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Ivermectin for Covid-19

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Discussion of scholarly papers published on Ivermectin, starting from the article of Caly et al. in Antiviral Research, available online April 3, 2020, and of some news that we can find about the use of this drug for the treatment of Covid-19. A list of clinical trials is also given. The proposed discussion was made in a series of versions from 14 June to 29 July 2020. Here updates (September 8, September 20). For what concerns scholarly papers, we report among them three preprints in MedRχiv. One, posted on 10 June, concludes that Ivermectin was associated with lower mortality during treatment of Covid-19. The other preprints, posted on 8 July and 15 September, are showing results of clinical studies. The preprint of July 8 tells, in its conclusions that add-on use of Ivermectin is giving better results when compared to controls, in particular a significant shorter hospitalization. The preprint of September 15 is reporting about the use of ivermectin, dexamethasone, enoxaparin and aspirin in the treatment of Covid-19. A preprint, posted in Research Square on July 14, is reported too. This preprint is giving the result of a trial regarding the combinations Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin. Among news, we consider especially the news regarding the use of Ivermectin in Peru. The case of Iquitos is discussed in detail. Epidemic data in this region are considered. News displaying the observation of rare symptoms of Covid-19, is also reported in detail. The observation was related to a large set of patients in Lima. The updates (8 September 2020 and 20 September 2020) are given in Appendix B and C.

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Before reading this work, please consider that I am not a physician. I do not suggest the use of ivermectin. I am not touting this drug. As previously told, the analysis of publications and news about ivermectin is made in the framework of a wider investigation about information concerning drugs used for Covid-19.

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1 - Introduction - In [SPA1], an article which is discussing the drugs used in Italy for the treatment of Covid-19, we mentioned Ivermectin. In [SPA1], published on 9 May 2020, we reported the news "Novità positive su Remdesivir e altri farmaci COVID-19/Farmaci", dated 7 May and written by Ernesto Carafoli and Enrico Bucci, archived http://archive.is/YdIqh . It is told that "L'ultimo farmaco giunto sulla scena del Covid-19 che vale la pena di citare è l'Ivermectina: un antiparassitario noto per la sua attività antivirale a largo spettro usato anche in terapia umana per affezioni dermatologiche. Un interessante studio australiano ha dimostrato che la sua aggiunta a cellule infettate con SARS_CoV-2 riduce in 48 ore il livello dell'RNA infettante di 5000 volte. Tuttavia, bisogna considerare alcune obiezioni che sono state sollevate, prima di essere sicuri che abbia senso iniziare dei trial su questo composto, come peraltro sembra si voglia fare in Francia". That is, the latest drug that arrived on Covid-19 scene, and which is worth mentioning, is Ivermectin. This drug is a pesticide known for its broad-spectrum antiviral activity and also used in human therapy for dermatological diseases. An interesting Australian study has shown that its addition to SARS_CoV-2 infected cells reduces the level of infectious RNA in 48 hours by 5000 times. However, it is necessary to consider some objections that have been raised, before being sure that it makes sense to start trials on this compound, as it seems to be done in France.

Let us see the scholarly papers published until September 7, 2020, on Ivermectin and some news, that we can find about its use for Covid-19. For what concerns scholarly papers, among them we

can find two preprints in MedRχiv. One, posted on 10 June, concludes that Ivermectin was associated with lower mortality during treatment of Covid-19. The other preprint, posted on 8 July, is showing the result of a clinical trial. This preprint tells, in its conclusions that add-on use of Ivermectin is giving better results when compared to controls, in particular a significant shorter hospitalization. A further preprint, posted in Research Square on July 14, is available too. This preprint is giving the result of a trial regarding the combinations Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin. The meaning of "lower mortality" and "better results" is detailed quantitatively in the preprint, according to the trial considered. *So please consider carefully the details given in the preprints.*

Among news, we consider especially the news regarding the use of Ivermectin in Peru. The case of Iquitos is discussed in detail. In Iquitos, capital city of the Department of Loreto, by May 25 Covid-19 cases and deaths had dropped notably, as reported on the web. Epidemic data in this region are considered, until September 7. News (July 27), displaying the observation of rare symptoms of Covid-19, is also reported in detail. The observation was related to a large set of patients in Lima.

The aim of the discussion is to understand the different approach to Covid-19 treatment, based on ivermectin, which is evident in Peru. In fact, the following discussion is made in the framework of an investigation, which started from drugs used in Italy [SPA1-SPA9]. For what concerns the news, in some cases, it has been preferred to left the original excerpt, to avoid misunderstanding.

2 - The Drug and the Nobel Prize - Before discussing literature and news relevant for the use of Ivermectin in Covid-19, let us remember the extraordinary history of the drug. Ivermectin is a drug derived from avermectin. Actually, the term "avermectin" represents a series of drugs and pesticides used to treat parasitic worms and insect pests. Its molecules are naturally occurring, being generated as fermentation products by Streptomyces avermitilis, a soil actinomycete. Half of the 2015 **Nobel Prize in Physiology or Medicine** was awarded to **William C. Campbell and Satoshi Ōmura**, for discovering avermectin, the derivatives of which have drastically lowered the incidence of river blindness and lymphatic filariasis. The other half of the prize was awarded to Tu Youyou for her discoveries concerning a novel therapy against Malaria. http://archive.is/JMRhi

About ivermectin, here what is told by WHO: "The treatment for onchocerciasis is ivermectin (brand name Mectizan®). Unlike previous treatments, which had serious – sometimes fatal – side effects, ivermectin is safe and can be used on a wide scale. It is also a very effective treatment, and has single-handedly transformed the lives of millions of people suffering from onchocerciasis since its introduction in 1987". https://www.who.int/apoc/cdti/ivermectin/en/ archived http://archive.is/FizVA .

3 - The trailblazer of the use of Ivermectin against onchocerciasis

In fact, Ivermectin was the new drug that "led to a revolutionary break-through in the late 1980s for human onchocerciasis control" [CUP1]. At the beginning of that decade, the ivermectin was observed as being "efficacious against the microfilariae of Onchocerca cervicalis, a common parasite of horses. Of particular interest was that none of the ivermectin-treated animals exhibited the gross or clinical reactions commonly associated with diethylcarbamazine treatment (Klei et al., 1980). Using that finding, Aziz et al. (1982) [AZI1] conducted a preliminary clinical trial of 32 patients in Senegal infected with O. volvulus and found the drug to be efficacious and safe. This seminal report led to a series of in-depth studies in Africa spanning 4–6 years aimed at determining dosage efficacy, tolerance and possible effects on parasite transmission" [CUP1]. Among the main results of these studies we find that ivermectin is highly tolerated and "therefore can be used in mass drug administration programs". "Controlled clinical studies have indicated that a single oral dose of ivermectin is safer and more effective therapy for onchocerciasis than the standard seven- to

10-day course of diethylcarbamazine" [AZI2]. As explained in [AZI3], the other drugs used against onchocerchiasis have serious side effects, but ivermectin was highly tolerated.

The "trialblazer" of the use of Ivermectin against onchocerciasis was **Mohammed Abdul Aziz**. " In 1981-1982, Dr. Mohammed Aziz at MDRL, an expert in River Blindness, conducted the first successful human trial (Aziz et al., 1982) [AZI1]. The results were clear - patients given a single dose of Ivermectin showed either complete elimination or near elimination of microfilariaload, while the adult parasites were untouched" [NPM1]. The success of Ivermectin in clinical trials had the following result. In 1982, Merck, the producer of Mectizan®, and WHO began a research program, the Mectizan Donation Program, under the guidance of Mohammed Aziz and Kenneth Brown, director of Merck's development of ivermectin for human use.

In 2015, "A Trailblazer in Medicine", written by Leedy Hoque, https://www.thedailystar.net/op-ed/trailblazer-medicine-179983 , gave a movingly memory of Dr. Aziz, Leedy's father.

4 -a - Scholarly Papers

Here we consider the papers on ivermectin in relation to Covid-19. In the above-mentioned article written by Carafoli and Bucci, it is told of an interesting Australian study concerning the drug. This study is published in [CAL1] (available from Apr 3, 2020).

Ref. [CAL1] is the origin of researches, trials and use of Ivermectin for Covid-19. The authors - Caly, L., Druce, J., Catton, M., Jans, D. & Wagstaff, K. - tell that this drug, an FDA-approved anti-parasitic, which has previously shown to have broad-spectrum anti-viral activity in vitro, "is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. **Ivermectin therefore warrants further investigation for possible benefits in humans**". The authors are also telling that, "Ultimately, development of an effective anti-viral for SARS-CoV-2, **if given to patients early in infection**, could help to limit the viral load, prevent severe disease progression and limit person-person transmission".

"The paper by Caly et al. has also elicited two letters to the editor," (Mike Bray, MD, Editor-in-chief) The letters are printed in [BRA1], followed by the authors' response to both letters. [BRA1] was published online 2020 Apr 21. "Readers should be aware that neither the letters nor the response has been peer-reviewed, so appropriate caution should be used in quoting or citing them".

Some objections concerning the use of Ivermectin for Covid-19 exist. We can find them given in [SCH1]. In the abstract it is told that "Caly, Druce [CAL1] reported that ivermectin inhibited SARS-CoV-2 in vitro for up to 48 h using ivermectin at 5 uM. The concentration resulting in 50% inhibition (IC50, 2 uM) was >35x higher than the maximum plasma concentration (Cmax) after oral administration of the approved dose of ivermectin when given fasted". Authors of [SCH1] conclude that "The likelihood of a successful clinical trial using the approved dose of ivermectin is low. Combination therapy should be evaluated in vitro. Re-purposing drugs for use in COVID-19 treatment is an ideal strategy but is only feasible when product safety has been established and experiments of re-purposed drugs are conducted at clinically relevant concentrations".

In [CHO1], it is told that "potential drugs like hydroxychloroquine, ivermectin and azithromycin have been tested by diverse group of researchers worldwide for their potential against novel coronavirus". The authors of [CHO1] are proposing a report derived from the major researches about the above-mentioned drugs. "Hydroxychloroquine and ivermectin were known to act by creating the acidic environment and inhibiting the importin (IMPα/β1) mediated viral import. Azithromycin was found to act similar to the hydroxychloroquine as an acidotropic lipophilic weak base. All the three categories of drugs seemed to potentially act against novel coronavirus infection. However, their efficacies need to be studied in detail individually and in combination in-vivo in

order to combat COVID-19 infection".

Ref. [CHO1] illustrates the action of Ivermectin, as we can also find in Ref. [CAL1]. "SARS-CoV-2 (causative agent of COVID-19) is a single stranded RNA virus (positive sense) which is closely related to SARS coronavirus (SARS-CoV). Recent study on ivermectin against SARS-CoV-2 under in vitro conditions revealed that it can inhibit the viral replication. The single treatment of this drug was able to reduce the virus up to 5000-fold in culture within 48h. However, no further reduction was reported with further increase in time period i.e up to 72h. Moreover, no toxicity was seen with the drug at any point of time" [CAL1]. "Mechanism by which ivermectin responded against the CoV-19 virus is not known and was believed to be working similarly as it acted on other viruses. It was known to inhibit the nuclear import of viral and host proteins. Integrase protein of viruses and the importin (IMP) α/β1 heterodimer was responsible for IN nuclear import which further increases the infection. As most of the RNA viruses are dependent upon IMPα/β1 during infection, Ivermectin acts on it and inhibits the import with the increase in antiviral response" [CAL1], [JAN1].

In Ref. [SHA1] the authors report, as [CAL1] and [CHO1], that the "antiviral potential of ivermectin against various viruses is mediated via the targeting of the following: importin α/β-mediated nuclear transport of HIV-1 integrase and NS5 polymerase; NS3 helicase; nuclear import of UL42; and nuclear localization signal-mediated nuclear import of Cap. As SARS-CoV-2 is an RNA virus, the antiviral activity of ivermectin may be mediated through the inhibition of importin α/β-mediated nuclear transport of viral proteins. The clinical efficacy and utility of ivermectin in SARS-CoV-2-infected patients are unpredictable at this stage, as we are dealing with a completely novel virus".

In [SHA1], it is told that it "has also been hypothesized that combination therapy using hydroxychloroquine and ivermectin may exert a synergistic inhibitory effect on SARS-CoV-2. In this combination, hydroxychloroquine acts by inhibiting the entry of SARS-CoV-2 into the host cells, whereas ivermectin further enhances the antiviral activity by inhibiting viral replication" [PAT1].

In [RIZ1], we find an article proposing "an alternative mechanism of action for this drug [Ivermectin] that makes it capable of having an antiviral action, also against the novel coronavirus, in addition to the processes already reported in literature".

In [CHA1], the dosage of Ivermectin is considered. "Caly et al. report a 5,000-fold reduction in SARS-CoV-2 RNA levels, compared with those in controls, after infected Vero/hSLAM cells were incubated for 48 hours with 5 μM ivermectin. ... Pharmacokinetic studies in healthy volunteers have suggested that single doses up to 120 mg of ivermectin can be safe and well tolerated. However, even with this dose," which is quite greater than those approved by the US FDA we are "one order of magnitude lower than effective in vitro concentrations against SARS-CoV-2. These findings may seem to discourage follow-up clinical trials with ivermectin. However, some in vivo effect may be possible even if efficacious in vitro concentrations are physiologically unattainable. ... Until we have a better understanding of ivermectin's antiviral mode of action and of appropriate in vitro systems for testing, we caution against using findings in Vero cells as more than a qualitative indicator of potential efficacy". The authors continue telling that they "believe the recent findings regarding ivermectin warrant rapidly implemented controlled clinical trials to assess its efficacy against SARS-CoV-2. These trials may open a new field of research on the potential use of avermectin antiparasitic drugs, including compounds with an improved pharmacokinetic profile, as antivirals". The authors are pointing out some points, that need to be considered "before testing ivermectin in severe disease". Three of the authors of [CHA1] are involved in trial [CHA2].

In [HEI1], abstract tells that "Ivermectin plays a role in several biological mechanisms, therefore it could serve as a potential candidate in the treatment of a wide range of viruses including COVID-19

as well as other types of positive-sense single-stranded RNA viruses. In vivo studies of animal models revealed a broad range of antiviral effects of ivermectin, however, clinical trials are necessary to appraise the potential efficacy of ivermectin in clinical setting". Ref. [HEI1] is a systematic review of the antiviral effects of Ivermectin. "Several studies reported antiviral effects of ivermectin on RNA viruses such as Zika, dengue, yellow fever, West Nile, ... Furthermore, there are some studies showing antiviral effects of ivermectin against DNA viruses". Playing a role in several biological mechanisms, Ivermectin "could serve as a potential candidate in the treatment of a wide range of viruses including COVID-19 as well as other types of positive-sense single-stranded RNA viruses. In vivo studies of animal models revealed a broad range of antiviral effects of ivermectin, however, clinical trials are necessary to appraise the potential efficacy of ivermectin in clinical setting".

In [ARU1], we find told that "There are many common observations between COVID-19 and dengue. Elevated levels of ferritin, interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), D-dimer, coagulopathy, urticaria and ARDS are reported in both diseases. There are many indicators that mast cell degranulation and histamine release may have a major role in COVID-19 and dengue severity. Mast cell stabilizers, antihistamines, Vitamin C, HCQ, azithromycin, ivermectin may address different aspects of this cascade and thus reduce disease severity. Disease mechanisms and immunopathology must be understood. Focusing on anti-viral action of drugs alone could be counter productive. For example, CQ had no effect on viraemia but decreased cases of DHF".

"The in vitro antiviral activity end-points are analyzed from the pharmacokinetic perspective. The available pharmacokinetic data from clinically relevant and excessive dosing studies indicate that the SARS-CoV-2 inhibitory concentrations are not likely to be attainable in humans". This is told in Ref. [MOM1].

In [ACH1], it is told that "Concerning the treatment outcome, adverse effect, and safety, Ivermectin - Doxycycline combination is a better alternative to Hydroxychloroquine - Azithromycin therapy in the case of mild to moderate degree of COVID19 patients. Though, both the treatment regimens were found to be effective in this study" (On July 14, 2020, the same group of researchers [ACH1] posted in Research Square the results of their clinical trial [ACH2]).

According to [GON1], the results are the following. "The search of the databases led to the retrieval of 25 articles. After the different phases of the selection process, eight articles were included in the present review for the extraction of relevant data. The results suggest that ivermectin inhibits the viral replication of SARS-CoV-2 through the action of the hypoxia-inducible factor (HIF-1α) and consequent destabilization of importin α/β1 proteins. Conclusions tell that "Ivermectin inhibits the viral replication of SARS-CoV-2. Laboratory and clinical studies are needed to provide more evidence in terms of the best posology and possible associations with other drugs for combatting COVID-19".

In [PAN1], authors tell that "Ivermectin acts by selectively binding to the glutamate-gated chloride on channels of the parasite and leads to hyperpolarization of the cell which results in the paralysis and death of the parasite". The anti-viral activity of ivermectin was first discovered with its ability to block the interaction between the nuclear transport receptor importin α/β(IMP) and integrase molecule of HIV. It is also known to block the viral replication of host of viruses including influenza, flavivirus and dengue virus. ... A phase-III, double blind, randomized clinical trial has been started with the aim to determine the safety and efficacy profile of the combination therapy of hydroxychloroquine and ivermectin I the treatment of hospitalized COVD-19 patients" (see the Clinical Trial https://clinicaltrials.gov/ct2/show/NCT04391127).

In [GUP1], we find a Letter to the Editor of The Brazilian Journal of Infectious Diseases, entitled "Ivermectin: potential candidate for the treatment of Covid 19". And a question is posed in [ECH1]:

Ivermectina: ¿La respuesta de Latinoamérica frente al SARS-CoV-2?

Ref. [MOL1] contains a discussion which is necessary to read, in particular because of the news that we will see in the following. A "word of caution is more than required and opportune specially for the use of IVM [ivermectin]. Although available data are coming from front-line medical personnel, and official sources, most of the evidences are based on entirely empirical facts".

In Ref. [WIJ1], the authors are reporting "three confirmed cases of COVID-19 infection with significant improvement clinically and radiologically following treatment with single dose of ivermectin".

