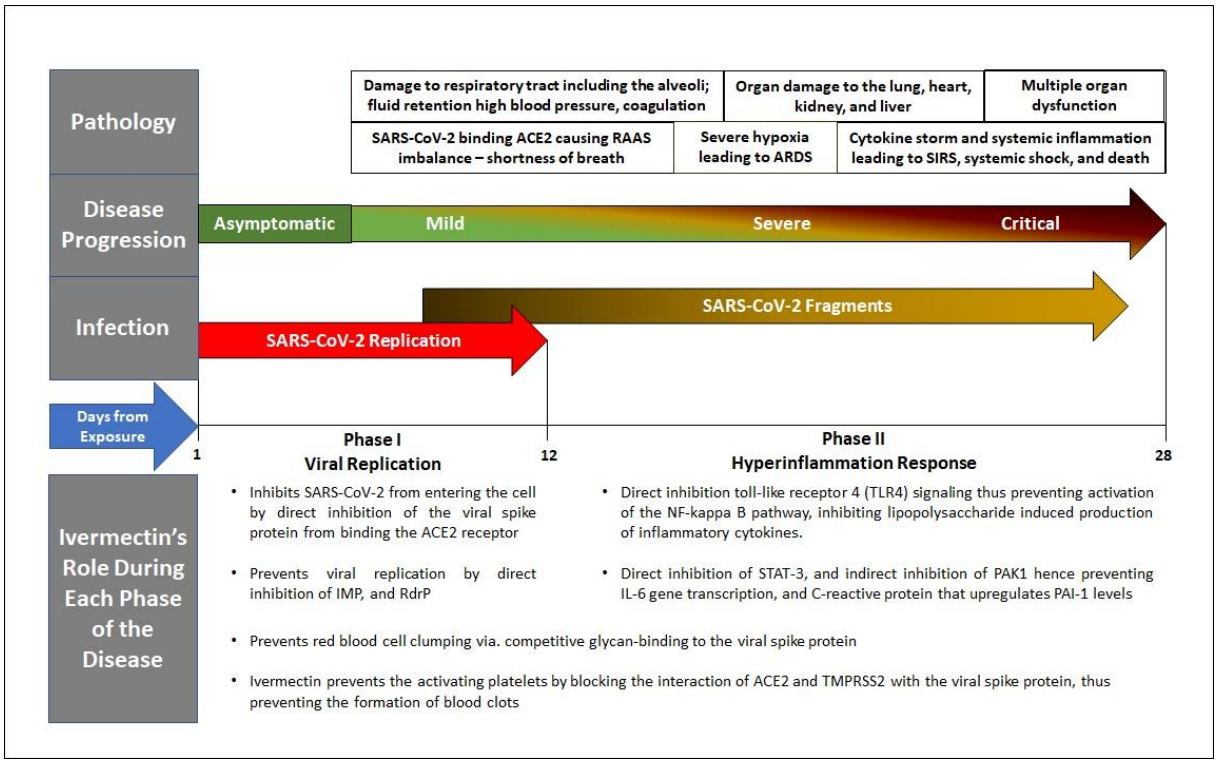

Figure 1. COVID-19 disease process, worst case scenario, and IVERMECTIN's role in its treatment

Legend of the Figure: ACE2: Angiotensin Converting Enzyme 2, RAAS: Renin-Angiotensin-Aldosterone System, ARDS: Acute Respiratory Distress syndrome; SIRS: Systemic Inflammatory Response syndrome; IMP: Importin, RdrP: RNA-dependent RNA polymerase, NF-kappa B: Nuclear factor kappa-light-chain enhancer of activated B cells, STAT-3: Signal transducer

and activator of transcription 3; PAK1: P21 activated kinase 1; PAI-1: Plasminogen activator inhibitor-1; TMPRSS2: Transmembrane protease serine 2.

Figure 1 gives a summary of the roles ivermectin has during each phase of the disease. Although it's not an all-inclusive list, it's clear that ivermectin can be used to treat patients with COVID-19 during each phase of the disease. The mechanisms are very complex and are further discussed in the references. Although most patients recover perfectly at home, Figure 1 illustrates the multi-functional roles ivermectin plays in treating patients with COVID-19, regardless of what stage the disease is at.

The mechanism of action with regard to blood clotting in COVID-19 infection

The pathology observed in COVID-19 patients, particularly the crucial role of red blood cell (RBC) clumping and its subsequent ramifications, leads to an understanding of the role of spike protein in COVID-19 patients and those suffering from COVID-19 vaccination injury. Several studies have underscored that a predominant cause of pathology in COVID-19 cases is the micro-clotting of blood [42]. Most notably, RBC clumps have been consistently identified in a majority of COVID-19 patients [42], with the rate of RBC micro-aggregates being 15 times higher in critically ill patients than in healthy controls [43]. Even among recovered COVID-19 patients who were hospitalised, there was a sixfold increase in occluded blood vessels compared to healthy individuals [44]. Of significant interest is the finding that, in nine such patients, 41% of RBCs contained traces of the SARS-CoV-2 spike protein [37]. Moreover, the presence of RBC clumps in the bloodstream appears to be at the epicentre of the most debilitating COVID-19 symptoms: from decreased oxygen saturation (SpO2 deficits) and microvascular occlusion to myocarditis. Notably, when RBC clumping was experimentally induced in vivo using high molecular weight dextran, it resulted in these same key morbidities [45]. A notable study from a Harvard hospital drew parallels between COVID-vaccinated subjects with myocarditis and detectable spike protein (SP) in their blood [46].

Furthermore, the findings by Boschi et al. (2022) emphasise the intricate interactions between the SARS-CoV-2 SP and human RBCs. When mixed in phosphate buffer solution (PBS), these components form clumps – a reaction that can wreak havoc in a host. IVM when added to this mix prevented RBC clumps from forming, and when added afterwards, reversed this aggregation and cleared all clumps [36] the biological mechanism being competitive binding with SARS-CoV-2 SP glycans [47]. Additionally, it is essential to appreciate the role of SA-tipped glycophorin A (GPA), densely coating the RBC surface, in these processes [42]. The ability of the virus's spike protein to latch onto human RBCs, leading to clumping and subsequently to clotting and inflammation, cannot be underestimated.

At a cellular level, the intricacies of glycan and ACE2 interactions with COVID-19 are paramount. While ACE2 serves as the virus's host target for replication, the glycan bindings of the SARS-CoV-2 spike protein predominantly dictate the virus's morbidity. Notably, blood cells have a significant density of SA-tipped glycans, though they lack ACE2. In contrast, endothelial cells exhibit a far higher concentration of SA-tipped CD147 glycan receptors than ACE2 receptors [42].

The lungs' vulnerability, especially the alveolar septal capillaries, is a grim reminder of how SARS-CoV-2 infiltrates the bloodstream. With most severe COVID-19 patients exhibiting damaged pulmonary capillaries and hypoxemia, the evident link between these morbidities and the clumping and clotting of blood cells is undeniable.

