Profound and persistent disparity in COVID-19 mortality rates between USA / Western Europe and sub-Saharan Africa: A crossover effect of antimalarial drugs?

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Abstract

Purpose: In May, 2020, one of the authors (GM) reported a profound initial disparity in COVID mortality rates between developed western nations (DWN) and countries in malaria-endemic regions.[1] We sought to confirm and understand this disparity.

Methods: We performed a comparative analysis of COVID-19 (hereinafter COVID) fatality rates from March 1, 2020, until July 1, 2021. We compared six sub-Saharan African countries (SSA),[fn1] selected for their high rates of malaria (Nigeria, DR Congo, Uganda, Mozambique, Côte d'Ivoire, and Niger), to four DWNs with essentially no malaria. Raw mortality data was obtained from Our World in Data.[2,3] The end-of-month numbers were cross checked for accuracy. We searched the scientific literature to determine uses and roles of antimalarial drugs in the COVID pandemic and the individual antimalarial agents used in these SSA countries.

Results: People living in the DWN died from COVID at a rate approximately 120 times that of people in the SSA group. When corrected for differences in age distribution, the DWN fatality rates were approximately twenty times those of SSA. (Figure 1.) [fn2] This profound disparity persisted over the study period. There is a strong correlation between a country's use of antimalarial drugs and low COVID death rates. Two antimalarial drugs, with reported anti-SARS-CoV-2 activity, artemisinin and the atovaquone - proguanil combination (AV-PG), were in widespread use in SSA. No antimalarial was in widespread use in the DWN. Hydroxychloroquine has a limited role in the treatment of autoimmune disease in DWN, but its use was largely prohibited for COVID treatment.

Conclusion : The profoundly lower mortality rates for people living in SSA versus the DWN appears to be explained by widespread use of antimalarial drugs which have crossover efficacy against SARS-CoV-2. The two most likely drugs are artemisinin and AV-PG. Such anti-COVID crossover effects of antimalarial drugs have been largely overlooked/ignored by those with health policy authority in DWN. Such crossover efficacy deserves urgent and thorough examination.

Keywords: COVID, artemisinin, Africa, malaria, atovaquone-proguanil, death, antimalarial,

Introduction

More than 4.3 million people have died from SARS-CoV-2 worldwide. This is a real-world, observational, epidemiological comparison of two similar-sized (427 and 501 million)

[1] For the purposes of this paper, the abbreviation "SSA" refers to the six sub-Saharan African countries studied.

[2] Overall A-A fatality rate ratio of DWN / SSA is 19. A-A fatality rate ratio of the US / SSA is 22.

populations with markedly disparate COVID outcomes. Using the best available data, we find that one group has about 900,000 more COVID deaths than the other group. This study seeks to find out why.

Early in the COVID pandemic, in March 2020, one of us (GM) observed the inverse relationship between malaria prevalance and COVID fatalities. He reported superior COVID outcomes in malaria-endemic countries and predicted that this success was due to antimalarial drugs and thus would continue.[1]

This work was always about the interplay between malaria and COVID. Six SSA countries studied were selected for study because of their high rates of malaria. This study began at a time when experts argued that Africa would have catastrophic COVID outcomes. The evidence of the inverse relationship between COVID and malaria is compelling. We sought to understand why.

When the initial paper was written in May, 2020, most experts opined that the COVID effects on Africa would be catastrophic. The news and the media were replete with articles anticipating and lamenting a catastrophic result for Africa and SSA in the COVID pandemic. No doubt African economies and countries are at risk on several levels, but the predicted catastrophic COVID outcomes have not materialized. Further documentation of this can be found below in the Discussion.

The U.S. Centers for Disease Control (CDC) asserted that, in the U.S., African Americans are more prone to infection and death from COVID than white Americans. If this were true, then Africans in Africa, who all too often had the same social determinants of poor health as well as essentially the same genetic makeup, would also experience catastrophic COVID outcomes. A follow-up analysis in June, 2020, demonstrated that COVID fatality rates for people living in Lagos, Nigeria, were much lower than for people in New York City. [4] The conclusion was that, at least on a worldwide scale, differences in COVID fatality rates are not readily explained by racial or social determinants, and that there must be some other explanatory factor.

The hypothesis of that first paper was that there exists an inverse relationship between endemic malaria and the incidence and severity of COVID. It was further hypothesized in that paper that the antimalarials "attenuated," were "effective against," or "inhibited" SARS-CoV-2, thus producing a "protective," "prophylactic," or "spill-over" effect. This was initially seen in the context of arriving travelers taking antimalarials. This would have been true of travelers arriving from China as well as the West. Thus, it was hypothesized that "antimalarial agents may play a role in preventing transmission or seeding of SARS-CoV-2 by incoming travelers to sub-Saharan Africa." [1]

This study was performed firstly, to determine whether the profoundly lower COVID fatality rates in SSA versus DWN as reported earlier were still present, sixteen months into the pandemic. Secondly, we searched the literature to discover any evidence to support the previous hypothesis that the use of antimalarial drugs, rather than the malaria infection itself or another variable, might explain the strikingly low COVID fatality rates in SSA.

This third paper now demonstrates that, sixteen months into this pandemic, the COVID outcomes in SSA remain profoundly and persistently superior to the U.S. and the DWNs. This is compelling evidence of the truth of the second hypothesis, that there exists a crossover efficacy of antimalarial drugs against SARS-CoV-2. That is to say, the prolonged superior COVID outcomes seen in the SSA countries, are due to the widespread availably and usage of other antimalarial

drugs initially understood to be atovaquone-proguanil ("AV-PG"), marketed as Malarone ® and now understood to include artemisinin as well.

Another, older antimalarial, hydroxychloroquine (HCQ), has always been an issue in the current pandemic. HCQ is the prototypical antimalarial, or at least was so in the past. Evidence demonstrates that HCQ has had success against SARS-CoV-2 in this present pandemic. This paper documents that the widespread prohibition and criminalization of early, outpatient treatment with HCQ has failed. (Figure 4.) We further note that HCQ is no longer widely used to treat malaria in SSA, so HCQ is not primarily responsible for the beneficial effect seen there. All these facts suggest that there exist other antimalarial agents used in the SSA countries which explain the profound 96% decrease in COVID mortality seen there. For the reasons which follow, we argue that two other drugs, artemisinin and AV-PG primarily explain the profoundly lower COVID mortality rates reported in SSA.

Material and Methods

Fatality Rates

This was an observational, epidemiological study. The experimental design was to tabulate, follow, and compare the COVID fatality rates of six sub-Saharan African countries (SSA) and four developed western nations (DWN) for the first sixteen months of the COVID pandemic from March 1, 2020 through July 1, 2021.

The six specific SSA countries of Nigeria, DR Congo, Uganda, Mozambique, Côte d'Ivoire, and Niger were not cherry-picked for inclusion because of low incidence of COVID. They were selected because they have the world's highest rates of endemic malaria as determined by the WHO's World Malaria Report for 2019. That report stated that "nineteen countries in sub-Saharan Africa and India carried almost 85% of the global malaria burden." These "six countries [studied here] accounted for more than half of all malaria cases worldwide." [5] The four developed Western nations chosen for comparison were Italy and Spain for their early experience and the U.S. and U.K. for their purported overall medical expertise.