In [KUM1], a review is proposed, published 6 July. The abstract tells that "documentations serve as a ray of hope for considering ivermectin in treating COVID-19 due to its suggested nuclear transport inhibitory mechanism".

Other working papers (see Refs. [SCD1], [SCD2], [AGU1], [ORT1], [SHW1], [SOT1]) are given in SSRN and Researchgate.

For what concerns Ivermectin in general, I strongly suggest the reading of articles [CRU1], [CAM1], [ACS1]. Let us add also [BUO1]. The Background of the article is the following: "Strongyloides stercoralis infection is a neglected condition that places people who are immunocompromised at risk of hyperinfection and death. Ivermectin is the drug of choice for the treatment of S stercoralis infection, but there is no definitive evidence on the optimal dose. This trial aimed to assess whether multiple doses of ivermectin were superior to a single dose for the treatment of non-disseminated strongyloidiasis". Then, this article is important for what concerns adverse effects of the drug. Authors tell that "Adverse events were generally of mild intensity and more frequent in the multiple-dose than in the single-dose group. The trial was terminated early due to futility". Interpretation: "Multiple doses of ivermectin did not show higher efficacy and was tolerated less than a single dose. A single dose should therefore be preferred for the treatment of non-disseminated strongyloidiasis".

Then, as we have seen, WHO tells that ivermectin is "safe and can be used on a wide scale", and adverse effects are "generally of mild intensity and more frequent in the multiple-dose".

From now on (that is, July 28, 2020), only scholarly articles with specific results and reporting on the treatment of Covid-19 patients, will be added.

4 - b - ChemRχiv preprints

Let us consider two preprints in ChemRχiv. In [SEN1], 12 different COVID-19 targets are studied. Among them, the RNA dependent RNA polymerase (RdRp) with RNA and Helicase NCB site show the strongest affinity to Ivermectin amounting -10.4 kcal/mol and -9.6 kcal/mol, respectively. "Molecular dynamics of corresponding protein-drug complexes reveals that the drug bound state of RdRp with RNA has better structural stability than the Helicase NCB site, with MM/PBSA free energy of -135.2 kJ/mol, almost twice that of Helicase (-76.6 kJ/mol). The selectivity of Ivermectin to RdRp is triggered by a cooperative interaction of RNA-RdRp by ternary complex formation. Identification of the target and its interaction profile with Ivermectin can lead to more powerful drug designs for COVID-19 and experimental exploration".

Ref. [MAU1] is the other ChemRχiv preprint. It is discussing the combination Ivermectin and Doxycycline. As we will see from news, "in Bangladesh, a group of doctors reported astounding success in treating patients suffering from COVID-19 with two commonly used drugs, Ivermectin and Doxycycline". In [MAU1], the author explored the possible mechanism by which the drugs

"might have worked for the positive response in the COVID-19 patients". To explore the mechanism, molecular docking and the molecular dynamics simulations have been used. The study "shows that both Ivermectin and doxycycline have significantly bind with SARS-CoV-2 proteins but Ivermectin was better binding than doxycycline. Ivermectin showed a perfect binding site to the Spike-RBD and ACE2 interacting region indicating that it might be interfering in the interaction of spike with ACE2 and preventing the viral entry in to the host cells. Ivermectin also exhibited significant binding affinity with different SARS-CoV-2 structural and non-structural proteins (NSPs) which have diverse functions in virus life cycle. ... Thus, our docking and simulation studies reveal that combination of Ivermectin and doxycycline might be executing the effect by inhibition of viral entry and enhance viral load clearance by targeting various viral functional proteins".

4 - c - MedRχiv preprints

Let us conclude the review of scholarly articles on the use of Ivermectin in Covid-19 patients with two preprint in MedRχiv.

In [RAJ1], the authors conclude that "Ivermectin was associated with lower mortality during treatment of COVID-19, especially in patients who required higher inspired oxygen or ventilatory support. These findings should be further evaluated with randomized controlled trials". Objective of [RAJ1]: "To determine whether Ivermectin is associated with lower mortality rate in patients hospitalized with COVID-19". Design and Setting are: "Retrospective cohort study of consecutive patients hospitalized at four Broward Health hospitals in South Florida with confirmed SARS-CoV-2. Enrollment dates were March 15, 2020 through May 11, 2020. Follow up data for all outcomes was May 19, 2020. Participants: 280 patients with confirmed SARS-CoV-2 infection (mean age 59.6 years [standard deviation 17.9], 45.4% female), of whom 173 were treated with ivermectin and 107 were usual care were reviewed".

In [GOR1], the results of the clinical trial NCT04343092C have been proposed (see the next section for all the clinical trials available at ClinicalTrials.gov). The preprint was posted on July 08, 2020. Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management (Pilot Trial), by Faiq I. Gorial et al. , preprint in MedRχiv.

From the Abstract. In vitro, studies indicated that ivermectin (IVM) has antiviral effect. The researchers made the clinical trial to assess the effectiveness of ivermectin (IVM) as add-on therapy to hydroxychloroquine (HCQ) and azithromycin (AZT) in treatment of COVID-19. "Methods: This Pilot clinical trial conducted on hospitalized adult patients with mild to moderate COVID-19 diagnosed according to WHO interim guidance. Sixteen Patients received a single dose of IVM 200Mcg /kg on admission day as add on therapy to hydroxychloroquine (HCQ) and Azithromycin (AZT) and were compared with 71 controls received HCQ and AZT matched in age, gender, clinical features, and comorbidities. The primary outcome was percentage of cured patients, defined as symptoms free to be discharged from the hospital and 2 consecutive negative PCR test from nasopharyngeal swabs at least 24 hours apart. The secondary outcomes were time to cure in both groups and evaluated by measuring time from admission of the patient to the hospital till discharge. Results: Of 87 patients included in the study, the mean age ± SD (range) of patients in the IVM group was similar to controls ... Majority of patients in both groups were male but statistically not significant ... All the patients of IVM group were cured compared with the controls [16 (100 %) vs 69 (97.2 %)]. Two patients died in the controls. The mean time to stay in the hospital was significantly lower in IVM group compared with the controls (7.62 ±2.75 versus 13.22 ±.90 days, p=0.00005, effect size= 0.82). No adverse events were observed Conclusions : Add-on use of IVM to HCQ and AZT had better effectiveness, shorter hospital stay, and relatively safe compared with controls. however, a larger prospective study with longer follow up may be needed to validate these results".

4 - d - Research Square preprints

On July 14, 2020, the same authors of [ACH1] posted in Research Square the results of their clinical trial [ACH2]. In their study, the authors "investigated and compared outcomes of Ivermectin-Doxycycline vs. Hydroxychloroquine-Azithromycin combination therapy COVID19 patients with mild to moderate disease". Patients with mild to moderate COVID-19 disease were tested positive by RT PCR for SARS-CoV-2 infection. "Patients were divided randomly into two groups: Ivermectin 200µgm/kg single dose + Doxycycline 100 mg BID for 10days in group A, and Hydroxychloroquine 400 mg 1st day, then200mg BID for 9days + Azithromycin 500 mg daily for 5 days in group B". "All subjects in the Ivermectin-Doxycycline group (group A) reached a negative PCR for SARS-CoV-2, at a mean of 8.93 days, and all reached symptomatic recovery, at a mean of 5.93 days, with 55.10% symptom-free by the 5th day. In the Hydroxychloroquine-Azithromcyin group (group B), 96.36% reached a negative PCR at a mean of 6.99 days and were symptoms-free at 9.33 days. Group A patients had symptoms that could have been caused by the medication in 31.67% of patients, including lethargy in 14(23.3%), nausea in 11(18.3%), and occasional vertigo in 7(11.66%) of patients. In Group B, 46.43% had symptoms that could have been caused by the medication, including 13(23.21%) mild blurring of vision and headache; 22(39.2%) increased lethargy and dizziness, 10(17.85%) occasional palpitation, and 9(16.07%) nausea and vomiting".

According to the researchers, "Ivermectin-Doxycycline combination showed a trend toward superiority to the Hydroxychloroquine-Azithromycin combination therapy in the case of patients with mild to moderate COVID19 disease, though the difference in time to becoming symptom-free and the difference in time to negative PCR was not statistically significant".

5 - Clinical trials regarding the use of Ivermectin for Covid-19

On July 28, 2020, we can find 33 clinical trials reported by ClinicalTrials.gov , at the following link **https://clinicaltrials.gov/ct2/results?cond=COVID&term=ivermectin+&cntry=&state=&city=&dist=**

For other trials about drugs for Covid-19, see [SPA4].

In the following list, the date is that when the trial was first posted on ClinicalTrials.gov .

1) 13 April 2020 - Efficacy of Ivermectin as Add on Therapy in COVID19 Patients - Drug: Ivermectin (IVM) - Locations: General Directorate of Medical City, Bagdad, Baghdad, Iraq - https://ClinicalTrials.gov/show/NCT04343092

2) 4 May 2020 - Max Ivermectin - COVID 19 Study Versus Standard of Care Treatment for COVID 19 Cases. A Pilot Study - Drug: Ivermectin - Locations: Max Super Speciality hospital, Saket (A unit of Devki Devi Foundation), New Delhi, Delhi, India - https://ClinicalTrials.gov/show/NCT04373824

3) 19 May 2020 - Efficacy of Ivermectin in COVID-19 - Drug: Ivermectin 6 MG Oral Tablet (2 tablets) - Locations: Combined Military Hospital Lahore, Lahore, Punjab, Pakistan - https://ClinicalTrials.gov/show/NCT04392713

4) 27 May 2020 - Ivermectin and Doxycycine in COVID-19 Treatment - Drug: Ivermectin, Doxycycline, Chloroquine - Locations: Sherief Abd-Elsalam, Tanta, Egypt - https://ClinicalTrials.gov/show/NCT04403555

5) 9 June 2020 - Prophylactic Ivermectin in COVID-19 Contacts - Drug: Ivermectin Tablets - Locations: Zagazig University, Zagazig, Sharkia, Egypt - https://ClinicalTrials.gov/show/NCT04422561

6) 11 June 2020 - Ivermectin In Treatment of COVID 19 Patients - Drug: Ivermectin - Locations: isolation and referal hospitals for COVID 19 patients, Cairo, Egypt - https://ClinicalTrials.gov/show/NCT04425707

7) 17 April 2020 - The Efficacy of Ivermectin and Nitazoxanide in COVID-19 Treatment - Drug: Chloroquine, Nitazoxanide, Ivermectin - Locations: Tanta University, Tanta, Egypt - https://ClinicalTrials.gov/show/NCT04351347

8) 22 May 2020 - Ivermectin-Azithromycin-Cholecalciferol (IvAzCol) Combination Therapy for COVID-19 - Drug: Ivermectin, Azithromycin, Cholecalciferol - Locations: Outpatient treatment, Mexico City, Mexico - https://ClinicalTrials.gov/show/NCT04399746

9) 11 May 2020 - Ivermectin Effect on SARS-CoV-2 Replication in Patients With COVID-19 - Drug: IVERMECTIN (IVER P®) arm will receive IVM 600 µg / kg once daily plus standard care. CONTROL arm will receive standard care. - Locations: Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno" CEMIC, Buenos Aires, Ciudad De Buenos Aires, Argentina - https://ClinicalTrials.gov/show/NCT04381884

10) 5 May 2020 - Trial to Promote Recovery From COVID-19 With Ivermectin or Endocrine Therapy - Drug: Bicalutamide 150 Mg Oral Tablet|Drug: Ivermectin 3Mg Tab - Locations: Johns Hopkins Hospital, Baltimore, Maryland, United States - https://ClinicalTrials.gov/show/NCT04374279

11) 24 April 2020 - Ivermectin and Nitazoxanide Combination Therapy for COVID-19 - Combination Product: Ivermectin plus Nitazoxanide, Other: Standard Care - https://ClinicalTrials.gov/show/NCT04360356

12) 18 May 2020 - New Antiviral Drugs for Treatment of COVID-19 - Drug: Treatment group: will receive a combination of Nitazoxanide, Ribavirin and Ivermectin for a duration of seven days - Locations: Mansoura University, Mansoura, Select A State Or Province, Egypt - https://ClinicalTrials.gov/show/NCT04392427

13) 16 June 2020 - A Comparative Study on Ivermectin and Hydroxychloroquine on the COVID19 Patients in Bangladesh - Drug: Ivermectin + Doxycycline | Drug: Hydroxychloroquine + Azithromycin - Locations: Chakoria Upazilla Health Complex, Cox's Bazar, Bangladesh - https://ClinicalTrials.gov/show/NCT04434144

14) 12 June 2020 - Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate COVID-19 - Drug: Ivermectin Oral Product - Locations: Sheba Medical Center, Ramat-Gan, Israel - https://ClinicalTrials.gov/show/NCT04429711

15) 18 May 2020 - Hydroxychloroquine and Ivermectin for the Treatment of COVID-19 Infection - Drug: Hydroxychloroquine, Ivermectin, Placebo - Locations: Jose Manuel Arreola Guerra, Aguascalientes, Mexico - https://ClinicalTrials.gov/show/NCT04391127

16) 28 May 2020 - Efficacy of Ivermectin in Adult Patients With Early Stages of COVID-19 - Drug: Ivermectin Oral Product, Placebo - https://ClinicalTrials.gov/show/NCT04405843

17) 29 May 2020 - Efficacy and Safety of Ivermectin and Doxycycline in Combination or IVE Alone in Patients With COVID-19 Infection. - Drug: Ivermectin + Doxycycline + Placebo, Ivermectin + Placebo, Placebo - https://ClinicalTrials.gov/show/NCT04407130

18) 15 May 2020 - Sars-CoV-2/COVID-19 Ivermectin Navarra-ISGlobal Trial - Drug: Ivermectin, Placebo - Clinica Universidad de Navarra, Pamplona, Navarra, Spain - https://ClinicalTrials.gov/show/NCT04390022

19) 17 June 2020 - Ivermectin vs Combined Hydroxychloroquine and Antiretroviral Drugs (ART) Among Asymptomatic COVID-19 - Drug: Ivermectin Pill, Combined

ART/hydroxychloroquine - Locations: Siriraj Hospital, Bangkok Noi, Bangkok, Thailand - https://ClinicalTrials.gov/show/NCT04435587

20) 29 May 2020 - Efficacy, Safety and Tolerability of Ivermectin in Subjects Infected With SARS-CoV-2 With or Without Symptoms - Drug: Ivermectin, Placebo - https://ClinicalTrials.gov/show/NCT04407507

21) 11 May 2020 - Novel Regimens in COVID-19 Treatment - Drug: Nitazoxanide, Ivermectin, Chloroquine, Azithromycin - https://ClinicalTrials.gov/show/NCT04382846

22) 11 June 2020 - IVERMECTIN Aspirin Dexametasone and Enoxaparin as Treatment of Covid 19 - Drug: Ivermectin 5 MG/ML - Locations: Hospital Eurnekian, Buenos Aires, Argentina - https://ClinicalTrials.gov/show/NCT04425863

23) 11 June 2020 - USEFULNESS of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19 - Device: iota carrageenan, Ivermectin - Locations: Hospital Eurnekian, Buenos Aires, Argentina - https://ClinicalTrials.gov/show/NCT04425850

24) 5 May 2020 - Novel Agents for Treatment of High-risk COVID-19 Positive Patients - Drugs: Hydroxychloroquine|, Hydroxychloroquine and Azithromycin, Hydroxychloroquine and Ivermectin, Camostat Mesilate - Locations: University of Kentucky Markey Cancer Center, Lexington, Kentucky, United States - https://ClinicalTrials.gov/show/NCT04374019

25) 14 June 2020 - A Real-life Experience on Treatment of Patients With COVID 19 - Drug: Chloroquine, Favipiravir, Nitazoxanide, Ivermectin, Niclosamide, Other drugs - Locations: Tanta university hospital, Tanta, Egypt - https://ClinicalTrials.gov/show/NCT04345419

26) 16 June 2020 - A Study to Compare the Efficacy and Safety of Different Doses of Ivermectin for COVID-19 - Drug: Ivermectin, Other: Standard treatment for COVID-19 - Locations: Hospital Univeristário da Universidade Federal de São Carlos (HU-UFSCar), São Carlos, São Paulo, Brazil - https://ClinicalTrials.gov/show/NCT04431466

27) 19 June 2020 - COVidIVERmectin: Ivermectin for Treatment of Covid-19 - Drug: Ivermectin - Other: Placebo - Locations: IRCCS Sacro Cuore Don Calabria hospital, Negrar, Verona, Italy, Policlinico S. Orsola, Bologna, Italy, Ospedale Luigi Sacco, Milan, Italy, Ospedale di Rovereto, Rovereto, Italy, Ospedale Amedeo di Savoia, Turin, Italy, Hospital Clinic/ISGlobal, Barcelona, Spain, Hospital La Paz-Carlos III, Madrid, Spain - https://ClinicalTrials.gov/show/NCT04438850

28) 24 June 2020 - Ivermectin in Treatment of COVID-19 - Drug: Ivermectin - Locations: Waheed Shouman, Zagazig, Sharkia, Egypt - https://ClinicalTrials.gov/show/NCT04445311

29) 25 June 2020 - Early Treatment With Ivermectin and LosarTAN for Cancer Patients With COVID-19 Infection. Drugs: Placebo, Ivermectin, Losartan - https://ClinicalTrials.gov/show/NCT04447235

30) 24 June 2020 - A Preventive Treatment for Migrant Workers at High-risk of Covid-19 - Interventions: Drug: Hydroxychloroquine Sulfate Tablets, Ivermectin 3Mg Tab, Zinc , Povidone-Iodine - Dietary Supplement: Vitamin C - Locations Tuas South Dormitory, Singapore - https://ClinicalTrials.gov/show/NCT04446104

31) 24 June 2020 - Anti - Androgen Treatment for COVID-19 - Interventions: Drug: Dutasteride - Drug: Ivermectin - Drug: Azithromycin - Locations: Corpometria Institute, Brasilia, Brazil - https://ClinicalTrials.gov/show/NCT04446429

32) 7 July 2020 - Worldwide Trends on COVID-19 Research After the Declaration of COVID-19 Pandemic - Drugs: Convalescent Plasma Transfusion, Hydroxychloroquine, DAS181, Ivermectin, Interferon Beta-1A - https://ClinicalTrials.gov/show/NCT04460547

33) 15 July 2020 - Efficacy of Subcutaneous Ivermectin With or Without Zinc and Nigella Sativa in COVID-19 Patients - Drug: Nigella Sativa / Black Cumin , Ivermectin Injectable Solution, Other: Placebo , Zinc - Location Shaikh Zayed Hospital, Lahore, Punjab, Pakistan - https://ClinicalTrials.gov/show/NCT04472585

6 - News from Bangladesh, Italy, US and Israel

Let us start for news coming from **Bangladesh**. https://worldhealth.net/news/ Anti Aging News - **May 25, 2020** - Bangladesh Medical Team Claims Ivermectin With Doxycycline Clears COVID-19 - Archived http://archive.is/wh6uE - "A Bangladeshi medical team is claiming that their research on the combination of two widely used and common drugs has yielded positive results in clearing COVID-19 patients with acute symptoms of the disease. "We have got astounding results. Out of 60 COVID-19 patients, all recovered as the combination of the two drugs were applied", said Professor Dr Md Tarek Alam, the head of medicine department at private Bangladesh Medical College Hospital (BMCH). According to Alam who is a reputed clinician in Bangladesh the antiprotozoal medicine **Ivermectin** in combination with one dose of the antibiotic **Doxycycline** yielded the results of COVID-19 patients being cleared as being negative from the disease".

