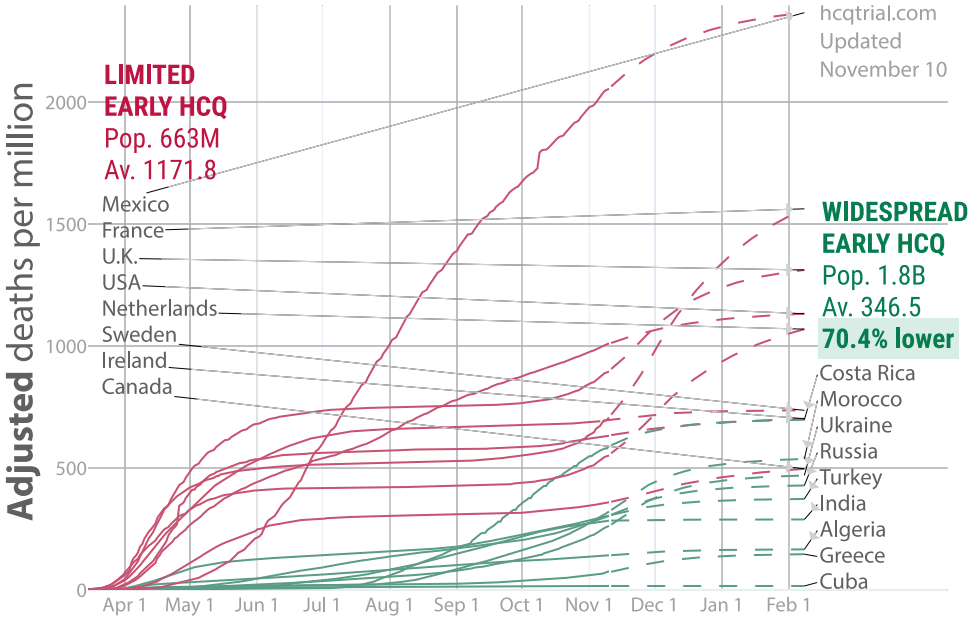
Early treatment with hydroxychloroquine: a country-based analysis

Covid Analysis, August 5, 2020 (Version 34, November 10, 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 November 10, 2020, an average of 130.8 per million in the treatment group have died, and 568.9 per million in the control group, relative risk 0.230. After adjustments, treatment and control deaths become 255.2 per million and 862.3 per million, relative risk 0.30. The probability of an equal or lower relative risk occurring from random group assignments is 0.031. Accounting for predicted changes in spread, we estimate a relative risk of 0.30. **The treatment group has a 70.4% lower death rate.** Confounding factors affect this estimate. We examined diabetes, obesity, hypertension, life expectancy, population density, urbanization, BCG vaccine use, 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 265 relevant references, shown in Appendix 13. 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 aggresive 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 13.

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 November 10, 2020, an average of 130.8 per million in the treatment group have died, and 568.9 per million in the control group, relative risk 0.230. After adjustments, treatment and control deaths become 255.2 per million and 862.3 per million, relative risk 0.30. If we combine all countries into single treatment and control groups, the relative risk is 0.25. Since the sample sizes are very large, $p < 0.0001$ (for the case of single combined treatment and control groups). 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 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 0.031.

Accounting for predicted changes in spread as detailed below, we estimate a relative risk of 0.30. The treatment group has a 70.4% lower death rate. For comparison, if there are no country exclusions, the estimated relative risk is 0.27. We examined diabetes, obesity, hypertension, life expectancy, population density, urbanization, BCG vaccine usage, 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.

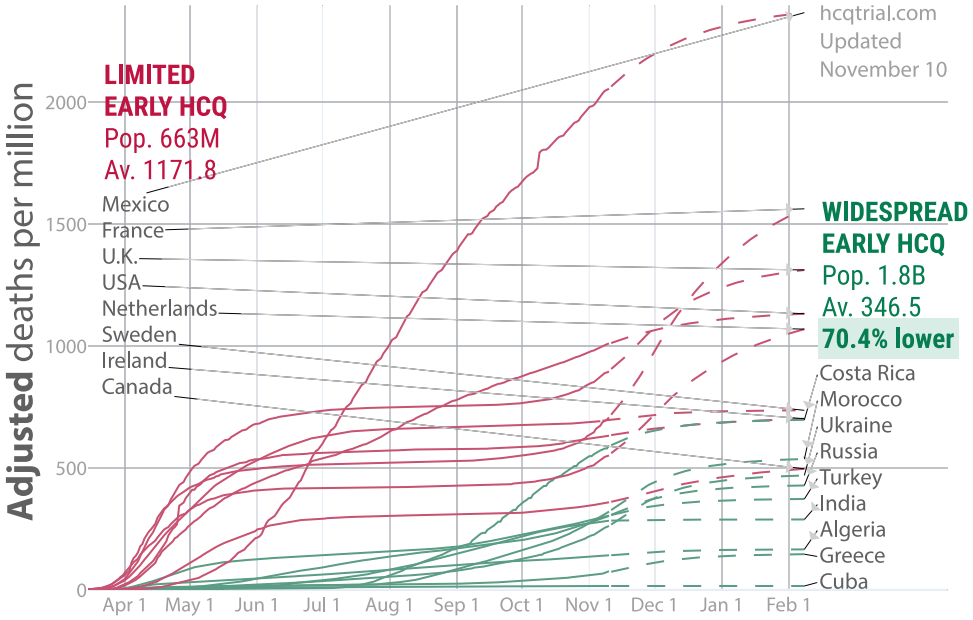


Figure 1. *Adjusted deaths per million for countries using widespread early HCQ versus those that do not, with a prediction for the following 90 days. As of November 10, 2020, countries using early HCQ are predicted to have a 70.4% lower death rate after adjustments.*

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.

