Real-World Evidence

Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions.

- FDA uses RWD and RWE to monitor postmarket safety and adverse events and to make regulatory decisions.
- The health care community is using these data to support coverage decisions and to develop guidelines and decision support tools for use in clinical practice.
- Medical product developers are using RWD and RWE to support clinical trial designs (e.g., large simple trials, pragmatic clinical trials) and observational studies to generate innovative, new treatment approaches.

The 21st Century Cures Act, passed in 2016, places additional focus on the use of these types of data to support regulatory decision making, including approval of new indications for approved drugs. Congress defined RWE as data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials. FDA has expanded on this definition as discussed below.

Why is this happening now?

The use of computers, mobile devices, wearables and other biosensors to gather and store huge amounts of health-related data has been rapidly accelerating. This data holds potential to allow us to better design and conduct clinical trials and studies in the health care setting to answer questions previously though infeasible. In addition, with the development of sophisticated, new analytical capabilities, we are better able to analyze these data and apply the results of our analyses to medical product development and approval.

What are RWD and where do they come from?

Real-world ***data*** are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources, for example:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings

- Data gathered from other sources that can inform on health status, such as mobile devices

What is RWE?

Real-world ***evidence*** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).

This Website was designed to capture up-to-date information about the status of FDA activities around the development and use of RWD and RWE.

Publications and Guidance

- Guidance: Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-utilizing-real-world-data-and-real-world-evidence-fda-drugs-and-biologics)
- Guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices)
- Guidance: Use of Electronic Health Records in Clinical Investigations (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry)
- Framework for FDA's Real-World Evidence Program (https://www.fda.gov/media/120060/download)
- Real-World Evidence — What Is It and What Can It Tell Us? (http://www.nejm.org/doi/full/10.1056/NEJMsb1609216) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) disclaimer icon (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm) *The New England Journal of Medicine*, Dec. 6, 2016
- Accelerating development of scientific evidence for medical products within the existing US regulatory framework (PDF - 180KB) (https://www.fda.gov/files/science%20&%20research/published/Accelerating-development-of-scientific-evidence-for-medical-products-within-the-existing-US-regulatory-framework.pdf)

Related Resources

- FDA Announces 4 Grant Awards for Projects Exploring the Use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making (/drugs/science-and-research-drugs/fda-announces-4-grant-awards-projects-exploring-use-real-world-data-generate-real-world-evidence)
- CDER Small Business and Industry Assistance Webinar: Framework for FDA's Real-World Evidence Program - Mar 15, 2019 (https://www.fda.gov/drugs/webinar-framework-fdas-real-world-evidence-program-mar-15-2019)

Contact

For more information on RWE, please contact CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov (mailto:CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov).

21st Century Cures Act

The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently.

The law builds on FDA's ongoing work to incorporate the perspectives of patients into the development of drugs, biological products, and devices in FDA's decision-making process. Cures enhances our ability to modernize clinical trial designs, including the use of real-world evidence (/science-research/science-and-research-special-topics/real-world-evidence), and clinical outcome assessments, which will speed the development and review of novel medical products, including medical countermeasures (/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/21st-century-cures-act-mcm-related-cures-provisions).

It also provides new authority to help FDA improve our ability to recruit and retain scientific, technical, and professional experts and it establishes new expedited product development programs, including:

- The Regenerative Medicine Advanced Therapy (/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation), or RMAT, that offers a new expedited option for certain eligible biologics products.
- The Breakthrough Devices program (/medical-devices/how-study-and-market-your-device/expedited-access-pathway-program), designed to speed the review of certain innovative medical devices.

In addition, the Cures Act directs FDA to create one or more intercenter institutes to help coordinate activities in major disease areas between the drug, biologics and device centers and improves the regulation of combination products.

- About the Oncology Center of Excellence (/oncology-center-excellence#AboutOCE)

Implementation

FDA is working hard to maximize the authorities and resources Congress granted us in Cures, as FDA Commissioner Scott Gottlieb outlined in an FDA Voice Blog.

- Blog: How FDA Plans to Help Consumers Capitalize on Advances in Science (https://blogs.fda.gov/fdavoice/index.php/2017/07/how-fda-plans-to-help-consumers-capitalize-on-advances-in-science/)

Work Plan

The Cures Act authorized $500 million over 9 years to help FDA cover the cost of implementing the law. We developed a draft work plan showing how FDA would use that funding, subject to annual appropriations. In keeping with the statutory requirements, we submitted the draft work plan to FDA's Science Board for their comments and recommendations at a public meeting in May. The final work plan, which includes the recommendations from the Science Board, was delivered to Congress on June 9.