The crucial role of RBC clumping in the pathology of COVID-19 and the interactions of the SARS-CoV-2 spike protein with glycans and its implications cannot be overlooked. As we further our understanding, refining our research methodologies will be essential.

The role of ivermectin in stopping clumping and clotting justifies its use in late-stage disease. So does its cardioprotective effect through mitochondrial support. SARS-CoV-2 has been a well-known cause for acute myocardial injury and hypoxic cardiac arrest.

In 2017, Nagai et al demonstrated that Ivermectin increased mitochondrial ATP production by inducing Cox6a2 expression. Ivermectin therefore maintains mitochondrial ATP production under hypoxic conditions and may therefore improve cardiac function under hypoxic conditions. https://pubmed.ncbi.nlm.nih.gov/28942281/

While Ivermectin does have antiviral activity, it also acts at all stages of the disease in SARS COV2. It has antiviral, anti-inflammatory and immunomodulatory effects, it stops haemagglutination, and is cardioprotective during hypoxia. The perception that it is reserved for early disease should be reviewed.

III. Clinical Evidence

As groups across the globe started using an ivermectin regimen for the treatment of COVID-19 through 2020 due to the evidence communicated of its efficacy from several quarters, regulatory authorities were scrambling to quickly approve COVID-19 vaccines. Publications from case studies, through to observational studies and small trials emerged, and with that the cry of 'insufficient evidence' from those in the regulatory and pharmaceutical industries who all had much to gain from a potentially successful vaccine. The evidence was not insufficient at the end of 2020 and through to 2021; it was just short on well-run large randomised control trials. The emphasis on large RCTs was misplaced in the emergency of the pandemic, but has a history in the indoctrination of the evidence-based medicine pyramid. The Evidence-Based Medicine (EBM) pyramid is a concept that originated from the field of evidence-based medicine. It was developed to help healthcare professionals and researchers visualise and understand the hierarchy of evidence certainty, with the idea that the certainty of evidence increases as you move up the pyramid. The pyramid typically places systematic reviews and meta-analyses at the top, followed by randomised controlled trials, cohort studies, case-control studies, case series/reports, and animal research or in vitro studies at the bottom. The EBM pyramid is widely used in medical education and clinical decision-making. However, it is an oversimplification of evidence and mistakenly replaces "certainty" with "quality". Therefore, people are comfortable in thinking that studies that are below a randomised control trial are of poor quality, and that randomised control trials epitomise good quality. Any thinking scientist knows that good quality case series have more value in the clinical setting that badly designed RCTs, but the knee jerk response that the lack of large RCTs in ivermectin meant insufficient evidence of 'high' quality.

The evidence has continued to mount showing the efficacy of ivermectin in case series and small studies carried out by clinicians treating COVID-19. Publication bias and information blocks in the lay and academic press and social media space since late 2020 has skewed the volume of true research data available in the public domain.

Summary of key clinical trials involving ivermectin

By Oct 3 2022, there were 265 published papers on the use of ivermectin in treating CoViD-19 in the PubMed database. These were classified into four types of studies:

- Systemic studies (systematic reviews, meta-analyses and clinical guidelines) use a structured approach to integrate, critically appraise and filter the primary evidence.
- Clinical studies (randomised controlled trials, cohort studies and case-control studies) relate to all trials on live humans. This is the primary evidence/ unfiltered information.
- Mechanisms-of-action are research studies that did not involve humans, i.e. in-silico (computer-based), in-vitro (human cells in a lab) and in-vivo (live animal) studies
- Reviews include literature or narrative reviews, case series, case reports and expert opinions

These papers were reviewed to understand the researchers' conclusions regarding whether or not ivermectin was useful in treating CoViD-19. This was coded on a spectrum from Yes to No:

- Yes: Ivermectin is useful in treating CoViD-19 (or, for mechanisms-of-action, there is a plausible reason why Ivermectin would work to treat CoViD-19)
- Promising: there is some evidence to support its use, though more research is advised
- Uncertain/Maybe: the evidence is insufficient/ conflicting; more research is required
- Not promising: the evidence does not support its use, though further research could identify its role e.g. at a certain dosage, infection stage, in combination with other drugs, etc.
- No: do not use Ivermectin to treat CoViD-19 (or, for mechanisms-of-action, no explanation was found about how Ivermectin can treat CoViD-19)

Table 2: Should Ivermectin be used in treating CoViD-19? Research findings by study type

	Level-of-evidence	**Total**	**Yes**	**No**	**Maybe**
Systematic	Clinical practice guidelines	5	0	4	1
Systematic	Meta-analyses and systematic reviews	31	1	3	27
Clinical	Randomised control trials	27	6	17	4
Clinical	Cohort & Case-Control studies	26	8	10	8
Clinical	Case reports and case series	8	1	0	7
Reviews	Narrative reviews, expert opinion, editorials	107	6	2	99
Mechanisms	In vivo, in silico and in vitro studies	61	31	10	20
		265	53	46	166

Looking at the totality of evidence, about 20% of research reports were for, and another 17% against, using Ivermectin to treat COVID-19. There are two points to note, however. By mid-2022, negative randomised control trials far outweighed those that showed positive results in published research. It has already been mentioned that many RCTs were poorly designed and misreported, but by this time there was a publication bias, and many positive outcome trials were unpublished. Meta-analyses that were published were selective in the articles they reviewed, with selection and interpretation of findings being subject to bias. Comparing the Bryant *et al* and the Popp *et al* systematic reviews of the literature shows that higher levels of evidence in the EBM pyramid can be subject to bias [48,49]. Most papers showed positive trends in therapeutic efficacy for ivermectin but concluded indecisively, reported as 'maybe' in Table 2. Many mentioned finding no major adverse events but recommending further research to confirm findings. Mechanism of action studies overwhelmingly supported functionality of ivermectin in treating COVID-19.

An argument for looking at the totality of evidence and not just at RCTs must be made. While it is clear that there was diversity in findings in the research on ivermectin efficacy, the trends towards showing efficacy were apparent if the totality of evidence rather than in the selection of only RCTS on which to make a judgement.

Ivermectin used for prophylaxis against COVID-19

A few studies indicated the potential use of ivermectin as a prophylactic treatment against COVID-19, but none were as unequivocal in their findings as the SAIVE trial. The SAIVE Trial (NCT 05305560) offers significant contributions to the body

of knowledge on the use of Ivermectin for COVID-19 [50]. This large, well-designed randomised control study demonstrated the efficacy of ivermectin in preventing COVID-19, showing a reduction in infection after exposure by 72%. The study was conducted among unvaccinated individuals exposed to people diagnosed with COVID-19, and it showed a much lower likelihood of contracting the illness after taking Ivermectin. The study was overseen by a U.S.-based independent Data Monitoring Committee, providing quality assurance for the study execution. The dosages used in the study were more than adequate, with daily doses of Ivermectin taken orally at 200 microgram/kg on Day 1, followed by 100 microgram/kg daily from Day 2 to Day 28. The SAIVE Trial added to the growing body of evidence supporting the efficacy of ivermectin in preventing and treating COVID-19.