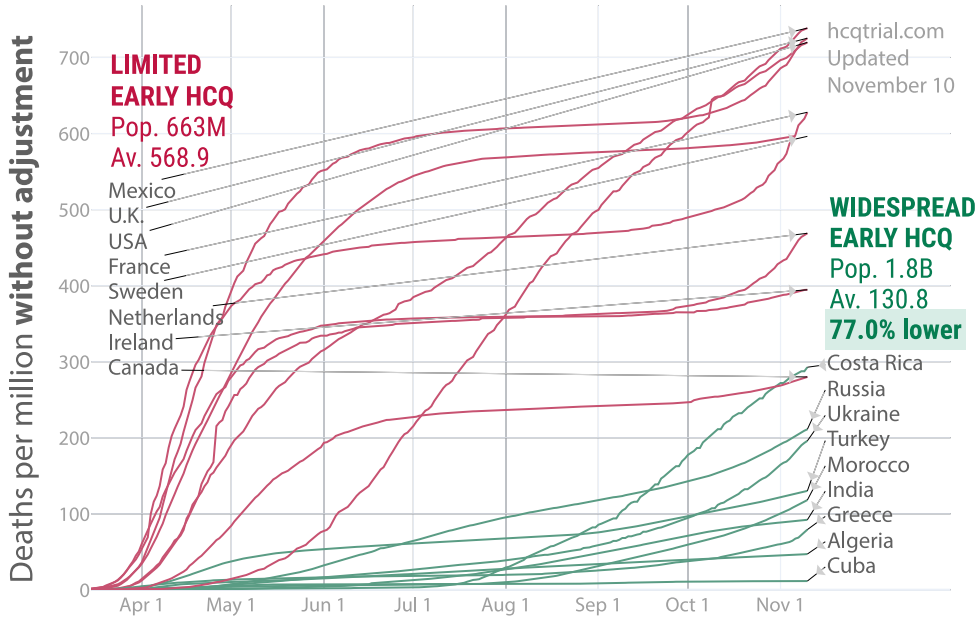


Figure 2. *Deaths per million for countries using widespread early HCQ versus those that do not,* ***before adjustments****.*

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**]*.

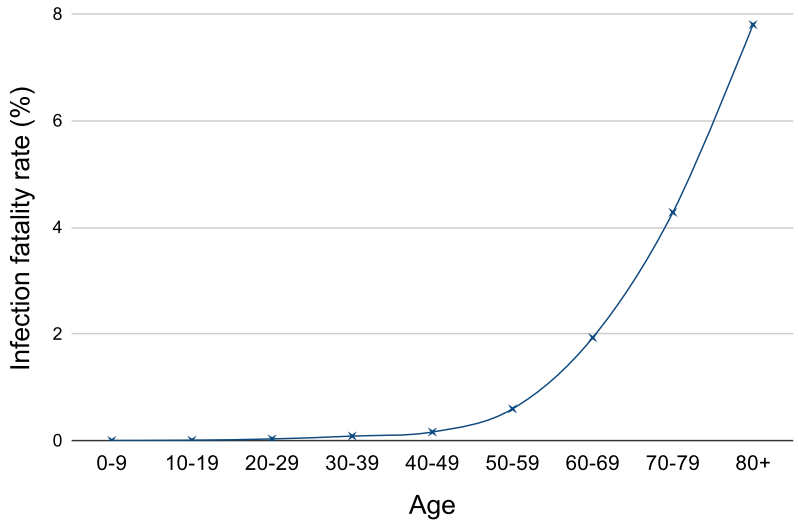


Figure 3. *Infection fatality rates from [**Verity**].*

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. Adusted mean treatment and control deaths become 255.2 per million and 862.3 per million, relative risk 0.30.

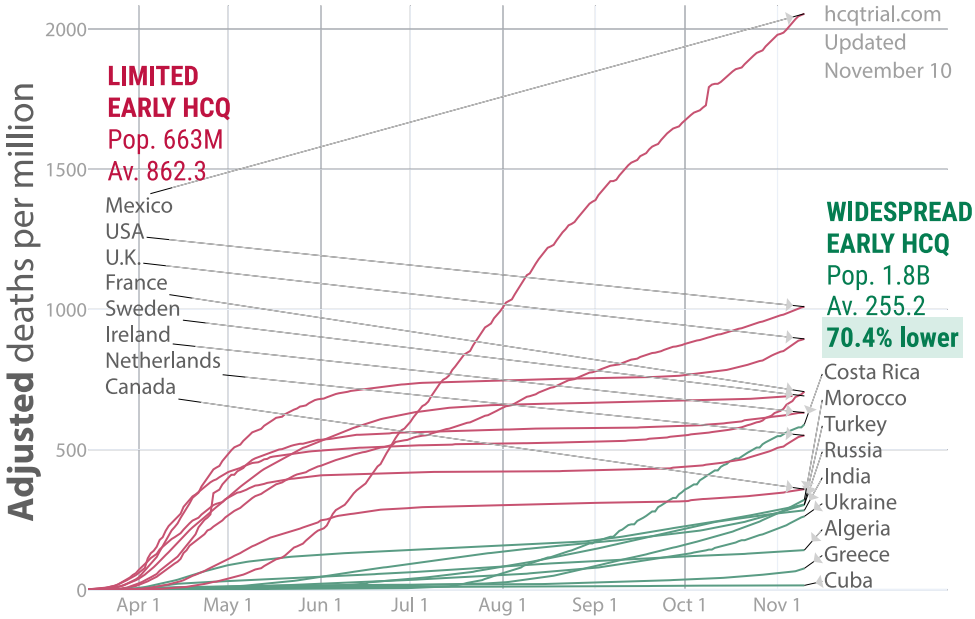


Figure 4. *Deaths per million for countries with widespread early HCQ versus those that do not, after adjustment for differences in demographics.*

Early isolation and masks. Many countries have taken an isolation approach, isolating themself from the world quickly and aggresively 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 12. 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 241.9 per million, and the relative risk decreases to 0.28.

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 = 0.12, obesity, r^2 = 0.07, or hypertension, r^2 = 0.08. 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 0.308, 0.304, 0.310 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 = 0.00, 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 11 shows a scatter plot, and the data can be found in Appendix 1. The correlation r^2 = 0.01, 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.

