

**Medical Studies Support MDs Prescribing
Hydroxychloroquine for Early Stage COVID-19
and for Prophylaxis**

**By
Vladimir Zelenko, M.D.
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Section 1

Vladimir Zelenko, M.D.

Item #1

Title and Authors of the Published Paper Entitled:

“COVID-19 Outpatients – Early Risk-Stratified Treatment with Zinc Plus Low Dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study”

“COVID-19 Outpatients – Early Risk-Stratified Treatment with Zinc Plus Low Dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study”

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Item #2

Published Preprint for the Article Entitled:

“COVID-19 outpatients – early risk-stratified treatment with zinc plus low dose hydroxychloroquine and azithromycin: a retrospective case series study”

“COVID-19 outpatients – early risk-stratified treatment with zinc plus low dose hydroxychloroquine and azithromycin: a retrospective case series study”

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ABSTRACT

Objective: To describe outcomes of patients with coronavirus disease 2019 (COVID-19) in the outpatient setting after early treatment with zinc, low dose hydroxychloroquine, and azithromycin (the triple therapy) dependent on risk stratification.

Design: Retrospective case series study.

Setting: General practice.

Participants: 141 COVID-19 patients with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in the year 2020.

Main outcome measures: Risk-stratified treatment decision, rate of hospitalization and all-cause death.

Results: Of 335 positively PCR-tested COVID-19 patients, 127 were treated with the triple therapy. 104 of 127 met the defined risk stratification criteria and were included in the analysis. In addition, 37 treated and eligible patients who were confirmed by IgG tests were included in the treatment group (total N=141). 208 of the 335 patients did not meet the risk stratification criteria and were not treated. After 4 days (median, IQR 3-6, available for N=66/141) of onset of symptoms, 141 patients (median age 58 years, IQR 40-67; 73% male) got a prescription for the triple therapy for 5 days. Independent public reference data from 377 confirmed COVID-19 patients of the same community were used as untreated control. 4 of 141 treated patients (2.8%) were hospitalized, which was significantly less ($p<0.001$) compared with 58 of 377 untreated patients (15.4%) (odds ratio 0.16, 95% CI 0.06-0.5). Therefore, the odds of hospitalization of treated patients were 84% less than in the untreated group. One patient (0.7%) died in the treatment group versus 13 patients (3.5%) in the untreated group (odds ratio 0.2, 95% CI 0.03-1.5; $p=0.16$). There were no cardiac side effects.

Conclusions: Risk stratification-based treatment of COVID-19 outpatients as early as possible after symptom onset with the used triple therapy, including the combination of zinc with low dose hydroxychloroquine, was associated with significantly less hospitalizations and 5 times less all-cause deaths.

Keywords: SARS-CoV-2, COVID-19, outpatients, treatment, zinc, hydroxychloroquine, azithromycin

ARTICLE SUMMARY

Strength and limitations of this study

- The first COVID-19 outpatient risk stratification and treatment study
- ▲ Repurposed antimalarial drug hydroxychloroquine at low dose in combination with zinc and azithromycin as a therapeutic approach early in the course of COVID-19 until specific drugs or vaccines are available
- Retrospective case series study with findings that have to be validated in prospective controlled clinical trials
- Only outcome data of the untreated control group of the same community based on public reference was available but no other patient characteristics, clinical symptoms, etc.
- ▲ No conclusion on the efficacy and safety of the used triple therapy related to severely ill hospitalized patients

Item #3

Full Text of the Article Entitled:

“COVID-19 outpatients – early risk-stratified treatment with zinc plus low dose hydroxychloroquine and azithromycin: a retrospective case series study”

INTRODUCTION

In December 2019, the new severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) started as an outbreak in Wuhan, China. This coronavirus has spread rapidly as a pandemic around the world,¹ causing coronavirus disease 19 (COVID-19) pneumonia, acute respiratory distress syndrome (ARDS), cardiac injury, liver and renal injury, thrombosis, and death.²

As of June, 2020, diagnosis and treatment of COVID-19 have been almost exclusively studied from an inpatient perspective, including intensive care with mechanical ventilation. Only one study has described characteristics and key health outcomes of COVID-19 diagnosed patients in an outpatient setting.³ This is surprising as primary care physicians see COVID-19 patients often first. They could play a critical role in early diagnosis, treatment, and management of disease progression and virus spread. This assumption is supported by the established principle in medicine that speed of eradication is linked to the outcome of life-threatening infections.⁴

The early clinical phase of COVID-19 has not been the focus of research until today even though timing of antiviral treatment seems to be critical.⁵ The more optimal window for therapeutic intervention is before the infection spreads from upper to lower respiratory tract and before the severe inflammatory reactions.⁶ Therefore, diagnosis and treatment of COVID-19 outpatients as early as possible, even based on clinical diagnosis only, may have been an underestimated first step to slow down or even stop the pandemic more effectively. Based on clinical application principles of antiviral therapies, as demonstrated in the case of influenza A,⁷ antiviral treatments should be used early in the course of infection.

Due to the lack of vaccines as well as SARS-CoV-2 specific therapies, the proposed use of repurposed antiviral drugs remains a valid practical consideration.⁸ One of the most controversial drugs during the current SARS-CoV-2 pandemic is the well-known oral antimalarial drug hydroxychloroquine (HCQ), routinely used in the treatment of autoimmune diseases like rheumatoid arthritis or lupus.^{9 10} HCQ is currently listed as an essential medication for lupus by the World Health Organization (WHO)¹¹. With more than 5.6 million prescriptions in the United States, HCQ was the 128th most commonly prescribed medication in 2017.¹² In the meantime, first observational studies concluding beneficial therapeutic effects of HCQ as monotherapy or in combination with the antibiotic azithromycin were reported just a few weeks after the start of the SARS-CoV-2 outbreak.¹³ All studies that used HCQ with rather

contradictory results were done with hospitalized and often sicker patients¹³⁻¹⁶ and one publication was recently withdrawn.^{17 18} As of June 2020, no studies with COVID-19 outpatients treated with HCQ at an early stage of the disease have been reported.

Antiviral effects of HCQ are well-documented.¹⁹ It is also known that chloroquine and probably HCQ have zinc ionophore characteristics, increasing intracellular zinc concentrations.²⁰ Zinc itself is able to inhibit coronavirus RNA-dependent RNA polymerase activity (RdRp).²¹ It has been hypothesized that zinc may enhance the efficacy of HCQ in treating COVID-19 patients.²² The first clinical trial results confirming this hypothesis were recently published as preprint.²³ Nevertheless, many studies with HCQ in monotherapy or in combination with the antibiotic azithromycin have been inconclusive so far.¹³⁻¹⁶ In all of these studies, HCQ was used later than 5 days after onset of symptoms when hospitalized patients most likely had already progressed to stage II or III of the disease.⁶ Regardless of the established antiviral effects of zinc and that many COVID-19 patients are prone to zinc deficiencies, dependent on comorbidities and drug treatments,²² none of these studies were designed to include zinc supplementation as combination treatment.

This first retrospective case series study with COVID-19 outpatients was done to show whether a) a simple to perform outpatient risk stratification might allow for rapid treatment decision shortly after onset of symptoms, and b) whether the triple 5-day therapy with zinc, low dose HCQ, and azithromycin might result in less hospitalizations and less fatalities compared with relevant public reference data of untreated patients.

METHODS

SETTING

This retrospective case series study analysed data from COVID-19 outpatients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in a community in New York State, USA. Outcome of patients who were treated with a specific triple therapy was compared to public reference data of patients in the same community who were not treated with this therapy.

CONFIRMATION OF COVID-19 DIAGNOSIS

COVID-19 diagnosis was confirmed if patients were positively tested for SARS-CoV-2 by means of PCR of nasal or pharyngeal swab specimens (majority of tests by Roche, Basel; 99,1% sensitivity and 99,7% specificity; other tests used with lower frequency included: Diasorin: 500 copies/mL; ThermoFisher: 10 genomic copy equivalents/reaction; Seegene: 1,250 copies/mL; Hologic: TCID₅₀/mL: 1X10⁻²) or retrospectively by IgG detection tests (DiaSorin: Sensitivity 97.6% (\geq 15 days after diagnosis), specificity 99.3%; Diazyme: Sensitivity 91.2%, specificity 97.3%). Only patients who did have a record of a positive test result were included in the analysis. The PCR assays were authorized by the Food and Drug Administration (FDA) without clinical sensitivity/specificity data due to the urgent nature of the pandemic. Only one positive test was necessary for the patient to be included in the retrospective analysis.

PATIENTS

Sequentially consecutive COVID-19 outpatients older than 18 years at diagnosis were included in the analysis as treatment group. All patients were white. Patients received a prescription for the triple therapy only if they met one of the following risk stratification requirements during a medical office-based or telehealth consultation:

Group A: age >60 years; with or without clinical symptoms;

Group B: age ≤ 60 years and shortness of breath (SOB);

Group C: age ≤ 60 years, clinically symptomatic and with at least one of the following comorbidities: hypertension, hyperlipidemia, diabetes, obesity (body mass index ≥ 30 kg/m²), cardiovascular disease, heart failure, history of stroke, history of deep vein thrombosis or pulmonary embolism, asthma, chronic

obstructive pulmonary disease (COPD), other lung disease, kidney disease, liver disease, autoimmune disease, or history of cancer. Pregnant women, if any, were to be included in this group as well.

Laboratory confirmed COVID-19 patients of the same community who were not treated with the described triple therapy and related outcome data represented the untreated control group (public reference data).

PROCEDURE AND TREATMENT

Data of treated patients was collected from electronic health records in the year 2020. Demographics, as reported by the patient, and a current medical history of hypertension, hyperlipidemia, diabetes, obesity (body mass index ≥ 30 kg/m²), cardiovascular disease, heart failure, stroke, asthma, COPD, other lung disease, kidney disease, liver disease, autoimmune disease, history of cancer, thyroid disease psychiatric disorder, or pregnancy were collected.

The presence of the following clinical symptoms of treated patients were documented:

cough/dry cough, fever, SOB, changes of or no smell or taste, sore throat, headache, runny nose/clear rhinorrhea, sinus congestion, diarrhea/vomiting, cold symptoms, feeling sick, weakness, and low back pain. If reported, number of days since onset of symptoms was documented.

The following vital signs, if available, were collected and documented: heart rate (beats per minute), breaths per minute (BPM), systolic and diastolic blood pressure (mmHg), body temperature (°C), oxygen saturation measured by pulse oximetry (O₂ %), body weight (kg), and/or body mass index (BMI).

Main co-medications were characterised based on primary care prescriptions active at the time of diagnosis, were documented as categorical variables and included: betablockers, angiotensin-converting enzyme inhibitors, angiotensin-2 antagonists, calcium channel blockers, hydrochlorothiazide, statins, bronchodilators, antidiabetics, and insulin.

Only diagnosed COVID-19 patients who met the defined risk stratification requirements of group A, B, or C got a prescription for the following triple therapy for 5 consecutive days in addition to standard supportive care: zinc sulfate (220 mg capsule once daily, containing 50 mg elemental zinc), HCQ (200 mg twice daily), and azithromycin (500 mg once daily). No loading dose was used. Patients who did not meet the risk stratification requirements received standard of care to treat common upper respiratory infection. Patients were not treated with HCQ if they had known contraindications, including QT prolongation, retinopathy, or glucose-6-phosphate dehydrogenase (G6PD) deficiency. As usual and

following best practice patients were informed about possible drug related side effects. Reported events, if any, were documented as required.

The selection of the used zinc supplement and drugs, dosages and the combination thereof, were based on treatment guidelines, positive reports from other countries like South Korea, emerging first clinical evidence, and based on the discretion of the treating physicians.

OUTCOME

Two outcomes were studied: COVID-19 related hospital admission and all-cause death during time of follow up of at least 28 days in the treatment group and in the untreated control group (public reference). The outcome of COVID-19 patients of the untreated control group was reported by the responsible health department.

STATISTICAL ANALYSES

Only patients of the treatment group who met the defined risk stratification requirements and who received at least a prescription for HCQ, with or without zinc, for 5 days, were included in the retrospective analysis and were categorized accordingly. If the patient's electronic health record did not include information on a clinical characteristic, it was assumed that the characteristic was not present. In the group of the public reference data only confirmed COVID-19 patients who were not treated in the respective general practice with the triple therapy were included in the analysis. For this untreated control group only outcome data for hospitalization and all cause death was available and used for the statistical comparison with the treatment group.

No sample-size calculations were performed. Descriptive statistics are presented as median and interquartile range (IQR) for continuous variables and frequencies for categorical variables. For comparison with results of other studies means and standard deviations were calculated as needed. Normality of distribution for continuous variables was assessed by the Shapiro-Wilk-Test. A 2-tailed Student's t-test was used for parametric analysis, and a Wilcoxon Signed-Rank test was used for nonparametric data analysis. For calculation of correlation the point biserial correlation coefficient was applied if one variable was dichotomous. Associations between two categorical variables were calculated with the Chi-Square test. Odds ratio (OR) were calculated for comparison of the outcome of the treatment group with the untreated control group. The α : 0.05 was considered as a significance level. The data were

analysed using Microsoft Excel for Microsoft 365 MSO (32-Bit), the Excel add-on Real Statistics, SigmaStat 4, and Sigma Plot 14.0.

PATIENT AND PUBLIC INVOLVEMENT

In this retrospective case series study no patients were involved in the study design or in setting the research questions or the outcome measures directly. No patients were asked to advise on interpretation or writing of results.

STUDY APPROVAL

The study was approved by the Western Institutional Review Board and it was exempt under 45 CFR § 46.104(d)(4). The analysis was conducted with de-identified patient data, according to the USA Health Insurance Portability and Accountability Act (HIPAA), Safe Harbor. For that reason exact dates and locations are not mentioned in this study.

RESULTS

PATIENTS

In accordance with available public reference data, 712 confirmed SARS-CoV-2 PCR positively tested COVID-19 patients were reported for the respective community at the defined time point of the analysis. Of these 712 patients, 335 presented as outpatients at a general practice and 127 were treated with the triple combination therapy. Of these 127 patients, 104 met the risk stratification criteria and were included in the analysis (table 1). 208 patients of the 335 did not meet the defined risk stratification criteria were treated with standard of care and recovered at home. The SARS-CoV-2 infection of 37 additional patients who met the risk stratification criteria and who were also treated with the triple therapy was later confirmed by IgG tests (table 1). These patients were included additionally in the analysis resulting in a total number of 141 patients, all with a confirmed SARS-CoV-2 infection by PCR or IgG tests. None of these patients were lost to follow-up for the defined outcome. The outcome of the remaining N=377 positively tested but not treated COVID-19 patients, e.g. from other practices of the community, served as public reference (fig 1). Analysis of the 141 patients in the treatment group showed that all of these patients (100%) got a prescription of HCQ, 136 (96.5%) of zinc sulfate, and 133 (94.3%) of azithromycin, while 1 patient (0.7%) got doxycycline instead.

BASELINE CHARACTERISTICS OF THE PATIENTS

Table 2 shows the baseline demographics and clinical characteristics of all 141 patients in the treatment group and for the risk stratification groups A, B, and C. 69 patients (49%) belonged to group A, 48 (34%) to group B, and 24 (17%) to group C. Age ranged from 18 to 80 years and the median age was 58 years with an interquartile range (IQR) of 40-67. The median age of group A, B, and C was 67, 39, and 45 years. A total of 103 patients (73.1%) were male with a male-to-female ratio of 2.71. Most common comorbidities included hypertension (28%), obesity (28%), hyperlipidemia (23%), and diabetes (18%), whilst least common ones were liver disease (2%), heart failure (1%), and stroke (1%). One patient was pregnant (1%) at initiation of treatment. There was a positive and significant correlation between age and hypertension ($r=0.3309$, $p=0.001$), hyperlipidemia ($r=0.26306$, $p<0.001$), and cardiovascular disease ($r=0.16757$, $p<0.05$), while asthma was negatively correlated with age ($r=-0.30867$, $p<0.001$).