Safety profile of Ivermectin

Since its introduction in 1987, Ivermectin (IVM) has been administered in an estimated 3.7 billion human doses, demonstrating a notable safety profile [7,51-54]. The conventional dosage for IVM is 200 µg/kg, commonly employed twice at weekly intervals for scabies [55], or administered one to three times annually for onchocerciasis, commonly known as river blindness [52,56]. The United States Centers for Disease Control and Prevention (CDC) endorse an oral regimen of up to 1.4 mg/kg over a one-month period as a viable treatment option for crusted scabies [55]. This low dose averts concern regarding potential Herxheimer reactions.

Multiple studies have substantiated the drug's tolerability at elevated dosages, including a single dose of 800 µg/kg [57], 1.6 mg/kg over a 12-week span [58], and 1.6 mg/kg administered over 13 days [50]. Guzzo et al. in 2002 reported that IVM remained tolerable even when administered at a dose tenfold higher than the standard 200 µg/kg [53]. Furthermore, clinical trials employing fixed doses as high as 120 mg (up to 2,000 µg/kg) in a single administration or 180 mg (up to 3,000 µg/kg) in divided doses across one week have shown IVM to be well-tolerated, with adverse event rates comparable to placebo [53].

A meta-analysis surveying the clinical utilisation of IVM found negligible differences in the frequency and severity of adverse events between standard dosages and elevated doses of up to 800 µg/kg [59]. Longitudinal studies examining IVM use in geriatric populations at dosages as high as 400 µg/kg reported no increased mortality rates [60,61]. Crump's 2011 review further corroborates the safety of IVM, emphasising its minimal side effects and suitability for administration by non-medical personnel following basic training. This has contributed to the drug's substantial positive impact on global public health [3].

VigiAccess is the world Health Organisations global database of reported potential side effects of medicines. In August 2023, after over 40 years of use in humans a total of 7 247 adverse drug responses were recorded in VigiAccess. Of these 26 were deaths. Table 3 below compares the safety in terms of adverse events and mortality with other drugs used during the COVID-19 pandemic.

Table 3: www.Vigiacces.org accessed 28 August 2023 (Deaths reported under "General disorders and administration site conditions")

Drug	Total Events	Total Deaths	Reported since
Remdesivir	10832	722	2020
Paxlovid	41902	73	2022

Malnupiravir	2578	16	2021
Ibuprofen	187459	1151	1969
Paracetamol	197669	4104	1983
Ivermectin	7247	26	1999

Type I or Type II error

Given the volume of peer reviewed information that was available on the safety of ivermectin by 2020 as well as the emerging data on efficacy by looking at the totality of evidence, one could question whether regulatory authorities could have made a humanitarian decision based on a Type 1 error rather than dismissing ivermectin based on their definition of quality research and hearsay from other authorities and awaiting data for a Type II error decision.

A Type I error can be safely considered if there is little risk of serious adverse reactions, and ivermectin has an already established safety profile. In the case of a Type I error decision the hypothesis would have been - **Ivermectin is rolled out and proven later to be ineffective.** The data showed that ivermectin is safe and effective for prophylaxis, early disease treatment, and advanced disease treatment. The costs of the drug could have been low, given that it is no longer under patent and could be produced in anywhere in the world. If it is was proven not to be effective at some later point, then there is a relatively small financial loss. There were unlikely to be any costs to human suffering due to the already well-established safety profile.

However, regulatory authorities decided to make a Type II error decision with the hypothesis **- Ivermectin is withheld until it is shown to work in a subsequent adequately robust RCT.** At the very least, looking at the totality of evidence and the failure of the vaccines to impact the pandemic as hoped, this decision can be shown to have incurred a higher mortality rate.

IV. Controversy and Challenges

Many controversies about evaluating the available empirical evidence for and against the use of ivermectin for the treatment of COVID-19, can be elucidated if the following basic considerations are taken into account:

First, by now it is well-understood that the pathophysiology of COVID-19 is that it is a triphasic illness with three overlapping stages of (a) viral replication; (b) hyperinflammatory cytokine storm (COVID-19 pneumonia); (c) thrombosis, making it necessary to use multiple drugs in combination to effectively treat patients through this disease process [62-66]. Consequently, when evaluating the role of ivermectin in treating COVID-19, evidence for or against the use of ivermectin to treat one stage of the disease does not necessarily extrapolate to the same conclusion for the other two stages. Furthermore, given the complexity of the illness, it is not reasonable to anticipate that ivermectin monotherapy alone will yield satisfactory outcomes. Studies investigating the use of ivermectin in the treatment of COVID-19 should do so in the context of incorporating ivermectin in sequenced multidrug protocols [67-71]. Likewise, as was noted by Risch [72], results on the efficacy and safety of any treatment from studies on outpatients do not extrapolate to inpatients and

vice versa, and results from studies testing the efficacy of a medication as monotherapy do not extrapolate to multidrug protocols. Furthermore, results claiming lack of efficacy in a cohort of low-risk patients do not necessarily extrapolate to high-risk patients. Studies focusing on high-risk patients are advantageous, because they tend to require smaller sample sizes in order to detect a positive efficacy signal, if one is there.

Second, the most relevant endpoints for the treatment of COVID-19 are the prevention of hospitalisation and death. Negative or neutral results on soft and subjective endpoints, such as duration of disease or time to viral clearance, are not decisive considerations when dealing with a potentially lethal disease. A treatment protocol, that may not reduce the duration of disease, or might even prolong it, would still be considered successful if it was shown to be effective in reducing both hospitalisations and deaths. Conversely, a treatment that may reduce the average duration or severity of the illness, but has no effect or even increases hospitalisations and/or deaths, would be considered unsuccessful.

Finally, the practical question that is relevant to clinical practice is to decide whether or not particular multidrug treatment protocols that incorporate the use of ivermectin should be adopted, and ultimately this is a yes or no question that is to be decided based on the strength of the evidence that evaluate the treatment protocols themselves as opposed to ivermectin monotherapy. The more theoretical academic question is to validate the biological mechanisms of action of ivermectin itself by providing convincing empirical arguments in support of the antiviral, anti-inflammatory, and anti-coagulant mechanisms of action.

Interpreting the literature

Kory et al [73] reviewed 7 RCTs on outpatients and 6 RCTs plus 5 OCTs on inpatients, did a meta- analysis of the studies that included a mortality rate reduction endpoint, and found that there is statistically significant efficacy for mortality rate reduction when these studies are combined together. The same paper also included a meta- analysis of several studies where ivermectin was used prophylactically and found a statistically significant decrease in the infection rate. The meta-analysis included the, now withdrawn, Elgazzar study [74], however the results remain robust after removing Elgazzar from the calculation [75]. Another meta-analysis by Bryant et al [48] confirmed the statistically significant reduction of all-cause mortality, and conducted an exhaustive sensitivity analysis showing the robustness of their conclusions. In both papers, studies of inpatients were mixed with studies of outpatients, and they should have been analysed separately. Bryant et al [48] considered that, but observed that separating the outpatients from inpatient trials was not helpful, because very few outpatient trials used mortality rate reduction as an endpoint. Consequently, the most reliable conclusion that we can draw from the Bryant et al [48] meta-analysis is that mortality rate reduction has been shown specifically for inpatients, when combining several available small studies, while it remains unclear whether the result also extends to outpatients. Several other meta-analyses of ivermectin also confirmed the existence of statistically significant mortality rate reduction efficacy [76].