BCG vaccine. Research suggests that the BCG vaccine may provide some protection against COVID-19 *[Escobar]*. A correlation was shown between a country's BCG vaccine use and mortality, although causation has not been established *[de Freitas e Silva, Escobar, Hegarty, Sharquie]*, and more recent analysis found the correlation was no longer significant *[Lindestam Arlehamn]*. We examined the correlation between the adjusted deaths and the mean BCG vaccine coverage as defined by *[Escobar]*. Appendix 7 shows the scatter plot for the BCG vaccine coverage and the adjusted deaths per million and the data is shown in Appendix 1. The correlation r^2 = 0.04 is low. Excluding countries with a BCG vaccine coverage below 50 (5 countries) reduces the correlation, r^2 = 0.01. Re-running the analysis in this case results in a relative risk of 0.23, i.e., the treatment group has 77.4% lower chance of death. Therefore we do not find evidence that differences in BCG vaccine use significantly affect the results.

Co-administered treatments. Several theories exist for why HCQ is effective *[Andreani, Brufsky, Clementi, de Wilde, Derendorf, Devaux, Fantini, 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 suppplements. 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 10 and Appendix 6, and data shown in Appendix 1. The correlation for population density r^2 = 0.00, and for urbanization, r^2 = 0.08. 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 9 shows a scatter plot, the correlation r^2 = 0.00, 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 0.30, i.e., the treatment group has 70.4% lower chance of death.

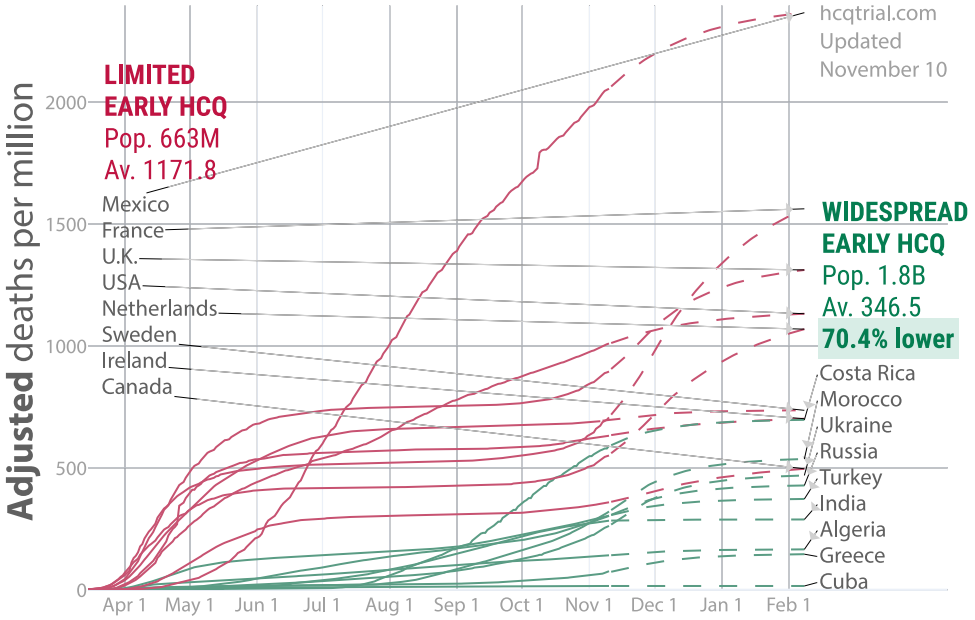


Figure 5. *Demographic adjusted deaths per million for countries using widespread early HCQ versus those that do not, with an extended prediction for the following 90 days.*

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**, **Fantini**, **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 α 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 μM; CC50 > 100 μM, 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; *[**Fantini (4/3/20)**]* ; *[**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 to 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-Delyle (5/8/20)**]* use human lung parenchymal explants, showing that CQ concentration clinically achievable in the lung (100 μM) inhibited the lipopolysaccharide-induced release of TNF-α (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 <= 4 log10 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 inital viral loads allow greater time to mount an immune response.

Human *in vivo* studies. We found 152 studies related to the human *in vivo* use of HCQ for treating COVID-19 *[Abd-Elsalam, Abella, Ahmad, Alamdari, Alberici, Almazrou, An, Aparisi, Arleo, Arshad, Ashinyo, Ashraf, Ayerbe, Barbosa, BaŞaran, Berenguer, Bernaola, Bhattacharya, Borba, Boulware, Bousquet, Carlucci, Carlucci (B), Catteau, Cavalcanti, Chamieh, Chatterjee, Chen, Chen (B), Chen (C), Chen (D), Choi, Coll, Cravedi, D'Arminio Monforte, Dabbous, Davido, de la Iglesia, Derwand (B), Derwand (C), Desbois, Di Castelnuovo, Dubee, Dubernet, Elbazidi, Esper, Faíco-Filho, Ferreira, Ferri, Fonseca, Fontana, Fried, Furtado, Gao (B), Gautret, Gautret (B), Geleris, Gendelman, Gentry, Giacomelli, Goenka, Goldman, Goldman (B), Gonzalez, Grau-Pujol, Guisado-Vasco, Gupta, Guérin, Heberto, Heras, Hong, Huang, Huang (B), Huang (C), Huh, Ip, Ip (B), Izoulet, Jiang, Kamran, Kelly, Khan, Khurana, Kim, Kirenga, Komissarov, Konig, Lagier, Lammers, Lano, Laplana, Lauriola, Lecronier, Lee, Lopes, Lopez, Luo, Ly, Lyngbakken, López, Macias, Magagnoli, Mahévas, Martinez-Lopez, McGrail, Membrillo de Novales, Meo, Mikami, Million, Mitchell, Mitjà, Mitjà (B), Molina, Nachega, Okour, Otea, Paccoud, Peters, Pinato, Pirnay, Podder, Rajasingham, RECOVERY, Rentsch, Rivera, Roomi, Rosenberg, Saleemi, Sbidian, Self, Serrano, Shoaibi, Singh, Skipper, Solh, SOLIDARITY, Soto-Becerra, Sulaiman, Synolaki, Sánchez-Álvarez, Tang, Tehrani, Trullàs, Ulrich, Wang (C), Xia, Xue (B), Yu, Yu (B), Zhong, Zhong (B), Ñamendys-Silva]*. 84 of these present positive results (of varying degrees and confidence) *[Ahmad, Alamdari, Alberici, Almazrou, Aparisi, Arleo, Arshad, Ashinyo, Ayerbe, Berenguer, Bernaola, Bhattacharya, Boulware, Bousquet, Carlucci, Carlucci (B), Catteau, Chamieh, Chatterjee, Chen (B), Chen (C), Coll, D'Arminio Monforte, Davido, Derwand (B), Derwand*