Raw mortality data was originally obtained from the total_deaths.csv file downloaded from Our World in Data.[2] This data source ceased being populated in November 2020. After that the data was migrated to a file named owid-COVID-data.csv.[3] The cumulative fatality rates were reviewed at the end of each month. The numbers were routinely cross checked for accuracy against the Coronavirus COVID Global Cases Dashboard from The Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) Whiting School of Engineering.[6] We performed a comparative analysis of death rates from COVID from the beginning of the pandemic until July 1, 2021. The cumulative fatality rates are reproduced graphically as Figure 1.

In the original May 2020, paper, the March and April, 2020 data were analyzed by epidemiologist and biostatistician, Dr. Khuder, one of the original authors. Dr. Khuder also verified the statistical significance of the data in the second, "Two Cities" paper in June 2020.[4] The more recent data, through July 1, 2021, was reverified using an online "Z score calculator for Two Population Proportions" at www.socscistatistics.com. [7]

To maximize the accuracy of the data, it was adjusted for age. We used a simplified age-adjustment method because age-banded fatality data was not found for the SSA countries. The

study country with the largest geriatric population is Italy at about 23%. The U.S. is 15.2%. The percentage of geriatric patients in the SSA countries averages about 3%. The fatality rates are adjusted accordingly. The age-adjusted fatality rates for the six SSA countries are a statistical fiction created to adjust for the differences in age demographics because these SSA countries have a lower percentage of elderly residents.

Review of Use/Efficacy of Antimalarial Drugs

To better understand the role of antimalarials in the treatment of SARS-CoV-2, the worldwide use of the antimalarials, HCQ, AV-PG and artemisinin was reviewed. To better understand the particular contributions of the three antimalarial drugs in achieving the extraordinarily low rates of COVID fatality in SSA, a review of their specific use in SSA was undertaken.

To review this material regarding COVID outcomes in SSA and the potential roles of antimalarial drugs in early, outpatient treatment, we employed various search engines including PubMed, Research Gate, Google Scholar, medRxiv, bioRxiv, Elsevier's SSRN and various sources of government and news data sources. Government and quasi-government health data sources included the World Health Organizations' Annual Malaria Report (2019 and 2020) and various countries' Presidential Malaria Initiatives for recent years.

Because this pandemic placed all of us in fast moving, uncharted waters, we had to use less overtly scientific sources such as newspapers and other periodicals. We were particularly searching for government policy pronouncements and other relevant materials to enable us to better understand what was happening in SSA. The various data sources were reviewed for information regarding the use of antimalarials to treat COVID in the study countries.

Results

COVID Fatality Rates

There are two classes of results. The first was statistical data collected and analyzed regarding the COVID fatality rates of the two groups of countries. The second class of results was the review of the use of particular antimalarial agents in the six SSA countries.

COVID fatality rates in SSA remain extraordinarily low and inversely related to the incidence of malaria. The COVID fatality rates utilized were those reported by their governments and collated by JHU and other respected sources. The COVID fatality rates in the SSA countries started low and stayed low over sixteen months of study. The data were reviewed and recalculated once a month on the first of the month. The data were finalized on July 1, 2021.

The cumulative age-adjusted COVID fatality rates for the two groups of countries, SSA and DWN are reproduced graphically as Figure 1 and also in Table 1. As of July 1, 2021, the average raw, population-adjusted COVID fatality rate of the four DWN was 1,904 deaths per million (dpm). The average raw, population-adjusted COVID fatality rate of the six SSA countries was 15.7 dpm. For comparison, the average raw, population-adjusted fatality rate for the entire world from Our World in Data (OWID) was 507 dpm. Thus, the raw, population-adjusted fatality ratio of DWN over SSA was 121:1 on July 1, 2021, sixteen months into the pandemic. It has remained persistently more than a hundred-fold. This remained highly statistically significant.

The abstract of the first article, "Markedly Lower Rates of Coronavirus Infection and Fatality in Malaria-Endemic Regions," began with the self-description as a "comparative analysis involving 2.4 billion persons across the world demonstrates a wide (two orders of magnitude or one hundred-fold) disparity in coronavirus fatality rates between well-developed and less-developed countries." Pg. 1. It ended with "This unexpected, hundred-fold, inverse disparity in fatality rates cannot be ignored." Pg. 9.[1] Thus, the data and the disparity remain persistent. Although the ratios have fluctuated a bit at times and decreased somewhat overall, the original hypothesis from the first paper remains intact over sixteen months of pandemic. The DWN have COVID fatality rates that exceed those of malaria-endemic SSA by two orders of magnitude or one hundred-fold.

COVID Fatality Rates - Age-Adjustment

The study country with the largest geriatric population is Italy at about 23%. The U.S. geriatric population is 15.2%. The percentage of geriatric patients in the SSA countries averages only about 3%. Seeking the greatest possible degree of accuracy, the fatality data was adjusted for age differences in the SSA population. When adjusted for age, the fatality rates of some of the DWN changed somewhat, but not nearly as much as the fatality rates in SSA. As of July 1, 2021, the average age-adjusted COVID fatality rate of the six SSA countries was 124 dpm. The average age-adjusted fatality rate for the DWN was 2,322. The average age-adjusted COVID fatality rate for the DWN was nineteen times greater than that for the SSA as of July 1 2021. The age-adjusted COVID fatality rate in SSA is 5.3% that of that of the DWN. The age-adjusted COVID fatality rate in SSA is 94.7% less than of that of the DWN.

When adjusted for age, the U.S. rate goes up as well as the African rate because the U.S. has significantly fewer elderly residents than Italy. Of the four DWN studied, on July 1, 2021, the U.S. had the highest age-adjusted fatality rate at 2,774. The age-adjusted fatality ratio of the U.S. over SSA was 22:1. The age-adjusted fatality rate of the U.S. is 22 times that of SSA. The age-adjusted COVID fatality rate in SSA is 4.5% that of the U.S. The age-adjusted COVID fatality rate in SSA is 95.5% less that of the U.S. This remains highly statistically significant. These results are summarized in Table 1.

Cumulative raw and age-adjusted COVID fatality rates in SSA remained extraordinarily low over the entire sixteen-month period of study from March 1, 2020 through July 1, 2021. This disparity is still confirmed by other data sources (e.g. JHU). [5 & fn3] The evidence presented here is what the FDA calls Real-World Data (RWD) or Real-World Evidence (RWE). The "FDA uses RWD and RWE to monitor post market safety and adverse events and to make regulatory decisions." The FDA notes that observational studies are increasingly being used to "generate innovative, new treatment approaches." [10]

Use Antimalarial Agents – Hydroxychloroquine

It is impossible to study the COVID pandemic without some consideration of hydroxychloroquine (HCQ). HCQ is the prototypical "antimalarial" agent. In the media, HCQ is often described as "the antimalarial drug HCQ." Though criticized and prohibited in the U.S.,

[3] E.g., the Lagos/NYC data as it was in the previous June 2020, "Two Cities" article. [4] On May 11, 2021, the total COVID fatality rate in Lagos was 439 total or 29 dpm. [8] The cumulative fatality rate reported in NYC was 28,000 total deaths (as of May 17, 2021) or 3,333 dpm. [9,20] Again, this is about a one-hundred-fold difference.

