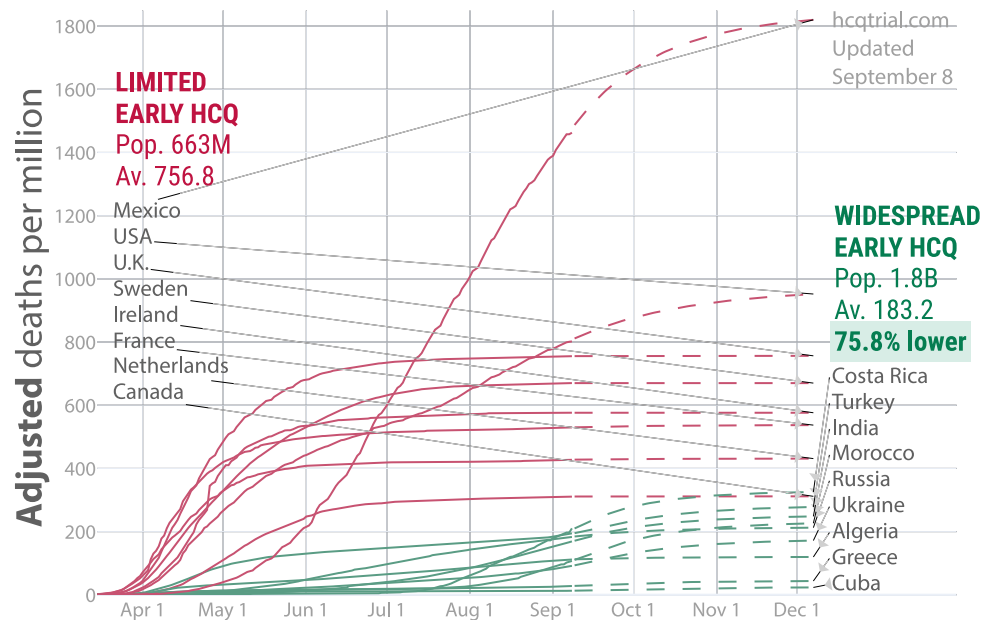


# Early treatment with hydroxychloroquine: a country-based analysis

Covid Analysis, August 5, 2020 (updated September 8, 2020)



Many countries either adopted or declined early treatment with HCQ, effectively forming a large trial with 1.8 billion people in the treatment group and 663 million in the control group. As of September 8, 2020, an average of 59.0 per million in the treatment group have died, and 465.5 per million in the control group, relative risk 0.127. After adjustments, treatment and control deaths become 123.1 per million and 691.7 per million, relative risk 0.18. The probability of an equal or lower relative risk occurring from random group assignments is 0.010. Accounting for predicted changes in spread, we estimate a relative risk of 0.24. **The treatment group has a 75.8% lower death rate.** Confounding factors affect this estimate. We examined diabetes, obesity, hypertension, life expectancy, population density, urbanization, testing level, and intervention level, which do not account for the effect observed.

## Trial Setup

**Treatment.** We investigate early or prophylactic treatment for COVID-19 with hydroxychloroquine (HCQ), which has been adopted or declined in different countries. Since the severity of COVID-19 varies widely based on age and comorbidities, treatment was generally only initiated in higher risk individuals. The primary endpoint was death.

**Treatment groups.** Entire countries made different decisions regarding treatment with HCQ based on the same information, thereby assigning their residents to the treatment or control group in advance. Since assignment is done without regard to individual information such as medical status, assignment of individuals is random for the purposes of this study.

We focus here on countries that chose and maintained a clear assignment to one of the groups for a majority of the duration of their outbreak, either adopting widespread use, or highly limiting use. Some countries have very mixed usage, and some countries have joined or left the treatment group during their outbreak. We searched government web sites, Twitter, and Google, with the assistance of several experts in HCQ usage, to confirm assignment to the treatment or control group, locating a total of 225 relevant references, shown in Appendix 12. We excluded countries with <1M population, and countries with <0.5% of people over the age of 80. COVID-19 disproportionately affects older people and the age based adjustments are less reliable when there are very few people in the high-risk age groups. We also excluded countries that quickly adopted aggressive intervention and isolation strategies and consequently have very little spread of the virus to date. This exclusion, based on analysis by [Leffler], favors the control group and is discussed in detail below. We also present results without these exclusions for comparison.

Collectively the countries we identified with stable and relatively clear assignments account for 31.1% of the world population (2.4B of 7.8B). Details of the groups and evidence, including countries identified as having mixed use of HCQ, can be found in Appendix 12.

**Analysis.** We analyze deaths per capita with data from [Our World in Data]. To determine the effectiveness of treatment we could compare the death rates for the entire populations in the treatment and control groups, however we use the average of the individual country rates in each group in order to minimize effects due to differences between countries. Since randomization was done at a coarse country level, we adjust for differences between countries and analyze confounding factors.

**Case statistics.** We analyze deaths rather than cases because case numbers are highly dependent on the degree of testing effort, criteria for testing, the accuracy and availability of tests, accuracy of reporting, and because there is very high variability in case severity, including a high percentage of asymptomatic cases.

## Results

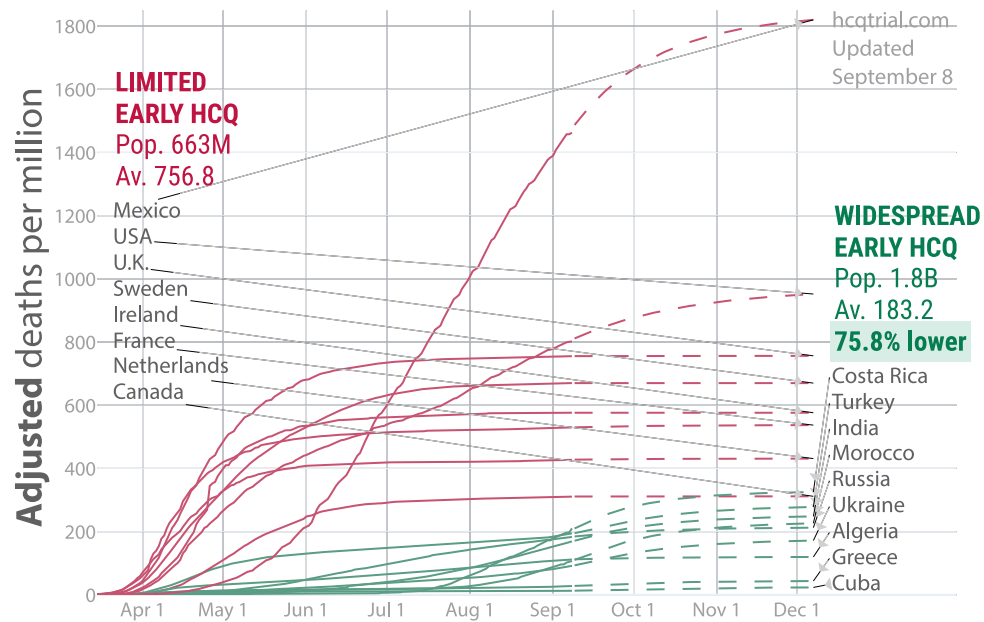
As of September 8, 2020, an average of 59.0 per million in the treatment group have died, and 465.5 per million in the control group, relative risk 0.127. After adjustments, treatment and control deaths become 123.1 per million and 691.7 per million, relative risk 0.18. For comparison, if we use the median of country death rates in each group rather than the mean, the relative risk is 0.18. If we combine all countries into single treatment and control groups, the relative risk is 0.19. Since the sample sizes are very large,  $p < 0.0001$  (for the case of single combined treatment and control groups, for the other cases it is less clearly defined). While the difference in death rates is statistically very significant, other factors affecting the results are more important which we analyze in the next section.

We ran a simulation to compute the probability of an equal or lower relative risk occurring due to chance. We randomly assigned the same number of countries to the treatment and control groups 1,000,000 times, from all countries reporting deaths to OWID. The probability of an equal or lower relative risk occurring is 0.010.

Accounting for predicted changes in spread as detailed below, we estimate a relative risk of 0.24. The treatment group has a 75.8% lower death rate. For comparison, if there are no country exclusions, the estimated relative risk is 0.20. We examined diabetes, obesity, hypertension, life

expectancy, population density, urbanization, testing level, and intervention level, which do not account for the effect observed.

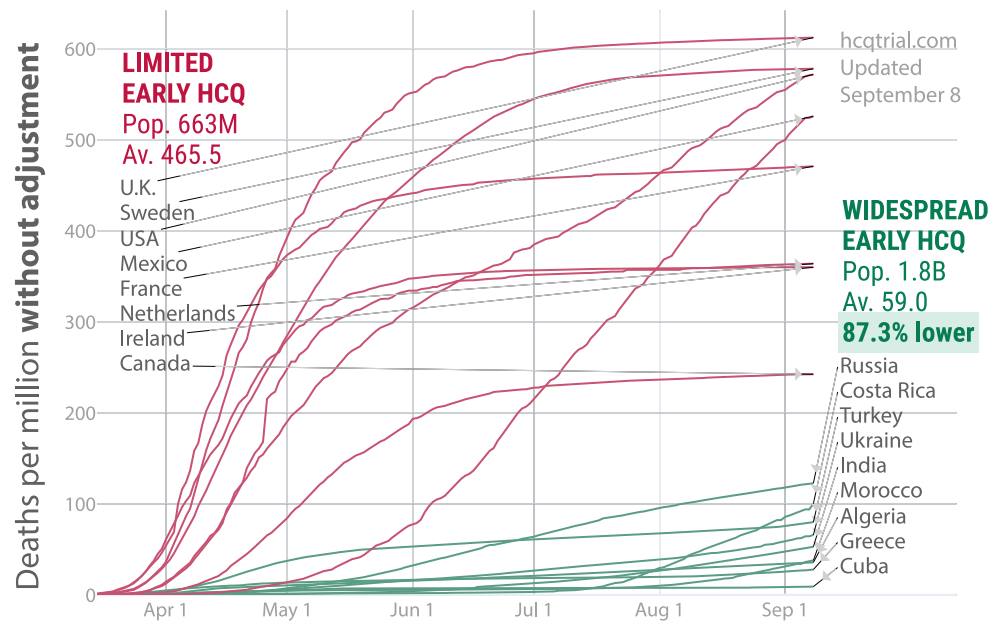
Figure 1 shows cumulative demographic adjusted death rates by country and trial group. Adjustments are detailed in the next section. Some analyses adjust graphs for the date since a specific milestone was reached, such as 0.1 deaths per million. We do not do this because an effective treatment will alter the time that such a milestone is reached.



**Figure 1.** Adjusted deaths per million for countries using widespread early HCQ versus those that do not, with a prediction for the following 90 days. As of September 8, 2020, countries using early HCQ are predicted to have a 75.8% lower death rate after adjustments.

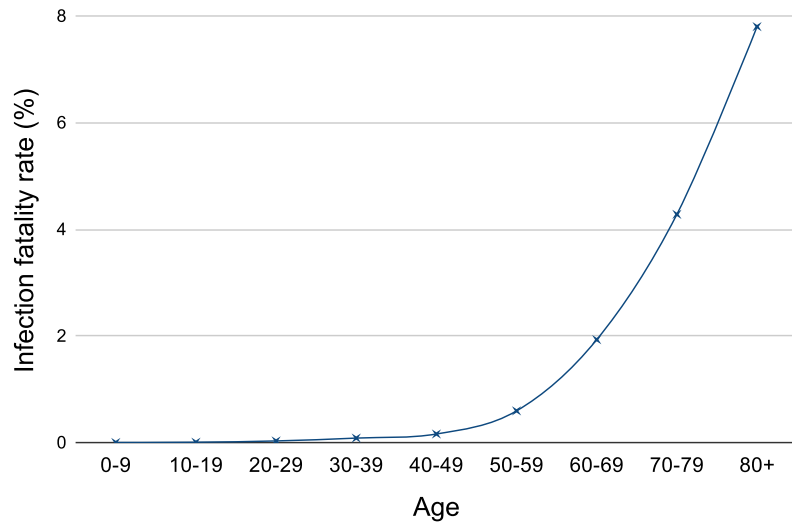
## Confounding Factors

A number of confounding factors affect the results, which we investigate here. For reference, the results before adjustments are shown in Figure 2.



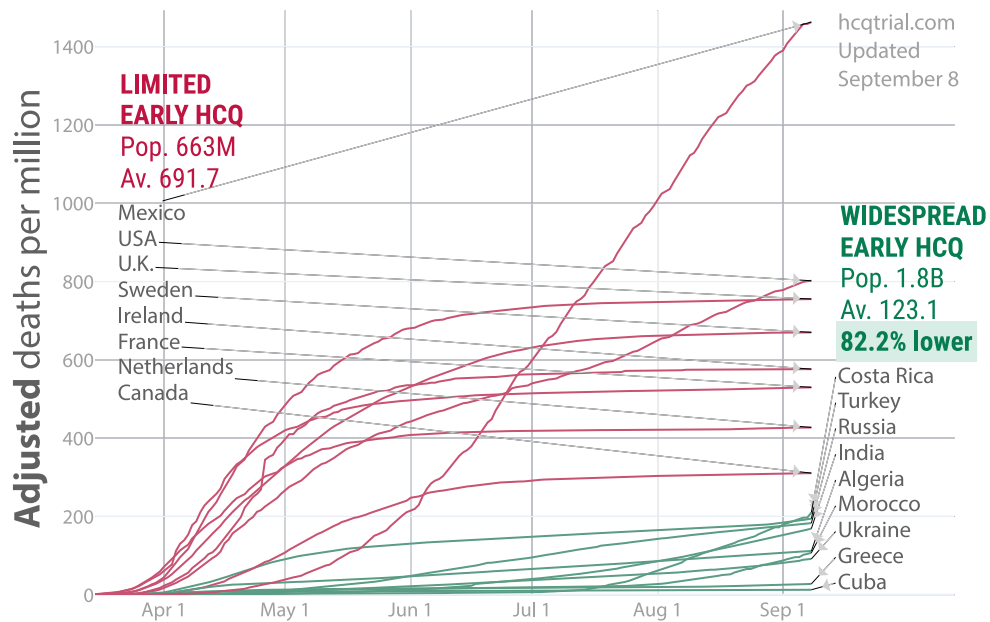
**Figure 2.** Deaths per million for countries using widespread early HCQ versus those that do not, *before* adjustments.

**Age.** The COVID-19 IFR varies around four orders of magnitude depending on age. Since the proportion of older adults varies significantly between countries, this is likely to have a significant effect on the results [Leffler]. We approximate the relative risk based on age using the infection fatality rates provided in [Verity], and shown in Figure 3. Due to the distribution, simple adjustment based on the median age, the proportion of people over 65, or similar may not be very accurate. We obtained age demographics from [United Nations] which provides a breakdown within 5 year age groups. Using the 9 age groups provided by [Verity], we computed an age adjustment factor for each country to normalize the observed deaths to the predicted number of deaths if the country's age distribution matched that of the country with the oldest population. The age distributions and computed age factors are provided in Appendix 1. These adjustments are relatively significant as in [Leffler].



**Figure 3.** Infection fatality rates from [Verity].

**Gender.** Risk differs significantly based on gender [Gebhard], so we also normalized for this in a similar fashion. Data is from [United Nations], and using the hazard ratio of 1.78 from [Williamson] the resulting adjustment factors are shown in Appendix 1. These adjustments are relatively minor as in [Leffler]. After adjusting for age and gender we obtain the results in Figure 4. Adjusted mean treatment and control deaths become 123.1 per million and 691.7 per million, relative risk 0.18.



**Figure 4.** Deaths per million for countries with widespread early HCQ versus those that do not, after adjustment for differences in demographics.

**Early isolation and masks.** Many countries have taken an isolation approach, isolating themselves from the world quickly and aggressively preventing any spread. With a very small and unknown fraction of the population infected, we can not easily analyze these countries. Many of these countries have also not taken a strong position on HCQ use. Mask usage was analyzed in [Leffler], which found 29 countries that widely and quickly adopted masks, as shown in Appendix 11. These countries in general took swift action with interventions and travel restrictions in order to prevent spread and have significantly lower spread of the virus to date. We excluded countries on this list, this excluded South Korea, Czech Republic, Indonesia, and Venezuela, which were provisionally identified as countries using early HCQ. This favors the control group. If we do not exclude these countries, the treatment group adjusted mean deaths is 100.3 per million, and the relative risk decreases to 0.15.

**Population health.** Health conditions such as diabetes, obesity, and hypertension significantly increase the risk of death with COVID-19 [Gao, Williamson]. This could affect the results because the prevalence of these conditions differs between countries. These conditions often occur together, for example [Iglay] found the most common comorbid conditions for diabetes were hypertension (82%) and obesity (78%), which makes combined country-level adjustment difficult, however we can first analyze the conditions individually. We examined the relationship of the diabetes, obesity, and hypertension levels with the adjusted deaths per million for the countries in our study, with data from [International Diabetes Federation], [CIA], and [Mills] respectively. Appendix 2, Appendix 3, and Appendix 4 show scatter plots, and the data can be found in Appendix 1. There was no significant correlation for diabetes,  $r^2 = 0.05$ , obesity,  $r^2 = 0.07$ , or hypertension,  $r^2 = 0.06$ . Based on this we do not expect adjustments to significantly affect the results. We re-ran the analysis adjusting for each of these factors individually (HR estimates: diabetes 1.63 [Williamson], obesity 1.4 [Williamson], hypertension 2.12 [Gao (B)]), which resulted in a relative risk of 0.178, 0.175, 0.179 respectively for diabetes, obesity, and hypertension. We also examined life expectancy with data from [Our World in Data (B)]. Appendix 5 shows a scatter plot and the data can be found in Appendix 1. The correlation,  $r^2 = 0.03$ , is relatively low, and is in the direction of higher life expectancy resulting in higher deaths. Therefore we do not find evidence that country-level differences in health have a significant effect on the results.

**Testing.** Countries with more widespread testing could potentially be more successful in minimizing deaths. We examined the relationship of testing per capita with adjusted deaths, with data from [Our World in Data (C)]. Appendix 10 shows a scatter plot, and the data can be found in Appendix 1. The correlation  $r^2 = 0.03$ , is very low and is also in the opposite direction of the expected potential correlation (we find that more testing is correlated with higher deaths). Therefore differences in testing do not appear to significantly affect the results.

**Co-administered treatments.** Several theories exist for why HCQ is effective [Andreani, Brufsky, Clementi, de Wilde, Derendorf, Devaux, Grassin-Delyle, Hoffmann, Hu, Keyaerts, Kono, Liu, Pagliano, Savarino, Savarino (B), Scherrmann, Sheaff, Vincent, Wang, Wang (B)], some of which involve co-administration of other medication or supplements. Most commonly used are zinc [Derwand, Shittu] and Azithromycin (AZ) [Guérin]. *In vitro* experiments report a synergistic effect of HCQ and AZ on antiviral activity [Andreani] at concentrations obtained in the human lung, and *in vivo* results are consistent with this [Gautret]. Zinc reduces SARS-CoV RNA-dependent RNA polymerase activity *in vitro* [te Velthuis], however it is difficult to obtain significant intracellular concentrations with zinc alone [Maret]. Combining it with a zinc ionophore such as HCQ increases cellular uptake, making it more likely to achieve effective intracellular concentrations [Xue]. Zinc deficiency varies and inclusion of zinc may be more or less important based on an individual's existing zinc level. Zinc

consumption varies widely based on diet [NIH]. To the extent that the co-administration of zinc, Azithromycin, or other medication or supplements is important, we may underestimate the effectiveness of HCQ because not all countries and locations are using the optimal combination.

**Population density and urbanization.** We tested the effect of population density [Our World in Data (D), Our World in Data (E)] and urbanization [World Bank], with scatter plots shown in Appendix 9 and Appendix 6, and data shown in Appendix 1. The correlation for population density  $r^2 = 0.00$ , and for urbanization,  $r^2 = 0.11$ . Differences in population density and urbanization do not appear to significantly affect the results.

**Treatment regimen.** There are differences in treatment regimens between and within countries. Details of timing, determination of risk, and dosages differ. Because not all locations are using the optimal regimen, this may reduce the effect observed.

**Adherence.** Some people in the control group obtained the treatment. This may reduce the effect observed.

**Counterfeit medication.** Counterfeit HCQ has been reported [Covid19Crusher]. This may reduce the effect observed.

**Seasonality.** Seasonality could affect results, although [Jamil] show there is currently little evidence for a large temperature dependence. We also note that the pandemic already covers more than one season and over time is likely to cover all seasons.

**Accuracy of death statistics.** The accuracy of reported death statistics varies across and within countries. Excess death statistics may be used in the future if they become available for more countries, however it may be difficult to separate deaths due to COVID-19 and changes to other causes of death related to interventions.

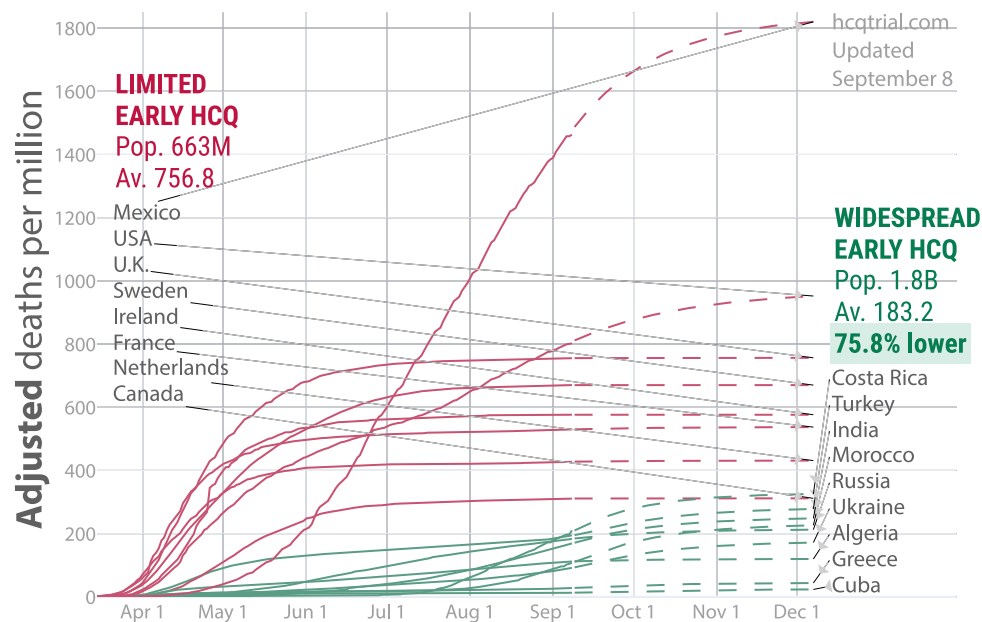
**Degree of spread.** The virus has spread throughout countries at different rates, due to differences in the initial number of infected persons arriving at the country, differences in treatments, population dynamics, cultural differences, and interventions including masks, social distancing, lockdowns, quarantine, and border restrictions. This factor is likely to be significant but will decline over time. Since it is unlikely that the virus will be eliminated soon, we expect that increasingly similar percentages of people will have been exposed over time, and we will update this analysis periodically to reflect the latest data. While interventions can temporarily slow the spread of the virus, it is unlikely that high intervention levels can be sustained indefinitely. Some countries, such as New Zealand, have highly contained the virus to date, essentially by quickly isolating themselves from the world with travel restrictions and strictly enforced quarantine rules. These countries may avoid significant spread while they remain isolated, however all of the countries in the treatment and control groups here have experienced significant spread of the virus.

We tested the effect of interventions using the average intervention stringency index [University of Oxford] over the period analyzed, as provided by [Our World in Data (E), Our World in Data (F)]. Appendix 8 shows a scatter plot, the correlation  $r^2 = 0.05$ , suggesting that the differences in non-medical interventions have a relatively minor affect on the results at present.

The treatment group countries generally show significantly slower growth in mortality which may be due to treatment, interventions, differences in culture, or the initial degree of infections arriving into the country. Over time we expect that increasingly similar percentages of people will have been

exposed, since it is unlikely that the virus will be eliminated soon.

To account for future spread, we created an estimate of the future adjusted deaths per million for each country, 90 days in the future, based on a second degree polynomial fit according to the most recent 30 days, enforcing the requirement that deaths do not decrease, and using an assumption of a progressively decreasing maximum increase over time. Figure 5 shows the results, which predicts a future relative risk of 0.24, i.e., the treatment group has 75.8% lower chance of death.



**Figure 5.** Demographic adjusted deaths per million for countries using widespread early HCQ versus those that do not, with an extended prediction for the following 90 days.

## Literature Review

**Introduction.** CQ and HCQ are 4-aminoquinoline synthetic alternatives to quinine, a naturally occurring compound found in cinchona bark, which has long been used for respiratory infections and other conditions [Burrows]. The cost of HCQ is around \$0.28 per dose according to [Centers for Medicare and Medicaid Services]. CQ, HCQ, and quinine are on the World Health Organization's list of essential medicines, the safest and most effective medicines needed in a health system [World Health Organization].