UNB NEWS DHAKA PUBLISH- **JUNE 06, 2020,** 06:21 PM UNB NEWS - UPDATE- JUNE 07, 2020, 10:35 AM - Covid-19: BMCH physician reports 'amazing results' using **Ivermectin**, **Doxycycline**. It is not the patients who decide the medication, says Dr Tarek Alam - Archived http://archive.is/A2rc2 - "Physicians from Bangladesh Medical College Hospital (BMCH), led by Dr Tarek Alam, claimed that a combination of the anti-parasitic drug '**ivermectin**' with antibiotic '**Doxycycline**' yielded amazing results against Covid-19".

https://www.thedailystar.net/ 12:00 AM, **June 14,** 2020 / LAST MODIFIED: 08:43 AM, June 14, 2020 - Use of **Ivermectin**: Hope held out, caution called for - Archived http://archive.is/Hup01 - "Physicians at a Dhaka hospital claimed they have observed "cumulative efficacy" of **ivermectin** in Covid-19 patients while using the drug in combination with **doxycycline**. They said although they were yet to be certain about the exact efficacy of the drug combination, they would seek permission from Bangladesh Medical and Research Council (BMRC) for a clinical trial to know further about its effectiveness."

The combination of ivermectin and doxycycline is used for the treatment of other diseases (see for instance [HOE1], [BAZ1]). Then, we have the proposal of a combination hydroxychloroquine and ivermectin.

From **Italy** - https://www.trialsitenews.com/university-of-naples-federico-ii-physicians-hypothesize-why-not-try-hydroxychloroquine-ivermectin-in-combo-against-covid-19/ **May 3,** 2020- Archived http://archive.is/yFsuG "University of Naples Federico II Physicians Hypothesize: Why Not Try **Hydroxychloroquine & Ivermectin** in Combo Against COVID-19?" - "Two researchers / physicians out of the University of Naples Federico II — one of the oldest universities in the world — introduce the use of two drugs classically used by dermatologists for the investigational use in fighting SARS-CoV-2, the virus behind the COVID-19 pandemic. The two doctors hypothesize that the use of **Hydroxychloroquine** (HCQ) and **Ivermectin** may evidence a consequential and synergistic action if administered simultaneously both for chemoprophylaxis and treatment of COVID-19". Physicians are Dr. Angela Patri and Dr. Gabriella Fabbrocini.

https://www.stampareggiana.it - **8 Aprile 2020** - Una novità importante è che oggi al San Raffaele inizia anche la sperimentazione di un nuovo farmaco, l'**Ivermectina**. Archived http://archive.is/tqnX7 - "Il suo utilizzo [Ivermectina] è stato approvato in via sperimentale dall'AIFA, l'ente Italiano del farmaco". Dopo l'annuncio della sua efficacia in vitro, "Adesso si ricerca la conferma clinica, si tratta di un farmaco da tempo usato contro la scabbia, i vermi ed altre

malattie prodotte da parassiti la cui specifica modalità di azione è stata chiarita. Aumenta la concentrazione di cloro all'interno delle cellule che hanno specifici recettori, Covid 19 compreso. Questo fatto determina la paralisi e poi la morte del virus. Ora resta la rapida sperimentazione clinica autorizzata in Italia essendo uno dei paesi più colpiti".

Then, news from **US**. https://www.newsmax.com/us/ - Breakthrough Drug: **Ivermectin** Shows 'Astounding' Results Against Coronavirus - By David A. Patten | Friday, **22 May** 2020 11:16 PM - Archived http://archive.is/uqrxr - "Doctors have administered the drug ivermectin in several simultaneous trials in several countries sometimes in combination with other common medications. Physicians who participated in the study report that patients' viral loads began declining almost immediately after they began administering ivermectin, a widely available prescription drug approved to combat parasites, scabies and head lice. ... Emergency medical physician Dr. Peter H. Hibberd, M.D., of Palm Beach County, Florida, told Newsmax Friday evening in an exclusive interview that he's optimistic the drug will prove to be an important therapeutic advance, although he expects more trials will be needed before it wins FDA approval for use as a COVID-19 medication. He noted it has impressed doctors in clinical trials on multiple continents. In some cases, doctors reported just one dose of ivermectin markedly improved a patient's condition. U. S. patients received a single oral dose, and some of them received a booster dose seven days later. The FDA-approved dose for parasitic infections was used. ... On Thursday, a team of U.S. doctors led by Dr. Jean-Jacques Rajter at the Broward Health Medical Center in Fort Lauderdale, Florida, submitted findings to an institutional review board. According to a medical source familiar with the study, some 250 coronavirus patients were involved in the Broward trial. The results were dramatic, with "statistically significant improvement in mortality," according to the source".

About the mentioned trial, see https://www.trialsitenews.com/broward-county-doctor-using-ivermectin-off-label-combo-on-covid-19-patients-it-is-working-secures-county-health-protocol-approval/ Archived http://archive.is/IQSts (See Ref. [RAJ1]).

From **Israel** - https://www.jpost.com/- Israeli researcher: Antiparasitic drug could 'cure' coronavirus - **JUNE 15**, 2020 - Archived http://archive.is/HADqB - "Prof. Eli Schwartz launched a clinical trial of the drug **Ivermectin**, a broad-spectrum antiparasitic agent that has also been shown to fight viruses. A tropical disease expert is testing a drug used to fight parasites in third-world countries that he said could help reduce the length of infection for people who catch coronavirus, enabling them to go back to work and life in as little as a few days. ... "At the onset of this virus, everyone was talking about the anti-malaria drug," he said, referring to hydroxychloroquine, which was first touted by US President Donald Trump, but has since been linked to increased risk of death in coronavirus patients, among other health risks. "We decided to look more widely for other medications and considered a few drugs that might have antiviral activity," he said; Ivermectin was selected".

https://www.trialsitenews.com/ - In Pursuit of Real-World **Ivermectin** Stories: Tales from Pathanamthitta **JUN 17**, 2020 - http://archive.is/iWQu6

https://www.trialsitenews.com/ - 100-Year-Old Discharged from Mumbai's Rajawadi Hospital after Successful Ivermectin Treatment - **JUN 18**, 2020- http://archive.is/hkuON - "Now apparently commonly in use in India, the medics at Rajawadi Hospital report that **Ivermectin** was the drug that actually worked, leading to the recent discharge of 100 year old Mr. Mali. It was to the thrill of all the staff to see this patient heal rapidly".

7 - The problem of Surgisphere - https://www.the-scientist.com/ - **16 June** 2020 - Surgisphere Sows Confusion About Another Unproven COVID-19 Drug - "The company behind a now-discredited study on hydroxychloroquine also posted a report that has been cited by Latin American governments recommending ivermectin as a possible coronavirus treatment. Clinicians there say the

effects have been extremely damaging". http://archive.is/G6JM6 .

This article is telling "One of the most influential studies on ivermectin's effect in COVID-19 patients was a large observational study that used a database owned by Surgisphere, a now-discredited Illinois-based company founded by vascular surgeon Sapan Desai. That study, published on the preprint server SSRN in early April and updated a couple weeks later, reported a strong positive association between ivermectin treatment and COVID-19 patient survival, and has been cited in white papers and reports by Latin American health researchers and governments as evidence of the drug's efficacy". The paper in SSRN is no more available[1]. About it, see please the discussion by Carlos Javier Chaccour (he is running a clinical trial about ivermectin). http://archive.is/d0VOd

www.the-scientist.com/ is highlighting in the web page the following: "With ivermectin firmly entrenched in political and public minds as a weapon against the pandemic, the question of evidence is now of secondary importance for some members of the medical and scientific communities". Even if mitigated by a "some members", this is a serious accusation against these communities. Let us observe that the sentence of the-scientist concerning ivermectin, that is "firmly entrenched in political and public minds as a weapon against the pandemic", could have been applied to hydroxychloroquine too, the "Trump's 'miracle' drug", as defined in The Guardian, http://archive.is/ToTIv . About this drug, "Praised by presidents", see "Three big studies dim hopes that hydroxychloroquine can treat or prevent COVID-19", Jun 9, 2020, in Science, http://archive.is/oVg7I .

What happened for hydroxychloroquine is happening for ivermectin.

8 - News from Peru and Bolivia

Let us continue with news - Fron CNN in Spanish - https://cnnespanol.cnn.com/ - **Ivermectina**, el arma sin validación científica que se usa en Bolivia para tratar covid-19 - Por Gloria Carrasco, CNN Publicado a las 16:23 ET (20:23 GMT) **29 mayo**, 2020 Archived http://archive.is/17R1Y - "**Bolivia** incluyó a la ivermectina dentro de la lista de medicamentos esenciales para que pueda ser usada en el tratamiento de pacientes con covid-19. En el departamento de Beni, en el norte del país, hay una campaña para distribuir gratuitamente este medicamento entre los pobladores del municipio de Trinidad".

https://cnnespanol.cnn.com/ - 17:17 ET(21:17 GMT) **10 Junio**, 2020 - Perú da impulso a **hidroxicloroquina** e **ivermectina** como tratamiento para covid-19 - Por Kiarinna Parisi Archived http://archive.is/w8KLw - **Bolivia** autoriza el uso de ivermectina contra covid-19 3:53 - "El Ministerio de Salud de Perú (Minsa) dio impulso como tratamiento para el nuevo coronavirus a dos medicamentos que carecen de autorización por parte de autoridades sanitarias o de consenso científico sobre su eficacia y seguridad para pacientes de covid-19. ... Por su parte, la ivermectina es un agente antiparasitario de amplio espectro, aprobado por la Administración de Medicinas y Alimentos de Estados Unidos para ciertos usos en humanos y animales, aunque la prevención o tratamiento contra el coronavirus no es uno de ellos. A principios de mayo, dicha autoridad desaconsejó su uso asociado al covid-19 tras afirmar que se necesitaban más estudios al respecto".

12/6/2020 https://www.eleconomistaamerica.pe/ "El hospital de San Juan de Lurigancho empezó a elaborar **ivermectina** para cubrir la demanda existente de este medicamento por parte de pacientes afectados por la COVID-19, que llegan al nosocomio que pertenece a la Dirección de Redes Integradas de Salud (Diris) Lima Centro, informó el Ministerio de Salud". Archived

1 As told in the introduction, the aim of this discussion is to understand the different approach to Covid-19 treatment, based on ivermectin, currently running mainly in Peru. in the framework of an investigation, which started from drugs used in Italy. It is not the discussion of SSRN paper for sure. For it, see Chaccour 's web article.

http://archive.is/hak3F

https://exitosanoticias.pe/ - **13/6/2020** Dr. Fernández: “Si más peruanos tomaran **ivermectina**, habría menos casos de COVID-19” - Usar la Ivermectina es como ponerte un chaleco antibalas contra la enfermedad. En el Perú, más de 1 millón de personas la consumen, y nadie se ha muerto”, indicó. Archived http://archive.is/fusra - ¿Qué hace la Ivermectina en el cuerpo? "Evita que el virus se multiplique en las células. Por eso, la **Ivermectina** y la **Hidroxicloroquina** trabajan muy bien en casos iniciales o cuando recién comienza la enfermedad”.

https://www.marca.com/claro-mx/ - **11/6/2020** - **Hidroxicloroquina** e **ivermectina**: ¿por qué llevan la delantera contra el coronavirus? "Por su parte, Marcelo Navajas, Ministro de Salud de Bolivia, emitió un permiso para la aplicación de la Ivermectina en los humanos para tratar el Covid-19 en dicho país, aunque aclaran que su uso contra el coronavirus no está avalado por la Organización Mundial de la Salud." ---------- web.archive.org/web/20200614112908/https://www.marca.com/claro-mx/trending/2020/06/11/5ee18c6d268e3eaf4b8b45a9.html

https://www.connuestroperu.com/ - Miscelánea **12 Junio** 2020 - La Libertad producirá 150 mil dosis de ivermectina para luchar contra el coronavirus - El Gobierno Regional de La Libertad producirá 150 mil dosis de **ivermectina** para combatir el coronavirus COVID-19 en los pacientes leves. Archived http://archive.is/BKf8q

Here also a **direct experience by Dr. A. Camargo** - https://www.connuestroperu.com/ - An interview with **Dr. Antonio Camargo**, **02 Junio** 2020 - Archived http://archive.is/Cy8Wc . "Usted contrajo la enfermedad y se curó con **ivermectina**, ¿podría narrarnos su experiencia? Me infecté en mis actividades laborales, atendiendo pacientes oncológicos. Un paciente que buscó ayuda y estuvo buen tiempo en nuestro centro contagió a dos trabajadoras y la trabajadora de limpieza me infectó. El diagnóstico de mi infección fue realizado el 8 o 9 de mayo. Tenía una carga viral terriblemente alta, como para hacer una especie de patrón de vigilancia. Tengo un laboratorio de biología molecular y recuerdo que el biólogo me dijo que mi carga viral era muy alta. Hasta ese momento no sentía nada, sólo una resequedad en la garganta, sin tos ni malestar general ni fiebre, pero sabía que se venía un “tsunami” sobre mí. Allí decidí probar en mí lo que estaba probando en otros pacientes. De inmediato tomé 60mg por día de **ivermectina, acompañando con hidroxicloroquina**: 200 mg por la mañana y 200mg por la noche, más 200mg de **sales de zinc** por día, que son dosis altas. Ese fue el tratamiento coronicida. A las 48 horas me realicé un control con PCR, test molecular para controlar mi carga viral y no había carga viral en mi faringe, no había virus".

In this interview, Dr. Camargo is reporting his experience and the use of ivermectin, hydroxychloroquine and zinc.

9 - The case of Iquitos (Peru)

This is a specific case which deserves a detailed discussion, because we can be sure that a large use of Ivermectin has been made. It is therefore very important for any possible statistical analysis.

https://www.connuestroperu.com/ - **13/6/2020** "El verdadero Comando COVID-19 de Iquitos: médicos independientes lograron contener el azote del coronavirus, no el Minsa ni Essalud" - Archived http://archive.vn/ePtmg

"Desde fines de abril a mayo las escenas diarias en los hospitales de Iquitos eran de avalancha de infectados con el coronavirus COVID-19, que sobrepasaron su capacidad y muchos pacientes no podían ser atendidos, mientras que otros hasta morían en los exteriores. ... Es gracias a los médicos independientes que Iquitos superó el desastre que causó la pandemia, que ahora está controlada, pues de no contener a muchísimos pacientes en sus domicilios con estos tratamientos exitosos, todos ellos habrían muerto". Interview by Con Nuestro Perú with **Dr. Sergio Bardon**, "uno de los

médicos independientes que participaron en esta lucha y fueron el verdadero Comando COVID-19 en Iquitos".

Question: "Desde **abril y mayo** hay un número creciente de médicos que usan exitosamente ivermectina, habiendo una cura. ¿A qué atribuye que internacionalmente no se difunda ello y se prefiera a fármacos que tienen menor efecto? Answer; "Con respecto a la **ivermectina** lo que se ha visto es que ha bajado en muchísimos pacientes la carga viral, es decir, la cantidad de virus que una persona tiene en el cuerpo, y por lo tanto, va a mejorar su cuadro clínico y disminuir drásticamente las posibilidades de que la persona se complique la infección viral".

Dr. Bardon tells also: "Lo cierto es que somos muchos los médicos que estamos usando ivermectina con muchísimo éxito. Por supuesto, estos medicamentos tienen mayor éxito cuanto antes se recetan y cuanto menos síntomas tiene el paciente, porque cuando llega a una fase de complicación aguda, con una disnea importante, allí ya empiezan a actuar muchas otras cosas que no son necesariamente la carga viral, porque es la respuesta inflamatoria que tiene cada paciente. Entonces la ivermectina ya no tiene mucho sentido, por eso es importante no solamente darla sino darla a tiempo ... Efectivamente, el éxito que he tenido con ivermectina es mucho. En general, a partir del tercero o cuarto día ya en la gran mayoría de los pacientes no se han visto síntomas ni signos de COVID-19, y con respecto a la negativización de la prueba, se obtiene también rápidamente a partir de una semana. ... Estoy tratando a todos los pacientes en forma ambulatoria. Solamente uno tuvo que recibir internamiento, que fue el primero. De allí todos han sido seguidos ambulatoriamente, especialmente porque trato pacientes en Amazonas, Loreto, en lugares donde ni siquiera tienen la posibilidad de ir a un hospital y estamos manejándolo básicamente con la asociación de **ivermectina-azitromicina**, y hasta ahora todos han sido exitosos".