For outpatients, Procter's case series [67,68] of 869 high-risk patients, with 20 hospitalisations (2.3%) and 2 deaths (0.2%), who were treated through December 2020 with the combination of hydroxychloroquine, ivermectin, zinc, azithromycin or doxycycline, budesonide, foliate, thiamine, and IV fluids, is particularly compelling due to the large sample size and the high-risk status of the patients. Here, the definition of high-risk is: age ≥ 50, or comorbidities associated with high COVID-19 mortality rates, or presenting with shortness of breath. A reanalysis by Gkioulekas et al [77] noted that during 2020, the expected mortality rate for high-risk COVID-19 patients with comorbidities or shortness of breath exceeded 5%, and the CDC estimate for expected mortality rate for COVID-19 patients, from the beginning of the pandemic through September 2021, with age ≥ 50 was at least 2.3%. Likewise, the probability of hospitalisation for high-risk patients can be lower bounded by at least 10%.

Gkioulekas et al [77] also introduced a new statistical technique where the hospitalisation and mortality rate lower bounds for untreated patients are compared against a corresponding 95% confidence efficacy threshold and a random selection bias threshold, which are calculated from the case series data. When the probability of an adverse outcome (death or hospitalisation) without treatment exceeds the efficacy threshold, then the observed reduction in adverse outcomes with

treatment is statistically significant with 95% confidence, and it is more likely than not that random selection bias cannot overturn this finding. When the higher random selection bias threshold is exceeded, then we can have 95% confidence that random selection bias cannot overturn the finding of the existence of some statistically significant reduction in adverse outcomes with treatment. Specifically for the Procter case series, the random selection bias threshold for mortality rate reduction is 1.82% and for hospitalisation rate reduction it is 5.2% (see Table 3 of Ref. [77]). Both are exceeded by the 2.3% mortality rate lower bound for high-risk patients and the 10% hospitalisation rate lower bound for high-risk patients. Thus, there is clear and convincing evidence that the multidrug treatment protocol used by Procter [67,68], which included the use of ivermectin and followed the principles of the McCullough protocol [3], was effective both with respect to mortality and hospitalisation rate reduction.

This leaves open the question of whether ivermectin itself is contributing in any way towards the effectiveness of outpatient multidrug protocols. As we shall explain in the following, evidence for the existence of an antiviral mechanism for ivermectin, is available from the Itaji prophylaxis studies [78,79], and evidence of benefit in hypoxic patients is available from several studies by Stone [80], Hazan [81], Babalola [82-84], which implies potential benefit for both outpatients and inpatients. Additional evidence supporting the hypothesis that ivermectin contributes to both hospitalisation and mortality rate reduction, when used prophylactically or in treatments, is given by the recently published ecological study of ivermectin use in Peru [85].

The prospective observational prophylaxis study that was undertaken in Itaji, Brazil [78] provides the strongest positive evidence that ivermectin has effective *in vivo* antiviral properties against COVID-19. The study involved a significant proportion of 159,561 out of the 223,128 citizens of Itaji, so there is low risk of confounding by selection bias. Between July 2020 and December 2020 the study tracked 113,845 ivermectin users who took 0.2mg⁄kg of ivermectin 42 consecutive days every 15 days over a period of 150 days, and 45,716 non-users of ivermectin, all during the same time period. From the ivermectin users, 4,311 (3.7%) were infected with 86 hospitalisations (2.0%) and 62 deaths (1.4%), and from the non-users, 3,034 (6.6%) were infected with 99 hospitalisations (3.3%) and 79 deaths (2.6%). This corresponds to statistically significant reduction of the infection risk in the ivermectin users (RR: 0.56; 95% CI: 0.53–0.58; $p < 0.0001$). From the infected patients, without making any adjustments, both statistically significant mortality rate reduction (RR: 0.55; 95% CI: 0.40–0.77; $p = 0.0004$) and hospitalisation rate reduction (RR:0.61; 95% CI: 0.46–0.81; $p = 0.0007$) have been observed. There is low risk of bias because the infected ivermectin users have a greater proportion of older high risk patients than the non-users (30.3% infected ivermectin users older than 50 vs 20.0% non-users older than 50). Furthermore, the findings continue to hold after adjustment with propensity score matching, yielding 68% mortality rate reduction (RR: 0.32; 95% CI: 0.20–0.49; $p < 0.0001$) and 56% hospitalisation rate reduction (RR: 0.44; 95% CI: 0.31– 0.63; $p < 0.0001$). Although the hospitalisation and mortality rate reduction effect can be attributed to a combination of mechanisms of action, the effectiveness of the prophylactic use of ivermectin in reducing the probability of infection signals the existence of robust antiviral mechanisms by ivermectin against the SARS-CoV-2 virus itself.

A follow-up study [79] showed a stronger mortality rate reduction effect with the subgroup of ivermectin users that used the medication regularly as opposed to the ivermectin users that used it irregularly. Compared against non-users the mortality rate reduction for regular users of ivermectin was 92% (RR: 0.08; 95% CI: 0.02–0.35; $p = 0.0008$). Furthermore, amongst the regular users of ivermectin, the hospitalisation rate was reduced 100%. The authors defined regular use as having taken a total of at least 180 mg over the study period of 150 days, and irregular use as having taken less than 60 mg in total over the same time period. The dose-response effect provides additional evidence of the overall capability of ivermectin to prevent hospitalisations and death amongst infected COVID-19 patients, when used prophylactically.

The results from the Itaji studies [78,79] confirm the findings of the SAIVE trial [50], and are corroborated by a recently published study [85] on the state-level use of ivermectin in Peru, and its effect on excess deaths, which were calculated from Peruvian national data for the age ≥ 60 population per each of the 25 states, where ivermectin was approved for both inpatient and outpatient treatment on May 8 2020, until Nov 17 2020 when the new president of Peru reintroduced restrictions on ivermectin use. A 14-fold reduction of excess deaths at the national level was observed after the deployment of ivermectin, which persisted until the reintroduction of restrictions on ivermectin use, at which point a 13-

fold increase in excess deaths was observed. More detailed analysis confirmed this pattern state by state, noting that there was variability on the extent and timing of the deployment of ivermectin from state to state, with the timing and magnitude of excess deaths being aligned with this state-by-state variability. Because the study was based on population level data, there is negligible risk of selection bias, although there are other possibilities for confounding. The authors considered and ruled out possible confounding by state-by-state variability in age distribution, viral strains, compliance with social distancing recommendations, herd immunity, and population density. The authors also ruled out possible confounding by a theoretical cross immunity with the dengue virus. One limitation of the study is that it is unclear to what extent the reduction in excess deaths can be attributed to prophylactic use of ivermectin or to use in outpatient or inpatient treatment of COVID-19 patients. Nevertheless, these results are sufficient for rejecting a null hypothesis of no benefit from ivermectin use for prophylaxis and treatment of COVID-19.