HCQ is effective against SARS-CoV-2 and related viruses *in vitro* [Keyaerts, Savarino, Savarino (B), Vincent, Wang], plasma concentrations that have been shown to be effective *in vitro* can be achieved safely [Keyaerts, Savarino, Vincent, Wang], and it has decades of use and a very well established safety profile [CDC].

**Theory, *in vitro*, and *ex vivo* results.** Several *in vitro* studies [Andreani, Clementi, de Wilde, Hoffmann, Keyaerts, Kono, Liu, Savarino, Sheaff, Vincent, Wang, Wang (B)] show that CQ inhibits related viruses and SARS-CoV-2, supported by several related theory articles [Brufsky, Derendorf, Devaux, Hu, Pagliano, Savarino (B), Scherrmann]. Theories for the mechanism of action include HCQ/CQ



protonation and accumulation in the endosome which prevents the acidification required for genome release [Fitch]; acting as an ionophoric agent that transports zinc ions into infected cells, where they inhibit viral RNA replicase enzyme [Xue]; dampening excess immune responses thereby mitigating the hyperactive immune response sometimes associated with COVID-19 [Schrezenmeier]; and inhibiting oxidative phosphorylation in mitochondria, likely by sequestering protons needed to drive ATP synthase [Sheaff]. [Savarino (B, 2003)] reviews the antiviral effects of CQ, noting that CQ inhibits the replication of several viruses including members of the flaviviruses, retroviruses, and coronaviruses. They note that CQ has immunomodulatory effects, suppressing the production/release of tumour necrosis factor  $\alpha$  and interleukin 6, which mediate the inflammatory complications of several viral diseases; [Keyaerts (2004)] show that the IC50 of CQ for inhibition of SARS-CoV *in vitro* approximates the plasma concentrations of CQ reached during treatment of acute malaria, suggesting that CQ may be considered for immediate use in the prevention and treatment of SARS-CoV; [Vincent (2005)] show that CQ has strong antiviral effects on SARS CoV infection when cells are treated either before or after exposure, suggesting prophylactic and treatment use, and describing three mechanisms by which the drug could work; [Savarino (2006)] in an update to their 2003 paper discuss the *in vitro* confirmation of CQ inhibiting SARS replication via two studies, and note that CQ affects an early stage of SARS replication; [Kono (2008)] showed that CQ inhibits viral replication of HCoV-229E at concentrations lower than in clinical usage; [de Wilde (2014)] show that CQ inhibits SARS-CoV, MERS-CoV, and HCoV-229E-GFP replication in the low-micromolar range; [Wang (B, 2/4/20)] showed that CQ (EC50 = 1.13  $\mu$ M; CC50 > 100  $\mu$ M, SI > 88.50) potently blocked virus infection at low-micromolar concentration and showed high selectivity *in vitro*; [Devaux (3/12/20)] discusses mechanisms of CQ interference with the SARS-CoV-2 replication cycle; [Liu (3/18/20)] show that HCQ is effective *in vitro* and less toxic than CQ. They note that in addition to the direct antiviral activity, HCQ is a safe and successful anti-inflammatory agent that has been used extensively in autoimmune diseases and can significantly decrease the production of cytokines and, in particular, pro-inflammatory factors. Therefore, in COVID-19 patients, HCQ may also contribute to attenuating the inflammatory response. They note that based on the selectivity index, careful design of clinical trials is important to achieve efficient and safe control of the infection; [Hu (3/23/20)] note that CQ is known in nanomedicine research for the investigation of nanoparticle uptake in cells, and may have potential for the treatment of COVID-19; [Pagliano (3/24/20)] note that CQ and HCQ inhibit replication at early stages of infection, that no similar effect is reported for other drugs which are only able to interfere after cell infection, and that there is a large volume of existing data on safety; [Clementi (3/31/20)] show a greater inhibition for combined pre and post-exposure treatment with Vero E6 and Caco-2 cells; [Brufsky (4/15/20)] present a theory on HCQ effectiveness with COVID-19, wherein HCQ blocks the polarization of macrophages to an M1 inflammatory subtype and is predicted to interfere with glycosylation of a number of proteins involved in the humoral immune response, possibly including the macrophage FcR gamma IgG receptor and other immunomodulatory proteins, potentially through inhibition of UDP-N-acetylglucosamine 2-epimerase. In combination with potential other immunomodulatory effects, this could blunt the progression of COVID-19 pneumonia all the way up to ARDS; [Andreani (4/25/20)] show that HCQ and AZ have a synergistic effect *in vitro* on SARS-CoV-2 at concentrations compatible with that obtained in the human lung; [Derendorf (5/7/20)] discuss pharmacokinetic properties of HCQ+AZ as a potential underlying mechanism of the observed antiviral effects; [Grassin-Delye (5/8/20)] use human lung parenchymal explants, showing that CQ concentration clinically achievable in the lung (100  $\mu$ M) inhibited the lipopolysaccharide-induced release of TNF- $\alpha$  (by 76%), IL-6 (by 68%), CCL2 (by 72%), and CCL3 (by 67%). In addition to antiviral activity, CQ may also mitigate the cytokine storm associated with severe pneumonia caused by coronaviruses; [Scherrmann (6/12/20)] propose a new mechanism supporting the synergistic interaction between HCQ+AZ; [Sheaff (8/2/20)] present a new theory on SARS-CoV-2 infection and why HCQ/CQ

provides benefits, which also potentially explains the observed relationships with smoking, diabetes, obesity, age, and treatment delay, and confirms the importance of accurate dosing. Metabolic analysis revealed HCQ/CQ inhibit oxidative phosphorylation in mitochondria (likely by sequestering protons needed to drive ATP synthase), inhibiting infection and/or slowing replication; and [Wang (9/2/20)] show that CQ and HCQ both inhibit the entrance of 2019-nCoV into cells by blocking the binding of the virus with ACE2.

[Hoffmann] perform an *in vitro* study of CQ and HCQ inhibition of SARS-CoV-2 into Vero (kidney), Vero-TMPRSS2, and Calu-3 (derived from human lung carcinoma) cells. They suggest a lack of effectiveness, but there appears to be three unsupported steps made to reach the conclusions in this paper. Firstly, authors conclude that CQ does not block infection of Calu-3 when the results show statistically significant inhibition at higher concentrations. Second, authors go from analysis of one specific type of pulmonary adenocarcinoma cells that resemble serous gland cells, *in vitro*, into a general claim of no inhibition in lung cells. Thirdly, they disregard existing theories of CQ/HCQ effectiveness to conclude a general lack of effectiveness.

Calu-3 is one of many cell lines derived from human lung carcinomas [Shen]. Calu-3 cells resemble serous gland cells (they do not express 15-lipoxygenase, an enzyme specifically localized to the surface epithelium, but they do express secretory component, secretory leukocyte protease inhibitor, lysozyme, and lactoferrin, all markers of serous gland cells). [Shen] note that the absence of systemic inflammation, circulatory factors, and other paracrine systemic influences is a potential limitation of the isolated cell system.

[Hoffmann] Fig. 1b @100uM shows CQ results in a ~4.5 fold decrease (note a log scale is used) in extracellular virus,  $p=0.05$ , after 24 hours (estimated from the graph). We note that the paper marks this as not significant because the value is 0.517, however the p value is unlikely to be accurate to this level. Additionally authors use Dunnett's test while other tests may have higher power [Sauder]. We further note that the 95% significance level is just a convention and results do not magically go from non-significant at  $p=0.051$  to significant at  $p=0.049$ . Results only apply to 24 hours later and we expect further decrease over time. Fig. 1a shows a ~45-50% entry inhibition @100uM for HCQ/CQ ( $p=0.0005/0.0045$ ), ~10-30% @10uM ( $p=0.13/0.99$ ). Inhibition is significantly better with Vero cells.

There are several theories on how HCQ may help with COVID-19, and we note that authors do not consider one of the most common theories where HCQ functions as a zinc ionophore, facilitating significant intracellular concentrations of zinc. Zinc is known to inhibit SARS-CoV RNA-dependent RNA polymerase activity, and is widely thought to be important for effectiveness with SARS-CoV-2 [Shittu].

**Animal *in vivo* studies.** [Keyaerts (B, 2009)] showed that CQ inhibits HCoV-OC43 replication in HRT-18 cells in a mouse study. Lethal HCoV-OC43 infection in newborn C57BL/6 mice was treated with CQ acquired transplacentally or via maternal milk, with the highest survival rate (98.6%) found when mother mice were treated daily with a concentration of 15 mg of CQ per kg of body weight. Survival rates declined in a dose-dependent manner, with 88% survival when treated with 5 mg/kg CQ and 13% survival when treated with 1 mg/kg CQ. They conclude that CQ can be highly effective against HCoV-OC43 infection in newborn mice and may be considered as a future drug against HCoVs; [Yan (2012)] show that CQ can efficiently ameliorate acute lung injury and dramatically improve the survival rate in mice infected with live avian influenza A H5N1 virus; and [Maisonnasse (5/6/20)] study treatment in monkeys. They report no effect, however the data has several signs of

effectiveness despite the very small sample sizes and 100% recovery of all treated and control monkeys. The final day lung lesion data shows 63% of control monkeys have lesions, while only 26% of treated monkeys do,  $p=0.095$  (missing data for 7 monkeys is predicted based on the day 5 results and the trend of comparable monkeys). After one week, 74% of treated monkeys have recovered with  $\leq 4 \log_{10}$  copies/mL viral load, compared to 38% of control monkeys,  $p=0.095$ . 38% of control monkeys also have a higher peak viral load than 100% of the 23 treated monkeys post-treatment. The group with the lowest peak viral load is the PrEP group. All animals in this study were infected with the same initial viral load, whereas real-world infections vary in the initial viral load, and lower initial viral loads allow greater time to mount an immune response.

**Human *in vivo* studies.** We found 93 studies related to the human *in vivo* use of HCQ for treating COVID-19 [Abd-El salam, Ahmad, Alberici, An, Arshad, Ashraf, Ayerbe, Barbosa, BaŞaran, Bernaola, Bhattacharya, Borba, Boulware, Carlucci, Castelnuevo, Catteau, Cavalcanti, Chamieh, Chatterjee, Chen, Chen (B), Chen (C), Colson, D'Arminio Monforte, Davido, de la Iglesia, Dubernet, Elbazidi, Esper, Ferreira, Ferri, Fried, Furtado, Gao (B), Gao (C), Gautret, Gautret (B), Geleris, Gendelman, Giacomelli, Gonzalez, Guérin, Heras, Hong, Horby, Huang, Huang (B), Huang (C), Huh, Ip, Ip (B), Izoulet, Jiang, Kamran, Kelly, Khurana, Kim, Lagier, Lecronier, Lee, Ly, Macias, Magagnoli, Mahévas, McGrail, Membrillo de Novales, Meo, Mikami, Million, Mitchell, Mitjà, Mitjà (B), Molina, Okour, Otea, Paccoud, Peters, Pinato, Pirnay, Roomi, Rosenberg, Saleemi, Sbidian, Scholz, Singh, Skipper, Synolaki, Sánchez-Álvarez, Tang, Xue (B), Yu, Yu (B), Zhong]. 56 of these present positive results (of varying degrees and confidence) [Ahmad, Alberici, Arshad, Ayerbe, Bernaola, Bhattacharya, Boulware, Castelnuevo, Catteau, Chamieh, Chatterjee, Chen, Chen (B), Colson, D'Arminio Monforte, Davido, Dubernet, Elbazidi, Esper, Ferreira, Ferri, Gao (B), Gao (C), Gautret (B), Gonzalez, Guérin, Heras, Hong, Huang, Huang (B), Huang (C), Ip, Izoulet, Jiang, Khurana, Kim, Lagier, Lee, Ly, Membrillo de Novales, Meo, Mikami, Million, Mitchell, Okour, Otea, Pinato, Pirnay, Sbidian, Scholz, Synolaki, Sánchez-Álvarez, Xue (B), Yu, Yu (B), Zhong], 19 present negative results (also of varying degrees and confidence) [An, Barbosa, Borba, Cavalcanti, Chen (C), Giacomelli, Horby, Ip (B), Kelly, Lecronier, Magagnoli, Mahévas, Molina, Peters, Roomi, Rosenberg, Saleemi, Singh, Tang], while the remainder are either inconclusive or were retracted. Table 1 shows a distribution of studies based on treatment time.

Study type	<i>In Vitro</i>	PrEP	PEP	Early treatment	Late treatment
Number of studies	12	12	3	21	59
Percentage positive	100%	100%	100%	100%	62%

**Table 1.** Distribution of studies regarding HCQ for COVID-19. Note that some studies are inconclusive, and also that the degree of positive or negative effect, and confidence therein varies widely.

**Late treatment studies.** Most studies focus on late treatment with hospitalized patients, and the results are very mixed. We found 31 of the studies reported positive effectiveness, while 19 reported negative effectiveness, both with varying degrees of effect and confidence. We do not consider the late treatment studies further here since we are concerned with early treatment, other than to note that these studies suggest HCQ may potentially be beneficial in a hospital setting if used very quickly and with patients that have not reached a more advanced stage of the disease; and it may

be of limited or negative value with later stage disease. Three studies consider higher dosages than typically used [Borba, Horby, World Health Organization (B)], and the results suggest that these dosages in late stage patients may be harmful.

**Pre-Exposure Prophylaxis (PrEP) studies.** We found 12 PrEP studies [Bhattacharya, Chatterjee, de la Iglesia, Ferreira, Ferri, Gendelman, Huang, Huh, Khurana, Macias, Mitchell, Zhong].

Several studies analyze HCQ usage by systemic autoimmune disease patients. SLE, RA, and other autoimmune conditions are associated with significantly increased susceptibility to and incidence of infections [Bouza, Bultink, Herrinton, Iliopoulos, Kim (B), Li, Listing]. For COVID-19 specifically, research confirms that the risk for systemic autoimmune disease patients is much higher, [Ferri] show OR 4.42,  $p < 0.001$ , which is the observed real-world risk, taking into account factors such as these patients potentially being more careful to avoid exposure.

[de la Iglesia] analyze autoimmune disease patients on HCQ, compared to a control group from the general population (matched on age and sex, but not adjusted for autoimmune disease), showing non-significant differences between groups. If we adjust for the different baseline risk, the mortality result becomes RR 0.35,  $p = 0.23$ , suggesting a substantial benefit for HCQ treatment; [Ferri] analyze 1641 autoimmune systemic disease (ASD) patients showing csDMARD (HCQ etc.) RR 0.37,  $p = 0.015$ . csDMARDs include HCQ, CQ, and several other drugs, so the effect of HCQ/CQ alone could be higher. This study also confirms that the risk of COVID-19 for ASD patients in general is much higher, OR 4.42,  $p < 0.001$ , which is the real-world risk, accounting for factors such as ASD patients potentially being more careful to avoid exposure; [Khurana] presents a study of hospital health care workers showing HCQ prophylaxis reduces COVID-19 significantly, OR 0.30,  $p = 0.02$ . 94 positive health care workers with a matched sample of 87 testing negative. The actual benefit of HCQ may be larger because the severity of symptoms are not considered; [Zhong] analyzed 6,228 patients with autoimmune rheumatic diseases with 55 COVID positive members of families exposed to COVID-19, showing that patients on HCQ had a lower risk of COVID-19 than those on other disease-modifying anti-rheumatic drugs with OR 0.09 (0.01–0.94),  $p = 0.044$ ; [Ferreira] analyze 26,815 patients showing that chronic HCQ treatment (77 patients) provides protection against COVID-19, odds ratio 0.51 (0.37–0.70); [Huang] analyze 1255 COVID-19 patients in Wuhan Tongji Hospital finding 0.61% with systemic autoimmune diseases, much lower than authors expected (3%–10%). Authors hypothesise that protective factors, such as CQ/HCQ use, reduce hospitalization; [Bhattacharya] shows PrEP HCQ reduced cases from 38% to 7% with 106 people; [Chatterjee] shows PrEP HCQ of 4+ doses was associated with a significant decline in the odds of getting infected, along with a dose-response relationship, based on 378 treatment and 373 control cases; [Mitchell] analyze COVID-19 amongst 2.4B people, showing a wide counterintuitive disparity between well-developed and less-developed countries, with more affluent countries about one hundred times more likely to be infected and die due to COVID-19. They find the effect is most apparent when comparing to countries with the highest rates of endemic malaria. Since travelers to malaria-endemic countries are likely to be taking antimalarial prophylaxis, authors find the data highly probative for the hypothesis that prophylactic antimalarial use by incoming visitors markedly attenuates a country's COVID-19 fatality rate. While authors do not adjust for age differences, those adjustments can only account for a small fraction of the observed difference; [Huh] perform a database analysis of many drugs and COVID-19 cases, with 23 cases taking HCQ, and 251 control patients not taking HCQ, showing OR 1.07,  $p = 0.77$ , and in multivariable analysis OR 1.48,  $p = 0.086$ . Patients taking HCQ are most likely taking it for systemic autoimmune diseases where the risk of COVID-19 is much higher. Adjusting the multivariable analysis result for the difference in baseline risk of systemic autoimmune patients results in RR 0.34. Details of the multivariable analysis are not

provided for assessment, but the analysis may be significantly affected by overfitting and/or multicollinearity. We note that many results in this study differ from other research, for example proton pump inhibitors show OR 0.47,  $p < 0.001$  whereas PPIs are classified as "no expected benefit" and other research suggests they increase risk; [Gendelman] presents a small study of rheumatic disease/autoimmune disorder patients showing no significant difference without adjusting for baseline risk. Adjusting for the difference in baseline risk using the result in Ferri et al. shows substantial benefit for HCQ, RR 0.211, but with only 3 HCQ cases the result is inconclusive; and [Macias] analyzes incidence among patients with rheumatic disease, however with only 3 confirmed cases, and not adjusting for significant differences between groups and the expected infection rates based on patient conditions, we consider this study inconclusive.

**Post-Exposure Prophylaxis (PEP) studies.** We found 3 PEP studies [Boulware, Lee, Mitjà]. [Lee] studies post exposure prophylaxis of 211 high-risk people in a long-term care hospital after a major exposure event, with no positive cases after 14 days.

[Boulware] reports a lack of efficacy due to statistical significance not being reached, however multiple secondary analyses show statistically significant and positive results. Due to this difference, we provide a detailed explanation. The paper shows a 17% reduction in cases,  $p = 0.35$  due to the small sample size - we can say this is inconclusive, but not negative (it is more likely to be positive than negative). Authors initially believed 3 days post exposure was the maximum enrollment delay of interest, however there was a mid-trial modification extending this to allow an additional day delay. With the original trial specification, they show a 30% reduction in cases for treatment,  $p = 0.13$ . If the trial was not ended early, and if the observed trend continued,  $p = 0.05$  would have been reached at ~840 patients total (the original trial specification was 1,242 patients).

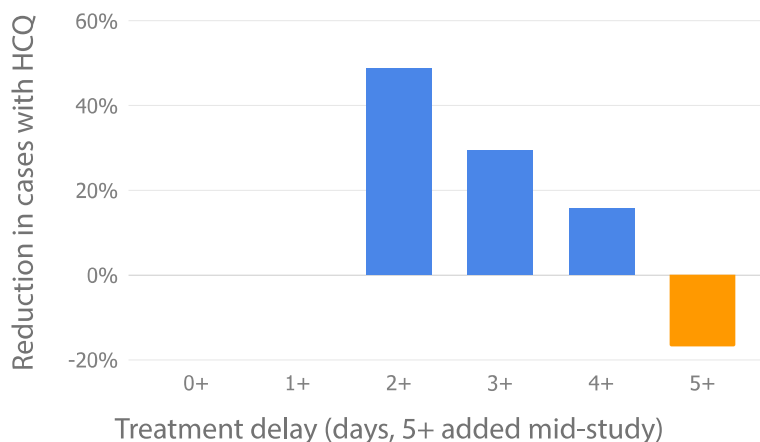
In the supplementary appendix, we can see that COVID-19 cases are reduced by [49%, 29%, 16%] respectively when taken within ~[70, 94, 118] hours of exposure (including shipping delay), as shown in Figure 6. *A priori* the most important cases to consider are the treatment delay-response relationship and the shortest delay to treatment (~70 hours on average in this case). The shortest delay to treatment is significant @94% versus all placebo. By simulation, assuming that cases occur randomly according to the observed frequency, we found the probability that the results follow the observed beneficial delay-reponse relationship is 0.2% [CovidAnalysis]. Since we have performed 2 tests, conservative Bonferroni adjustment [Jafari] gives us  $p = 0.004$ . The efficacy of treatment has also been shown in another secondary analysis [Watanabe].

*A priori* we expect an effective treatment here to be more effective when administered sooner [Cohen]. Extrapolating the treatment delay-response trend suggests 93% reduction in cases for immediate treatment, of course we have little confidence in this prediction, however it would be consistent with the data and can not be ruled out.

The effectiveness found is even more notable considering the limitations of the study. Treatment was relatively late, with enrollment up to 4 days after exposure, and an unspecified shipping delay. While the paper does not provide shipping details, the study protocol gives some information. While not clear, it indicates no shipping on the weekends and a possible 12pm cutoff for same day dispensing and mailing, from which we estimate the treatment delay as ~70 to 140 hours after exposure on average for the 1-4 days since enrollment specified in the paper (we will update this when authors respond to our request for details). There was only 75% medication adherence,

including 16% who did not take the medication at all, so the actual effectiveness is likely to be higher. The study relies on Internet surveys, and false surveys were received (identified by 555 numbers), suggesting there could be additional unidentified false entries.

The accompanying editorial to this paper also notes that in a small-animal model of SARS-CoV-2 [Sheahan], prevention of infection or more severe disease was observed only when the antiviral agent was given before or shortly after exposure [Cohen]. Research also shows that the placebo used in the US (folate) may be protective for COVID-19 [Acosta-Elias]. More details on this analysis can be found in [CovidAnalysis].



**Figure 6.** Treatment delay-response relationship from [Boulware].

[Mitjà] perform a highly delayed PEP treatment study which suggests efficacy but lacks statistical significance due to the small number of cases. Death rates reduced from 0.6% to 0.4%, RR 0.71, not statistically significant due to low incidence (8 control cases, 5 treatment cases).

Enrollment was up to 7 days after exposure and the treatment delay in this study is unclear, without details of the exposure event timing or medication dispensing. They appear to identify index cases based on the date of a positive test for a contact, which is likely to be much later than the actual exposure time. Due to quarantine at the time and likely cohabitation of a majority of the contacts, it is likely that the actual exposure time was significantly earlier. 13.1% of patients already tested positive at baseline, which is consistent with the actual exposure time being significantly earlier. Nasopharyngeal viral load analysis is subject to test unreliability and temporo-spatial differences in viral shedding [Wang (C)]. PCR testing has a very high false-negative rate in early stages (e.g., 100% on day 1, 67% on day 4, and 20% on day 8 [Kucirka], hence it is likely that a much higher percentage were infected at an unknown time before enrollment.

Given the enrollment delay, PCR test delay, and PCR false negative rate at early stages, the treatment delay in general for this study was very long and could be over 2 weeks.

This study focuses on the existence of symptoms or PCR-positive results, however severity of symptoms is more important. Research has shown HCQ concentrations may be much higher in the lung compared to plasma [Browning], which may help minimize the occurrence of severe cases and death. The outcome analyzed here may not be highly relevant to the goal of reducing mortality. For

positive symptomatic cases, they find  $RR=0.89$ , favoring treatment but not statistically significant. The  $RR$  for non-PCR positive at baseline is 0.74, which is consistent with earlier treatment being more effective. A greater effect is seen for nursing home residents,  $RR=0.49$ , possibly because the exposure events are identified faster in this context, versus home exposure where testing of the source may be more delayed. There is a treatment-delay response relationship consistent with an effective treatment.

The paper does not mention zinc. Zinc deficiency in Spain has been reported at 83% [Olza], this may significantly reduce effectiveness to the extent that zinc is important for the success of HCQ treatment.

The definition of COVID-19 symptoms is very broad - just existence of a headache alone or muscle pain alone was considered COVID-19. There was an overall very low incidence of confirmed COVID-19 (138 cases across both arms). There were no serious adverse events that were adjudicated as being treatment related. Authors exclude those with symptoms in the previous two weeks, however, those with symptoms up to several months before may still test PCR-positive even though there may be no viable virus. There appears to be inaccurate data in the paper. Table 2, secondary outcomes, control, hospital/vital records shows that 8 of 1042 is 9.7%.

In summary, this study appears positive in the context of very delayed treatment and the small number of cases.

