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COVID-19 and Repurposed Drugs How Much is A Human Life?.

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ABSTRACT

The current pandemic due to COVID 19 (SARS COV2) has revealed a disturbing reality most of the world's health systems, and the organizations that govern health policies at a global level, have not been able to meet the expectations that were set on them. On the one hand, W.H.O has shown hesitations, orders, counter-orders, delays and errors that have made it lose credibility. The terrible images of corpses piled up in the corridors of healthcare centers (from underdeveloped countries to the most powerful ones in the planet); will remain forever in our memory. The enormous financial effort made was not always well targeted, and rarely benefited the patients. The cost / benefit ratio was inverted, contributing fortunes in the final monitoring of severe cases, when logic indicates that emphasis should be placed on not reaching severe stages, and must be solved earlier. In this article, we establish a comparison between what is done and what - in our opinion - should be done.

Introduction

The answer to the question in the subtitle, about the value of a human life, is simple: a human life, all-human lives, any human life, are priceless. However, if we refer to the cost of healthcare for that human life, there are values that must always be taken into account, not to lower costs, but to optimize benefits. The sustainability of health policies over time is what differentiates utopia from reality. The current pandemic has confirmed a truism: the more advanced a clinical stage, the greater the resources that must be applied (Figure 1).

We are seeing that - during the current pandemic - health services (primary care, general hospitalization and admission to the ICU) are overcrowded, personnel in charge are at the limit of their strength, and the population does not find a response in time. The division of those infected into mild, moderate, severe and critical forms is not tight, since even the most serious cases began as mild, because a percentage of them will inevitably evolve into severe and even lethal forms (Figure 2).

In addition to the lethality of this virus, there are those due to exacerbation of pre-existing comorbidities, and the appearance of new entities, associated with the methods used in its attempt to mitigate it (Figures 3 and 4).

Also, the attention of all pathologies other than COVID are being put off, in an unprecedented neglectfulness (Figure 5).

A very important point is the level of contagion between Health Care Agents. This is far from being an abundant resource; rather, it is disturbingly rare (Figure 6). The higher the level of hospitalization of COVID cases, the greater the risk of contagion from Health Agents, which, in turn, will negatively affect the quality of care of those hospitalized (whatever the cause of their admission). Nor is it a minor or isolated detail the stigmatization to which Health Agents working in the first line of defense against the pandemic have been subjected, who are rewarded in public and rejected or avoided in private (Figure 7).

In another aspect, quarantines have yielded most contradictory results, but -in general terms- it has been shown that their prolonged duration has caused more damage (to the physical and mental health of populations and to the economy of the population
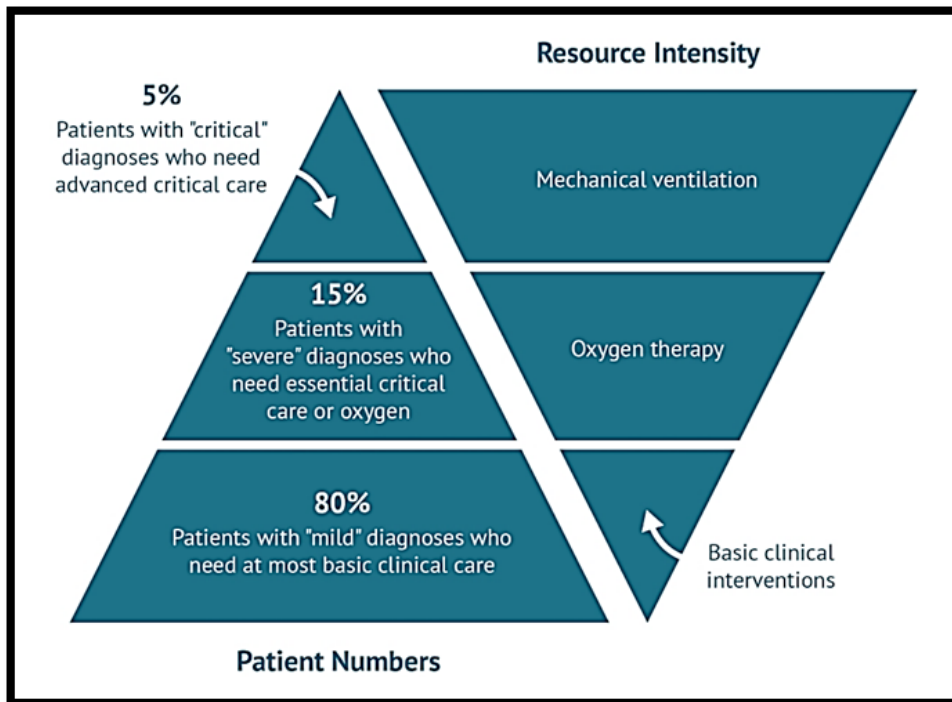
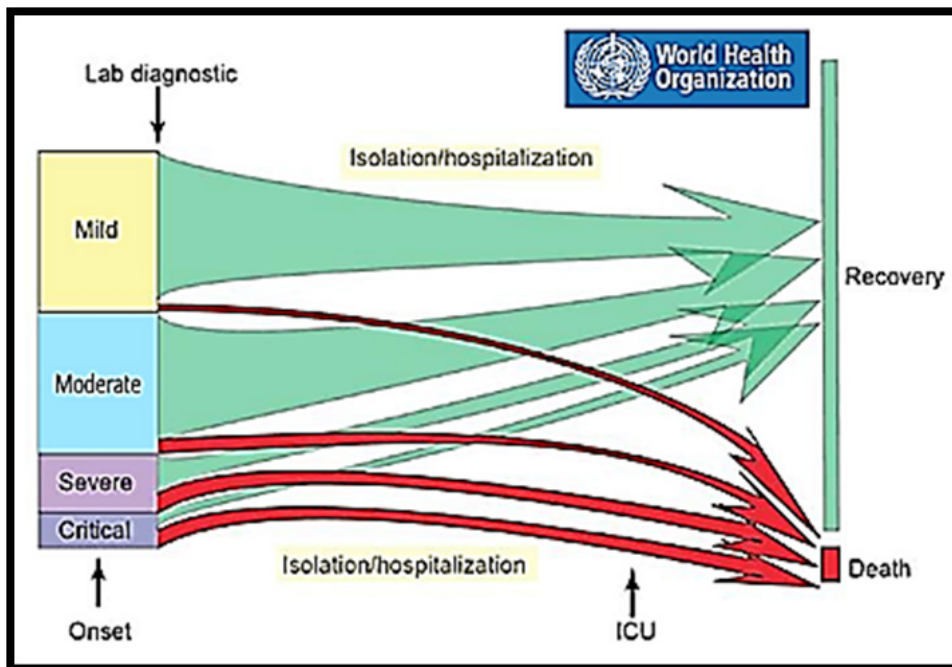**Figure 1:** Relation between severity of cases and need of health measures [1].

