Written Evidence Submitted by Dr Theresa Anne Lawrie, Director, The Evidence-based Medicine Consultancy Ltd

(CLL0115)

I am the Director of the Evidence-based Medicine Consultancy Ltd in Bath, United Kingdom. I have a medical degree (MBBCh) and a Doctorate in Philosophy (PhD) from the University of the Witwatersrand in Johannesburg, South Africa. Whilst I have practiced clinical Medicine in both the United Kingdom and South Africa, I now perform non-clinical research work only. My United Kingdom General Medical Council registration number is 3634680.

As the director of E-BMC Ltd, which I established in 2013, I am committed to improving the quality of healthcare globally through rigorous research. My research expertise is drawn from experience in both developing and developed countries, which uniquely positions me to evaluate and design research for a variety of healthcare settings. As a result, I am a frequent member of Technical Teams responsible for developing international clinical practice guidelines and am currently employed as the Guideline Methodologist on two World Health Organization (WHO) clinical practice guidelines due to be published in 2021. My peer-reviewed publications have received in excess of 3000 citations and my ResearchGate score is among the top 5% of ResearchGate members. Please note that E-BMC Ltd does not undertake pharmaceutical industry-sponsored work and I have no conflicts of interest to declare.

<u>My involvement in the ivermectin story</u>

On the 26th of December 2020, I watched Dr Pierre Kory's testimony on ivermectin before the United States Senate in which he asked that ivermectin be approved for the treatment of covid-19. Dr Pierre Kory is an intensive care specialist physician who is part of a group of called the Frontline Covid-19 Critical Care Alliance that has been monitoring potential treatments for covid-19. This group was the first to identify dexamethasone as a useful treatment for covid-19.

I obtained a copy of the Kory/FLCCC review on ivermectin on the 26th December and was impressed with the number of studies included on ivermectin – I was surprised that I had not heard about ivermectin in the context of covid-19 before. I noted that a limitation of the FLCCC review was that the authors had not performed a meta-analysis of the included trials. Meta-analysis is a research method that involves pooling data from different studies to produce an overall estimate of the effect of a treatment for critical and important health outcomes. Evidence synthesis is one of my areas of expertise. Given the urgent need for therapeutics against covid-19, I undertook to do this evidence synthesis work for free during my Christmas holiday because I thought it might help to clarify whether ivermectin would be useful against covid-19 and in the context of the pandemic, speed was of the essence. I approached this work with professional equipoise.

Following my evaluation of the evidence, I concluded that ivermectin was an essential drug to reduce the morbidity and mortality from covid-19. Therefore, on Monday the 4th of January 2021, I emailed my report on ivermectin to Mr. Hancock, Mr. Ashworth, Mr. Rees Mogg (my MP based on my home address) and Mrs. Wera Hobhouse (my MP based on my business address). I titled the email 'URGENT - Ivermectin

for COVID-19 will save lives and prevent COVID-19 infection'. I also emailed the report to one of my usual commissioning employers at the WHO, asking her to forward the report to the dedicated WHO Covid-19 Team. I enclose a summary excerpt from page 16 of the report:

This review and meta-analysis confirms that ivermectin substantially reduces the risk of a person dying from COVID-19 by probably somewhere in the region of 65% to 92% according to RCT data. The uncertainty in the evidence relates to the precise extent of the reduction, not in the effectiveness of ivermectin itself. Similarly, when ivermectin is used as prophylaxis among health care workers and contacts, it is clear that ivermectin substantially reduces COVID-19 infections, probably somewhere in the region of 88% (82% to 92%). Data from numerous currently active RCTs will help to determine the precise extent of its protective effect in these at-risk groups.

Despite the FLCCC's strong recommendation that ivermectin should be implemented globally to save lives from COVID-19, most governments and health professionals still appear to be unaware of this profoundly effective COVID-19 treatment. Not only is ivermectin a safe, effective and well-known medicine, at an estimated cost of less than 10 pence per person treated with a 12 mg tablet, it does indeed seem like a miracle drug in the context of the current global COVID-19 situation. Guidance and protocols on using ivermectin for COVID-19 can be found on the FLCCC website https://covid19criticalcare.com.