**Early treatment studies.** We found 21 early treatment studies [Ahmad, Ashraf, Chen, Elbazidi, Esper, Gautret, Gautret (B), Guérin, Heras, Hong, Huang (C), Ip, Izoulet, Lagier, Ly, Meo, Million, Mitjà (B), Otea, Scholz, Skipper] which all show some degree of effectiveness. [Heras] perform a retrospective analysis of 100 confirmed COVID-19 elderly nursing home patients, median age 85, showing HCQ+AZ mortality 11.4% versus control 61.9%,  $RR$  0.18,  $p<0.001$ . Details of differences between groups are not provided, and no adjustments are made. Authors indicate treatment was early but do not specify the treatment delay; [Elbazidi] analyze US states and countries. For countries they find a significant correlation between the dates of decisions to adopt/decline HCQ, and corresponding trend changes in CFR. For US states they find a significant correlation between CFR and the level of acceptance of HCQ; [Ip] perform a retrospective analysis of 1,274 outpatients, finding a 47% reduction in hospitalization with HCQ with propensity matching, HCQ OR 0.53 [0.29-0.95]. Sensitivity analyses revealed similar associations. Adverse events were not increased (2% QTc prolongation events, 0% arrhythmias); [Ly] perform a retrospective analysis of retirement homes with 1690 elderly residents (226 infected, 116 treated, mean age 83), showing HCQ+AZ  $\geq 3$  days resulted in 41% lower mortality (15.5% vs. 26.4%), OR = 0.39,  $p=0.026$ . Detection via mass screening also showed significant improvements (16.9% vs. 40.6%, OR = 0.20,  $p=0.001$ ), suggesting that earlier detection and treatment is more successful; [Hong] showed that HCQ 1-4 days from diagnosis was the only protective factor against prolonged viral shedding found, OR 0.111,  $p=0.001$ . 57.1% viral clearance with 1-4 days delay vs. 22.9% for 5+ days delayed treatment. Authors report that early administration of HCQ significantly ameliorates inflammatory cytokine secretion and that COVID-19 patients should be administered HCQ as soon as possible. 42 patients with HCQ 1-4 days from diagnosis, 48 with HCQ 5+ days from diagnosis; [Scholz] performs a retrospective analysis of 518 patients (141 treated, 377 control) showing that early treatment with HCQ+AZ+Z results in 84% lower hospitalization and 80% lower death - hospitalization OR 0.16 ( $p<0.001$ ), death OR 0.2 ( $p=0.16$ ); [Lagier] analyzed 3,737 patients showing that early treatment leads to significantly better clinical outcome and faster viral load reduction with matched sample mortality HR 0.41  $p=0.048$ ; [Chen] showed significantly faster clinical recovery and shorter time to RNA negative (from 7.0 days

to 2.0 days (HCQ),  $p=0.01$  with 67 mild/moderate cases; [Otea] showed HCQ+AZ appears to reduce serious complications and death with 80 patients; [Guérin] performed a small retrospective study with 88 patients and found mean recovery time reduced from 26 days to 9 days with HCQ+AZ,  $p<0.0001$  or to 13 days with AZ, including a case control analysis with matched patients; [Ahmad] treated 54 patients in long term care facilities with 6% death, compared to 22% using a naive indirect comparison; [Million] showed HCQ+AZ is safe and results in a low fatality rate with a retrospective analysis of 1,061 patients; [Ashraf] concluded that HCQ improved clinical outcome with a small limited trial of 100 patients in Iran; [Izoulet] compares the dynamics of daily deaths in the 10 days following the 3rd death in countries using and not using [H]CQ. They show dramatically lower death in [H]CQ countries, but do not attempt to account for other differences between the countries; [Esper] analyzed 636 patients showing HCQ+AZ reduced hospitalization 79% when used within 7 days (65% overall); [Gautret (B)] presented a pilot study suggesting improvement with HCQ+AZ and recommending further study; [Huang (C)] analyzed 22 patients with all CQ patients discharged by day 14 versus 50% of Lopinavir/Rotinavir patients, and all CQ patient's pneumonia improved, versus 75% of Lopinavir/Rotinavir patients.; and [Gautret] in an early and small trial with significant limitations, showed that HCQ was associated with viral load reduction and that this was enhanced with AZ. [Gautret] also performed an early and small trial, showing that HCQ was associated with viral load reduction and that this was enhanced with AZ, however this study has significant limitations [Machiels, Rosendaal]. In addition, [Risch] presents an updated meta analysis that includes several studies that are currently unpublished. 7 new studies of high-risk outpatients are reported, for a total of 12 studies, all showing significant benefit.

[Mitjà (B)] present a randomized trial of 293 low-risk patients with no deaths, no serious adverse events, and no statistically significant improvements. There was a 25% reduction in hospitalization and 16% reduction in the median time to symptom resolution for HCQ, without statistical significance due to small samples. However, this paper has inconsistent data - some of the values reported in Table 2 and the abstract correspond to 12 control hospitalizations, while others correspond to 11 control hospitalizations, hence we are unsure of other data reported here. This paper also does not specify the treatment delay, reporting only an enrollment delay of up to 120 hours post symptoms, plus an additional unspecified delay where medication was provided to patients at the first home visit. They do not break down results by treatment delay. Undetectable viral load was changed to 3 log<sub>10</sub> copies/mL potentially partially masking effectiveness. For viral load with nasopharyngeal swabs, we note that viral activity in the lung may be especially important for COVID-19, and that HCQ concentration in the lung may be significantly higher (for example, about 30 times blood concentration in [Chhonker]). Nasopharyngeal viral load analysis is subject to test unreliability and temporo-spatial differences in viral shedding [Wang (C)]. Viral detection by PCR does not equate to viable virus [Academy of Medicine]. PCR testing does not distinguish between live virus and fragments of dead virus cells, which may take months to clear [Bo-gyung].

[Skipper] present an RCT with Internet surveys of 423 patients. As with the companion PEP study, we find the results significantly more positive than typically reported. They show ~70 to 140 hour delayed treatment with HCQ reduced combined hospitalization/death by 50%,  $p=0.29$  (5 HCQ cases, 10 control cases), and reduced hospitalization by 60%,  $p=0.17$ . There was one hospitalized control death and one non-hospitalized HCQ death. It is unclear why there was a non-hospitalized death, external factors such as lack of standard care may be involved. Excluding that case results in one control death and zero HCQ deaths (not statistically significant but noted as reducing mortality is the most important outcome). Details for the hospitalizations and deaths such as medication adherence and treatment delay may be informative but are not provided.



The paper states the end point was changed from hospitalization/death to symptom severity because they would have required 6,000 participants. However, if the observed trend continued, they would hit 95% significance on the reduction in hospitalization at ~725 patients, and 95% on the reduction in combined hospitalization/death at ~1,145 patients, both of which are less than the original plan of 1,242 patients. We hope this trial can be continued for statistical significance.

As with the companion PEP trial, treatment in this trial was relatively late, with an unspecified shipping delay, which we estimate as ~70 to 140 hours after symptoms for enrollment days 1 to 4. We note there is no overlap with the more typical delays used such as 0 - 36 hours for oseltamivir.

The paper compares 0 - 36 hour delayed treatment with oseltamivir (influenza) and ~70 to 140 hour delayed treatment with HCQ (COVID-19), noting that oseltamivir seemed more effective. However, a more comparable study is [McLean] who showed that 48 - 119 hour delayed treatment with oseltamivir has no effect. This suggests that HCQ is more effective than oseltamivir, and that HCQ may still have significant effect for some amount of delay beyond the delay where oseltamivir is effective.

6 people were included that enrolled with >4d symptoms, although they do not match the study inclusion criteria. This reduces observed effectiveness. Patients in this study are relatively young and most of them recover without assistance. This reduces the room for a treatment to make improvements. The maximum improvement of an effective treatment would be expected before all patients approach recovery. For symptoms, authors focus on the end result where most have recovered, but it is more informative to examine the curve and the point of maximum effectiveness. Authors did not collect data for every day but they do have interim results for days 3, 5, 10. The results are consistent with an effective treatment and show a statistically significant improvement,  $p = 0.05$ , at day 10 (other unreported days might show increased effectiveness). Results also show a larger treatment effect for those >50, not statistically significant due to the small sample, but noted as COVID-19 risk dramatically increases with age.

As with the companion PEP trial, this study relies on Internet surveys. Known fake surveys were submitted to the PEP trial and there could be an unknown number of undetected fake surveys in both trials. Research shows the placebo used in the US may be protective for COVID-19 [Acosta-Elias] so the true effectiveness of HCQ could be higher than observed. Medication adherence was only 77% also making the true effect of treatment likely to be higher. Authors note that the results are not generalizable to the COVID high-risk population.

## Discussion

We originally used the term "country-randomized controlled trial" for this study - a medication is being trialled, there is a control group, and a person in the study has their group randomly assigned in advance, independent of their medical status. As distinct from a retrospective study, the control population is not related to the treatment decisions of the treatment population. People do not get to choose their group, and that is controlled by the countries (who are effectively running the trial), as opposed to occurring in a natural experiment. This is perhaps a unique time in history where the world bifurcated over a treatment for a disease, with countries choosing to accept or decline treatment based on the same information, resulting in random selection for patients. We also note one can make a comparison with cluster-randomized controlled trials, and that the bar for "RCT" is relatively low. For example, Internet survey studies with unknown survey bias, unknown percentage

of fake responses, and low adherence are accepted as RCTs. However, it is possible that some people misinterpreted the nature of this study as a clinical trial if they did not read the paper, hence we modified the name to avoid any confusion.

All studies have some limitations, for HCQ study limitations may include confounding factors; sample sizes that are too small; sub-optimal treatment regimens; dosing regimens that may be too low, too high, or insufficiently account for the long half-life of HCQ; excessive treatment delays; reliance on Internet surveys; inclusion/exclusion criteria; using tests that may be inaccurate or poor measures of disease severity; and patient characteristics that are very different from the most at-risk population.

There are distinct advantages and disadvantages to this trial, with several details discussed earlier. Benefits include the very large scale, lack of barriers to implementation, and lack of inclusion/exclusion criteria. The primary disadvantage is the coarse country-based randomization which requires us to address differences between countries, and the most significant limitation at present is likely to be the varying degrees of spread between countries. We have reviewed available seroprevalence data [*BBC, CDC (B), Eckerle, European University, Fontanet, Fontanet (B), Havers, Ioannidis, Lewis, Public Health England, Salje, Skowronski, Slot, Swedish Public Health Agency, The Hindu, The Indian Express, The Irish Times, The Jerusalem Post, Valenti*], but the sparse nature, different time periods, and different geographic coverage prevents conclusions at this time. We expect that increased seroprevalence data will allow improved analysis over time.

While this is not a double-blind trial, this should not significantly affect the results. [*Wood*], based on an analysis of 1,346 trials, show that allocation concealment and blinding are only important for subjective outcomes, and should not significantly effect the objective outcome here.

Imperfect medication adherence, imperfect co-administration of treatments, imperfect dosing regimens, and counterfeit HCQ may decrease the observed effectiveness of treatment.

In terms on early treatment, we consider this to be PrEP or PEP prophylaxis, and treatment within about 48 hours of symptoms. Details of the effectiveness based on treatment delay are not well known at this time. For comparison, oseltamivir is generally considered to only be effective within about 48 hours, and within that time period earlier is considered to be better. [*Nicholson, Treanor*] for example, find effectiveness for oseltamivir based on 0-36 hour delayed treatment, while [*McLean*] finds no effect for 48 - 119 hour delayed treatment.

The results here are consistent with the positive results of other early treatment trials as discussed in the previous section. There are many other examples that are consistent with effectiveness, some of these in Brazil and Switzerland are discussed by [*Rafaeli, Risch (B)*]. We provide a few more examples.

[*Mitchell (B)*] provide an extensive discussion of the differences between the death rates of New York City and Lagos, Nigeria, which both received infected travelers around the same time. NYC's high rate has been linked to population density, poverty, overcrowding, and ethnicity. Lagos is a crowded urban center of about 22 million people with 30 families often in a single building sharing the same bathroom, and none of the factors mentioned favor reduced death rates in Lagos. Lagos further has lower quality of medical care. Yet NYC had a death rate 600 times higher. The younger population can only account for a small part of this difference. Mitchell concludes that there is a crossover prophylactic effect of antimalarial agents against COVID-19.

In France, early treatment with HCQ has not been widely used, but one exception is in Marseille. Table 2 shows the death statistics until the end of May for these two locations for 2020 and compared with the previous two years. Paris shows a large increase, while Marseille does not [Covid19Crusher (B)].

	Change from previous years				
	2018	2019	2020	2020/2018	2020/2019
Paris	6,055	5,927	7,972	+32%	+35%
Marseille	1,321	1,509	1,304	-1%	-14%

**Table 2.** Deaths as of the end of May each year for Marseille (using early treatment with HCQ) vs. Paris (generally not using early treatment with HCQ) [Covid19Crusher (B)].

For countries that started and/or stopped early HCQ treatment it is possible to examine the resulting change in statistics. Many examples can be found from [Covid19Crusher (C)].

We welcome feedback and will improve and update this study over time.

## Revisions

This study is updated regularly. The paper is entirely data-driven - all graphs and numbers are dynamically generated based on the latest data. As discussed previously, the limitation from varying degrees of spread should reduce over time, allowing a continually improving analysis. Numbers may change as new statistics are released each day. OWID also periodically updates statistics for earlier days, sometimes these changes are significant. The prediction for future spread will change based on the latest trend.

9/8: We added references [Synolaki].

9/7: We added references [BaŞaran, Elbazidi].

9/6: Since the previously minor correlation for the intervention stringency index has disappeared as the data evolves, we no longer test removing stringency outliers. We added references [Burrows, Elbazidi, Furtado, Huang, Sánchez-Álvarez].

8/31: We added references [de la Iglesia, Fried, Heras, Huh].

8/28: We added reference [Ferri].

8/27: We added a comparison of results without the country exclusions.

8/26: We added reference [Ip].

8/25: We added reference [Castelnuovo].

8/24: We added references [Catteau, Grassin-Delyle].

8/21: We added a reference *[Gonzalez]*.

8/20: We removed Israel because multiple reports indicated usage has not been as widespread as believed. Reference *[Dubernet]* was added. We changed "/million" to "per million" to avoid any confusion.

8/19: Corrected a typo in the responses - "widespread" should have been "not widespread". Historical data for the United Kingdom was updated in the OWID data, allowing removal of the special case for the change in their counting method.

8/18: We added references *[Abd-El salam, Ly, Peters, Saleemij]*.

8/17: Some countries identified by Leffler were missing in Appendix 11. Notably, Leffler identified Indonesia, which should therefore be excluded but which we had previously included. This error has been corrected.

8/15: We noted that the United Kingdom modified their counting method around August 13.

8/13: We added references *[Machiels, Mitchell, Rosendaal]* and details on the definition of early treatment.

8/12: We updated the title and corresponding discussion. We added analysis of the probability of random allocation resulting in the observed difference or better. We clarified the exclusion of countries that widely and quickly adopted masks, which is focused on excluding those countries that have taken an aggressive intervention and isolation approach and have very little spread of the virus.

8/10: We added a section to respond to common questions. This will be expanded over time. An appendix numbering error was fixed for urbanization.

8/9: We clarified the p-value for the entire treatment and control groups. We updated the medication cost reference to link directly to the relevant data.

8/8: We clarified the mask based exclusions at the earlier mention because feedback indicated many people did not read the confounding factors section and misinterpreted this. Feedback also indicated that many people missed the discussion of case statistics, so we moved that into a separate named section.

8/7: We updated and clarified terminology related to the trial. We believe it was clear originally from the title on, with clear explanation of how the trial came about, however some people reported misunderstanding. We didn't think that anyone would misinterpret the wording to think that 2.4B enrolled in a clinical trial, that's impossible. It seems self-evident that the countries are trialling this treatment (and we explain this in the first sentence of the abstract). It's not clear how much people really misinterpreted this due to the combination with other baseless accusations. One for example claims this must be fake because it looks too professional. We appreciate the feedback on our basic design skills (hopefully clean and easy to navigate), but we don't follow the logic. In any case, we want to be as clear as possible.

## Responses

**Why is country x not included?** Our goal is to identify countries that have taken a strong decision on treatment. Countries without clear decisions are much harder to analyze - to create any meaningful results we need to know the proportion of usage to some reasonable degree. One possibility for further research would be to analyze prescription data if available.

Countries like Italy or Brazil have extremely mixed usage, with differences during major time periods of their outbreak and/or major geographic differences. Analyzing these countries would be much more complex. Data broken down by intra-country geography is typically unavailable, and analysis before/after treatment decision changes is complicated by different rates of spread over time.

Analysis of countries that have avoided significant spread of the virus is difficult because we have very little ability to predict the final death rate when the virus is not widespread, and the virus may never become widespread in these countries, for example if they maintain isolation long enough and a very effective vaccine becomes available. These countries also tend not to have made a strong decision for or against treatment.

**Israel should not be in the widespread use category.** We received some reports that usage in Israel is not as high as believed. We would like to receive confirmation of usage. Removing Israel would not significantly change the observed effect (it would benefit the treatment group slightly).

## References

1. **Abd-Elisalam** et al., American Journal of Tropical Medicine and Hygiene, 10.4269/ajtmh.20-0873, *Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study*, <https://www.ajtmh.org/content/journals/10.4269/ajtmh.20-0873>.
2. **Academy of Medicine**, *Position Statement from the National Centre for Infectious Diseases and the Chapter of Infectious Disease Physicians, Academy of Medicine, Singapore – 23 May 2020*, [https://www.ams.edu.sg/view-pdf.assetment+\(final\)+23-5-20+\(logos\).pdf](https://www.ams.edu.sg/view-pdf.assetment+(final)+23-5-20+(logos).pdf).
3. **Acosta-Elias** et al., Front. Pharmacol., 16 July 2020, doi:10.3389/fphar.2020.01062, *The Folate Concentration and/or Folic Acid Metabolites in Plasma as Factor for COVID-19 Infection*, <https://www.frontiersin.org/articles/10.3389/fphar.2020.01062/full>.
4. **Ahmad** et al., doi:10.1101/2020.05.18.20066902, *Doxycycline and Hydroxychloroquine as Treatment for High-Risk COVID-19 Patients: Experience from Case Series of 54 Patients in Long-Term Care Facilities*, <https://www.medrxiv.org/content/10.1101/2020.05.18.20066902v1>.
5. **Alberici** et al., Kidney Int., 98:1, 20-26, July 1, 2020, doi:10.1016/j.kint.2020.04.030 (preprint 5/10), *A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection*, [https://www.kidney-international.org/abstract/S0085-2538\(20\)30508-1/fulltext](https://www.kidney-international.org/abstract/S0085-2538(20)30508-1/fulltext).
6. **An** et al., medRxiv, doi:10.1101/2020.07.04.20146548, *Treatment Response to Hydroxychloroquine and Antibiotics for mild to moderate COVID-19: a retrospective cohort study from South Korea*, <https://www.medrxiv.org/content/10.1101/2020.07.04.20146548v1>.

7. **Andreani** et al., Microbial Pathogenesis, doi:/10.1016/j.micpath.2020.104228, *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, <https://www.sciencedirect.com/science/article/pii/S0882401020305155>.
8. **Arshad** et al., Int. J. Infect. Dis., July 1 2020, doi:10.1016/j.ijid.2020.06.099, *Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19*, [https://www.ijidonline.com/article/S1201-9712\(20\)30534-8/fulltext](https://www.ijidonline.com/article/S1201-9712(20)30534-8/fulltext).
9. **Ashraf** et al., medRxiv doi:10.1101/2020.04.20.20072421.t, *COVID-19 in Iran, a comprehensive investigation from exposure to treatment outcomes*, [https://www.researchgate.net/publication/exposure\\_to\\_treatment\\_outcomes](https://www.researchgate.net/publication/exposure_to_treatment_outcomes).
10. **Ayerbe** et al., Journal of Thrombosis and Thrombolysis, doi: 10.1007/s11239-020-02162-z, *The association between treatment with heparin and survival in patients with Covid-19*, <https://doi.org/10.1101/2020.05.27.20114694>.
11. **Barbosa** et al., Preprint, *Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: a quasi-randomized comparative study*, <https://bibliovid.org/en/clinical-hospitalized-patients-with-covid-19-a-302>.
12. **Başaran** et al., Turk. J. Med. Sci., doi:10.3906/sag-2006-173, *Outcome of Non-Critical COVID-19 Patients with Early Hospitalization and Early Antiviral Treatment Outside the ICU*, <https://pubmed.ncbi.nlm.nih.gov/32718127/>.
13. **BBC**, *India coronavirus: Nearly one in four in Delhi had Covid-19, study says*, <https://www.bbc.com/news/world-asia-india-53485039>.
14. **Bernaola** et al., medRxiv, doi:10.1101/2020.07.17.20155960, *Observational Study of the Efficiency of Treatments in Patients Hospitalized with Covid-19 in Madrid*, <https://www.medrxiv.org/content/10.1101/2020.07.17.20155960v1>.
15. **Bhattacharya** et al., medRxiv, doi:10.1101/2020.06.09.20116806, *Pre exposure Hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers*, <https://www.medrxiv.org/content/10.1101/2020.06.09.20116806v1>.
16. **Bo-gyung**, K., The Korea Herald, *Tests in recovered patients found false positives, not reinfections, experts say*, <http://www.koreaherald.com/view.php?ud=20200429000724>.
17. **Borba** et al., JAMA Network Open, doi:10.1001/jamanetworkopen.2020.8857, *Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study)*, <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765499>.
18. **Boulware** et al., NEJM, June 3 2020, doi:10.1056/NEJMoa2016638, *A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19*, <https://www.nejm.org/doi/full/10.1056/NEJMoa2016638>.
19. **Bouza** et al., Infect. Dis. Clin. North. Am., 2001 Jun, 15:2, 335-61, doi:10.1016/s0891-5520(05)70149-5, *Infections in Systemic Lupus Erythematosus and Rheumatoid Arthritis*, <https://pubmed.ncbi.nlm.nih.gov/11447699/>.
20. **Browning**, D., Hydroxychloroquine and Chloroquine Retinopathy, April 4, 2014, 35–63, doi:10.1007/978-1-4939-0597-3\_2, *Pharmacology of Chloroquine and Hydroxychloroquine*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7122276/>.
21. **Brufsky**, A., J. Medical Virology, doi:10.1002/jmv.25887, *Hyperglycemia, hydroxychloroquine, and the COVID-19 pandemic*, <https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.25887>.

22. **Bultink** et al., *Rheumatology*, doi:10.1093/rheumatology/keaa267, *Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus vs matched controls*, <https://academic.oup.com/rheumatol...1093/rheumatology/keaa267/5870413>.
23. **Burrows**, E., *Medical Record*, 97:6, 235, Feb 7, 1920, *A confirmatory report upon the abortive action of quinine dihydrochloride*, <https://twitter.com/EdmundFordham/status/1301801632443887616>.
24. **Carlucci** et al., doi:10.1101/2020.05.02.20080036, *Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients*, <https://www.medrxiv.org/content/10.1101/2020.05.02.20080036v1>.
25. **Castelnuovo** et al., *European J. Internal Medicine*, doi:10.1016/j.ejim.2020.08.019, *Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study*, <https://www.sciencedirect.com/scie..../article/abs/pii/S0953620520303356>.
26. **Catteau** et al., *Int. J. Antimicrobial Agents*, doi:10.1016/j.ijantimicag.2020.106144, *Low-dose Hydroxychloroquine Therapy and Mortality in Hospitalized Patients with COVID-19: A Nationwide Observational Study of 8075 Participants*, <https://www.sciencedirect.com/scie..../article/abs/pii/S0924857920303423>.
27. **Cavalcanti** et al., *NEJM*, July 23, 2020, doi:10.1056/NEJMoa201901, *Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19*, <https://www.nejm.org/doi/full/10.1056/NEJMoa2019014>.
28. **CDC**, *Medicines for the Prevention of Malaria While Traveling Hydroxychloroquine (Plaquenil™)*, <https://www.cdc.gov/malaria/resour..f/fsp/drugs/Hydroxychloroquine.pdf>.
29. **CDC (B)**, *Commercial Laboratory Seroprevalence Survey Data*, <https://www.cdc.gov/coronavirus/20..pdates/commercial-lab-surveys.html>.
30. **Centers for Medicare and Medicaid Services**, *National Average Drug Acquisition Cost*, <https://data.medicare.gov/Drug-Pri..AC-as-of-2019-08-07/m7ng-9e3x/data>.
31. **Chamieh** et al., *medRxiv* 2020.05.28.20114835, doi:10.1101/2020.05.28.20114835, *Viral Dynamics Matter in COVID-19 Pneumonia: the success of early treatment with hydroxychloroquine and azithromycin in Lebanon*, <https://www.medrxiv.org/content/10.1101/2020.05.28.20114835v1>.
32. **Chatterjee** et al., *Indian J. Med. Res.*, June 20, 2020, doi:10.4103/ijmr.IJMR\_2234\_20, *Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19*, <http://www.ijmr.org.in/preprintarticle.asp?id=285520>.
33. **Chen** et al., *medRxiv*, doi:10.1101/2020.06.19.20136093, *Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study*, <https://www.medrxiv.org/content/10.1101/2020.06.19.20136093v1>.
34. **Chen (B)** et al., *medRxiv* doi:10.1101/2020.03.22.20040758, *Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial*, <https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v3>.
35. **Chen (C)** et al., *J. Zhejiang University (Med Sci)*, doi:10.3785/j.issn.1008-9292.2020.03.03, *A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)*, <http://www.zjujournals.com/med/EN/..cleFile.do?attachType=PDF&id=41137>.
36. **Chhonker** et al., *Journal of Chromatography B, Analytical Technologies in the Biomedical and Life Sciences*, 22 Nov 2017, 1072:320-327 doi:10.1016/j.jchromb.2017.11.026, *Simultaneous quantitation of hydroxychloroquine and its metabolites in mouse blood and tissues using LC-ESI-MS/MS: An application for pharmacokinetic studies*, <https://europepmc.org/article/med/29207305>.