Figure 2: Evolution of confirmed cases [2].

and Countries), than the eventual and hypothetical benefit that was initially expected from them (Figure 8). Last but not least, restrictions on free movement have caused not only a limitation on human rights, but also a fatal blow to local economies, mainly those that depend on tourism (Figure 9). Therefore, we want to warn the World Health Authorities that these inequities cannot and should not continue, and that there is a way to avoid them.

Material and Method

THE REPURPOSING OF DRUGS we propose pharmacological alternatives that can be applied with immediate results (waiting for the vaccines to demonstrate - after the necessary time - their respective efficacy and safety). **A. I.D.E.A. PROTOCOL** The IDEA protocol, consisting of the sequenced use of Ivermectin (IVM), Aspirin (ASA), Dexamethasone (DM) and Enoxaparin
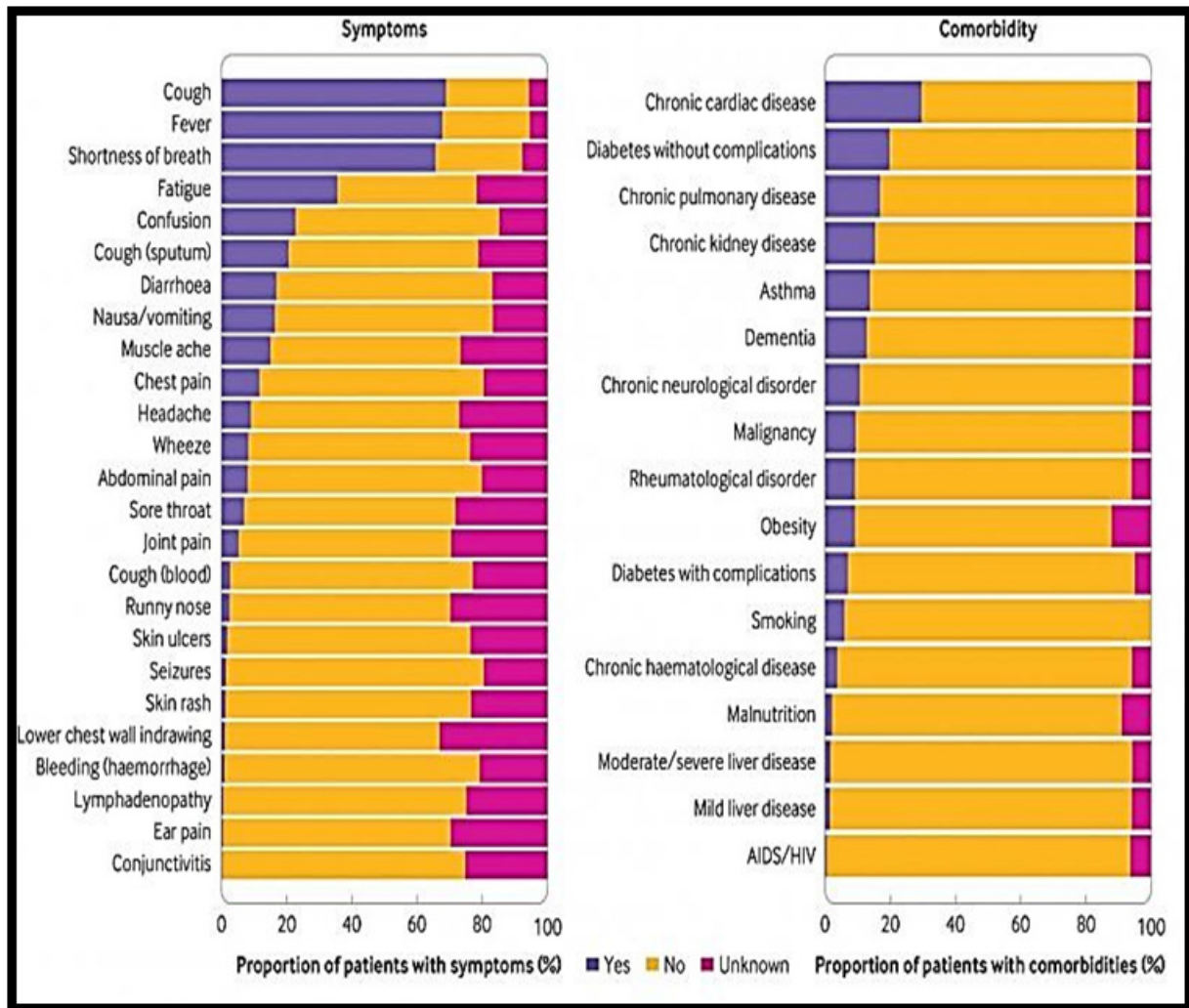
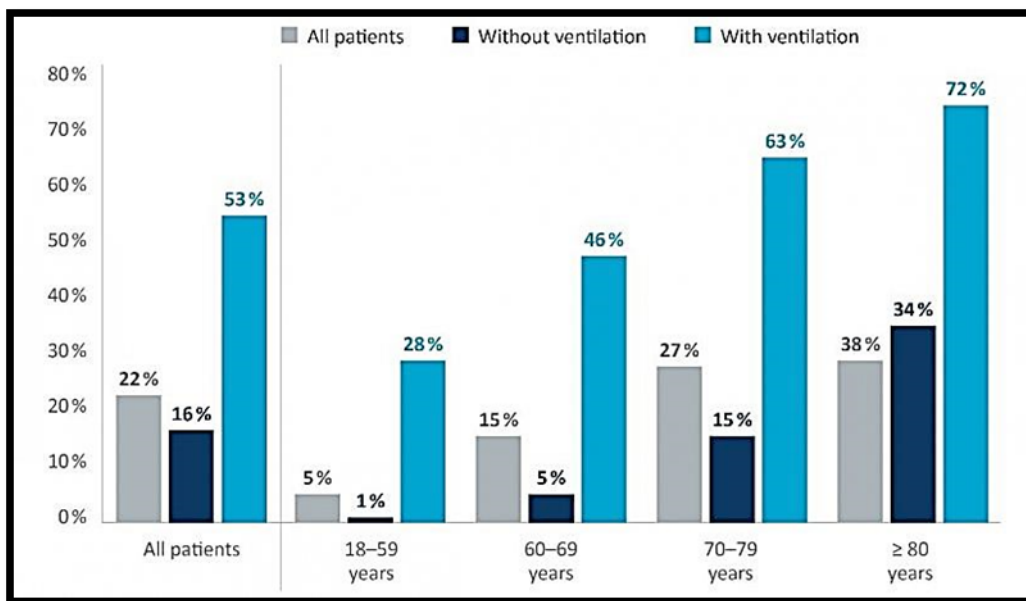**Figure 3:** Comorbidities, which worsen prognosis [3].
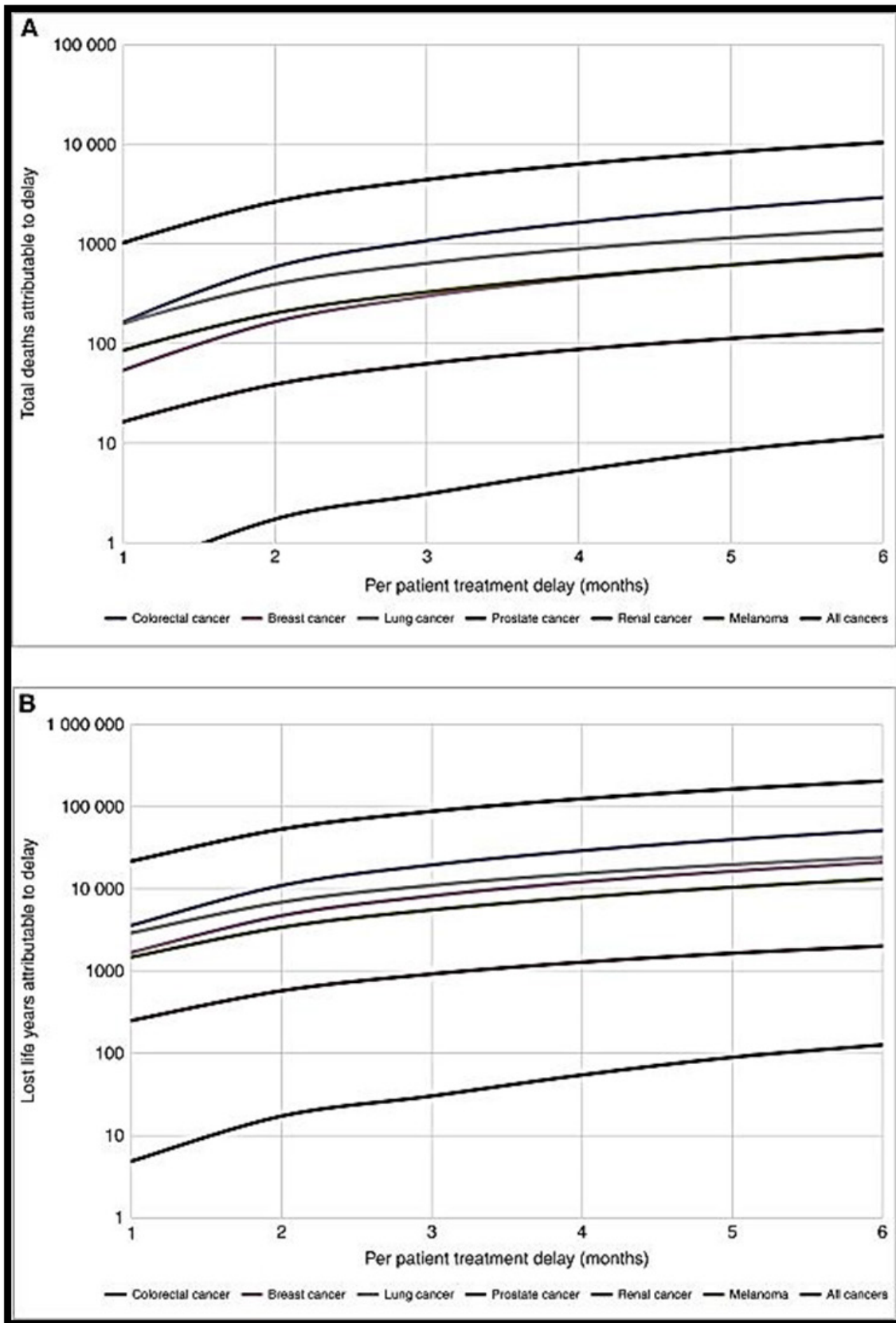