I received automated replies from the MPs but nothing more. As a medical doctor, I have a moral duty to help in times of health emergencies; I therefore recorded a brief appeal to the Prime Minister on the 6th of January 2021, in the hope of expediting communication about ivermectin with the Health Minister and authorities. The appeal can be found at this link:

https://www.youtube.com/channel/UCcCrBQZqQ1FTZ60WnC6JjDA

Since early January 2021, I and my team have continued to write to members of your cabinet and government health and regulatory agencies regarding the promising evidence on ivermectin's effectiveness against Covid-19, and its substantial safety record. We have been urging the British government to consider the rapid implementation of ivermectin for the prevention and treatment of Covid-19. We were therefore delighted to hear that the UK government is setting up a taskforce on anti-virals to develop a treatment against Covid-19 that can be deployed in the early stages of the infection and in outpatient settings.

Meanwhile, I led a team of experts in conducting a systematic review and meta-analysis of the evidence on ivermectin for Covid-19. This review has been accepted for publication in a peer-reviewed journal and will be published in the coming days. Please find an abstract for this review in the attached 'Summary of the evidence' document.

Guideline development in response to a health and social care emergency requires an acceleration of the process while maintaining transparency of decision-making and reporting. This is one of the core principles underpinning the development of all NICE guidance and standards. NICE issued guidance on covid research in March 2020 stating that the hierarchy of evidence for evaluating interventions for covid would be systematic reviews, followed by randomized trials, observational studies and expert opinion. In the context of the pandemic, NICE states that they will not evaluate risk of study bias or grade (assess the quality or certainty of the evidence). Thus, the evidence provided by our systematic review and meta-analysis, with risk of bias assessment and grading of the certainty of the evidence represents the highest level of evidence that is used under normal circumstances and goes beyond the level of evidence required by NICE to make a recommendation on ivermectin during a pandemic.
https://www.nice.org.uk/process/pmg35/chapter/finding-evidence

Ivermectin, if it had been implemented when the evidence was presented, could have proven to be a very useful tool that, in combination with other measures, could have substantially ameliorated the devastating impact of Covid-19 on the population, NHS staff, the economy, etc.

Since health authorities in the UK already justify off-label usage of ivermectin for scabies, a less dangerous disease than Covid-19 with less evidence, doctors could have been advised to use ivermectin off-label for Covid-19, while procedures for formal approval were underway.

A number of countries around the world have already implemented ivermectin and seen the impact it can have in terms of reducing mortality and morbidity. Similarly, the UK could have prevented tens of thousands of deaths if it had only taken a close look at the evidence on ivermectin that we repeatedly brought to the attention of government, health and regulatory agencies. We have yet to have a considered response from any UK Health Authorities, including the MHRA, Therapeutics Task Force, Public Health England, NICE, SAGE,etc.

I reiterate that the evidence in support of using ivermectin for treatment of covid-19 is far stronger than the evidence on any other medicine given emergency use authorization to treat covid-19. In addition, ivermectin can be used in asymptomatic, mild, moderate and severe covid-19 infection – no other treatment has been shown to do this. In addition, ivermectin is very safe – it is currently being used by millions of people around the world for covid and other infections.

Data retrieved from WHO/Uppsala VigiAccess pharmacovigilance database (22.03.2021)				
Medicine	**Year reporting started**	**Deaths**	**Deaths per year**	**Adverse events**
Ivermectin	1992	16	< 1	4702
Aspirin	1968	1432	8	177606
Remdesivir	2020	467	467	5733
Tocilizumab	2005	769	48	47545
COVID-19 vaccines	2020	2402	9612	309403
Tetanus vaccine	1968	32	< 1	14725

I therefor ask the members of the Science and Technology Committee to please answer the following questions:

1. Why has no one from the UK government, health and regulatory agencies engaged with me to discuss the evidence on ivermectin?
2. Why did the Therapeutics Taskforce not engage with the evidence we sent them, and invite Dr. Tess Lawrie to testify before the relevant entities?
3. Why have novel treatments approved (e.g. remdesivir) based on less evidence, when they are less effective, more expensive and with a worse safety record?
4. Why did the government ignore its own instructions for developing guidelines during the pandemic, as set out in March 2020 in NICE's document entitled "Interim process and methods for developing rapid guidelines on Covid-19"?