As it is evident from previous news, in Iquitos the ivermectin was used. Iquitos is the capital of Peru's Maynas Province and Loreto Region. It is the largest metropolis in the Peruvian Amazon, east of the Andes, and it is the ninth most populous city of Peru.

In [FRA1], it was told that the health system in this town was subjected to a very high stress for Covid-19. "The first COVID-19 case in the Peruvian Amazon, detected on March 17, seemed to be a one-off — a tour guide who apparently caught it from foreign visitors. Within weeks, however, Carlos Calampa [Regional Health Director] saw patients overflowing into the corridors of the Loreto Regional Hospital in Iquitos, where he was director". After describing the situation in the town and Peru, the article [FRA1] ends telling "By May 25, COVID-19 cases and deaths had dropped in Iquitos but were rising in remote areas accessible only by river or light plane, Calampa said. He is reinforcing staff and coordinating with the military to deliver medicine, oxygen, and other supplies to health centres on the Marañón, Corrientes, and Tigre rivers, where much of the population is Indigenous".

It seems that something happened **before May 25**. And in fact, in the article of **June 8, 2020**, entitled "Effective formula knocks out Covid-19 in the Peruvian Amazon", by **Juan J Chamie** https://medium.com/@juanjchamie/effective-formula-knocks-out-covid-19-in-the-peruvian-amazon-150565e9b6c6 archived http://archive.is/pI5x6 , we find the proper question "How did they get through it so quickly?". "The numbers don't lie. While the coastal departments (Sí Covid) haven't stopped the growing number of reported deaths, the main departments in the jungle region (Ex-Covid), for example in Loreto and Ucayali, broke the trend and within three weeks drastically lowered the rise in mortality rates. Although they still need more time to reach normal values, the trend indicates that they'll manage it very soon". - And then: How did they get through it so quickly? - The author of the article in Medium tells that the "drop in deaths in the region is attributed to the general use of a medication, and that without even having scientific evidence, according to local residents, it has saved many lives". The drug is Ivermectin.

"In mid-April, a group of volunteers initiated a campaign in the department of Ucayali to deliver

ivermectin to residents. They openly acknowledged that they were using veterinarian ivermectin and confirmed positive results, as well. ... Similarly, in the city of Iquitos ... an independent group of volunteer doctors initiated a public campaign plus free vaccinations with ivermectin". This is told in medium.com.

As we have seen in news published by www.connuestroperu.com, there are physicians such a Dr. Bardon that, in medical clinics, are administrating the drug under their medical supervision. However, there are also different experiences, based on groups of volunteers, that used the drug in the veterinary formulation. Here news in http://www.perulactea.com/ on 16/05/2020 - "En Iquitos vienen aplicando Ivermectina de uso veterinario con buenos resultados frente a Covid19". Archived http://archive.is/yx24r

"La dosificación que se está utilizando es 1ml x 2 días. Una botella de 1000 ml Ivermecticina al 1% de uso en ganadería, se consigue en 130 soles en las veterinarias. En pocas palabras con 130 soles se pueden inyectar a 500 personas. [1 Sol equals 0.26 Euro] Se afirma que ya atendieron más de 2000 personas con este tratamiento, quedando claro que la Ivermectina está dando resultados favorables para pacientes covid 19 en etapas 1 y 2. ... Desde el día martes 12 de mayo se esta aplicando la inyección de IVERMECTINA a personas con síntomas leves de Covid 19, la atención será totalmente GRATUITA". The article tells that the dosage of the drug that is being used is 1ml x 2 days. A bottle of 1000 ml Ivermectin at 1% of use in livestock, is available in 130 soles in veterinary medicine. In short, with 130 soles, 500 people can be injected. It is stated that more than 2000 people have already been treated with this treatment, making it clear that Ivermectin is giving favorable results for covid 19 patients in stages 1 and 2. Since Tuesday, May 12, the Ivermectin injection is being applied to people with mild symptoms of Covid 19, the care will be totally for free.

Let us stress once more. A large use of ivermectin has been made in this province of Peru. It would be very interesting to have further reports about the results of the treatment, besides the report mentioned above.

For the moment, about the Department of Loreto, we can show data from https://bing.com/covid/local/loreto_peru?vert=graph

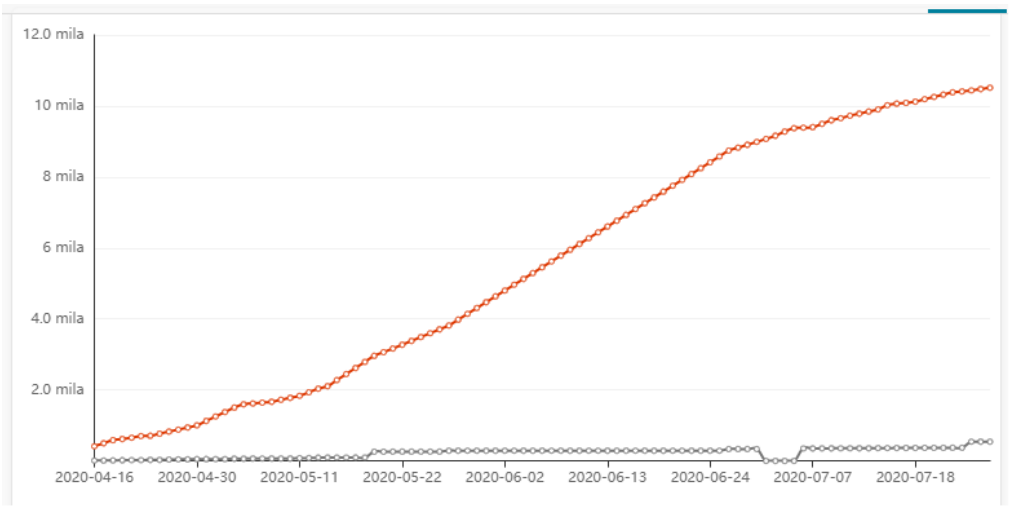

Fig.1 - Red dots represents the confirmed cases, the black dots the victims of the virus. Data from 16 April to 26 July.

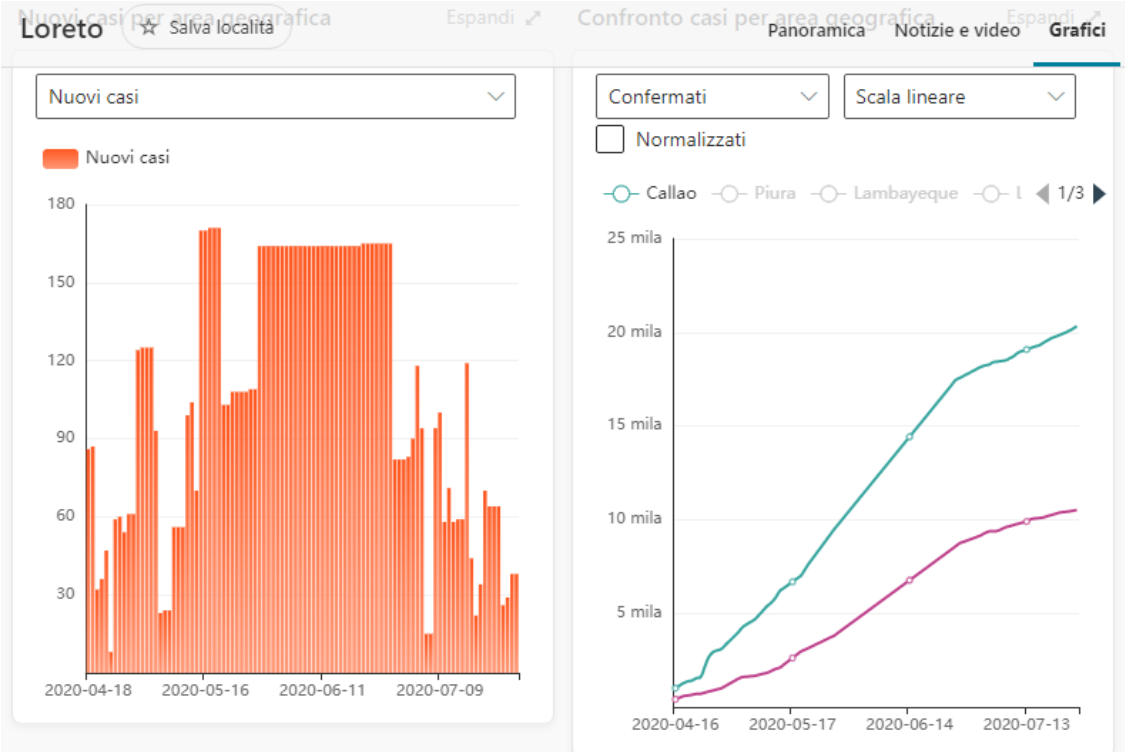

Fig.2 - Daily new cases in Loreto, on the left- https://bing.com/covid/local/loreto_peru?vert=graph. On the right, the purple curve represents data from Loreto, the blue curve from Callao.

The number of victims in Loreto was 259 (20 May), 288 (20 June), 368 (20 July). The last number is 544. Then, in Loreto the percentage of fatal cases was: 544/10721=0.05 , that is 5% . What could we deduce from the graph and numbers, about a possible effect of ivermectin? It is difficult, and we need further investigation. However, the curve of the confirmed cases seems to approach the plateau.

The image given previously (on the right) shows the comparison of cases in Loreto and Callao, which is much more densely populated than Loreto. It seems that in Loreto, the curve is closer to the plateau than in Callao. From https://coronalevel.com/Peru/Loreto/ , the following plot is available. Data: Johns Hopkins University CSSE. Data from 29 May to 28 July.

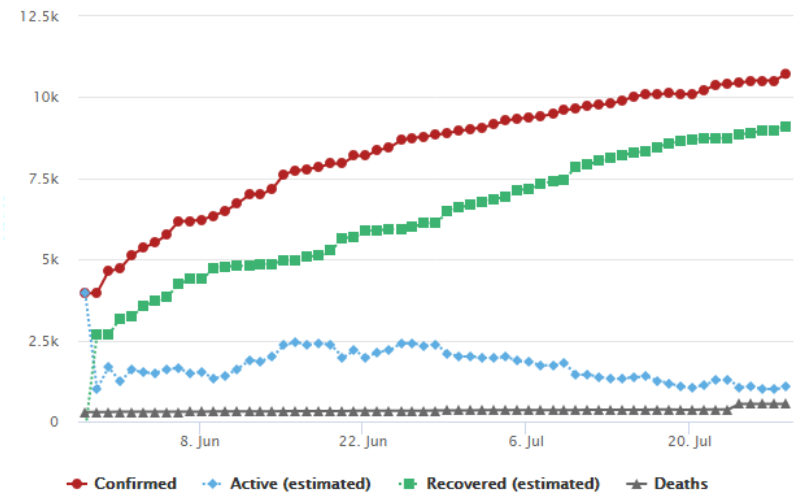

Fig.3 - Data from Johns Hopkins University CSSE.

20 June 2020 - https://ojo-publico.com/1909/medicos-piden-cautela-en-uso-de-hidroxicloroquina-e-ivermectina - archived http://archive.is/Vdy90 - "Juan Carlos Celis Salinas es médico infectólogo en el hospital regional de Loreto, en donde las últimas semanas han atendido a cientos de personas con Covid-19 y a muchas otras que han llegado con síntomas de haberse automedicado con ivermectina, un fármaco usado como parte del tratamiento experimental contra el Sars-Cov-2 y que necesita un acompañamiento clínico. "Hay personas que llegan luego de haber tomado dosis excesivas de ivermectina, y otros que se aplican la de uso veterinario; en ambos casos llegan con efectos adversos. Llegan con mareos, taquicardia", sostiene".

The drug must be used under medical supervision.

10 - A drug for humans

About the concerns of using a drug involved in veterinary use, an answer was the following. "La Ivermectina fue creada para el tratamiento de humanos" - El médico trujillano Gustavo Elera ha frenado en seco al coronavirus en unos mil 200 pacientes en Chanchamayo con este fármaco, muy empleado en medicina veterinaria". http://www.laindustria.pe/nota/16073-la-ivermectina-fue-creada-para-el-tratamiento-de-humanos - dated **7 June 2020** - Archived http://archive.is/beTgM

"Desde abril a la fecha, el médico Gustavo Elera Arévalo, trujillano él, ha tratado con excelentes resultados a mil 200 pacientes, todos en su momento afectados por el coronavirus, en La Merced, Chanchamayo, Junín". In this article, the reporter asks Dr. Elera about the difference between Ivermectin for human and veterinary use. Question: "En el mercado encontramos la Ivermectina para uso humano y animal. La de uso humano ha escaseado y las pocas que se encuentran, tienen un costo muy elevado. Así las cosas, ¿se puede emplear la veterinaria?" Answer: "Claro. No es tóxica. Nosotros hemos utilizado la de uso veterinario para el penal de La Merced (Chanchamayo), para la Policía Nacional, para todos los pacientes que estamos viendo sin ningún problema y la vamos a utilizar en el barrido que haremos en algunos otros sectores del mismo Chanchamayo. La diferencia entre la Ivermectina de uso humano y la de uso veterinario es que la de uso humano es Ivermectina más agua y Sorbitol, que es un saborizante que la vuelve dulce, y la de uso veterinario es Ivermectina más agua y punto".

We can find Ivermectin in the formulation for human and veterinary use. The formulations for human use are in short supply and at a very high cost. So, a question is "Can we use veterinary medicine?" Elera's answer is the following: "Sure. It is not toxic. We have used the formulation for veterinary use for the ... The difference (in the formulation) of Ivermectin for human use and for veterinary use is the following. The formulation for human use is Ivermectin plus water and Sorbitol, which is a flavouring that makes it sweet. The formulation for veterinary use is Ivermectin plus water, plain and simple. Elera' answer is translated because, in a following sections, the two formulations of ivermectin will be discussed in detail.

Let us stress that it is necessary to check carefully the formulations, and avoid self-medication (the use of drugs needs medical supervision). At this is clear because of different concentrations. "El médico veterinario Eleazar Vargas señaló que la ivermectina que viene siendo usada para humanos difiere en concentración del empleado para animales". **18 Junio**, 2020 - http://archive.is/1qN3N

Dr. Eleazar Vergas is dean of the Colegio Médico Veterinario. Let us report some sentences from this article "Hay una sola ivermectina, que se dedique para animales o para humanos ya es un tema de concentración. Aunque creo que para humanos lo utilizan solo de vía oral", señaló el experto a Exitosa. It is also told, "Por otro lado, el decano del Colegio Médico Veterinario hizo un llamado a

los médicos a respetar la profesión veterinaria, luego que se generaran algunos comentarios despectivos de algunos de ellos respecto a los puntos de vista de veterinarios sobre la ivermectina: “creo que es una contraposición inoportuna, no es momento para decir yo soy más o yo soy menos. He escuchado que incluso hablan del veterinario de forma despectiva, no debería ser así. Nosotros somos profesionales de la salud”.

We can find further information about the use of ivermectin in Peru in the recent https://elcomercio.pe/tecnologia/ciencias/ivermectina-gustavo-elera-ivermectina-el-medico-que-se-ha-convertido-en-el-referente-nacional-de-una-campana-anticovid-19-que-carece-de-base-cientifica-noticia/ - **26 June** 2020. Ivermectina - El rostro de una campaña contra el COVID-19 que crece en el Perú pero que no tiene base científica - El médico Gustavo Elera impulsa el uso de ivermectina en diversas regiones del país con el apoyo de alcaldes. Pese a la opinión de expertos, asegura tener la evidencia suficiente para ello". In the article, we find that Gustavo Elera is preparing an article to be submitted to Lancet, where he will describe the results of the use of ivermectin. It is also stressed that "En diversos medios regionales, el médico [Elera] ha defendido el uso de ivermectina veterinaria en lugar de la fabricada para humanos, con el argumento de que la primera es mucho más barata. Ha asegurado, además, que “la de uso veterinario es Ivermectina más agua y punto”. The article continues telling "Pero especialistas consultados por este Diario advirtieron que su consumo puede traer efectos secundarios y que bajo ninguna circunstancia un medicamento para animales debe ser usado en humanos".

And a link is given: https://elcomercio.pe/tecnologia/ciencias/coronavirus-ivermectina-covid-19-en-ucayali-autoridades-reparten-ivermectina-para-animales-para-tratar-pacientes-con-coronavirus-noticia/?ref=ecr/ - dated **26 May** 2020, where it is told that "Dos consejeros regionales, uno de ellos del partido Alianza para el Progreso, publicitan su iniciativa como “un acto filantrópico”. Sin embargo, expertos subrayan que la medicina veterinaria puede ser nociva en humanos". The article has the title: COVID-19 | Autoridades reparten ivermectina para vacas para tratar pacientes con coronavirus en Ucayali". Veterinary medicine is a branch of medicine, working with drugs, like the ivermectin, which can have formulations both for humans and animals. "Although the majority of veterinary dosage forms contain the same drug as human dosage forms, some veterinary preparation contain drugs that are not widely used in humans. ... Some types of dosage forms are suitable for used in humans and certain animal species. They include parenteral solution; conventional tablets and capsules; oral solution and suspensions" [RAM1].

Then, like many other drugs, ivermectin is not only a drug "para vacas". The highlight of elcomercio.pe is therefore misleading. In any case, we find there a discussion about the different formulations.

“[La presentación para animales] podría tener ivermectina como principio activo, pero no se sabe qué más tiene. Esos otros componentes son los que pueden producir efectos no deseados”, explica Alfonso Zavaleta, profesor de Farmacia y Bioquímica de la Universidad Peruana Cayetano Heredia (UPCH). ... El modo de aplicación en humanos es oral, mientras que en los animales es intramuscular. ... Ricardo Grandez, profesor de la Facultad de Medicina Veterinaria y Zootecnia de la UPCH, alerta que si se administra esta droga por vía subcutánea e intramuscular y “se aplica inadecuadamente, puede producir necrosis en la zona de aplicación”. “La presentación inyectable [usada en animales] es de larga duración, tiene sustancias que liberan lentamente el principio activo. Algunos de estos productos podrían generar reacciones en algunos individuos o en todos los individuos".