Figure 4: Ventilator-related deaths [4].

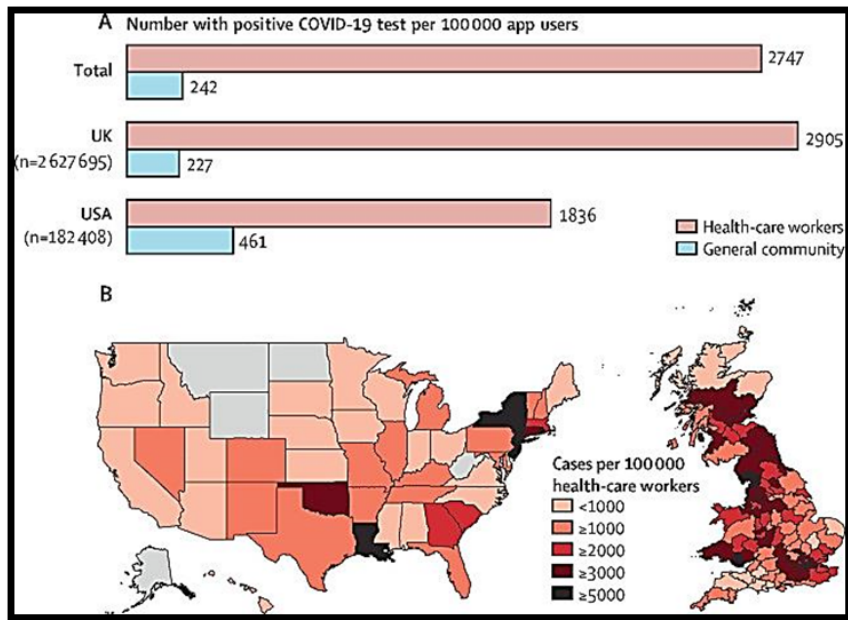**Figure 5:** Delays in the assistance of breast cancer cases.

Figure 6: Relation between contagion of patients and health care workers in two different scenarios [5].
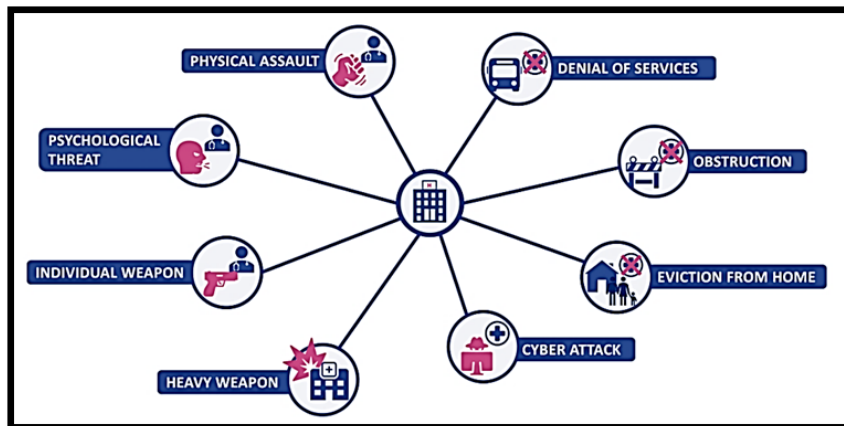

Figure 7: Attacks suffered by health care workers during the pandemic [6].

Figure 8: Lockdowns in different countries [7].

Figure 9: Travel restrictions in different scenarios (multiple sources).