Separately from the antiviral mechanism of ivermectin, case series of severely hypoxic COVID-19 patients by Stone [80] and Hazan [81] have shown that ivermectin, when used in combination with other medications, can result in rapid recovery of SpO2 levels, with a statistically significant normalisation trend being observed within 24 hours. The Stone case series [80] consisted of 34 hypoxic COVID-19 patients presenting with room-air baseline SpO2 ≤ 93%, of which 28 patients presented with SpO2 ≤ 90%, who were treated between August 2020 and May 2021 in Harare, Zimbabwe, using the SID protocol [86], a 10-day treatment regiment with ivermectin, nanosilver, doxycycline, and zinc, and in particularly severe cases also corticosteroids and anticoagulants. The Hazan case series [81] consisted of 23 patients presenting with room-air baseline SpO2 ≤ 90%, who were treated in the United States between August 2020 and February 2021 with a 10-day course of ivermectin, doxycycline, zinc, Vitamin C, and Vitamin D. The patients in the Hazan case series [81] enrolled in a clinical trial for outpatient COVID-19 treatment, but were excluded due to room-air baseline SpO2 ≤ 90% and advised to seek hospital care, but declined to be hospitalised for a variety of personal reasons, and were thus treated via telemedicine while quarantined at home. The patients in the Stone case series [80] were by necessity treated at home, via visiting nurses, or in an outpatient clinic setting, due to the unavailability of hospital resources in Harare, Zimbabwe. With both case series, the outcome was zero hospitalisations and zero deaths, mediated by the rapid recovery of SpO2 levels.

Out of 57 hypoxic patients in both case series combined, 51 patients initially presented with room-air baseline SpO2 ≤ 90%, so the expected counterfactual hospitalisation rate, in the absence of treatment and assuming the willingness of the patients to be hospitalised and the availability of hospital resources, should have been at least 51 out of 57. Obviously, all of these hospitalisations were successfully prevented with treatment, and the corresponding hospitalisation rate reduction is statistically significant with $p = 10^{-25}$. Another case series of younger hypoxic COVID-19 patients by Babalola [82–84], where ivermectin was used as a monotherapy over a period of 5 days, also showed a statistically significant rapid recovery in SpO2 levels, however the rate of recovery observed in the Hazan [81] and Stone [80] case series was more intense.

These results, when considered together, show that the rapid recovery of SpO2 levels can be attributed, in part, to ivermectin. However, using it synergistically, as part of a multidrug protocol, intensifies the effect. Because the drop in SpO2 levels is a consequence of microscopic blood clots accumulating in the lungs, from the toxicity of the spike protein, ivermectin's anticoagulant mechanisms of action are the most likely explanation for the rapid increase in SpO2 levels [36,42,47]. These results provide good reason to recommend the use of the SID multidrug protocol [86] for inpatients. They also point to another rationale for using ivermectin for the treatment of outpatients, separately from antiviral action; if ivermectin is capable of restoring SpO2 levels on hypoxic patients, when used in combination with nanosilver, doxycycline, and zinc, then it is a reasonable extrapolation that this combination of medications would also prevent the SpO2 levels from dropping if given to COVID-19 patients before they develop hypoxia. Indeed, some of the empirical observations of mortality and hospitalisation rate reduction for infected ivermectin users from the Itaji studies [78,79], where ivermectin was used prophylactically, could be resulting not only from the antiviral action but also from this additional protective effect.

Trails showing ivermectin failure to treat COVID-19

Six randomised control trials, published in high impact journals, have been cited as evidence against the use of ivermectin in the treatment of COVID-19 [87–92]. Four of these tested ivermectin monotherapy against placebo [89–92] so the results are not relevant to the multidrug treatment protocols used by practicing doctors. From the remaining two studies, the COVID-OUT trial [87] is methodologically flawed, because it compared a combination therapy of three consecutive days of ivermectin combined with a 14-day course of metformin against a mixed control group of patients that received only the 14-day course of metformin or a placebo. Because the trial did demonstrate some efficacy for metformin monotherapy, this comparison, as well as the under-dosing of ivermectin in the study, biases the results towards the null hypothesis, therefore a neutral result is inconclusive, and cannot be reliably interpreted as evidence against the use of ivermectin.

The I-Tech study [88] is interesting because it recruited high-risk patients with age ≥ 50 and at least one comorbidity, the treatment group was treated with a realistic multidrug protocol combining ivermectin with corticosteroids, antibiotics, and anticoagulants with 1.2% mortality rate, the control group was treated only with corticosteroids, antibiotics, and anticoagulants, with 4.0% mortality rate. The authors claim that this was a negative result due to *p*-value $p = 0.09$, and also due to negative results in irrelevant soft endpoints other than hospitalisation and death. Using the methodology by Gkioulekas et al [77] on the treatment group of 241 patients with three deaths, the corresponding efficacy threshold is calculated at 3.7%. Furthermore, Gkioulekas et al [77] noted that the expected mortality rate for untreated high-risk patients with comorbidities exceeds 5%, and even more so with the addition of the age ≥ 50 restriction. Consequently, comparison of the treatment group against the known historical control of untreated high-risk patients shows that it is more likely than not that there is a mortality rate reduction benefit when ivermectin is used as part of a multidrug protocol. The study allowed a 7-day window from the beginning of symptoms before initiating treatment, however Fazio et al [93] showed that the ideal window of opportunity for the outpatient treatment of COVID-19 is approximately 3 days from the beginning of symptoms. Thus, we can expect stronger results if the protocol used in the I-Tech study [88] is initiated within the 3-day window from the onset of symptoms.

With regards to the remaining RCTs, the Lopez-Medina [91] and ACTIV-6 [89, 90] trials have very low mortality rate in the control groups, so prima facie, on both arms of the trial the patients are in the low-risk category thus, a negative result with respect to mortality rate reduction cannot be justified by these studies. Likewise, because the treatment was monotherapy not initiated within the first 3 days from the onset of symptoms, these studies cannot be relied on to conclude the lack of hospitalisation rate reduction benefit from early outpatient multidrug treatment protocols that incorporate the use of ivermectin. Finally, the TOGETHER trial [92] tested a 3-day ivermectin monotherapy against placebo with negative results with respect to hospitalisation and mortality rate reduction. Prima-facie, the study shows that a 3-day ivermectin monotherapy where more than half of the patients initiated treatment at 4-7 days from onset of symptoms is insufficient, which can be attributed to underdosing, short duration of treatment, and given too late. More concerning is an asymmetric loss of patients in the control arm from intention-to-treat patients to per-protocol patients, compared to a negligible loss of patients in the treatment arm, indicating a possible loss of blinding. The study authors did not do a per protocol analysis for hospitalisation and mortality rate reduction and refused to release their data for independent per-protocol analysis [94].