(C), Di Castelnuovo, Dubernet, Elbazidi, Esper, Ferreira, Ferri, Fonseca, Fontana, Gao (B), Gautret (B), Goenka, Gonzalez, Guisado-Vasco, Guérin, Heberto, Heras, Hong, Huang, Huang (B), Huang (C), Ip, Izoulet, Jiang, Khan, Khurana, Kim, Lagier, Lammers, Lauriola, Lee, Lopes, Ly, López, Martinez-Lopez, Membrillo de Novales, Meo, Mikami, Million, Mitchell, Nachega, Okour, Otea, Pinato, Pirnay, Sbidian, Serrano, Shoaibi, Sulaiman, Synolaki, Sánchez-Álvarez, Tehrani, Xia, Xue (B), Yu, Yu (B), Zhong, Zhong (B), Ñamendys-Silva], 30 present negative results (also of varying degrees and confidence) *[An, Barbosa, Borba, Cavalcanti, Chen (D), Choi, Cravedi, Giacomelli, Gupta, Ip (B), Kelly, Komissarov, Lecronier, Magagnoli, Mahévas, Molina, Peters, RECOVERY, Rentsch, Rivera, Roomi, Rosenberg, Saleemi, Self, Singh, Solh, SOLIDARITY, Soto-Becerra, Tang, Ulrich]*, while the remainder are either inconclusive or were retracted. Table 1 shows a distribution of studies based on treatment time.

Study type	*In Vitro*	PrEP	PEP	Early treatment	Late treatment
Number of studies	12	22	3	26	104
Percentage positive	100%	91%	100%	100%	65%

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 53 of the studies reported positive effectiveness, while 29 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, RECOVERY, SOLIDARITY]*, and the results suggest that these dosages in late stage patients may be harmful.

Pre-Exposure Prophylaxis (PrEP) studies. We found 22 PrEP studies *[Abella, Arleo, Bhattacharya, Chatterjee, de la Iglesia, Desbois, Ferreira, Ferri, Gendelman, Gentry, Goenka, Grau-Pujol, Huang, Huh, Khurana, Konig, Laplana, Macias, Mitchell, Rajasingham, Rentsch, 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.

[Arleo] perform a retrospective analysis of hospitalized rheumatic disease patients showing 50% lower mortality for patients on HCQ; *[Goenka]* study SARS-CoV-2-IgG antibodies in 1122 health care workers in India, finding 87% lower positives for adequate HCQ prophylaxis, 1.3% HCQ versus 12.3% for no HCQ prophylaxis; *[Abella]* report on a very small early-terminated underpowered PrEP RCT with 64/61 HCQ/control patients and only 8 infections, HCQ infection rate 6.3% versus control 6.6%, RR 0.95 [0.25 - 3.64]. There was no hospitalization or death, no significant difference in QTc, no severe adverse events, no cardiac events (e.g., syncope and arrhythmias) observed. Medication

adherence was 81%. Therapeutic levels of HCQ may not have been reached by the time of the infection in the first week. 2 infections were reported to be after discontinuation of the medication, but the authors do not specify which arm these were in. Hypothetically, if these were both in the HCQ arm, the resulting RR for treatment would be much lower; *[**Gentry**]* perform a retrospective analysis of patients with rheumatologic conditions showing zero mortality with HCQ, odds ratio OR 0.0, p=0.10. 0 of 10,703 COVID-19 deaths for HCQ patients versus 7 of 21,406 for control patients. COVID-19 cases OR 0.79, p=0.27. There are several significant differences in the propensity matched patients that could affect results, e.g., 20.9% SLE versus 24.7%; *[**Rajasingham**]* show HCQ COVID-19 case HR 0.73, p = 0.12 with a PrEP RCT. This trial was halted after 47% enrollment, p < 0.05 will be reached at ~75% enrollment if similar results continue. HR 0.66/0.68 for full medication adherence (1x/2x dosing). Efficacy for first responders was higher, OR 0.32, p = 0.01. First responders had a much higher incidence, allowing greater power, and reducing the effect of confounders such as misdiagnosis of other conditions or survey issues. Performance is similar to placebo for the first 3 weeks. The effect may be greater with a dosage regimen that achieves therapeutic levels faster. ~40% of participants suspected they might have had COVID-19 before the trial, the effect in people without prior COVID-19 may be higher. Authors note that the trial was underpowered, investigation into more frequent dosing may be warranted, and there was insufficient dosing with no participants achieving more than the *in vitro* EC50; *[**Grau-Pujol**]* performed a small PrEP RCT showing that PrEP with HCQ is safe at the dosage used. No deaths, hospitalizations, or serious adverse events occurred. With only one case (in the placebo arm), efficacy was not evaluated; *[**Rentsch**]* perform an observational database study of RA/SLE patients in the UK, HCQ HR 1.03 [0.80-1.33] after adjustments. 70 patients with HCQ prescriptions died. One major problem is that there is no knowlege of medication adherence for these 70 - for example, it is possible that they were all part of the expected percentage of patients that did not take the medication as prescribed, invalidating the result. Both confirmed and suspected deaths were included. It is not clear why the authors did not report the result for only confirmed cases. Other limitations include confounding by use of bDMARDs, confounding by severity of rheumatological disease, and incorrectly classified deaths; *[**Laplana**]* survey 319 autoimmune disease patients taking CQ/HCQ finding 5.3% COVID-19 incidence, compared to a control group from the general population (matched on age, sex, and region, but not adjusted for autoimmune disease), with 3.4% incidence. It not clear why authors did not compare with autoimmune patients not on CQ/HCQ. If we adjust for the different baseline risk, the result would become RR 0.36, p<0.001, suggesting a substantial benefit for HCQ/CQ treatment; *[**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; *[**Desbois**]* retrospectively analyze 199 sarcoidosis patients, showing HCQ RR 0.83, p=1.0; *[**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; *[**Konig**]* analyzed 80 SLE patients diagnosed with COVID-19, showing the frequency of hospitalisation did not differ significantly between individuals using an antimalarial versus non-users. Authors suggest that the dosage used may be too low to reach therapeutic levels; *[**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 multivarible 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 addional 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 multiple other secondary analyses *[**Luco**, **Watanabe**, **Wiseman**]*.

