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Promising Antimicrobial Hope for "Coronavirus", but is it Working Against A Virus?

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Figure 1: *Chaos in Italy*

- Antivirals did not play a significant role in helping curb previous coronavirus outbreaks — SARS and MERS largely went away on their own, through public health measures that helped contain the spread.
- Present coronavirus trials using antivirals have to this point on the whole proved either inconclusive or disappointing.
- Azithromycin, an antibiotic with no antiviral activity whatsoever, is proving quite efficacious in treating the disease behind the "COVID-19" pandemic. Azithromycin is a first-line drug against *Mycobacterium avium*, which can simulate obstructive lung disease, and every other sign or symptom of COVID-19 documented to date. In addition azithromycin is a second or third-line drug against drug-resistant *Mycobacterium tuberculosis*.
- There was and still is a Pandemic going on in the world which dwarfs coronavirus. A Pandemic which kills one person every 21 seconds. A pandemic which in 2018 alone killed at least 1.5 million people annually. A mycobacterial pandemic, from *Mycobacterium tuberculosis*.
- In the United States, pulmonary *Mycobacterium avium* complex (MAC) disease or "fowl tuberculosis" is more common than tuberculosis.
- Furthermore, *Mycobacterium avium* complex is now the leading mycobacterial cause of chronic pneumonia in the United States.

- Infections due to non-tuberculous mycobacteria (NTM) such as *Mycobacteria avium* are increasing *worldwide*, and are particularly important to take into account when considering a zoonosis, which COVID-19 was originally thought to be.
- Not only does the drug hydroxychloroquine inhibit intracellular TB, but it acts synergistically against mycobacterial disease when combined with certain antimycobacterials. Azithromycin is also used as an antimycobacterial.
- The BCG tuberculosis vaccine is currently the focus of an international 4 country study to combat the Coronavirus pandemic.
- In the present Coronavirus pandemic, tubercular infection is by far the most common co-morbidity or underlying condition.
- A Recent preliminary Chinese study shows that tubercular infection likely increases susceptibility to SARS-CoV-2, and also increases COVID-19 severity.

Introduction

The FDA cleared the way for hard hit New York to experiment with the malaria and lupus drug hydroxychloroquine and the antibiotic Zithromax (generic name azithromycin) as a treatment for COVID-19 There is no doubt that the disease presently being attributed to "coronavirus" (which not long ago was best known for the common cold), has the potential to be deadly. Besides New York, witness Italy, where on March 21, 2020 alone 793 people died. And the next day, 651 lives were lost again…… with no sign of let up in sight. But was this from a virus? Not all illnesses with non-specific flu-like symptoms are from viruses. And this despite the many virologists at the head of the CDC, NIH, and others that insist that if it's an epidemic or pandemic, it's a virus.

Questions persist as to whether these deaths were as a direct result of the virus itself. There is little credible evidence that present coronavirus tests are picking up the RNA of a virus alone. The most accurate of these tests to this point is a measure of RNA. Such RNA could come from other sources such as the cells of the patient, bacteria, and other pathogens. For example, there are RNA elements in both mycobacteria. [1] and their mycobacteriophages or bacterial viruses [2] which live inside of all virulent mycobacteria such as *M. avium* and *M. tuberculosis* (a true global killer), both of which were on the upswing in the Italian peninsula and Wuhan considerably prior to the COVID-19 (SARS-CoV-2).[3,4] This same RNA could also account for the RNA being detected in COVID testing. According to the *World Health Organization* (WHO), mycobacterial disease is presently responsible for one death every 21 seconds around the world. In the package inserts of all coronavirus RT-PCR test, it is clearly stated that this test will not rule out bacterial or mycobacterial disease. Furthermore any mycobacterial cross- reactivity studies done between *M. tuberculosis* and COVID-19 by manufacturers have to this point been unclear, ambiguous and incomplete.