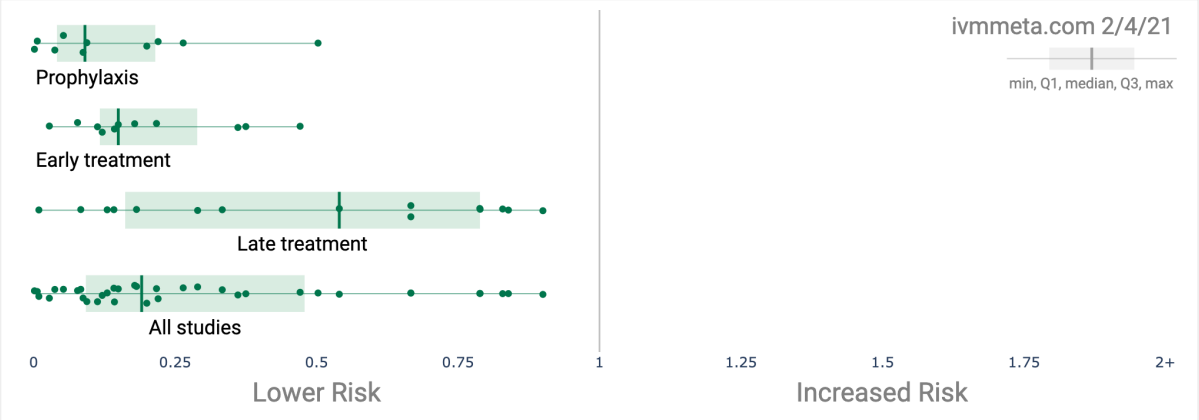
- Submission to Congress: Food & Drug Administration Work Plan and Proposed Funding Allocations of FDA Innovation Account (PDF - 233KB) (/media/105635/download) *Required by Section 1002 of the 21st Century Cures Act (Public Law 114-255)*

Resources For You

- 21st Century Cures Act (https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf) (Congress.gov)
- Technical Corrections include also in FDA Reauthorization Act of 2017 (FDARA) (https://www.congress.gov/115/plaws/publ52/PLAW-115publ52.pdf) (Congress.gov)

Swiss Policy Research

On the Treatment of Covid-19



Effectiveness of ivermectin against covid-19 (IVMMETA)

Updated: February 2021
Languages: German, English
Share on: Twitter / Facebook

Based on the available scientific evidence and current clinical experience, the SPR Collaboration recommends that physicians and authorities consider the following covid-19 treatment protocol for the **prophylactic and early treatment** of people at high risk or high exposure.

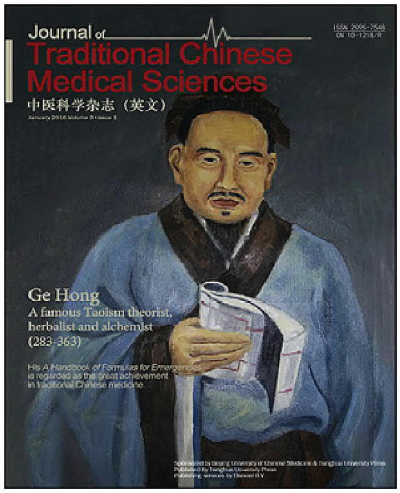
ATTEMPTING TO PREVENT ADDITIONAL SARS-CoV-2 UNNECESSARY CHRONICITY & DEATH

It is my great frustration and deep regret not to be a practicing physician during this pandemic, to more effectively fight against the medical tyranny imposed on us all by people of the lie also called the gods of money, whose devious machinations unconscionably and successfully have deprived the afflicted of safe, effective, and inexpensive—prophylactic as well as curative—treatment with medication.