The totality of the evidence indicates that a combination of chemoprophylaxis using ivermectin along with use of multidrug protocols that incorporate the use of ivermectin, could have reduced both hospitalisations and deaths by at least one order of magnitude. The empirical evidence supports the use of ivermectin-based protocols in both outpatients and inpatients, and points to the importance of initiating early outpatient treatment as soon as possible, and ideally within the first 3 days from the onset of symptoms. The TOGETHER trial [92] raises doubt on the efficacy of ivermectin monotherapy, when given over a short 3-day period and with significant delays, but their findings cannot be considered settled without a per protocol analysis of hospitalisation and mortality rate reduction, and they do not extrapolate to prophylactic use or to use in multidrug outpatient and inpatient treatment protocols.

The controversy surrounding Ivermectin's use

In spite of the available and accumulating positive evidence supporting the use of ivermectin in the treatment of COVID-19, especially in the context of prophylactic use as well as use in multidrug treatment protocols, the World Health Organization has been cited in calls to use regulatory agencies to restrict doctors from using this medication in accordance with their better judgment [95]. Practicing physicians involved in the development of multidrug treatment protocols have faced increased levels of censorship and professional consequences. These developments may be indicative of a broader trend where public health measures are being leveraged for the establishment of political authority on an international scale.

In the US, the FDA issued a statement titled, "Why You Should Not Use Ivermectin to Treat or Prevent COVID-19,[96]" and subsequently disseminated correspondence to both the Federation of State Medical Boards and the National Association of Boards of Pharmacy, urging their attention to the document's contents.

In addition to formal channels, the FDA leveraged social media platforms using the PR company Weber Shandwick, the same PR company used by Moderna to disseminate succinct messages such as, "Ivermectin is Intended for Equine Parasitic Infections, Not COVID-19," and "Humans Are Not Livestock: The Dangers of Using Veterinary Products for Human Medical Conditions." These messages were accompanied by juxtaposing imagery of a veterinary professional embracing an equine patient and a medical doctor conducting a human patient examination. Social media platforms have international reach, particularly throughout the English speaking world. Regulatory authorities in smaller countries mimicked the FDA in their refusal to entertain the used of ivermectin in COVID-19 treatment regimens based on the parroted call that there was 'insufficient evidence'. Regulatory authorities hid behind their stubborn requirement for a large randomised control trial to show efficacy. We have already pointed out above that those RCTs that were considered adequately designed were flawed.

Merck put out a statement On February 4 2021, stating that they did not believe the data available provided sufficient therapeutic and efficacy data, but alarmingly they stated there was a concerning lack of safety data in the majority of studies. The Guzzo study of 2002 had already shown the data on dosage safety levels, the WHO VigiAccess database had shown its safety, the majority of papers that were published on the use of ivermectin in COVID-19 all stated that there were few or no adverse responses and those that existed were mild and transient. This after Prof Omura showed enthusiasm to carry out a large randomised control trial in Japan, which they denied. Merck's response to using ivermectin for COVID-19 is anathema, unless one cynically considers that they would rather have backed a product that ivermectin was in opposition too, molnupiravir perhaps? The patent to ivermectin expired years ago, molnupiravir is a new drug. It does not take deep thinking to see which drug could be more profitable for Merck.

Misinformation and disinformation

In looking at regulatory oversight, it is clear that many regulatory bodies discounted the potential utility of ivermectin, ostensibly due to concerns regarding the quality of supporting studies. These bodies appear to align their stances closely with guidance from globally recognised entities such as the Food and Drug Administration (FDA) and the World Health Organization (WHO). Nevertheless, the FDA has rejected claims suggesting its influence over other regulatory institutions. This rejection came in the form of a legal brief filed against three clinicians challenging the FDA's position on ivermectin. In the document, the FDA disavowed any role in directing clinicians' off-label prescribing practices and refuted claims that it swayed other independent regulatory authorities. Additionally, the FDA contended that its social media communications were intended for informal public engagement, rather than as definitive guidance.

As of August 8, 2023, the authority for physicians to prescribe ivermectin off-label has been reinstated. This development raises questions about the FDA's earlier communications, suggesting that they may have been a source of inaccurate information regarding off-label prescribing rights for ivermectin. When authoritative bodies disseminate misleading or false information, they risk undermining public trust and could potentially pose societal risks.

V. Potential Applications

Since it has been shown that ivermectin has multiple mechanisms of action, it is no wonder that it has potential uses beyond being an anti-parasitic and used off-label during the COVID-19 pandemic. ivermectin is approved as an anti-parasitic for the treatment of:

- Strongyloidiasis of the intestinal tract is due to the nematode parasite Strongyloides stercoralis and is contracted through the skin. Other organs in the body may also be affected.
- Onchocerciasis, commonly known as river blindness, is caused by the parasitic worm Onchocerca volvulus.
- Rosacea is a chronic inflammatory disorder that affects the face, and although not life-threatening, it does have a phycological effect on patients. IVERMECTIN is approved as a 1% cream used as an anti-inflammatory applied to the skin once a day.

In recent years, ivermectin has been or will be accessed in several clinical trials (Table 1) for various indications.

Implications for global health

So, here's the problem: ivermectin is a 40-year-old anti-parasitic, off-patent medication with a long track record of being safe. Several clinical studies and real-world experience have confirmed is effective against several viruses. Therefore, ivermectin should also be considered for other viral infections, particularly those in which a vaccine would be useless once the infection takes hold. The following is an ideal example because this virus adversely affects the immune system.

Potential Application for Treating Patients with Ebola Hemorrhagic Fever (Ebola Virus Disease)

We do not know when or what the next pandemic will be. However, while researching for this particular section of the book, we came across another indication that, to our knowledge, has not been considered but is nonetheless important. That is the potential for ivermectin to treat people infected with the Ebola virus. Should the Ebola virus become airborne while retaining its pathogenic properties, it would make the SARS-CoV-2 pandemic seem like "a walk in the park". Ebola is a filovirus that causes hemorrhagic fever in 30–50% of cases. With the severe form of the disease, multi-organ failure occurs, and blood vessels leak their contents into the surrounding tissues. The mortality rate can be as high as 90%. A cytokine storm initiated by an excessive increase of proinflammatory cytokines and chemokines is a key feature of the disease via the activation of T-cell lymphocytes, but not before disabling the patient's innate immune system by targeting macrophages and dendritic cells. [97-99]

Before ivermectin, there was suramin, a drug dating back 100 years, used to treat river blindness and anti-parasitic infections. Suramin, like ivermectin, also has antiviral and a lot more indications. It was considered that suramin had too many targets, resulting in serious adverse side effects. Therefore, suramin was replaced with ivermectin, which is safer and could be given orally. Suramin has effectively prevented the Ebola virus from entering cells and replicating *in vitro*. [99,100]

We already know from previous sections of this chapter that ivermectin is effective against the SARS-CoV-2 virus, which is also an RNA virus. Unlike suramin, which is highly toxic, ivermectin can be administered safely at higher dosages and is, therefore, potentially more effective than suramin, assuming that both drugs have the same mode of action for Ebola. When normal cells are damaged, they express phosphatidylserine (PS), a phospholipid on their surface, activating the innate immune system to produce proinflammatory cytokines, the normal physiological response for removing damaged or dead cells. The Ebola virus expresses PS on its surface, mimicking a damaged cell, causing a cytokine storm and disseminated intravascular coagulation. [102] The Ebola virus can also initiate a cytokine storm via Toll-4 receptors and other mechanisms similar to those of COVID-19. [98] However, the most devastating action of the virus is its ability to inactivate the immune response to the Ebola virus itself [102]. Therefore, a vaccine would be ineffective once an outbreak takes place.