Actually, for animals too, it is necessary to be careful and in fact, it is told "Dosis y vía de administración: ... **Vía subcutánea (S. C.) únicamente**"., as at the web page of this company https://www.vecol.com.co/productos/veterinaria/antiparasitarios/ivermectina-1, http://archive.is/YAEVk . See also https://www.ema.europa.eu/en/documents/referral/bovimectin-injection-article-33-referral-annex-i-

ii-iii_it.pdf . For veterinary use, subcutaneous injections[2] are the proper route of administration for aqueous solutions, as we will see in the next section. Novel oil formulations can be used for intramuscular injection too. Let us add also that it is true that ivermectin for humans is in the form of tablets, but we have case reports about the use of subcutaneous ivermectin too, as a safe salvage therapy [PAC1],[BAR1].

11 - Stabilized aqueous formulation

Gustavo Elera tells that the drug for veterinary use is "Ivermectina más agua y punto". Of course, as soon as we can read the report that he promised we will know the specific drug, the dosage, and the route of administration. However, we have to note the following. In Ref. [KSH1], which is discussing about ivermectin for veterinary use, it is told that "Ivermectin is generally insoluble and unstable in aqueous preparations. Hence, to overcome the problem of poor water solubility and obtain a stable injectable formulation of ivermectin, several commercial preparations have been developed which use organic solvents as vehicles". High concentrations of organic solvents have been reported to induce significant side effects [DON1], and pain and inflammation at the injection site were commonly observed side effects of commercial ivermectin preparations [FRO1]. "The commercially available ivermectin preparations employ different vehicles that help in stabilizing the compound".

Table 1 of [KSH1] is giving details. One of the formulations, **for parenteral and oral routes of administration**, is the following. "**Stabilized aqueous formulation** containing 0.1-7.5% w/v ivermectin (Parenteral administration) with other components such as surface active agent – 0.5-2.5% (polyoxyethylene sorbitan monoisostearate, polyoxyethylene sorbitan monostearate, and polysorbate 80). Cosolvent – 10-60% (glycerol formal, glycerin, and polyethylene glycol) and Substrate – 1-5% w/v (benzyl alcohol, lidocaine, parabens, and choline)". The solubilization of ivermectin in water is described in the patent (Inventors Pak-Kan A. Lo , James B. Williams, Merck and Co Inc), https://patents.google.com/patent/US4389397A/en . Abstract: "Ivermectin, an antiparasitic agent which is insoluble and unstable in water, is solubilized by the formation of colloidal particles, called micelles, with surface active agents as solubilizers and stabilized by using cosolvents and/or appropriate substrates in the aqueous formulation. The liquid formulations are suitable for use as parenteral or oral administration for the treatment of parasitic infections".

In [KSH1], among the several formulations for veterinary use, in the Table 1, we can find also the following: "Subcutaneous and intramuscular administration of a novel oil-based formulation of ivermectin was found to be superior to the commercially available standard preparation" [LIF1].

12 - "There are no parenteral antihelminthic drugs licensed for use in humans"

Since we are talking about ivermectin for veterinary use by means of a parenteral route of administration, we have also to add an important observation. In [MAR1], it is told that "There are no parenteral antihelminthic[3] drugs licensed for use in humans. [The authors of [MAR1]] report the successful treatment of disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin in a patient presenting with severe malabsorption and paralytic ileus. To [authors'] knowledge, ivermectin levels are reported for the first time in this situation". The year of publication of the article is 2005. In [ROG1], a book of 2010, it is stressed that patients "who are unable to absorb oral therapy present a difficult challenge as no parental preparations" of ivermectin are licensed for use in human. However, parenteral ivermectin exists and it is that for animals.

2 Subcutaneous and intramuscular injections are different techniques of injection.

3 Anthelmintics or antihelminthics are a group of antiparasitic drugs that expel parasitic worms and other internal parasites from the body by either stunning or killing them and without causing significant damage to the host.

The same, that is that "At present there are no parenteral anthelminthics licensed for use in humans", is also told in [BAR1], an article published in 2016. And in 2020, "Regarding the treatment, oral ivermectin is recommended for uncomplicated strongyloidiasis and is usually well-tolerated with a higher cure rate than with albendazole. In patients with hyperinfection, and no available oral route, therapeutic options are limited. No parenteral anti-helminthic drugs are licensed for use in humans, but parenteral ivermectin is used in veterinary medicine. Although drug-related toxicity, parenteral ivermectin has been used in humans as rescue therapy, appearing to be effective and safe" ([CIP1], and references therein).

It seems to me that the only parenteral ivermectin is that for veterinary use. The use of it in rescue therapy is effective and safe, according to publications. If this ivermectin can be the proper bullet for Sars-Cov-2, why not use it?

13 - News propagation

As we have seen, in the region of Iquitos, Peru, physicians in their clinics used, under their control, ivermectin. However, there were also some volunteers, in particular an evangelical group, that treated people having Covid-19 symptoms, with ivermectin for veterinary use.

"Un grupo evangélico peruano inyecta un medicamento veterinario a miles de personas para la covid-19". This is the title of an article in El Pais that started a sequence of news. "En Nauta, al menos 5.000 personas la han recibido [ivermectin]", cuenta Leonardo Tello, director de Radio Ucamara, la principal emisora de la ciudad ubicada a dos horas de la capital de la región, Iquitos". https://elpais.com/sociedad/2020-06-19/un-grupo-evangelico-peruano-inyecta-un-medicamento-veterinario-a-miles-de-personas.html dated 19 June 2020, archived http://archive.is/l4IhL .

"Tello cuenta que muchas personas sintieron el aceleramiento del corazón tras recibir la inyección. "Ha sido horroroso el efecto secundario", relata. El director de Radio Ucamara explica que algunos pastores evangélicos de Loreto han vinculado al nuevo coronavirus con el demonio y el fin del mundo, ofreciendo esas inyecciones "como una salvación". El Pais continues explaining that "En la comunidad de Cuninico, donde gran parte de la población tenía síntomas de la covid-19, el técnico del módulo de salud ... dijo a los voluntarios de las denominadas Misiones Evangélicas de la Amazonía, que ya no necesitaban la "vacuna" porque la mayoría de personas se estaba cuidando con la medicina tradicional, con plantas. Sin embargo, los enviados por el grupo evangélico decidieron administrar la ivermectina veterinaria. "La explicación de los voluntarios fue clara y directa de que está aprobado mediante una ley, y que es un tratamiento animal que da resultados positivos como vacuna", refirió el apu –jefe indígena– de Cuninico, Wadson Trujillo Acosta. "Dijeron que lo están haciendo a nivel nacional y también en Nauta, y alertaron de los efectos secundarios como la diarrea. A algunas personas sí les produjo esa reacción", describió".

Adverse effects were observed, and this is due to the dose of the drug. Ivermectin is safe, if used in the proper manner, under the control of a physician. For the side effects of accidental self-injection and ingestions of injectable solutions, see please what is reported in the web page on ivermectin at http://www.inchem.org/documents/pims/pharm/ivermect.htm archived http://archive.is/awBXE .

In any case, it is clear from El Pais that Tello and Acosta are giving two different versions, and that the behaviour of the evangelical group (or better, of some of the members of the group) was wrong.

Let us see how the SUN reduces the text: https://www.thesun.co.uk/news/11934870/sick-amazon-evangelicals-animal-drug-coronavirus-ivermectin/ archived http://archive.is/IIxsF

"He [Tello] said that many of those who had received the treatment had suffered an increase in their heart rate whilst others have warned of diarrhoea as a side effect." The SUN is reporting only what was told by Tello. From the SUN, we can see a further propagation in Italy. The

information was proposed by the Messaggero in the following article https://www.ilmessaggero.it/mondo/coronavirus_farmaco_animali_amazzonia_indigeni_ultime_notizie_24_giugno_2020-5307039.html , dated 24 June 2020, archived http://archive.is/3wAic in the following manner: "Leonardo Tello, direttore della stazione radio locale Radio Ucamara, racconta: «Gli effetti collaterali sono stati terribili: attacchi cardiaci, diarrea e molto altro»." That is: Leonardo Tello, director of the local radio station Radio Ucamara, says: «The side effects were terrible: heart attacks, diarrhea and much more».

This is not what Tello told to El Pais, and it is also quite different from what is told in the SUN. Nobody died after having received the drug. And this is clear form the news in El Pais.

14 - Discussion in TrialSite - A Health Movement

An interesting discussion is given in the article "How a Grassroots Health Movement Led to Acceptance of Ivermectin as a COVID-19 Therapy in Peru", https://www.trialsitenews.com/how-a-grass-roots-health-movement-led-to-acceptance-of-ivermectin-as-a-covid-19-therapy-in-peru/ , 12 June 2020, archived http://archive.is/e9t8k - The discussion is published in TrialSite News, a digital media dedicated to the coverage of clinical research and clinical trials, investigators and pharma. A section is devoted to Ivermectin. Here the link https://www.trialsitenews.com/category/ivermectin/ .

"Perhaps Peru is the epicentre of the movement for off-label use of Ivermectin to treat COVID-19 patients. The doctors there swear by it. In fact, some of them curse the government for not embracing the anti-parasite drug sooner as they believe more lives could have been saved. ... This grassroots medical movement for Ivermectin as a treatment for COVID-19 in many ways has been driven out of Peru as the story continues to unfold".

The web page tells that "For many weeks now, TrialSite News researchers heard a greater number of stories about the use of Ivermectin in both Bolivia and Peru". And also "TrialSite News has interviewed doctors around the world using the anti-parasitic drug to treat COVID-19 with significant success. ... an informal network of many doctors around Peru drove a kind of community movement to use the medicine to treat COVID-19. The government came to the conclusion that a sufficient number of experts in that country had formed a consensus that couldn't be ignored".

TrialSite News tells that university-based documents exist, "floating around in Peru that may have led to the off-label use and, ultimately, the approval". A title is given "Therapeutic Plan that includes Ivermectin in the First Line of Action" (see https://archive.vn/aCprF). To my best knowledge, no document is available in English. Gustavo A. Aguirre-Chang seems to be the author of the document entitled "INCLUSIÓN DE LA IVERMECTINA EN LA PRIMERA LÍNEA DE ACCIÓN TERAPÉUTICA PARA COVID-19. Se reporta una muy significativa disminución de la Tasa de Letalidad con su uso". Lima, Perú. 2 de Mayo del 2020. Available at https://megalabs.global/ - http://archive.is/x12Co . In the paper, the author is telling that "Por su parte, en República Dominicana, el Médico Neumólogo J. Tavares reporta que va tratando 247 pacientes con Ivermectina con respuesta favorable en todos los casos y no ha manifestado ningún caso fatal. De manera similar, a nivel local, si bien a la fecha aún no son muchos los casos documentados, la Tasa de Letalidad viene siendo 0% y además se observa que en el 100% de los casos tratados con Ivermectina se presenta una mejoría de la enfermedad y resolución de la fiebre dentro de las 48 horas de iniciado el tratamiento". Aguirre-Chang is detailing of 82 cases in Peru[4].

The TrialSite is also telling that Gustavo A. Aguirre-Chang, in mid May, commented in a Reddit group "that his group had treated 39 COVID-19 cases and that the Ivermectin regimen was quite

4 Aguirre-Chang is also reporting the interest of MedinCell for an injectable formulation of ivermectin, see https://www.trialsitenews.com/medincell-continues-its-investigational-pursuit-of-ivermectin-targeting-covid-19-patients/

successful for “those who complete the indicated treatment and undergo medical follow-up.” Dr. Aguirre-Chan reported that 1) patients with the disease were showing improvement within 2 and 3 days of starting treatment (100% of the 36); 2) fever resolution rate at 36 hours of taking ivermectin was at 94% and 3) resolution rate of dyspnea (difficulty breathing) at 72 hours was 86%."

Let us continue with the discussion in TrialSite. In Peru, "Doctors went about using Ivermectin and reporting on positive results to colleagues. Conservative forces there resisted noting, after all, this drug was for animals". "For Animals: Humans Need Not Try. ... the first line of defense against this drug, at least in the developed “first world,” was that Ivermectin was an “animal drug.” This sort of bias was evidenced clearly by the FDA’s Ivermectin warning. Titled “FAQ : COVID-19 and Ivermectin Intended for Animals,” the FDA took overt advantage of a loaded headline to convey an underlying point. ... But did they think anyone would take them seriously? But it was Created for Humans. In reality, Ivermectin was in fact created for humans. In Peru, doctors are treating COVID-19 patients with one drop every 24 hours for two days and many physicians report within a month they see patients fully recovered". *We have discussed before the formulations for humans and veterinarian use.*

TrialSite tells that "Prominent researchers and industry observers were obviously skeptical and downplayed the Monash findings[5], arguing that studies in humans weren’t feasible due to dosage and other factors". *This is not ture. As we have seen, many scientists and physicians are running 33 clinical trials with ivermectin.* TrialSite continues: "However, in nations that struggle with poverty and lack of access to more expensive drugs, such as remdesivir, physicians had to chart their own course. Hence, dozens if not hundreds of doctors around the world are prescribing ivermectin in COVID-19 patients; Peru perhaps can be considered the epicentre of that movement. TrialSite News has interviewed a handful of these doctors and they all report the same thing: that the anti-parasite drug ... actually works better than remdesivir. This finding is heard from doctors all over the world; TrialSite News has interviewed physicians in Bangladesh, France, India, Brazil and the United States not to mention Peru, Bolivia and Mexico. ... TrialSite News recently interviewed a contact in Peru, a PhD in Public Administration and Computer Science, that happens to be active in the Ivermectin movement there. He reports that in the city of Iquitos, a place known for scary tropical diseases, the widespread use of Ivermectin has led to a steep drop in the number COVID-19 cases".

As we have seen, we can find news telling that there is a large use in Peru of ivermectin. In the TrialSite it is stressed that the use of this drug is linked to a health movement, which has government support. When compared to the number of physicians in the world, the "dozens if not hundreds of doctors around the world" is a small number, but it important to know, when possible, their experiences in specific reports, in particular for the case of Iquitos.

15 - Further news until 20 July and a report from Dr. T. Alam

Trafficking drugs: a problem related to pandemic. SANTA CRUZ - Arrestan a dos personas por venta de ivermectina con precio sextuplicado - 29 June 2020 - http://archive.vn/GWW7f and also Ivermectin trafficking - "Dois homens são flagrados com 250 caixas de ivermectina contrabandeada da Bolívia em MT [Mato Grosso]; remédio é usado contra Covid-19 - Além de ivermectina, eles também contrabandearam 25 caixas de levofloxacino hemi- hidrato, nove caixas de Paracetamol e 14 caixas de Ibuprofeno. Toda a mercadoria está avaliada em R$ 8 mil. - 29/06/2020 10h51 - http://archive.vn/K4pLG

The Gorvernor of **Mato Grosso** - “Não tomei cloroquina. Nada contra, mas ... ”. O governador afirmou que fez uso de dois comprimidos de Ivermectina por um dia. O remédio é um anti-

5 That is, the results reported in [CAL1].

helmíntico (vermífugo), que em estudo in vitro teria demonstrado capacidade de reduzir a duplicação do vírus e impedir a entrada dele nas células. No entanto, poucas evidências demonstram sua eficácia". 09/06/2020 - http://archive.vn/sHWX5

Once more we find - On Jul 7, 2020 - "Animal products not intended for COVID-19 treatment" - https://www.kmaland.com/ag/animal-products-not-intended-for-covid-19-treatment/article_a7e78cdd-c7df-572c-8a95-2f1194761e52.html - archived http://archive.vn/aWjsQ - "As the public became aware of the research paper there were growing concerns about people wanting ivermectin to treat COVID-19 -- and self-medicating by taking ivermectin products intended for animals".

"Latin America is battling some of the world's most devastating coronavirus outbreaks, and is also facing the scourge of fake cures and unproven treatments promoted on social media across the region." 12 July 2020 - https://www.bbc.com/news/53361876 - "Along with many other drugs, ivermectin's effectiveness against Covid is being evaluated in clinical trials. But the PAHO has said studies so far "were found to have a high risk of bias, very low certainty of the evidence, and that the existing evidence is insufficient to draw a conclusion on benefits and harms. Ivermectin "is incorrectly being used for the treatment of Covid-19" says the PAHO, "without any scientific evidence of its efficacy and safety for the treatment of this disease". Despite this, health officials in Peru, Bolivia and parts of Brazil have endorsed and administered the drug - and it has been widely sold".

In the Section 6, we have already seen that Dr. Alam reported of results on the use of Ivermectin. Here further news - Dr Tarek Alam: Unleashing the potential of Ivermectin - UNB NEWS DHAKA PUBLISH- JULY 19, 2020, 12:22 PM - https://unb.com.bd/category/special/dr-tarek-alam-unleashing-the-potential-of-ivermectin/54846 - archived http://archive.is/XFQLe . For Covid-19, as we have previously seen, it was used a combination of "two cheap, easily available drugs". The article tells that the combination of drugs eas success in reducing the viral load and restricting the severity of disease.

"Apparently 98 percent of Covid-19 patients get cured with the combined use of anti-parasitic drug Ivermectin and antibiotic Doxycycline within 4-14 days, said Dr Tarek Alam, the renowned doctor who has been leading a team of BMC physicians in a study during the course of treating patients at the hospital attached to BMC. They recently reported tremendous success with the two-drug combination treatment against the virus during its study that started on April 15 last. “What we’ve found is that it’s better to use the two drugs as soon as possible after a person is tested positive or symptom is seen,” Dr Alam said in a virtual interview with UNB. “We used the drugs within 5-6 days on all patients (and almost all got cured). Actually it needs to conduct further study whether these (drugs) will be effective in case of use after the time,” he said, adding that so far the drugs have been used on “some 400-500 Covid patients” since April. But only “4-5 patients” having diabetes and heart problems or who delayed in getting the treatment needed to go to Intensive Care Unit (ICU). And two patients died despite being administered with Remdesivir and plasma therapy".