Median time between onset of clinical symptoms and medical consultation was 4 days (IQR 3-6; available for 66/141 patients, mean 4.8 days \pm 2.7) (table 3). There was no significant correlation between age and days of onset of clinical symptoms to consultation ($p>0.05$). Days from onset of symptoms to consultation were not significantly different between groups ($p>0.05$).

Most common clinical symptoms included cough (87.2%), fever (77.3%), SOB (46.1%), and changes of or no smell or taste (30%), whilst least common ones were sinus congestion (16%), diarrhea/vomiting (5%), and low back pain (3%). Table 4 shows symptoms of all patients and stratified by groups A, B, and C. There was a significant negative correlation between age and changes of smell or taste ($r=-0.43$, $p<0.001$). No patient had a clinical diagnosis of pneumonia.

Table 5 shows vital signs, as they were available, for all patients and by group A, B, and C. Many patients consulted the general practice during the COVID-19 crisis via telehealth so vital signs were not available for all of these patients. The highest proportion of patients had available measurements for heart rate (63%) and pulse oximetry (60%). Vital signs were not significantly different between risk stratification groups ($p>0.05$) except for systolic blood pressure of group A and B ($p<0.05$).

Table 6 summarizes most important co-medications. 16% of patients were taking angiotensin-converting enzyme inhibitors, angiotensin-2-antagonists, hydrochlorothiazide or a combination thereof. The most common long-term therapies at the time of COVID-19 diagnosis were statins (20%), beta-blockers (12%), and insulin (18%).

HOSPITALIZATIONS AND ALL-CAUSE DEATH

In the treatment group 4 of 141 patients were hospitalized, which was significantly less than in the untreated group with 58 of 377 patients (15.4%), (fig 2.), (OR 0.16; [95% CI, 0.06 to 0.5]; $p < 0.001$), (table 7, fig 4). Therefore, the odds of hospitalization of treated patients were 84% less than in the untreated patients. All hospitalized patients were male, one in his twenties, two in their forties, and one in his seventies. Three of the 4 hospitalized patients (75%) belonged to risk stratification group B and one to group A (25%). All patients (100%) reported SOB at time of consultation. Median days from onset of symptoms to consultation were 4 days. Of the treatment group 1 patient had to stay only one day in hospital, 2 other patients were discharged as cured, and 1 patient died (s. below). No patient was on a ventilator.

One of the 141 patients (0.71%) who belonged to treatment group A died after being hospitalized. This patient had a history of cancer and did only take one daily dose of the triple therapy before hospital admission. With 13 of 377 patients (3.5%, fig 3) more patients died in the untreated group (OR 0.2; [95% CI, 0.03 to 1.5]) (table 7, fig 4). The odds of all-cause death of treated patients were 80% less ($p = 0.16$) than in the untreated group.

The 208 patients presenting at the general practice who did not meet the risk stratification requirements and who were not treated with the triple therapy recovered at home and no hospital admissions or deaths were reported.

SAFETY

In general, the triple therapy with zinc, low dose HCQ, and azithromycin was well tolerated. After initiation of treatment 30 of 141 patients (21%) reported weakness, 20 (14%) nausea, 15 (11%) diarrhea, and 2 (1%) rash (table 8). No patient reported palpitations or any cardiac side effect.

DISCUSSION

This first retrospective case series study with COVID-19 outpatients in primary care setting showed that risk-stratified treatment early after onset of clinical symptoms, with the triple therapy zinc, low dose HCQ, and azithromycin was associated with significantly less hospitalizations (odds ratio 0.16; $p < 0.001$) and less all-cause deaths (odds ratio 0.2; $p = 0.16$) in comparison to untreated patients (public reference data) of the same community. Based on the performed risk stratification prevalence of the comorbidities hypertension, hyperlipidemia, and diabetes were the highest in group A (>60 years and clinical

symptoms), asthma and other lung diseases were the highest in group B (<60 years and SOB), and obesity and autoimmune disease were the highest in group C (<60 years, clinical symptoms, and defined comorbidities). Most frequent symptoms of these COVID-19 patients were cough followed by fever while available median body temperature measurements were in a normal range. Almost 50% of risk-stratified and treated patients were suffering from SOB while breaths per minute and blood oxygen saturation were still in the normal range. Median time from onset of symptoms to first medical consultation was 4 days (IQR 3-6). Approximately 16% of patients received co-medications known to be associated with zinc deficiency, such as antihypertensive drugs. No patient experienced any known severe adverse events that were considered drug related during treatment or follow up.

STRENGTHS AND WEAKNESSES OF THE STUDY

At the time of this manuscript submission, only one peer-reviewed study had analyzed the key health outcomes of COVID-19 patients diagnosed in primary care setting.³ Because of this gap in data, the value of this study is multifold. It provides much needed recommendations for risk stratification and a treatment regimen to prevent hospitalization and death of COVID-19 patients. Diagnosis of COVID-19 for all patients in this analysis was confirmed by PCR or IgG tests compared with a recent study in which less than 3% had a diagnosis confirmed by laboratory tests.²⁴ To start the triple therapy as early as possible after symptom onset is critical for treatment success, because SARS-CoV-2 viral load seems to peak at day 5 to 6 after symptom onset²⁵⁻²⁷ and severe cases progress to acute respiratory distress syndrome (ARDS) after only 8 to 9 days.^{28 29} Early antiviral treatment is an established protocol to manage severe disease progression, as was shown, for example, by a cumulative case control study during the 2009 H1N1 influenza pandemic in Canada.³⁰ For patients at high risk for severe viral disease progression, it is recommended to start antiviral therapy as early as possible.^{31 32} Early treatment might be also critically important to effectively reduce SARS-CoV-2 viral load,⁵ and this underscores the role of early intervention by primary care physicians as reported herein.

Further strength of this approach was the simple risk stratification of symptomatic outpatients to determine the need for therapy, a strategy not yet applied in COVID-19 primary care,³³ but routinely implemented in primary care for other diseases.³⁴ Underlying assumptions of the risk stratification used in this setting are different than other recommendations.³⁵ Here, age stratified high risk was defined as >60 years (typically defined as >65 years) to encompass the common increase of comorbidity incidences

in this age group.³⁶ Patients ≤ 60 years with SOB, even without reduced pulse oximetry values, were treated because it was assumed virus will likely spread from upper to lower respiratory tract.³⁷ Also treated were patients ≤ 60 years with clinical symptoms and prognostically relevant comorbidities.³⁵ By applying this risk stratification approach, respective care was tailored to patients with a higher likelihood for hospitalizations or fatalities, which ensured that the medical principles of “patient first” and “doing no harm” were maintained.³⁸ As a result, 62% of COVID-19 patients were treated with standard of care only and recovered at home, and only 38% needed treatment with the triple therapy.

The antiviral potential of HCQ was broadly described *in vitro* and *in vivo*.³⁹⁻⁴¹ HCQ has a long terminal elimination half-life of 32 days in plasma and 50 days in blood.⁴² Therefore, the treatment approach was conservative, with starting dose being the same as maintenance dose and with a short treatment duration of only 5 days, being even more conservative than other recommendations.⁴⁰ HCQ-dependent intracellular increases in pH might directly interfere with pH-dependent SARS-CoV-2 replication.¹⁹ Also, chloroquine and probably HCQ have characteristics of a zinc ionophore resulting in increasing intracellular zinc concentrations.²⁰ The dose of elementary zinc in this study was similar to doses previously studied to successfully prevent infections in the elderly.⁴³ Antiviral effects of zinc against a variety of viruses have been demonstrated during the last decades.⁴⁴ Zinc, in addition to its role as a general stimulant of antiviral

immunity, is known to specifically inhibit coronavirus RNA-dependent RNA polymerase.²¹ Based on HCQ’s ionophore properties, it has been hypothesized that zinc may enhance the efficacy of HCQ in treating COVID-19 patients.²² In addition, zinc might inhibit the serine protease furin.⁴⁵ Furin is expressed on endothelial cells, monocytes/macrophages, and smooth muscle cells in human atherosclerotic plaques⁴⁶ and therefore might play a critical role for the severe cardiovascular complications of COVID-19. As furin might be responsible to favor SARS-CoV-2 spreading compared with other beta coronaviruses^{47 48} and as furin-inhibition protects from certain viral-dependent infections⁴⁹, it may be important to evaluate the potential role of zinc in inhibiting this pathway.

Azithromycin was added to the treatment regimen as preliminary data provides evidence for more efficient or synergic virus elimination in conjunction with bacterial superinfection.^{13 50} Although there is a synergistic antiviral effect between zinc, HCQ, and azithromycin, zinc supplementation may be instrumental for the outcome of patient

populations with severe clinical courses. Zinc deficiency was confirmed in a large number of healthy elderly⁵¹ and in diabetic patients.⁵² In addition, it has been documented that the antihypertensive drugs hydrochlorothiazide, angiotensin-converting-enzyme inhibitors, and angiotensin 2 receptor antagonists can result in an increased urinary excretion of zinc with subsequent systemic zinc deficiency.⁵³ Age, comorbidities, and relevant co-medications align well with the majority of described COVID-19 patients at high risk, including the risk-stratified population of this analysis. Zinc deficiency might explain why certain patient groups seem not to benefit from HCQ in monotherapy. During the 5-day treatment with the triple therapy and during follow up, no severe adverse events were observed and no cases of cardiac arrhythmia were reported in this general practice, which is in accordance with available safety data of more than 300,000 patients.⁵⁴

Inherent to all retrospective analyses, our study has certain limitations such as nonrandomization and blinding of treatment. Also, only the outcome data of the untreated control group based on the public reference was available but no other patient characteristics or clinical symptoms and so no risk adjustment was possible. Therefore, confounding factors and selection bias, among other issues, do exist. The demographic composition of the treatment group might have also had an influence on our findings. Because many physician appointments had to be managed by telehealth, vital parameters were not available for the majority of patients. Viral load and ECG data were not analyzed. Treatment with the triple therapy resulted in a numerically lower rate of all-cause deaths. In the absence of clinical details about the untreated patient group, the lower rate of all-cause death in the treated group was not statistically significant. However, the patients in the treated group were all positively risk-stratified while the risk of the untreated group was obviously lower as this group included high and low-risk patients.

STRENGTHS AND WEAKNESSES IN RELATION TO OTHER STUDIES, DISCUSSING IMPORTANT DIFFERENCES IN RESULTS

In this study, the ratio of males and average age was comparable with a relevant number of other studies, but distribution of comorbidities was not.⁵⁵ The latter was expected because outpatients usually have a different distribution of age and especially of comorbidities than critically ill inpatients. As expected the prevalence of hypertension, hyperlipidemia, and cardiovascular disease correlated positively with age while asthma correlated negatively. Approximately 50% of risk-stratified and treated patients presented with SOB while the parameters breaths per minute and blood oxygen saturation were still within the

normal range. These patients would usually not be considered for hospital admission, although SOB might be considered an alarming early sign of disease progression. Based on the implemented risk stratification, these patients were identified and treated immediately.

In contrast to many other studies, the most frequent symptom was cough and not fever.^{56 57} Changes in smell or taste in one third of patients and a negative correlation with age were similar to findings from other groups.⁵⁸ While mean time from onset of symptoms to treatment was only 4.8 days (median 4 days), previously reported time spans range from 6.3 days,⁵⁹ to 8 days,¹⁶ up to 16.6 days,¹⁴, or was often even not reported.⁶⁰ In most of these studies, COVID-19 disease had most likely already progressed at the time of presentation to stages II or even stage III of the disease.⁶ In

many studies, often only limited information is provided about co-medications and specifically about clinical symptoms at admission.⁶⁰ The latter would be very important to better understand the differences of clinical presentation between inpatients and outpatients, and thus the urgency for early anti-COVID-19 treatment in outpatient setting.⁶¹ The potential of zinc to enhance the antiviral efficacy of HCQ was already described in detail elsewhere.²² This hypothesis was recently confirmed by a study using a similar triple therapy and treatment duration.²³ Zinc added to HCQ and azithromycin resulted in a significantly increased number of patients being discharged, a reduction in mortality, or transfer to hospice. In another study, when a lower dose of 200 mg HCQ twice daily was added to basic treatment, mortality of even critically ill patients was significantly reduced.⁶² These and our findings indicate that proper dosing of HCQ with its long half-life might be key for the favourable outcome of COVID-19 patients. In critical care, drugs with short half-lives are usually preferred. Especially in critically ill COVID-19 patients, higher doses of HCQ may have unforeseeable effects, for example, on insulin sensitivity in obese patients⁶³ and glucose levels in diabetics.⁶⁴

⁶⁵ Besides glucose levels, it is important to closely monitor renal function which is increasingly affected during progression of COVID-19.⁶⁶ Because HCQ is substantially excreted by the kidneys, the risk of toxic reactions is greater in patients with impaired renal function.⁶⁷

POTENTIAL IMPLICATIONS FOR CLINICIANS AND POLICY MAKERS

Clinical experience from severely ill inpatients with pneumonia who were treated with high dose HCQ are not readily transferable to the outpatient setting with upper respiratory disease only. For outpatients

with a median of only 4 days after onset of symptoms, COVID-19 represents a totally different disease and needs to be managed and treated differently.⁶¹ A simple to perform outpatient risk stratification, as shown here, allows rapid treatment decisions and treatment with the triple therapy zinc, low dose HCQ, and azithromycin and may prevent a large number of hospitalizations and probably deaths during the SARS-CoV-2 pandemic. This might also help to avoid overwhelming of the health care systems.

UNANSWERED QUESTIONS AND FUTURE RESEARCH

Almost no general clinical data of COVID-19 outpatients exists and hence responsible experts and stakeholders should ensure a common effort to close this gap by designing studies specifically for primary care setting. Ongoing studies with HCQ should be amended to include combination with zinc. Based on our and others preliminary data, the triple therapy zinc, low dose HCQ, and azithromycin should be used and tested to generate prospective data as soon as possible. As zinc deficiency may play an important role during infection, development, and the clinical course of COVID-19, zinc supplementation in accordance with defined recommended dietary allowances should be evaluated as a simple option for primary prevention. Zinc has a high safety margin and it would be physiologically already available if for example treatment with HCQ is initiated.

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Conflict of interest

The author Roland Derwand is/was at the time of writing an employee of Alexion Pharma Germany GmbH. His engagement and contribution to this study and publication was private and independent from his employer. The author Martin Scholz is/was at the time of writing External Senior Advisor for the company LEUKOCARE in Munich, Germany, and is/was Managing Director at Starts- and -Ups

Consulting, Frankfurt, Germany. Vladimir Zelenko is/was general practitioner in New York State. All three authors confirm that this article content has no conflict of interest.