HCQ is successfully used to treat COVID around the world. HCQ remains perhaps the greatest controversy in the COVID pandemic. HCQ was always touted as an antimalarial agent. A search on PubMed reveals the existence of 2,588 articles on HCQ and COVID in about sixteen months' time. [11]

HCQ has been widely successful in the treatment of COVID around the world. In a metanalysis of 1.8 billion patients, the c19study group reported that "the treatment group has a 69.9% lower death rate."[12] There is arguably no institution more representative of modern "science," especially contemporary western science than the American Association for the Advancement of Science ("AAAS"). The AAAS is epitomized by its (rather audaciously named) flagship publication "Science." Now in the COVID pandemic, even the AAAS has acknowledged the association between the use of HCQ and superior COVID outcomes worldwide. In an AAAS EurekAlert! The AAAS cited a c19 study of the use of HCQ around the world as Figure 2. [13,14] Figure 3 shows the corollary, the COVID outcomes of those same countries around the world.[15,fn4]

Despite the criticisms and prohibitions by the purported best and brightest of U.S. physicians and scientists, HCQ is successfully used in the U.S. as well. Its precursor, quinine, has been used for 220 years. HCQ is said to have been used to treat malaria for 65 years. The public and many in the scientific community appear to have a continued interest in HCQ. Shortly after Dr. Raoult's first publication in March 2020,[16] Dr. Zev Zelenko, practicing near the U.S. COVID epicenter in New York, began to report his success in treating COVID with HCQ. [17] In June 2020, well-known Yale epidemiologist, Harvey Risch, MD, PhD, published his epidemiologic evidence of the efficacy of HCQ. [18] At least by October 2020, Dr. Brian Tyson was publicly reporting his success in treating COVID in southern California. [19] Dr. Tyson was one of the coauthors on Dr. McCullough's paper (below). His associate Dr. Fareed was one of the treating physicians appearing along with Dr. McCullough and Dr. Risch before the Senate Homeland Security Committee. [21] In August 2020, Peter McCullough, MD, PhD, and a large group of coauthors published the seminal article, at least in the U.S., on early, outpatient treatment of COVID in the American Journal of Internal Medicine. [22] Space does not permit the cataloging of the many other physicians who have reported success in treating SARS-CoV-2 with HCQ. When a dozen physicians staged a social media press conference in Washington, D.C. on July 27, 2020, NBC reported that they were viewed 20 million times on Facebook before they were censored.[23] The public has a real interest in HCQ.

Results of Outpatient Treatment Prohibition

In the U.S. especially, early outpatient treatment of COVID with the antimalarial HCQ was widely criticized by health agencies and experts. This includes: the FDA,[24] the CDC,[25] Dr. Fauci, the director of the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH and advisor to presidents Biden and Trump,[26,27] Dr. Fauci's agency, the NIH,[28] and the World Health Organization.[29] Studies from North America are 3.7 times more likely to report negative results than studies from the rest of the world combined.[30]

HCQ was not only criticized, it was widely banned throughout the U.S., often under the full weight of law. In Ohio, for example, this included the Board of Pharmacy,[31] the Ohio Attorney

[4] The issue here is not an absolute one-to-on correspondence between a country's use or prohibition of HCQ and its COVID outcome. The issue here is that the AAAS has begun to acknowledge the role of HCQ in this pandemic.

General and both of Ohio's two federal prosecutors.[32,33]

America's prohibition and even criminalization of HCQ has failed. This can be seen not just in the OWID graph (Figure 4, below), but also in the now infamous May 22, 2020, Lancet article entitled – "Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID: a multinational registry analysis." [34] Its lead author was the endowed chair of cardiology at Harvard, Prof. Mandeep R Mehra, MD. The newly released article was touted on CCN on Friday afternoon, May 22, 2020.[35] On the basis of the Lancet article, the WHO immediately terminated all HCQ research worldwide.[36] The data for the Lancet article was reportedly collected and held by a company called Surgisphere.[37] Surgisphere turned out to be a complete fraud, and it vanished when the fraud was exposed.[38] The article, later known as "Lancetgate," was subsequently withdrawn.[39] A related article was retracted from the New England Journal of Medicine. [40] In an interview with The New York Times, Dr. Richard Horton, the editor in chief of The Lancet, "called the paper retracted by his journal a 'fabrication' and 'a monumental fraud.'" [41]

There is now overwhelming evidence the U.S. COVID outcomes are far worse than the rest of the world. Figure 4 can easily be produced on the OWID website. [5,42,] [fn5] The poor U.S. outcomes can easily be confirmed by the most widely used data source, the JHU COVID Dashboard. [5] If this data is not accurate, how can we trust any data in the COVID pandemic? Even if the SSA data is disregarded, there remain some 185 other countries to compare to the U.S. It is indisputable that U.S. results are at least twice as bad as the rest of the world – maybe four times worse.

For the purposes of this paper one must consider the role of HCQ. HCQ is used to fight COVID in Africa, but the prevalence of HCQ in Africa to treat Malaria or COVID is not precisely known. The authors make no claim of possessing exhaustive knowledge of the usage rates of HCQ to treat either malaria or COVID in these SSA countries. A few things have been discovered. For approximately the past fifteen years, HCQ has been supplanted as the recommended antimalarial drug in SSA. Artemisinin is the preferred drug. However, change is slow and there are anecdotal reports of continued use of HCQ in many countries for various reasons, especially for confirmed or suspected malaria.

About twenty reports of HCQ use by governments or groups for the treatment of COVID in SSA have been documented by the c19study group.[43] There is additional documentation of intentional use of HCQ to treat COVID in SSA. [fn6] Even if there is significant HCQ use in SSA,

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[5] OWID not just some guy on the internet. OWID is the flagship publication for the Oxford Martin Programme on Global Development at Oxford University. Oxford University is the oldest university in the English-speaking world, effectively established in 1096. Our World in Data's mission is "Research and data to make progress against the world's largest problems." Oxford seems to be a reliable institution. Oxford/OWID's evaluation of U.S. performance during the pandemic is the best available evidence. The U.S. has been significantly outperformed by the rest of the world during the COVID pandemic.

[6] Writing in the journal, *Research and Reports in Tropical Medicine* Ethiopian pharmacist Anteneh Belayneh reported that "many African countries have already approved at the national level to use these drugs to treat COVID by opposing WHO warnings." Belayneh specifically noted that HCQ was used to treat COVID in Nigeria, Uganda, and Mozambique. [52] Belayneh reported that "the Anadolu Agency showed that Nigeria goes into clinical trials with hydroxychloroquine." A Nigerian medical director was quoted as saying, "The narrative might change later, but for now, we believe in hydroxychloroquine." Belayneh reported, "Uganda recorded good results by treating COVID patients with hydroxychloroquine or chloroquine." Dr. Diana Atwine, secretary of the Ministry of Health stated,

the fact of the reported COVID outcomes in these six countries being so much better than anywhere else, argues for another explanation besides HCQ. There is no sufficient evidence that HCQ alone could explain the very low fatality rates seen in these six SSA countries. This is especially true because, as seen below, the available evidence indicates that other antimalarial agents may be more widely used than HCQ in SSA.