From our experience with COVID-19, ivermectin would be a useful candidate to use off-label to treat patients infected with the Ebola virus and prophylactically in the geographical areas affected because of its apparent similarities to suramin. That being the case, ivermectin would be used to treat the patient during the replication and hyper-inflammation phases of the disease, as would be the case with COVID-19. [103-107] Any treatment should be in combination with nano-silver to prevent PS and glycoproteins on the surface of the virus from adversely modulating the immune system. [108,109].

VI. Conclusion

In today's society where information is available from many sources of varying reliability, from social media to independent or controlled press media, there is a predilection for superficial interpretations and quick categorisations of information, often favouring straightforward solutions to complex questions. There is a tendency to rely on authoritative figures and celebrities for pre-packaged opinions, rather than engaging in independent, critical thinking. To genuinely understand complex issues, it is imperative to adopt an evolving thought process characterised by curiosity and critical evaluation.

Unfortunately, society generally encourages swift judgment and discourages inquisitive exploration, which fosters a climate of intellectual complacency. This inclination toward immediate, emotionally gratifying conclusions obfuscates the value of objective thought that necessitates more rigorous thinking. The act of thinking, particularly when it challenges pre-existing beliefs or the status quo, can be both cognitively demanding and emotionally uncomfortable, particularly for individuals accustomed to outsourcing their work of thinking to external authorities. It is therefore easy to manipulate people through controlling social media, the press and embargoes on academic publication.

The COVID-19 pandemic provided a maelstrom of alternatives and extremes of thought. Conspiracy theories soon emerged and with that an almost binary approach to thinking to every measure taken to curb the disease. There were arguments about lockdowns working or not working, masks preventing disease transmission or indeed causing pneumonia, vaccines saving lives or vaccines killing numbers of people, ivermectin working, or not working. Social media and censorship tried to control the narrative, but not in an effort to balance debate. It had the effect of deepening the divide between extreme arguments. In retrospect we will be able to see how in certain circumstances lockdowns were necessary, but in others damaging. Vaccines certainly do have serious adverse events and it is our duty to understand how and why they occurred, not to dismiss vaccines as ineffective or dismiss the adverse events as irrelevant. We have shown in this chapter that there was research indicating that ivermectin was effective in treating COVID-19. We need critically reflect on why in 2023, a Google search or a ChatGPT question will always shine a negative light on ivermectin as a potential therapeutic for COVID-19.

What we knew in 2020 that would have allowed a Type 1 error decision to use ivermectin

In 2019, ivermectin's primary recognised use was as an anti-parasitic drug, particularly for treating various parasitic infections in humans and animals. The drug's efficacy and safety in treating parasitic infections were well established and had been widely used for decades. However, as an antiviral agent, knowledge about ivermectin's efficacy and safety in 2019 was limited. While some studies had suggested potential antiviral effects of ivermectin against certain viruses, including some RNA viruses, the evidence was based mainly on in vitro (laboratory-based) experiments or studies in animal models. In cell culture experiments, the antiviral activity of ivermectin was mainly observed against viruses like dengue, Zika, and other flaviviruses. In these studies, ivermectin inhibited viral replication in a laboratory setting. However, translating these findings from in vitro studies to effective antiviral therapy in humans is a complex process that requires further investigation.

By 2019, few clinical trials evaluated ivermectin's potential as an antiviral in humans. Most of the available data were preclinical or based on observational studies, meaning that the drug's antiviral properties had not been thoroughly established in humans then.

It's important to emphasise that scientific knowledge evolves, and research on drugs like ivermectin continues progressing. Since 2019, there may have been new studies and clinical trials investigating the antiviral potential of ivermectin, especially in the context of the COVID-19 pandemic. It's best to consult reputable sources and medical literature to obtain the most recent information.

By the pandemic's start, ivermectin dosages for its approved anti-parasitic uses were well-established and widely known. The drug had been used for decades to treat various parasitic infections in humans and animals, and its dosing guidelines were well documented. For treating onchocerciasis (river blindness) and lymphatic filariasis, the standard oral dose of ivermectin was 150 to 200 micrograms per kilogramme of body weight. This dose was typically administered as a single dose and repeated annually or as per the specific treatment programme in regions where these diseases were prevalent. For other parasitic infections like scabies and head lice, topical formulations of ivermectin were available, and the dosages varied based on the product's concentration and the individual's age and weight.

It's important to note that the dosages for approved anti-parasitic uses were well established through extensive clinical trials and research. However, the dosing and safety profile might differ when considering using ivermectin for potential off-label purposes or as an antiviral agent. In such cases, consulting with a qualified healthcare professional who can provide appropriate guidance and monitor for potential side effects or interactions is essential.

The propaganda against ivermectin and the TNI

There have been discussions and controversies surrounding the use of ivermectin for various medical purposes, including its potential use as a treatment for COVID-19. Some of these discussions have involved accusations of misinformation, biased reporting, or propaganda on both sides. Some medical professionals, researchers, and advocates have expressed support for using ivermectin as a potential treatment for COVID-19 based on their experience and analysis of emerging literature.

Major health organisations, including the World Health Organisation (WHO), the U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA), have not approved ivermectin for the treatment of COVID-19. These organisations have emphasised that the available data on ivermectin's efficacy and safety as a COVID-19 treatment are insufficient and inconclusive, ignoring the totality of the evidence. They have actively warned against its use outside of approved indications or clinical trials and have highlighted potential risks associated with self-medication or inappropriate dosing. Their stance led to the off-label use of ivermectin, while legal and within the purview of a qualified doctor, being criminalised, with some doctors losing their right to practice medicine after prescribing ivermectin off-label.

In the context of COVID-19, there have been continued efforts to discredit or dismiss ivermectin and instances of misinformation and propaganda surrounding ivermectin. Several systematic reviews and meta-analyses have attempted to assess the existing evidence on ivermectin's role in COVID-19 treatment. It is essential to be critical of information from all sources. It became apparent during the pandemic that one should not rely on health regulators and every piece of scientific literature without critical thought for reliable and evidence-based information.