37. **CIA**, *Obesity - Adult Prevalence Rate*, <https://www.cia.gov/library/publications/factbook/rankorder/2228rank.html>.
38. **Clementi** et al., *Front. Microbiol.*, 10 July 2020, doi:10.3389/fmicb.2020.01704 (preprint 3/31), *Combined Prophylactic and Therapeutic Use Maximizes Hydroxychloroquine Anti-SARS-CoV-2 Effects in vitro*, <https://www.frontiersin.org/article/abstract/10.3389/fmicb.2020.01704>.
39. **Cohen**, M., *NEJM*, doi:10.1056/NEJMe2020388, *Hydroxychloroquine for the Prevention of Covid-19 – Searching for Evidence*, <https://www.nejm.org/doi/full/10.1056/NEJMe2020388>.
40. **Colson** et al., *Int. J. Antimicrob. Agents*, doi: 10.1016/j.ijantimicag.2020.105932. Epub 2020 Mar 4., *Chloroquine and Hydroxychloroquine as Available Weapons to Fight COVID-19*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7135139/>.
41. **Covid19Crusher**, *Fake Hydroxychloroquine has appeared in Brazil*, <https://twitter.com/Covid19Crusher/status/1277526066152837122>.
42. **Covid19Crusher (B)**, *Marseille vs. Paris Death Statistics*, <https://twitter.com/Covid19Crusher/status/1278009960115376129>.
43. **Covid19Crusher (C)**, <https://twitter.com/Covid19Crusher>.
44. **CovidAnalysis**, *Boulware et al. comments*, <https://c19study.com/boulware.html>.
45. **D'Arminio Monforte** et al., *Int. J. Infectious Diseases*, doi:10.1016/j.ijid.2020.07.056, *Effectiveness of Hydroxychloroquine in COVID-19 disease: A done and dusted situation?*, [https://www.ijidonline.com/article/S1201-9712\(20\)30600-7/fulltext](https://www.ijidonline.com/article/S1201-9712(20)30600-7/fulltext).
46. **David** et al., *Int. J. Antimicrobial Agents*, 2020, doi:10.1016/j.ijantimicag.2020.106129, *Impact of medical care including anti-infective agents use on the prognosis of COVID-19 hospitalized patients over time*, <https://www.sciencedirect.com/science/article/pii/S0924857920303125>.
47. **de la Iglesia** et al., *medRxiv*, doi:10.1101/2020.08.31.20185314, *Hydroxychloroquine for pre-exposure prophylaxis for SARS-CoV-2*, <https://www.medrxiv.org/content/10.1101/2020.08.31.20185314v1>.
48. **de Wilde** et al., *Antimicrobial Agents and Chemotherapy*, Jul 2014, 58:8, 4875-4884, doi:10.1128/AAC.03011-14, *Screening of an FDA-Approved Compound Library Identifies Four Small-Molecule Inhibitors of Middle East Respiratory Syndrome Coronavirus Replication in Cell Culture*, <https://aac.asm.org/content/58/8/4875>.
49. **Derendorf**, H., *Int. J. Antimicrobial Agents*, 7 May 2020, doi:10.1016/j.ijantimicag.2020.106007, *Excessive lysosomal ion-trapping of hydroxychloroquine and azithromycin*, <https://www.sciencedirect.com/science/article/pii/S0924857920301655>.
50. **Derwand** and Scholz, *Medical Hypotheses*, 142, doi:10.1016/j.mehy.2020.109815, *Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19?*, <https://www.sciencedirect.com/science/article/pii/S0306987720306435>.
51. **Devaux** et al., *International Journal of Antimicrobial Agents*, doi:10.1016/j.ijantimicag.2020.105938, *New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?*, <https://www.sciencedirect.com/science/article/pii/S0924857920300881>.
52. **Dubernet** et al., *J. Global Antimicrobial Resistance*, doi:10.1016/j.jgar.2020.08.001, *A comprehensive strategy for the early treatment of COVID-19 with azithromycin/hydroxychloroquine and/or corticosteroids: results of a retrospective observational study in the French overseas department of Reunion Island*, <https://www.sciencedirect.com/science/article/pii/S221371652030206X>.
53. **Eckerle** et al., *Lancet*, July 6, 2020, doi:10.1016/S0140-6736(20)31482-3, *SARS-CoV-2 seroprevalence in COVID-19 hotspots*, [https://www.thelancet.com/pdfs/journal/PIIS0140-6736\(20\)31482-3.pdf](https://www.thelancet.com/pdfs/journal/PIIS0140-6736(20)31482-3.pdf).



54. **Elbazidi** et al., *New Microbes and New Infections*, doi:10.1016/j.nmni.2020.100749, *Pandemic and social changes, political fate*, <https://www.sciencedirect.com/science/article/pii/S2052297520301013>.
55. **Esper** et al., Prevent Senior Institute, São Paulo, Brazil, *Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine*, <https://www.dropbox.com/s/5qm58cd4..20journal%20manuscript%20final.pdf>.
56. **European University** at St. Petersburg, *6% of People in St. Petersburg, Russia have had COVID-19*, <https://eusp.org/en/news/press-rel..ersburg-russia-have-had-covid-19-0>.
57. **Ferreira** et al., *J. Medical Virology*, July 9, 2020, doi:10.1002/jmv.26286 (preprint 6/29), *Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection*, <https://www.medrxiv.org/content/10.1101/2020.06.26.20056507v1>.
58. **Ferri** et al., *Clinical Rheumatology*, doi:10.1007/s10067-020-05334-7, *COVID-19 and rheumatic autoimmune systemic diseases: report of a large Italian patients series*, <https://link.springer.com/article/10.1007/s10067-020-05334-7>.
59. **Fitch**, C., *Trans. Am. Clin. Climatol. Assoc.*, 1997, 109:97-105, PMID:PMC2194336, *Involvement of heme in the antimalarial action of chloroquine*, <https://europepmc.org/article/med/9601131>.
60. **Fontanet** et al., medRxiv, 10.1101/2020.04.18.20071134, *Cluster of COVID-19 in northern France: A retrospective closed cohort study*, <https://www.medrxiv.org/content/10.1101/2020.04.18.20071134v1>.
61. **Fontanet (B)** et al., medRxiv, doi:10.1101/2020.06.25.20140178, *SARS-CoV-2 infection in primary schools in northern France: A retrospective cohort study in an area of high transmission*, <https://www.medrxiv.org/content/10.1101/2020.06.25.20140178v2>.
62. **Fried** et al., *Clinical Infectious Disease*, doi:10.1093/cid/ciaa1268, *Patient Characteristics and Outcomes of 11,721 Patients with COVID19 Hospitalized Across the United States*, <https://academic.oup.com/cid/advance/doi/10.1093/cid/ciaa1268/5898276>.
63. **Furtado** et al., *The Lancet*, doi:10.1016/S0140-6736(20)31862-6, *Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial*, [https://www.thelancet.com/journals../PIIS0140-6736\(20\)31862-6/fulltext](https://www.thelancet.com/journals../PIIS0140-6736(20)31862-6/fulltext).
64. **Gao** et al., *European Heart Journal*, Volume 41, Issue 22, 7 June 2020, 2058–2066, doi:10.1093/eurheartj/ehaa433, *Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study*, <https://academic.oup.com/eurheartj/article/41/22/2058/5851436>.
65. **Gao (B)** et al., *BioScience Trends*, 2020, doi:10.5582/bst.2020.01047, *Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies*, [https://www.jstage.jst.go.jp/article..dvpub/0/advpub\\_2020.01047/\\_article](https://www.jstage.jst.go.jp/article..dvpub/0/advpub_2020.01047/_article).
66. **Gao (C)** et al., *Biosci Trends*, May 21, 2020, 14:2, 156-158, doi:10.5582/bst.2020.03072, Epub Apr 13, 2020, *Update on Use of Chloroquine/Hydroxychloroquine to Treat Coronavirus Disease 2019 (COVID-19)*, <https://pubmed.ncbi.nlm.nih.gov/32281583/>.
67. **Gautret** et al., *Int. J. of Antimicrobial Agents*, 17 March 2020, doi:10.1016/j.ijantimicag.2020.105949, *Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an openlabel non-randomized clinical trial*, [https://www.mediterranee-infection..roxychloroquine\\_final\\_DOI\\_IJAA.pdf](https://www.mediterranee-infection..roxychloroquine_final_DOI_IJAA.pdf).
68. **Gautret (B)** et al., *Travel Medicine and Infectious Disease*, doi:10.1016/j.tmaid.2020.101663, *Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study*,

<https://www.sciencedirect.com/science/article/pii/S1477893920301319>.

69. **Gebhard** et al., *Biol. Sex Differ.*, 2020, 11:29, doi:10.1186/s13293-020-00304-9, *Impact of sex and gender on COVID-19 outcomes in Europe*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7247289/>.
70. **Geleris** et al., *NEJM*, May 7, 2020, doi:10.1056/NEJMoa2012410, *Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19*, <https://www.nejm.org/doi/full/10.1056/NEJMoa2012410>.
71. **Gendelman** et al., *Autoimmunity Reviews*, 19:7, July 2020, doi:10.1016/j.autrev.2020.102566, *Continuous Hydroxychloroquine or Colchicine Therapy Does Not Prevent Infection With SARS-CoV-2: Insights From a Large Healthcare Database Analysis*, <https://www.sciencedirect.com/science/article/pii/S1568997220301282?via%3Dihub>.
72. **Giacomelli** et al., *Journal of Medical Virology*, doi:10.1002/jmv.26407 (preprint 6/12), *Early administration of lopinavir/ritonavir plus hydroxychloroquine does not alter the clinical course of SARS-CoV-2 infection: a retrospective cohort study*, <https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.26407>.
73. **Gonzalez** et al., *medRxiv*, doi:10.1101/2020.08.18.20172874, *The Prognostic Value of Eosinophil Recovery in COVID-19: A Multicentre, Retrospective Cohort Study on Patients Hospitalised in Spanish Hospitals*, <https://www.medrxiv.org/content/10.1101/2020.08.18.20172874v1>.
74. **Grassin-Delye** et al., *Clinical Infectious Diseases*, doi:10.1093/cid/ciaa546, *Chloroquine Inhibits the Release of Inflammatory Cytokines by Human Lung Explants*, <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa546/5831983?redirectedFrom=fulltext>.
75. **Guérin** et al., *Asian J. Medicine and Health*, July 15, 2020, doi:10.9734/ajmah/2020/v18i730224 (preprint 5/31), *Azithromycin and Hydroxychloroquine Accelerate Recovery of Outpatients with Mild/Moderate COVID-19*, <https://www.preprints.org/manuscript/202005.0486/v1>.
76. **Havers** et al., *JAMA Intern. Med.*, July 21, 2020, doi:10.1001/jamainternmed.2020.4130, *Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020*, <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2768834>.
77. **Heras** et al., *Research Square*, 10.21203/rs.3.rs-70219/v1, *COVID-19 mortality risk factors in older people in a long-term care center*, <https://www.researchsquare.com/article/rs-70219/v1>.
78. **Herrinton** et al., *J. Rheumatology*, 2016, 43(8), doi:10.3899/jrheum, *Risk of Serious Infection for Patients With Systemic Lupus Erythematosus Starting Glucocorticoids With or Without Antimalarials*, <https://pubmed.ncbi.nlm.nih.gov/27370880/>.
79. **Hoffmann** et al., *Nature*, (2020), doi:10.1038/s41586-020-2575-3, *Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2*, <https://www.nature.com/articles/s41586-020-2575-3>.
80. **Hong** et al., *Infect. Chemother.*, 2020, 52:e43, *Early Hydroxychloroquine Administration for Rapid Severe Acute Respiratory Syndrome Coronavirus 2 Eradication*, <https://icjournal.org/DOIx.php?id=10.3947/ic.2020.52.e43>.
81. **Horby** et al., *medRxiv*, 7/15/2020, doi:10.1101/2020.07.15.20151852 (press release 6/5), *Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial*, <https://www.medrxiv.org/content/10.1101/2020.07.15.20151852v1>.
82. **Hu** et al., *Nature Nanotechnology*, 15, 247–249, 2020, doi:10.1038/s41565-020-0674-9, *Insights from nanomedicine into chloroquine efficacy against COVID-19*, <https://www.nature.com/articles/s41565-020-0674-9>.
83. **Huang** et al., *Annals of the Rheumatic Diseases* 2020:79, 1163-1169, doi:10.1136/annrheumdis-2020-217425, *Clinical characteristics of 17 patients with COVID-19 and systemic autoimmune diseases: a retrospective study*, <https://ard.bmj.com/content/79/9/1163>.

84. **Huang (B)** et al., National Science Review, nwaa113, doi:10.1093/nsr/nwaa113, *Preliminary evidence from a multicenter prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19*, <https://academic.oup.com/nsr/advance-article/doi/10.1093/nsr/nwaa113/5848167>.
85. **Huang (C)** et al., Journal of Molecular Cell Biology, Volume 12, Issue 4, April 2020, 322–325, doi:10.1093/jmcb/mjaa014, *Treating COVID-19 with Chloroquine*, <https://academic.oup.com/jmcb/article/12/4/322/5814655>.
86. **Huh** et al., medRxiv, doi:10.1101/2020.05.04.20089904, *Association of previous medications with the risk of COVID-19: a nationwide claims-based study from South Korea*, <https://www.medrxiv.org/content/10.1101/2020.05.04.20089904v2>.
87. **Iglay** et al., Curr. Med. Res. Opin., July 2016, 32:7, 1243-52, doi:10.1185/03007995.2016.1168291, *Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus*, <https://pubmed.ncbi.nlm.nih.gov/26986190/>.
88. **Iliopoulos** et al., Semin. Arthritis Rheum., 1996 Apr, 25(5):318-36, *Immunopathogenesis and Spectrum of Infections in Systemic Lupus Erythematosus*, <https://pubmed.ncbi.nlm.nih.gov/8778988/>.
89. **International Diabetes Federation**, Diabetes Atlas, World Bank Diabetes Prevalence, <https://data.worldbank.org/indicator/SH.STA.DIAB.ZS>.
90. **Ioannidis**, J., medRxiv, doi:10.1101/2020.05.13.20101253, *The infection fatality rate of COVID-19 inferred from seroprevalence data*, <https://www.medrxiv.org/content/10.1101/2020.05.13.20101253v3>.
91. **Ip** et al., medRxiv, doi:10.1101/2020.08.20.20178772, *Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: A multi-center observational study*, <https://www.medrxiv.org/content/10.1101/2020.08.20.20178772v1>.
92. **Ip (B)** et al., medRxiv, doi:10.1101/2020.05.21.20109207, *Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients - An Observational Study*, <https://www.medrxiv.org/content/10.1101/2020.05.21.20109207v1>.
93. **Izoulet M.**, SSRN, doi:10.2139/ssrn.3575899, *Countries which Primarily Use Antimalarial Drugs As COVID-19 Treatment See Slower Dynamic of Daily Deaths*, [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3575899](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3575899).
94. **Jafari** et al., Cell J. 2019, 20:4, 604–607, doi:10.22074/cellj.2019.5992, *Why, When and How to Adjust Your P Values?*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6099145/pdf/Cell-J-20-604.pdf>.
95. **Jamil** et al., medRxiv, doi:10.1101/2020.03.29.20046706, *No evidence for temperature-dependence of the COVID-19 epidemic*, <https://www.medrxiv.org/content/10.1101/2020.03.29.20046706v2>.
96. **Jiang** et al., Chin. J. Tuberc. Respir. Dis., 2020, 43, doi:10.3760/cma.j.issn.1001-0939.2020.0019, *Expert Consensus on Chloroquine Phosphate for the Treatment of Novel Coronavirus Pneumonia*, <http://rs.yiigle.com/yufabiao/1182323.htm>.
97. **Kamran** et al., medRxiv, doi:10.1101/2020.07.30.20165365, *Clearing the fog: Is HCQ effective in reducing COVID-19 progression: A randomized controlled trial*, <https://www.medrxiv.org/content/10.1101/2020.07.30.20165365v1>.
98. **Kelly** et al., British Journal of Clinical Pharmacology, doi:10.1111/bcp.14482, *Clinical outcomes and adverse events in patients hospitalised with COVID-19, treated with off-label hydroxychloroquine and azithromycin*, <https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bcp.14482>.
99. **Keyaerts** et al., Biochem. Biophys. Res. Comm., 323:1, 8 October 2004, doi:10.1016/j.bbrc.2004.08.085, *In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine*, <https://www.sciencedirect.com/science/article/pii/S0006291X0401839X>.

100. **Keyaerts (B)** et al., *Antimicrob. Agents Chemother.*, August 2009, 53(8), doi:0.1128/AAC.01509-08, *Antiviral Activity of Chloroquine against Human Coronavirus OC43 Infection in Newborn Mice*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2715625/>.
101. **Khurana** et al., medRxiv, doi:10.1101/2020.07.21.20159301, *Prevalence and clinical correlates of COVID-19 outbreak among healthcare workers in a tertiary level hospital*, <https://www.medrxiv.org/content/10.1101/2020.07.21.20159301v1>.
102. **Kim** et al., medRxiv, doi:10.1101/2020.05.13.20094193, *Treatment Response to Hydroxychloroquine, Lopinavir/Ritonavir, and Antibiotics for Moderate COVID 19: A First Report on the Pharmacological Outcomes from South Korea*, <https://www.medrxiv.org/content/10.1101/2020.05.13.20094193v1>.
103. **Kim (B)** et al., *Rheumatology (Oxford)*, 2018 Jul, 57:26–33, doi: 10.1093/rheumatology/kex523, *Risk of human papillomavirus infection in women with rheumatic disease: cervical cancer screening and prevention*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6099129/>.
104. **Kono** et al., *Antiviral Research*, 77:2, February 2008, 150-152, 10.1016/j.antiviral.2007.10.011, *Inhibition of human coronavirus 229E infection in human epithelial lung cells (L132) by chloroquine: Involvement of p38 MAPK and ERK*, <https://www.sciencedirect.com/science/article/pii/S0166354207004597>.
105. **Kucirka** et al., *Annals of Internal Medicine*, doi:10.7326/M20-1495, *Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction–Based SARS-CoV-2 Tests by Time Since Exposure*, <https://www.acpjournals.org/doi/10.7326/M20-1495>.
106. **Lagier** et al., *Travel Med. Infect. Dis.* 101791, Jun 25, 2020, doi:10.1016/j.tmaid.2020.101791, *Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis*, <https://www.sciencedirect.com/science/article/pii/S1477893920302817>.
107. **Leclercq** et al., *Critical Care*, 24:418, 2020, doi:10.1186/s13054-020-03117-9, *Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis*, <https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03117-9>.
108. **Lee** et al., *Int. J. Antimicrob. Agents*, 2020, Apr 17, doi:10.1016/j.ijantimicag.2020.105988, *Can Post-Exposure Prophylaxis for COVID-19 Be Considered as an Outbreak Response Strategy in Long-Term Care Hospitals?*, <https://pubmed.ncbi.nlm.nih.gov/32305587/>.
109. **Leffler** et al., Preprint, *Association of country-wide coronavirus mortality with demographics, testing, lockdowns, and public wearing of masks (Update June 15, 2020)*, [https://www.researchgate.net/publication/347100000\\_Association\\_of\\_country-wide\\_coronavirus\\_mortality\\_with\\_demographics\\_testing\\_lockdowns\\_and\\_public\\_wearing\\_of\\_masks\\_Update\\_June\\_15\\_2020](https://www.researchgate.net/publication/347100000_Association_of_country-wide_coronavirus_mortality_with_demographics_testing_lockdowns_and_public_wearing_of_masks_Update_June_15_2020).
110. **Lewis, N.**, *Climate Etc.*, *The progress of the COVID-19 epidemic in Sweden: an analysis*, <https://judithcurry.com/2020/06/28/covid-19-epidemic-in-sweden-an-analysis/>.
111. **Li** et al., *Ann. Rheum. Dis.*, 2019 Jul, 78:7, 941-946, doi:10.1136/annrheumdis-2018-214844, *Risk of Severe Herpes Simplex Virus Infection in Systemic Lupus Erythematosus: Analysis of Epidemiology and Risk Factors Analysis in Taiwan*, <https://pubmed.ncbi.nlm.nih.gov/30954968/>.
112. **Listing** et al., *Rheumatology (Oxford)*, 2013 Jan, 5:1, 53-61, doi:10.1093/rheumatology/kes305, *The Risk of Infections Associated With Rheumatoid Arthritis, With Its Comorbidity and Treatment*, <https://pubmed.ncbi.nlm.nih.gov/23192911/>.
113. **Liu** et al., *Cell Discovery* 6, 16 (2020), doi:10.1038/s41421-020-0156-0, *Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro*, <https://www.nature.com/articles/s41421-020-0156-0>.

114. **Ly** et al., Preprint, 2020, *Pattern of SARS-CoV-2 infection among dependant elderly residents living in retirement homes in Marseille, France, March-June 2020*, <https://www.mediterranee-infection.com/article/S0924857920302260>.
115. **Machiels** et al., *Int. J. Antimicrobial Agents*, 56:1, July 2020, doi:10.1016/j.ijantimicag.2020.106056, *Reply to Gautret et al: hydroxychloroquine sulfate and azithromycin for COVID-19: what is the evidence and what are the risks?*, <https://www.sciencedirect.com/science/article/pii/S0924857920302260>.
116. **Macias** et al., medRxiv, 10.1101/2020.05.16.20104141, *Similar incidence of Coronavirus Disease 2019 (COVID-19) in patients with rheumatic diseases with and without hydroxychloroquine therapy*, <https://www.medrxiv.org/content/10.1101/2020.05.16.20104141v1.full.pdf>.
117. **Magagnoli** et al., *Med* (2020), doi:10.1016/j.medj.2020.06.001 (preprint 4/21), *Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19*, [https://www.cell.com/med/pdf/S2666-6340\(20\)30006-4.pdf](https://www.cell.com/med/pdf/S2666-6340(20)30006-4.pdf).
118. **Mahévas** et al., *BMJ* 2020, 369, doi: <https://doi.org/10.1136/bmj.m1844>, *Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data*, <https://www.bmj.com/content/369/bmj.m1844>.
119. **Maisonnasse** et al., *Nature*, 2020, doi:10.1038/s41586-020-2558-4 (preprint 5/6), *Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates*, [https://www.nature.com/articles/s41586-020-2558-4\\_reference.pdf](https://www.nature.com/articles/s41586-020-2558-4_reference.pdf).
120. **Maret** W., *Int. J. Mol. Sci.* 2017, 18:11, doi:10.3390/ijms18112285, *Zinc in Cellular Regulation: The Nature and Significance of "Zinc Signals"*, <https://www.mdpi.com/1422-0067/18/11/2285>.
121. **McGrail** et al., medRxiv, doi:10.1101/2020.07.17.20156521, *COVID-19 Case Series at UnityPoint Health St. Luke's Hospital in Cedar Rapids, IA*, <https://www.medrxiv.org/content/10.1101/2020.07.17.20156521v1>.
122. **McLean** et al., *Open Forum Infect. Dis.* September 2015, 2:3, doi:10.1093/ofid/ofv100, *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4525010/>.
123. **Membrillo de Novales** et al., Preprints 2020, 2020050057, doi:10.20944/preprints202005.0057.v1, *Early Hydroxychloroquine Is Associated with an Increase of Survival in COVID-19 Patients: An Observational Study*, <https://www.preprints.org/manuscript/202005.0057>.
124. **Meo** et al., *Eur. Rev. Med. Pharmacol. Sci.* 2020, 24 (8), 4539-4547, doi:10.26355/eurrev\_202004\_21038, *Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19*, <https://www.europeanreview.org/article/21038>.
125. **Mikami** et al., *J. Gen. Intern. Med.*, doi:10.1007/s11606-020-05983-z, *Risk Factors for Mortality in Patients with COVID-19 in New York City*, <https://link.springer.com/article/10.1007/s11606-020-05983-z>.
126. **Million** et al., *Travel Med Infect Dis.*, 2020 May 5, doi:10.1016/j.tmaid.2020.101738, *Early Treatment of COVID-19 Patients With Hydroxychloroquine and Azithromycin: A Retrospective Analysis of 1061 Cases in Marseille, France*, <https://pubmed.ncbi.nlm.nih.gov/32387409/>.
127. **Mills** et al., *Circulation*, Aug 9, 2016, 134:6, 441–450, doi:10.1161/circulationaha.115.018912, *Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-based Studies from 90 Countries*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4979614/>.
128. **Mitchell** et al., SSRN, doi:10.2139/ssrn.3586954, *Markedly Lower Rates of Coronavirus Infection and Fatality in Malaria-Endemic Regions – A Clue As to Treatment?*, [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3586954](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3586954).