Use of Antimalarial Agents in SSA – Atovaquone-Proguanil

A second antimalarial agent, AV-PG, appears to be effective against SARS-CoV-2 as well.[fn7] The efficacy of other antimalarial agents was hypothesized in the author's first paper (May 2020).[1] We know that the SARS-CoV-2 virus originated in China, and there was significant exchange of travelers between China and SSA.[44] In the first paper, we hypothesized that this seeding of SSA was inhibited by the use of prophylactic antimalarial agents. In the second paper, we identified AV-PG (Malarone) by name as the suspected antimalarial prophylactic drug used by arriving travelers. It is reported that most visitors (95%) to the six SAA countries are taking prophylactic antimalarial drugs.[45] It is publicized that 70% of the time the antimalarial drug taken is AV-PG.[46] This would have been true of travelers from China as well. [fn8] AV-PG is the CDC recommended antimalarial prophylaxis for all six of the studied SSA countries. [47]

Since the first paper, there have been studies demonstrating in vitro efficacy of AV-PG against SARS-COV-2. [48,49,50] This corroborates the hypothesized diminished seeding of SARS-COV-2 in the SSA countries because of the use of antimalarial AV-PG in arriving travelers. AV-PG's effectiveness is further suggested by this epidemiologic evidence and in vitro evidence as well. The authors are unaware of any current confirming human studies.[51]

The inhibition of seeding of SARS-CoV-2 by arriving travelers would have had the most impact early in the pandemic. Later, COVID would be expected to be spread by person-to-person transmission within the country. Experts now agree that the profoundly superior COVID outcomes have persisted, month after month. The persistence of superior outcomes seen in this SSA countries after an initial period of seeding by travelers and the success of HCQ elsewhere suggests that there is some in-country factor which is inhibiting person-to-person transmission of SARS-CoV-2 in these SSA countries. This epidemiologic evidence suggests that another mechanism, a third antimalarial drug, is inhibiting person-to-person transmission in the SSA countries. That

"Uganda has scored good results from using these drugs. She also added that these drugs are not new for them, and they know well about the side effects." [52]

[7] Malarone® (GlaxoSmithKline (GSK), London England) is the brand name for the combination of atovaquone and proguanil, effective in the treatment of and especially the prophylaxis against malaria. This paper will use the accepted generic abbreviation AV-PG.

[8] The Chinese know malaria. [53] Malaria has been known to be present in China for hundreds of years. In 1940, China had 3 million cases of malaria with 300,000 deaths. [54] Malaria has now been entirely eradicated from China. China would be highly motivated to prevent its travelers from importing malaria back to China. China has a sophisticated CDC believed to be modeled after the U.S. CDC. [55] As part of their CDC, the Chinese have a National Institute of Parasitic Diseases (NIPD) "designated as the WHO Collaborative Center for Malaria, Schistosomiasis and Filariasis since 1980." [56] The Chinese generally follow US CDC and WHO recommendations, and China has a master plan to eliminate malaria. This would include strong antimalarial prophylaxis among its many citizens traveling to Africa. [57] Like other world travelers to SSA, Chinese travelers would have followed CDC guidelines and used AV-PG as prophylaxis. This explains the low initial COVID infection rate in the six SSA countries. [58, 59]

third drug is believed to be artemisinin. This may be the most effective treatment of COVID yet. Like AV-PG, artemisinin is an antimalarial used aggressively and continuously in the six SSA countries.

Use of Antimalarial Agents in SSA - Artemisinin

Artemisinin is an antimalarial agent widely and continuously used in SSA. Artemisinin is usually given as combination therapy (ACT) as the first-line therapy for treatment of malaria. Figure 5 is a graph published by Ezenduka, et al in the *Malaria Journal*.[60] It is illustrative of the use of artemisinin usage in the treatment of malaria in Nigeria. There, the President's Malaria Initiative for 2021 indicates that in a country of about 223 million people, there is need for about 30 million ACT courses.[61] Artemisinin use is reported to be widely available in Nigeria.[62] Artemisinin is also widely used in DR Congo,[63,64] Uganda,[65] Mozambique,[66] Côte d'Ivoire,[67] and Niger.[68] Thus, all the six SSA countries studied utilize large amounts of artemisinin - about 200,000,000 ACT courses, about two thirds of the global artemisinin production.[69] Artemisinin's widespread use is epidemiologically associated with superior COVID outcomes in the six SSA countries.

Finally, this crossover efficacy of artemisinin is supported by the fact that, as with AV-PG, there is not only epidemiological evidence of artemisinin's effectiveness against COVID, there is newly emerging in vitro evidence of efficacy as well. [fn9] We are aware of increasing interest in artemisinin, typically computer modeling and in vitro studies. We are aware of no other sources linking the widespread use of the two antimalarials with the profoundly disparate COVID outcomes between SSA and DWN.

There is also increasing interest in the use of ivermectin in the treatment of COVID. [70] Ivermectin, used to treat river blindness (onchocerciasis), is not an antimalarial, but the geographical distribution of onchocerciasis almost exactly parallels that of malaria in SSA. "More than 99% of infected people live in 31 countries in sub-Saharan Africa" including all six of the countries studied here.[71,72,73,74] The use of Ivermectin seems to produce a 66-73% reduction in mortality rate overall, not the 96% reduction reported in SSA.[75,76]

Amodiaquine, like HCQ, is another congener of chloroquine that is no longer recommended for single drug chemoprophylaxis of P. falciparum malaria because of toxicity.[77] Amodiaquine is used in some artemisinin-based ACT malaria therapies.[71,74] This is further evidence of the efficacy of antimalarial drugs, even chloroquine congeners, in the treatment of COVID. The potential role of amodiaquine per se is only beginning to be elucidated and like ivermectin, is beyond the scope of this paper.

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[9] Nair, et. al. found that "artemisinin alone showed an estimated IC50 of about 70 μM." "In contrast, the antimalarial drug amodiaquine had an IC50 = 5.8 μM." [9] Chuanxiong Nie, et. al. reported that artemisinin inhibited a variety of viruses including SARS-CoV-2. The authors found that the artemisinin derivative Artesunate was most effective and that the commercial drink, COVID-Organics may be effective as well.[9] Ruiyuan et. al. found the artemisinin derivative Arteannuin B showed the highest anti-SARS-CoV-2 potential with an EC50 of 10.28±1.12μM.[9] Thus, there is developing in vitro evidence of efficacy of artemisinin against SARS-Cov-2. This is corroborative of the epidemiologic evidence presented above. In short, the antimalarial agent, artemisinin, is widely used to treat malaria in SSA countries. Artemisinin's broad usage is associated with the world's best COVID outcomes and supported by in vitro as well as epidemiological evidence.

Our review of antimalarials used in SSA through various search engines found some expected but limited consideration of the repurposing of AV-PG and artemisinin as treatments for COVID. These SSA antimalarials have attracted little attention for the treatment of COVID. Across multiple databases, there are about 80 studies of HCQ for every study of artemisinin. There are a few in vitro studies, even fewer still human studies.

COVID Vaccines in Africa

With the new year in 2021, there came a shift emphasis to vaccines for COVID treatment. Vaccines which had been in development are now being administered. Vaccines were emphasized by both American presidents. Vaccines are heavily promoted, even mandated. Because this is the most recent intervention, the most recent data is collected. Vaccination rates through 08/10/21 are as follows. Full vaccination rates for DWN: U.S. 50%, U.K. 58%, Italy 56%, and Spain 60%, for an average of 56%. Full vaccination rates for SSA: Nigeria 0.69%, Congo 0%, Uganda 0%, Mozambique 1.53%, Côte d'Ivoire 0%, and Niger 0.13% for an average of 0.39%. [78]

Discussion

Over sixteen months of pandemic, the raw, population-adjusted fatality ratio of US/Western nations over SSA remains greater than 100:1 at 121:1. This is the "two orders of magnitude" reported more than a year ago.[1] It remains strikingly constant. [fn10]

To obtain the most reliable data, we adjusted for age. It is critical to note that the percentage of elderly residents in the SSA countries is not zero. It is about 20% of the number found in the U.S. Thus, the expected COVID death rate in SSA is not zero. The death rate expected in SSA would be about 20% of the U.S. COVID death rate. Thus, based upon 20% of the U.S. rate of 1,833 dpm, the expected fatality rates in the six SSA countries would be about 367 dpm. It is not. It is reported to be 15.7 dpm. The statistically created age-adjusted average fatality rate for the SSA countries is 124 dpm. The age-adjusted fatality ratio of the DWNs over SSA remained approximately 20:1. The age-adjusted COVID fatality rates in SSA are about 5% that of the U.S. and the other DWN. The disparity in COVID outcomes (fatality rates) between the US/Western nations and SSA is profound and persistent. This disparity contradicts the commonly perceived social determinates of disease. Another paper discussing that subject (Two Cities) was produced last year.[6] The data disparity was and remains highly statistically significant with a p value < 0.0001.[7] The evidence presented here is what the FDA calls Real-World Data (RWD) or Real-World Evidence (RWE). It is useful and reliable.