The Trusted News Initiative (TNI) is a partnership founded by the BBC that includes news agencies and organisations from around the globe, including Google, YouTube, Meta, Microsoft and Twitter. TNI members work together to build audience trust and to find solutions to tackle the challenges of disinformation. However, the question remains: Who decides what is disinformation or misinformation? They have endeavoured to control a global narrative by including media organisations and social media platforms. The TNI prides itself on being "… the only forum in the world of its kind designed to take on disinformation in real-time." There is a very fine line between controlling a narrative that may be false and removing journalistic freedom. Many YouTube videos covering peer-reviewed published papers were removed from the platform, and their channel owners were punished. Twitter removed tweets and tweeters from their platform if any positive scientific information on ivermectin in COVID-19 treatment was shared. The popular press would carry no story about ivermectin unless it were negative. The TNI made a central decision that any information on the efficacy of ivermectin in treating COVID-19 was mis or disinformation, and all members across the globe acted to remove ivermectin

from any story. Who was the first person or group to decide to make ivermectin efficacy news mis or dis-information, regardless of the research? That is a question we may never find the answer to. There have been some of the more cynical who would say that the pharmaceutical industry influenced this decision because no vaccine could be used without the regular pre-launch research if an already existing therapeutic was available [110]

The role of medical doctors in scientific discovery

The development of medical science must follow the scientific method, the core principle of which is that the sole judge of scientific truth is experiment, and more broadly the accumulated available empirical evidence, not the WHO, not the FDA, not the EMA, not the TNI, not the medical boards, not the news agencies, not social media companies, not governments. New fundamental discoveries often begin from a single practicing doctor formulating a hypothesis based on direct empirical observations from his efforts to save patients, combined with experience, inspiration, and insight. Article 37 of the 2013 Helsinki declaration [111,112] codifies the ethics of the role of medical doctors in scientific discovery by stating that: *"In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available."*

New discoveries that begin with the sole practicing doctor, are then investigated, developed and published by academic scientists, and then public health agencies like the WHO, FDA, CDC, and others periodically evaluate and conduct systematic reviews of the resulting research literature, and news agencies may report the most impactful results to the general public. With scientific knowledge flowing from the practicing doctor, to academics, and then to the large public health agencies, it is a logical fallacy of circular reasoning for the public health agencies to accuse the practicing doctor or the academic researcher of disseminating misinformation, when the latter bring forth new scientific findings that are backed by the empirical evidence that conflict with the currently accepted consensus promulgated by the agencies. Just as it is unscientific for medical boards to give higher weight to the current scientific consensus or to opinions of public health organizations, when reviewing doctors whose diverging practices are backed by the empirical outcomes of their efforts. If doctors and academic researchers are not allowed to explore, communicate, and discover, under the ethical conditions of article 37 of the 2013 Helsinki Declaration, then the scientific method of discovery itself is disrupted, at the cost of increased suffering, hospitalization, and death.

Ethics of the dismissal of the use of ivermectin by authorities

Ethical considerations are vital in ensuring that healthcare decisions consider the population's well-being. Denying a population access to a drug that could work against a disease can raise several ethical concerns, particularly in a public health crisis or when dealing with life-threatening conditions. Access to potentially life-saving treatments is considered a fundamental human right. Denying a population access to a drug that might be effective against a disease can be seen as a violation of this right, especially if limited or no alternative treatments are available. The ethical principles of beneficence (acting in the best interest of patients) and non-maleficence (doing no harm) guide medical decision-making. If evidence suggests that a drug could be beneficial and safe, withholding it from those who may benefit could be seen as failing to uphold these principles. Ethical considerations of fairness and distributive justice come into play when deciding who gets access to potentially life-saving treatments. If individuals are aware of a drug's potential benefits and risks and are willing to take it, they should be allowed to make informed decisions about their healthcare. Denying access to a drug might limit their autonomy and right to make choices about their health.

In some cases, the denial of a drug could be justified due to a lack of robust evidence supporting an appropriate balance of safety and efficacy or due to credible evidence signaling the existence of unacceptable safety concerns. Ethical considerations involve ensuring that treatments are based on sound scientific research and that decisions are not

influenced by vested interests or misinformation. In infectious diseases, denying access to a potentially effective drug could have broader public health implications. Limiting the spread of the disease and protecting vulnerable populations are critical considerations in deciding drug access. Healthcare professionals have an ethical duty to provide the best available care to their patients. If a drug is available and supported by *credible* evidence, healthcare providers may face ethical challenges in withholding it from their patients.

In the context of ivermectin in the COVID-19 pandemic, we can see that these ethics were scarce in those who actively denigrated the drug. By denying the use of the drug, people died. Their human right to make a decision on whether to take it or not was removed before they could make an informed decision. The safety data was there, and there was credible evidence at *in silico, in vitro, in vivo* and clinical levels. The decision to make a Type II error decision shows a lack of beneficence.

Future prospects for ivermectin

In his Nobel acceptance speech, Prof Omura referred to ivermectin as a gift from the earth. History has shown this to be true. It's not only a gift to Merck to make money for the period of a patent or a gift from them to those who need it but who cannot afford it. It is a valuable medicine for the future, and we need to invest in further research into its efficacy across many pathologies. The problem is the patent no longer protects anybody's financial investment into research. An International Research Institute for Ivermectin would not be feasible as a self-funded entity. It would need to be funded from humanitarian sources, and the research products would have to be made freely available to all. As we enter the age of artificial intelligence, we will likely be able to carry out many *in-silico* experiments to find new mechanisms of action for ivermectin across all living creatures. Ivermectin could have saved many lives during the pandemic; it could have reduced the time it took for the pandemic to burn itself out. What else could it do for us in the future?

Final thoughts and recommendations

It is becoming increasingly clear that Ivermectin is a safe and highly versatile agent with a wide variety of pharmacological targets. It has multiple modes of action, including (but not restricted to) anti-viral, anti-inflammatory, anti-thrombosis, and cardioprotective, which may act together to elicit synergistic therapeutic effects, thereby providing significant benefits to those who use it, at sufficient dosage, at any stage of the disease.

The research, published in peer-reviewed journals, it is becoming increasingly clear that ivermectin could have saved many lives, reduced morbidity and prevented infection during the pandemic. Who decided to prevent this information from reaching the general public? Who decided to introduce a disparaging narrative against the drug to misdirect the attention from ivermectin? There will never be a clear answer to these questions, but what is clear is that beneficence was rejected, and opportunists from industrial and political arenas made enormous financial gains.

An extended period of reflection is required for those of us who can think independently. We need to unite and plan ways to help others to think for themselves. To develop critical thinking skills. We do not want to convert people from one way of thinking to another; we want them to be genuinely able to seek reliable information and make informed decisions. We need to move away from polarised thinking that becomes binary thinking, which is not helpful. We need to find a way to protect independent journalism. Whilst the TNI may have had noble intentions initially, their control of the narrative became an attack on freedom of information. In essence, we need to protect true democracy.

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