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**]*.

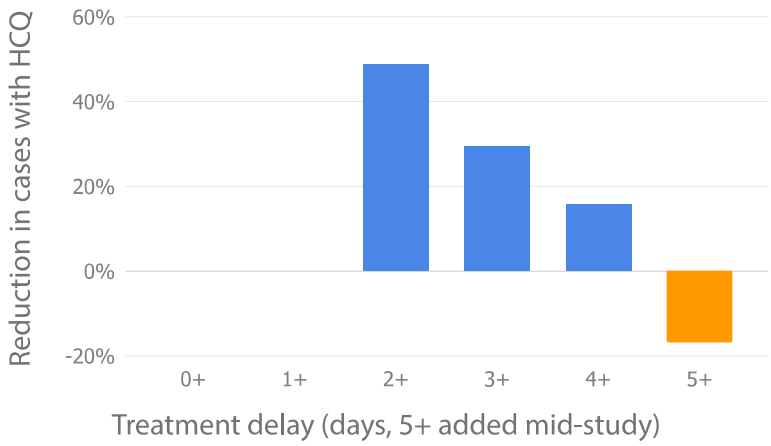


Figure 6. *Treatment delay-response relationship from [**Boulware**].*

*[**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 (D)**]*. 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 26 early treatment studies *[**Ahmad**, **Ashraf**, **Chen (B)**, **Derwand (B)**, **Derwand (C)**, **Elbazidi**, **Esper**, **Fonseca**, **Gautret**, **Gautret (B)**, **Guérin**, **Heras**, **Hong**, **Huang (C)**, **Ip**, **Izoulet**, **Kirenga**, **Lagier**, **Ly**, **Meo**, **Million**, **Mitjà (B)**, **Otea**, **Pirnay**, **Skipper**, **Sulaiman**]* which all show some degree of effectiveness. *[**Fonseca**]* show 64% lower hospitalization with HCQ. Retrospective 717 patients in Brazil with early treatment, adjusted OR 0.32, p=0.00081, for HCQ versus no medication, and OR 0.45, p=0.0065, for HCQ vs. anything else; *[**Derwand (B)**]* ; *[**Derwand (C)**]*

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); *[**Sulaiman**]* perform a prospective analysis of 5,541 patients in Saudi Arabia showing adjusted HCQ mortality OR 0.36, p = 0.012, and adjusted HCQ hospitalization OR 0.57, p < 0.001; *[**Kirenga**]* retrospectively analyze 56 patients in Uganda, 29 HCQ and 27 control, showing 25.6% faster recovering with HCQ, 6.4 vs. 8.6 days (p = 0.20). There was no ICU admission, mechanical ventilation, or death; *[**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 >= 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 administrated HCQ as soon as possible. 42 patients with HCQ 1-4 days from diagnosis, 48 with HCQ 5+ days from diagnosis; *[**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 (B)**]* 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; *[**Pirnay**]* analyze 68 very high risk nursing home residents, median age 86, using HCQ+AZ early treatment within 2.5 days onset, showing significantly less mortality than other nursing homes in France and the same as the median death for the same period in 2019/2018; *[**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 log10 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 (D)**]*. 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 pecentage 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 disdavantage 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 seroprevalance 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.

11/10: We added *[Dhibar, Mathai, Self]*.

11/4: We added *[Behera, Cadegiani]*.

11/1: We added *[Desbois, Trullàs]*.

10/31: We added *[Arleo, Choi, Coll, Fonseca, Frontera, Tehrani]*.

10/24: We added *[Barnabas, Goenka]*.

10/23: We added references *[Dubee, Lano, Solh, Ñamendys-Silva]*.

10/16: We added references *[Annie, Aparisi, DISCOVERY, Guisado-Vasco, Nachega, Sili, SOLIDARITY, Soto-Becerra]*.

10/6: We added analysis of BCG vaccine usage and references *[Abella, Almazrou, Ayerbe, Dabbous, de Freitas e Silva, Escobar, Hegarty, Lammers, Luco, Sharquie, Wiseman]*.

9/25: We added references *[Ashinyo, Axfors, Gentry, Grau-Pujol, Karatza, Rajasingham, Shoaibi]*.

9/15: We added reference *[Lauriola]*.

9/13: We added references *[Alamdari, Sulaiman]*.

9/9: We added references *[Kirenga, Laplana, Rentsch]*.

9/8: We added reference *[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 *[Di 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-Elsalam, Ly, Peters, Saleemi]*.

8/17: Some countries identified by Leffler were missing in Appendix 12. 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 aggresive 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 done 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).

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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	BCG vaccine usage	Gender factor
Algeria	44M	73.2	0.32	17	102.1	94	1.00
Canada	38M	81.5	0.29	4	98.5	0	1.00
Costa Rica	5M	80.1	0.29	96	99.8	86	1.00
Cuba	11M	77.1	0.33	110	98.6	98	1.00
France	65M	80.7	0.27	123	93.8	80	1.01
Greece	10M	79.4	0.25	83	96.4	72	1.01
India	1.4B	34.5	0.34	450	108.2	76	0.99
Ireland	5M	63.4	0.29	70	98.6	79	1.00
Mexico	129M	80.4	0.31	66	95.8	85	1.01
Morocco	37M	63.0	0.33	80	98.5	91	1.00
Netherlands	17M	91.9	0.25	509	99.3	0	1.00
Russia	146M	74.6	0.28	9	86.4	94	1.02
Sweden	10M	87.7	0.16	25	100.4	17	1.00
Turkey	84M	75.6	0.26	105	97.5	73	1.00
U.K.	68M	83.7	0.29	273	97.7	37	1.00
USA	331M	82.5	0.29	36	97.9	0	1.00
Ukraine	44M	69.5	0.27	77	86.3	92	1.02