The First "Virus" in History Claimed to Respond to Antibiotics

Figure 2: *A Promising Trial*

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Professor Didier Raoult, a French virologist who heads the Mediterranean Infectious and Tropical Disease Institute in Marseille, had an idea. He would create a cocktail of hydroxychloroquine, a less toxic derivative of chloroquine, used to treat malaria, lupus and rheumatoid arthritis and combine it with azithromycin, an antibiotic used against bacterial pneumonia– and then give it to Covid-19 patients. The only problem was that antibiotics like azithromycin by definition have no activity against viruses. Never mind.

Raoult would fashion his own explanation tailored as to why his potion would work. The antibiotic Azithromycin (Zithromax®) was added, he claimed, not only because it is known to be effective against complications from bacterial lung disease, but "because it has been shown to be effective in the laboratory against a large number of viruses". Since it is universally known that antibiotics do not have any effect on viruses, including COVID-19 (later renamed SARS-CoV-2), then if the antibiotic azithromycin was effective against COVID-19, then COVID-19 could not be a virus. [5]

Figure 3: *Professor and Virologist Didier Raoult*

Azithromycin has activity against many of the mundane bacterial pneumonias, such as *Haemophillus influenza* (once called *Mycobacterium Influenzae*). It is also probably the most widely used first-line drug against *Mycobacterium avium*, which can simulate obstructive lung disease, and every other sign or symptom of coronavirus documented to this date. [3] In addition azithromycin is a second or third-line drug against drug-resistant *Mycobacterium tuberculosis*. [6] In the United States, pulmonary *Mycobacterium avium* complex (MAC) disease or "fowl tuberculosis" is more common than tuberculosis. [7] Furthermore, *Mycobacterium avium* complex is now the leading mycobacterial cause of chronic pneumonia in the United States. [8]

But why the hydroxychloroquine? Raoult was encouraged by the in vitro results treating COVID-19 with hydroxychloroquine obtained by a Chinese team led by Xueting Yao, from Peking University Hospital, in Beijing, and published by the journal *Clinical Infectious Diseases* [9] on March 9th. The Chinese proposed that the hydroxychloroquine worked by a vague "immunomodulatory effect" to control the "cytokine storm" that occurs in the late-phase of patients critically ill from coronavirus [AKA COVID-19, AKA SARS- CoV-2]. They admitted that currently, there is no evidence to support the use of hydroxychloroquine in SARS-CoV-2 infection. It just seemed to help, to one extent or another. Raoult thus thought that it might be a good idea to include hydroxychloroquine in his trial. But when he compared untreated patients, those receiving hydroxychloroquine and those given hydroxychloroquine plus the antibiotic azithromycin, his results showed "a spectacular reduction in the number of positive cases" with the combination therapy with the antibiotic azithromycin [See sharp drop in % of PCR positive patients represented in green just below]:

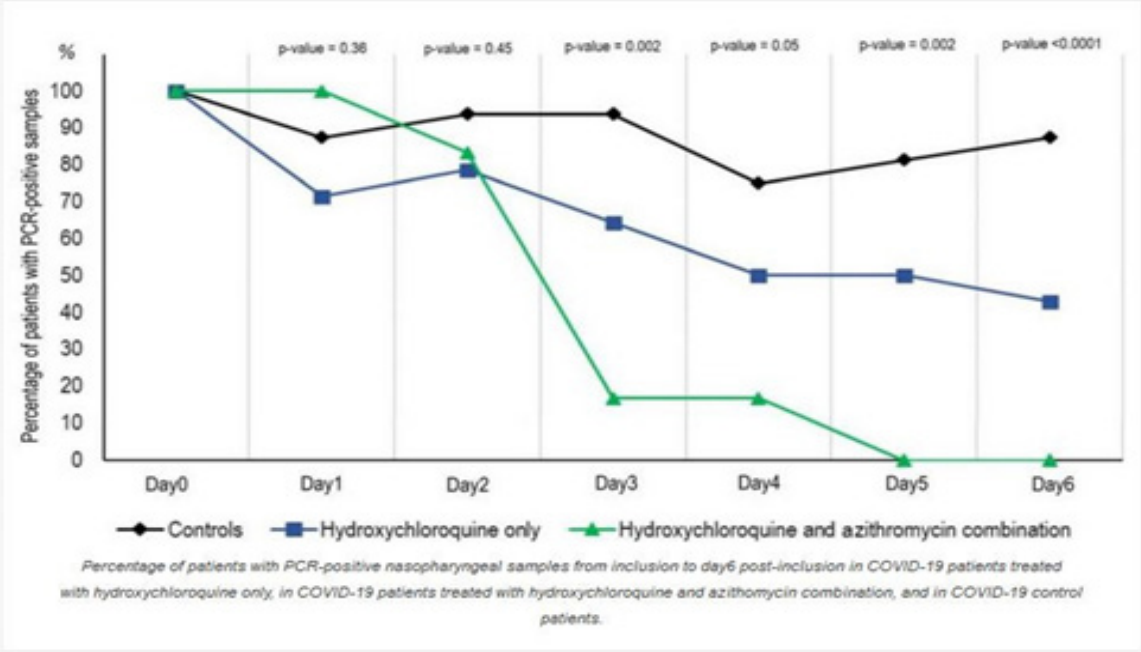


Figure 4: *The Study's Results*

Why did this happen? Obviously the antibiotic azithromycin in combination with the hydroxychloroquine was having an effect not within reach by just using hydroxychloroquine alone. It would have been nice to have a 4th colored line graph just above with only azithromycin being used, but this Raoult., *et al.* shied away from performing. After all, should just azithromycin used alone mimic closely the results for azithromycin with chloroquine, this would have created pandemonium in the field of virology, which Didier Raoult is very much a part of. Instead after receiving 600mg of Plaquenil® (hydroxychloroquine) with 250mg of azithromycin for six days, three-quarters of Raoult's patients tested negative for the virus, while 90 per cent of the control group who did not take the drugs still tested positive. [10] But even here, aside from its anti-inflammatory impact, it is doubtful that hydroxychloroquine was having much power on reducing or eliminating COVID-19. After all, in the past, among HIV-infected AIDS patients not taking antiretroviral therapy, the use of hydroxychloroquine alone compared with placebo actually increased viral replication. [11] So why should it be that in the case of COVID-19 it magically decreased viral replication? As the hydroxylated version of chloroquine, with a similar mechanism of action, hydroxychloroquine is preferred due to its safer profile.

The uproar from fellow virologists, regarding Didier Raoult's new find, was a beauty to behold. Unswayed, Raoult fired back in an interview with *La Provence* newspaper that "In my field, I am a star, worldwide". "I don't give a damn what others think. I am not an outsider. I'm streaks ahead of the others." Perhaps, but at times his statements antibiotic-wise seemed to be "streaks ahead" of all known facts as well.

So on the surface, it seemed that the major effect that hydroxychloroquine was probably related to its well-documented anti-inflammatory properties. Although Hydroxychloroquine (Plaquenil®) is a 4-amino- quinoline antimalarial medication, it is also widely used to treat systemic lupus erytheromatosis (SLE), rheumatoid arthritis, and related inflammatory conditions. Inflammation of the aveoli of the lungs with their subsequent flooding through the fluids that form accompanied by difficulty in breathing has a major role in the deaths resulting from the present pandemic. But first superficial 'surface' impressions do not always tell the whole story. Did hydroxychloroquine do more?