DISEASE SEVERITY	IVERMECTIN	CORTICOID		VENTILATION
Confirmed Mild case (and close contacts)	24 mg orally at a dose of 300 ug / kg in a single dose, to be repeated a week later	No	Aspirin 250 mg orally, on a daily basis	No
Moderate clinical stage	36 mg orally at a dose of 450 ug / kg in a single dose, to be repeated a week later	Dexamethasone 4 mg (parenteral)	idem	Low Flow Oxygen or Oxygen Concentrator
Severe case with bilateral pneumonia	48 mg via gastric cannulae, at a dose of 600 ug / kg to be repeated a week later	idem	Enoxaparin 100 UI/kg (1 mg/kg)	Mechanical Ventilation

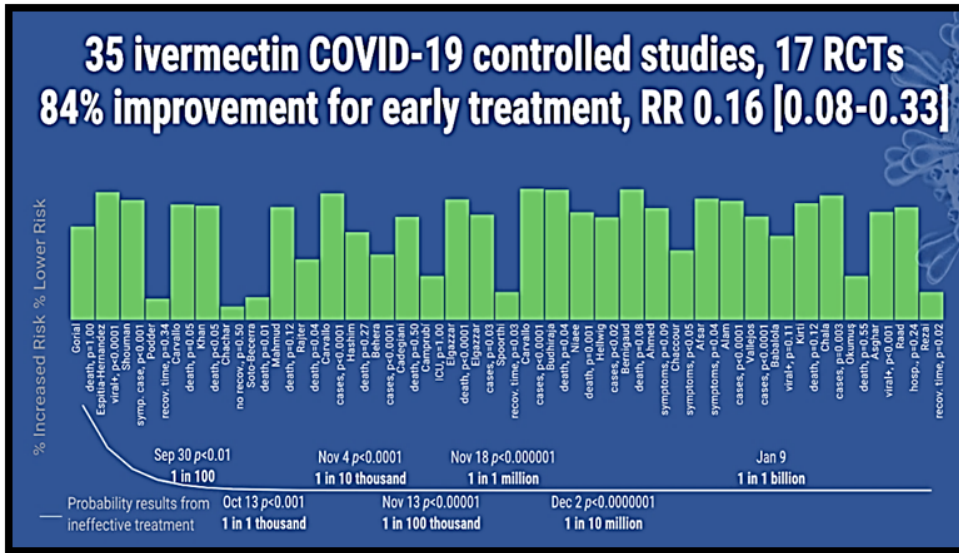**Figure 10:** I.D.E.A. PROTOCOL [8,9].

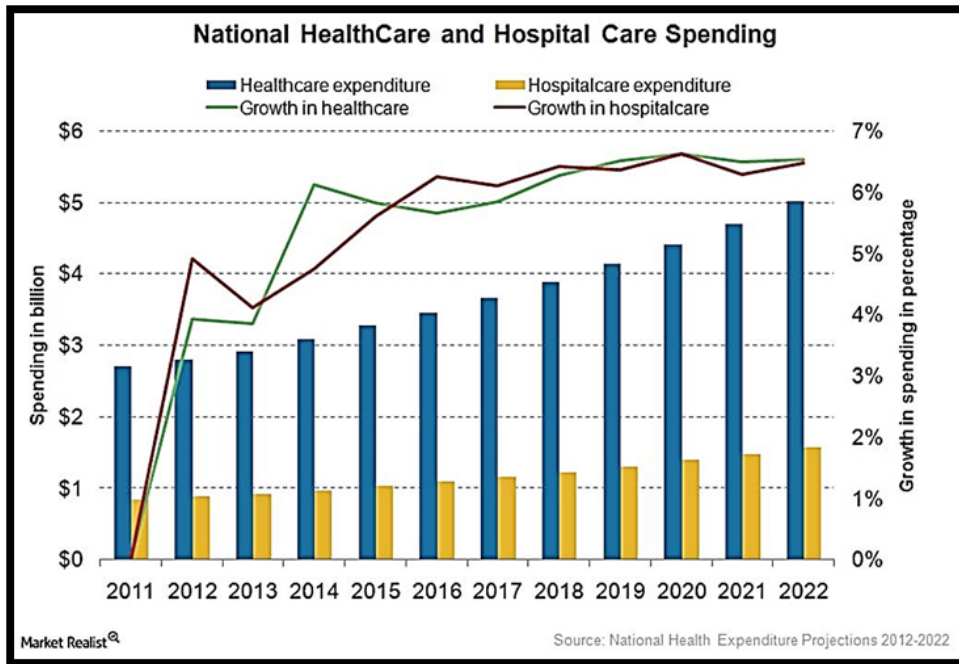**Figure 11:** Effectiveness of IVM on COVID 19 [10].

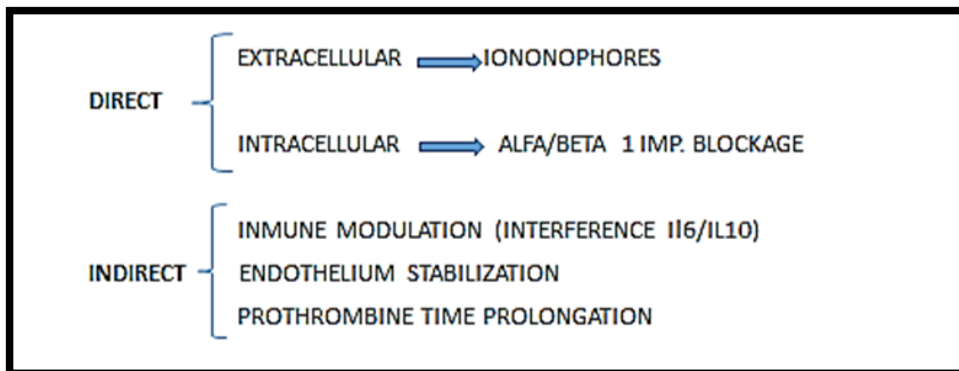**Figure 12:** Permanent increase in hospital costs [11].