Table 4. *Country statistics [Escobar, 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	263.2
Costa Rica	80.3	9.1	25.7	24.0	47.6
Cuba	78.8	9.6	24.6	38.8	80.3
France	82.7	4.8	21.6	38.2	337.3
Greece	82.2	4.7	24.9	37.8	186.3
India	69.7	10.4	3.9	27.5	85.3
Ireland	82.3	3.2	25.3	39.1	347.5
Mexico	75.0	13.5	28.9	28.9	16.4
Morocco	76.7	7.0	26.1	33.2	93.5
Netherlands	82.3	5.4	20.4	36.5	157.2
Russia	72.6	6.1	23.1	40.7	446.8
Sweden	82.8	4.8	20.6	39.4	174.4
Turkey	77.7	11.1	32.1	36.7	179.4
U.K.	81.3	3.9	27.8	30.8	450.5
USA	78.9	10.8	36.2	31.5	475.2
Ukraine	72.1	6.1	24.1	49.2	83.4

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

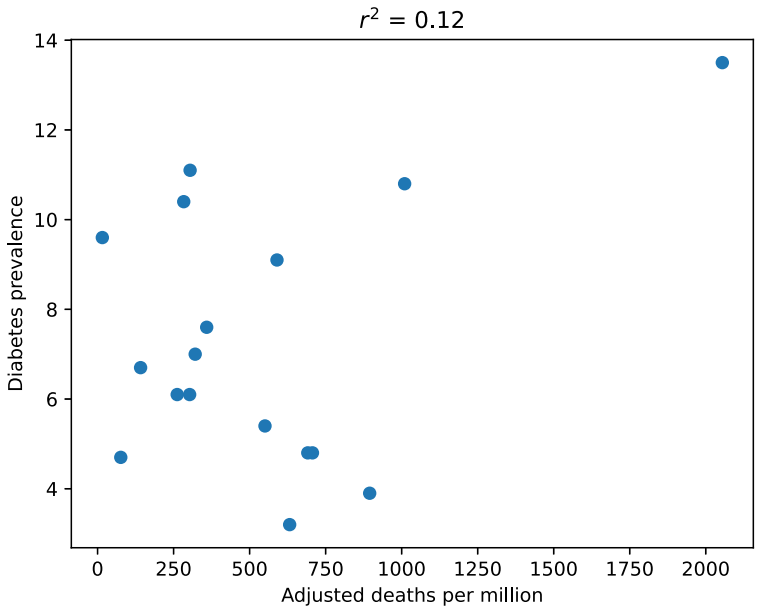

Figure 7. *Diabetes prevalence [**International Diabetes Federation**] versus adjusted deaths per million, r^2 = 0.12.*

Appendix 3. Obesity

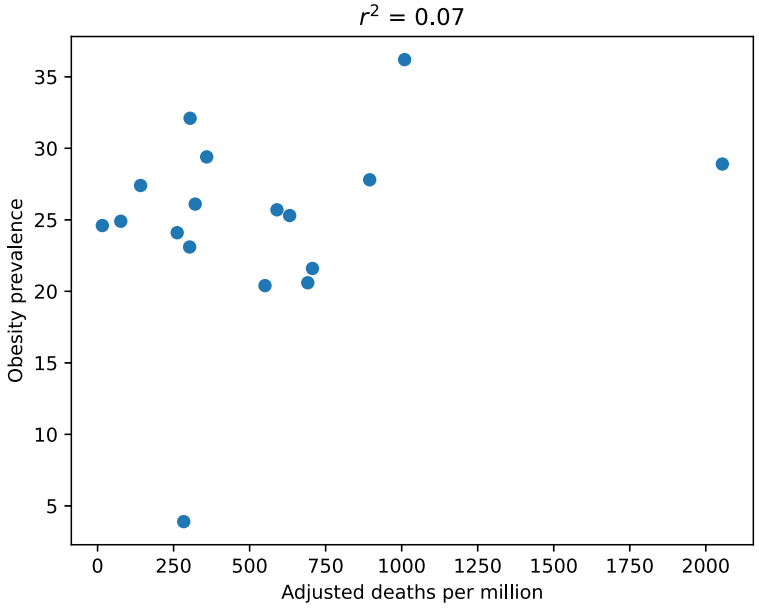

Figure 8. *Obesity prevalence [**CIA**] versus adjusted deaths per million, r^2 = 0.07.*

Appendix 4. Hypertension

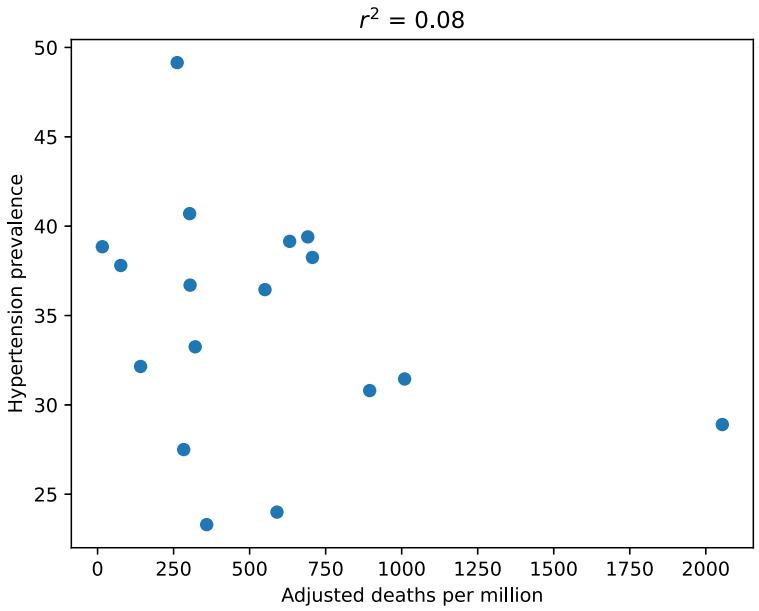

Figure 9. *Hypertension prevalence [**Mills**] versus adjusted deaths per million, r^2 = 0.08.*