Ernesto Vasquez, MD

Ivermectin— 1700 years of 'the pharmacological basis of therapeutics'

Highlights Compiled by
Ernesto Vasquez, MD



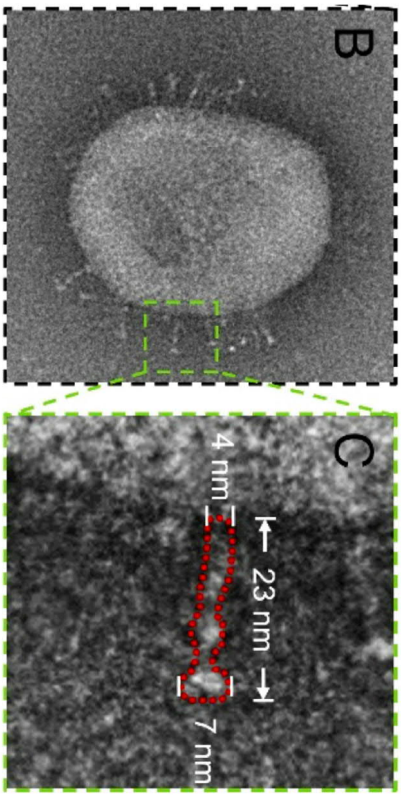
FROM

— Ge Hong (A.D. 283-363). *Handbook of Formulas for Emergencies.* Journal of Traditional Chinese Medical Sciences (2016) 3:1-2. https://doi.org/10.1016/j.jtcms.2016.09.001

— Andy Crump & Satoshi Omura. *Invermectin, 'Wonder drug' from Japan: the human use perspective*. Proc. Jpn. Acad., Ser. B 87 (2011). https://doi.org/10.2183/pjab.87.13

— The 2015 Nobel Price in Medicine for novel therapies *(Ivermectin)* for *roundworm infections* (William C. Campbell and Satoshi Omura) and *malaria* (Youyou Tu). www.pnas.org/cgi/doi/10.1073/pnas.1520952112

— Chen, I-S & Kubo, Y. (2018). *Ivemectin and its target molecules.* J. Physiol. https://doi.org/10.1113/jp275236



SARS-CoV-2 Architecture by Cryo-EM
https://doi.org/10.1101/2020.03.02.972927

TO

— Kory P, Meduri GU, Iglesias, J, Varon J, et al. (2021). *Review of the emerging evidence demonstrating the efficacy of Ivermectin in the prophylaxis and treatment of COVID-19.* Front. Pharmacol. https://doi.org/10.31219/osf.io/wx3zn -as a result of which,

— NIH REVISED on 01-15-2021 the Ivermectin Treatment Guidelines: the previous recommendation *against* has been REMOVED. *IF SO INCLINED* , the clinician has the choice now of attempting to prevent additional unnecessary chronicity and death!
https://www.covid19treatmentguidelines.nih.gov/statement-on-ivermectin/

— FLCCC Alliance Response to the NIH Guideline Committee Recommendation on Ivermectin use in COVID-19 dated January 14th, 2021
https://covid19criticalcare.com/wp-content/uploads/2021/01/FLCCC-Alliance-Response-to-the-NIH-Guideline-Committee-Recommendation-on-Ivermectin-use-in-COVID19-2021-01-18.pdf

[New post] Update on ivermectin for covid-19

1 message

Sebastian Rushworth M.D. <donotreply@wordpress.com>
To: evself@gmail.com

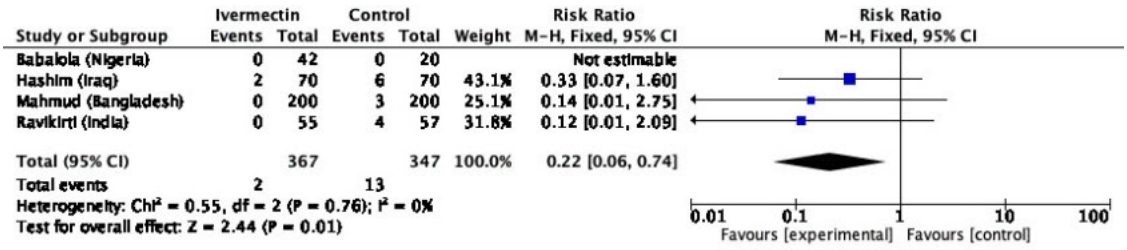
Sun, May 9, 2021 at 4:03 AM

New post on **Sebastian Rushworth M.D.**

Update on ivermectin for covid-19

by Sebastian Rushworth, M.D.

Back in January I wrote an article about four randomized controlled trials of ivermectin as a treatment for covid-19 that had at that time released their results to the public. Each of those four trials had promising results, but each was also too small individually to show any meaningful impact on the hard outcomes we really care about, like death. When I meta-analyzed them together however, the results suddenly appeared very impressive. Here's what that meta-analysis looked like:



It showed a massive 78% reduction in mortality in patients treated with covid-19. Mortality is the hardest of hard end points, which means it's the hardest for researchers to manipulate and therefore the least open to bias. Either someone's dead, or they're alive. End of story.