16 - Not all doctors use ivermectin

Not all the physicians are using or suggesting the use of ivermectin and hydroxychloroquine.

Let us go back to news from Peru. As we have previously seen, there is a health movement - as defined by TrialSite - in Peru, driven by physicians. From news we know that it is supported by the Government. However, some "Médicos peruanos piden detener el uso de la hidroxicloroquina e ivermectina en pacientes COVID-19" - 30 June 2020 ---------- https://larepublica.pe/sociedad/2020/06/29/coronavirus-peru-medicos-piden-detener-el-uso-de-la-hidroxicloroquina-e-ivermectina-en-pacientes-covid-19-carta-abierta-al-minsa/ , http://archive.vn/YbsuR - "Los doctores ... se mostraron preocupados por el uso de la hidroxicloroquina y la ivermectina que

impulsan las autoridades sanitarias en el país como tratamiento para la COVID-19". This is important. And also here https://www.estrelladigital.es/articulo/america/medicos-peruanos-piden-detener-uso-hidroxicloroquina-ivermectina-pacientes-covid-19/20200630102348422556.html archived http://archive.is/7UAD0 - "Los doctores Julio Chirinos, médico internista y cardiólogo (Universidad de Pensilvania), Vicente Corrales, médico internista e infectólogo (The Ottawa Hospital) y Germán Málaga, médico internista (Universidad Peruana Cayetano Heredia) se mostraron preocupados por el uso de la hidroxicloroquina y la ivermectina que impulsan las autoridades sanitarias en el país como tratamiento para la COVID-19. Los especialistas precisaron que ambos medicamentos son recomendados por el Minsa, pero numerosos estudios de importante credibilidad han reportado una falta de efectividad por parte de los fármacos cuando se aplican con la finalidad de tratar la COVID-19. Tras haber difundido la misiva el pasado 17 de junio, el grupo de galenos no ha obtenido una respuesta concreta, pero confía en que establecerá un diálogo oficial y sincero con los representantes de la cartera ministerial".

The Carta Abiertas is available at https://it.scribd.com/document/466257700/Carta-Abiertas-sobre-las-recomendaciones-del-MINSA-sobre-el-tratamiento-con-medicamentos-de-COVID-19-en-el-Peru#from_embed

17 - US monopolises Remdesivir

A very interesting discussion - **US monopolises COVID-19 treatment drug**. Which countries are missing out? - https://www.sbs.com.au/news/dateline/us-monopolises-covid-19-treatment-drug-which-countries-are-missing-out (web site visited 8 July 2029) - "The US has bought most of the globes' supply of remdesivir, an antiviral drug that could help treat COVID-19. The Trump administration has purchased more than 500,000 doses of remdesivir -- that's almost all of the world's supply for the next three months. The antiviral could help treat COVID-19 by improving the recovery time for hospitalised patients. It is not a cure". About Peru it is told - "Unless the country has its own stocks of remdesivir, it's unlikely Peru will have access to the drug in the next months. Last month, officials spruiked ivermectin, an antiparasitic commonly used in tropical medicine, as a COVID-19 treatment. The Pan American Health Organization, a regional office of the World Health Organization, has issued a statement warning against the use of ivermectin to treat COVID-19. The Peruvian Ministry of Health also promoted hydroxychloroquine has an effective treatment". If US possesses Remdesivir - if it is useful or not is another problem - what can the rest of humankind use?

18 - From Bulgaria, India and Brazil

On July 6, 2020 - "**Bulgarian Team Close to Finding a Treatment for COVID-19**" - https://www.novinite.com/articles/205180/Bulgarian+Team+Close+to+Finding+a+Treatment+for+COVID-19 , archived http://archive.vn/EBN7l - "In May, a clinical trial with the drug Ivermectin was launched in Bulgaria. The team is Bulgarian, and so is the manufacturing company. So far, 30 patients have been recruited for it. The clinical trial is being conducted in 9 hospitals in Bulgaria," Kirilov [director of Bulgarian Drug Agency] said. "Bulgaria was the first country in the EU to launch such a clinical trial, followed by Spain, Brazil and the United States. We hope to have primary results by the end of the month." "

7 July 2020 - "Grupo de 478 médicos do DF elabora protocolo para tratamento precoce da Covid-19 Documento com sugestão de medicamentos foi entregue à Secretaria de Saúde e inclui hidroxicloroquina e ivermectina" - https://www.metropoles.com/colunas-blogs/grande-angular/grupo-de-478-medicos-do-df-elabora-protocolo-para-tratamento-precoce-da-covid-19 - "Um grupo com 478 médicos da rede pública e privada do Distrito Federal se reuniu para elaborar e propor um protocolo

de tratamento precoce de pacientes infectados pelo novo coronavírus. Na lista de medicamentos a serem ofertados aos doentes está a hidroxicloroquina, além do vermífugo ivermectina e do antibiótico azitromicina. ... “Temos medicações que estão disponíveis, são de baixo custo, baixa toxicidade e que podem ser prescritas pelos médicos no primeiro estágio da Covid-19 para diminuir a replicação viral. É claro que todos nós gostaríamos de trabalhar com base em estudos científicos sólidos. Mas vivemos uma situação atípica, de guerra. O novo coronavírus não está na bula, porque ele não existia quando os medicamentos foram criados”, explica a otorrinolaringologista Carine Petry, uma das integrantes do grupo.

On 3 July 2020 - https://www.nationalheraldindia.com/india/delhis-ln-hospital-to-discontinue-anti-viral-drug-favipiravir-for-covid-19-treatment - "**Delhi’s LN Hospital** decides against using anti-viral drug Favipiravir for COVID-19 treatment. The LN Hospital committee approved the use of three other drugs – Remdesivir, Tocilizumab and Ivermectin – and plasma therapy in the treatment of COVID-19. ... The committee acknowledges that though Ivermectin has shown only laboratory evidence as an inhibitor of the COVID-19 causative virus, it should be considered for hospitalised patients because it is a cheap drug, easily available and is known to be safer than other drugs. Its side effects are only fever and skin rash. This drug, which has been approved by the US FDA for parasitic infections, could help in limiting the viral load and prevent severe disease progression, according to the doctors at LN Hospital".

19 - a - SSRN or Antiviral Research

As we have previously seen, a working paper was published in SSRN and then retracted by the authors. For this reason, I have not discussed it above. In Google Scholar it appears as "Ivermectin in COVID-19 related critical illness, SSRN 3570270, 2020 - papers.ssrn.com - "A pre-clinical study, demonstrated that ivermectin, FDA approved as an anti-parasitic agent with an established safety profile …". I repeat, the paper was withdrawn from SSRN by the authors. However, we have to mention SSRN for the following news.

5 July 2020 - "San Marcos: tratamiento con ivermectina tiene menos tasa de letalidad" - https://www.radionacional.com.pe/noticias/locales/san-marcos-tratamiento-con-ivermectina-tiene-menos-tasa-de-letalidad - La tasa de letalidad en los pacientes que usaron ivermectina en su tratamiento contra el covid-19 fue 6.1 veces menor en comparación con los pacientes que no lo usaron, según un estudio realizado por el médico egresado de la Universidad Nacional Mayor de San Marcos (UNMSM), Gustavo Aguirre". The same in http://laindustria.pe/nota/16663-tratamiento-con-ivermectina-tiene-menos-tasa-de-letalidad and in https://libero.pe/ocio/1570733-coronavirus-peru-estudio-revela-100-pacientes-covid-19-trato-ivermectina-mejoraron-minsa - After two days - **7 July 2020** - "Ivermectina y COVID-19: los errores y mentiras detrás de un “estudio” viral de dudosa calidad" - https://elcomercio.pe/tecnologia/ciencias/ivermectina-covid-19-coronavirus-los-errores-y-mentiras-detras-de-un-estudio-viral-de-dudosa-calidad-noticia/ .

The elcomercio.pe is not giving links to documents. However, it seems - due to published screenshot - it is the same of that at http://archive.is/x12Co). The elcomercio.pe tells the research "había sido publicada en Antiviral Research. El Comercio comprobó que el estudio no figura en esta revista médica internacional". In the document, Dr. Aguirre Chang does not tell that his work has been published in the Antiviral Research journal. The document seems being a working paper. In any case, **let us stress that the paper published in the Antiviral Research journal is Ref. [CAL1]**. In Aguirre's working paper (http://archive.is/x12Co), there was a mistake in abstract and text. It was told that the document in SSRN has been placed on the web site of Antiviral Research[6].

6 Aguirre-Chang has revised the text. The new version is at https://www.researchgate.net/publication/342466502_INCLUSION_DE_LA_IVERMECTINA_EN_LA_PRIMERA_LINEA_DE_ACCION_TERAPEUTICA_PARA_COVID-19_Se_reporta_una_muy_significativa_disminucion_de_la_Tasa_de_Letalidad_con_su_uso - See also

This mistake raised confusion, enhanced by elcomercio in the news. *SSRN working paper is no more available, because it has been withdrawn. Let us forget it, but ask for results obtained by physicians that used ivermectin.*

It seems to me that Aguirre's document to consider is [AGU1]. "RESULTADOS: Se trataron con Ivermectina 33 pacientes adultos con Síntomas Persistentes de COVID-19. En el 97% de los 33 pacientes tratados con Ivermectina se encontró mejoría clínica después de las 2 dosis de Ivermectina. La mejoría clínica fue total en el 87.9% de los pacientes después de la 2da dosis de Ivermectina. En el 12.1% de los pacientes se requirió dar más días de tratamiento con Ivermectina, pero con esto se logró una mejoría clínica y remisión de los síntomas en el 100% de los casos. CONCLUSIÓN: El resultado del presente estudio encuentra efectividad del tratamiento con Ivermectina de los pacientes con Síntomas Persistentes de COVID-19, observándose una mejoría clínica en el 100% de los casos".

As we have previously told, Dr. Aguirre is reporting, in the previously mentioned documents, of several cases in Peru. We are also waiting for the report of Dr. Elera, as he promised to elcomecio.pe (see the news previously mentioning him) and from all the other doctors engaged in the Health Movement. The reason is the following: to test the efficacy of ivermectin.

19 - b - Un breve commento sul documento in SSRN, ora ritirato

Il lavoro pubblicato su SSRN (16 Aprile) ed ora ritirato, autori con affiliazioni negli Stati Uniti, sosteneva l'efficacia dell'ivermectina in pazienti ricoverati per Covid-19 in terapia intensiva. Lo studio era retrospettivo tra il primo Gennaio del 2020 ed il 31 Marzo del 2020. Si dice che si sono analizzati in Europa 107+120=227 casi. Guardate i dati delle vittime in Italia, Francia, Spagna, Regno Unito. Vi sembra possibile che in Europa, avendo ottenuto in qualche caso buoni risultati con l'ivermectina, essa non sia stata usata per evitare le stragi da Covid-19? Pensate a questo. In ogni caso, i dati non potevano provenire dall'Italia, dove, secondo le notizie, solo da Aprile, nello specifico l'8 Aprile, si sarebbe autorizzato l'uso dell'ivemectina in test clinici, a seguito della ricerca pubblicata in [CAL1].

The work published on SSRN (April 16) and now withdrawn, authors with affiliations in the United States, supported the efficacy of ivermectin for patients in hospital intensive care units for Covid-19. The study was retrospective, between 1 January 2020 and 31 March 2020. 107 + 120 = 227 cases are said to have been analysed as coming from Europe. Look at the data of the victims in Italy, France, Spain, and in the United Kingdom. Does it seem possible to you that in Europe, having in some cases obtained good results with ivermectin, it has not been used to avoid the massacres of Covid-19? Think about this. In any case, data could not come from Italy, where, according to the news, the use of ivermectin in clinical trials was authorized just from April, the 8 of April, after the results published in [CAL1].

In my opinion, but I have to check it, ivermectin was not used in Europe to treat Covid-19 from the first of January to the end of March, not used at all. Therefore, I want to tell once more to forget this damned SSRN preprint. There is no point in the news continuing to bring it up. Let us concentrate on the results obtained by physicians who are using ivermectin.

http://archive.is/vwHOs

20 - Rare symptoms of Covid-19 - a report from Dr. E. Durand, Lima

As previously told, ivermectin has a large use in Peru. This fact gives the possibility to receive specific reports from physicians about the efficacy of it in the treatment of Covid-19 patients. At the same time, these reports can evidence new facts about the disease and consequently improve the knowledge about the effects of Sars-Cov-2 on human bodies. Here in the following an important example.

"Perú: médico que ha tratado más de 3,000 pacientes de coronavirus reporta raro síntoma en mujeres y confirma eficacia de la ivermectina" - Lima, Peru - 27 Julio 2020 - https://www.connuestroperu.com/ciencia-y-tecnologia/salud/66246-peru-medico-que-ha-tratado-mas-de-3-000-pacientes-de-coronavirus-reporta-raro-sintoma-en-mujeres-y-confirma-eficacia-de-la-ivermectina ------- archived http://archive.is/YKGWv

"Un síntoma raro ha sido observado en pocos pacientes contagiados con el coronavirus COVID-19 en Lima y se presenta en mujeres. El doctor Eduardo Durand, quien ha atendido en la práctica privada a más 3,000 pacientes con coronavirus, reporta síntomas raros en pocos pacientes. Consisten en debilidad de los miembros inferiores acompañada de dolor lumbar, que hasta el momento ha observado en cinco pacientes mujeres. El galeno, de Consultorios Médicos San Luis, Lima, señala que junto con estos síntomas, las pacientes presentaron también dolor de oído, sensación de frío en la espalda y ardor en los ojos. Las pacientes, de edades de 30 a 65 años, pasaron por análisis de prueba rápida y radiografía de tórax. Todas recibieron tratamiento que resultó satisfactorio con su recuperación gradual en un promedio de diez días."

Rare symptoms have been observed in few Covid-19 patients in Lima and occurred in women. Dr. Eduardo Durand, who has treated more than 3,000 patients with coronavirus in his private practice, reports about them. The symptoms consist of weakness of the lower limbs accompanied by low back pain, which have been observed in five female patients so far. Dr. Durand, Consultorios Médicos San Luis, Lima, pointed out that, along with these symptoms, the patients also presented ear pain, a feeling of cold in the back and burning eyes. The patients, aged 30 to 65 years, underwent rapid test analysis and chest radiography. They all received a treatment that was effective for their gradual recovery in an average of ten days.

The reports continues about ivermectin. "Eficacia de la ivermectina - El doctor Durand destaca la eficacia de la ivermectina y considera a este fármaco un gran y rápido aliado, y destaca su fácil accesibilidad. Tanto las pacientes con estos síntomas raros, como más de tres mil pacientes, superaron la enfermedad en estados leve a moderado, a los cuales prescribió de una a dos gotas de ivermectina por kilo de peso, según el grado de complicación, sin haberse observado efectos adversos, salvo un caso de diarrea. Recomendación a la ciudadanía ante el aumento de contagios y fallecimientos. El galeno recomienda a la ciudadanía estar alerta a los síntomas de esta enfermedad y no dejar que avance, pues puede requerir hospitalización en un momento en que los hospitales están saturados. De igual forma, no deje pasar el tiempo con calmantes. Indica que si en la zona en que se encuentra no hay pruebas de descarte, deje que con diagnóstico de síntomas su médico inicie el tratamiento, pues por televisión se ve a personas esperando días por la prueba sin inicio de tratamiento, con lo cual van camino al agravamiento porque es una enfermedad que avanza a gran velocidad."

Eduardo Durand highlights the efficacy of ivermectin and considers this drug a great and fast allied agent, of easily availability, against Covid-19. The patients with rare symptoms, such as his other Covid-19 patients - more than 3,000 -, overcame the disease in mild to moderate states. Ivermectin was prescribed according to the state of patient. Adverse effects have not been observed, except for a case of diarrhea. Actually, Dr. Durand recommends not letting the symptoms of the disease progress, in order to avoid hospitalization. In the case that it is not possible to test for Sars-Cov-2 infection, when symptoms are observed, it is better to ask a doctor for starting a treatment as soon

as possible to avoid the aggravation of the disease. Covid-19 is a disease that progresses rapidly.

The rare symptoms observed and reported by Dr. E. Durand, Consultorios Médicos San Luis, Lima, Peru, have to be added to the list of the neurological associations of the disease published in [ELL1].

21 - Making ivermectin for oral use (6mg/mL)

As we have discussed before (see Section 13), it happened that ivermectin for veterinary use had been injected in many persons with Covid-19. In fact, ivermectin for parenteral route of administration is existing only in the veterinary formulation. The use of this formulation in rescue therapy is effective and safe, according to publications. In fact, the drug for veterinary use **must** be safe, because accidental self-injection and ingestions are possible. See cases in http://archive.is/awBXE . Ivermectin is generally well tolerated. "Only side effects have been reported: itching, swollen lymph glands, dizziness, hypotension, fever, headache and myalgia. Side effects are more frequent and severe in patients with high microfilaria counts. Other persons at risk include veterinarians and farm workers involved in treating animals for worms and ectoparasites. Most cases reported involve accidental self-injection and some ingestions of injectable solutions. No human deaths have been reported".

However, some web sites of newspapers raised concerns about the use of ivermectin for parenteral route of administration, in particular elcomercio.pe as we have seen. On 28 June, the same web site gives the important news. https://elcomercio.pe/peru/coronavirus-peru-san-martin-essalud-moyobamba-comenzo-a-producir-ivermectina-con-capacidad-de-20-mil-dosis-mensuales-nnpp-noticia/ , we read that ivermectin for oral use is produced in a local hospital. "Una excelente noticia para la región San Martín dio a conocer EsSalud-Moyobamba, tras anunciar que viene produciendo ivermectina para el tratamiento de pacientes con COVID-19, a cargo del área de Farmacotecnia del Hospital II-1 Alto Mayo que está en capacidad de elaborar 20 mil dosis mensuales. ... Asimismo, la composición de ivermectina incluye alcohol etílico, propilenglicol, sorbitol e ivermectina de uso médico (sólido), y será suministrado bajo prescripción médica". The same, that is the production of ivermectin for oral use to treat Covid-19, is happening in other hospitals is Peru.