Appendix 5. Life Expectancy

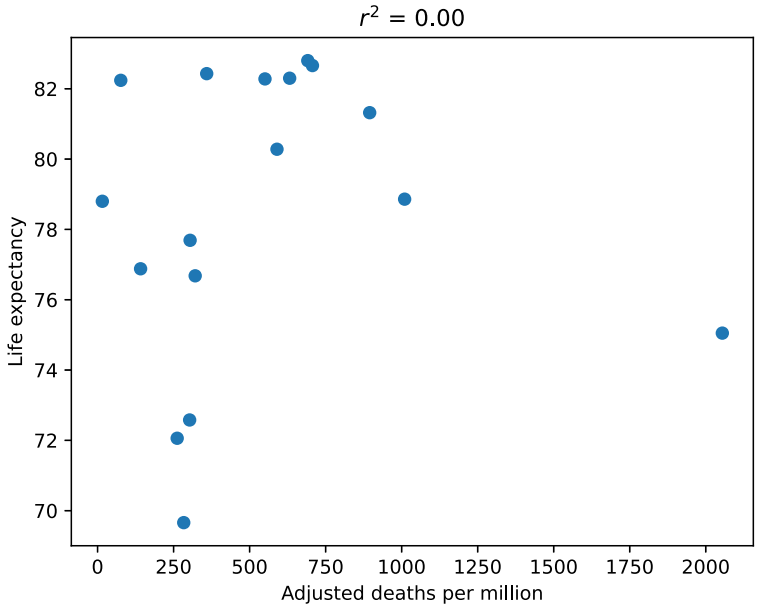

Figure 10. *Life expectancy [**Our World in Data (B)**] versus adjusted deaths per million, r^2 = 0.00.*

Appendix 6. Urbanization

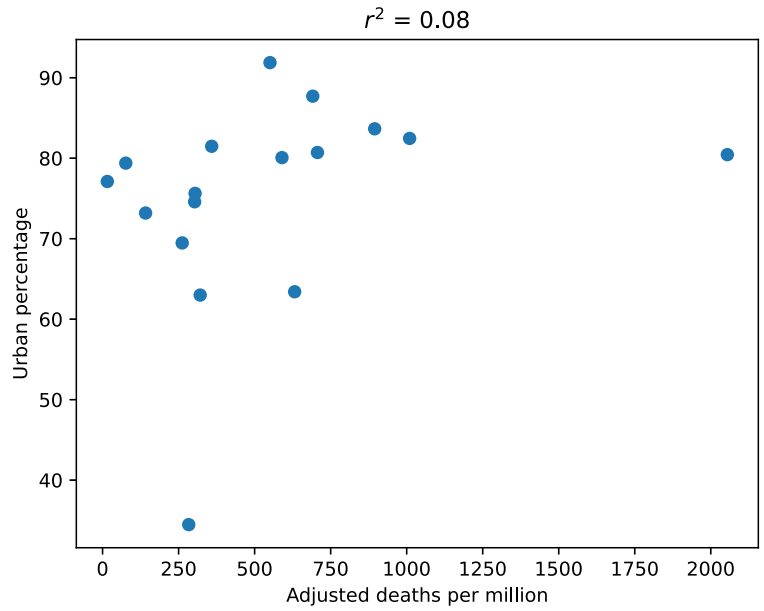

Figure 11. *Urban percentage [**World Bank**] versus adjusted deaths per million, r^2 = 0.08.*

Appendix 7. BCG Vaccine

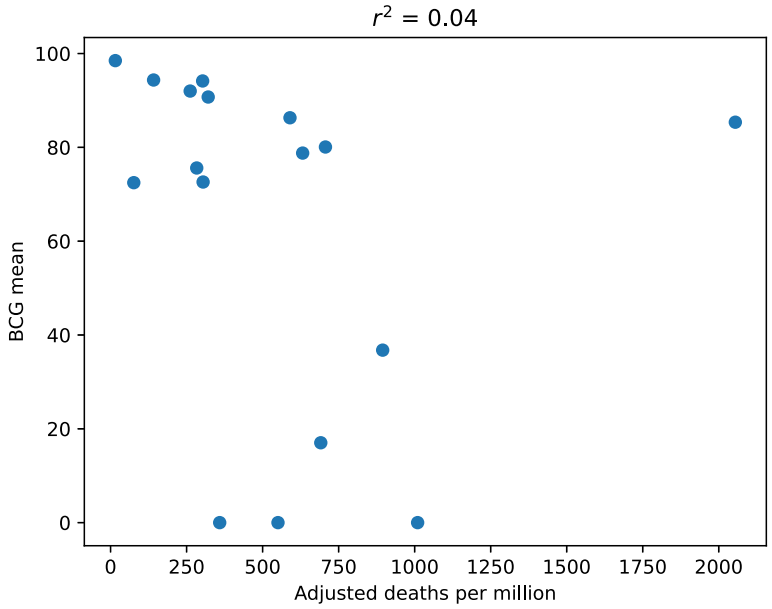

Figure 12. *BCG vaccine usage [**Escobar**] versus adjusted deaths per million, r^2 = 0.04.*

Appendix 8. Gender

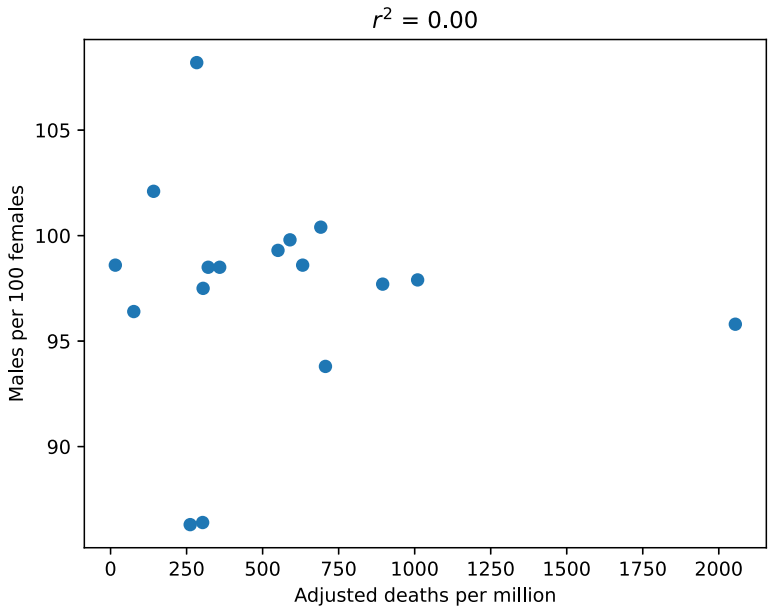

Figure 13. *Males per 100 females [**United Nations (B)**] versus adjusted deaths per million, r^2 = 0.00.*