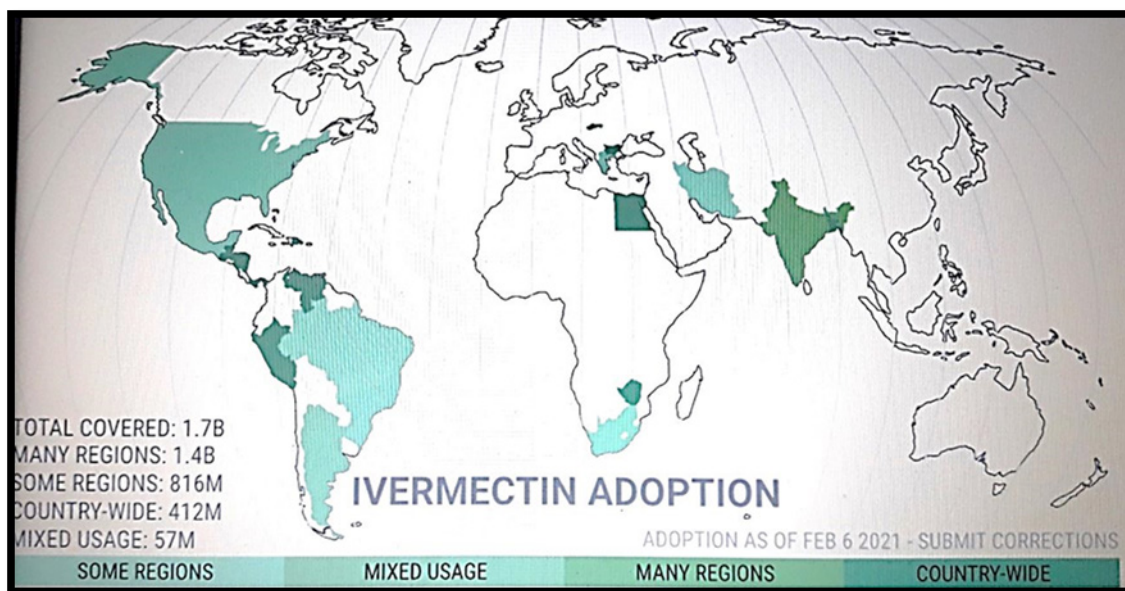**Figure 13:** IVM Mechanisms of action on COVID 19 [8,9]

Figure 14: Regions, which adopted IVM as treatment against COVID 19 at february 2021.
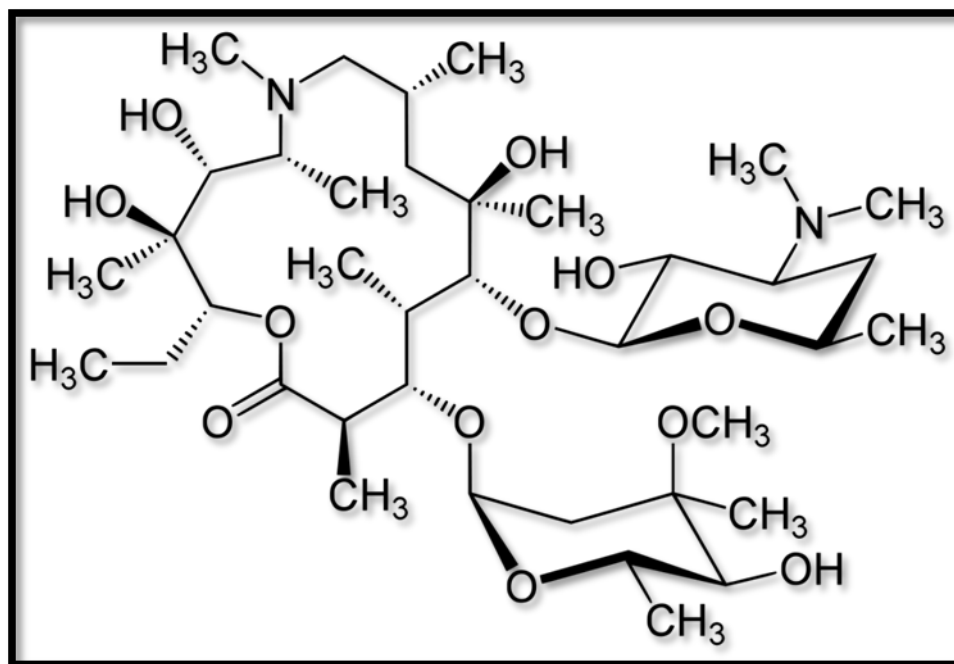

Figure 15: Azithromycin chemical structure.

(ENP), implies a clear advance in the management of COVID patients, particularly in mild patients with recent diagnosis, but also in all its stages (Figure 10).

The present protocol, as all medical interventions, has proved to be more effective if applied at early stages of disease (Figure 11).