In fact, a document dated 23 June 2020 of the Peruvian Government exists which is giving the formulation. https://cdn.www.gob.pe/uploads/document/file/874053/RM_426-2020-MINSA.pdf

Ivermectina USP.....	0.6 g
Propilenglicol USP.....	70.0 mL
*Alcohol Etílico 96°.....	10.0 mL
Sorbitol 70%.....csp	100.0 mL

**En preparados para niños se debe reemplazar los 10 mL de Alcohol Etílico 96° por Propilenglicol*

Formulation from MINSA, Peru.

22 - Data

As we can appreciate in the news from Peru - and South-America, in general - it seems that a large use of ivermectin is and will be made for Covid-19. It is therefore clear that an efficacy of the drug can be easily evidenced by the numbers about new, active cases and victims in the country. In the plots given below, proposed by the www.worldometers.info for Peru, it is reasonable to imagine

that the curves, about new and active cases, and victims, can be influenced by any efficacy of the drug.

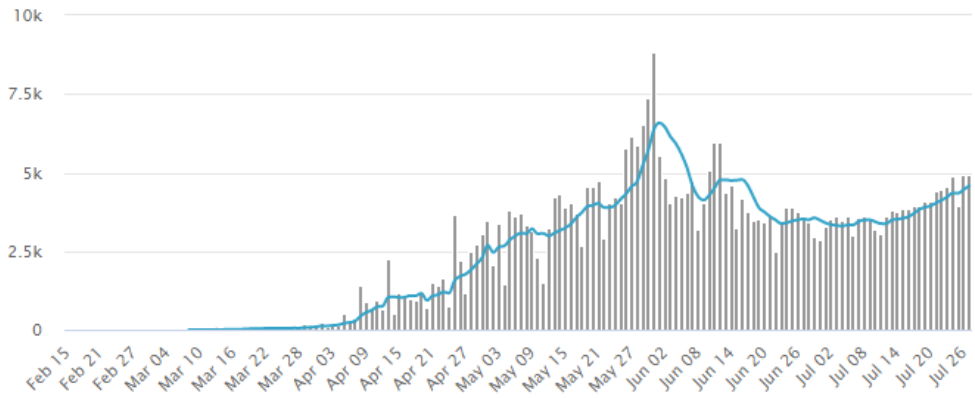

Fig.4 - Daily New Cases. The blue line represents a 7-days moving average.

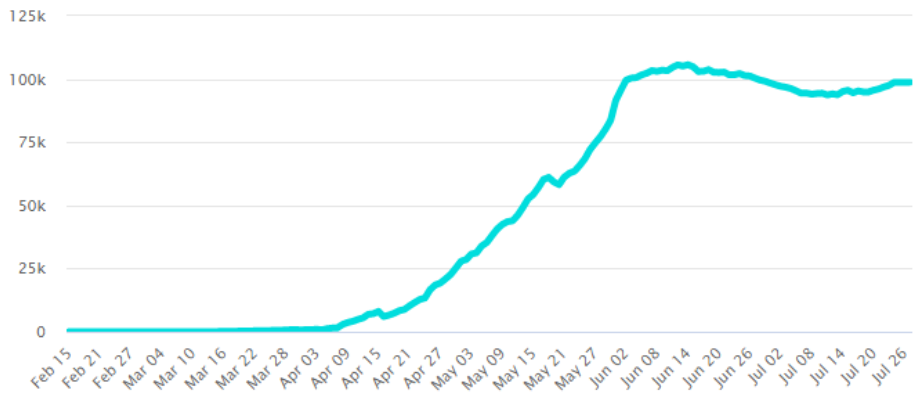

Fig.5 - Number of infected people (active cases).

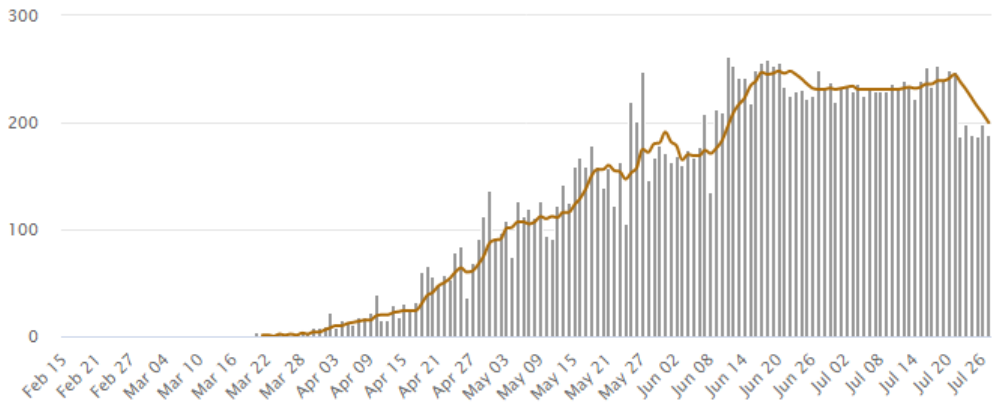

Fig.5 - Daily victims. Red line represents a 7-days moving average.

The data (15 February - 27 July, are a courtesy of worldometers.info, available at https://www.worldometers.info/coronavirus/country/peru.

The number of the daily cases is increasing, but the number of victims of the virus seems to have a decreasing trend in the last days of July.

Acknowledgement

I would like to offer my special thanks to Dr. Rocio Ferrel for her precious support on literature and news concerning Ivermectin.

Appendix A

Not only ivermectin is under investigation. 16 June 2020 - "Broad-Spectrum Antiparasitic Drug Ivermectin Could Help `Cure` COVID-19" is told" by https://www.hospimedica.com/covid-19/articles/294782974/broad-spectrum-antiparasitic-drug-ivermectin-could-help-cure-covid-19.html archived http://archive.vn/mOV0b - The article is reporting about the clinical trial led by Eli Schwartz, Sheba Medical Center (Tel Hashomer, Israel). But it is also telling the following. "Another anti-parasitic drug **niclosamide** tested on ferrets in a study by Daewoong Pharmaceutical Co., Ltd. (Seoul, Korea) was found to have eliminated the novel coronavirus from their lungs. According to Daewoong, its experimental anti-viral drug completely cleared up the disease in the lung tissues of ferrets and the company now plans to start human clinical trials in July with approval of the COVID-19 treatment drug expected by the end of this year". Niclosamide is nentioned in trial https://ClinicalTrials.gov/show/NCT04345419 .

In [XIN1], a study of possible drugs against Sars-Cov-2, it is told "Interestingly, three anti-parasitic drugs pyrvinium, ivermectin, and niclosamide were ranked among the top 30 predicted drugs. Both **ivermectin** and **niclosamide** were shown to inhibit the replication of SARS-CoV-2 in vitro (Caly et al. 2020; Jeon et al. 2020), and pyrvinium and niclosamide were shown to be effective against MERS-CoV and SARS-CoV (Shen et al. 2019; C.-J. Wu et al. 2004)".

In [KAN1], it is told: "**Niclosamide**: Another medication undergoing repurposing investigations for SARS-CoV-2 is niclosamide, an oral anthelmintic drug used worldwide at a single dose of 2 g/d. Niclosamide exerts anti-MERS activity, inhibits SARS-CoV replication and abolishes viral antigen synthesis in vitro, (Refs. 51,52 of [KAN1]) and therefore, is considered a possible treatment option. However, **it is cytotoxic** and has low absorption including low oral bioavailability (10%) and although efforts have been made to formulate derivatives to overcome these obstacles, its extensive clinical development as an antiviral agent may still be hindered. An interventional trial has been registered to evaluate the use ...". As we have told before, Ivermectin is safe.

See also Ref. [PAU1]: "Clinical trials on the repurposing of some **anthelmintics** (Nitazoxanide, NTZ; Ivermectin, IVT; Niclosamide, NCL) for COVID-19 seem to be based on in vitro data showing that these compounds inhibit replication of a variety of viruses in cell culture assays. NTZ, for instance, was active in cell culture assays against a broad range of influenza A and B, as well as other RNA and DNA viruses, such as RSV, parainfluenza, coronavirus, rotavirus, norovirus, hepatitis B and C viruses, dengue, yellow fever, Japanese encephalitis and HIV. Likewise, in in vitro tests, IVM inhibited the replication of a broad range of viruses (dengue, West Nile virus, HIV, simian SV-40, influenza and others) and strongly repressed SARS-CoV-2 virus replication in Vero-hSLAM cells. Also in in vitro assays, NCL proved to be a potent inhibitor (nanomolar to micromolar range) of replication of SARS-CoV, MERS-CoV, zika virus, hepatitis C virus and human adenovirus. NCL had been reported to be active (in vitro) against SARS-CoV at

concentrations as low as 1.56 µM in 2003". See also [JXU1] , [POO1].

APPENDIX B - Update of 8 September 2020

Now, it is time to consider if something new on the use of Ivermectin exists.

23 - Literature

When reporting the literature, I told that only scholarly articles with specific results and reporting on the treatment of Covid-19 patients, would be added. However, the publication of reviews and discussions of repurposing of Ivermectin continues. So here new articles (and also some lost in the first round, probably at the time not available from Google Scholar).

[KSH2]: It is a short review published on May 30, 2020, on the antiviral activity of Ivermectin. The authors conclude that " Ivermectin exerts broad-spectrum antiviral activity against several animal and human viruses, including both RNA and DNA viruses. - The antiviral potential of ivermectin against various viruses is mediated via the targeting of the following: importin α/β-mediated nuclear transport of HIV-1 integrase and NS5 polymerase; NS3 helicase; nuclear import of UL42; and nuclear localization signal-mediated nuclear import of Cap. - As SARS-CoV-2 is an RNA virus, the antiviral activity of ivermectin may be mediated through the inhibition of importin α/β-mediated nuclear transport of viral proteins. - The clinical efficacy and utility of ivermectin in SARS-CoV-2-infected patients are unpredictable at this stage, as we are dealing with a completely novel virus".

[SIN1] is a letter to the Editor, published on line Jue 4, 2020. The long letter starts from [CAL1], ending with this sentence. "The study provides baseline information of ivermectin against SARS-CoV-2 action only; therefore, there is a need of extensive analysis at preclinical level regarding efficacy and safety in the treatment of COVID-19 in different group of population before moving to clinical trials and off-label use".

[BAN1]: In it the authors "have fished and compiled the needed information on the drug, that will help readers and prospective investigators in having a quick overview. Though the primordial biological action of the drug is allosteric modulation of helminthic ion channel receptor, its in vitro activity against both RNA and DNA viruses is known for almost a decade. In the past two years, efficacy study in animal models of pseudorabies and zika virus was found to be favourable and unfavourable respectively. Only one clinical study evaluated the drug in dengue virus infection without any clinical efficacy. However, the proposed mechanism of drug action, by inhibiting the importin family of nucleus-cytoplasmic transporters along with favourable pharmacokinetics, warrants exploration of its role in COVID 19 through safely conducted clinical trials".

[RIC1]: "While the findings by Caly and colleagues provide some promise, several pharmacokinetic factors limit the immediate translation of their findings, and there is no evidence that the 5µM concentration of ivermectin used by Caly and colleagues in their in vitro SARS-CoV-2 experiment, can be achieved in vivo. ... Although high doses of ivermectin in adults or children are well tolerated, the clinical effects of ivermectin at a concentration of 5µM range are unknown and may be associated with toxicity. Consequently, ivermectin has in vitro activity against SARS-CoV-2, but this effect is **unlikely to be observed in vivo** using current dosing".

[DEC1]: A letter to the Editor, entitled "Continuous high-dose ivermectin appears to be safe in

patients with acute myelogenous leukemia and could inform clinical repurposing for COVID-19 infection".

[RAH1]: The reader caa find a "**Comparison of Viral Clearance between Ivermectin with Doxycycline and Hydroxychloroquine with Azithromycin in COVID-19 Patients**". "Viral clearance is 132 (66%) on day 5 and 167 (83.5%) on day 6. Among them 33(16.5%) remain PCR positive after 6th day of Ivermectin ingestion in Group A. Whereas there is154 (77.0%) viral clearance at 11th day and 163(81.5%) viral clearance at 12th day of Hydroxychloroquine ingestion in Group B. Among them 37 (18.5%) remain PCR positive after 12 day in group B. The P value is 0.000427 which is significant considering 5th day viral clearance of Ivermectin ingestion and 11th day of Hydroxychloroquine ingestion. But considering 6th day and 12th day the P-value is 0.59 which is not significant".

[RAH2]: We find a **"wake-up call" on re-purposive use of drugs**. "Meanwhile, Bangladesh National Guidelines on Clinical Management of Coronavirus Disease-2019 reviewed its medication list. People are using many drugs without any definite proof of benefit. So, high-powered, randomized, double-blind, placebo-controlled trials recruiting larger numbers of COVID-19 patients with different severity groups, is expected to provide a reliable statement in this issue. Till then, it would remain as a wake-up call towards the treating physicians to remain very much cautious in re-purposive use of drugs against COVID-19 and “do no harm” to the patients.

[TAR1]: We find in this reference a study concerning the **combination of Ivermectin and Doxycycline, to be evaluated therapeutically to treat COVID-19 patients**. "Methods: 100 COVID-19 patients were enrolled in this study with a predefined inclusion and exclusion criteria. RT- PCR of the SARS-CoV-2 will be done at designated government hospitals. The clinical features and response to treatment were noted according to a dedicated protocol. Results: In this study male and female were 64 and 36 respectively, the age ranged between 8 to 84 years. Retesting was done between 4 and 18 days of starting medication. All patients tested negative and their symptoms improved within 72 hours. There were no noticeable side effects. Conclusion: Combination of Ivermectin and doxycycline was found to be **very effective in viral clearance** in mild and moderately sick COVID-19 patients. Medical societies and institutions should undertake larger multi center studies to validate and recommend this combination therapy to include in national guidelines".

[WHP1]: "A group of senior doctors with vast clinical experience met on 19th July’20 under the aegis of Academy of Advanced Medical Education. **The panel looked at Ivermectin**, one of the old molecule and evaluated it's use in COVID 19 (Novel Coronavirus Disease 2019) management. After critical panel discussion, all the attending doctors came to a conclusion that Ivermectin can be a potential molecule for prophylaxis and treatment of people infected with Coronavirus, owing to its anti-viral properties coupled with effective cost, availability and good tolerability and safety".

[CNW1]: A remarkable discussion by Claire Njeri Wamae entitled "Mass Drug Administration and Worms Experience in Africa: Envisage Repurposing Ivermectin for SARS-COV-2". Incipit: "I have spent over 40 years studying parasitic worms and the drugs we use to treat them. With this background, I suggest that large-scale annual mass drug administration for preventive chemotherapy of neglected tropical diseases may be contributing to keeping COVID-19 cases in check and below projections in Africa".

[ALK1]: A work on the **combination azithromycin–ivermectin.** "Different experimental and approved drugs were tested for coronavirus infection disease (COVID-19) to detect effective one that attenuates or prevents the pathogenesis of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). Repurposing of old approved drugs with the potential arrhythmogenic effect such as chloroquine in COVID-19 may increase the risk of sudden cardiac death due to torsadogenic potential. The Food and Drug Administration approved the drugs, such as ivermectin, which can

kill SARS-CoV-2 within 48 h". et us remember that this is an in-vitro result. "Azithromycin augments the antiviral activity of chloroquine in COVID-19 with a high risk of morbidity and mortality through torsadogenic potential. There were no obvious interactions between ivermectin and azithromycin and without risk of torsadogenic effect despite the prolongation of QT by azithromycin. Therefore, azithromycin–ivermectin is regarded as an effectual combo for COVID-19 in elderly patients with underlying cardiac abnormalities".

[YAV1]: It is a review of antiviral treatment of COVID-19.

[REB1] is the reply to [CAR1]. [RAS1] is a view-point.

[KHA1]: "There are no approved drugs or vaccine. Ivermectin, an FDA-approved anti-parasitic, was shown to inhibit action against SARS-CoV-2 in vitro. Of the several drugs under investigation Ivermectin was shown to inhibit JEV by targeting its helicase. **To understand the mechanism of inhibition, we used an in silico structure-based screening of Ivermectin** and Ivermectin like drugs. The approach helped us in identifying Ivermectin and Nystatin as potential inhibitor of SARS-CoV2 helicase. Combined with the above results, known safety profiles for oral doses and its wide availability, Ivermectin warrants further investigation in clinical settings".

[MUD1]: It is a literature review. Scientia Pharmaceutia received the article on 20 July 2020., the revised version on 31 July 2020. It was published 17 August 2020.

[NGC1]: "This document sets out the **results of a study aimed at estimating the therapeutic efficacy of ivermectin** as an adjuvant in the treatment of COVID-19 patients treated at the Specialty Hospital Vida Mejor of the Institute of Social Security for Workers of the State of Chiapas, ISSTECH, Mexico. Ivermectin as an adjuvant in the treatment of COVID-19 patients is more effective (92%) outpatient patients. In critical hospitalized and severe hospitalized patients, ivermectin had a significant impact, both in improving patients' health and decreasing lethality". July 2020.

[VAS1]: The aim of the discussion is "Identificar evidências quanto ao enfoque profilático do **uso da nitazoxanida e ivermectina na COVID-19**. Métodos: Sumário de evidências com busca realizada na Pubmed. Resultados: Foram incluídos quatro artigos sobre nitazoxanida e 12 sobre ivermectina. Conclusões: Não existem estudos sobre o uso da nitazoxanida e ivermectina como uso profilático pré-exposição ao vírus. Para o uso profilático pós-exposição bem como para tratamento da COVID-19, a ivermectina e a nitazoxanida devem fazer parte de um protocolo de pesquisa com termo de consentimento. A dose da medicação deve ser levada em consideração, a dose aprovada atualmente não seria o suficiente para atuar na inibição viral".