5. In ignoring the systematic review and meta-analysis, as well as the real-world data, observational studies and expert opinion, overwhelmingly favoring ivermectin against Covid-19, was the government aware of the tens of thousands of lives it could have saved?
6. Given the safety record of ivermectin at a range of dosage regimes, why was the government so reluctant to trial ivermectin when the worst that could have happened was that trial participants would have been rid of any parasites they may have had?
7. Finally, and most importantly, why is ivermectin not part of the toolkit for clinicians against Covid-19?

Finally, I am ready and willing to provide oral evidence before the Committee, and hope you will invite me to do so.

Yours Sincerely

Dr. Theresa Anne Lawrie

(Attachment: Summary of the Clinical Trials Evidence for Ivermectin in COVID-19)

Summary of the Clinical Trials Evidence
for Ivermectin in COVID-19

Ivermectin, an anti-parasitic medicine whose discovery won the Nobel Prize in 2015, has documented anti-viral and anti-inflammatory properties in laboratory studies. In the past 4 months, numerous, controlled clinical trials from multiple centers and countries worldwide are reporting consistent, large improvements in COVID-19 patient outcomes when treated with ivermectin. Several comprehensive scientific reviews of these and more recent referenced trials can be found here:

- Kory et al, 2021: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8088823/
- Bryant et al, 2021: accepted for publication in the American Journal for Therapeutics (June 2021)
- Karale et al, 2021: https://www.medrxiv.org/content/10.1101/2021.04.30.21256415v1

Properties of Ivermectin
1) Ivermectin inhibits the replication of many viruses, including SARS-CoV-2, influenza, and others;
2) Ivermectin has potent anti-inflammatory properties with multiple mechanisms of inhibition;
3) Ivermectin diminishes viral load and protects against organ damage in animal models;
4) Ivermectin prevents transmission of COVID-19 when taken either pre- or post-exposure;
5) Ivermectin hastens recovery and decreases hospitalization and mortality in patients with COVID-19;
6) Ivermectin leads to far lower case-fatality rates in regions with widespread use.

Meta Analyses to date:

- Kory, P. *et al.* (2021). Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19, American Journal of Therapeutics May/June 2021.
- Hill, A. *et al.* (2021). Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. *Research Square* preprint. DOI: 10.21203/rs.3.rs-148845/v1
- Cobos-Campos, R. *et al.* (2021). Potential use of Ivermectin for the treatment and profilaxis. *Clinical Research and Trials*, 7, 1-5. DOI: 10.15761/CRT.1000333 (over-ridden)

- Bryant, A., Lawrie, T.A., Dowswell, T., Fordham, E.J., Mitchell, S., Hill, S.R. & Tham, T.C. (2021). Ivermectin for prevention and treatment of COVID-19 infection: a systematic review and meta-analysis. *OSF* preprint, https://osf.io/k37ft/
- Castañeda-Sabogal, A. *et al.* (2021). Outcomes of Ivermectin in the treatment of COVID-19: a systematic review and meta-analysis. *medRxiv* preprint, DOI: 10.1101/2021.01.26.21250420
- Nicolas, P., Maia, M. F., Bassat, Q., Kobylinski, K. C., Monteiro, W. & Rabinovich, N. R. (2020). Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis. *The Lancet Global Health*, 8, E92 – E100. doi: https://doi.org/10.1016/S2214-109X(19)30453-X
- Navarro, M. et al. (2020). Safety of high-dose ivermectin: a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy,* DOI: 10.1093/jac/dkz524
- Karale, S. et al. (2021). A Meta-analysis of Mortality, Need for ICU admission, Use of Mechanical Ventilation and Adverse Effects with Ivermectin Use in COVID-19 Patients. medRxiv 2021.04.30.21256415; doi: https://doi.org/10.1101/2021.04.30.21256415

Quick facts:

- Meta-analysis of 13 trials, assessing 1892 participants, found that ivermectin reduced the risk of death by an average of 68% compared with no ivermectin treatment.
- Meta-analysis of 3 trials, assessing 738 participants, found that ivermectin prophylaxis among health care workers and covid-19 contacts probably reduces the risk of covid-19 infection by an average of 86%
- Ivermectin has a well-established safety profile with billions of doses of ivermectin having been used worldwide for parasitic indications. Various WHO documents on parasitic infections refer to ivermectin's long safety record.
- Ivermectin is affordable, and can be distributed by various means, e.g. post, and self-administered. It can therefore effectively reach traditionally 'hard-to-reach' and vulnerable populations such as undocumented migrants, homeless, the elderly living alone or in care homes, those lacking transport to reach health facilities, and those who lack access to adequate health care for other reasons.