Some have criticized or rejected the reported African COVID outcomes as inaccurate – for a variety of reasons. They seem too good to be true. The SSA data reported here runs contrary to virtually all American scientists who assert that African Americans are more prone to

[10] The SSA data remained strikingly constant with the slight exception of Mozambique. Its rate began to pull away from the crowd a bit about three months ago. Mozambique's rate has been about three times that of the other five SSA countries. Those other five SSA countries have remain tightly homogenous.

SARS-CoV-2 infection. [fn11] The disparity in the COVID outcomes between SSA and the DWN remained profound and persistent and a great surprise to the experts as seen below.

In our review of antimalarial used in SSA through various search engines, we did not find similar epidemiological studies linking the superior clinical outcomes of SSA with the widespread use of these specific antimalarials. Nor did we find similar papers emphasizing poor COVID outcomes with the prohibition and criminalization of early, outpatient antimalarial treatment. Nor did we find similar papers contrasting the prohibition of early, outpatient COVID treatment in the West with the superb clinical outcomes associated with the widespread use of AV-PG and artemisinin as we see in SSA. We did find the consideration of HCQ to be inescapable with 2,588 citations in Pub Med.[10] There are three aspects of HCQ which impact this study of SSA.

HCQ is widely and successfully used around the world to treat COVID. The c19study group documents 1.8 billion patients studied with those treated with HCQ having a 70% decrease in mortality.[11] America's prohibition and criminalization of early, outpatient treatment, notably with the antimalarial drug HCQ (and ivermectin) has failed with the U.S. having a fatality rate nearly four times the rest of the world. (Figure 4.)

HCQ has some use in SSA as noted above, but that use is thought insufficient to explain SSA's remarkably superior COVID outcomes. (Figure 1.) HCQ's success elsewhere opens the door for consideration of other drugs, possibly antimalarials. AV-PG is a likely candidate. AV-PG is most recommended for malaria prophylaxis in all arriving foreign travelers. AV-PG is the drug most widely used as malarial prophylaxis by travelers arriving to the six SSA countries. AV-PG explains some of the surprise.

Discussion of Atovaquone-Proguanil

Initial SARs-CoV-2 transmission in a country is due to seeding by arriving travelers. Here, SARs-CoV-2 transmission to SSA early in the pandemic was essentially nonexistent. People traveled to SSA from Europe and especially from China before and at least initially during the pandemic. AV-PG is efficacious for prophylaxis and treatment of malaria and, like HCQ, appears to have a shared, crossover efficacy in prophylaxis and treatment of SAR-Cov-2. The low rates of COVID fatality seen here in SSA are thus associated with the world's highest per capita use rates of antimalarial drug AV-PG in arriving travelers. There is no reason to believe that traveling Chinese do anything differently. The evidence indicates that virtually all travelers arriving in SSA were taking AV-PG. About 95% of travelers to SSA take antimalarial prophylaxis and about 70%

[11] American scientists typically attribute increased COVID incidence to social determinates of disease such as poverty, poor access to health care, etc. Thus, the crossover hypothesis, that antimalarial drugs are effective against COVID, and even the inverse relationship to malaria itself, both run uphill or against the tide of conventional wisdom. Some say the African death rates are falsely low because of a lack of testing. If so, where are the bodies of those who died of the misattributed cause? Some say deaths are being concealed. Either way, it seems implausible that six countries are conspiring to hide tens of thousands of corpses. It is arrogant, insulting, or worse to assert that Africans hide, ignore, or cannot count COVID deaths. There is evidence that Africans and others are monitoring for unreported COVID deaths. We must accept that the fatality rates reported by multiple government agencies and reflected on the JHU Dashboard are real. Other explanations have been offered: climate, genetics, the BCG vaccine, or the malarial infection itself. These alternative explanations have generally fallen to the wayside and are beyond the scope of this paper. No other alternative explanation discredits the crossover hypothesis suggested here by the data. The second, Lagos paper ("Two Cities," 06/15/20) provides a more comprehensive analysis of the assertion that persons of African descent are more susceptible to SARS-Cov-2 infection and death.[4]

of those are taking AV-PG. High usage rates of the antimalarial AV-PG are associated with superior COVID outcomes. The countries with the world's highest per capita use of the antimalarial AV-PG have the world's best COVID outcomes. However, AV-PG probably does not play nearly as big a role in persistence of the disparity of outcomes as it did in producing the low fatalities seen in SSA in the early days of the pandemic. A third antimalarial drug is thought to explain the persistence of the disparity; a third antimalarial drug is thought to be even more effective and impactful. It is artemisinin.

The 20-fold disparity in COVID fatality between the DWN and SSA is not only profound but also persistent over sixteen months. These persistently superior COVID outcomes in SSA were of great surprise to the experts. The degree of their surprise cannot be overstated. The unexpected superior COVID outcomes in SSA argue for the beneficial effectiveness of a third antimalarial drug, artemisinin.

Early in the pandemic, most experts opined that COVID's effects on Africa would be catastrophic.[79,80,81,82,83,84] At the time of the first paper suggesting better COVID outcomes in SSA, the news and the media were replete with articles anticipating and lamenting a catastrophic result for Africa and SSA in the COVID pandemic. [85,86,87,88,89,90] No doubt African economies and countries are at risk on several levels but the feared and predicted catastrophic COVID outcomes simple did not materialize (at least thus far in the fifteen months of observation in this study). The U.S. CDC was perhaps the loudest in a chorus of voices who authoritatively asserted that, in the U.S., African Americans are more prone to infection and death from COVID than whites. [91,92,93,94,95] Against this backdrop, it was nearly impossible to consider that Black Africans could possibly have better COVID outcomes than white Westerners, but this is what the data was beginning to show.

Instead, the experts were uniformly surprised at the superior COVID outcomes produced in SSA and now reported here to be continuing sixteen months into the pandemic. For example, by October 2020, Professor Salim Abdool Karim, South Africa's COVID ministerial advisory committee chair stated, "Most African countries do not have a peak. I do not understand why. I'm completely at sea." [96] Perhaps most dramatic were the admissions of Steven Phillips, M.D., MPH, a medical epidemiologist, and pandemic preparedness expert formerly with the CDC. He would go on to make the same observations that other authors have begrudgingly admitted over the past year, describing the "stunning observation," that African death rates are "exponentially lower." He described the "amazing performance" and "spectacular success" of Africa and reported that Africa's superior COVID outcomes are "no longer hypothetical." [97] Thus, about six months after the author's original "Markedly Lower Rates of Coronavirus" paper, [fn12] Dr. Phillips affirmed the author's original hypothesis, the one hundred-fold superior outcomes in SSA. The inverse relationship between malaria endemicity and COVID fatalities is affirmed by former CDC expert Dr. Phillips and further borne out now by another six months of epidemiologic data.

