British Ivermectin Recommendation Development Panel – Response to EMA Statement on Ivermectin for Covid-19

On 22 March, the European Medicines Agency (EMA) issued a statement [0] that, after reviewing the evidence, they recommend against the use of ivermectin for the prevention and treatment of covid-19, outside of 'well-designed' clinical trials. The EMA claims evidence from laboratory studies, clinical trials, observational studies, and meta-analysis, but provides no sources, specifics or citations. We fill these omissions below.

The British Ivermectin Recommendation Development (BIRD) panel was set up in January 2021 by Dr Tess Lawrie of the Evidence-Based Medicine Consultancy Ltd (E-BMC), an independent medical research company based in Bath, UK. A systematic review and meta-analysis of ivermectin for covid-19 was recently conducted by Dr Lawrie, the director, with a team of expert systematic reviewers. A preliminary report was released in the public domain on 3 January [1]. A comprehensive paper including 21 RCTs has been submitted to a peer-reviewed journal, and meanwhile is available on two pre-print servers [2 ,3]. Moreover, on 20 February 2021, a panel of 65 clinicians, researchers and patient representatives from 16 countries attended the BIRD panel meeting, convened by Dr. Lawrie and her team, to evaluate the evidence on ivermectin for covid-19.

Following the standard "DECIDE" Evidence-to-Decision framework [4] for clinical recommendations, BIRD concluded that there was enough evidence to recommend the rapid implementation of ivermectin for covid-19 [5, 6]. This recommendation is by implication global and not restricted to the UK or the EU. Indeed, the low cost and widespread use make ivermectin uniquely placed to tackle covid-19 worldwide, including very low income countries.

BIRD provides a detailed response to the EMA statement, with citations to the evidence.

EMA advice against ivermectin for the prevention or treatment of COVID-19:

1. Review of the evidence

> ***EMA has reviewed the latest evidence on the use of ivermectin for the prevention and treatment of COVID-19 and concluded that the available data do not support its use for COVID-19 outside well-designed clinical trials. … Results from clinical studies were varied, with some studies showing no benefit and others reporting a potential benefit. Most studies EMA reviewed were small and had additional limitations, including different dosing regimens and use of concomitant medications. EMA therefore concluded that the currently available evidence is not sufficient to support the use of ivermectin in COVID-19 outside clinical trials.***

Ivermectin's potential therapeutic utility has expanded over the last decade as broad-spectrum anti-viral and even anti-neoplastic properties have been discovered [7, 8]. Since April 2020, the evidence base of observational and randomised trials of ivermectin for covid-19 has accumulated. A review [9, 10] by the Front Line Covid-19 Critical Care Alliance (FLCCC) summarised findings from 27 randomised controlled trials (RCTs) and 16 observational studies on ivermectin both for prevention and treatment of covid-19. They conclude that ivermectin "*demonstrates a strong signal of therapeutic efficacy.*" Moreover, ivermectin is the sole therapeutic so far to have demonstrated efficacy at all stages of the very complex clinical course of the covid-19 disease, from prophylaxis through to critical care.

A systematic review and meta-analysis [2, 3] was subsequently conducted by Dr Lawrie and a team of experts. Twenty-one RCTs involving 2741 participants met review inclusion, according to strict criteria, and subsequent meta-analysis of 13 trials found that ivermectin reduced risk of death (compared to no ivermectin) with an average Risk Ratio 0.32 [95% confidence interval (CI) 0.14 to 0.72; n=1892; I^2=57%] with "low to moderate-certainty." Low certainty evidence found ivermectin prophylaxis reduced the risk of covid-19 infection by an average of 86% [95% CI 79% to 91%]. Adverse events were rare and usually attributable to other adjunct medications.

In practical terms this means that ivermectin reduces the risk of death from covid-19 to about *one-third* of the risk of death without using this medication. In the long run, of every *nine* patients who would otherwise die from covid-19, *six* can now be saved by using ivermectin. Similarly the risk of contracting covid-19 is reduced to *one-seventh* of the risk faced by other healthy people with similar exposure, when using ivermectin as prophylaxis. For every *seven* people who would catch covid-19 from an infected person, only *one* is likely to catch the illness, when using ivermectin.