There, the rapid improvement and resolution of the COVID 19 pictures has allowed the early discharge of affected patients, while avoiding the need for hospitalizations, which has a crucial impact in the following areas: bio-psycho-improvement of patients and their affective environments, reduction of the potential risk of contagion among participating Health Personnel, cutting the chain of transmission / contagion, and lower health costs. The latter, which continues to grow, is summarized in figure 12.

In mild patients, and even in early moderate ones, only IVM, ASA and DM will be used, and this will mean –in most cases- that there will be no need to hospitalize them. Statistically speaking, up to 10% of mild cases, and up to 40% of moderate cases, require hospitalization. For this reason, avoiding this instance is crucial, not only to decompress health systems, but also to drastically

lower their costs, which will result in the possibility of sustaining these health policies indefinitely (Figure 14). We carried out a cost survey to support what has been stated so far: **Hospitalization Costs, in Europe**: Daily hospitalization (average): 2,932 euros this figure doubles, if the ICU admission is considered. **IDEA Protocol costs**: IVM container for 20 ml (for two weeks): 5 euros AAS, 200 mg / day (for two weeks): 5 euros Dexamethasone (1 shot / day, for 10 days): 45 euros ENP (2 shots / day, for 10 days: 1800 euros. It should be reiterated that mild cases will only require IVM and ASA, and DM will be added to moderate cases, all of which can be treated on an outpatient basis, with which the daily costs of outpatient management of such patients will be approximately 20 euros, on average.

B. Azithromycin Recent publications by French and Italian researchers have raised interest in azithromycin as a treatment for SARS-CoV-2 infection. In one of these articles, the efficacy of combined hydroxychloroquine and azithromycin therapy in patients with COVID-19 is evaluated. In addition, hopes of successfully finding an effective causal therapy against COVID-19 rose after the comment of the co-author of the article, Professor Didier Raoult of the Mediterranean Infection University Hospital Institute, who announced a "significant reduction in the number of positive cases" before the official publication of the study results. It included 42 patients with laboratory-confirmed SARS-CoV-2 infection (RT-PCR) with different clinical symptoms (asymptomatic infection, rhino pharyngitis symptoms, pneumonia), mainly adults in need
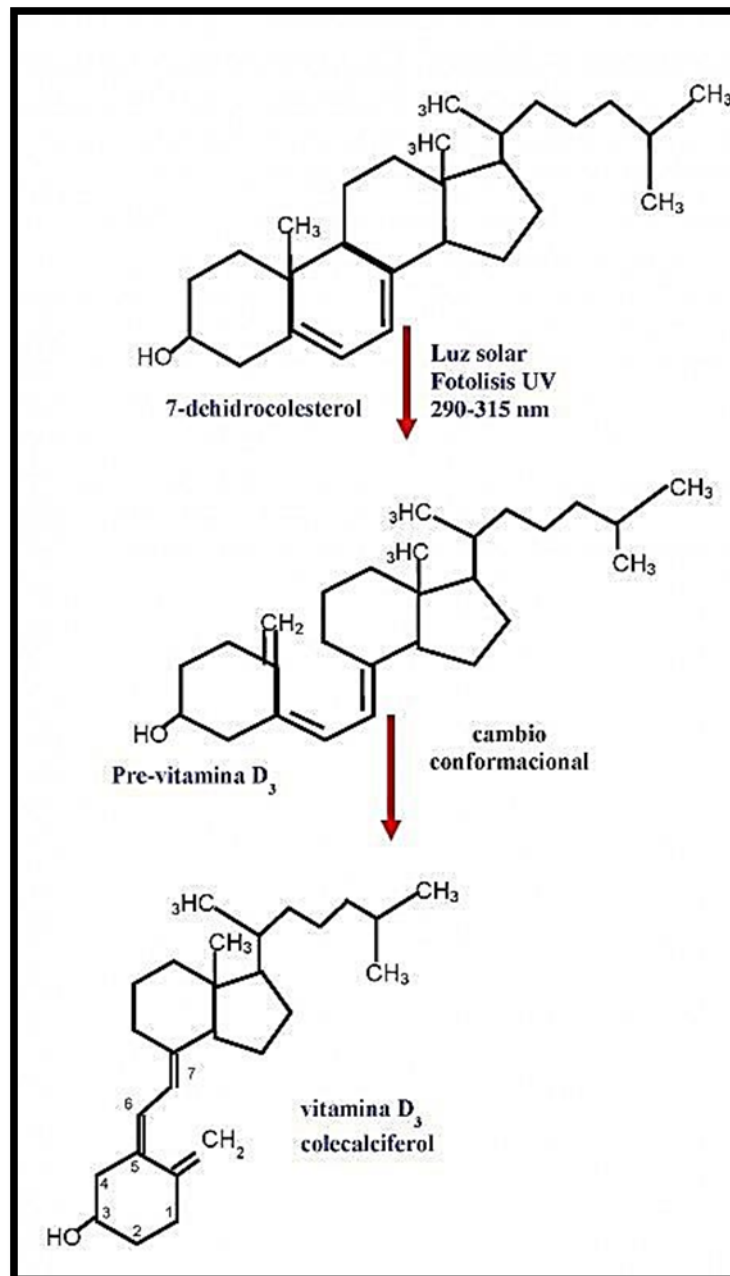