Summaries of most recent systematic reviews on ivermectin for Covid-19:

Bryant & Lawrie et al, 2021 (accepted for publication in peer-reviewed journal)

Background Re-purposed medicines may have a role against the SARS-CoV-2 virus. The antiparasitic ivermectin, with anti-viral and anti-inflammatory properties, has now been tested in numerous clinical trials.

Areas of uncertainty We assessed the efficacy of ivermectin treatment in reducing mortality, in secondary outcomes, and in chemo-prophylaxis, among people with, or at high risk of, covid-19 infection.

Data sources We searched bibliographic databases up to April 25 2021. Two review authors sifted for studies, extracted data and assessed risk of bias. Meta-analyses were conducted and certainty of the evidence was assessed using the GRADE approach and additionally in trial sequential analyses for mortality. Twenty-four RCTs involving 3406 participants met review inclusion.

Therapeutic Advances Meta-analysis of 15 trials found ivermectin reduced risk of death compared with no ivermectin (average Risk Ratio 0.38, 95% confidence interval (CI) 0.19 to 0.73; n=2438; I2=49%; moderate-certainty evidence). This result was confirmed in a trial sequential analysis (TSA) using the same DerSimonian-Laird method that underpinned the unadjusted analysis. This was also robust against a TSA using the Biggerstaff-Tweedie method. Low-certainty evidence found ivermectin prophylaxis reduced

covid-19 infection by an average 86% (95% CI 79% to 91%). Secondary outcomes provided less certain evidence. Low certainty evidence suggested that that there may be no benefit with ivermectin for 'need for mechanical ventilation', whereas effect estimates for 'improvement' and 'deterioration' clearly favoured ivermectin use. Severe adverse events were rare among treatment trials and evidence of no difference was assessed as low certainty. Evidence on other secondary outcomes was very low certainty.

Conclusions Moderate-certainty evidence finds that large reductions in covid-19 deaths are possible using ivermectin. Employing ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally.

Kory et al, 2021 (published in the *American Journal of Therapeutics*)

Background After COVID-19 emerged on U.S shores, providers began reviewing the emerging basic science, translational, and clinical data to identify potentially effective treatment options. In addition, a multitude of both novel and repurposed therapeutic agents were used empirically and studied within clinical trials.

Areas of Uncertainty The majority of trialed agents have failed to provide reproducible, definitive proof of efficacy in reducing the mortality of COVID-19 with the exception of corticosteroids in moderate to severe disease. Recently, evidence has emerged that the oral antiparasitic agent ivermectin exhibits numerous antiviral and anti-inflammatory mechanisms with trial results reporting significant outcome benefits. Given some have not passed peer review, several expert groups including Unitaid/World Health Organization have undertaken a systematic global effort to contact all active trial investigators to rapidly gather the data needed to grade and perform meta-analyses.

Data Sources Data were sourced from published peer-reviewed studies, manuscripts posted to preprint servers, expert meta-analyses, and numerous epidemiological analyses of regions with ivermectin distribution campaigns.

Therapeutic Advances A large majority of randomized and observational controlled trials of ivermectin are reporting repeated, large magnitude improvements in clinical outcomes. Numerous prophylaxis trials demonstrate that regular ivermectin use leads to large reductions in transmission. Multiple, large "natural experiments" occurred in regions that initiated "ivermectin distribution" campaigns followed by tight, reproducible, temporally associated decreases in case counts and case fatality rates compared with nearby regions without such campaigns.

Conclusions Meta-analyses based on 18 randomized controlled treatment trials of ivermectin in COVID-19 have found large, statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance. Furthermore, results from numerous controlled prophylaxis trials report significantly reduced risks of contracting COVID-19 with the regular use of ivermectin. Finally, the many examples of ivermectin distribution campaigns leading to rapid population-wide decreases in morbidity and mortality indicate that an oral agent effective in all phases of COVID-19 has been identified.

(June 2021)