To our knowledge, in addition to the narrative review of Kory *et al.* [9, 10] and the rigorous meta-analysis of Bryant *et al* [2,3] , three[1] other systematic reviews have so far been conducted *viz.*: Hill *et al* [11] (commissioned by the WHO); Castañeda-Sabogal *et al* [12]; and Nardelli *et al* [13]. That of Nardelli is brief, but consistent with our own[2]. Hence, of the *five* reviews to date, only Castañeda-Sabogal is negative, and in methodological assessment against the AMSTAR 2 criteria [15] scores very poorly, as does that of Hill [11, 2, 3]. Hill *et al* nevertheless report a 75% reduction in mortality, whilst inconsistently opining that the "*results are insufficient for review by regulatory authorities.*" This is not a conclusion that follows from the evidence.

[1] A fourth review (Cobos-Campos *et al.* [14]) is available at https://t.co/EDRx8vyqoe but its DOI reference 10.15761/CRT.1000333 has been over-ridden, contrary to the principles of the Digital Object Identifier system.
[2] Though reporting an Odds Ratio rather than Risk Ratio. The difference is merely the choice of a different metric.

It is significant that the review by Bryant *et al* [2, 3] (on which the recommendation of BIRD is based) is the most up-to-date systematic review and meta-analysis. It is also the first, and to date the only one, to use the strict Cochrane systematic review methodology [16]. These review procedures interpret findings in light of risk of bias in individual trials and thereby derive a "certainty of the evidence" for each of the clinical outcomes for which data exists. "Low Certainty" in this context has a technical meaning: that further research is "likely" to change the quantitative estimate of the effect and "very likely" to change our confidence in it. "Moderate" certainty means that further research "may" change the estimate, and is "likely" to change our confidence in it. The low-to-moderate certainties reported do *not* mean that the therapeutic effect is weak: on the contrary, the observed effect is strong and consistent for all of the clinical "outcomes" for which evidence is available.

The evidence base does not end with the trials covered by Bryant *et al* [2, 3] which deliberately restricted itself to reports from Randomised Controlled Trials (RCTs). These are considered the highest quality of evidence by regulators, but other high-quality observational trials (OCTs) are available, covering many more patients, and which endorse the findings of the RCTs. Comparisons between the reliability of RCTs versus OCTs (such comparisons being themselves reviewed by strict Cochrane methods [17]) show that high-quality OCTs are as reliable as RCTs in their findings. It is illogical not to consider them in addition.

Finally 'real world' whole-country case studies, of which the most completely described is that of Peru [18], show striking reductions of covid-related deaths and infections as soon as ivermectin distribution is implemented on a wide scale. 25 countries are now using ivermectin against covid-19, 15 of them country-wide with official endorsement [19]. Several Indian States have adopted ivermectin as official policy, serving a total population of around 400 million. Within the EU itself, ivermectin has already been adopted by three countries (Bulgaria, Czech Republic, Slovakia).

In summary: The EMA's position is inconsistent with the findings of 4/5 reviews, the fifth being methodologically poor. It is inconsistent with policy already adopted in 25 countries, including three Member States of the EU itself.

2. Dosage and Safety

Although ivermectin is generally well tolerated at doses authorised for other indications, side effects could increase with the much higher doses that would be needed to obtain concentrations of ivermectin in the lungs that are effective against the virus. Toxicity when ivermectin is used at higher than approved doses therefore cannot be excluded.

Two distinct claims are implied: (i) That efficacy against covid-19 requires higher concentrations than in the anti-parasitic indications; (ii) That safety in those higher concentrations is not established. Neither assumption is borne out by the evidence.

(i) That adequate lung or serum concentrations (derived from initial *in vitro* EC_{50} values reported by Caly *et al* [20]) may not be achievable *in vivo* is a well-known controversy in the literature (e.g. [21]). It is however already refuted by the clinical trials showing a consistent therapeutic effect in dosages either no higher, or up to double, the standard dose of 200 μg/kg recommended for strongyloidiasis [22]. Schedules [5] do not exceed 5 doses, and in most protocols just 2 or 3 are recommended. Many protocols standardize on a fixed 12 mg dose, corresponding to 200 μg/kg only at a body weight of 60 kg, light-weight for many adults.