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Tables and Figures

| Table 1. COVID-19 Diagnostics by PCR and IgG tests of Patients in the Treatment Group | | | | |
|--|---------------------------------------|---------------------------------------|---------------------------------------|---|
| COVID-19 Diagnostics – no. (%) | Risk Stratified Group A (N=69) | Risk Stratified Group B (N=48) | Risk Stratified Group C (N=24) | All Patients Treatment Group (N=141) |
| SARS-CoV-2 – PCR Test | 51 (74) | 39 (81) | 14 (58) | 104 (74) |
| SARS-CoV-2 – IgG Test | 18 (26) | 9 (19) | 10 (42) | 37 (26) |

| Table 2. Baseline Demographics and Clinical Characteristics of Patients in the Treatment Group* | | | | |
|--|---------------------------------------|---------------------------------------|---------------------------------------|---|
| Characteristics | Risk Stratified Group A (N=69) | Risk Stratified Group B (N=48) | Risk Stratified Group C (N=24) | All Patients Treatment Group (N=141) |
| Median age (IQR) – years | 67 (64-69) | 39 (24-47) | 45 (36-50) | 58 (40-67) |
| Male sex – no. (%) | 46 (67) | 40 (83) | 17 (71) | 103 (73) |
| Coexisting conditions – no. (%) | | | | |
| Any condition | 44 (64) | 31 (65) | 24 (100) | 99 (70) |
| Hypertension | 27 (39) | 4 (8) | 8 (33) | 39 (28) |
| Hyperlipidemia | 21 (30) | 7 (15) | 5 (21) | 33 (23) |
| Diabetes | 16 (23) | 4 (8) | 5 (21) | 25 (18) |
| Obesity | 20 (29) | 10 (21) | 10 (42) | 40 (28) |
| Cardiovascular Disease | 9 (13) | 1 (2) | 3 (13) | 13 (9) |
| Heart Failure | 2 (3) | 0 (0) | 0 (0) | 2 (1) |
| Stroke | 1 (2) | 0 (0) | 0 (0) | 1 (1) |
| Asthma | 2 (3) | 9 (19) | 2 (8) | 13 (9) |
| COPD | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Other Lung Disease | 6 (9) | 5 (10) | 4 (17) | 15 (11) |
| Kidney Disease | 1 (2) | 3 (6) | 2 (8) | 6 (4) |
| Liver Disease | 1 (2) | 2 (4) | 0 (0) | 3 (2) |
| Autoimmune Disease | 2 (3) | 4 (8) | 4 (17) | 10 (7) |
| History of Cancer | 6 (9) | 2 (4) | 1 (4) | 9 (6) |
| Thyroid Disease | 7 (10) | 4 (8) | 2(8) | 13 (9) |
| Psychiatric Disorder | 7 (10) | 4 (8) | 5 (21) | 16 (11) |
| Pregnancy | - | - | 1 (4) | 1 (1) |

*IQR interquartile range

Table 3. Patients with Reported Days Since Onset of Symptoms in the Treatment Group

| Characteristics | Risk Stratified Group A (N=69) | Risk Stratified Group B (N=48) | Risk Stratified Group C (N=24) | All Patients Treatment Group (N=141) |
|---|---------------------------------------|---------------------------------------|---------------------------------------|---|
| Patients with reported days – no. (%) | 32 (46) | 25 (48) | 9 (38) | 66 (47) |
| Median days since onset of symptoms – (IQR) | 4 (3-6) | 3 (3-6.5) | 4 (3-5.5) | 4 (3-6) |

Table 4. COVID-19 Diagnostics and Baseline Reported Clinical Symptoms of Patients in the Treatment Group

| Clinical Symptoms – no. (%) | Risk Stratified Group A (N=69) | Risk Stratified Group B (N=48) | Risk Stratified Group C (N=24) | All Patients Treatment Group (N=141) |
|---------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------------|
| Cough/Dry Cough | 60 (87) | 39 (81) | 24 (100) | 123 (87) |
| Fever | 53 (77) | 38 (79) | 18 (75) | 109 (77) |
| Shortness of Breath (SOB) | 17 (25) | 48 (100) | 0 (0) | 65 (46) |
| Changes of or no smell or taste | 21 (30) | 19 (40) | 2 (8) | 42 (30) |
| Sore Throat | 19 (28) | 8 (17) | 7 (29) | 34 (24) |
| Headache | 19 (28) | 6 (13) | 7 (29) | 32 (23) |
| Runny Nose/Clear Rhinorrhea | 16 (23) | 8 (17) | 4 (17) | 28 (20) |
| Sinus Congestion | 10 (15) | 9 (19) | 4 (17) | 23 (16) |
| Diarrhea/Vomiting | 1 (2) | 5 (10) | 1 (4) | 7 (5) |
| Cold Symptoms | 31 (45) | 16 (33) | 12 (50) | 59 (42) |
| Feels Sick | 40 (58) | 38 (79) | 17 (71) | 95 (67) |
| Weakness | 44 (64) | 22 (46) | 11 (46) | 77 (55) |
| Low Back Pain | 3 (4) | 0 (0) | 1 (4) | 4 (3) |

Table 5. Physical Examination – Vital Signs of Patients in the Treatment Group

| Parameter | | Patients with available Parameters – no. (%) of N=141 |
|---|------------------|--|
| Median Heart Rate – beats per minute – (IQR) | 86 (80-94) | 89 (63) |
| Median Breaths per Minute [BPM] – (IQR) | 16 (15-18) | 43 (31) |
| Median Systolic Blood Pressure [mmHg] – (IQR) | 126 (120-139) | 66 (47) |
| Median Diastolic Blood Pressure [mmHg] – (IQR) | 80 (74-85.5) | 66 (47) |
| Median Body Temperature [°C] – (IQR) | 37.2 (37-37.8) | 79 (56) |
| Median Pulse Oximetry [O ₂ %] – (IQR) | 97 (96-98) | 85 (60) |
| Median Body Weight [kg] – (IQR) | 88 (72.6-98.4) | 43 (31) |
| Median Body Mass Index [kg/m ²] – (IQR) | 32.2 (28.5-36.3) | 30 (21) |

Table 6. Co-Medications of Patients in the Treatment Group

| Drug Class | Patients – no. (%) of N=141 |
|--|--|
| Betablockers | 17 (12) |
| Angiotensin-converting enzyme inhibitors | 8 (6) |
| Angiotensin-2 Antagonists | 13 (9) |
| Calcium channel blockers | 8 (6) |
| Hydrochlorothiazide | 6 (4) |
| Statins | 28 (20) |
| Bronchodilators | 10 (7) |
| Antidiabetics | 11 (8) |
| Insulin | 26 (18) |

Table 7. Clinical Outcome in the Treated Patient Group versus the Untreated Patient Group

| Outcome | Treated Group – no. (%) of N=141 | Untreated Group – no. (%) of N=377 | Odds Ratio | 95% CI | P-value |
|-----------------|---|---|-----------------------|---------------|----------------|
| Hospitalization | 4 (2.8) | 58 (15.4) | 0.16 | 0.06- 0.5 | <0.001 |
| All-cause death | 1 (0.71) | 13 (3.5) | 0.2 | 0.03- 1.5 | 0.16 |

CI=Confidence Interval

| Event | Patients – no. (%) of N=141 |
|-------------------|--|
| Any adverse event | 67 (48) |
| Weakness | 30 (21) |
| Nausea | 20 (14) |
| Diarrhea | 15 (11) |
| Rash | 2 (1) |

Figure 1

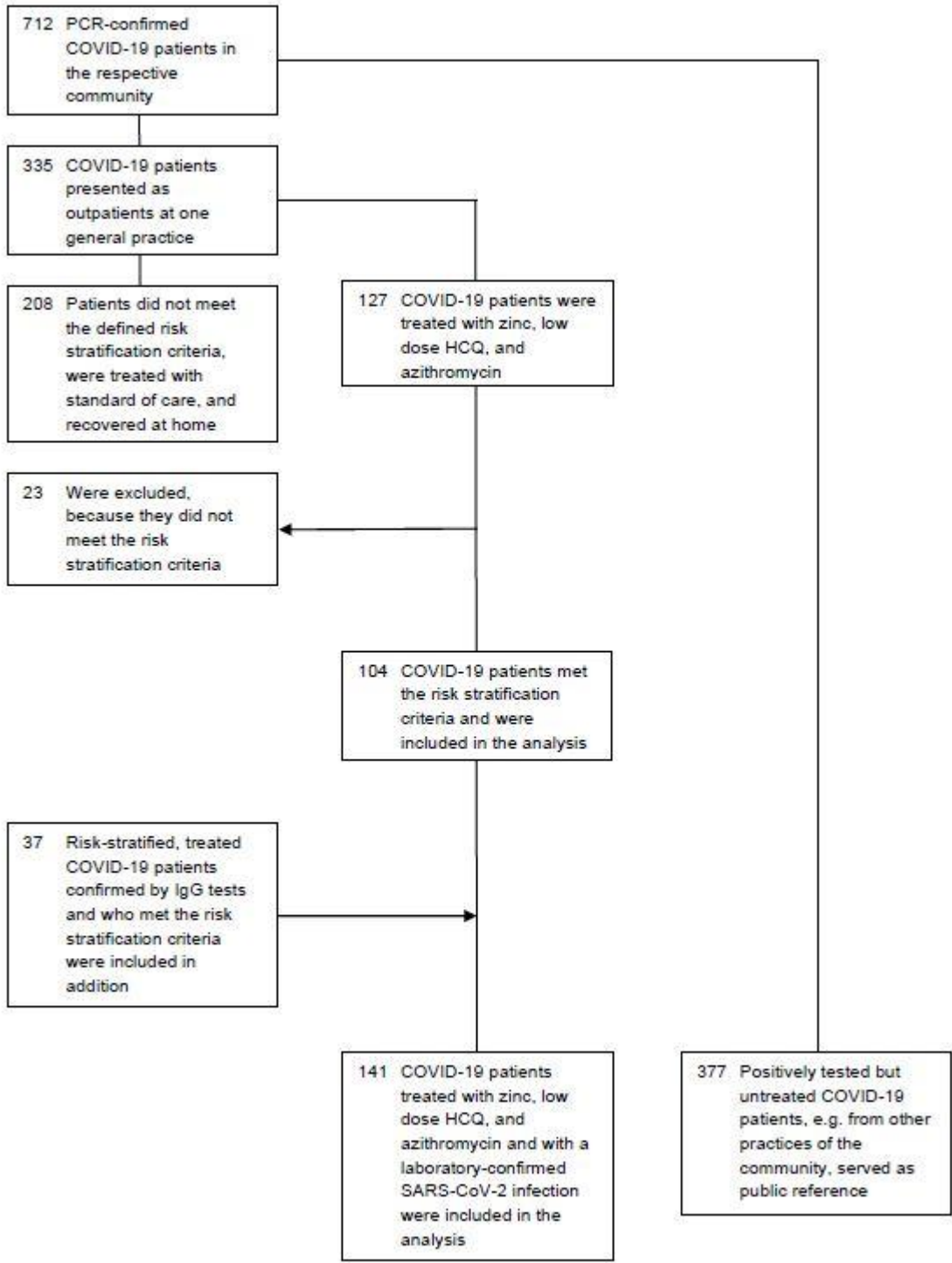


Figure 1: Study population. N=141 COVID-19 patients, all with a laboratory-confirmed SARS-CoV-2 infection, were included in the analysis as treated group. N=377 positively tested COVID-19 patients of the public reference were included in the analysis as untreated group.

Figure 2

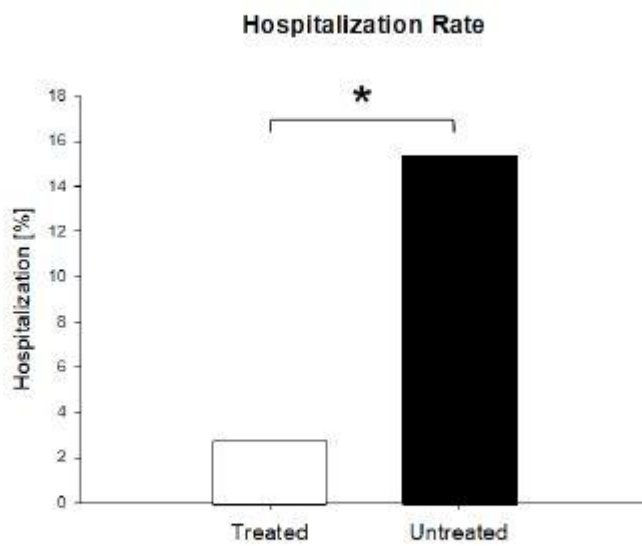


Figure 2: Treatment with the triple therapy zinc, low dose HCQ, and azithromycin was associated with significantly less hospitalizations in comparison to untreated patients of the public reference data. $\chi^2(1, N=518)=14.17, *P<0.001$

Figure 3

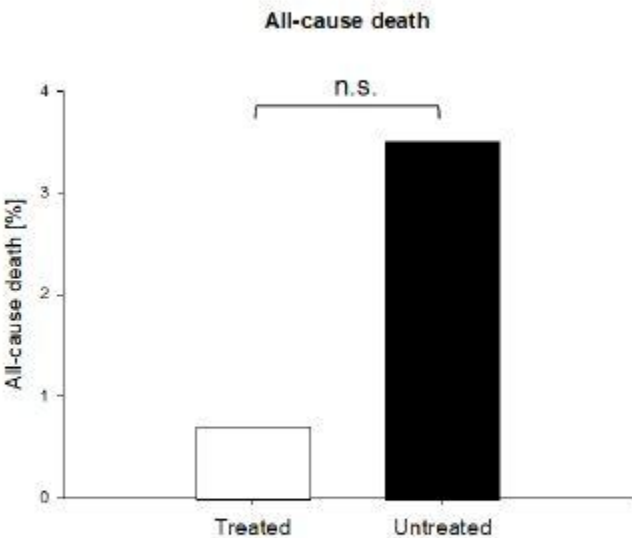


Figure 3: Treatment with the triple therapy zinc, low dose HCQ, and azithromycin was associated with numerically less all-cause deaths in comparison to untreated patients of the public reference data. n.s.=not significant. $\chi^2(1, N=518)=1.98, P=0.16$

Figure 4

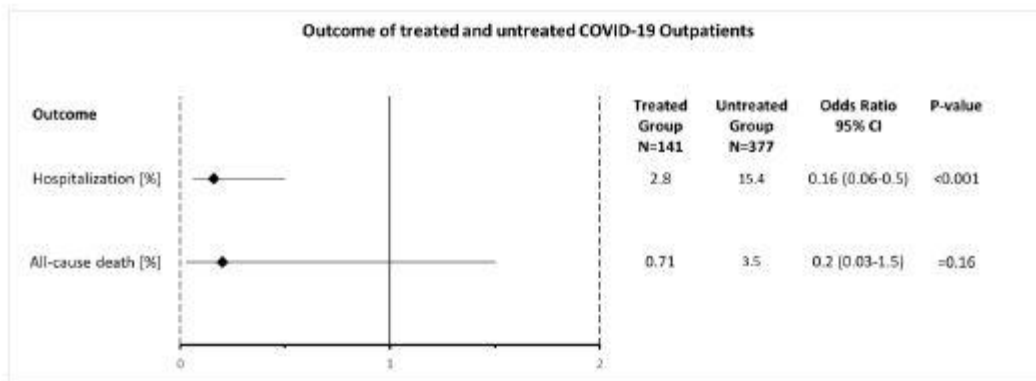


Figure 4: The odds of hospitalization of the treated patient group were 84% less than in the untreated patient group, and was statistically significant ($p < 0.001$). The odds of all-cause death of the treated patient group were 80% less than in the untreated patient group, but did not reach statistical significance ($p = 0.16$). CI=Confidence Interval.

Section Two

Harvey A. Risch, M.D., PH.D.