129. **Mitchell (B)**, G., SSRN Preprint, June 16, 2020, doi:10.2139/ssrn.3628644, *A Tale of Two Cities – Lagos, Nigeria's Apparent Success in the War Against COVID-19*, [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3628644](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3628644).
130. **Mitjà** et al., medRxiv, doi:10.1101/2020.07.20.20157651, *A Cluster-Randomized Trial of Hydroxychloroquine as Prevention of Covid-19 Transmission and Disease*, <https://www.medrxiv.org/content/10.1101/2020.07.20.20157651v1>.
131. **Mitjà (B)** et al., Clinical Infectious Diseases, ciaa1009, doi:10.1093/cid/ciaa1009, *Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial*, <https://academic.oup.com/cid/article..a1009/5872589#.XxCYIMdGoJM.twitter>.
132. **Molina** et al., Médecine et Maladies Infectieuses, 50:4, June 2020, 10.1016/j.medmal.2020.03.006 (preprint 3/28), *No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection*, <https://www.sciencedirect.com/science/article/pii/S0399077X20300858>.
133. **Nicholson** et al., Lancet, 355:9218, 1845-1850, May 27, 2000, doi: 10.1016/S0140-6736(00)02288-1, *Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial*, <https://www.thelancet.com/journals..icle/PIIS0140673600022881/fulltext>.
134. **NIH**, *Zinc Fact Sheet for Health Professionals*, <https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/>.
135. **Okour** et al., Journal of Pharmacokinetics and Pharmacodynamics, May 13, 2020, doi:10.1007/s10928-020-09689-x, *Hydroxychloroquine and azithromycin as potential treatments for COVID-19; clinical status impacts the outcome*, [https://www.ncbi.nlm.nih.gov/pmc/a..12/pdf/10928\\_2020\\_Article\\_9689.pdf](https://www.ncbi.nlm.nih.gov/pmc/a..12/pdf/10928_2020_Article_9689.pdf).
136. **Olza** et al., Nutrients 2017, 9:7, 697, doi:10.3390/nu9070697, *Reported Dietary Intake and Food Sources of Zinc, Selenium, and Vitamins A, E and C in the Spanish Population: Findings from the ANIBES Study*, <https://www.mdpi.com/2072-6643/9/7/697>.
137. **Otea** et al., medRxiv, doi:10.1101/2020.06.10.20101105, *A short therapeutic regimen based on hydroxychloroquine plus azithromycin for the treatment of COVID-19 in patients with non-severe disease. A strategy associated with a reduction in hospital admissions and complications.*, <https://www.medrxiv.org/content/10.1101/2020.06.10.20101105v1>.
138. **Our World in Data**, *Data on COVID-19 (coronavirus) by Our World in Data*, <https://github.com/owid/covid-19-data/tree/master/public/data>.
139. **Our World in Data (B)**, *Life Expectancy*, <https://ourworldindata.org/life-expectancy>.
140. **Our World in Data (C)**, *Total COVID-19 tests per 1,000 people*, <https://ourworldindata.org/grapher..total-tests-per-thousand-bar-chart>.
141. **Our World in Data (D)**, *Population Density*, <https://ourworldindata.org/grapher/population-density>.
142. **Our World in Data (E)**, *Coronavirus Source Data*, <https://ourworldindata.org/coronavirus-source-data>.
143. **Our World in Data (F)**, *COVID-19: Government Response Stringency Index*, <https://ourworldindata.org/grapher/covid-stringency-index>.
144. **Paccoud** et al., Clinical Infectious Diseases, doi:10.1093/cid/ciaa791, *Compassionate use of hydroxychloroquine in clinical practice for patients with mild to severe Covid-19 in a French university hospital*, <https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa791/5859555>.
145. **Pagliano** et al., Clin. Infect. Dis., 2020 Mar 24, doi:10.1093/cid/ciaa320, *Is Hydroxychloroquine a Possible Post-Exposure Prophylaxis Drug to Limit the Transmission to Health Care Workers Exposed to COVID19?*, <https://pubmed.ncbi.nlm.nih.gov/32211764/>.

146. **Peters** et al., medRxiv, doi:10.1101/2020.08.14.20173369, *Outcomes of Persons With COVID-19 in Hospitals With and Without Standard Treatment With (Hydroxy)chloroquine*, <https://www.medrxiv.org/content/10.1101/2020.08.14.20173369v1>.
147. **Pinato** et al., Cancer Discovery, doi:10.1158/2159-8290.CD-20-0773, *Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients*, <https://cancerdiscovery.aacrjournals.org/2020/08/18/2159-8290.CD-20-0773>.
148. **Pirnay** et al., Hosp. Pharm. and Clinician, doi:10.1016/j.phclin.2020.06.001, *Beneficial effect of Hydroxychloroquine-Azithromycin combination in the treatment of elderly patients with Covid-19: results of an observational study*, <https://www.sciencedirect.com/science/article/pii/S2211104220300771>.
149. **Public Health England**, *Sero-surveillance of COVID-19*, <https://www.gov.uk/government/publications/sero-surveillance-of-covid-19>.
150. **Rafaelli**, F., Medium, July 23, 2020, *Hydroxychloroquine: The Narrative That it Doesn't Work is the Biggest Hoax in Recent Human History*, <https://truthaboutshc.com/hcq-works/>.
151. **Risch**, H., American Journal of Epidemiology, July 20, 2020, doi:10.1093/aje/kwaa152, *Response to: "Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients" and "Re: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis"*, <https://academic.oup.com/aje/article/doi/10.1093/aje/kwaa152/5873640>.
152. **Risch (B)**, H., Newsweek, July 23, 2020, *The Key to Defeating COVID-19 Already Exists. We Need to Start Using It*, <https://www.newsweek.com/key-defeating-covid-19-already-exists-we-need-to-start-using-it-opinion-1519535>.
153. **Roomi** et al., J. Medical Internet Research, doi:10.2196/21758, *Efficacy of hydroxychloroquine and tocilizumab in patients with COVID-19: A single-center retrospective chart review*, <https://www.jmir.org/preprint/21758/accepted>.
154. **Rosenberg** et al., JAMA, May 11, 2020, doi:10.1001/jama.2020.8630, *Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State*, <https://jamanetwork.com/journals/jama/fullarticle/2766117>.
155. **Rosendaal** F., Int. J. Antimicrobial Agents, 56:1, July 2020, doi:10.1016/j.ijantimicag.2020.106063, *Review of: "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial Gautret et al 2010*, <https://www.sciencedirect.com/science/article/pii/S0924857920302338>.
156. **Saleemi** et al., medRxiv, doi:10.1101/2020.08.05.20151027, *Time to negative PCR from symptom onset in COVID-19 patients on Hydroxychloroquine and Azithromycin - A real world experience*, <https://www.medrxiv.org/content/10.1101/2020.08.05.20151027v1>.
157. **Salje** et al., Science 10 Jul 2020, 369:6500, 208-211 doi:10.1126/science.abc3517, *Estimating the burden of SARS-CoV-2 in France*, <https://science.sciencemag.org/content/369/6500/208>.
158. **Sauder** et al., Advances in Methods and Practices in Psychological Science, 2:1, 26-44, 2019, doi:10.1177/2515245918808784, *An Updated Recommendation for Multiple Comparisons*, <https://journals.sagepub.com/doi/full/10.1177/2515245918808784>.
159. **Savarino** et al., Lancet Infect. Dis., doi:10.1016/S1473-3099(06)70361-9, *New insights into the antiviral effects of chloroquine*, [https://www.thelancet.com/journals./PIIS1473-3099\(06\)70361-9/fulltext](https://www.thelancet.com/journals./PIIS1473-3099(06)70361-9/fulltext).
160. **Savarino (B)** et al., Lancet Infect. Dis., doi:10.1016/S1473-3099(03)00806-5, *Effects of chloroquine on viral infections: an old drug against today's diseases*, [https://www.thelancet.com/journals./PIIS1473-3099\(03\)00806-5/fulltext](https://www.thelancet.com/journals./PIIS1473-3099(03)00806-5/fulltext).

161. **Sbidian** et al., medRxiv, doi:10.1101/2020.06.16.20132597, *Hydroxychloroquine with or without azithromycin and in-hospital mortality or discharge in patients hospitalized for COVID-19 infection: a cohort study of 4,642 in-patients in France*, <https://www.medrxiv.org/content/10.1101/2020.06.16.20132597v1>.
162. **Scherrmann**, AAPS J 22, 86 (2020), doi:10.1208/s12248-020-00465-w, *Intracellular ABCB1 as a Possible Mechanism to Explain the Synergistic Effect of Hydroxychloroquine-Azithromycin Combination in COVID-19 Therapy*, <https://link.springer.com/article/10.1208/s12248-020-00465-w>.
163. **Scholz** et al., Preprints 2020, 2020070025, doi:10.20944/preprints202007.0025.v1, *COVID-19 Outpatients – Early Risk-Stratified Treatment with Zinc Plus Low Dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study*, <https://www.preprints.org/manuscript/202007.0025/v1>.
164. **Schrezenmeier** et al., Nature Reviews Rheumatology, 16, 155–166, doi:10.1038/s41584-020-0372-x, *Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology*, <https://www.nature.com/articles/s41584-020-0372-x>.
165. **Sheaff**, R., bioRxiv, doi:10.1101/2020.08.02.232892, *A New Model of SARS-CoV-2 Infection Based on (Hydroxy)Chloroquine Activity*, <https://www.biorxiv.org/content/10.1101/2020.08.02.232892v1>.
166. **Sheahan** et al., Science Translational Medicine, 29 Apr 2020, 12:541, doi:10.1126/scitranslmed.abb5883, *An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice*, <https://stm.sciencemag.org/content/12/541/eabb5883>.
167. **Shen** et al., Am. J. Physiol., May 1994, 266, 493-501, doi:10.1152/ajplung.1994.266.5.L493, *Calu-3: a human airway epithelial cell line that shows AMP-dependent Cl<sup>-</sup> secretion*, <https://journals.physiology.org/doi/10.1152/ajplung.1994.266.5.L493>.
168. **Shittu** et al., Le Infezioni in Medicina, 28:2, 192-197, 2020, *Improving the efficacy of chloroquine and hydroxychloroquine against SARS-CoV-2 may require zinc additives - A better synergy for future COVID-19 clinical trials*, [https://www.infezmed.it/index.php/..loDaVisualizzare=Vol\\_28\\_2\\_2020\\_192](https://www.infezmed.it/index.php/..loDaVisualizzare=Vol_28_2_2020_192).
169. **Singh** et al., medRxiv, doi:10.1101/2020.05.12.20099028, *Outcomes of Hydroxychloroquine Treatment Among Hospitalized COVID-19 Patients in the United States- Real-World Evidence From a Federated Electronic Medical Record Network*, <https://www.medrxiv.org/content/10.1101/2020.05.12.20099028v1>.
170. **Skipper** et al., Annals of Internal Medicine, doi:10.7326/M20-4207, *Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial*, <https://www.acpjournals.org/doi/10.7326/M20-4207>.
171. **Skowronski** et al., medRxiv, doi:10.1101/2020.07.13.20153148, *Low SARS-CoV-2 sero-prevalence based on anonymized residual sero-survey before and after first wave measures in British Columbia, Canada, March-May 2020*, <https://www.medrxiv.org/content/10.1101/2020.07.13.20153148v1>.
172. **Slot** et al., Research Square, doi:10.21203/rs.3.rs-25862/v1, *Herd immunity is not a realistic exit strategy during a COVID-19 outbreak*, <https://www.researchsquare.com/article/rs-25862/v1>.
173. **Swedish Public Health Agency**, *Första resultaten om antikroppar efter genomgången covid-19 hos blodgivare*, <https://www.folkhalsomyndigheten.s.nomgangen-covid-19-hos-blodgivare/>.
174. **Synolaki** et al., medRxiv, doi:10.1101/2020.09.05.20184655, *Activin/Follistatin-axis deregulation is independently associated with COVID-19 in-hospital mortality*, <https://www.medrxiv.org/content/10.1101/2020.09.05.20184655v1>.
175. **Sánchez-Álvarez** et al., Nefrología, doi:10.1016/j.nefro.2020.04.002, *Status of SARS-CoV-2 infection in patients on renal replacement therapy. Report of the COVID-19 Registry of the Spanish Society of Nephrology (SEN)*, <https://www.sciencedirect.com/science/article/pii/S201325142030050X>.



176. **Tang** et al., BMJ 2020, 369, doi:10.1136/bmj.m1849, *Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial*, <https://www.bmj.com/content/369/bmj.m1849>.
177. **te Velthuis** et al., PLOS Pathogens 2010, 6:11, doi:10.1371/journal.ppat.1001176, *Zn<sup>2+</sup> Inhibits Coronavirus and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture*, <https://journals.plos.org/plospath..le?id=10.1371/journal.ppat.1001176>.
178. **The Hindu**, *Initial results of survey show 'high' seroprevalence in Delhi: officials*, <https://www.thehindu.com/news/citi..officials/article32025471.ece/amp/>.
179. **The Indian Express**, *India not in community transmission stage, states cannot lower guard, says ICMR*, <https://indianexpress.com/article/..stage-yet-health-ministry-6454183/>.
180. **The Irish Times**, *The Irish Times view on Ireland's Covid-19 antibody study: still susceptible*, <https://www.irishtimes.com/opinion..-study-still-susceptible-1.4309176>.
181. **The Jerusalem Post**, *Coronavirus herd immunity? Not in Israel, according to a serological study*, <https://www.jpost.com/israel-news/..ding-to-a-serological-study-630059>.
182. **Treanor** et al., JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016, *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, <https://jamanetwork.com/journals/jama/fullarticle/192425>.
183. **United Nations**, *Population Dynamics*, <http://population.un.org/wpp/Download/Standard/Population/>.
184. **University of Oxford**, *Intervention Stringency Index*, <https://www.bsg.ox.ac.uk/research/..avirus-government-response-tracker>.
185. **Valenti** et al., medRxiv, doi:10.1101/2020.05.11.20098442, *SARS-CoV-2 seroprevalence trends in healthy blood donors during the COVID-19 Milan outbreak*, <https://www.medrxiv.org/content/10.1101/2020.05.11.20098442v2>.
186. **Verity** et al., Lancet Infect. Dis., 2020, doi:10.1016/S1473-3099(20)30243-7, [https://www.thelancet.com/journals../PIIS1473-3099\(20\)30243-7/fulltext](https://www.thelancet.com/journals../PIIS1473-3099(20)30243-7/fulltext).
187. **Vincent** et al., Virol. J. 2:69, 2005, doi:10.1186/1743-422X-2-69, *Chloroquine is a potent inhibitor of SARS coronavirus infection and spread*, <https://virologyj.biomedcentral.com/articles/10.1186/1743-422X-2-69>.
188. **Wang** et al., Phytomedicine, doi:10.1016/j.phymed.2020.153333, *Chloroquine and hydroxychloroquine as ACE2 blockers to inhibit viropexis of 2019-nCoV Spike pseudotyped virus*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7467095/>.
189. **Wang (B)** et al., Cell Res. 30, 269–271, doi:10.1038/s41422-020-0282-0, *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro*, [https://www.nature.com/articles/s4..iVs8\\_7R1KkwOuqjRh7psfHV6iSDRD1cM0](https://www.nature.com/articles/s4..iVs8_7R1KkwOuqjRh7psfHV6iSDRD1cM0).
190. **Wang (C)** et al., Chest Journal, June 19, 2020, doi:10.1016/j.chest.2020.06.015, *Differences of SARS-CoV-2 Shedding Duration in Sputum and Nasopharyngeal Swab Specimens Among Adult Inpatients With COVID-19*, [https://journal.chestnet.org/article/S0012-3692\(20\)31718-9/fulltext](https://journal.chestnet.org/article/S0012-3692(20)31718-9/fulltext).
191. **Watanabe, M.**, arXiv.org, arXiv:2007.09477, *Efficacy of Hydroxychloroquine as Prophylaxis for Covid-19*, <https://arxiv.org/abs/2007.09477>.
192. **Williamson** et al., Nature, 2020, doi:10.1038/s41586-020-2521-4, *OpenSAFELY: factors associated with COVID-19 death in 17 million patients*, <https://www.nature.com/articles/s41586-020-2521-4>.

193. **Wood** et al., BMJ, 2008, 336, doi:10.1136/bmj.39465.451748.AD, *Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study*, <https://www.bmj.com/content/336/7644/601.full>.
194. **World Bank**, *World Bank, Urban population (% of total population)*, <https://data.worldbank.org/indicator/SP.URB.TOTL.IN.ZS>.
195. **World Health Organization**, *WHO Model Lists of Essential Medicines*, <https://www.who.int/medicines/publications/essentialmedicines/en/>.
196. **World Health Organization (B)**, study not available yet, *"Solidarity" clinical trial for COVID-19 treatments*, <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/clinical-trial-for-covid-19-treatments>.
197. **Xue** et al., PLoS One, 9:10, 2014, 10.1371/journal.pone.0109180, *Chloroquine Is a Zinc Ionophore*, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4182877/>.
198. **Xue (B)** et al., J. Med. Virology, June 17, 2020, doi:10.1002/jmv.26193, *Hydroxychloroquine treatment in COVID-19: a descriptive observational analysis of 30 cases from a single center in Wuhan, China*, <https://onlinelibrary.wiley.com/doi/10.1002/jmv.26193>.
199. **Yan** et al., Cell Research, 23, 300–302, doi:10.1038/cr.2012.165, *Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model*, <https://www.nature.com/articles/cr2012165>.
200. **Yu** et al., Science China Life Sciences, 2020 Aug 3, doi:10.1007/s11427-020-1782-1, *Beneficial effects exerted by hydroxychloroquine in treating COVID-19 patients via protecting multiple organs*, <https://link.springer.com/content/pdf/10.1007/s11427-020-1782-1.pdf>.
201. **Yu (B)** et al., Science China Life Sciences, 2020 May 15, 1-7, doi:10.1007/s11427-020-1732-2, *Low Dose of Hydroxychloroquine Reduces Fatality of Critically Ill Patients With COVID-19*, <https://pubmed.ncbi.nlm.nih.gov/32418114/>.
202. **Zhong** et al., Lancet Rheumatology, 10.1016/S2665-9913(20)30227-7, *COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study*, [https://www.thelancet.com/journals./PIIS2665-9913\(20\)30227-7/fulltext](https://www.thelancet.com/journals./PIIS2665-9913(20)30227-7/fulltext).

## Appendix 1. Country Statistics

Country	Age 0-9	Age 10-19	Age 20-29	Age 30-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79	Age 80+	Age factor
Algeria	22.1%	15.3%	15.0%	16.6%	12.4%	8.7%	5.8%	2.8%	1.3%	3.14
Canada	10.5%	10.5%	13.5%	14.0%	12.8%	13.7%	12.5%	8.0%	4.4%	1.28
Costa Rica	13.9%	14.1%	16.2%	16.2%	12.8%	11.8%	8.3%	4.5%	2.2%	2.10
Cuba	10.6%	11.0%	12.5%	13.4%	13.8%	17.4%	10.4%	7.1%	3.8%	1.42
France	11.5%	12.1%	11.3%	12.3%	12.8%	13.2%	11.9%	8.8%	6.2%	1.12
Greece	8.5%	10.3%	10.1%	12.8%	15.1%	14.4%	12.1%	9.2%	7.5%	1.00
India	17.0%	18.3%	17.4%	15.6%	12.3%	9.3%	6.3%	2.8%	1.0%	3.24
Ireland	13.6%	13.5%	11.5%	14.1%	15.5%	12.2%	9.7%	6.7%	3.2%	1.60
Mexico	17.2%	17.3%	16.9%	14.6%	12.8%	9.9%	6.4%	3.2%	1.6%	2.77
Morocco	18.3%	16.5%	15.9%	15.2%	12.1%	10.1%	7.4%	3.2%	1.2%	2.83
Netherlands	10.2%	11.4%	12.2%	12.2%	12.6%	14.7%	12.4%	9.3%	4.9%	1.17
Russia	12.8%	10.5%	10.7%	16.8%	14.0%	12.9%	12.7%	5.9%	3.9%	1.46
Sweden	11.8%	11.2%	12.6%	13.1%	12.5%	12.8%	10.8%	9.8%	5.3%	1.16
Turkey	15.9%	16.1%	15.6%	15.1%	13.6%	10.6%	7.3%	4.0%	1.7%	2.43
U.K.	11.8%	11.3%	12.6%	13.7%	12.7%	13.5%	10.7%	8.6%	5.1%	1.23
USA	12.0%	12.8%	13.9%	13.5%	12.2%	12.7%	11.6%	7.3%	4.0%	1.40
Ukraine	10.5%	10.0%	11.2%	16.5%	14.6%	13.5%	12.7%	6.8%	4.2%	1.36

**Table 3.** Country age distributions [United Nations] and the computed age factor.

Country	Population	Urban percentage	Average intervention stringency index	Population density	Males per 100 females	Gender factor
Algeria	44M	73.2	0.29	17	102.1	1.00
Canada	38M	81.5	0.29	4	98.5	1.00
Costa Rica	5M	80.1	0.28	96	99.8	1.00
Cuba	11M	77.1	0.30	110	98.6	1.00
France	65M	80.7	0.27	123	93.8	1.01
Greece	10M	79.4	0.26	83	96.4	1.01
India	1.4B	34.5	0.34	450	108.2	0.99
Ireland	5M	63.4	0.28	70	98.6	1.00
Mexico	129M	80.4	0.29	66	95.8	1.01
Morocco	37M	63.0	0.31	80	98.5	1.00
Netherlands	17M	91.9	0.25	509	99.3	1.00
Russia	146M	74.6	0.30	9	86.4	1.02
Sweden	10M	87.7	0.16	25	100.4	1.00
Turkey	84M	75.6	0.26	105	97.5	1.00
U.K.	68M	83.7	0.28	273	97.7	1.00
USA	331M	82.5	0.28	36	97.9	1.00
Ukraine	44M	69.5	0.28	77	86.3	1.02

**Table 4.** Country statistics [Our World in Data (D), Our World in Data (F), United Nations (B), University of Oxford, World Bank] and the computed gender factor.

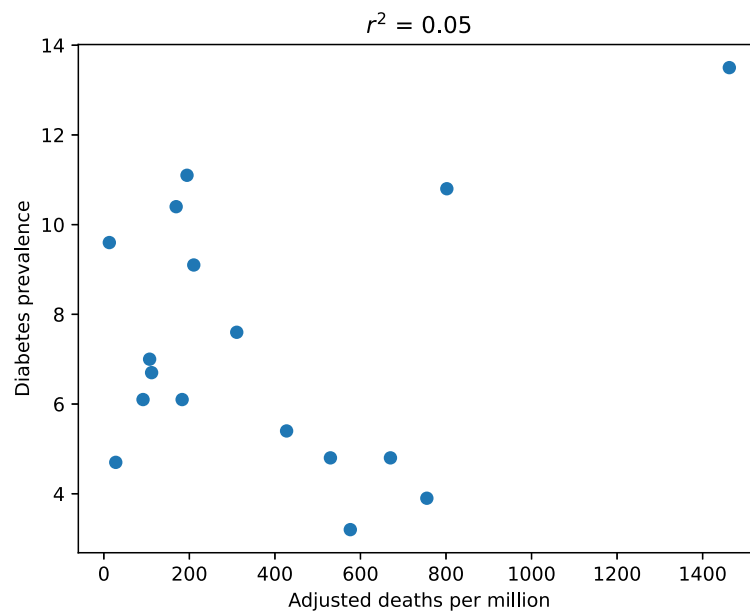
Country	Life expectancy	Diabetes prevalence	Obesity prevalence	Hypertension prevalence	Tests per thousand
Algeria	76.9	6.7	27.4	32.1	N/A
Canada	82.4	7.6	29.4	23.3	153.2
Costa Rica	80.3	9.1	25.7	24.0	28.1
Cuba	78.8	9.6	24.6	38.8	38.1
France	82.7	4.8	21.6	38.2	105.8
Greece	82.2	4.7	24.9	37.8	97.4
India	69.7	10.4	3.9	27.5	35.4
Ireland	82.3	3.2	25.3	39.1	180.2
Mexico	75.0	13.5	28.9	28.9	10.3
Morocco	76.7	7.0	26.1	33.2	54.2
Netherlands	82.3	5.4	20.4	36.5	96.2
Russia	72.6	6.1	23.1	40.7	265.6
Sweden	82.8	4.8	20.6	39.4	59.8
Turkey	77.7	11.1	32.1	36.7	92.2
U.K.	81.3	3.9	27.8	30.8	215.8
USA	78.9	10.8	36.2	31.5	276.5
Ukraine	72.1	6.1	24.1	49.2	39.1

**Table 5.** Country statistics [CIA, International Diabetes Federation, Mills, Our World in Data (B), Our World in Data (C)].