Spotlight on Hydroxychloroquine in 2019, But Not for a Virus

Figure 5: *An Overlooked Anti-Mycobacterial Property for Hydroxychloroquine*

As it turns out, chloroquine and its congener hydroxychloroquine do much more then virologists and others seemed to be able to fathom. Beyond anti-malarial, anti-inflammatory properties, chloroquine and its congener hydroxychloroquine, even by 1990, were found, by themselves to inhibit intracellular TB. [12] They are also being closely considered for their activity against *Mycobacterium avium*. [13]

But that is not all. Chloroquine and hydroxychloroquine happen to have a distinct effect in potentiating other anti-mycobacterial antibiotics to kill virulent mycobacteria. The latest reference to this came in a November of 2019 study published in *Science Translational Medicine*, a journal of *American Association for the Advancement of Science*. When added to an antibiotic active against mycobacteria, chloroquine seemed to reduce resistance to the antibiotic once introduced into the system. And that, in turn, seemed to help fight drug-resistant mycobacteria. In effect chloroquine lowers the acidic PH inside the bodies' macrophages [a type of white blood cell] therefore allowing anti-mycobacterial antibiotics [such as azithromycin] to better kill organisms such as *M. avium* and *Mycobacterium tuberculosis*, potentiating the efficacy of these antibiotics in vivo. The research was conducted in vivo only; and the researchers admitted that human trials with the regimen may be a long way off. [14]

Enter the BCG Vaccination

Figure 6: *The Bacillus Calmette-Guérin (BCG) vaccine (pictured) is used to fend off tuberculosis (TB)*

In March of 2020, it was announced that research teams from four different countries will join in clinical trials using the TB vaccine BCG (Bacillus Calmette-Guérin) to see if it fends off the signs and symptoms of COVID-19.

BCG is thinned-out bovine (cattle) tuberculosis derived from the pathogen *Mycobacterium bovis*. It is also the only approved vaccination for TB in the world.

Although trials will start in the Netherlands, Germany and the UK, the Australian arm of the trial will be one of the largest, where 4,000 healthcare workers, doctors and nurses will participate, half of them getting the vaccine and the other half not getting it. Healthcare workers and the elderly are particularly vulnerable to infection and many, many of them have fallen sick or worse from "the virus". It is projected that some sign of the effectiveness of giving this vaccination designed to combat tuberculosis will be in evidence by 3 months into this study's trials, with researchers claiming that the vaccine works by somehow "boosting the body's immune system". Australia's lead investigator Dr. Nigel Curtis said: "If I didn't think [the TB vaccine] would work, I wouldn't have been here seven days a week for the last month with a team of 20 people." Granted that it might very well work, the larger question is specifically how it is going to work?

The thought that the tubercular BCG vaccine "stimulates" the immune system and protects against approximately 30% of a wide range of other diseases, including viruses is an extremely controversial view, first espoused by Danish researchers Peter Aaby and Christine Stabell Benn, in Guinea-Bissau. [15]

However, there is a much more scientifically satisfying reason for how the *Mycobacterium bovis* in BCG (dilute cow tuberculosis) does what it does in the real world.

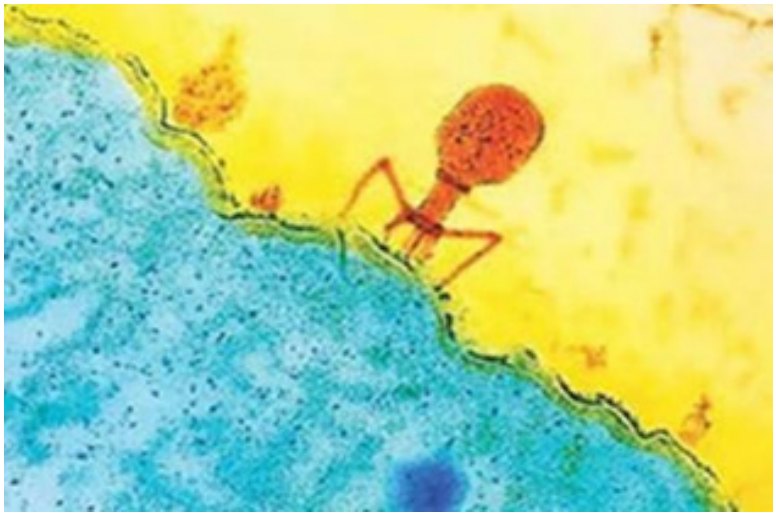


Figure 7: *A TM4 Mycobacteriophage virus from another mycobacteria, injecting its DNA through the cell wall of Mycobacterium tuberculosis– an event which can lead to the eventual destruction of the TB microbe.*