Item #1

Abstract for:

“Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis”

ABSTRACT

More than 1.6 million Americans have been infected with SARS-CoV-2 and >10 times that number carry antibodies to it. High-risk patients presenting with progressing symptomatic disease have only hospitalization treatment with its high mortality. An outpatient treatment that prevents hospitalization is desperately needed. Two candidate medications have been widely discussed: remdesivir, and hydroxychloroquine+azithromycin. Remdesivir has shown mild effectiveness in hospitalized inpatients, but no trials have been registered in outpatients. Hydroxychloroquine+azithromycin has been widely misrepresented in both clinical reports and public media, and outpatient trials results are not expected until September. Early outpatient illness is very different than later hospitalized florid disease and the treatments differ. Evidence about use of hydroxychloroquine alone, or of hydroxychloroquine+azithromycin in inpatients, is irrelevant concerning efficacy of the pair in early high-risk outpatient disease. Five studies, including two controlled clinical trials, have demonstrated significant major outpatient treatment efficacy. Hydroxychloroquine+azithromycin has been used as standard-of-care in more than 300,000 older adults with multicomorbidities, with estimated proportion diagnosed with cardiac arrhythmias attributable to the medications 47/100,000 users, of which estimated mortality is <20%, 9/100,000 users, compared to the 10,000 Americans now dying each week. These medications need to be widely available and promoted immediately for physicians to prescribe.

Item #2

Original Unedited Accepted Manuscript for

“Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis”

Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis

Harvey A. Risch

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Conflict of Interest: Dr. Risch acknowledges past advisory consulting work with two of the more than 50 manufacturers of hydroxychloroquine, azithromycin and doxycycline. This past work was not related to any of these three medications and was completed more than two years ago. He has no ongoing, planned or projected relationships with any of these companies, nor any other potential conflicts-of-interest to disclose.

Running Head: Outpatient Treatment of High-Risk Covid-19

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Abstract

More than 1.6 million Americans have been infected with SARS-CoV-2 and >10 times that number carry antibodies to it. High-risk patients presenting with progressing symptomatic disease have only hospitalization treatment with its high mortality. An outpatient treatment that prevents hospitalization is desperately needed. Two candidate medications have been widely discussed: remdesivir, and hydroxychloroquine+azithromycin. Remdesivir has shown mild effectiveness in hospitalized inpatients, but no trials have been registered in outpatients.

Hydroxychloroquine+azithromycin has been widely misrepresented in both clinical reports and public media, and outpatient trials results are not expected until September. Early outpatient illness is very different than later hospitalized florid disease and the treatments differ. Evidence about use of hydroxychloroquine alone, or of hydroxychloroquine+azithromycin in inpatients, is irrelevant concerning efficacy of the pair in early high-risk outpatient disease. Five studies, including two controlled clinical trials, have demonstrated significant major outpatient treatment efficacy. Hydroxychloroquine+azithromycin has been used as standard-of-care in more than 300,000 older adults with multicomorbidities, with estimated proportion diagnosed with cardiac arrhythmias attributable to the medications 47/100,000 users, of which estimated mortality is <20%, 9/100,000 users, compared to the 10,000 Americans now dying each week. These medications need to be widely available and promoted immediately for physicians to prescribe.

Keywords: Azithromycin; Covid-19; Doxycycline; Hydroxychloroquine; Remdesivir; SARSCoV-2; Zinc

Abbreviations: AZ, azithromycin; CDC, US Centers for Disease Control; FAERS, FDA Adverse Events Reporting System database; FDA, US Food and Drug Administration; HCQ, hydroxychloroquine; NIH, US National Institutes of Health; QTc, corrected electrocardiogram Q-T-wave duration; RCT, randomized controlled trial; RR, relative risk; R_t , epidemic reproduction number at time t .

Introduction

Aside from the now more than 1.6 million Americans found through testing and public health reporting to be infected with SARS-CoV-2, seropositivity studies in California (1, 2), Colorado (3) and New York City and State (4) suggest that some 10-50-fold larger numbers of people carry antibodies to the virus. The workforce and effort required to carry out contact tracing on these tens of millions of Americans is not practical. While these studies have generated some media criticism, recent similar studies of blood donor samples in the Netherlands found 3% with SARS-CoV-2 antibodies (5), and 5% among household volunteers in Spain (6). Even allowing for some degree of false-positivity of these antibody tests, they still indicate that appreciably larger fractions of the population have been infected than have been characterized by identified reported cases. “Flattening the curve,” by social distancing, mask wearing and staying at home, serves to reduce hospital loads and spread them out over time, but to-date has pushed infection reproduction numbers R_t down only to about 1.0 (7), thus even if maintained, over time very large numbers of people in the US may eventually get the infection. The great majority of infected people are at low risk for progression or will manifest the infection asymptotically. For the rest, outpatient treatment is required that prevents disease progression and hospitalization. Exposures will occur as isolation policies are lifted and people begin to mix, even with various degrees of public isolation such as mask usage and physical separation still in place. Thus, *the key to returning society toward normal functioning and to preventing huge loss of life, especially among older individuals, people with comorbidities, African Americans and Hispanics and Latinos, is a safe, effective and proactive outpatient treatment that prevents hospitalization in the first place.*

All treatments have costs and benefits. In an ideal world, randomized double-blinded controlled clinical trials establish evidence for the relative degree of benefit, and if large enough, for estimates of the frequencies of adverse events. These trials take time to conduct: to get formal approval, to get funding, to enroll enough eligible patients, to wait for the outcomes to occur, and to analyze the data. In the context of the Covid-19 pandemic, we are presently averaging about 10,000 deaths per week in the US, under moderately strong isolation policies that have put more than 36 million people out of work. Results of currently ongoing or planned randomized trials for use of a number of outpatient medications are many weeks or months off, and there are no guarantees that the results for these agents, even if statistically significant, will show sufficient magnitudes of effectiveness to be useful clinically. We are rapidly reaching a breaking point in the ability to maintain the status quo; states have begun the process of lifting their restrictions, and we thus need to evaluate what evidence we do have for promising outpatient treatments.

Review of Evidence

Based on laboratory and other preliminary evidence to-date, among many others, two candidate medication regimens have been widely discussed for outpatient treatment: remdesivir (Gilead Sciences, Inc., Foster City, California), and hydroxychloroquine (HCQ) plus azithromycin (AZ). Remdesivir has been studied extensively in laboratory work and in animals (8) and for other viral diseases and has good biological properties, suggesting utility for SARS-CoV-2 infection. In a study of remdesivir compassionate use in 53 hospitalized patients with severe disease (9), 13% died, which appears lower than what might have been expected without treatment, though greater than the deaths in the placebo arm of the Adaptive COVID-19 Treatment Trial (more below). In a randomized, controlled but relatively underpowered trial in severe non-ventilated hospitalized patients in China (10), benefit vs placebo was not able to be

shown either in improvement or mortality. An appreciable fraction of the remdesivir patients left the trial early because of serious adverse events. The Adaptive COVID-19 Treatment Trial of hospitalized patients with advanced lung disease has released initial results (11) showing that patients on remdesivir had 31% faster recovery than patients on placebo, medians 11 vs 15 days, which difference was statistically significant, but these results involve patients who did indeed survive. Mortality of the two groups, 8.0% vs 11.6%, respectively, was better for remdesivir but not significantly so (P -value=.059). More specific for consideration here, remdesivir has not been studied in outpatient use. The Scientists to Stop Covid-19 “secret” Report (12, p. 7) recommends widespread use of remdesivir, and “as early in infection as possible,” but no actual evidence as yet shows in humans that it would be helpful for routine outpatient circumstances and disease. The FDA recently approved use of remdesivir in the current public-health emergency circumstances (13), but only for patients with “severe disease defined as $SpO_2 \leq 94\%$ on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)” and “administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider.” This approval seems specifically not to allow outpatient use. Symptomatic outpatient infection is a pathologically and clinically different disease than the life-threatening inpatient acute respiratory distress syndrome caused by SARS-CoV-2, thus there is little reason to think that the same treatment would be useful for both (14). In any event, none of 20 currently registered trials is scheduled to provide data on outpatient use of remdesivir, thus we may not know whether it could be used effectively to prevent hospitalization of symptomatic outpatients unless or until it is actually tried that way.

The other suggestion is the combined regimen of HCQ+AZ (or its variant HCQ+doxycycline). The FDA has recently issued guidance (15) to physicians and the general public advising that the combination HCQ+AZ should not generally be used except by critically ill hospital inpatients or in the context of registered clinical trials. The NIH panel for Covid-19

treatment guidelines say essentially the same (16), and a similar statement has been released by the major cardiology societies (17). Numerous reviews of HCQ efficacy and adverse events have been and continue to be published. To my knowledge, *all of these reviews have omitted the two critical aspects of reasoning about these drugs: use of HCQ combined with AZ or with doxycycline, and use in the outpatient setting.* For example, the Veterans' Administration Medical Centers study (18) examined treated *hospitalized* patients and was fatally flawed (19). The same point about outpatient use of the combined medications has been raised by a panel of distinguished French physicians (20) in petitioning their national government to allow outpatient use of HCQ+AZ. It appears that the FDA, NIH and cardiology society positions have been based upon theoretical calculations about potential adverse events and from measured physiologic changes rather than from current real-world mortality experience with these medications and that their positions should be revised. In reviewing all available evidence, I will show that HCQ+AZ and HCQ+doxycycline are generally safe for short-term use in the early treatment of most symptomatic high-risk outpatients, where not contraindicated, and that they are effective in preventing hospitalization for the overwhelming majority of such patients. If these combined medications become standard-of-care, they are likely to save an enormous number of lives that would otherwise be lost to this endemic disease.

What is the evidence for these assertions? Similar to remdesivir, 16 clinical trials of HCQ+AZ are listed in the ClinicalTrials.gov database (21). Of these, only five involve treating outpatients with the combined HCQ+AZ regimen (Web Table 1). For the earliest trial, between now and September, assuming a flat epidemic curve of 10,000 deaths per week, I estimate that approximately 180,000 more deaths will occur in the US before the trial results are known. The CDC has estimated substantially greater numbers of deaths (22).

In this context, we cannot afford the luxury of perfect knowledge and must evaluate, now and on an ongoing basis, the evidence for benefit and risk of these medications (23). Available

evidence of efficacy of HCQ+AZ has been repeatedly described in the media as “anecdotal,” but most certainly is not. The evidence is not perfect either. Each piece of evidence, contained in each study, must be carefully considered and not dismissed because in an ideal world such evidence would fall in a lower part of the evidence-quality triangle. Furthermore, and most critical to the correct understanding of what evidence is available, *evidence for single agents cannot be extrapolated to apply to combined agents, evidence for one biochemical form of a drug cannot be extrapolated to another form, and even more importantly, evidence for utility or lack thereof or toxicity in hospitalized patients cannot be extrapolated to apply to outpatient use*, outpatient use comprising the sole argument for application that I am making in this review.

Thus for example, studies of chloroquine or HCQ used alone do not bear upon evidence for efficacy of HCQ+AZ or HCQ+doxycycline. This point has been argued forcefully by the French doctors (20). The first study of HCQ+AZ (24) was controlled but not randomized or blinded, and involved 42 patients in Marseilles, France. This study showed a 50-fold benefit of HCQ+AZ vs standard-of-care, with P -value=.0007. In the study, six patients progressed, stopped medication use and left the trial before the day-6 planned outcome measure of swabsampled nasopharyngeal viral clearance. Reanalysis of the raw study data elsewhere (25) and by myself shows that including these six patients does not much change the 50-fold benefit. What does change the magnitude of benefit is presentation with asymptomatic or upper respiratorytract infection, vs lower respiratory-tract infection, the latter cutting the efficacy in half, 25-fold vs standard-of-care. This shows that the sooner these medications are used, the better their effectiveness, as would be expected for viral early respiratory disease. The average start date of medication use in this study was day-4 of symptoms. This study has been criticized on various grounds that are not germane to the science, but the most salient criticism is the lack of randomization into the control and treatment groups. This is a valid general scientific criticism, but does not represent epidemiologic experience in this instance. If the study had shown a 2-fold

or perhaps 3-fold benefit, that magnitude of result could be postulated to have occurred because of subject-group differences from lack of randomization. However, the 25-fold or 50-fold benefit found in this study is not amenable to lack of randomization as the sole reason for such a huge magnitude of benefit. Further, the study showed a significant, 7-fold benefit of taking HCQ+AZ over HCQ alone, P -value=.035, which cannot be explained by differential characteristics of the controls, since it compares one treatment group to the other, and the treated subjects who received AZ had more progressed pneumonia than the treated subjects receiving HCQ alone, which should otherwise have led to worse outcomes. The study has also been described as “small,” but that criticism only applies to studies not finding statistical significance. Once a result has exceeded plausible chance finding, greater statistical significance does not contribute to evidence for causation (26). No different conclusion would have resulted had a study with 1000 patients found the same 50-fold benefit but with a P -value of 10^{-10} . Study size limitation only applies to studies having findings within the play of chance. That is not the case here.

A second study of the Marseilles group (27) involved 1061 patients tested positive for SARS-CoV-2 and treated with HCQ+AZ for at least 3 days and followed for at least 9 days. The authors state “No cardiac toxicity was observed.” Good clinical outcome and virological cure were seen in 973 patients (92%). Five patients died, and the remainder were in various stages of recovery.

The third piece of evidence involves the cohort of 1450 patients treated by Dr. Vladimir Zelenko of Monsey, NY. Dr. Zelenko has released a two-page report (28) describing his clinical reasoning and procedures, dosing conditions and regimen, and patient results through April 28. Symptomatic patients presenting to Dr. Zelenko were treated with five days of HCQ+AZ+zinc sulfate if they were considered high-risk, as evidenced by one or more of: age 60 years or older; high-risk comorbidities; body-mass index>30; mild shortness of breath at presentation. Patients

were considered to have Covid-19 based on clinical grounds and started treatment as soon as possible following symptom onset, rather than delaying for test results before starting treatment. Of the 1450 patients, 1045 were classified as low-risk and sent home to recuperate without active medications. No deaths or hospitalizations occurred among them. Of the remaining 405 treated with the combined regimen, 6 were ultimately hospitalized and 2 died. No cardiac arrhythmias were noted in these 405 patients.

The fourth relevant study was a controlled non-randomized trial of HCQ+AZ in 636 symptomatic high-risk outpatients in São Paulo, Brazil (29). All consecutive patients were informed about the utility and safety profile of the medications and offered the treatment, and those who declined (n=224) comprised the control group. Patients were monitored daily by telemedicine. The study outcome was need for hospitalization, defined as clinically worsening condition or significant shortness of breath (blood oxygen saturation <90%). Even though the severities of all of the recorded flu-like signs and symptoms and of important comorbidities (diabetes, hypertension, asthma, stroke) were substantially greater in the treated patients than the controls, the need for hospitalization was significantly lower, 1.2% in patients starting treatment before day 7 of symptoms, 3.2% for patients starting treatment after day 7, and 5.4% for controls, P -value<.0001. No cardiac arrhythmias were reported in the 412 treated patients. The most common side effect of treatment was diarrhea (16.5%), but 12.9% of treated patients presented with diarrhea before treatment began.

Finally, a small study is ongoing in a long-term care facility in Long Island, NY. This study has been employing HCQ+doxycycline rather than HCQ+AZ for treatment of high-risk Covid-19 patients. Doxycycline itself has antiviral activity against SARS-CoV-2 at in vitro concentrations 5.6 μ M median (30). Among the first 54 residents treated in the Long Island study, 6 were hospitalized and 3 (5.6%) died (31). An unofficial update of these data indicates that of about 200 high-risk patients treated with HCQ+doxycycline, 9 (4.5%) have died.