[12] Originally submitted April 27, 2020. [1]

Discussion of Artemisinin

Artemisinin is the drug most widely used to treat malaria throughout the six SSA countries. Artemisinin, like HCQ's precursor quinine, is another natural products story. [fn13] Artemisinin has been used for hundreds of years to treat malaria. Artemisinin is the active ingredient in a traditional Chinese herb called Artemisia annua, or sweet wormwood. Artemisinin has been considered a COVID treatment but is often described condescendingly as an herbal remedy.[98] Artemisinin is not to be trivialized. Artemisinin is utilized for the treatment of malaria and is the drug most widely recommended for malaria treatment in the six SSA countries studied. Tons of artemisinin are produced worldwide, and most is used to treat malaria in SSA. The crossover efficacy of artemisinin is supported by the fact that, as with AV-PG, there is not only epidemiological evidence of artemisinin's effectiveness against COVID, but also newly emerging in vitro evidence of efficacy as well. Artemisinin, of course, is not used in the West. High usage rates of the antimalarial artemisinin are associated with superior COVID outcomes. Thus, the countries with the world's highest per capita use of the antimalarial artemisinin have the world's best COVID outcomes. A year's worth of epidemiological data, presented here, strongly suggests that it is artemisinin whose crossover efficacy caused the 96% reduction in COVID deaths in SSA.

Three other facts pertaining to the potential use of artemisinin should be borne in mind. One, artemisinin is available in a parenteral formulation. It might be an antimalarial which has potential for use in patients with more advanced disease. Two, increased use of artemisinin to treat COVID might lead to increased malarial resistance to the drug. This will have to be monitored carefully. Three, malaria is still a catastrophic disease. Any use of artemisinin to treat COVID must not detract from the drug's availability to treat malaria. The repurposing of other antimalarial agents such as artemisinin and AV-PG should be thoroughly investigated by the world's medical and scientific experts.

Ivermectin and Other Issues

Ivermectin and amodiaquine both show promise in the treatment of COVID but consideration of these agents is generally beyond the scope of this paper. [99] It is pertinent to note that ivermectin seems to produce a 66-73% reduction in mortality rate overall, not the 95% reduction reported in SSA. (Figure 1.) For this reason, the crossover efficacy of the antimalarials is thought to be the more important causal factor and the more efficacious COVID treatment. The success of ivermectin is, at minimum, a further example of how other various drugs like antimalarials may be repurposed to treat COVID. If ivermectin is the causal factor in the superior outcomes of SSA, this is more reason to study ivermectin and SSA as vigorously as possible. [90, 91] Amodiaquine is important as another congener of chloroquine; it was shown in at least one study to have the greatest in vitro efficacy against SARS-CoV-2, greater than artemisinin alone. [68, 74]

[13] Artemisinin is the active agent derived from the Artemisia annua plant. It is commonly used in combination regimens known as ACTs, e.g. artemether-lumefantrine, artesunate-amodiaquine, etc. Because of these multiple combinations and compound names, for the purpose of this paper, these drugs will be lumped together under the name artemisinin.

Failure of Treatment Prohibition and Criminalization of COVID Treatment

Some have attempted to ignore the SSA experience completely. There is no legitimate reason to assume that such a profound disparity is "mere correlation."

Perhaps the greatest surprise has been the utter failure of western medicine and science in the COVID pandemic. As noted above in the results, the U.S. and the West produced COVID outcomes which are approximately four times (300%) worse than the rest of the world. No one saw this coming. Western criticism, prohibition, and criminalization of HCQ has failed. (Figure 4.) The SSA experience is greatly corroborated by the failure of HCQ prohibitions in the West. Even if the SSA experience is ignored, Western prohibitions of HCQ treatment have still failed. The SSA experience is real and cannot be ignored. HCQ has been successfully used in many parts of the world. It appears to be used to some degree in SSA and may contribute to SSA's success, but there exists no convincing evidence that HCQ is the primary cause of the superior COVID outcomes seen there. For this reason, the authors submit that two other antimalarial drugs produce better COVID outcomes than HCQ. They are AV-PG and artemisinin.

There is no doubt that SSA is fragile, both in terms of health care and economically. This is what so many experts saw and feared early in the pandemic. Nothing in this paper should be construed to trivialize these concerns. Whatever value artemisinin and other antimalarials may bring to the early, outpatient treatment of COVID must be balanced against their necessity and requisite availability of these drugs for the treatment of malaria. Perhaps the supply of artemisinin will be required to treat malaria. Perhaps the efficacy of AV-PG and artemisinin in treating and preventing COVID will promote further use of HCQ and further investigation of the repurposing of other antimalarial drugs. Perhaps some antimalarial to which malaria has become resistant will be found to be effective against COVID. Any use of artemisinin or other currently used antimalarial in the treatment of COVID must be managed with great care.

Discussion of Unnecessary Deaths / Lives Saved

In the sixteen months of the pandemic, the COVID outcomes were vastly superior in SSA. In those sixteen months, there were 140,834 lives saved in SSA and there were 897,351 lives unnecessarily lost in DWN. The population of the DWN is 501 million. The population of SSA is 427 million. The total deaths in the DWN are 941,950. The total deaths in SSA are 5,507.

The expected age-adjusted death rate for DWN using the SSA (x15.7 x 5.67) rate is 44,599. The number of actual deaths (941,950) minus the number of SSA rate predicted deaths, equals the number of unnecessary DWN deaths (897,351). The expected age-adjusted death rate for SSA using the DWN (x1904 x 0.18) rate is 146,341. The expected age-adjusted death rate for SSA (146,341) minus the actual number of SSA deaths (5,507) is the number of SSA lives saved (140,834). Thus, there were 140,834 lives saved in SSA and there were 897,351 lives unnecessarily lost in DWN.

Discussion of Vaccinations

With the new year in 2021, there came a shift emphasis to vaccines for COVID treatment. Vaccines which had been in development were now being administered. Vaccines were emphasized by both American presidents. Vaccines are heavily promoted, even mandated.

Because this is the most recent intervention, data is analyzed up to the time of submission. Vaccination rates through 08/10/21 are as follows. Full vaccination rates for DWN are: U.S. 50%, U.K. 58%, Italy 56%, and Spain 62%, for an average of 56%. Vaccine use in the SSA is essentially zero. Only three of the six SSA countries report any vaccine use at all. For SSA the full vaccination rates are: Nigeria 0.69%, Congo 0%, Uganda 0%, Mozambique 1.53%, Côte d'Ivoire 0%, and Niger 0.13%, for an average of 0.39%.

Vaccines are supposed to be effective in preventing death. With regard to the SSA, the expected inverse correlation between vaccination rates and death rates is not found. Just the opposite is true. Paradoxically, the counties with the lowest vaccination rates also have the lowest death rates. This observational, epidemiological study strongly suggests that the Sars-CoV-2 vaccines are not effective in preventing COVID death.[69]

Conclusion

A country's COVID fatality rate is inversely related to its prevalence of malaria. This is a real-world, observational, epidemical comparison of two populations with markedly disparate COVID outcomes. Using the best available data from JHU, we find that one group has 900,000 more COVID deaths than the other group. The countries with the world's highest per capita use of the antimalarial AV-PG have the world's best COVID outcomes. The countries with the world's highest per capita use of the antimalarial artemisinin have the world's best COVID outcomes. The best available compilation of data demonstrates that countries which prohibit early, outpatient treatment with antimalarials and other agents have poor COVID outcomes.