In nature there is a phenomena which happens probably millions of times a day in which one colony of bacteria or mycobacteria sends out its viral phages (bacteriophages or mycobacteriophages) that live inside it to kill another colony of the same type of organism.....a sort of natural lysogeny. The bacterial viruses called phages are the most plentiful viruses on earth. But they are species specific in that they only attack like species. The *Mycobacterium bovis* in BCG are closely related to and in fact part of the *Mycobacterium tuberculosis complex*. Therefore, the phages inside BCG have the potential to destroy TB and other related mycobacteria. The destruction of TB bacilli in the body is in and of itself "bolstering the immune system", as there is no other microbe known to man that is quite as immunosuppressive.

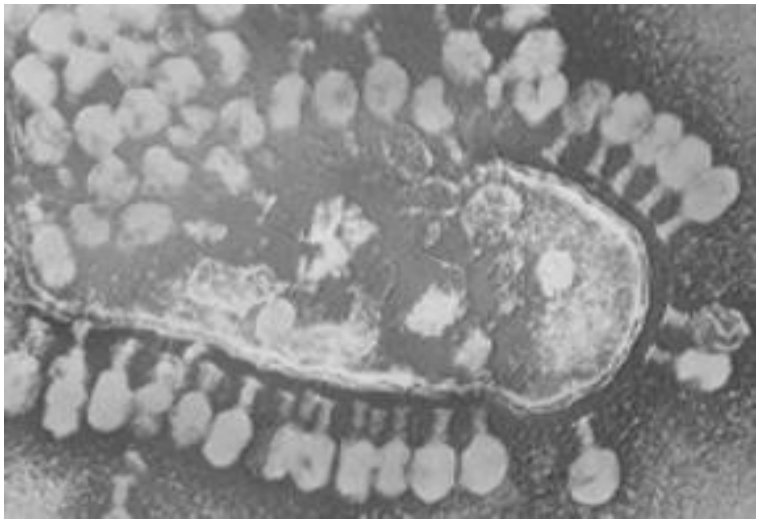


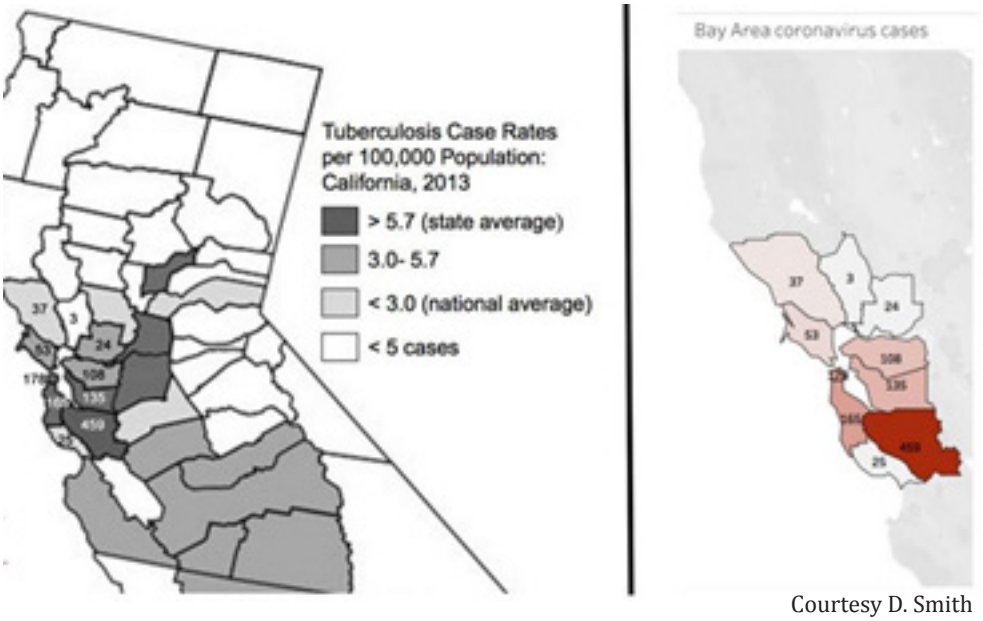
Figure 8*: Transmission Electron Micrograph (TEM) of many phages Attacking a bacterium*