The two non-randomized but controlled trials provide important evidence, if not “proof,” for the major efficacy of early use of HCQ+AZ against SARS-CoV-2 infection in symptomatic high-risk outpatients. What can be said about the uncontrolled large case series of treated patients? Standard published case reports provide clinical evidence of the possibility of an exposure-outcome relationship, but not of the regularity, magnitude or representativeness of such a relationship. The same can be said of case series reports, meaning that subject entry into the series is not necessarily well-defined and no denominator information is provided from which to gauge what the series represents. However, a large series in the context of known risks of mortality or adverse events can allow for ballpark estimates of the denominator and thus provide a reasonable frame of reference for whether the outcomes likely represent beneficial or harmful results. For example, among Connecticut cases 60 years of age or older, at present the mortality is 20% (32). Thus, it would be ballpark to estimate that some 20% of the 1466 treated high-risk patients in the Zelenko and Marseilles cohorts would have died without outpatient HCQ+AZ treatment, 293 patients, compared to the 7 who did die. An alternative is to use the 12-13% mortality of hospitalized patients in the placebo arms of the remdesivir trials (10, 11). This would give about 180 expected deaths.

Adverse Events

Both proposed drug regimens have shown side effects. Remdesivir, in its phase-3 trial of 10-day vs 5-day therapeutic courses in hospitalized patients, produced a range of adverse events in more than 70% of patients in both treatment arms (33). Adverse events requiring medication discontinuation were many fewer, 5% in the 5-day group and 10% in the 10-day group. In the Chinese trial, 12% of remdesivir patients stopped the medication before the end of the 10-day treatment because of drug-related adverse events (10).

For HCQ+AZ use, the argued issue concerns fatal cardiac arrhythmias: the warnings issued by the FDA, the NIH and the cardiology societies. Indeed, both HCQ and AZ produce QT prolongation, rare instances of fatal Torsades de Pointes and long QT-interval syndrome. A number of essays by cardiologists published in *JAMA* and other journals have anxiously warned about these risks, but have not examined mortality from them. The sole question is whether these fatal events, or even any fatal cardiac arrhythmia events, would occur with enough frequency that general treatment of non-contraindicated high-risk outpatients by HCQ+AZ would outweigh benefit in preventing hospitalization and mortality. A number of studies have examined hospital inpatient use, but these studies have had major flaws discussed at length in the literature, not least of which is that patients hospitalized with multiple medical problems and more-advanced disease do not represent the mortality experience of outpatient use of these medications in patients otherwise well enough not to be hospitalized. One source of data on mortality associated with these medications is the FDA FAERS database (34). Examination of the database for adverse events reported from the beginning of the database in 1968 through 2019 and into the beginning of 2020, shows for hydroxychloroquine 1064 adverse event reports including 200 deaths for the total of cardiac causes that could be both specifically and broadly classified as rhythm-related. Of these, 57 events including 10 deaths were attributed to Torsades de Pointes and long QT-interval syndrome combined. This concerns the entirety of HCQ use over more than 50 years of data, likely millions of uses and of longer-term use than the 5 days recommended for Covid-19 treatment. For AZ use, the numbers of reported Torsades de Pointes and long QT-interval syndrome events total 37, of which 2 deaths. FAERS data are generated by patient, physician and pharmacist report initiation and likely underrepresent true event occurrences. However, even if the true numbers were 10-fold larger, they would still be minuscule compared to the amounts of medication usage. How much the risk of QT prolongation would be enhanced with HCQ and AZ taken together is unknown, but the

Physicians' Desk Reference (35) says that coadministration of these medications risks “additive QT prolongation.” Not multiplicative. “Pharmacokinetic drug interactions associated with the highest risk of TdP include antifungal agents, macrolide antibiotics (except azithromycin)” (36, p. 139). Nevertheless, even if the combined HCQ+AZ produced a 10-fold higher incidence of fatal Torsades de Pointes and long QT-interval syndrome than either agent alone, and even if both events were 10-fold underreported in FAERS, thus hypothetically giving 1200 fatal events, that would still be very small compared to the millions of uses of these medications that the FAERS database represents. Therefore, while it is established that HCQ+AZ lengthens the QTc interval by 18-55ms on average (37-40), in 40, 84, 90 and 98 hospitalized severely ill patients in the four studies, respectively, treated with these medications and having this lengthening, a total of one case of Torsade de Pointes occurred and it was not fatal—there were no deaths.

Substantial fractions of these hospitalized patients were taking diuretics, which may be contraindicated for HCQ+AZ use in the first place. This arrhythmia issue is a real, physiologically measurable effect of the use of these combined medications, but fatal arrhythmia outcomes are so rare that they are of much lesser clinical significance than the hospitalization and mortality that the drugs prevent. This fact is also clear from the lack of any cardiac arrhythmia events or arrhythmia mortality noted in the 405 Zelenko patients or the 1061 Marseilles patients or the 412 Brazil patients. Patients were not enrolled in these studies if they had known histories of QTc prolongation. History of cardiac arrhythmia or other possible contraindications for use of HCQ or AZ or doxycycline is a normal part of workup and clinical judgement in physician choice to use these medications and how to monitor the patients (see Web Appendix).

Further evidence of the real-world unimportance of arrhythmia and other cardiovascular adverse event endpoints of HCQ+AZ use is given in the large Oxford-based record-linkage study (41, 42). Fourteen large medical-records databases were examined for all-cause mortality and

for 15 specified classes of adverse events among hundreds of thousands of patients with rheumatoid arthritis who had used these drugs. First, 323,122 users of HCQ+AZ were compared to 351,956 users of HCQ+amoxicillin. No significant difference in all-cause mortality was seen: as reported by the authors, relative risk (RR)=1.36, P -value=.10, and as I calculate from the data provided by the authors in their supplement to the paper (42), RR=1.18, P -value=.37; either way, a null association within the range of chance. However, the authors selectively presented from among the 15 analyzed endpoints the three most significant associations: cardiovascular mortality RR=2.19, P -value=.0088; chest pain/angina RR=1.15, P -value=.0027; and heart failure RR=1.22, P -value=.027. What is misrepresented in the authors' presentation of these data in this way is that these three outcomes were not individually specified to be of more interest than any of the other 12 specific outcomes that they examined, and they did not correct their calculated levels of statistical significance for the 15 classes of outcomes. In lay terms, a fishing expedition. When accounting is done, by the standard Bonferroni correction of multiple comparisons, the respective P -values are .12, .040 and .35. The large amount of data in this study thus shows that there is no significant relationship of HCQ+AZ use vs HCQ+amoxicillin use for any of the 15 outcomes specified or for all-cause mortality, except a just-barely significant association with chest pain/angina, with a 15% higher risk which even if a true finding would still be of little clinical import for a relatively infrequent outcome in the context of the mortality to be saved by HCQ+AZ use in widespread symptomatic high-risk outpatient Covid-19 treatment.

Second, the stated concern of the FDA and NIH advisories and the cardiology society opinion restricting use of HCQ+AZ was for fatal Torsades de Pointes and long QT-interval syndrome, two rare types of cardiac arrhythmias, as well as for cardiac arrhythmias in general. The Oxford study (41, 42) examined cardiac arrhythmia outcomes and obtained for its random effects meta-analysis result, RR=1.08, P -value=.36 for HCQ+AZ use vs HCQ+amoxicillin use.

The fixed-effects meta-analysis $RR=1.04$, $P\text{-value}=.41$. This study clearly demonstrates that cardiac arrhythmia adverse events are not appreciably increased by combining HCQ with AZ. The same study compared HCQ use to sulfasalazine use and again found no difference in cardiac arrhythmia risk: for HCQ, a slightly lower $RR=0.89$, $P\text{-value}=.13$. The subjects analyzed in the Oxford study were largely older adults with multiple comorbidities in addition to rheumatoid arthritis.

Finally, the Oxford study allows for a direct estimate of the number of arrhythmia events attributable to HCQ+AZ use (41, 42). Among 306,106 people taking sulfasalazine (which is known not to produce QT prolongation), 877 with cardiac arrhythmias were identified, 0.287%. In 320,589 people taking HCQ+AZ, 1,068 had arrhythmias, 0.333%. The difference, 0.047% or 47/100,000 older multicomorbidity patients taking HCQ+AZ, is attributable to the HCQ+AZ use. These are events, not fatalities. As noted above, fatalities according to FAERS comprise <20% of HCQ-related arrhythmia events. The maintenance HCQ dose in the Oxford study patients, 200 mg/day, gives as large or larger plasma drug levels as five days of HCQ at 400 mg/day, the recommended dose for outpatient Covid-19. These very small numbers of arrhythmias, as well as the null results in this very large empirical study should therefore put to rest the anxieties about population excess mortality of HCQ+AZ outpatient use, either from cardiac arrhythmias, or as mortality from all causes.

This discussion thus shows that the FDA, NIH and cardiology society warnings about cardiac arrhythmia adverse events, while appropriate for theoretical and physiological considerations about use of these medications, are not borne out in mortality in real-world usage of them. Treatment-failure mortality will be much higher, but even that pales in comparison to the lives saved. It would therefore be incumbent upon all three organizations to reevaluate their positions as soon as possible. It is unclear why the FDA, NIH and cardiology societies made their recommendations about HCQ+AZ use now, when the Oxford study (41, 42) analyzed

323,122 users of HCQ+AZ compared to 351,956 users of HCQ+amoxicillin, i.e., that the combination of HCQ+AZ has been in widespread standard-of-care use in the US and elsewhere for decades, use comparable to HCQ+amoxicillin as if it just involved an alternate antibiotic choice, this use predominantly in older adults with multiple comorbidities, with no such strident warnings about the use given during that time. I note that since doxycycline is believed to cause even fewer cardiac arrhythmias than AZ, in patients where that is a concern (43), the long-term care-facility evidence suggests that HCQ+doxycycline likely will work about as well.

Discussion

Given that a detailed and dispassionate review of all of the available relevant evidence leads to conclusions about outpatient HCQ+AZ use different than those of the FDA and NIH panels (which comprise wider expertise than the cardiology societies), I address how different underlying scientific worldviews might be involved. This is particularly reflected in the Scientists to Stop Covid-19 position about remdesivir use “as early as possible,” i.e., early outpatient use implied (12, p. 5). All but one of the scientists on the Scientists to Stop Covid-19 panel are laboratory or clinical scientists; only one is an epidemiologist. Their recommendation for remdesivir use as early as possible was made without either FDA approval or RCT evidence of efficacy in the outpatient context. This recommendation therefore appears to be an extrapolation from animal and laboratory data and from use in severely ill hospitalized patients. However, a history of epidemiology shows numerous instances of failed extrapolation from animals to humans. “Animal research on almost any topic of epidemiologic interest is so heterogeneous and inadequately synthesized that it is possible to selectively assemble a body of evidence from the animal and in-vitro studies that support almost any epidemiologic result.” (44, p. 221) For example, some carcinogens have been affirmed in animal studies but not shown in human studies (acrylamide, alar, cyclamate, red dye #2, saccharin) (44). This is in part why the

FDA has an approval system of phased RCTs leading to safety and efficacy of use in humans, *in the specific contexts* in which the drug is intended. It is not a question of off-label use, but of who are the patients for which to use the medication. For Covid-19, inpatient acute respiratory distress syndrome is typically a florid immune-system overreaction, whereas initial outpatient illness is a viral multiplication problem involving the beginnings of immune response. These are different diseases. Thus, how well remdesivir might perform in outpatients won't be known until it is tried in typical outpatient circumstances, whether in RCTs or in any other unbiased systematic study of such use. Further, to the degree that remdesivir is similar in temporal characteristics to an antiviral like Tamiflu, it would be used in general societal contexts where patients must first recognize that they might have symptoms of the disease and not something else and go to their physicians or clinics for care, and either be rapidly tested positive with an assay that has negligible false negatives, or be symptomatic enough for the disease to be clinically distinguished and diagnosed, but definably positive in this way not more than two days after symptoms start. This is a very narrow temporal window to be definitive and to obtain full antiviral effectiveness, and could be difficult to achieve in general in the mass-treatment circumstances that we are facing. So regardless of the strength of the *implied* evidence of outpatient efficacy when given shortly after the start of symptoms, remdesivir efficacy might be substantially less in the context of actual population outpatient usage. This is another reason why empirical studies of medication use in the full context of application are needed.

The extrapolation from laboratory theory to empirical use also seems to underlie resistance to the idea that combined HCQ regimens could work for early outpatient use. HCQ is known to interfere with toll-like receptor signaling, reducing dendritic cell activation and immune response. This would seem to be counterproductive for suppressing SARS-CoV-2 multiplication in early treatment. Again, in extrapolation from physiologic theory to human data, the epidemiologic data are definitive. The fact that epidemiologic data to-date show strong

evidence for efficacy of combined HCQ+AZ in early outpatient treatment, even if not “proof” yet at the level of several successful RCTs, is evidence that this medication regimen works in that context. The clash in scientific worldviews is that basic and clinical scientists seem to feel that biological and drug-development evidence for medication use in non-human and nonoutpatient contexts can be extrapolated to recommendations for outpatient use without benefit of RCT evidence but don’t accept epidemiologic evidence without RCTs, whereas epidemiologists have had career experience with laboratory and animal evidence that did not hold up under epidemiologic study, but do reason by including all types of epidemiologic study designs and derive causal conclusions in the standard way following Hill’s Aspects (26) on the basis of strong totality of evidence, sometimes even without RCT evidence. There are contexts where each approach is valid. However, it is not my point to say that remdesivir has little evidence to support its potential outpatient utility, only efficacy considerations that have not been addressed and that could lead to lack of efficacy under general use, but that HCQ+AZ has been directly studied in actual early high-risk outpatient use with all of its temporal considerations and found empirically to have sufficient epidemiologic evidence for its effective and safe employment that way, and that requiring delay of such general use until availability of additional RCT evidence is untenable because of the ongoing and projected continuing mortality. No studies of Covid-19 outpatient HCQ+AZ use have shown higher mortality with such use than without, cardiac arrhythmias included, thus there is no empirical downside to this combined medication use.

Some of my medical colleagues still prefer to wait until more studies are done and stronger evidence such as from RCTs becomes available, and government and professional advisory panels do reevaluate the evidence. I strongly urge these panels to reconsider the data and arguments discussed above. Substantial fractions of physicians treating Covid-19 patients in Europe and elsewhere report use of HCQ+AZ: 72% in Spain, 49% in Italy, 41% in Brazil, 39% in Mexico, 28% in France, 23% in the US, 17% in Germany, 16% in Canada, 13% in the UK

(45), much of the non-US use in outpatients. HCQ+AZ has been standard-of-care treatment at the four New York University hospitals, where a recent study showed that adding zinc sulfate to this regimen significantly cut both intubation and mortality risks by almost half (46). The French physicians are insistent that with careful clinical judgement and supervision, these medications are safe and should be used as early as possible for outpatients, and they provide a detailed clinical guide to their use (20). Until we have quantitative evidence for the utility and safety of other medications for preventing hospitalization and mortality in high-risk Covid-19 outpatients, the urgency of current mass mortality requires an immediate application of the best that we have available, even if knowledge is imperfect and even if yet unproven to the standards of doubleblinded RCTs. This problem will get even worse as states and cities yield to the acute pressure at this moment to begin lifting stay-at-home restrictions and even more people become infected. Some people will have contraindications and will need other agents for treatment or to remain in isolation. But for the great majority, I conclude that HCQ+AZ and HCQ+doxycycline, preferably with zinc (47) can be this outpatient treatment, at least until we find or add something better, whether that could be remdesivir or something else. It is our obligation not to stand by, just “carefully watching,” as the old and infirm and inner city of us are killed by this disease and our economy is destroyed by it and we have nothing to offer except high-mortality hospital treatment. We have a solution, imperfect, to attempt to deal with the disease. We have to let physicians employing good clinical judgement use it and informed patients choose it. There is a small chance that it may not work. But the urgency demands that we at least start to take that risk and evaluate what happens, and if our situation does not improve we can stop it, but we will know that we did everything that we could instead of sitting by and letting hundreds of thousands die because we did not have the courage to act according to our rational calculations.