You would have thought that this strong overall signal of benefit in the midst of a pandemic would have mobilized the powers that be to arrange multiple large randomized trials to confirm these results as quickly as possible, and that the major medical journals would be falling over each other to be the first to publish these studies.

That hasn't happened.

Rather the opposite, in fact. South Africa has even gone so far as to ban doctors from using ivermectin on covid-19 patients. And as far as I can tell, most of the discussion about ivermectin in mainstream media (and in the medical press) has centred not around its relative merits, but more around how its proponents are clearly deluded tin foil hat wearing crazies who are using social media to manipulate the masses.

In spite of this, trial results have continued to appear. That means we should now be able to conclude with even greater certainty whether or not ivermectin is effective against covid-19. Since there are so many of these trials popping up now, I've decided to limit the

discussion here only to the ones I've been able to find that had at least 150 participants, and that compared ivermectin to placebo (although I'll add even the smaller trials I've found in to the updated meta-analysis at the end).

As before, it appears that rich western countries have very little interest in studying ivermectin as a treatment for covid. The three new trials that had at least 150 participants and compared ivermectin with placebo were conducted in Colombia, Iran, and Argentina. We'll go through each in turn.

The Colombian trial (Lopez-Medina et al.) was published in JAMA (the Journal of the American Medical Association) in March. There is one thing that is rather odd with this study, and that is that the study authors were receiving payments from Sanofi-Pasteur, Glaxo-Smith-Kline, Janssen, Merck, and Gilead while conducting the study. Gilead makes remdesivir. Merck is developing two expensive new drugs to treat covid-19. Janssen, Glaxo-Smith-Kline, and Sanofi-Pasteur are all developers of covid vaccines. In other words, the authors of the study were receiving funding from companies that own drugs that are direct competitors to ivermectin. One might call this a conflict of interest, and wonder whether the goal of the study was to show a lack of benefit. It's definitely a little bit suspicious.

Anyway, let's get to what the researchers actually did. This was a double-blind randomized controlled trial that recruited patients with mildly symptomatic covid-19 who had experienced symptom onset less than 7 days earlier. Potential participants were identified through a statewide database of people with positive PCR-tests. By "mildly symptomatic" the researchers meant people who had at least one symptom but who did not require high-flow oxygen at the time of recruitment in to the trial.

Participants in the treatment group received 300 ug/kg body weight of ivermectin every day for five days, while participants in the placebo group received an identical placebo. 300 ug/kg works out to 21 mg for an average 70 kg adult, which is quite high, especially when you consider that the dose was given daily for five days. For an average person, this would work out to a total dose of 105 mg. The other ivermectin trials have mostly given around 12 mg per day for one or two days, for a total dose of 12 to 24 mg (which has been considered enough because ivermectin has a long half-life in the body). Why this study gave such a high dose is unclear. However, it shouldn't be a problem. Ivermectin is a very safe drug, and studies have been done where people have been given ten times the recommended dose without any noticeable increase in adverse events.

The stated goal of the study was to see if ivermectin resulted in more rapid symptom resolution than placebo. So participants were contacted by telephone every three days after inclusion in the study, up to day 21, and asked about what symptoms they were experiencing.

398 patients were included in the study. The median age of the participants was 37 years, and they were overall very healthy. 79% had no known co-morbidities. This is a shame. It means that this study is yet another one of those many studies that will not be able to show a meaningful effect on hard end points like hospitalization and death. It is a bit strange that studies keep being done on young healthy people who are at virtually zero risk from covid-19, rather than on the multi-morbid elderly, who are the ones we actually need an effective treatment for.

Anyway, let's get to the results.

In the group treated with ivermectin, the average time from inclusion in the study to becoming completely symptom free was 10 days. In the placebo group that number was 12 days. So, the ivermectin treated patients recovered on average two days faster. However, the difference was not statistically significant, so the result could easily be due to chance. At 21 days after inclusion in the study, 82% had recovered fully in the ivermectin group, as compared to 79% in the placebo group. Again, the small difference was not statistically significant.

In terms of the hard end points that matter more, there were zero deaths in the ivermectin group and there was one death in the placebo group. 2% of participants in the ivermectin group required "escalation of care" (hospitalization if they were outside the hospital at the start of the study, or oxygen therapy if they were in hospital at the start of the study) as compared with 5% in the placebo group. None of these differences was statistically significant. But that doesn't mean they weren't real. Like I wrote earlier, the fact that this was a study of healthy young people meant that, even if a meaningful difference does exist in risk of dying of covid, or of ending up in hospital, this study was never going to find it.