Appendix 9. Average Intervention Stringency Index

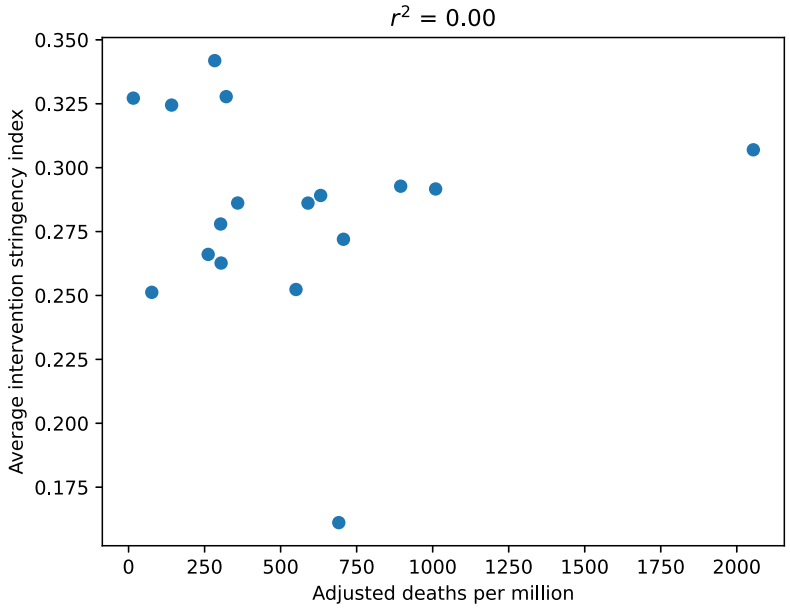

Figure 14. *Average intervention stringency index [**Our World in Data (F)**, **University of Oxford**] versus adjusted deaths per million, r^2 = 0.00.*

Appendix 10. Population Density

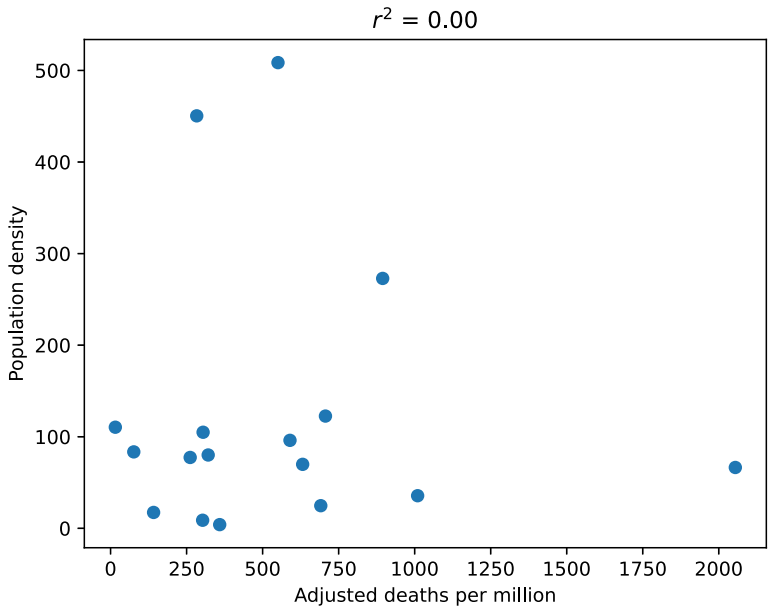

Figure 15. *Population density [**Our World in Data (D)**] versus adjusted deaths per million, r^2 = 0.00.*

Appendix 11. Test Volume

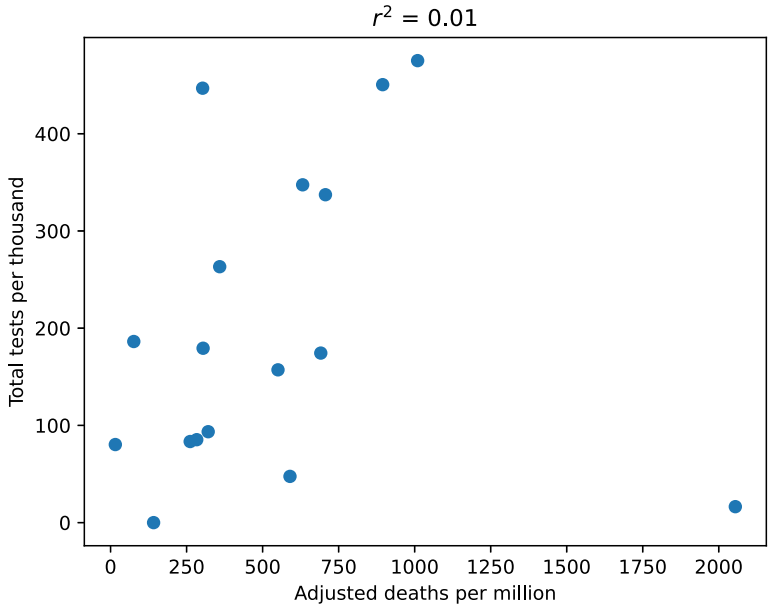

Figure 16. *Tests per thousand [**Our World in Data (C)**] versus adjusted deaths per million, r^2 = 0.01.*

Appendix 12. 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.68 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. (S225)
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 26.102 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 13. 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, Marshall Islands, 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, Congo, Democratic Republic of the, Cote d'Ivoire, Côte d'Ivoire, DR Congo, 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, Palestine, State of, Papua New Guinea, Qatar, Republic of Congo, Rwanda, Sao Tome and Principe, Saudi Arabia, Senegal, Sierra Leone, Solomon Islands, 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.

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

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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.

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Belarus - mixed use of early treatment with HCQ

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

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Canada - limited early treatment with HCQ

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Chile - mixed use of early treatment with HCQ

Stopped use after WHO/Lancet reports around May 26.

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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.

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

Using to treat at an early stage.

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

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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.

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Germany - mixed use of early treatment with HCQ

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

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

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

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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.

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

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

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

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Switzerland - early HCQ treatment was adopted relatively late

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United Kingdom - limited early treatment with HCQ

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United States - limited early treatment with HCQ

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