Country	Diabetes factor	Obesity factor	Hypertension factor
Algeria	1.04	1.11	1.36
Canada	1.05	1.12	1.26
Costa Rica	1.06	1.10	1.27
Cuba	1.06	1.10	1.44
France	1.03	1.09	1.43
Greece	1.03	1.10	1.42
India	1.07	1.02	1.31
Ireland	1.02	1.10	1.44
Mexico	1.09	1.12	1.32
Morocco	1.04	1.10	1.37
Netherlands	1.03	1.08	1.41
Russia	1.04	1.09	1.46
Sweden	1.03	1.08	1.44
Turkey	1.07	1.13	1.41
U.K.	1.02	1.11	1.34
USA	1.07	1.14	1.35
Ukraine	1.04	1.10	1.55

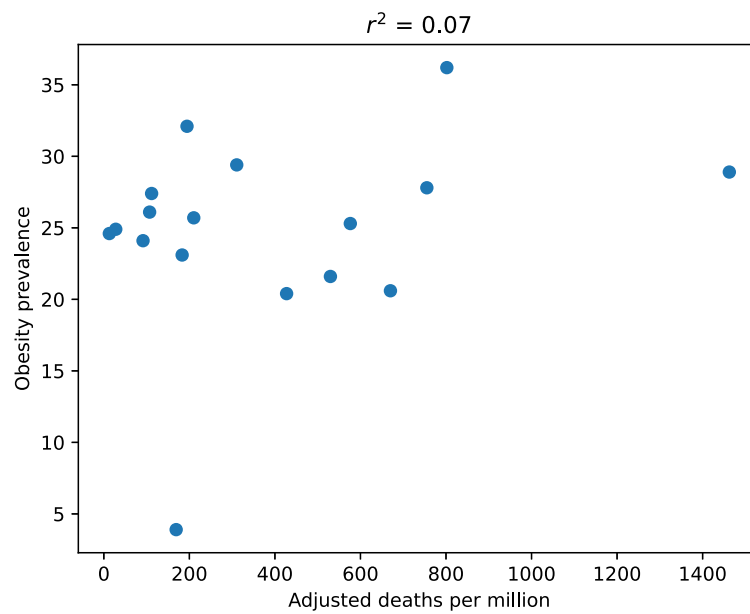
**Table 6.** *Health adjustment factors.*

## Appendix 2. Diabetes



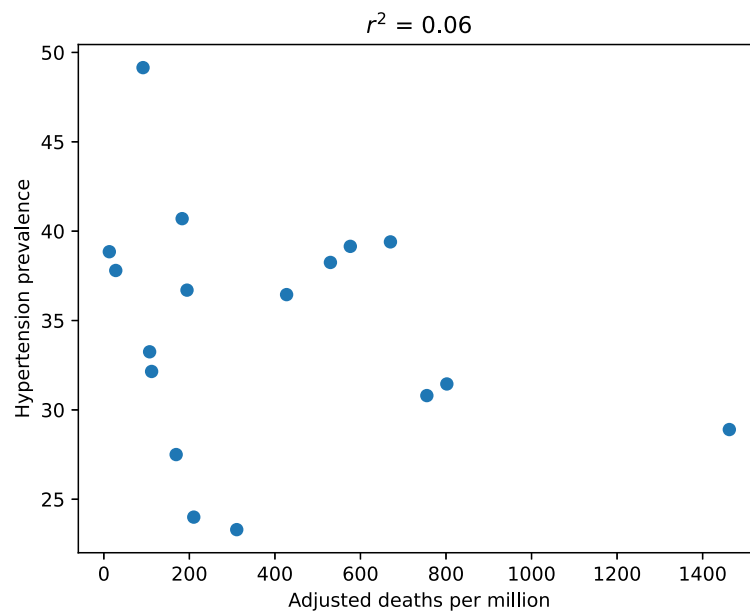
**Figure 7.** Diabetes prevalence [International Diabetes Federation] versus adjusted deaths per million,  $r^2 = 0.05$ .

## Appendix 3. Obesity



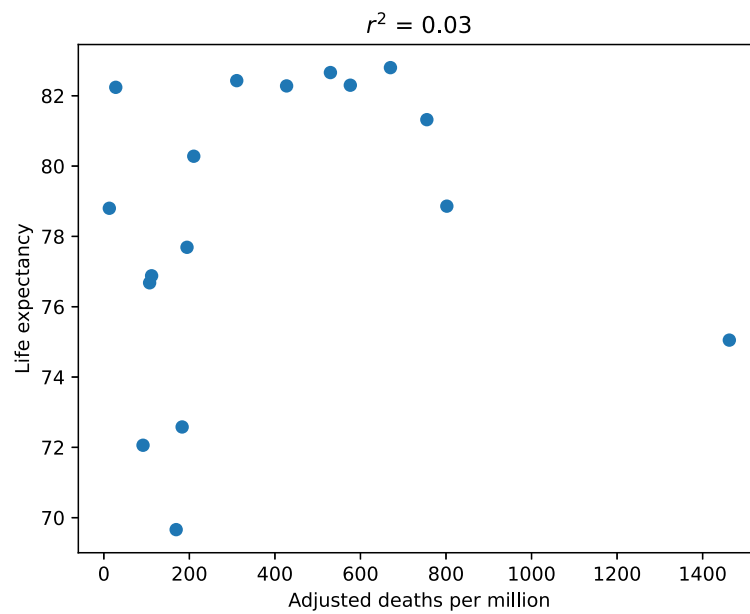
**Figure 8.** Obesity prevalence [CIA] versus adjusted deaths per million,  $r^2 = 0.07$ .

## Appendix 4. Hypertension



**Figure 9.** Hypertension prevalence [Mills] versus adjusted deaths per million,  $r^2 = 0.06$ .

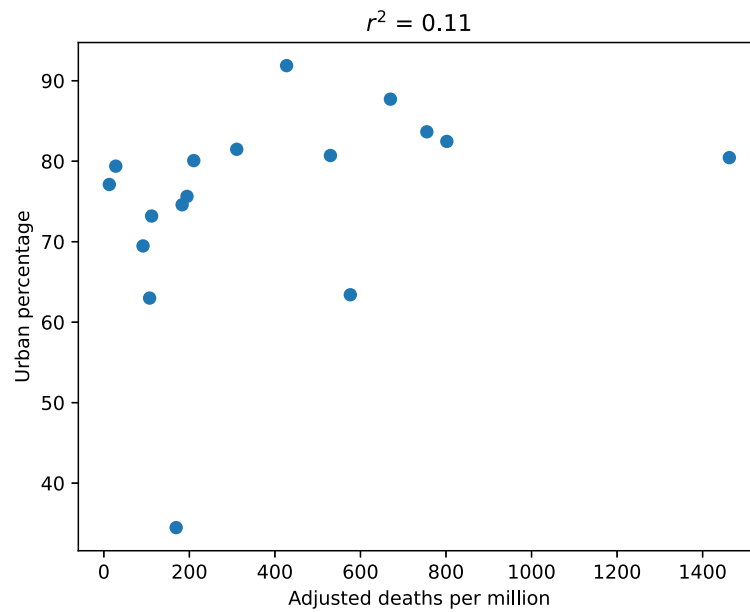
## Appendix 5. Life Expectancy



**Figure 10.** Life expectancy [Our World in Data (B)] versus adjusted deaths per million,  $r^2 = 0.03$ .

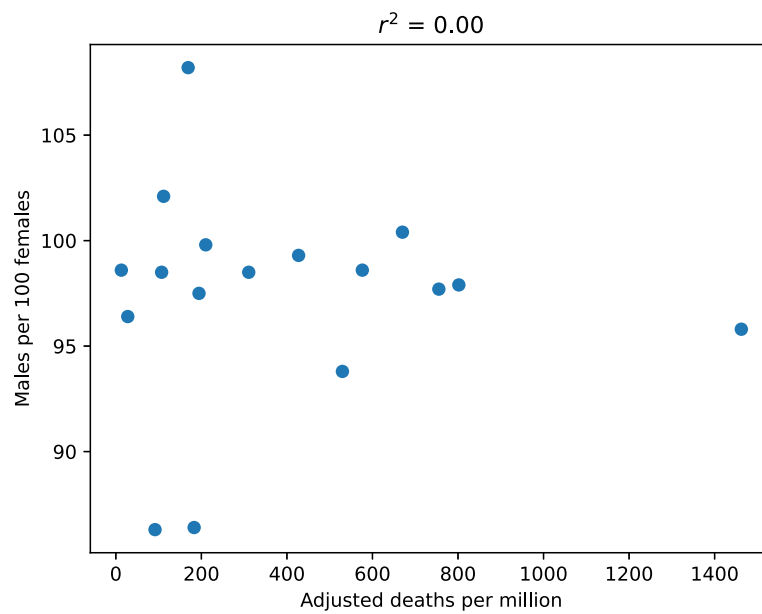


## Appendix 6. Urbanization



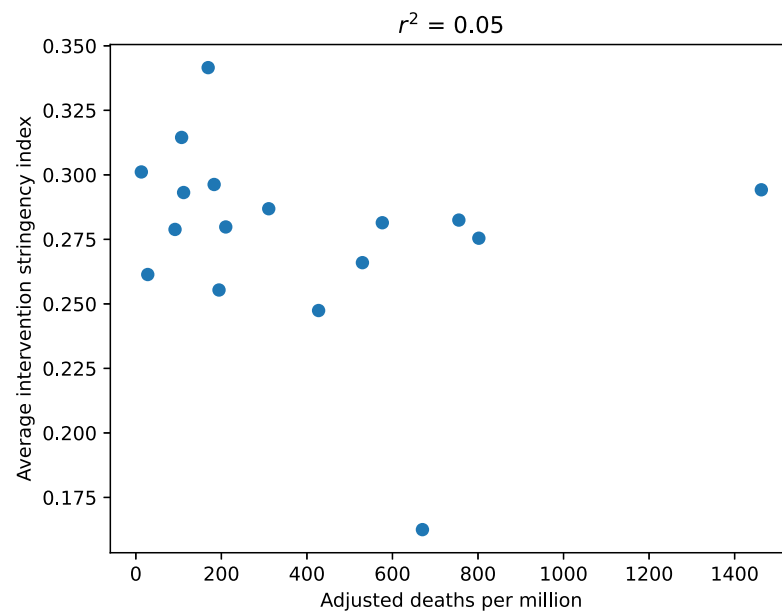
**Figure 11.** Urban percentage [World Bank] versus adjusted deaths per million,  $r^2 = 0.11$ .

## Appendix 7. Gender



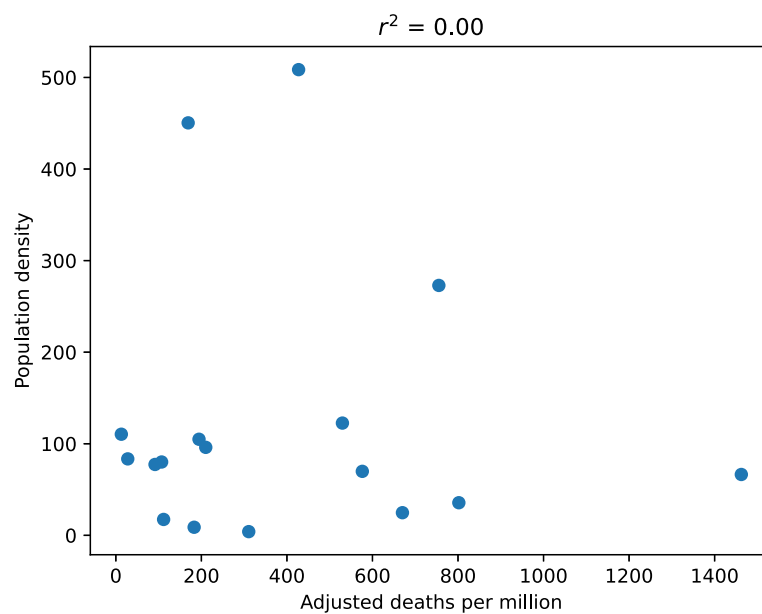
**Figure 12.** Males per 100 females [United Nations (B)] versus adjusted deaths per million,  $r^2 = 0.00$ .

## Appendix 8. Average Intervention Stringency Index



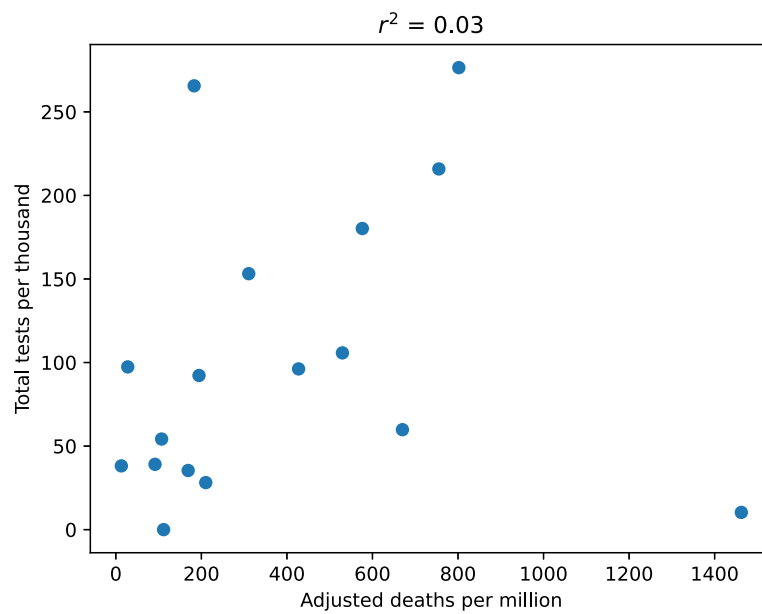
**Figure 13.** Average intervention stringency index [Our World in Data (F), University of Oxford] versus adjusted deaths per million,  $r^2 = 0.05$ .

## Appendix 9. Population Density



**Figure 14.** Population density [Our World in Data (D)] versus adjusted deaths per million,  $r^2 = 0.00$ .

## Appendix 10. Test Volume



**Figure 15.** Tests per thousand [Our World in Data (C)] versus adjusted deaths per million,  $r^2 = 0.03$ .

## Appendix 11. Early Mask Adoption

Country	Days adopted within	Comments
Antigua and Barbuda	28	Masks were required in all public spaces on April 5.
Bangladesh	24	The first death occurred on March 18. From March 11-19, 2020, when students age 17 to 28 were asked if they were wearing a surgical face mask in public, 53.8% responded “yes” and an additional 6.6% responded “occasionally”. A survey from March 29 to April 29 found that 98.7% reported wearing a face mask in crowded places.
Benin	26	Masks were recommended in public on April 6, mandated on April 7, and enforced by police beginning April 8.
Bhutan	10	On Mar. 11, the Ministry of Health advised wearing of masks in “a crowded place”.
Bosnia and Herzegovina	29	Masks were required in public by March 29.
Brunei	18	On March 22, Sultan Hassanal Bolkiah advised the people to wear masks in public.
Cambodia	6	Masks were widely used by the public by January 28.
Chad	24	On April 13, the office of the president announced that a mask or suitable alternative (e.g. turban, veil) would be mandatory in public on April 14. On April 14, the government had to backtrack on enforcement due to lack of supplies. Specific penalties for failing to wear a mask in public were announced on May 7.
Czechia	23	Masks were required in public on March 19.
Côte d'Ivoire	29	On April 4, senior health officials recommended masks when in public.
Dominica	23	Prime Minister Skerrit and Health Minister McIntyre wore masks during an interview on March 30. When Dr. Adis King demonstrated mask-wearing to the legislative assembly on April 7, all in attendance wore masks. S76 President Savarin recommended the wearing of masks in public on April 9. Others, including the state epidemiologist, repeated this recommendation in coming days. On April 21, physician Sam King estimated that 95% of the population was wearing masks in public. Masks were mandated on public transport on April 25.
El Salvador	31	The first death was reported March 31. Masks were mandated in public on April 8.
Grenada	18	On April 3, the Ministry of Health recommended all wear a mask, which could be purchased at a pharmacy, to “prevent asymptomatic people from transmitting the disease unknowingly”. Masks were mandated outside the home on April 6.
Hong Kong	6	Surgical masks were traditionally used, and also were recommended on public transport and in crowded places, on January 24, 2020. Surveys indicated that masks were worn by about 73% in the week of Jan. 21, and by 98% of the public by mid-February, which persisted into May. In February 2020, 94.8% of pedestrians were observed to wear masks, and 94.1% believed mass masking reduces the chance of community outbreak. A poll consistently found that 85% or more wore masks in public between Feb. 25 and Apr. 21, 2020.

Country	Days adopted within	Comments
Indonesia	15	The first death occurred on March 3. The public scrambled to buy face masks in early February. The proportion of Indonesian adults wearing a mask in public was 54% on Feb. 24, 2020, 47% on March 9, 59% on March 23, 71% on March 30, 79% on April 13, 81% on April 20, and from 82%-84% from May 4 to June 9. During March and April, 76% of students indicated that they wore a mask outside the home. Masks were mandated in public on April 5.
Japan	5	Public use of masks is traditional. Surveys indicate that 64% of adults habitually wore a mask in Winter. Public masking was manifest by Jan. 16 when the first domestic case was announced. The government initially recommended masks when in "confined, badly ventilated spaces". One survey documented mask wear prevalence over 60% by March 14, increasing to over 75% by April 12. In another poll, 62% indicated wearing a mask in public by March 17, and 76% by April 13, 2020.
Kenya	30	The March 12 case had arrived from the U.S. on March 5. The first death was on March 26, of a man who arrived in Kenya on March 13. Masks were mandated in Kenya on public transport on April 2, and more broadly in public on April 4. A survey in Nairobi published on May 5, 2020 found that 89% had worn a face mask in the previous week, and 73% said they always did so outside the home.
Laos	0	Health officials in Laos advised mask-wearing by March 6 and the public began wearing masks even before any cases were reported in the country.
Macau	6	Mask use is traditional. By Jan. 23, the government had implemented a mask distribution program for the public.
Malawi	20	The first death was on April 7. The public was required to wear masks on April 4. A survey in Karonga from April 25 to May 23 found that 22% of urban residents and 5% of rural residents wore a mask.
Malaysia	10	Masks were used by the public by January 30. A poll reported 55% wore a mask in public on Feb. 24, 69% on Mar. 23, and 82% on Apr 6.
Mongolia	0	Mongolians began wearing masks in January.
Mozambique	18	Masks were recommended by health authorities on April 4, and were required on public transport or in gatherings on April 8.
Myanmar	28	In Myanmar, the first death occurred on March 31. A study from March 3-20, 2020 found that 72% of adults were confident they would wear a surgical mask whenever visiting a crowded area. <sup>68</sup> On April 5, the Ministry of Health recommended masks in crowded places, and cited the US CDC recommendation for the use of cloth masks by the public. On April 7, State Counsellor Daw Aung San Suu Kyi announced that she would make a mask for herself. By April 16, some regions mandated masks in public. A survey from May 7-23, 2020 conducted by the Ministry of Health found that 80% of the public wore a mask each time they went out.
Philippines	5	Masks were used extensively as early as Jan. 30. In a poll, 60% indicated wearing a mask in public on Feb. 24, and 82% by March 30. Masks were mandated on April 2.
Sierra Leone	6	Masks were recommended in public on April 1. Compliance has been incomplete.
Slovakia	13	Masks were mandated in shops and transit on March 15, and more broadly in public on March 25.

Country	Days adopted within	Comments
South Korea	15	Use of masks is traditional. The alert level was raised from yellow to orange on Jan. 27. Children were advised to wear masks at school by January 30. By Feb. 2, mask sales increased 373 times year-over-year. Stores were selling out of masks by February 3. A superspreader event in mid-February was associated with a religious group which did not use masks at their gatherings. South Korea initially had trouble obtaining enough masks, but at the end of February the government began to control the distribution of masks to the public. On Feb. 22, the government instructed the wearing of masks in the epidemic area.
South Sudan	29	On April 29, the High Level Task Force approved the use of locally-manufactured cloth masks to be worn in public.
St. Kitts and Nevis	14	On April 2, Chief Medical Officer Dr. Hazel Laws recommended wearing a mask in public on the grounds that masks could block droplets, and viral particles could remain suspended for 3 hours. The requirement to wear masks in public became mandatory on April 7. (\$225)
Sudan	27	The first death occurred on March 12. Masks were dispensed by pharmacists for free in Sudan by March 16. A survey from March 25 to April 4 of 2336 adults found that 703 (30.1%) had been to a crowded area, and 1153 (49.4%) had worn a mask outside the home in the previous few days.
São Tomé and Príncipe	21	On April 22, it was announced that masks would be mandatory in public beginning April 24.
Taiwan	11	Use of masks is traditional. By January 24, Taiwan banned the export of surgical masks. By January 27, the government had to limit mask exports and limit sales from pharmacies to those needed for personal use. On January 28, the government began releasing 6 million masks daily, with each resident able to purchase 3 masks weekly at a set price. A poll consistently found over 80% wore a mask from Feb. 25 to Apr 21, 2020.
Thailand	20	Masks, including N95 masks, were already worn outdoors in early January to combat smog. The Thai government was handing out masks and advising wearing of masks in public to prevent coronavirus by January 28, 2020. The recommendation of cloth masks for the public was reaffirmed by the Ministry of Public Health on March 3, 2020. Enforcement of a mask mandate on public transport began on March 26. <sup>102</sup> One survey reported high mask-wearing: 73% by Feb. 24, 80% by March 23, and 89% by March 30. During March 2020, another survey found masks were worn "all the time" by 14% of COVID19 cases and 24% of controls, and "some of the time" by 38% of cases and 15% of controls.
Timor-Leste	7	Masks were required in stores and other venues as part of a state of emergency beginning March 28.
Uzbekistan	19	The first coronavirus death was on March 29. Masks were mandated on March 25.
Venezuela	5	President Maduro demonstrated wearing of masks on live television on March 13 (the day the first case was confirmed), and required masks on public transport. Masks were required in any public space by March 20.
Vietnam	9	Masks were widely used by the public by January 27 and were mandated by the government on March 16. One survey found the prevalence of mask wear consistently from 85-90% from March 12 to April 14. A poll reported 59% wore a mask on March 23, and over 80% from March 30 to Apr. 20. From March 31 to April 6, 2020, 99.5% of respondents reported using a mask when outside.
Zambia	24	The first death was recorded on April 2. On April 4, masks were recommended for the public "at all times" by the Zambian Minister of Health. This spurred the manufacture of cloth masks. On April 16, masks were mandated for the public.

**Table 7.** Countries that adopted masks early, and the number of days from the estimated start of their outbreak, from [Leffler].

## Appendix 12. Country HCQ Status

**Andorra, Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, Bermuda, British Virgin Islands, Brunei, Brunei Darussalam, Cayman Islands, Curacao, Curaçao, Dominica, French Polynesia, Gibraltar, Greenland, Grenada, Guam, Iceland, Isle of Man, Liechtenstein, Malta, Monaco, Montserrat, New Caledonia, Northern Mariana Islands, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, San Marino, Sao Tome and Principe, Seychelles, Sint Maarten (Dutch part), Turks and Caicos Islands, United States Virgin Islands**

These countries were excluded because their population is <1M.

**Afghanistan, Angola, Bahrain, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Congo, Cote d'Ivoire, Côte d'Ivoire, Democratic Republic of Congo, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Iraq, Kenya, Kuwait, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, Oman, Palestine, Papua New Guinea, Qatar, Republic of Congo, Rwanda, Sao Tome and Principe, Saudi Arabia, Senegal, Sierra Leone, Somalia, South Sudan, State of Palestine, Sudan, Tajikistan, Tanzania, Togo, Uganda, United Arab Emirates, United Republic of Tanzania, Western Sahara, Yemen, Zambia, Zimbabwe**

These countries were excluded because <0.5% of the population is >80.

**Mongolia, Laos, Japan, Philippines, Macau, Hong Kong, Sierra Leone, Cambodia, Timor-Leste, Vietnam, Malaysia, Bhutan, Venezuela, Taiwan, Slovakia, St. Kitts and Nevis, South Korea, Indonesia, Brunei, Grenada, Mozambique, Uzbekistan, Thailand, Malawi, São Tomé and Príncipe, Czechia, Dominica, Bangladesh, Zambia, Chad, Benin, Sudan, El Salvador, Antigua and Barbuda, Myanmar, Bosnia and Herzegovina, Côte d'Ivoire, South Sudan, Kenya**

These countries were excluded because they quickly adopted widespread mask use.

## **Australia, New Zealand, North Korea, Turkmenistan, Solomon Islands, Vanuata, Samoa, Kiribati, Federated States of Micronesia, Tonga, Marshall Islands, Palua, Tuvalu, Nauru**

These countries were excluded because they have no or very little spread to date. They may be included in the future if they experience significant spread.

## **Algeria - widespread early treatment for high-risk patients for most of the outbreak**

Adopted HCQ in early April and continued to use after WHO warning.

*The Africa Report*, <https://www.theafricareport.com/2020/04/15/coronavirus-didier-raoult-the-african-and-chloroquine-from-dakar-to-brazzaville/>, Coronavirus: Didier Raoult the African and chloroquine, from Dakar to Brazzaville, 4/15.