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Web Material

Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis

Harvey A. Risch

Web Table 1: Randomized Controlled Trials of Hydroxychloroquine plus

Azithromycin in Outpatients, Registered in ClinicalTrials.gov2

Web Appendix: General Contraindications for Use of Hydroxychloroquine

plus Azithromycin Together3

Web Table 1. Randomized Controlled Trials of Hydroxychloroquine plus Azithromycin in Outpatients, Registered in ClinicalTrials.gov

| Trial Number | Location | Current Status | Planned Enrollment Completion | Planned Results |
|---------------------|--|---|--------------------------------------|------------------------|
| NCT04371406 | Paris, France | Recruiting | August 2, 2020 | September 2, 2020 |
| NCT04354428 | Multi-site US, based at Univ. Washington | Recruiting | End of July, 2020 | October, 2020 |
| NCT04370782 | St. Francis Hospital, Roslyn, New York | Recruitment of patients presenting at emergency room; starting soon | September 30, 2020 | October, 2020 |
| NCT04324463 | Hamilton, Ontario, Canada | Recruiting | September 30, 2020 | December, 2020 |
| NCT04358068 | Multi-site US, based at UCLA and UCSD | Recruitment starting soon | October 9, 2020 | March, 2021 |

Web Appendix:

General Contraindications for Use of Hydroxychloroquine plus Azithromycin Together

Some patients may have contraindications for taking hydroxychloroquine+azithromycin together. Typical contraindications include: history of QT prolongation or cardiac arrhythmia, psoriasis, porphyria, hepatic disease, alcoholism, G6PD deficiency, HIV, neurological diseases with myopathy, seizure disorders, women breastfeeding, hypoglycemia or diabetes mellitus, uncorrected hypocalcemia, hypokalemia or hypomagnesemia, hypothyroidism, history of myocardial infarction or cardiac failure, and various interacting medications including diuretics, antifungals, etc. (1). Some patients with these conditions may be able to take HCQ+doxycycline safely. All of these circumstances need to be evaluated by treating physicians, who may elect to obtain screening ECGs prior to treatment and at some point or points during treatment if indicated. Portable cell-phone based FDA-approved ECG sensors with QTc functionality are available (2, 3) and could be loaned out on an outpatient basis and mailed back in and disinfected.

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Item #3

AJE-00843-2020

RESPONSES TO PUBLISHED ARTICLE

Response to: "Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients" and "Re: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis"

| | |
|------------------|---|
| Journal: | <i>American Journal of Epidemiology</i> |
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**Response to: “Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients”
and “Re: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that
Should be Ramped-Up Immediately as Key to the Pandemic Crisis”**

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Abbreviations: AZ, azithromycin; Dox, doxycycline; HCQ, hydroxychloroquine; SOC, standard-of-care

Financial Support: None

Running Head: Outpatient Treatment of High-Risk Covid-19

Conflicts of Interest: Dr. Risch acknowledges past advisory consulting work with two of the more than 50 manufacturers of hydroxychloroquine, azithromycin and doxycycline. This past work was not related to any of these three medications and was completed more than two years ago. He has no ongoing, planned or projected relationships with any of these companies, nor any other potential conflicts-of-interest to disclose.

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4 Dr. Korman's thesis is that no available treatments are effective in preventing hospitalization for
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6 the overwhelming majority of COVID-19 patients, and that potential hazards are associated with
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8 use of hydroxychloroquine (HCQ) + azithromycin (AZ) (1). The studies that I reviewed (2)
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10 contradict this. Dr. Korman superficially describes the same studies that I discussed at length,
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12 except with negative adjectives and numerous terms in "quotation" marks to imply, without
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14 evidence, their lack of validity. He calls all these studies "anecdotal," to distinguish from the
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16 "magic" of randomized controlled trials (3), when government medical and scientific regulatory
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18 agencies of western countries around the world routinely use epidemiologic evidence to establish
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20 facts of causation, benefit and harm (4). This disingenuous argument has been discussed at
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22 length elsewhere (5). Dr. Korman's only novel point is that macrolide antibiotics such as AZ can
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24 lead to development of antibiotic resistance. Such instances can occur but are uncommon, and
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26 this issue has seemingly not been of substantial concern in the hundreds of millions of uses of
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28 AZ world-over during the past 30 years.
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34 Drs. Peiffer-Smadja and Costagliola (6) discuss the data in some of the studies that I reviewed.
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36 They first question the small non-randomized trial by Gautret et al. (7). I also have concerns
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38 about subject baseline differences between the treated and untreated subjects in that study and
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40 thus limit my conclusions to the 26 treated patients. Gautret et al. (7) provided individual-
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42 subject data on all 26 which enabled me to carry out my own Cox-regression analyses. The data
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44 are that 14 patients received HCQ only, 6 received HCQ+AZ, and under intention-to-treat
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46 principles, 6 were lost to follow-up and had received 3 days or fewer of HCQ but were
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48 unspecified as to receipt of AZ. I conducted my analyses starting with the 20 subjects with
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50 completed medication usage, and then included bracketing of the unknown-exposure subjects,
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52 first assuming all had taken HCQ+AZ and then only HCQ, and in each case, whether the 6
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3 subjects presented with upper vs lower respiratory infections. In the 20 main subjects, for
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5 HCQ+AZ vs HCQ alone, the hazard ratio for viral clearance = 7.4 (95%CI 1.12-48.4). Across
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7 the four bracketed-combination analyses, the hazard ratios ranged from 3.5 to 8.0 and *P*-values
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9 from .078 to .021. Drs. Peiffer-Smadja and Costagliola need to use the outcome event times in
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11 Cox regression in order to obtain proper *P*-values. They also say that the trial was not conducted
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13 in outpatients and therefore cannot be applied to outpatients. However, the Marseille hospital
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15 was used as both an outpatient clinic and a small inpatient facility for a city-wide COVID-19
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17 population screening and treatment program and patients were seen as daily “inpatients” as well
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19 as stayed overnight in it. Many of the patients in the Gautret et al. study were asymptomatic or
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21 very mildly symptomatic and would be treated as outpatients in most circumstances.
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27 Second, Drs. Peiffer-Smadja and Costagliola refer to the larger Marseille screening program (8).
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29 I have discussed those data at length in my response (9) to Dr. Fleury (10). Third, they label a
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31 carefully performed, sequential-patient non-randomized controlled clinical trial an “unpublished,
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33 poorly designed studies whose quality is even lower than the papers discussed above.” I disagree
34
35 with this characterization as it is unsupported by the evidence. Fourth, Drs. Peiffer-Smadja and
36
37 Costagliola assert that the Boulware prevention trial (11) demonstrates lack of treatment
38
39 efficacy. That prevention trial is not relevant to treatment of high-risk outpatients, because
40
41 virtually all its subjects were low-risk; it would be difficult for any active treatment to do much
42
43 better than the one hospitalization observed among the 58 test-positive placebo patients. In fact,
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45 a preventive medication that allows subjects to develop antibodies while protecting them from
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47 severe disease and hospitalization is a better goal than blocking infection altogether. Fifth, Drs.
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49 Peiffer-Smadja and Costagliola take issue with the use of case series of treated patients. In the
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3 mass-mortality circumstances we face, a cohort of 400 treated high-risk outpatients with one or
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5 two deaths can only be considered informative about the fact of treatment efficacy.
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8 Finally, in pandemic times when months and years of delay cannot be tolerated before large
9
10 randomized controlled trials are completed, it is possible to quibble with apparent imperfections
11
12 in almost any study. That misses the forest for the trees. Since my paper (2) discussing five
13
14 studies was published, data from seven other studies of high-risk outpatients have become
15
16 available, all showing the same substantial and significant benefit of use of HCQ along with AZ
17
18 or other companion medications (Table 1). Two additional large studies of hospital patients
19
20 given HCQ within 48 hours of admission show significant benefit adjusted for age and
21
22 comorbidities (12, 13), and a meta-analysis of studies to-date completely demonstrates this
23
24 benefit (14). Perhaps even more important, the exponential COVID-19 mortality explosion in
25
26 the northern state of Pará, Brazil (15), reversed direction, downward dramatically about 5 weeks
27
28 after a shipment of 75,000 doses of AZ and 90,000 doses of HCQ began to be distributed to
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30 infected individuals (Figure 1). No such decline has been observed in the rest of Brazil. This is
31
32 a compelling, large-scale experiment demonstrating efficacy of HCQ+AZ in saving lives of
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34 high-risk people infected with SARS-CoV-2.
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For Peer Review

Table 1. Studies Examining High-Risk Outpatient COVID-19 Disease Treated Early with HCQ

| Principal Investigator | Location | Subject Status | Number Treated with HCQ | Number of Comparison Subjects | Other Medications with HCQ | Comparison-Subject Medications | Outcome | Direction of Benefit | RR (95% CI), Statistical Significance or Number of Deaths | Reference |
|------------------------|------------------------------|--------------------|-------------------------|-------------------------------|----------------------------|--|--------------------------------|----------------------|---|-----------------------|
| P. Gautret | Marseille, France | Mixed older adults | 6 | 14 | AZ | HCQ alone | Nasopharyngeal viral clearance | Reduced risk | 7.4 (1.12-48.4) | (6) |
| V. Zelenko | Kiryas Joel, NY | High-risk | 405 (series 1) | -- | AZ, zinc sulfate | -- | Mortality | Reduced risk | 2 deaths/405 | (16) |
| V. Zelenko | Kiryas Joel, NY | High-risk | 400 (series 2) | -- | AZ, zinc sulfate | -- | Mortality | Reduced risk | 0 deaths/400 | PC ^a |
| R. Barbosa Esper | São Paulo, Brazil | Mixed older adults | 412 | 224 | AZ | SOC | Hospitalization | Reduced risk | 0.35 (0.14-0.87) | (17) |
| I. Ahmad | Long Island, NY Nursing Home | High-risk | 200 | -- | Dox | -- | Mortality | Reduced risk | 9 deaths/200 | (18), PC ^b |
| J.-C. Lagier | Marseille, France | High-risk | 199 | 199 | AZ | Propensity-score matched; HCQ or AZ alone or neither | Mortality | Reduced risk | 0.41 (0.17-0.99) | (19) |

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| 4 | | | | | | | | | | | |
| 5 | M. Leriger | Indiana Nursing Homes | High-risk | 105 | 113 | None, AZ, Dox | SOC, +AZ or Dox | Mortality | Reduced risk | $P < .05$ | PC ^c |
| 6 | | | | | | | | | | | |
| 7 | | | | | | | | | | | |
| 8 | | | | | | | | | | | |
| 9 | L. Kacmar | Aurora, IL | High-risk | 68 | -- | AZ | -- | Mortality | Reduced risk | 0 deaths/68 | PC ^d |
| 10 | | | | | | | | | | | |
| 11 | | | | | | | | | | | |
| 12 | S. Fonseca | Brazil HMO | High-risk | 159 | 558 | Prednisone | Neither HCQ nor Prednisone | Hospitalization | Reduced risk | $P < .05$ | PC ^e |
| 13 | | | | | | | | | | | |
| 14 | | | | | | | | | | | |
| 15 | | | | | | | | | | | |
| 16 | B. Procter | McKinney, TX | High-risk | 50 | -- | AZ, zinc sulfate, losartan, aspirin | -- | Mortality | Reduced risk | 0 deaths/50 | PC ^f |
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| 20 | | | | | | | | | | | |
| 21 | S. Crawford | Festus, MO Nursing Home | High-risk | 52 | -- | Rehydration | -- | Mortality | Reduced risk | 0 deaths/52 | (20) |
| 22 | | | | | | | | | | | |
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| 24 | | | | | | | | | | | |
| 25 | | | | | | | | | | | |
| 26 | B. Tyson | El Centro, CA | High-risk | 219 | -- | AZ (2 with Dox) | -- | Mortality | Reduced risk | 0 deaths/219 | PC ^g |
| 27 | | | | | | | | | | | |
| 28 | | | | | | | | | | | |

Abbreviations: AZ, azithromycin; Dox, doxycycline; HCQ, hydroxychloroquine; PC, personal communication as described in the following footnotes; SOC, standard-of-care.

^a Vladimir Zelenko MD, PC, Family Practice, Monroe, NY, personal communication, 2020.

^b Imtiaz Ahmad, 21st Century Oncology, Inc., Fort Myers, FL, personal communication, 2020.

^c Monica Leriger, American Senior Communities, Indianapolis, IN, personal communication, 2020.

^d Lawrence Kacmar, The Center for Primary Care and Sports Medicine, Aurora IL, personal communication, 2020.

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^e Sílvia Fonseca, Hospital São Francisco, Ribeirão Preto, Brazil, personal communication, 2020.

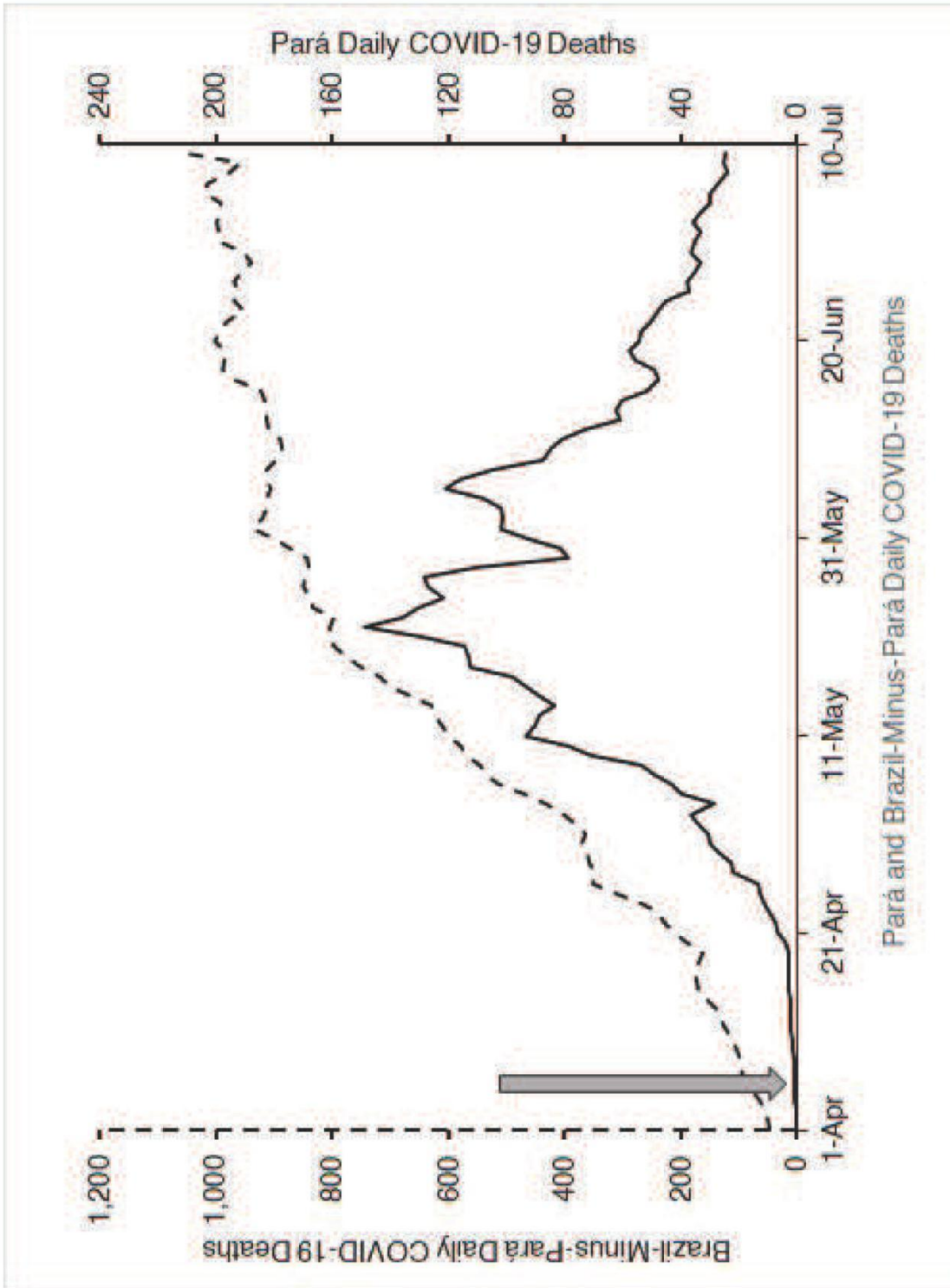
^f Brian Procter, McKinney Family Medicine, McKinney TX, personal communication, 2020.