(ii) The safety of ivermectin is better-established than almost any other medicine in the pharmacopaeia, having been distributed worldwide in "Mass Drug Administration" (MDA) campaigns for the control and elimination of tropical parasites [23]. The cumulative number of doses now exceeds 3.8 billion [24], approximately half of the world's population. Moreover detailed safety studies [25] show that ivermectin is well-tolerated in doses up to 10 × the FDA maximum indicated for strongyloidiasis, giving a more than adequate therapeutic range.

Several other safety studies are available. An expert review report of over 500 studies assessed reported adverse events associated with the use of ivermectin, and found that adverse events were rare, and mostly mild to moderate [26]. Many of the adverse reactions relate to the treatment of parasitic infections with inflammation and irritation caused by the decay of dead or dying internal parasites; these are of course completely irrelevant to the treatment of covid-19.

An extreme example of continuous administration of ivermectin is its use in treatment of childhood leukaemia, where daily doses of 1 mg/kg or 60 mg (5 x the strongyloidiasis dose, repeated daily) were continued for six months. The 13-yr old patient's only complaint related to the smell of ivermectin [27] (dispensed as an oral solution in some countries, rather than a tablet).

A Phase 1 clinical trial validating the safety of continuous administration of ivermectin, authorised by the Medicines & Healthcare products Regulatory Agency (MHRA, the UK regulator), found no side effects with the first two doses administered [28].

Records [29] show only 16 deaths from ivermectin ingestion since 1992. This drug that has been used for 30 years, for a range of indications, in colossal quantities, with adverse reaction reports that are either at a very low rate, or mild to trivial (e.g. headache).

In summary: (i) High doses are plainly not essential (though dose-optimising trials should certainly be welcomed. Current covid-19 protocol doses are well within previously established safe ranges. (ii) Likewise, whilst further pharmacovigilance is always welcome, ivermectin is an exceptionally safe drug, with negligible rates of serious adverse events, and only trivial common side effects, which must of course be compared to the symptoms and risks of the disease itself.

3. Recommendation that Ivermectin be restricted to clinical trials

EMA therefore concluded that use of ivermectin for prevention or treatment of COVID-19 cannot currently be recommended outside controlled clinical trials.

As discussed above, this recommendation is based upon a review of the evidence that is inconsistent with five of out of six positive reviews of ivermectin already available, and consistent only with a single review that is methodologically poor. It is a recommendation in defiance of decisions in 25 countries, including three Member States of the EU itself.

A restriction to clinical trials supposes that the effect of ivermectin remains unknown. This is simply not so. Many important clinical trials have already been done. The reported effects are strong, and overwhelmingly in the beneficial direction. Whilst the "certainty" of the evidence is low, or "low to moderate" (as reported in the review [2, 3] on which the BIRD recommendation is based) this does not mean the effect is weak. It means that further and better-quality evidence may change either the quantitative measure of benefit, or our confidence in it. The evidence that some positive benefit exists is already clear.

When a treatment has been found to be effective, it is unethical to perform further controlled clinical trials for a potentially life-threatening illness using a placebo arm. They would also violate international law protocols such as the *Helsinki Protocols* for clinical trials [30]. Further clinical trials should be restricted to (i) dose-optimising trials, (ii) trials comparing the effect of various adjunct medications commonly used at various disease stages (antibiotics, other anti-virals, vitamins and minerals, anti-inflammatories and anti-coagulants) and (iii) contact trials quantifying reduction of contagion when used as a prophylactic.

Emergency authorization has been granted for therapeutics (e.g. remedesivir) with less positive evidence and more negative safety profiles than we currently have for ivermectin. Ivermectin itself has been approved by the WHO in the scabies indication, and added to the Essential Medicines list (including the Children's list) in that indication, on an evidence base plainly weaker than the systematic reviews already available for covid-19 [31].

In summary: It is time for regulatory authorities to recognize that ivermectin's effectiveness in covid-19 has already been demonstrated, and that its general safety profile is extremely well-known. In a pandemic situation, regulators should approve this very safe medicine for routine use, at the clinical discretion of any licensed medical practitioner. Further delay can lead only to further unnecessary loss of life.

The Evidence-Based Medicine Consultancy Ltd, Bath, England 26 March 2021

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