*Afrik.com*, <https://www.afrik.com/edouard-ychloroquine-et-le-remdesivir>, Edouard Philippe emporté par le Covid, Didier Raoult, l'hydroxychloroquine et le... remdésivir, *Follows the Raoult protocol*, 7/6.

*Gummi Bear*, <https://twitter.com/gummibear737/status/1256676533638479872>, Adopted early April, 5/2.

*Barron's*, <https://www.barrons.com/news/dividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *continue to promote*, 6/1.

*Covid19Crusher*, <https://twitter.com/Covid19Crusher/status/1258469706442444804>, Algeria's Health Minister praises HCQ used since the end of March, 5/7.

*Franceinfo*, [https://www.francetvinfo.fr/magazine/le-magazine/les-pays-africains-qui-ont-decide-de-continuer-a-soigner-le-covid-19-avec-lhydroxychloroquine\\_3983239.html](https://www.francetvinfo.fr/magazine/le-magazine/les-pays-africains-qui-ont-decide-de-continuer-a-soigner-le-covid-19-avec-lhydroxychloroquine_3983239.html), Ces pays africains qui ont décidé de continuer à soigner le Covid-19 avec l'hydroxychloroquine, *continue to use after WHO warning, positive results*, 5/28.

## **Bahrain - widespread early treatment (excluded due to young population)**

*Hydroxychloroquine News*, <https://twitter.com/niro60487270/status/1260588201179144193>, Adopted as standard treatment very early, 5/13.

*Al Arabia*, <https://english.alarabiya.net/en/News/middle-east/2020/05/26/hydroxychloroquine-to-treat-coronavirus-bahrain-among-first-countries-to-use-hydroxychloroquine-to-treat-coronavirus-Used-since-the-first-case-3/26>, Bahrain among first countries to use Hydroxychloroquine to treat coronavirus, *Used since the first case*, 3/26.

*GulfInsider*, <https://www.gulf-insider.com/2020/05/25/coronavirus-bahrain-therapeutic-medication-proved-effective/>, Coronavirus: Bahrain's Therapeutic Medication Proved Effective, *Effectiveness of HCQ confirmed*, 5/25.

*Barron's*, <https://www.barrons.com/news/dividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *use not suspended post WHO/Lancet*, 6/1.

*Marie94167358*, <https://twitter.com/Marie94167358/status/1260661671816835082>, Fully on HCQ, 5/13.



*Hydroxychloroquine News*, <https://twitter.com/niro60487270/status/1256675338853072896>, Used early, 5/2.

## **Belarus - mixed use of early treatment with HCQ**

There was early HCQ use but it was suspended outside of hospitals on WHO recommendation 6/2.

*Jared Young*, <https://twitter.com/jtyoung18/status/1258279092010586113>, In inpatient and outpatient protocols, 5/6.

*BelTA*, <https://eng.belta.by/society/..vid-19-treatment-130102-2020/>, Belarus to receive potential effective drug for COVID-19 treatment, 4/29.

*BelTA*, <https://eng.belta.by/society/..ide-of-hospitals-130777-2020/>, Belarus suspends use of chloroquine for COVID-19 outside of hospitals, 6/2.

## **Brazil - early HCQ treatment was adopted relatively late**

Late and very mixed use, increasing over time.

*Filipe Rafaeli*, <https://medium.com/@filiperaf..nt-human-history-2685487ad717>, Hydroxychloroquine: the narrative that it doesn't work is the biggest hoax in recent human history, *almost unanimity of Brazilian scientists are against the application of these drugs and repeat that "there is no scientific evidence" of the functioning*, 7/23.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1273878906785972224>, Clinical outcomes improve after adoption of HCQ starts, 6/19.

*CNN*, <https://www.cnnbrasil.com.br/..-para-casos-leves-de-covid-19>, Government changes protocol and authorizes hydroxychloroquine for mild cases of Covid-19, 5/20.

*Último Segundo*, <https://ultimosegundo.ig.com...tao-zerados-diz-pazuello.html>, Estoques de hidroxiclороquina no país estão zerados, diz Pazuello, *government has run out of HCQ. Distribution data indicates only a small portion of cases receive HCQ*, 8/13.

*The Verge*, <https://www.theverge.com/2020..navirus-jair-bolsonaro-maduro>, Twitter removes tweets by Brazil, Venezuela presidents for violating COVID-19 content rules, 3/30.

*Agência Brasil*, <https://agenciabrasil.ebc.com..dicoes-para-uso-da-cloroquina>, CFM estabelece critérios e condições para uso da cloroquina, *there is no "solid evidence" to confirm the effect of CQ and HCQ*, 4/23.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1279445536685383680>, One by one municipalities are adopting HCQ, 7/4.

*Diário de Uberlândia*, <https://diariodeuberlandia.co..tada-a-pacientes-com-covid-19>, Farmacêuticos não podem negar venda de cloroquina receitada a pacientes com Covid-19, *high degree of controversy in Brazil*, 7/3.

## **Burkina Faso - widespread early treatment (excluded due to young population)**

*Franceinfo*, [https://www.francetvinfo.fr/m..droxychloroquine\\_3983239.html](https://www.francetvinfo.fr/m..droxychloroquine_3983239.html), Ces pays africains qui ont décidé de continuer à soigner le Covid-19 avec l'hydroxychloroquine, *continue to use after WHO warning, positive results*, 5/28.

*LifeSiteNews*, <https://www.lifesitenews.com/..loss-of-life-from-covid-virus>, Doctors insist this cheap, safe drug is "key to preventing huge loss of life" from Wuhan virus, *widely used*, 6/5.

*The Africa Report*, <https://www.theafricareport.c..ne-from-dakar-to-brazzaville/>, Coronavirus: Didier Raoult the African and chloroquine, from Dakar to Brazzaville, 4/15.

## **Cameroon - widespread early treatment (excluded due to young population)**

*Covid19Crusher*, <https://twitter.com/Covid19Cr..atus/1257626384782053377?s=20>, , 5/5.

*France 24*, <https://www.france24.com/fr/2..%A9e-en-protocole-d-%C3%A9tat>, Covid-19 : au Cameroun, la méthode Raoult érigée en protocole d'État, *adopted the Raoult protocol*, 5/2.

## **Canada - limited early treatment with HCQ**

Physicians not allowed to use. New Brunswick used briefly until stopped by Health Canada.

*Maclean's*, <https://www.macleans.ca/socie..e-rise-of-hydroxychloroquine/>, The incalculable rise of hydroxychloroquine, *Health Canada has not permitted physicians to administer HCQ for COVID*, 5/21.

*CBC*, <https://www.cbc.ca/news/health..experimental-drugs-1.5511244>, Doctors face sanctions for prescribing unproven COVID-19 drugs to friends and family, regulators warn, *except when there is a clinical trial, the statement instructs both doctors and pharmacists not to provide the drugs as a treatment for COVID-19*, 3/27.

*Acadie Nouvelle*, <https://www.acadienouvelle.co..e-la-covid-19-deploye-au-n-b/>, EXCLUSIF: un traitement expérimental contre la COVID-19 déployé au N.-B., *New Brunswick adopts HCQ*, 4/2.

*Acadie Nouvelle*, <https://www.acadienouvelle.co..experimental-de-la-covid-19/>, Le Nouveau-Brunswick fait marche arrière sur le traitement expérimental de la COVID-19, *Health Canada ended New Brunswick's use of HCQ on 4/17*, 5/10.

*CBC*, <https://www.cbc.ca/news/canad..ur-gill-tweets-cps-1.5680122>, Ontario doctor subject of complaints after COVID-19 tweets, *HCQ has been shown to be ineffective. Medical bodies such as the Canadian Pediatric Society say HCQ has no significant benefit in fighting COVID-19. Health Canada has not authorized HCQ to treat or cure COVID-19. It says HCQ can have serious side effects*, 8/10.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1256869896014704640>, New Brunswick broke ranks with Canada adopting HCQ, 5/3.

*ChloroquineGorilla*, <https://twitter.com/Prolongin..id/status/1277927519203635205>, Quebec has some of the harshest anti-HCQ rules in the world, 6/30.

## **Chad - widespread early treatment (excluded due to young population)**

*Barron's*, <https://www.barrons.com/news/...ividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *continue to promote*, 6/1.

*Franceinfo*, [https://www.francetvinfo.fr/m...droxychloroquine\\_3983239.html](https://www.francetvinfo.fr/m...droxychloroquine_3983239.html), Ces pays africains qui ont décidé de continuer à soigner le Covid-19 avec l'hydroxychloroquine, *continue to use after WHO warning, positive results*, 5/28.

## **Chile - mixed use of early treatment with HCQ**

Stopped use after WHO/Lancet reports around May 26.

*Cristian Navarro Merino*, <https://twitter.com/cnnavarro1/status/1272207814749020160>, Stopping because of WHO/Lancet, 6/14.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1265400801507315712>, Chile stops HCQ, 5/26.

*Barron's*, <https://www.barrons.com/news/...ividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *banned*, 6/1.

*Veronica Riveros*, <https://twitter.com/veronicar...oc/status/1270558291714867200>, People fear HCQ, 6/9.

## **Costa Rica - widespread early treatment for high-risk patients for most of the outbreak**

Used early based on recommendation from China 3/18.

*The Tico Times*, <https://ticotimes.net/2020/06...nue-partnership-with-coursera>, News briefs: Reopening plans on-track, hydroxychloroquine use to continue, partnership with Coursera, *HCQ use continuing after FDA revoked EUA*, 6/15.

*Q Costa Rica*, <https://qcostarica.com/hydrox...ccessfully-to-fight-covid-19/>, Hydroxychloroquine: The Drug Costa Rica Uses Successfully To Fight Covid-19, 4/19.

*Hydroxychloroquine News*, <https://twitter.com/niro60487270/status/1256675338853072896>, Used early, 5/2.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1264837406802444288>, First and only Central American country to immediately adopt, 5/25.

*Rich Drake*, <https://twitter.com/drakerich/status/1284219391140343809>, Available OTC, 7/17.

*J David*, <https://twitter.com/badlandj/status/1267509994368503814>, Costa Rica refuses WHO recommendation to stop using HCQ, 6/1.

## **Cuba - widespread early treatment for high-risk patients for most of the outbreak**

Using to treat at an early stage.

*Pleno.News*, <https://pleno.news/saude/coro..id-com-hidroxicloroquina.html>, Cuba stands out in combating Covid with hydroxychloroquine, *using low doses of HCQ to treat Covid-19 at an early stage*, 7/12.

*Anadolu Agency*, <https://www.aa.com.tr/en/amer..tent-against-covid-19/1905650>, Cuba: Early hydroxychloroquine potent against COVID-19, *"We are aware of the polemics around this product. Physicians here mostly have a good opinion of the results it has achieved, provided that it is used at an early stage in low doses and only with patients without comorbidities, which could be complicated by hydroxychloroquine"*, 7/10.

## **Czech Republic - widespread early treatment (excluded due to early isolation)**

Supported use since early March.

*Expats.cz*, <https://news.expats.cz/weekly..hospitals-to-treat-covid-19/>, Czech Health Ministry permits temporary use of hydroxychloroquine to treat COVID-19, *temporary permit for 8 months*, 4/7.

*Rozhodnutí Ministerstva zdravotnictví*, <https://www.mzcr.cz/rozhodnut..ychloroquine-sulfate-tablets/>, Rozhodnutí o dočasném povolení neregistrovaného humánního léčivého přípravku HYDROXYCHLOROQUINE SULFATE TABLETS, *authorization of HCQ*, 4/30.

*Hydroxychloroquine News*, <https://twitter.com/niro60487270/status/1257696987576557568>, Support for HCQ in early March, 5/4.

## **Djibouti - widespread early treatment (excluded due to small population)**

*VOA*, [https://www.voanews.com/covid..ce=dlvr.it&utm\\_medium=twitter](https://www.voanews.com/covid..ce=dlvr.it&utm_medium=twitter), Djibouti is Treating All COVID Patients with Chloroquine, But Scientists Urge Caution, 5/21.

## **France - limited early treatment with HCQ**

Banned post WHO/Lancet. Used late stage in hospitals. Limited early treatment, some exceptions, especially in Marseille. Media very negative.

*Reuters*, <https://www.reuters.com/artic..fety-fears-grow-idUSKBN2340A6>, EU governments ban malaria drug for COVID-19, trial paused as safety fears grow, *banned May 27, previously generally only in hospitals*, 5/27.

*Afrik.com*, <https://www.afrik.com/edouard..ychloroquine-et-le-remdesivir>, Edouard Philippe emporté par le Covid, Didier Raoult, l'hydroxychloroquine et le... remdésivir, *HCQ prohibited outside hospitals*, 7/6.

*CBS News*, <https://www.cbsnews.com/news/..NM-00-10aab7e&linkId=89534081>, France bans use of hydroxychloroquine, drug touted by Trump, in coronavirus patients, 5/27.

*Ian56*, <https://twitter.com/Ian56789/status/1272844272769867777>, Not used early, 6/16.

## **Germany - mixed use of early treatment with HCQ**

We found several reports of early treatment early in the outbreak, confirmed by Sermo, later reports of trials paused post WHO/Lancet, current status of early treatment is unclear.

*Andreas Backhaus*, <https://twitter.com/AndreasSh..ed/status/1295790850790895621>, Off-label prescriptions were banned between early April and early July, 8/18.

*Col Pavan Nair*, <https://twitter.com/pavannair/status/1289884254365655043>, Used early in the outbreak, 8/2.

*DAZ.online*, <https://www.deutsche-apotheke..dnungen-von-hydroxychloroquin>, BfArM: Keine ambulanten Off-Label-Verordnungen von Hydroxychloroquin, 6/4.

*pressenza*, <https://www.pressenza.com/fr/..voie-du-movimento-ippocrate/>, Vaincre la peur : la voie du "Movimento Ippocrate", "in Germany, the extensive use of HCQ, AZ, and a large amount of hyperimmune plasma has kept the death rate below 3%. But in great silence, as the Germans know how to do", 7/10.

*Andreas Backhaus*, <https://twitter.com/AndreasSh..ed/status/1295752761095618569>, Federal institute for disease control and prevention advises against the use of HCQ, 8/18.

*Munchensenton*, <https://twitter.com/Munchensenton/status/1286659832741867520>, Started using early, 7/24.

*Christopher Kidwell*, <https://twitter.com/Lerianis1/status/1288039709218922496>, Early treatment used, 7/28.

*Reuters*, <https://www.reuters.com/artic..ovid-19-spiegel-idUSKBN2343AL>, Germany pauses anti-malaria drug study for COVID-19: Spiegel, two week pause in trial, 5/28.

## **Ghana - widespread early treatment (excluded due to young population)**

*TheGuardian*, <https://guardian.ng/news/nige..id-19-prevention-says-nafdac/>, Chloroquine potent for COVID-19 prevention, says NAFDAC, 8/26.

## **Greece - widespread early treatment for high-risk patients for most of the outbreak**

Approved for use April 15, they disregarded WHO's recommendation to stop.

*Medical Xpress*, <https://medicalxpress.com/new..versy-greece-chloroquine.html>, Amid global controversy, Greece moves forward with chloroquine, *greek epidemiologists consider chloroquine effective, especially in the early stages of COVID-19*, 6/10.

*Barron's*, <https://www.barrons.com/news/..-with-chloroquine-01591781707>, Amid Global Controversy, Greece Moves Forward With Chloroquine, *the ongoing debate over the drugs has had little impact in Greece, where epidemiologists consider chloroquine effective, especially in the early stages of COVID-19*, 6/10.

*Afrik.com*, <https://www.afrik.com/edouard..ychloroquine-et-le-remdesivir>, Edouard Philippe emporté par le Covid, Didier Raoult, l'hydroxychloroquine et le... remdésivir, *Follows the Raoult protocol*, 7/6.

## **Guinea - widespread early treatment (excluded due to young population)**

*Mosaïque Guinée*, <https://mosaïqueguinée.com/tr..vec-lhydroxychloroquine-anss/>, Traitement des malades de covid19 en Guinée: « nous continuons avec l'hydroxychloroquine » (ANSS), *ignoring WHO recommendation*, 5/25.

## **India - widespread early treatment for high-risk patients for most of the outbreak**

Widespread early use. Prophylaxis for healthcare workers and household contacts of confirmed cases.

*Rathi et al. Lancet Infect. Dis. doi:10.1016/S1473-3099(20)30313-3*, [https://www.thelancet.com/jou..1473-3099\(20\)30313-3/fulltext](https://www.thelancet.com/jou..1473-3099(20)30313-3/fulltext), Hydroxychloroquine prophylaxis for COVID-19 contacts in India, *ICMR recommends chemoprophylaxis with HCQ for asymptomatic health-care workers and asymptomatic household contacts of confirmed cases*, 4/17.

*Atikh Rashid*, [https://indianexpress.com/art..te/?\\_\\_twitter\\_impression=true](https://indianexpress.com/art..te/?__twitter_impression=true), Maharashtra expands use of hydroxychloroquine as preventive measure, 4/23.

*Ministry of Health and Family Welfare*, <https://twitter.com/Billtheicon/status/1262508966321496066>, Advised all front line health care workers to take HCQ prophylactically, 3/28.

*Oneindia*, <https://www.oneindia.com/indi..-health-ministry-3111048.html>, No COVID-19 death in Manipur, Mizoram, Nagaland, Sikkim so far: Govt, *HCQ widely distributed*, 6/26.

*Dina Goldin*, <https://www.facebook.com/grou..e/permalink/2367454293560817/>, Summary of HCQ usage in India from an MD in India, *everyone diagnosed with COVID-19 gets HCQ, it is the standard of care country-wide. The only problem is some patients come very late, deaths are from those who wait too long before seeking medical help. Everyone at high risk, including policemen, firemen, healthcare workers, and nursing home patients, take HCQ, all contacts of positive cases also get HCQ prophylaxis. HCQ is OTC in India, so everyone else is also welcome to use it*, 8/21.

AFP, <https://www.msn.com/en-ph/new..eventon/ar-BB14EloP?ocid=st2>, India backs hydroxychloroquine for virus prevention, 5/27.

AAPS, <https://aapsonline.org/hcq-90-percent-chance/>, Hydroxychloroquine Has about 90 Percent Chance of Helping COVID-19 Patients, *many nations, including Turkey and India, are protecting medical workers and contacts of infected persons prophylactically*, 4/28.

*The Indian Express*, <https://indianexpress.com/art..s-as-analysis-begins-6486049/>, Vadodara administration drive: HCQ helping in containing Covid-19 cases, say docs as analysis begins, *used prophylactically in Vadora with positive results*, 7/2.

*Barron's*, <https://www.barrons.com/news/..ividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *used as preventative measure*, 6/1.

*Government of India*, <https://www.mohfw.gov.in/pdf/..edHomelsolationGuidelines.pdf>, The caregiver and all close contacts of such cases should take HCQ prophylaxis, 7/2.

*The Australian*, <https://www.theaustralian.com..56d1371697fe69e4fcc39d7f1f97c>, India and Indonesia stand by antimalarials, 5/29.

## **Indonesia - widespread early treatment (excluded due to early isolation)**

Used early. Disregarded WHO request to stop using HCQ.

*Reuters*, <https://www.reuters.com/artic..o-stop-using-it-idUSKBN23227L>, Exclusive: Indonesia, major advocate of hydroxychloroquine, told by WHO to stop using it, *Indonesia told doctors to use HCQ to treat all COVID-19 patients with symptoms from mild to severe*, 5/26.

*The Australian*, <https://www.theaustralian.com..56d1371697fe69e4fcc39d7f1f97c>, India and Indonesia stand by antimalarials, 5/29.

*Sag Leyos*, <https://twitter.com/sagleyos/status/1274856392902533120>, Used early, 6/21.

*Sag Leyos*, <https://twitter.com/sagleyos/status/1274992969549037569>, Treatment given early, do not need to wait for test results, 6/22.

*Sag Leyos*, <https://twitter.com/sagleyos/status/1274505486180782080>, Used early, 6/20.

## **Ireland - limited early treatment with HCQ**

No early treatment.

*Robert Nugent*, <https://twitter.com/RobertANu..t1/status/1268877953825419264>, Nobody treated early with HCQ in Italy, 6/5.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1255194379255504897>, Ireland waits for clinical trials, 4/28.

## Israel - mixed use of early treatment with HCQ

We initially believed that Israel had widespread early use for the majority of the outbreak, but we received reports that Israel's use for early treatment has not be as widespread as believed.

*The Times of Israel*, <https://www.timesofisrael.com..fit-in-virus-treatment-study/>, Malaria drug stockpiled by Israel shows no benefit in virus treatment — study, *no official guidance but doctors can prescribe*, 4/22.

*Anatoly Lubarsky*, <https://twitter.com/anatoly/status/1295791524131766273>, Prescriptions of HCQ off-label was banned in late March, 8/18.

*Judy Breton*, <https://twitter.com/JudyBreton/status/1293768018087104513>, Israeli Ministry of Health has forbidden doctors from writing scripts for HCQ for COVID-19, 8/12.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1256949969036214275>, Received 2 million doses from Teva mid April, 5/3.

*Haaretz*, <https://www.haaretz.com/israel..o-treat-coronavirus-1.8712940>, Israel Preparing to Use Unapproved Medication to Treat Coronavirus, *preparing to use HCQ*, 3/26.

*Association of American Physicians and Surgeons*, <https://www.prnewswire.com/ne..-surgeons-aaps-301098030.html>, More Evidence Presented for Why Hydroxychloroquine Should be Made Available, in a New Court Filing by the Association of American Physicians & Surgeons (AAPS), *greater access to HCQ*, 7/22.

*Xinhua*, [http://www.xinhuanet.com/english/2020-04/09/c\\_138961933.htm](http://www.xinhuanet.com/english/2020-04/09/c_138961933.htm), Israel brings anti-malarial drug from India to fight COVID-19, 4/9.

*Luke Mor*, <https://twitter.com/LukeMor19..10/status/1271442135720615938>, Used early, 6/12.

## Italy - early HCQ treatment was adopted relatively late

Banned post WHO/Lancet. Some early treatment started late in Italy's outbreak.

*Reuters*, <https://www.reuters.com/artic..fety-fears-grow-idUSKBN2340A6>, EU governments ban malaria drug for COVID-19, trial paused as safety fears grow, *banned May 27*, 5/27.

*Talking Points Memo*, <https://talkingpointsmemo.com..the-use-of-hydroxychloroquine>, Italian Pharmacological Agency Warns Against The Use Of Hydroxychloroquine, 5/22.

*Trustnodes*, <https://www.trustnodes.com/20..tment-with-hydroxychloroquine>, Italy Finally Starts Mass Treatment with Hydroxychloroquine, *early treatment starts in some areas*, 3/29.

*Barron's*, <https://www.barrons.com/news/..ividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *banned except clinical trials*, 6/1.

*CBC*, <https://www.cbc.ca/news/world..9-over-safety-fears-1.5586220>, France, Italy, Belgium act to stop use of hydroxychloroquine for COVID-19 over safety fears, 5/27.



## Malaysia - mixed use of early treatment with HCQ

Used early since January until about 6/22.

*Reuters*, <https://www.reuters.com/article/fight-covid-19-idUSKCN21X0YQ>, Exclusive: India agrees to sell hydroxychloroquine to Malaysia to help fight COVID-19, *Malaysia has been using hydroxychloroquine for mild to severe COVID-19 cases along with other drugs, according to its treatment protocol seen by Reuters*, 4/15.

*CNA*, <https://www.channelnewsasia.com/till-using-treatment-12771770>, Malaysia still using hydroxychloroquine to treat COVID-19 patients; health ministry monitoring side effects, *did not halt based on WHO recommendation*, 5/26.

*CodeBlue*, <https://codeblue.galencentre.com/e-can-slow-covid-19-progress/>, Malaysia Finds Hydroxychloroquine Can Slow Covid-19 Progress, 6/9.

*Malay Mail*, <https://www.malaymail.com/news/st-wave-says-health-d/1851457>, 'Chloroquine' used to treat Covid-19 patients since first wave, says Health D-G, 3/29.

*CodeBlue*, <https://codeblue.galencentre.com/ine-from-covid-19-treatment/>, Malaysia Drops Hydroxychloroquine From Covid-19 Treatment, *stopped using based on study with stage 2/3 patients, not clear if stopped for early use*, 6/22.

*New Straits Times*, <https://www.nst.com.my/news/n-e-hydroxychloroquine-covid-19>, Dr Noor Hisham: Malaysia drops use of hydroxychloroquine for Covid-19, 6/22.

*Hydroxychloroquine News*, <https://twitter.com/niro60487270/status/1261701176665337857>, Used since the start, 5/16.

## Mexico - limited early treatment with HCQ

Not authorized outside of clinical trials. Doctors outside hospitals not allowed to prescribe. Some limited exceptions.

*Mark F. McCarty*, <https://twitter.com/markfmccarty/status/1270421880697044993>, Doctors outside hospitals not allowed to prescribe, 6/9.

*El subsecretario de Prevención y Promoción*, <https://jalisco.quadratin.com/ara-uso-de-hidroxiclороquina/>, Not authorized for COVID-19 outside of clinical trials, 5/27.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1281912523470643200>, Mexico is anti-HCQ, 7/11.