No one can predict the future. COVID deaths may increase in SSA. It's hard to imagine that any future increase in SSA COVID deaths would erase the disparity of 900,000 deaths between SSA and DWN. This data strongly suggests that antimalarial agents have a crossover efficacy in the treatment of COVID. The best available data compilations indicates that countries with the highest usage rates of these two newer antimalarial agents, artemisinin and AV-PG, experienced 95% fewer COVID deaths than DWN.

Recommendations for Further Study

Despite Africa's health vulnerability and economical fragility, this may be a window of opportunity for SSA to be of great benefit to the rest of the world. Whatever the future may hold, SSA had superior COVID outcomes for the first sixteen months of this pandemic. This paper is a plea for further investigation. While protecting the supplies needed to treat malaria, medical researchers should proceed, with haste and vigor, to further investigate the repurposing of antimalarial agents, especially artemisinin and AV-PG, for the treatment of COVID.

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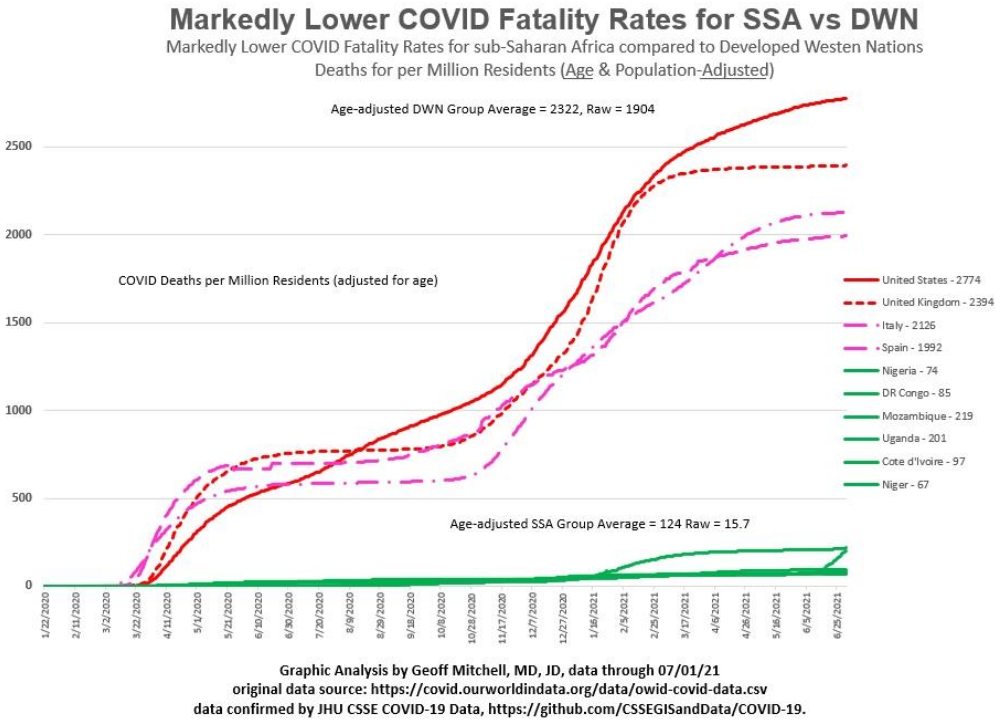


Figure 1. Superior COVID Outcomes in sub-Saharan Africa (07/01/21)

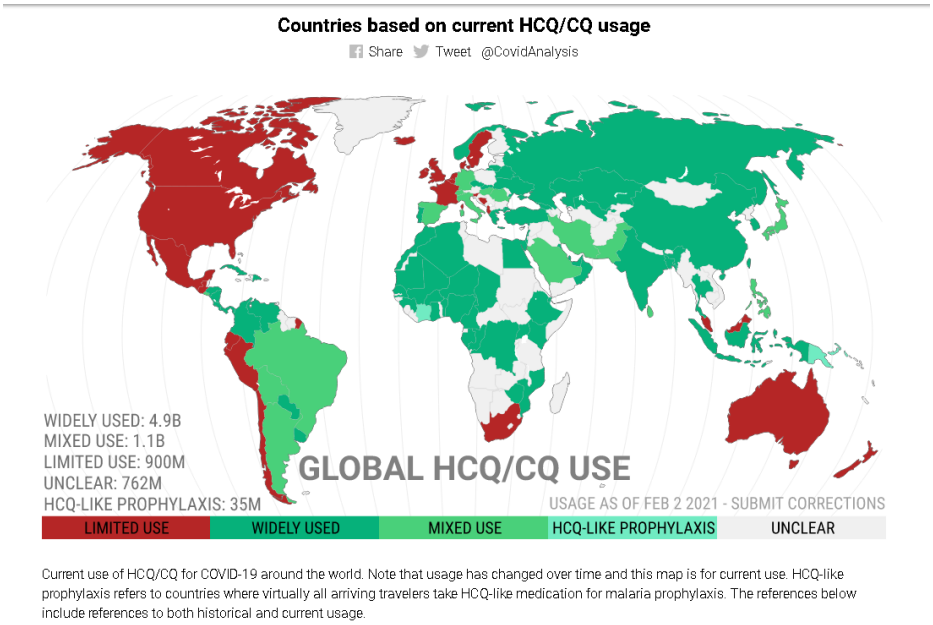


Figure 2 – Global HCQ/CQ Use c19study.com. Copyrights Dr. Alberto Boretti, Dr. Bimal Banik, Dr. Stefania Castelletto, Bentham Science. Also published by AAAS as a "EurekAlert!" https://sciencesources.eurekalert.org/multimedia/pub/250198.php?from=485555

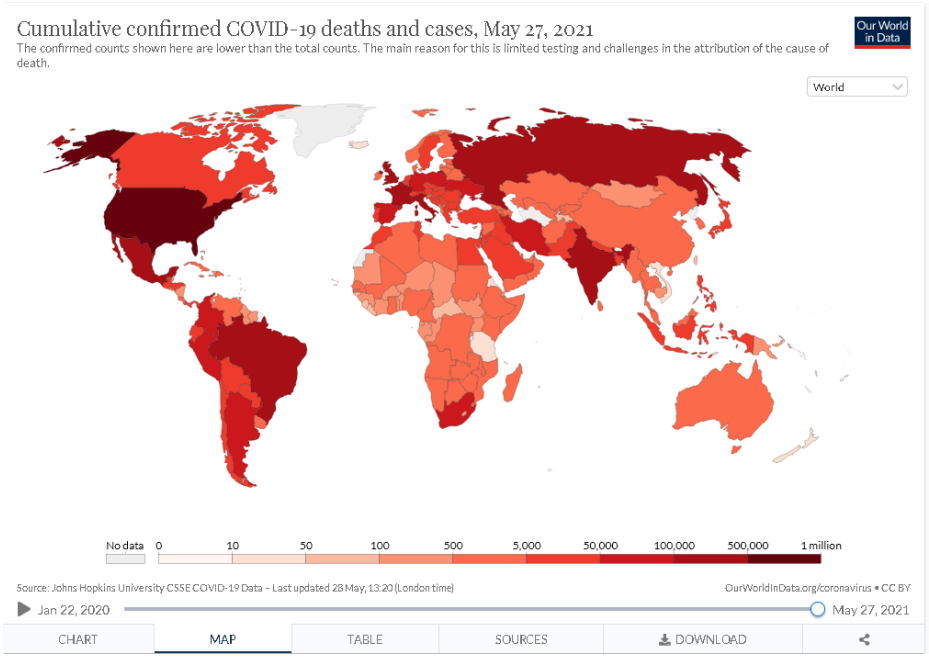


Figure 3 - Cumulative confirmed deaths from COVID 19, OWID https://ourworldindata.org/grapher/cumulative-deaths-and-cases-covid-19?tab=map&country=~OWID_WRL. Also published by AAAS as a "EurekAlert!" https://sciencesources.eurekalert.org/multimedia/pub/250198.php?from=485555, Copyright attributed to Dr. Alberto Boretti, Dr. Bimal Banik, Dr. Stefania Castelletto, Bentham Science Publishers.