Let me remember ***ChemRχiv, MedRχiv and Research Square preprints***

24 - Research Square is proposing a new approach

[CHA3] of 26 August 2020. The title is "**Nebulized ivermectin for COVID-19** and other respiratory diseases, a proof of concept, dose-ranging study in rats". From Abstract. "An ethanol-based ivermectin formulation was administered once to 14 rats using a nebulizer capable of delivering particles with alveolar deposition. ... Results: There were no relevant changes in behavior or body weight. There was a delayed elevation in muscle enzymes compatible with rhabdomyolysis, that was also seen in the control group and has been attributed to the ethanol dose which was up to 11 grams/kg in some animals. There were no histological anomalies in the lungs of any rat. Male animals received a higher ivermectin dose adjusted by adipose weight and reached higher plasma concentrations than females in the same dosing group (mean Cmax 86.2 ng/ml vs 26.2 ng/ml in the lower dose group and 152 ng/ml vs 51.8 ng/ml in the higher dose group). All subjects had detectable ivermectin concentrations in the lungs at seven days post intervention, up to 524.3 ng/g

for high-dose male and 27.3 ng/g for low-dose females. Conclusion: nebulized ivermectin can reach pharmacodynamic concentrations in the lung tissue of rats, additional experiments are required to assess the safety of this formulation in larger animals".

25 - Ivermectin and Adenoviruses

[KIN1] "Human adenoviruses (HAdV) are ubiquitous within the human population and comprise a significant burden of respiratory illnesses worldwide ... no approved antiviral therapies specific to HAdV exist. Ivermectin is an FDA-approved broad-spectrum antiparasitic drug that also exhibits antiviral properties against a diverse range of viruses. Its proposed function is inhibiting the classical protein nuclear import pathway mediated by importin-α (Imp-α) and -β1 (Imp-β1). Many viruses, including HAdV, rely on this host pathway for transport of viral proteins across the nuclear envelope". In [KIN1], it is shown that ivermectin inhibits HAdV-C5 early gene transcription. Similarly, ivermectin inhibits genome replication of HAdV-B3. "Mechanistically", the auhotrs have shown that "ivermectin disrupts binding of the viral E1A protein to Imp-α without affecting the interaction between Imp-α and Imp-β1".

26 - Update of Clinical trials regarding the use of Ivermectin for Covid-19

On July 28, 2020, we had found 33 clinical trials reported by ClinicalTrials.gov , at the link **https://clinicaltrials.gov/ct2/results?cond=COVID&term=ivermectin+&cntry=&state=&city=&dist=** that we reported before. For other trials about drugs for Covid-19, see [SPA4].

Now we find new trials.

1) Ivermectin **Nasal Spray** for COVID19 Patients - First Posted **August 12, 2020** - Drug: Ivermectin nasal | Drug: Ivermectin oral - Other: standard care - https://ClinicalTrials.gov/show/NCT04510233 - Principal Investigator: Kamal Okasha, PhD Tanta Univesity faculty of Medicine

2) Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection - Drug: Ivermectin and Doxycycline, Locations: Dhaka Medical College, Dhaka, Bangladesh - https://ClinicalTrials.gov/show/NCT04523831

3) Outpatient Use of Ivermectin in COVID-19 - Drug: Ivermectin Pill|Drug: Placebo, Locations: Temple University Hospital, Philadelphia, Pennsylvania, United States - https://ClinicalTrials.gov/show/NCT04530474

4) Ivermectin to Prevent Hospitalizations in COVID-19 - Drug: Ivermectin | Placebo - Locations: Ministry of Public Health of the Province of Corrientes, Corrientes, Argentina - https://ClinicalTrials.gov/show/NCT04529525

5) Effectiveness and Safety of Ivermectin for the Prevention of Covid-19 Infection in Colombian Health Personnel - Drug: Ivermectin - Locations: Pontificia Universidad Javeriana, Cali, Valle Del Cauca, Colombia - https://ClinicalTrials.gov/show/NCT04527211

6) Trial of Combination Therapy to Treat COVID-19 Infection Drug: Ivermectin Doxycycline Hcl Dietary Supplement: Zinc Vitamin D3 Vitamin C - Locations: ProgenaBiome, Ventura, California, United States - https://ClinicalTrials.gov/show/NCT04482686

In **https://www.clinicaltrialsregister.eu/** we find also the following trials.

EudraCT Number: 2020-001994-66 Sponsor Protocol Number: ECIT-PRO19- Start Date: 2020-05-06 - Sponsor Name:Fundació Assistencial Mútua Terrassa - Full Title: Randomised clinical trial of ivermectin for treatment and prophylaxis of COVID-19

EudraCT Number: 2020-001971-33 Sponsor Protocol Number: CORIVER Start Date: 2020-06-02 - Sponsor Name:Carmen Hidalgo - Full Title: Pragmatic study "CORIVER": Ivermectin as antiviral treatment for patients infected by SARS-COV2 (COVID-19)

EudraCT Number: 2020-001474-29 Sponsor Protocol Number: SAINT Start Date: 2020-05-07 - Sponsor Name:Clínica Universidad de Navarra/Universidad de Navarra - Full Title: Pilot study to evaluate the potential of ivermectin to reduce COVID-19 transmission

EudraCT Number: 2020-002091-12 Sponsor Protocol Number: HUVE-19-CT-001 Start Date: 2020-05-15 - Sponsor Name: HUVEPHARMA EOOD - Full Title: Multicenter, randomized, double-blind, placebo-controlled study investigating efficacy, safety and tolerability of ivermectin HUVE-19 in patients with proven SARS-CoV-2 infection (COVID-19) and man...

EudraCT Number: 2020-002283-32 Sponsor Protocol Number: 2020-34 Start Date: 2020-06-12 - Sponsor Name:OSPEDALE CLASSIFICATO EQUIPARATO SACRO CUORE DON CALABRIA - PRESIDIO OSPEDALIERO ACCREDITATO - Full Title: Randomized, Double-blind, Multi Centre Phase II, Proof of Concept, Dose Finding Clinical Trial on Ivermectin for the early Treatment of COVID-19.

We can see, from the new clinical trials that there is an interest for the nasal use on ivermectin. We anca see again the investigation of the combination of ivermectin and doxycycline is used for the treatment of other diseases (see for instance [HOE1], [BAZ1]).

27 - News

Previously, we have seen some of the many news about ivermectin. In particular, in August a large number of news was coming from Australia. A "wonder drug" to cure the virus, as https://www.skynews.com.au/details/_6179108952001 . "Gastroenterologist Professor Thomas Borody says Ivermectin used in conjunction with two other drugs is making it look like “corona is very simple to kill”." **Actually, the virus is not so simple to kill as told by Bodory, and Ivermectin cannot be defined a "wonder drug" for the treatment of Covid-19: let us wait for results from clinical trials.** https://archive.is/fPZ3R

Of course, we have to stress once more that ivermectin is an extraordinary drug. "Over the past decade, the global scientific community have begun to recognize the unmatched value of an extraordinary drug, ivermectin, that originates from a single microbe unearthed from soil in Japan. ... Today, ivermectin is continuing to surprise and excite scientists, offering more and more promise to help improve global public health by treating a diverse range of diseases, with its unexpected potential as an antibacterial, antiviral and anti-cancer agent being particularly extraordinary". And this is told in [CRU2]. However, in the case of Covid-19, we have to receive further results from clinical trials to understand the role of this drug in all the stages of the disease.

Borody (4 August 2020) is proposing the triple Ivermectin, Zinc, Doxycycline. In https://www.medianet.com.au/ releases/189953/ , it is told that "He [Borody] said he knows of medical professionals already using it as a preventative therapy themselves", and also "These 3 medications are already approved. They do not need pre-clinical or clinical trials nor additional TGA approvals unless the aim is to combine in a single capsule, for example. Patient treatment programs have been done in the US and elsewhere which indicate it can work within 4-6 days.” Archived https://archive.is/uR4sR .

Now, I prefer to continue avoiding simply PRO or CONTRO announcements. Then, only a few are given.

Colombia - Requieren pacientes para estudio sobre ivermectina en Cali Agosto 24, 2020 - 11:55 p. m. Por: Redacción de El País - https://www.elpais.com.co/cali/requieren-pacientes-para-estudio-

sobre-ivermectina-en.html - "Desde el Centro de Estudios de Infectología Pediátrica (Ceip) en Cali, donde se lidera el único estudio clínico en el país aprobado por el Invima para verificar la seguridad y eficacia de ivermectina en pacientes con covid, se hizo un llamado a los caleños con la enfermedad en fase temprana para participar en dicha investigación. El doctor Eduardo López, director científico del Ceip, invitó a las personas que estén en estadios iniciales del Covid-19 y que quieran hacer parte del estudio con ivermectina, a que se contacten con el Centro de Estudios de Infectología Pediátrica de Cali para hacer la prueba PCR y así poder iniciar el tratamiento con el antiparasitario". In fact, we have mentioned this clinical trial before.

US - Clinical Testing Underway In Calif. For Ivermectin - OAN Newsroom - UPDATED 7:37 PM PT – Wednesday, August 26, 2020 - "Clinical testing is now underway in California for a powerful new drug in the fight against coronavirus. One America's Pearson Sharp has more on the medicine that researchers believe could cure the virus in just 48 hours". Again, let us stress that the 48 hours is **in vitro** [CLA1].

Australia - Merck : Ivermectin Triple Therapy Protocol for COVID-19 Released to Australian GPs for Infected Elderly and Frontline Workers - 08/19/2020 | 03:24am EDT "SYDNEY, Aug 19, 2020 - (ACN Newswire) - https://www.marketscreener.com/quote/stock/MERCK-CO-INC-13611/news/Merck-Ivermectin-Triple-Therapy-Protocol-for-COVID-19-Released-to-Australian-GPs-for-Infected-Elde-31142061/ - Triple therapy specialist Professor Thomas Borody, famous for curing peptic ulcers using a triple antibiotic therapy saving millions of lives, today released the COVID-19 treatment protocol to Australian GPs, who can legally prescribe it to their COVID-19 positive patients, and can also prescribe it as a preventative medication. Borody says this could be the fastest and safest way to end the pandemic in Australia within 6-8 weeks". - archived https://archive.is/U3DL5

And here I have to stress this fact, that one of the references given in the article is not concerning Ivermectin for Covid-19. The article tells that "There are currently 28 COVID-19 Ivermectin treatment studies running globally. Research papers include: WHO: Mass treatment with ivermectin: an underutilized public health strategy ... " The given link is the following https://www.who.int/bulletin/volumes/82/8/editorial30804html/en/ . The article entitled "Mass treatment with ivermectin: an underutilized public health strategy, by Rick Speare & David Durrheim [SPE1] was published in 2004. No Covid-19 in 2004. The other articles are properly reported.

From TrialSiteNews, https://www.trialsitenews.com/?s=ivermectin, we have several results about ivermectin. The last is the following on the "Zagazig University Randomized Controlled Ivermectin Study Results Confirms PI Hypothesis: Drug Effective Against COVID-19" - AUG 28, 2020

28 - News from Peru and Iquitos, and the use of corticosteroids

We considered news coming from Iquitos, in the Loreto region.

Now, a news: September 1- 2020 - ¡Buena noticia! Disminuye número de fallecidos y contagiados por coronavirus en Loreto - https://www.andina.pe/agencia/noticia-buena-noticia-disminuye-numero-fallecidos-y-contagios-coronavirus-loreto-812089.aspx - archived

"Una buena noticia. La región Loreto registra un notable descenso de fallecidos y contagiados por la pandemia de coronavirus (covid-19), destacó el titular de la Dirección Regional de Salud (Diresa) de Loreto, Carlos Calampa. Sostuvo que en Iquitos y otras ciudades y comunidades de Loreto, como Yurimaguas y Caballococha, se registra un descenso en el número de casos de covid-19 gracias al manejo efectivo de la pandemia, a la entrega oportuna de medicamentos y una mayor preparación del personal de salud para enfrentar la pandemia".

Reasons exist for this positive result. In particular, because of a better approach to the treatment.

What about ivermectin?

https://caretas.pe/nacional/coronavirus-las-lecciones-no-aprendidas-de-loreto/ archived https://archive.is/IJNiV

Coronavirus: las lecciones no aprendidas de Loreto. "Iquitos fue duramente golpeada por la COVID-19. Después de varias semanas de pandemia, un grupo de médicos entendió cómo enfrentar el virus y reducir el número de muertos drásticamente. El periodista Juanjo Fernández entrevistó a uno de ellos". 28 de agosto del 2020 en Nacional

The journalist interviews Dr. Juan Carlos Celis, Hospital Regional de Iquitos. The physician observes that, in the first phase of the disease, "El empleo de medicamentos corticoides en esta primera fase puede ser fatal porque son inmunomoduladores y pueden exponer el organismo a la expansión de la carga viral llegando a poder producir la muerte". About ivermectin, "Al constatar el galope de la epidemia empezamos a darnos cuenta que hay un grupo de ellos - incluida la ivermectina, que fue una explosión - que se unió al grupo de cloroquina, hidroxicloroquina, azitromicina, que aunque hubieran sido ya tomados los enfermos igualmente morían. Observamos que los pacientes van a peor cuando usan todas estas drogas juntas". As all physicians observed, it is very difficult to treat Covid-19 when patients need hospitalization, and this is also evidenced by the clinical trials discussed before. *The observation about the use of the combination of three drugs Ivermectin, Hydroxychloroquine and Azithromycin is very important.*

Also what Dr. Celis tells needs further discussion: "Vimos que era especialmente grave el uso de corticoides en una primera fase de la enfermedad. En Perú hay una tradición en su uso, las faringitis, los dolores de gargantas, hasta los golpes se curan con la famosa triple: megacilina, metamizol y dexametasona intramuscular. La gente ya sabe lo que es una triple sin necesidad de ir al médico. Eso es lo que creo que nos está matando. Una realidad de que médicos y pacientes se llevan automedicando con corticoides toda la vida. Nosotros lo hemos visto y estamos documentándolo, como pacientes que han venido habiendo tomado corticoides llegaron con lesiones más graves que los que no habían tomado nada. Habría que llevar esa recomendación a una guía nacional ¿Cómo hacerlo?". Dr. Celis is telling that in Peru there is a large use of the "famous triple: megacillin, metamizole, and intramuscular dexamethasone. People already know what a triple is without going to the doctor". According to Dr. Celis, this is a reason for the large number of victims. "[It is] a truth that doctors and patients have been self-medicating with corticosteroids all their lives. We have seen it and we are documenting it, as patients who have been taking corticosteroids arrived with more serious injuries than those who had not taken anything".

With great relief, in the fortnight of May the cases began to decline.

Any future update will be devoted to the results of clinical trials.

APPENDIX C - Update of 20 September 2020

29 - A combination used in treating Covid-19

On September 15, 2020, a clinical study has been published on the use of ivermectin combined with other drugs: dexamethasone, enoxaparin and aspirin [HEC1]. The authors are telling in the abstract that "No treatment tested worldwide has shown unquestionable efficacy in the fight against COVID 19, according to NICE reports". Then, the authors have designed an experimental treatment, that they have called IDEA, "based on four affordable drugs already available on the market in Argentina, based on the following rationale: -Ivermectin solution at a relatively high dose to lower

the viral load in all stages of COVID 19 -Dexamethasone 4-mg injection, as anti-inflammatory drug to treat hyperinflammatory reaction to COVID-infection -Enoxaparin injection as anticoagulant to treat hypercoagulation in severe cases. -Aspirin 250-mg tablets to prevent hypercoagulation in mild and moderate cases. Except for Ivermectin oral solution, which was used in a higher dose than approved for parasitosis, all other drugs were used in the already approved dose and indication". So we see that a different dose was used for ivermectin. The authors tells also that "Regarding Ivermectin safety, several oral studies have shown it to be safe even when used at daily doses much higher than those approved already". The clinical study has been conducted on patients at Eurnekian Hospital in the Province of Buenos Aires, Argentina. The study protocol and its final outcomes are described in [HEC1]. "Results were compared with published data and data from patients admitted to the hospital receiving other treatments. None of the patient presenting mild symptoms needed to be hospitalized. Only one patient died (0.59 % of all included patients vs. 2.1 % overall mortality for the disease in Argentina today; 3.1 % of hospitalized patients vs. 26.8 % mortality in published data). IDEA protocol appears to be a useful alternative to prevent disease progression of COVID-19 when applied to mild cases and to decrease mortality in patients at all stages of the disease with a favorable risk-benefit ratio".

In the article [HEC1] we read a comparison with other treatments: "Overall mortality rate of patients treated according to IDEA protocol was 0.59 % (1 death in 167 treated cases). As a comparison, estimated overall mortality rate in Argentina is approximately 2.1 % (official data by September 2nd, 2020). Regarding moderate to severe cases, i.e. patients needing hospitalization, only 1 patient out of 32 receiving IDEA treatment died (3.1 %), whereas mortality rate published in articles from Spain, Italy and Spain [?] is ca. 25 %. Moreover, a group of 12 patients were hospitalized in Eurnekian hospital in the same period but did not receive IDEA treatment. Three of them died, thus presenting a mortality rate of 25 %, i.e. significantly higher than that of those receiving IDEA treatment". A comment in the related web page of medRxiv is telling "Small Argentinian study (n=167) without control group suggests favorable outcomes for COVID patients treated with ivermectin+dexamethasone+aspirin or enoxaparin".

I would like also to stress the fact that comparison with data from Spain and Italy needs to be considered and discussed carefully. First of all, it is necessary to give reference to the source of data. Moreover, data concerning the same average age have to be compared. It is also very important to consider properly the evolution of the disease. Then, any rate involved in the discussion cannot be considered as a constant. Italy was the first country, outside China, where Covid-19 had severely hit the population, and this is a fact. However, the efficacy of cures in intensive care units increased during the time.

About data, let me suggest also the reading of [ALI1].

30 - Conclusions

As I told at the beginning, I am not a physician, I do not suggest the use of ivermectin, I am not touting this drug. The aim of this work was the analysis of publications and news about ivermectin, made in the framework of a wider investigation about information concerning drugs used for Covid-19. In the news, we can read of physicians telling that ivermectin is helpful, and of physicians telling to be cautious and avoid self-medication. In fact, ivermectin is under investigations in many clinical trials, which are providing and will provide information about the role of Ivermectin for Covid-19.

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