*Government of Mexico*, <https://www.gob.mx/cofepris/a-la-poblacion-251030?idiom=es>, Actualmente no existe un medicamento eficaz y seguro para la cura del paciente con Covid-19 y tampoco una vacuna para prevenirlo., *still claiming no drug is effective*, 8/25.

*The World*, <https://www.pri.org/file/2020-over-unfounded-covid-19-link>, Mexico runs out of malaria drugs over unfounded COVID-19 link, 5/27.

## **Morocco - widespread early treatment for high-risk patients for most of the outbreak**

All patients treated on first symptoms.

*Le Nouvel Afrik*, <https://www.afrik.com/covid-1..nt-plus-en-europe-qu-au-maroc>, Covid-19 : pourquoi les Marocains décèdent plus en Europe qu'au Maroc, *All COVID patients treated with HCQ as soon as the first symptoms appear. Moroccans more likely to die in Europe than Morocco*, 5/5.

*The Africa Report*, <https://www.theafricareport.c..ne-from-dakar-to-brazzaville/>, Coronavirus: Didier Raoult the African and chloroquine, from Dakar to Brazzaville, 4/15.

*Afrik.com*, <https://www.afrik.com/edouard..ychloroquine-et-le-remdesivir>, Edouard Philippe emporté par le Covid, Didier Raoult, l'hydroxychloroquine et le... remdésivir, *Follows the Raoult protocol*, 7/6.

*Morocco World News*, <https://www.moroccoworldnews...ss-reveals-european-failures/>, Moroccan Scientist: Morocco's Chloroquine Success Reveals European Failures, *Zemmouri believes approximately 78% of Europe's coronavirus-related deaths "could have been avoided" if European countries had applied the "same chloroquine strategy as Morocco."*, 6/22.

*Challenge*, <https://www.challenge.ma/coro..que-le-maroc-a-reussi-144484/>, Coronavirus : ce que le Maroc a réussi, *Ignored WHO recommendation*, 6/13.

*Barron's*, <https://www.barrons.com/news/..ividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *continue to promote*, 6/1.

*Franceinfo*, [https://www.francetvinfo.fr/m..droxychloroquine\\_3983239.html](https://www.francetvinfo.fr/m..droxychloroquine_3983239.html), Ces pays africains qui ont décidé de continuer à soigner le Covid-19 avec l'hydroxychloroquine, *continue to use after WHO warning, positive results*, 5/28.

*Marie94167358*, <https://twitter.com/Marie94167358/status/1260661671816835082>, Fully on HCQ since February, 5/13.

## **Netherlands - limited early treatment with HCQ**

Doctors will be fined if prescribing HCQ for COVID-19. Used for hospitalized patients.

*De Limburger*, <https://www.limburger.nl/cnt/..e-behandelng-coronapatienten>, Inspectie: Meijelse huisarts moet stoppen met experimentele behandeling coronapatiënten, *doctors will be fined if prescribing HCQ for COVID*, 4/8.

*AD - Nieuws*, <https://www.ad.nl/binnenland/..-aan-coronapatient~a0ddaabbd/>, Ziekenhuizen gaven massaal omstreden malariamedicijn aan coronapatient, *used for hospitalized patients*, 5/20.

## **Nigeria - widespread early treatment (excluded due to young population)**

Reportedly everyone diagnosed is treated. Available OTC.

Nosa Imagbenikaro, <https://twitter.com/nosamagbe/status/1261706460750364672>, Everyone diagnosed is treated with HCQ, 5/16.

Vanguard, <https://www.vanguardngr.com/2020/05/chloroquine-effective-as-prophylaxis/>, COVID-19: Nigerian study finds Chloroquine, Hydroxychloroquine effective as Prophylaxis, 6/23.

Robin J., <https://twitter.com/RobinJHel..dt/status/1281080419241332738>, Available OTC, 7/8.

Medical World Nigeria, <https://medicalworldnigeria.com/2020/05/27/nafdac-says-chloroquine-potential-for-covid-19-prevention/>, Chloroquine potent for COVID-19 prevention, says NAFDAC, *The National Agency for Food and Drug Administration and Control (NAFDAC), yesterday, declared that chloroquine prevents the dreaded coronavirus. Its Director General, Prof. Christianah Mojisola Adeyeye, during an online interactive session with journalists said: "We realise that chloroquine can be used in the early stage of the COVID-19 infection as prophylactic treatment. Science does not lie."*, 8/27.

Pilot News, <https://www.westafricanpilotnews.com/2020/05/26/chloroquine-cqb-treat-coronavirus-at-early-stage-nafdac-dg/>, Chloroquine cqb Treat Coronavirus at Early Stage – NAFDAC DG, *the Director-General of the National Agency for Food and Drug Administration and Control (NAFDAC), Mojisola Adeyeye has said chloroquine is effective for the treatment of COVID-19 at the early stage of infection*, 8/26.

Franceinfo, [https://www.francetvinfo.fr/monde/afrique/ces-pays-africains-qui-ont-decide-de-continuer-a-soigner-le-covid-19-avec-lhydroxychloroquine\\_3983239.html](https://www.francetvinfo.fr/monde/afrique/ces-pays-africains-qui-ont-decide-de-continuer-a-soigner-le-covid-19-avec-lhydroxychloroquine_3983239.html), Ces pays africains qui ont décidé de continuer à soigner le Covid-19 avec l'hydroxychloroquine, *continue to use after WHO warning, positive results*, 5/28.

TheGuardian, <https://guardian.ng/news/nigeria-chloroquine-potent-for-covid-19-prevention-says-nafdac/>, Chloroquine potent for COVID-19 prevention, says NAFDAC, 8/26.

Nigeria News World, <https://nigeriannewsworld.com/2020/05/17/jigawa-govt-reveals-secret-behind-mass-recovery-of-patients-secret-behind-recoveries-is-hcq-az-z/>, COVID-19: Jigawa govt reveals secret behind mass recovery of patients, *secret behind recoveries is HCQ+AZ+Z*, 5/17.

## Pakistan - mixed use of early treatment with HCQ

Obtained from India, later banned.

Government of Pakistan, [http://covid.gov.pk/new\\_guide...COVID-19\\_infections\\_1203.pdf](http://covid.gov.pk/new_guide...COVID-19_infections_1203.pdf), Clinical Management Guidelines for COVID-19 Infections, *HCQ not recommended for early or late treatment*, 7/2.

OpIndia, <https://www.opindia.com/2020/05/15/hydroxychloroquine-india-coronavirus/>, Pakistan seeks Hydroxychloroquine from India to curb the Coronavirus pandemic, 4/15.

The News, <https://www.thenews.com.pk/pr...ts-claims-top-medicine-expert>, HCQ tablets proving effective in treatment of COVID-19 patients, claims top medicine expert, *trials suspended but some use continues*, 6/3.

ARY News, <https://arynews.tv/en/coronavirus-panel-dexamethasone-actemra/>, Experts rule against plasma, Dexamethasone, Actemra as viable COVID-19 cures, *all licenses related to stocking and selling of Hydroxychloroquine in Pakistan have been revoked and all human trials to verify its potency have been stopped*, 6/22.

## **Panama - mixed use of early treatment with HCQ**

Dropped usage at the end of May, started again in July

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1280772619034398721>, Panama dropped HCQ at the end of May, 7/8.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1295618863535710208>, Ban ended around Jul 22, 8/18.

*Sistema Estatal de Radio y Televisión*, <https://sertv.gob.pa/nacionalfm/comunicado-185/>, Comunicado #185, "Since the Ministry of Health authorized the use of HCQ and/or AZ as drugs to treat positive COVID-19 patients, a significant decrease in cases of this disease has been noted, said the minister", Luis Francisco Sucre, 8/27.

*PanaTimes*, <https://panatimes.com/proposa..oquine-again-against-covid-19>, Proposal is being prepared to use hydroxychloroquine again against COVID-19, *group of infectious disease doctors in the front line of battle against Covid-19 signed a proposal for HCQ+AZ for early stage patients*, 7/14.

*Radio Panamá*, <https://twitter.com/radiopanama/status/1281691420659679234>, Scientific adviser to Panama's President sees no reason to reconsider the negative stance on HCQ, 7/10.

## **Peru - early HCQ treatment was adopted relatively late**

Some use, adopted late ~May 8. Reportedly more used in upper/middle classes. Health ministry promoted on June 8, but usage is controversial.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1265595929383534599>, Adopted May 8, 5/27.

*Ministerio de Salud*, [https://cdn.www.gob.pe/upload/694719/RM\\_270-2020-MINSA.PDF](https://cdn.www.gob.pe/upload/694719/RM_270-2020-MINSA.PDF), Adopting HCQ, 5/8.

*Minister of Health*, <https://rpp.pe/peru/actualida..ia-cientifica-noticia-1270896>, Minsa sobre uso de Hidroxicloroquina e Ivermectina: No tenemos tiempo para "esperar evidencia científica", *Recommended for use*, 6/4.

*CNN*, <https://cnnespanol.cnn.com/20..mo-tratamiento-para-covid-19/>, Perú da impulso a hidroxycloroquina e ivermectina como tratamiento para covid-19, *Recommended for use*, 6/10.

*Manuelcv*, <https://twitter.com/manuelcl10/status/1265632450794979328>, Only middle class and high class receiving proper HCQ treatment, 5/27.

## **Portugal - mixed use of early treatment with HCQ**

Banned post WHO/Lancet.

*ZAP Notícias - Aeiou*, <https://zap.aeiou.pt/portugal..enda-hidroxicloroquina-328362>, Portugal ainda não recomenda uso de hidroxicloroquina, *Portugal still does not recommend the use of HCQ*, 6/4.

*Portugal Resident*, <https://www.portugalresident...nd-use-of-hydroxychloroquine/>, , *suspended post WHO/Lancet*, 5/29.

*Barron's*, <https://www.barrons.com/news/..ividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *continue to promote*, 6/1.

*Covid19Crusher*, <https://twitter.com/Covid19Cr..er/status/1258408833640267776>, Portugal has less than half the ICU beds per capita of France or Spain and treatment at home quickly became the only option. With HCQ, the death rate was minimized, 5/7.

## **Qatar - widespread early treatment (excluded due to young population)**

*Hydroxychloroquine News*, <https://twitter.com/niro60487..atus/1263731107578515457?s=20>, Qatar health minister says they found HCQ to be highly effective, 5/22.

*Hydroxychloroquine News*, <https://twitter.com/niro60487270/status/1256675338853072896>, Used early, 5/2.

## **Russia - widespread early treatment for high-risk patients for most of the outbreak**

Approved for use April 15, they disregarded WHO's recommendation to stop.

*The Moscow Times*, <https://www.themoscowtimes.co..g-to-treat-coronavirus-a70025>, Russia Approves Unproven Malaria Drug to Treat Coronavirus, 4/17.

*Russian Government*, <http://publication.pravo.gov...t/View/0001202004160037#print>, Распоряжение Правительства Российской Федерации от 16.04.2020 № 1030-р, 4/16.

*The Moscow Times*, <https://www.themoscowtimes.co..ug-for-coronavirus-bbc-a69877>, Moscow Doctors Forced to Self-Test Risky Malaria Drug for Coronavirus – BBC, 4/6.

*Gummi Bear*, <https://twitter.com/gummibear737/status/1279874373046939649>, Russian treatment protocol showing HCQ used early, 7/5.

*Barron's*, <https://www.barrons.com/news/..ividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *use not suspended post WHO/Lancet*, 6/1.

*The BL*, <https://thebl.com/world-news/..ine-drug-ccp-virus-trump.html>, Russia supports the use of hydroxychloroquine, the drug to treat the CCP Virus suggested by Trump, *will not follow WHO recommendation*, 5/28.

## Senegal - widespread early treatment for high-risk patients for most of the outbreak

Used early. Prof. Raoult was born in Senegal.

*NPR News*, <https://wfuv.org/content/sene..%80%94-and-their-contacts-too>, Senegal pledges a bed for every coronavirus patient, *country's treatment plan uses HCQ despite warning from WHO*, 5/17.

*Teller Report*, <http://www.tellerreport.com/n..ychloroquine.BJeet4Kst8.html>, Coronavirus: a study in Senegal confirms the effectiveness of hydroxychloroquine, 5/2.

*Africanews*, <https://www.africanews.com/20..heal-faster-senegalese-medic/>, Coronavirus patients on chloroquine heal faster - Senegalese medic, 6/4.

*Medical Xpress*, <https://medicalxpress.com/new..oroquine-virus-treatment.html>, Senegal says hydroxychloroquine virus treatment is promising, 4/2.

*Afrik.com*, <https://www.afrik.com/edouard..ychloroquine-et-le-remdesivir>, Edouard Philippe emporté par le Covid, Didier Raoult, l'hydroxychloroquine et le... remdésivir, *Follows the Raoult protocol*, 7/6.

*The Africa Report*, <https://www.theafricareport.c..ne-from-dakar-to-brazzaville/>, Coronavirus: Didier Raoult the African and chloroquine, from Dakar to Brazzaville, 4/15.

*Barron's*, <https://www.barrons.com/news/..ividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *continue to promote*, 6/1.

*Franceinfo*, [https://www.francetvinfo.fr/m..droxychloroquine\\_3983239.html](https://www.francetvinfo.fr/m..droxychloroquine_3983239.html), Ces pays africains qui ont décidé de continuer à soigner le Covid-19 avec l'hydroxychloroquine, *continue to use after WHO warning, positive results*, 5/28.

*Hydroxychloroquine News*, <https://twitter.com/niro60487270/status/1256675338853072896>, Used early, 5/2.

## South Korea - widespread early treatment (excluded due to early isolation)

Promoted and prophylaxis for health care workers.

*Hydroxychloroquine News*, <https://twitter.com/niro60487270/status/1256675338853072896>, Used early, 5/2.

*Luke Mor*, <https://twitter.com/LukeMor19..10/status/1271442135720615938>, Used early, 6/12.

*American RN*, [https://twitter.com/rn\\_american/status/1272812657142349826](https://twitter.com/rn_american/status/1272812657142349826), Prohylactic use, 6/16.

*ChloroquineGuerilla*, <https://twitter.com/Prolongin..id/status/1279874993153662977>, Standard of care from the beginning, 7/5.

*Businessrizz*, <https://twitter.com/businessrizz/status/1261092622312955904>, Promoted since January and used for prophylaxis with healthcare workers, 5/14.

## **Spain - early HCQ treatment was adopted relatively late**

We found limited information for Spain suggesting it was initially not used during rapid spread, was adopted later, and later became controversial.

*Newsweek*, <https://www.newsweek.com/spain-vid-19-health-workers-1497277>, Spain Launches Large-scale Study of Hydroxychloroquine and Antiretrovirals to Prevent COVID-19 in Health Workers, 4/10.

*Robert McDonald*, <https://twitter.com/robbymcd1/status/1275152353298087936>, Initially not used but started later, 6/22.

*Free News*, <https://freenews.live/spain-h..trials-of-hydroxychloroquine/>, Spain has stopped most clinical trials of hydroxychloroquine, 6/23.

## **Sweden - limited early treatment with HCQ**

Doctors instructed not to use.

*Breaking News Today*, <https://www.breakingnewstoday..ng-used-in-swedish-hospitals/>, Trump's "Miracle Drug" Chloroquine No Longer Being Used in Swedish Hospitals, *trials canceled*, 4/8.

*AJMC*, <https://www.ajmc.com/newsroom..ardiovascular-disease-covid19>, Caution Strongly Recommended When Using Chloroquine, Hydroxychloroquine in Patients With Cardiovascular Disease, COVID-19, *clinicians instructed not to use [H]CQ for COVID outside of trials*, 4/17.

*Barron's*, <https://www.barrons.com/news/..ividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *banned, used in the early phases of the pandemic for patients with severe symptoms, but halted in April after the European Medicines Agency recommended it only be used in clinical trials*, 6/1.

*Ian56*, <https://twitter.com/Ian56789/status/1272844272769867777>, Not used early, 6/16.

*Henrik Wallen*, <https://twitter.com/henrikwal..atus/1280439318109184000?s=21>, Generally no treatment at all outside hospitals, 7/7.

## **Switzerland - early HCQ treatment was adopted relatively late**

Started using May 1.

*É Mo Scél*, [https://twitter.com/e\\_scel/status/1262737713725239298](https://twitter.com/e_scel/status/1262737713725239298), Using since May 1, 5/19.

## **Tunisia - mixed use of early treatment with HCQ**

Was using but banned post WHO/Lancet.

Barron's, <https://www.barrons.com/news/dividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *banned*, 6/1.

France 24, <https://www.france24.com/en/europe/manufacturing-hydroxychloroquine>, Coronavirus pandemic: Tunisia begins manufacturing hydroxychloroquine, 4/10.

## Turkey - widespread early treatment for high-risk patients for most of the outbreak

Science board suggested beneficial in early stages. Reported everyone testing positive receives HCQ. Gradual adoption at the beginning.

Middle East Eye, <https://www.middleeasteye.net/news/turkey-malaria-treatment-progress>, Coronavirus: Turkey says hydroxychloroquine dramatically reduces pneumonia cases, *used early - "our science board suggested that the drug is really beneficial in the early stages to prevent the spread of the virus in the body"*, 4/8.

BBC, <https://www.bbc.com/news/world-europe-52831017>, Coronavirus: How Turkey took control of Covid-19 emergency, *"controversially that includes the anti-malarial drug, hydroxychloroquine, as standard"*, 5/29.

David Stringer, <https://twitter.com/davidstri11/status/1264995116785246210>, Everyone testing positive gets HCQ, 5/25.

The Palmer Foundation, <https://www.palmerfoundation.org/hydroxychloroquine-ministry-of-health/>, Turkey: Highest COVID-19 cases and lowest fatalities in middle east, broad use hydroxychloroquine – Ministry of Health, *"Doctors prescribe hydroxychloroquine to everyone who is tested positive for coronavirus" Dr. Sema Turan, a member of the Turkish government's coronavirus advisory board*, 5/2.

Hydroxychloroquine News, <https://twitter.com/niro60487270/status/1256675338853072896>, Treating early with HCQ, 5/2.

CBS News, <https://www.msn.com/en-au/news/g-touted-by-trump/ar-BB13oMXS>, Turkey claims success treating virus with drug touted by Trump, 4/30.

AAPS, <https://aapsonline.org/hcq-90-percent-chance/>, Hydroxychloroquine Has about 90 Percent Chance of Helping COVID-19 Patients, *many nations, including Turkey and India, are protecting medical workers and contacts of infected persons prophylactically*, 4/28.

Barron's, <https://www.barrons.com/news/dividing-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *continue to promote*, 6/1.

Covid19Crusher, <https://twitter.com/Covid19Crusher/status/1257921469914517505>, Turkey has adopted early HCQ use, 5/5.

Covid19Crusher, <https://twitter.com/Covid19Crusher/status/1255516638033608710>, Gradually adopted early HCQ, 4/29.

Association of American Physicians and Surgeons, <https://www.prnewswire.com/news-releases/more-evidence-presented-for-why-hydroxychloroquine-should-be-made-available-in-a-new-court-filing-by-the-association-of-american-physicians-and-surgeons-aaps-301098030.html>, More Evidence Presented for Why Hydroxychloroquine Should be Made Available, in a New Court Filing by the Association of American Physicians & Surgeons (AAPS), *greater access to HCQ*,



7/22.

Luke Mor, <https://twitter.com/LukeMor19..10/status/1271442135720615938>, Turkey advocates early use, 6/12.

## **Ukraine - widespread early treatment for high-risk patients for most of the outbreak**

Government treatment protocol shows early use.

*Ukrinform*, <https://www.ukrinform.net/rub..own-in-ukraine-on-june-3.html>, Ukraine receives batch of hydroxychloroquine tablets from India, *received additional shipment*, 5/5.

*Ukraine Ministry of Health Care*, [https://www.dec.gov.ua/wp-con..20\\_762\\_protokol\\_covid19-f.pdf](https://www.dec.gov.ua/wp-con..20_762_protokol_covid19-f.pdf), ПРОТОКОЛ «НАДАВАННЯ МЕДИЧНОЇ ДОПОМОГИ ДЛЯ ЛІКУВАННЯ КОРОНАВІРУСНОЇ ХВОРОБИ (COVID-19)», *government treatment protocol showing early use*, 4/2.

*Ministry of Health of Ukraine*, [https://twitter.com/MoH\\_Ukraine/status/1248268122332766208](https://twitter.com/MoH_Ukraine/status/1248268122332766208), Ukraine will receive an additional 320 thousand tablets with the active substance Hydroxychloroquine for symptomatic treatment of patients with #COVID—19, 4/9.

## **United Kingdom - limited early treatment with HCQ**

Use is banned outside of clinical trials. Media very negative.

*U.K. Government*, <https://www.gov.uk/government..oronavirus-covid-19-treatment>, Chloroquine and Hydroxychloroquine not licensed for coronavirus (COVID-19) treatment, *use is banned outside of clinical trials*, 3/25.

*Daily Mail*, <https://www.dailymail.co.uk/n..despite-doctors-using-it.html>, US health regulator approves two malaria drugs as a last resort for coronavirus patients in hospital - but the UK will only let doctors use the promising medications in trials, 3/30.

*Ian56*, <https://twitter.com/Ian56789/status/1272844272769867777>, Not used early, *blocked almost completely*, 6/16.

## **United States - limited early treatment with HCQ**

FDA has warned against use, several states prohibit early use. Doctors may risk censure and their license for prescribing. Media very negative. Usage in late treatment in hospitals. Relatively minimal usage for early treatment.

FDA, <https://www.fda.gov/drugs/drug-safety/9-outside-hospital-setting-or-fda-cautions-against-use-of-hydroxychloroquine-or-chloroquine-for-covid-19-outside-of-the-hospital-setting-or-a-clinical-trial-due-to-risk-of-heart-rhythm-problems>, FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems, 4/24.

*The Washington Post*, [https://www.washingtonpost.com/health/fda-warns-about-hydroxychloroquine-dangers-citing-serious-heart-issues-including-death/](https://www.washingtonpost.com/health/fda-warns-about-hydroxychloroquine-dangers-citing-serious-heart-issues-including-death/2020/04/24/), FDA warns about hydroxychloroquine dangers, citing serious heart issues, including death, 4/24.

National Academy for State Health Policy, <https://www.nashp.org/wp-content/uploads/2020/03/State-Rules-and-Recommendations-Regarding-Chloroquine-Hydroxychloroquine-and-Other-Drugs-Related-to-COVID-19.pdf>, State Rules and Recommendations Regarding Chloroquine, Hydroxychloroquine and Other Drugs Related to COVID-19, 3/27.

Association of American Physicians and Surgeons, <https://www.prnewswire.com/news-releases/more-evidence-presented-for-why-hydroxychloroquine-should-be-made-available-in-a-new-court-filing-by-the-association-of-american-physicians-surgeons-aaps-pharmacists-may-be-prevented-from-filling-hcq-prescriptions-most-americans-are-unable-to-obtain-hcq-for-early-treatment-and-virtually-no-americans-are-able-to-access-it-as-preventive-medicine-301098030.html>, More Evidence Presented for Why Hydroxychloroquine Should be Made Available, in a New Court Filing by the Association of American Physicians & Surgeons (AAPS), *pharmacists may be prevented from filling HCQ prescriptions, most Americans are unable to obtain HCQ for early treatment, and virtually no Americans are able to access it as preventive medicine*, 7/22.

Texas Scorecard, <https://texasscorecard.com/stories/limited-coronavirus-medicine/>, Physician Says Texas Pharmacy Board Limited Coronavirus Medicine, 5/12.

Harvey Risch, MD, PhD, <https://www.newsweek.com/key-start-using-it-opinion-1519535>, The Key to Defeating COVID-19 Already Exists. We Need to Start Using It, *doctors have been threatened by medical boards with the chance of losing their license for prescribing HCQ*, 7/23.

## Venezuela - widespread early treatment (excluded due to early isolation)

Efecto Cocuyo, <https://efectococuyo.com/coronavirus-19-anuncia-jorge-rodriguez/>, Venezuela empieza a usar la cloroquina para tratar COVID-19, anuncia Jorge Rodríguez, *used prophylactically*, 3/23.

Association of American Physicians and Surgeons, <https://www.prnewswire.com/news-releases/more-evidence-presented-for-why-hydroxychloroquine-should-be-made-available-in-a-new-court-filing-by-the-association-of-american-physicians-surgeons-aaps-pharmacists-may-be-prevented-from-filling-hcq-prescriptions-most-americans-are-unable-to-obtain-hcq-for-early-treatment-and-virtually-no-americans-are-able-to-access-it-as-preventive-medicine-301098030.html>, More Evidence Presented for Why Hydroxychloroquine Should be Made Available, in a New Court Filing by the Association of American Physicians & Surgeons (AAPS), *available OTC*, 7/22.

Barron's, <https://www.barrons.com/news/avoiding-the-world-01591006809>, Hydroxychloroquine: A Drug Dividing The World, *used as preventative measure*, 6/1.