And that is exactly how BCG works–not against "a virus" and not through "training" or "bolstering" the immune system, but by BCG (*Mycobacterium bovis*) shooting off phages to kill closely related mycobacteria or mycobacterial colonization, latent or active, in the system. Since phages are species specific, they are often used for diagnostic purposes. So just the mere successful use of dilute mycobacteria (BCG) with its mycobacteriophages is evidence in itself that the target, the coronavirus, is not of a spontaneous occurrence, but a mycobacterial generated disease. That is, if BCG works, which it probably will.

Conclusion

Preliminary results of a new Chinese study published in medRxiv, (pronounced "med-archive"), an online server founded by Cold Spring Harbor Laboratory (CSHL), Yale University, and the BMJ [*British Medical Journal*], showed that a history of tuberculosis (either active or latent) is an important risk factor for SARS-CoV-2 infection. Patients with active or latent TB were more susceptible to SARS-CoV-2, and COVID-19 symptom development and progression were more rapid and more severe. The authors therefore maintained that tubercular status should be assessed carefully at patient admission, and management and therapeutic strategies adjusted accordingly to prevent rapid development of severe COVID-19 complications. [16]

But did this study go far enough? There is a fine line of difference in the judgement/reasoning to conclude that an initial disease (mycobacterial, tubercular) can lead to increased susceptibility and the rapid development of severe complications in a second disease (COVID-19), and yet not be its underlying cause to begin with. Also, while the study above acknowledges that tuberculosis lays the fertile ground for increase COVID-19 susceptibility and severity, it does not take into account that non-tubercular mycobacteria (NTM) such as *Mycobacterium avium*, deeply suspect for playing a role in the current pandemic and whose signs and symptoms are often identical to COVID-19, can team up with classical tuberculosis to present just the deadly scenario we are now witnessing. [3,4] In the United States, not only is pulmonary *Mycobacterium avium* complex (MAC) disease or fowl tuberculosis more common than tuberculosis, but *Mycobacterium avium* complex is now the leading mycobacterial cause of chronic pneumonia. Traditionally, Italy has a low incidence of tuberculosis (TB); and in 2008, the incidence of notified cases was only 7.6/100,000 population. Yet even by 2009, in Milan, the largest urban area and the birthplace of Italian COVID-19, in Lombardy, the incidence climbed steeply to 20.44/100,000 population. By 2019, Cuomo., *et al*. attributed this to rising immigration patterns. There is evidence that immigration patterns are also at work elsewhere. Take San Francisco [See Figure 9 below]:



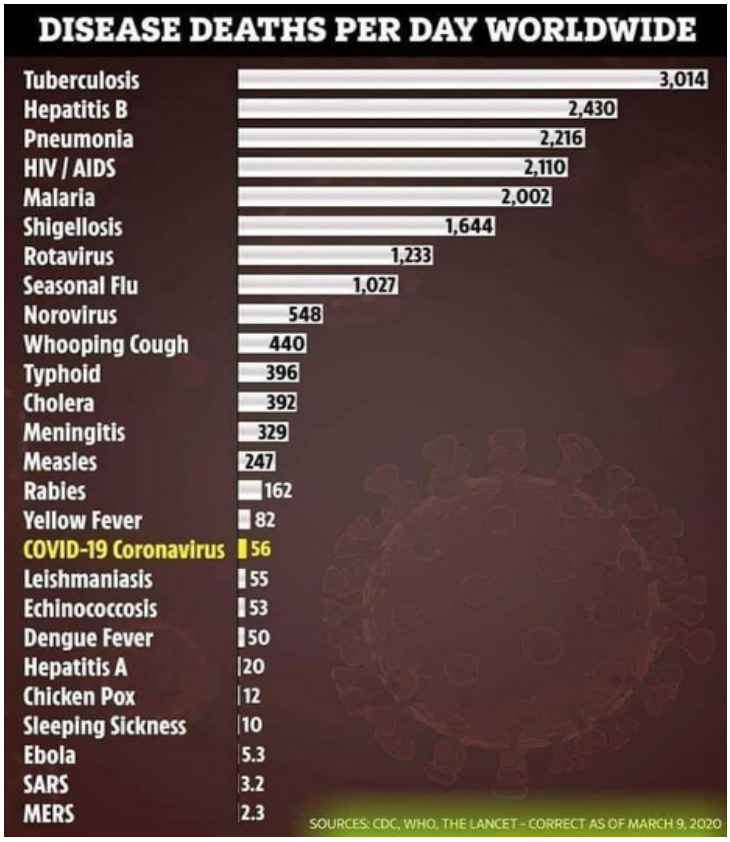
Courtesy D. Smith

Figure 9: *Graphic comparing TB cases and current Covid-19 cases in the San Francisco Bay Area*

Admittedly, the current pandemic has different levels of morbidity and aggression, depending upon where you are referring to. And the question crops up as to whether TB and the mycobacteria can strike as quickly and destructively as is seen in certain instances in the present pandemic?

Historian/researcher René Dubos, of the *Rockefeller Institute for Medical Research*, assured his readers that "galloping consumption" was not an isolated, but a frequent diagnosis in the 19th Century. [17] Despite persistent myths to the contrary, in the early phase of any new TB epidemic from a new and virulent strain, tuberculosis manifests itself as an acute disease and only much later as the chronic pulmonary tuberculosis that we know in today's Western world. An example of this was found in the high mortality during the 1918 "influenza" pandemic, when African-Americans were brought to fight in France during World War I, large numbers of them dying from accelerated tubercular "galloping consumption". But was it only this specific group that was affected circa 1918? Thomas Mays' study of galloping consumptive involved cases in America that were caucasian. [18] Mays, an infectious disease specialist at Philadelphia polyclinic during the Pandemic of 1890, spoke of such "acute" tuberculosis formerly called "galloping consumption" which not only "invariably" resulted in death but depending upon its intensity, could kill within two or three days –although the majority of cases lived 11 days to five weeks, and could even endure for three or four months.

Even though it has been 27 years since the World Health Organization [WHO] declared the "white plague" a Global Emergency, a Global Emergency which it never lifted, a Global Emergency which to this point dwarfs the COVID-19 pandemic. For human life to be snuffed out, whether it be from mycobacterial disease or COVID-19 is a terrible thing. But it is in the possibility of inaccurate diagnosis or lack of desire to get to the real underlying cause that far, far more lives are lost. To combat this, as COVID-19 raged and while nations around the world confronted the COVID-19 pandemic, the World Health Organization (WHO) reminded people and scientists alike that another respiratory illness— tuberculosis (TB)—remains the world's leading infectious disease killer and urged more action to prevent the disease. [19] While many cases are latent, and require no treatment, tuberculosis and its related mycobacteria can complicate other health conditions, such as HIV, diabetes, COPD, cancer, and many others. And preliminary data suggests that combined, mycobacterial disease plays a much greater role in "underlying conditions" then any of the others presently attributed to COVID-19. Perhaps it's time to rethink COVID-19.



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