So, what can we conclude?

Ivermectin does not meaningfully shorten duration of symptoms in healthy young people. That's about all we can say from this study. Considering the conflicts of interest of the authors, my guess is that this was the goal of the study all along: Gather together a number of young healthy people that is too small for there to be any chance of a statistically significant benefit, and then get the result you want. The media will sell the result as "study shows ivermectin doesn't work" (which they dutifully did).

It is interesting that there were signals of benefit for all the parameters the researchers looked at (resolution of symptoms, escalation of care, death), but that the relatively small number and good health status of the participants meant that there was little chance of any of the results reaching statistical significance.

Let's move on to the next study, which is currently available as a pre-print on Research Square (Niaee et al.). It was randomized, double-blind, and placebo-controlled, and carried out at five different hospitals in Iran. It was funded by an Iranian university.

In order to be included in the trial, participants had to be over the age of 18 and admitted to hospital because of a covid-19 infection (which was defined as symptoms suggestive of covid plus either a CT scan typical of covid infection or a positive PCR test).

150 participants were randomized to either placebo (30 people) or varying doses of ivermectin (120 people). The fact that they chose to make the placebo group so small is a problem, because it makes it very hard to detect any differences even if they do exist, by making the statistical certainty of the results in the placebo group very low.

The participants were on average 56 years old and the average oxygen saturation before initiation of treatment was 89% (normal is more than 95%), so this was a pretty sick group. Unfortunately no information is provided on how far along people were in the disease course when they started receiving ivermectin. It stands to reason that the drug is more likely to work if given ten days after symptom onset than when given twenty days after symptom onset, since death usually happens around day 21. If you, for example, wanted to design a trial to fail, you could start treating people at a time point when there is no time

for the drug you're testing to have a chance work, so it would have been nice to know at what time point treatment started in this trial.

So, what were the results?

20% of the participants in the placebo group died (6 out of 30 people). 3% of the participants in the various ivermectin groups died (4 out of 120 people). That is an 85% reduction in the relative risk of death, which is huge.

So, in spite of the fact that the placebo group was so small, it was still possible to see a big difference in mortality. Admittedly, this is a pre-print (i.e. it hasn't been peer-reviewed yet), and the absolute numbers of deaths are small, so there is some scope for random chance to have created these results (maybe people in the placebo group were just very unlucky!). However, the study appears to have followed all the steps expected for a high quality trial. It was carried out at multiple different hospitals, it used randomization and a control group that received a placebo, and it was double-blinded. And death is a very hard end point that is not particularly open to bias. So unless the researchers have falsified their data, then this study constitutes reasonably good evidence that ivermectin is highly effective when given to patients hospitalized with covid-19. That's great, because it would mean that the drug can be given quite late in the disease course and still show benefit.

Let's move on to the third trial (Chahla et al.), which is currently available as a pre-print on MedRxiv. It was carried out in Argentina, and funded by the Argentinean government. Like the first trial we discussed, this was a study of people with mild disease. It literally boggles my mind that so many researchers choose to study people with mild disease instead of studying those with more severe disease. Especially when you consider that these studies are all so small. A study of people with mild disease needs to be very large to find a statistically significant effect, since most people with covid do well regardless. The risk of false negative results is thus enormous. If you're going to do a small-ish study, and you want to have a reasonable chance of producing results that reach statistical significance, it would make much more sense to do it on sick hospitalized patients.

The study was randomized, but it wasn't blinded, and there was no placebo. In other words, the intervention group received ivermectin (24 mg per day), while the control group didn't receive anything. This is a bad bad thing. It means that any non-hard outcomes produced by the study are really quite worthless, since there is so much scope for the placebo effect and other confounding factors to mess up the results. For hard outcomes, in particular death, it should be less of a problem (although we wouldn't expect any deaths in such a small study of mostly healthy people with mild disease anyway).

The study included people over the age of 18 with symptoms suggestive of covid-19 and a positive PCR test. The average age of the participants was 40 years, and most had no underlying health issues. A total of 172 people were recruited in to the study.

The researchers chose to look at how quickly people became free of symptoms as their primary endpoint. This is enormously problematic, since the study, as already mentioned, wasn't blinded and there was no placebo. Any difference between the groups could easily be explained by the placebo effect and by biases towards treatment benefit among the researchers.