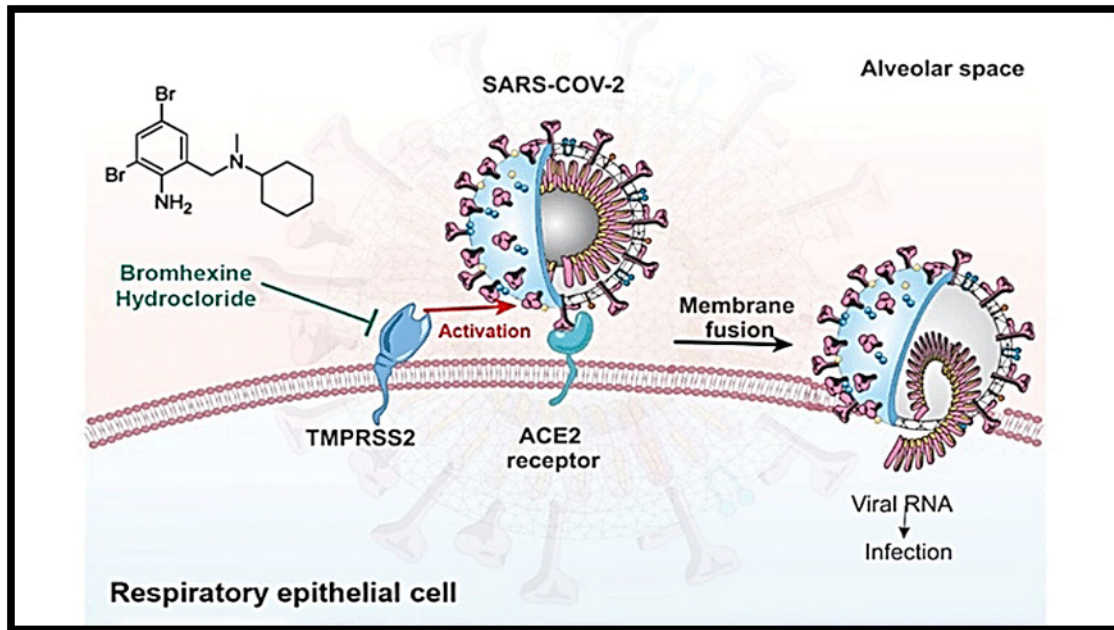**Figure 16:** Vitamin d progressive reactions.

Figure 17: Bromehine interference with virus/tmprss2 membrane receptors.

of treatment or hospital isolation. The authors of the current guidelines of the Polish Association of Epidemiologists and Physicians of Infectious Diseases have also commented on reports on azithromycin, stating that in COVID-19 patients, administration of azithromycin may be considered in justified situations with concomitant bacterial infections and following the general protocols of antibiotic therapy. In this framework, considering the results, and facing the reality that is presented to us in this year 2021, it is possible to recommend the treatment of patients diagnosed positive for coronavirus and before the first symptoms of disease with oral administration of azithromycin, to mitigate the damage induced by said condition, giving them a 500 milligram tablet from the first day until the seventh day of treatment. Always recording the clinical evolution of patients for statistical purposes of clinical research. It should be remembered that this antibiotic is available as a generic drug in the world pharmaceutical market, at an affordable price (Figure 15).

C. Vitamin D (VD): VD has antiviral, anti-inflammatory and lung protection properties, demonstrating that it could play a role in enhancing the immune response.

Hypovitaminosis D is associated with a higher prevalence of diseases that increase the risk for COVID-19: diabetes, hypertension, obesity, cardiovascular diseases, and has a high incidence in the risk group of older adults. The endocrine system of vitamin D can have a variety of actions on the cells and tissues involved in the progression of COVID-19.

The administration of calciferol or 25-hydroxyvitamin D to hospitalized patients with COVID-19 significantly reduced their need for admission to United Intensive Care.

Calciferol seems to be able to reduce the severity of the disease, again to a value so low that it would be sustainable indefinitely in time (Figure 16).

An open-label randomized controlled trial (RCT) in institutionalized but asymptomatic adults older than 60 years is evaluating the effect of 2000 IU (50 µg) of vitamin D plus 30 mg of zinc gluconate per day for two months versus usual care. The primary outcome measure is mortality; the incidence of COVID-19 infection is a secondary outcome.

A trial is testing whether a single oral dose of 25,000 IU (625 µg) of vitamin D (form not specified) improves mortality in SARS-CoV-2 infected patients without severe symptoms, compared to usual care.

Another RCT compared single doses of vitamin D3, 50,000 IU to 200,000 IU (1250 vs 5000 µg) in people with COVID-19 pneumonia who are older than 75 years or older than 70 with low oxygen saturations; the primary outcome measure is mortality at 14 days.

D. Bromhexine (BMH): Bromhexine is a mucolytic drug used in the treatment of respiratory disorders associated with viscid or excessive mucus. It has also proved to be a potent inhibitor of COVID 19 binding to TMPRSS2 membrane receptors, which is crucial for further virus interaction with ACE2 receptors, in order to invade host cells (Figure 17).

Its oral, early administration reduces the ICU transfer, intubation, and the mortality rate in patients with COVID-19. This affordable medication can easily be administered everywhere with a huge positive impact(s) on public health and the world economy.

Discussion / Conclusions

The early application of repurposed drugs, whose primary and secondary effects are widely known, whose efficacy in the current pandemic is being accepted worldwide, and whose costs make them accessible to any health policy over time, forces us to rethink the strategy applied so far, where test drugs have been prioritized, almost invariably with disappointing results.

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