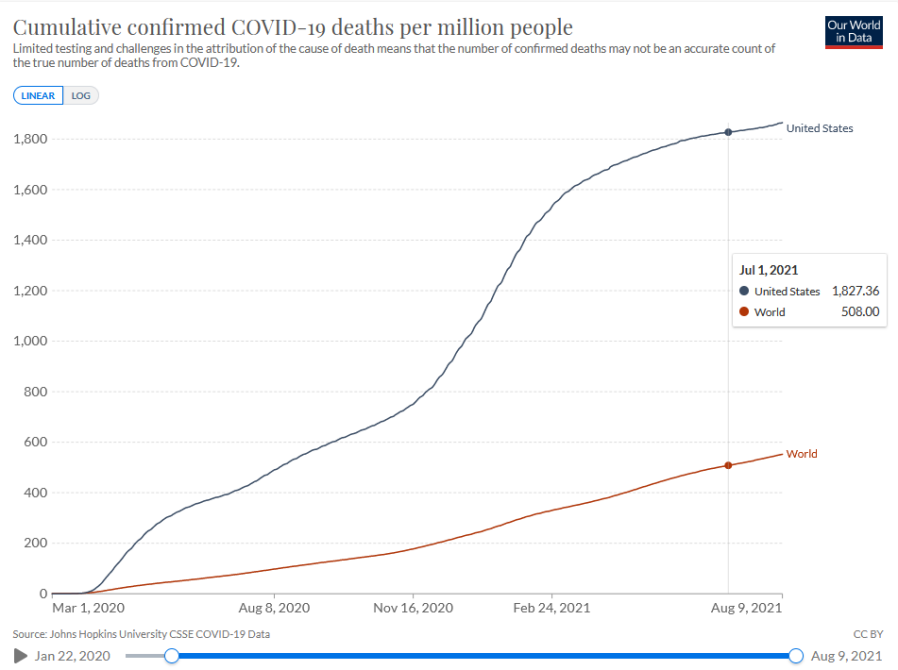
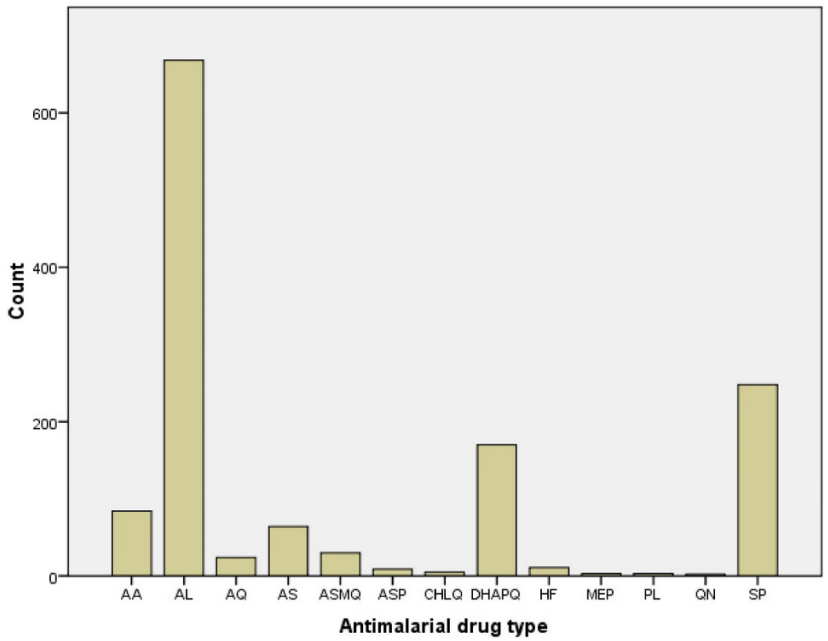


Figure 4. COVID Outcomes, U.S. v. World (U.S. Fatalities nearly 4x worse)

From: Drugs use pattern for uncomplicated malaria in medicine retail outlets in Enugu urban, southeast Nigeria: implications for malaria treatment policy



The utilization pattern of anti-malarial drugs dispensed, by types. AA = artesunate-amodiaquine; AL = artemether-lumefantrine; AQ = amodiaquine; AS = artesunate; ASMF = artesunate-mefloquine; ASSP = artesunate-sulphadoxine + pyrimethamine; CHLQ = chloroquine; DHAPQ = dihydroartemisin-piperaquine; HF = halofantrine; MEP = mepacrine; PL = proguanil; QN = quinine; SP = sulphadoxine + pyrimethamine.

Figure 5. Artemisinin Use in Nigeria. Ezenduka, C.C., Ogbonna, B.O., Ekwunife, O.I. *et al.* Drugs use pattern for uncomplicated malaria in medicine retail outlets in Enugu urban, southeast Nigeria: implications for malaria treatment policy. *Malar J* **13,** 243 (2014). https://doi.org/10.1186/1475-2875-13-243.

Disparate COVID-19 Fatality Rates Between SSA and DWN

The risk of death from SARS-CoV-2 is approximately 120 times greater in U.S. than in poor, malaria prone countries.
When adjusted for age, the COVID-19 fatality rate is still about 20 times greater in the Developed Western Countries.

Country	Population	Cases (07/01/21)	COVID-19 Deaths	COVID-19 Fatality Rate	Deaths /million	Raw Fatality Ratio	% Elderly	Age-adjusted death rate	Age-Adjusted Fatality Ratio	CDC Malaria Prophylaxis Instructions
Developed Western Countries (with good to excellent healthcare infrastructure/resources)										
Italy	60 million	4260788	127587	0.212645%	2126		23 %	2126		Not recommended
Spain	46.7 million	3821305	80883	0.173197%	1732		20%	1992		Not recommended
United Kingdom	66.6 million	4844944	128426	0.191681%	1917		18.5 %	2383		Not recommended
United States	330 million	33679433	605054	0.183350%	1833	**117 x**	15.2 %	2774	**22 x**	Not recommended
Average of Four DWNs				0.190218%	**1904**	**124 x**		**2322**	**19 x**	
High Malaria Prevalent Sub-Saharan Africa (with poor healthcare infrastructure/resources)										
Nigeria	205 million	167692	2121	0.000964%	9.6		3 %	74		All areas are at risk of malaria. Prophylaxis is recommended
Congo	89 million	41353	933	0.001111%	11.1		3 %	85		All areas are at risk of malaria. Prophylaxis is recommended
Uganda	45 million	81034	1061	0.002358%	23.6		2.7 %	201		All areas are at risk. Prophylaxis is recommended
Mozambique	31 million	77205	884	0.002852%	28.5		3 %	219		All areas are at risk of malaria. Prophylaxis is recommended
Côte d'Ivoire	25 Million	48378	315	0.001260%	12.6		3 %	97		All areas are at risk. Prophylaxis is recommended
Niger	22 Million	5492	193	0.000877%	8.8		3 %	67		All areas are at risk. Prophylaxis is recommended
Average of Six SSA Countries				0.001570%	**15.7**			**124**		

Table 1. Disparate Fatality Rates (07/01/21)