Anyway, the study found that 49% in the treatment group were free of symptoms at five to nine days after the beginning of treatment, compared with 81% in the control group.

However, the lack of blinding means that this result is worthless. The methodology is just too flawed.

No data is provided on the number of people who died in each group. Since it isn't reported, I think it's safe to assume that there were no deaths in either group. Nor is any data provided on the number of hospitalizations in each group.

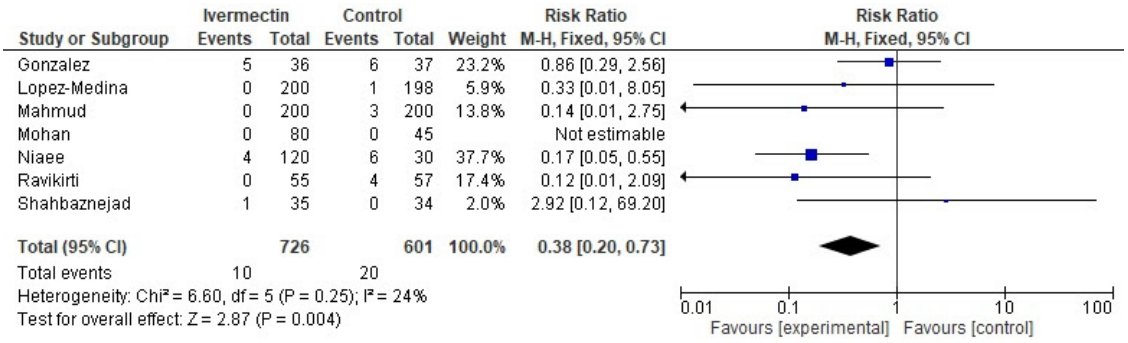
So, what does this study tell us?

Absolutely nothing at all. What a waste of time and money.

Let's move on and update our meta-analysis. The reason we need to do a meta-analysis here is that none of the trials of ivermectin is large enough on its own to provide a definitive answer as to whether it is a useful treatment for covid-19 or not. For those who haven't heard of meta-analyses before, basically what you do is just take the results from all different studies in existence that fulfill your pre-selected criteria, and then put them together, so as a to create a single large "meta"-study. This allows you to produce results that have a much higher level of statistical significance. It is particularly useful in a situation where all the individual trials you have to work with are statistically underpowered (have too few participants), as is the case here.

In this new meta-analysis, I've included every double-blind randomized placebo-controlled trial I could find of ivermectin as a treatment for covid. Using only double-blind placebo-controlled trials means that only the highest quality studies are included in this meta-analysis, which minimizes the risk of biases messing up the results as far as possible. In order to be included, a study also had to provide mortality data, since the goal of the meta-analysis is to see if there is any difference in mortality.

I was able to identify seven trials that fulfilled these criteria, with a total of 1,327 participants. Here's what the meta-analysis shows:



What we see is a 62% reduction in the relative risk of dying among covid patients treated with ivermectin. That would mean that ivermectin prevents roughly three out of five covid deaths. The reduction is statistically significant (p-value 0,004). In other words, the weight of evidence supporting ivermectin continues to pile up. It is now far stronger than the evidence that led to widespred use of remdesivir earlier in the pandemic, and the effect is much larger and more important (remdesivir was only ever shown to marginally decrease length of hospital stay, it was never shown to have any effect on risk of dying).

I understand why pharmaceutical companies don't like ivermectin. It's a cheap generic drug. Even Merck, the company that invented ivermectin, is doing it's best to destroy the drug's reputation at the moment. This can only be explained by the fact that Merck is

currently developing two expensive new covid drugs, and doesn't want an off-patent drug, which it can no longer make any profit from, competing with them.

The only reason I can think to understand why the broader medical establishment, however, is still so anti-ivermectin is that these studies have all been done outside the rich west. Apparently doctors and scientists outside North America and Western Europe can't be trusted, unless they're saying things that are in line with our pre-conceived notions.

Researchers at McMaster university are currently organizing a large trial of ivermectin as a treatment for covid-19, funded by the Bill and Melinda Gates foundation. That trial is expected to enroll over 3,000 people, so it should be definitive. It's going to be very interesting to see what it shows when the results finally get published.

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Sebastian Rushworth, M.D. | 9 May, 2021 at 10:03 | Tags: Ivermectin | Categories: Covid 19, Medications | URL: https://wp.me/pcdgfy-Uc

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