^g Brian Tyson, All Valley Urgent Care, El Centro, CA, personal communication, 2020.

For Peer Review

Figure Legend

Figure 1. Pará and Brazil-Minus-Pará Daily COVID-19 Deaths, April 1, 2020 through July 9, 2020. Points plotted are 7-day symmetrical moving averages of the raw data, which are available from CORONAVÍRUS BRASIL as posted daily (15). Solid line, daily COVID-19 deaths in Pará; dashed line, daily COVID-19 deaths in the rest of Brazil. The daily numbers of newly identified COVID-19 cases in Pará were increasing through May 28 and then have stayed roughly flat at about 2,100 per day, whereas the daily numbers of new cases in the rest of Brazil have risen throughout the period (data not shown). On April 6, the public hospital network of Pará purchased 75,000 doses of azithromycin (AZ) and 90,000 doses of hydroxychloroquine (HCQ) and started distributing them to infected individuals over the next few weeks; the Hapvida HMO hospitals in the state also acquired the medications and started using them in the same period (Alexandre Wolkoff, Hapvida Saúde HMO, Fortaleza, Brazil, personal communication, 2020). The gray arrow denotes when the medications were initially purchased. Approximately five weeks after the medications began distribution, the mortality numbers in Pará turned down dramatically. In Pará, the July 2 mortality ($n=40$) as a fraction of June 2 incidence ($n=2,068$) = 1.9%, whereas the same for the rest of Brazil was $1,026/23,733 = 4.3\%$. Brazil outside of Pará was not systematically using HCQ and AZ over the time period shown in the figure.



Item #4

Resume CV

Curriculum Vitae for: HARVEY A. RISCH, M.D., PH.D.

Professor of Epidemiology
Yale School of Public Health, Yale School of Medicine

Business Address: Yale School of Public Health
60 College Street, LEPH 413
P.O. Box 208034, New Haven, CT 06520-8034
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E-mail: harvey.risch@yale.edu

Education:

| <i>Date</i> | <i>School</i> | <i>Degree, Major</i> |
|-------------|------------------------------------|-------------------------------------|
| 9/80-12/82 | University of Washington | Postdoctoral Fellow, Epidemiology |
| 9/76-8/80 | University of Chicago | Ph.D., Biomathematics |
| 9/72-6/76 | UC San Diego School of Medicine | M.D., Medicine |
| 9/67-6/72 | California Institute of Technology | B.S. (Honors), Biology; Mathematics |

Professional Appointments:

7/01- Professor of Epidemiology, Department of Chronic Disease Epidemiology, Yale School of Public Health, Yale School of Medicine, New Haven, CT.

1/12- Director, Molecular Cancer Epidemiology Laboratory and Shared Resource, Yale Comprehensive Cancer Center and Yale School of Public Health

9/06-8/07 Lady Davis Visiting Professor, Department of Community Medicine and Epidemiology, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

1/91-6/01 Associate Professor of Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine.

1/83-12/90 Epidemiologist-Biostatistician, Epidemiology Unit, National Cancer Institute of Canada, Toronto, Ontario.

7/90-12/90 Associate Professor, Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario (Concurrent Appointment).

1/83-6/90 Assistant Professor, Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario (Concurrent Appointment).

9/80-12/82 Postdoctoral Fellow, Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, Washington.

7/79-8/80 Postdoctoral Fellow, Department of Pathology, University of Chicago, Chicago, Illinois.

h-Index: 88. Publication citations: more than 36,200 research citations as of June 1, 2020.

Awards, Memberships, etc.:

NSF Undergraduate Research Fellowship, Department of Mathematics, California Institute of Technology, Pasadena (6/70-9/70)

General Medicine Stipended Externship, UC San Diego School of Medicine, La Jolla (6-9/73)

Theoretical Biology Predoctoral Traineeship, University of Chicago (9/76-6/79)

Pathobiology Postdoctoral Traineeship (GM 7190), University of Chicago (7/79-8/80)

Cancer Epidemiology Postdoctoral Traineeship (CA 9168), University of Washington (9/80-12/82)

Member, Society for Epidemiologic Research (1982-)

Member, American Society of Preventive Oncology (1984-)

Full Member, Sigma Xi (1986-)

Fellow, American College of Epidemiology (1991-); Member (1984-91)

Member, Yale Cancer Center (1992-), Sections: Cancer Prevention and Control; Gynecologic Oncology; Cancer Genetics

“Best of the AACR Journals” for “Aspirin Use and Reduced Risk of Pancreatic Cancer,” one of the most highly cited *Cancer Epidemiology, Biomarkers & Prevention (CEBP)* articles published in 2016 (April 2018) (<http://aacrjournals.org/h-a-risch-bio>)

The Ruth Leff Siegel Award for Excellence in Pancreatic Cancer Research (2018), \$50,000 (<http://columbiasurgery.org/pancreas/ruth-leff-siegel-award>)

Member, [Connecticut Academy of Science and Engineering](#) (2019-)

Highest attention paper ever published in the American Journal of Epidemiology (2020) (<https://oxfordjournals.altmetric.com/details/82900954>)

Consortia:

BEACON: Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (2005-)

OCAC: Ovarian Cancer Association Consortium (International Consortium of Case-Control Studies of Ovarian Cancer) (2005-)

PanC4: Pancreatic Cancer Case-Control Consortium (2006-); Elected Steering Committee Member (2008-2013, 2014-2017, 2018-2021)

Panscan: Pancreas Cancer Genome-wide Association Study Consortium (2008-)

CIMBA: Consortium of Investigators of Modifiers of BRCA1/2 (2017-)

Research Interests:

Cancer epidemiology and etiology—Pancreas, Ovary, Lung, Breast, Stomach, Bladder, etc.

Cancer genetic epidemiology: polymorphisms, major genes; Hormonal factors and cancer; Occupational/environmental exposures and cancer; Diet and cancer; *Helicobacter pylori* and cancer

Epidemiologic methods; Causal inference; Cancer registration, control and prevention

Teaching Experience:

Advanced Epidemiologic Research Methods (Yale University CDE 619a) (Course developer)

Fundamentals of Epidemiology (Yale University CDE/EMD 508) (Course developer)

Principles of Epidemiology II (Yale University CDE 516) (Course developer)

Research Methods in Epidemiology I (University of Toronto CHL 4102f) (Course co-developer)

Research Methods in Epidemiology II (University of Toronto CHL 4105s) (Course developer)

Cancer Epidemiology (University of Toronto CHL 4103f; Yale University CDE 532b)

Trainees

PhD: Advisor to five students; dissertation committee member for 11 students.

MPH or MSc: Advisor to 36 students.

Postdoctoral Fellows: Advisor to 16 fellows.

Visiting Faculty: Host to four visiting professors.

Service Activity:

Grant Review Panels:

Health Canada, National Health Research and Development Program: Epidemiology, Occupational Health and Chronic Disease Panel (1987-91)
NIH External Site Reviewer (1995)
NIH Study Section Regular Member: Epidemiology and Disease Control (EDC2) (1997)
US Army MRMC Ovarian Cancer Research Program Integration Panel Member (1997-2002)
American Cancer Society Extramural Grant Reviewer (1998)
Chair, Epidemiology Grant Review Panel, National Cancer Institute of Canada (2000-2)
Dutch Cancer Society Extramural Research Grant Reviewer (2000, 2001, 2008)
Cancer Council Australia Extramural Research Grant Reviewer (2004)
Pancreatic Cancer Action Network-AACR Career Development Awards Scientific Review Committee (2016-8)
NIH Study Section Member: Epidemiology and Disease Control (EDC2) (2000)
NIH Study Section Member: Epidemiology Special Emphasis Panel (ZRG4, 1998; ZRG1, 2001-3)
NIH Study Section Member: Pancreas SPORE Panel (ZCA1 GRB-V, 2002-3)
NIH Study Section Member: Small Grants Program for Cancer Epidemiology Panel (ZCA1 SRRB-Q, 2003)
NIH Study Section Member: Cancer Genetics Panel (CG) (2004, 2006)
NIH Study Section Member: Cancer Epidemiology, Prevention and Control (NCI-E X1) (2005)
NIH Study Section Member: Breast and Ovarian Cancer Genetics (ZRG1 ONC-U 03M) (2005)
NIH Study Section Member: Gene-Environment Interactions (ZHL1 CSR-D S1 R) (2007)
NIH Study Section Member: Epidemiology of Cancer Member Conflicts (ZRG1 HOP-Q, 2009; ZRG1 PSE-B, 2010)
NIH Study Section Member: Barrett's Esophagus Translational Research Network (ZCA1 SRLB-1 (O1) R, 2011)
NIH Study Section Member: Core Infrastructure and Methodological Research for Cancer Epidemiology Cohorts (ZCA1 SRLB-9 (M2) B, 2013; ZCA1 TCRB-9 (J2) R, 2014; ZCA1 SRBJ (O2) S, 2015)
NIH Study Section Member: Cancer Management, Epidemiology, and Health Behavior (ZCA1 SRLB-B (J1) S, 2013)
NIH Study Section Member: Population Science (U01) (ZCA1 RTRB-Z M1 R, 2016)
Medical Research Council UK External Reviewer (2019)

Journal Editor:

Associate Editor, *American Journal of Epidemiology* (1997-2014)
Editor pro tem, *American Journal of Epidemiology* (2002-2014)
Member, Board of Editors, *American Journal of Epidemiology* (2014-)
Associate Editor, *Journal of the National Cancer Institute* (2000-)
Editor, *International Journal of Cancer* (2008-)

Journal Referee:

Alimentary Pharmacology & Therapeutics (2015-)
American Journal of Epidemiology (1986-)
American Journal of Medical Genetics (2004-)
American Journal of Obstetrics and Gynecology (2015-)
American Journal of Preventive Medicine (1988-)

Annals of Epidemiology (1992-)
Annals of Oncology (2001-)
Annals of Surgical Oncology (2011-)
Biodemography and Social Biology (2018-)
Biometrics (1990-)
Blood Transfusion (2015-)
BMC Cancer (2007-)
BMC Public Health (2007-)
British Journal of Cancer (2003-)
Canadian Journal of Public Health (1987-)
Canadian Medical Association Journal (1983-)
Cancer (1996-)
Cancer Causes and Control (1992-)
Cancer Detection and Prevention (2003-2009)
Cancer Epidemiology (2009-)
Cancer Epidemiology, Biomarkers and Prevention (1995-)
Cancer Genetics (2012-)
Cancer Research (1988-)
Carcinogenesis (2008-)
Clinical Cancer Research (2015-)
Clinical Gastroenterology and Hepatology (2007-)
Current Pharmacogenomics (2007-)
DNA and Cell Biology (2019-)
Environmental Pollution (2018-)
Epidemiology (1989-)
European Journal of Cancer (2001-)
European Journal of Epidemiology (1995-)
European Journal of Human Genetics (2008-)
Gastroenterology (2007-)
Gynecologic Oncology (1997-)
International Journal of Cancer (1995-)
International Journal of Epidemiology (1995-)
JAMA (1990-)
Journal for Nurse Practitioners (2018-)
Journal of Clinical Epidemiology (2006-)
Journal of Clinical Gastroenterology (2010-)
Journal of Clinical Medicine (2019-)
Journal of Epidemiology (2016-)
Journal of Infectious Diseases (2002-)
Journal of the National Cancer Institute (1992-)
Menopause (2011-)
Molecular Carcinogenesis (2009-)
Nature Clinical Practice Oncology (2005-)
Nature Scientific Reports (2016-)
New England Journal of Medicine (2017-)
Oncology Research (2001-)
Oncotarget (2017-)
Preventive Medicine (1994-)

Reproductive Sciences (2008-)
Science (2004-)
Treatments in Endocrinology (2003-)
Tumor Biology (2015-)
World Journal of Gastroenterology (2013-)

Other Review and Service:

Society for Epidemiologic Research Student Prize Paper Review Committee (1987, 1994)
American Society for Clinical Oncology Cancer Prevention Curriculum (2006)
External Advisory Board Member, Multiple Myeloma Prevention Program Project, Washington University (2014-2015)
Mayo Clinic SPORE in Pancreatic Cancer External Advisory Committee (2018-2023)
Connecticut Academy of Science and Engineering (CASE) Advisory Committee on Covid-19 for Reopening Connecticut (2020)

Academic and Professional Standing Committees:

Yale School of Public Health:

Doctoral (Admissions and Progress; 1991-1999)
MPH (Academic Progress; 1991-1995)
Computer (1999-2001)
Medical Studies (2000-2005)
Chair, Genetics and Public Health Interest Group (2003-2006)
Chair, C.E.A. Winslow Medal Committee (2007-2010)
Chair, Hildreth Memorial Fund Committee (2007-2012)
The Honorable Tina Brozman Foundation Small Grant Proposal Review Committee (2010)
Chair, MPH Thesis Dean's Prize Committee (2010-)
Chair, Department of Chronic Disease Epidemiology, Epidemiology Competencies Committee (2015-)
Committee for Academic and Professional Integrity (2018-2021)
Education Committee (2019-)

Yale School of Medicine:

Program in Investigative Medicine Doctoral Committee (1999-2007)
Mentored Clinical Research Scholar Program Advisory Board (2003-2008)

Yale Cancer Center:

Rapid Case Ascertainment System Shared Resource (1995-)
American Cancer Society Institutional Research Award Review Committee (1996-2001)

American College of Epidemiology:

Education Committee (1996-2002)
Policy Committee (1997-2003)

Peer-Reviewed Research Publications:

Accepted for Publication or In-Press

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Research Grants Held:

- 2020-2025 AP Klein (Principal Investigator), G Petersen, D Li, **HA Risch**, P Bracci, S Gallinger, R Hung, M Meng, E Jacobs, J Manjer, M Sund, V Katzke, A Arslan, L Le Marchand, R Milne, R Stolzenberg-Solomon, C Kooperberg, S van den Eeden, J Genkinger, A Schwartz, J Brody, S Lynch, A Tjønneland, X-O Shu, L Amundadottir, K Visvanathan, B Wolpin. *Multi-Ancestry Mapping of Pancreatic Cancer Susceptibility Loci*. (National Cancer Institute, \$112,843 total direct costs to Yale subcontract over 60 months)
- 2018-2020 CY Jeon (Principal Investigator), S Freedland, S Kim, NY Kyeong, TK Nuckols, SJ Pandol, **HA Risch**, B Spiegel. *Predicting the Diagnosis of Pancreatic Cancer by Leveraging Big Data*. (National Cancer Institute, \$235,000 total direct costs over 24 months)
- 2018-2018 ML Irwin (Principal Investigator), L Lu, **H Risch**. *Impact of exercise and diet-induced weight loss on immunosuppression in breast cancer survivors*. (Cynthia Barnett Breast Cancer Foundation, \$25,000 total costs over 12 months)
- 2017-2018 **HA Risch** (Principal Investigator), L Lu. *Feasibility of circulating exosomal proteins in ovarian cancer diagnosis*. (Brozman Ovarian Cancer Foundation, \$25,000 total costs over 12 months)
- 2016-2021 AP Klein (Principal Investigator), P Bracci, S Cleary, S Gallinger, R Hung, D Li, R Neale, S Olson, G Petersen, **HA Risch**, G Scelo. *Validation and Fine-scale Mapping of Pancreatic Cancer Susceptibility Loci*. (National Cancer Institute, \$220,000 total direct costs to Yale subcontract over 60 months)
- 2013-2017 Y Guan, X Ma (Principal Investigators), D Zimmerman, P Diggle, T Holford, **H Risch**, L Mueller, Y Zhang. *New Statistical Methods to Handle Spatial Uncertainty in Cancer Risk Estimation*. (National Cancer Institute, \$1,100,000 total direct costs over 48 months)
- 2011-2016 R Kurman (Principal Investigator), H Berman, L Cope, T Diaz-Montes, M Gauthier, D Huso, D Levine, E Matloff, S Narod, V Parkash, **H Risch**, G Rosner, P Shaw, I-M Shih, R Soslow, R Vang, K Visvanathan, T-L Wang, et al. *Prevention of Ovarian High-Grade Serous Carcinoma by Elucidating Its Early Changes*. (Department of Defense USMRMC, \$9,166,162 total direct costs, of which \$199,000 total direct to Yale epidemiology subcontract, over 60 months).
- 2011-2015 AP Klein (Principal Investigator), P Bracci, P Brennan, E Duell, S Gallinger, D Li, R Neale, S Olson, G Petersen, **HA Risch**. *Validation and Fine-scale Mapping of Pancreatic Cancer Susceptibility Loci*.

- (National Cancer Institute, \$197,000 total direct costs to Yale subcontract over 48 months)
- 2011-2013 AP Klein, **HA Risch** (Co-Principal Investigators). *Validation and Fine-Scale Mapping of Pancreatic Cancer Susceptibility Loci*. (National Human Genome Research Institute, covers costs of large-scale high-throughput genotyping of collaborative multi-center pancreatic cancer study (see previous grant) at the Center for Inherited Disease Research (CIDR)).
- 2010-2016 H Yu (Principal Investigator), M Irwin, X Ma, S Mayne, **H Risch**, H Zhao, J Lim. *Epidemiologic Study of Hepatocellular Carcinoma in the US*. (National Cancer Institute, \$5,385,000 total direct costs over 60 months)
- 2010-2014 T Sellers (Principal Investigator), A Berchuck, G Bloom, M Clyde, D Fenstermacher, B Fridley, S Gayther, W Ge, E Goode, E Iversen, H-Y Lin, S Mears, A Monteiro, T Moorman, L Pearce, P Pharoah, C Phelan, **H Risch**, MA Rossing, J Schildkraut, G Trench, Y-Y Tsai. *Follow-up of Ovarian Cancer Genetic Association and Interaction Studies (FOCI)*. (National Cancer Institute, \$108,926 total direct costs to Yale subcontract 2012-2014)
- 2010-2013 CL Pearce (Principal Investigator), JA Doherty, S Gayther, VM McGuire, **H Risch**, MA Rossing, J Schildkraut, TA Sellers, W Sieh, D Stram, G Trench, P Webb, A Whittemore, A Wu. *Identifying Ovarian Cancer Susceptibility Alleles Using Genome-Wide Scan Data*. (National Cancer Institute, \$22,500 total direct costs to Yale subcontract)
- 2009-2014 M Irwin (Principal Investigator), J Dziura, R McCorkle, G Mor, **H Risch**, P Schwartz, H Yu. *Impact of Exercise on Ovarian Cancer Prognosis*. (National Cancer Institute, \$2,045,493 total direct costs over 59 months)
- 2009-2012 T Vaughan, D Whiteman (Principal Investigators), L Bernstein, D Corley, MD Gammon, L Hardie, N Hayward, G Liu, L Murray, O Nyrén, U Peters, B Reid, **HA Risch**, Y Romero, N Shaheen, D Stram, D Van Den Berg, B Weir, A Wu. *Barrett's and Esophageal Adenocarcinoma Consortium Genetic Susceptibility Study*. (National Cancer Institute, \$3,750,000 total direct costs over 36 months)
- 2009-2010 M Goodman (Principal Investigator), A Berchuck, J Chang-Claude, D Cramer, CM Garcia, E Goode, S Krueger Kjaer, R Ness, P Pharoah, **HA Risch**, M Rossing, R Sutphen, K Terry, G Trench, A Whittemore. *Collaborative Genetic Study of Ovarian Cancer Risk*. (National Cancer Institute, \$17,419 total direct costs over 12 months, to Yale subcontract)
- 2007-2014 **HA Risch** (Principal Investigator), Y-T Gao, MS Kidd, H Yu. *Case-Control Study of Pancreas Cancer in Shanghai, China*. (National Cancer Institute, \$1,858,377 total direct costs over 75 months)
- 2007-2012 P Salovey (Principal Investigator), M Irwin, ST Mayne, **HA Risch**. *Promoting Cancer Prevention/Control with Message Framing: III*.

- Extending Tailored Cancer Information Service-Delivered Messages Across the Cancer Continuum.* (National Cancer Institute: \$1,525,215 total direct costs over 58 months)
- 2007-2012 R Neale (Principal Investigator), D Whiteman, J Young, L Fritschi, J Fawcett, P Webb, **H Risch**. *Case-Control Study of Genetic and Environmental Risk Factors for Pancreatic Carcinoma.* (National Health and Medical Research Council (Australia): AU\$946,475 total nonacademic direct costs over 60 months)
- 2007-2011 T Sellers (Principal Investigator), D Ballinger, J Barnholtz-Sloan, ME Colter, Y Huang, E Iversen, J Lancaster, J McLaughlin, S Narod, VS Pankratz, **H Risch**, J Schildkraut, R Sutphen. *Haplotype-Based Genome Screen for Ovarian Cancer Loci.* (National Cancer Institute, \$5,726,016 total direct costs over 60 months)
- 2006-2007 R Neale (Principal Investigator), D Whiteman, L Fritschi, J Young, J Fawcett, P Webb, **H Risch**. *A Case-Control Study of the Environmental and Genetic Causes of Pancreatic Carcinoma.* (Queensland Cancer Fund: AU\$258,339 total nonacademic direct costs over 16 months)
- 2003-2012 **HA Risch** (Principal Investigator), FS Gorelick, D Jain, MS Kidd, ST Mayne, MD Topazian, H Yu. *Case-Control Study of Pancreas Cancer Etiologic Factors.* (National Cancer Institute: \$2,578,672 total direct costs over 80 months, in NCE)
- 2003-2010 H Yu (Principal Investigator), **HA Risch**, ST Mayne, M Irwin, B Cartmel. *Role of Genetic and Lifestyle Interplay in Uterus Cancer.* (National Cancer Institute: \$2,185,432 total direct costs over 60 months, in NCE)
- 2003-2006 SA Narod (Principal Investigator), B Rosen, JR McLaughlin, P Shaw, **HA Risch**. *The contribution of BRCA2 to ovarian cancer.* (National Cancer Institute of Canada: \$375,000 total nonacademic direct costs over 36 months)
- 2002-2005 H Yu (Principal Investigator), **HA Risch**. *DNA Methylation, Aging, and Prostate Cancer Risk.* (National Cancer Institute: \$600,000 total direct costs over 48 months)
- 2002-2006 JP Concato (Principal Investigator), W Li, P Peduzzi, **HA Risch**, D Jain. *Risk of Mortality in Prostate Cancer.* (USVA: \$424,000 total direct costs over 48 months)
- 2001-2007 P Salovey (Principal Investigator), **HA Risch**, ST Mayne, M Morra. *Promoting Cancer Prevention/Control with Message Framing. II.* (National Cancer Institute: \$1,324,481 total direct costs over 72 months)
- 1999-2005 **HA Risch** (Principal Investigator), AE Bale. *DNA Polymorphisms in Ovarian Cancer: Case-Control Study.* (National Cancer Institute: \$325,168 total direct costs over 58 months)

- 1998-2002 JP Concato (Principal Investigator), W Li, P Peduzzi, S Flynn, C Howe, **HA Risch**, D Esrig. *Risk of Mortality in Prostate Cancer*. (USVA: \$425,245 total direct costs over 48 months)
- 1997-2003 **HA Risch** (Principal Investigator), L DiPietro, AF Saftlas, A Duleba, ML Carcangiu. *Case-Control Study of Ovarian Cancer Hormonal Etiology*. (National Cancer Institute: \$1,445,806 total direct costs over 70 months)
- 1997-2000 SA Narod (Principal Investigator), **HA Risch**. *Risk-Factor Analysis of BRCA1 and BRCA2 Carriers*. (National Cancer Institute: \$1,228,000 total direct costs over 36 months)
- 1997-2001 P Salovey (Principal Investigator), **HA Risch**, M Morra. *Promoting Cancer Prevention/Control with Message Framing*. (National Cancer Institute: \$498,295 total direct costs over 48 months)
- 1996-1999 P Salovey (Principal Investigator), **HA Risch**, M Morra. *Message Framing, Persuasion, and Cancer Prevention/Detection*. (American Cancer Society: \$198,000 total direct costs over 24 months)
- 1994-2000 **HA Risch** (Principal Investigator), JR McLaughlin, SA Narod, NJ Risch, EJ Holowaty, BP Rosen, DEC Cole. *Genetic-Epidemiology Study of Epithelial Ovarian Tumors*. (National Cancer Institute: \$799,551 total direct costs over 69 months)
- 1994-1997 SA Narod (Principal Investigator), HT Lynch, **HA Risch**, DE Goldgar. *The Prevention of Hereditary Breast and Ovarian Cancer*. (National Cancer Institute: \$356,875 total direct costs over 34 months)
- 1992-1996 **HA Risch** (Principal Investigator), ST Mayne, R Dubrow, AB West. *Epidemiologic Study of Esophageal/Gastric Adenocarcinoma*. (National Cancer Institute: \$536,163 total direct costs over 43 months)
- 1991-1992 **HA Risch** (Principal Investigator). *Latency-Temporality Analysis in Case-Control Studies of Chronic Exposures*. (National Institutes of Health (BSRG): \$19,000 total direct costs over 12 months)
- 1990-1991 **HA Risch** (Principal Investigator), GR Howe, R West, LM Strand. *A Record-Linkage Cohort Study of Menopausal Hormone Usage and Endometrial Cancer in Saskatchewan*. (National Health Research and Development Program, Health and Welfare Canada: \$50,476 total nonacademic direct costs over 8 months)
- 1990-1994 JAJ Stolwijk (Principal Investigator), **HA Risch**, ST Mayne, R Dubrow, T Holford. *Cancer Prevention Research Unit for Connecticut at Yale*. (National Cancer Institute: \$3,865,000 total direct costs over 60 months)
- 1989-1993 **HA Risch** (Principal Investigator), LD Marrett, GR Howe, M Jain. *A Case-Control Study of Dietary Factors and Epithelial Ovarian Cancer*. (National Health Research and Development Program, Health and Welfare Canada: \$343,766 total nonacademic direct costs over 41 months)

1986-1990 GR Howe (Principal Investigator), **HA Risch**, M Jain, JD Burch, C Wall. *Research Project Support of the NCIC Epidemiology Unit*. (National Cancer Institute of Canada: total nonacademic direct costs \$228,093 in 1986-7; \$440,454 in 1987-8; \$205,617 in 1988-9, etc.)

Selected Scholarly Presentations and Workshops:

- 5/19 "Pancreatic Cancer and Diet." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.
- 3/19 "Reducing Mortality of What Will Be the #3 Cause of Cancer Death Two Years from Now." Virus and Other Infection-associated Cancers Research Seminar, Yale School of Medicine, New Haven, CT.
- 5/18 "New Concepts in Causation." Keynote speaker, Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.
- 2/18 "Risk Factors for Pancreatic Cancer." Yale Pancreas Symposium 2018: Multidisciplinary Management of Pancreatic Cancer. New Haven, CT.
- 4/17 "Reducing Mortality of what will be the #2 Cause of Cancer Death Four Years from Now." Gastroenterologic Oncology Service, Yale Cancer Center, New Haven, CT.
- 3/17 "Genomewide Association Study of Pancreatic Cancer in American Jews." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.
- 3/17 "New Markers and Approaches in Predicting Risk of Pancreatic Cancer." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.
- 12/16 "Genomewide Association Study of Pancreatic Cancer in American Jews." Pancreatic Cancer Case-Control Consortium (PanC4) GWAS Study Annual Meeting, Bethesda, MD.
- 10/16 "Reducing Mortality of Pancreatic Cancer in the International Context." Inaugural Global Oncology Seminar Series speaker, Yale Cancer Center, New Haven, CT.
- 6/16 "Prevention of Pancreatic Cancer." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Milan, Italy.
- 1/16 "Reducing Mortality of what will be the #2 Cause of Cancer Death Five Years from Now." Department of Therapeutic Radiation, Yale School of Medicine, New Haven, CT.
- 10/15 "Reducing Mortality of what will be the #2 Cause of Cancer Death Five Years from Now." Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Rockville, MD.
- 3/15 "Absolute Risk Models for Pancreatic Cancer." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.

- 12/12 Keynote Speaker, “From Cancer Registration to Cancer Etiology to Cancer Prevention.” Cancer Registrars Association of New England Annual Meeting, Norwich, CT.
- 3/12 “Pancreatic Cancer Risk Models.” Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.
- 3/12 Cancer Center Grand Rounds: “*Helicobacter pylori*, ABO Blood Group and the Etiology of Pancreatic Cancer in China and the US.” Yale University School of Medicine, New Haven, CT.
- 9/11 “Etiology of Pancreatic Cancer: Theory and Evidence.” Seminar, Division of Chronic Disease Epidemiology, Yale University School of Public Health, New Haven, CT.
- 3/11 “Genetic Effects and Modifiers of Radiotherapy and Chemotherapy on Survival in Pancreatic Cancer,” Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, New York, NY.
- 1/11 Keynote Speaker, “Why is Pancreatic Cancer Less Frequent in Asia than in the US, in Spite of the Higher Prevalence of Risk Factors in Asia? Observations on the Etiology of Pancreatic Cancer.” Japan Epidemiology Association National Meetings, Sapporo, Japan.
- 1/11 Department Seminar: “*BRCA1* and *BRCA2* Mutations: Population Frequencies and Associations with a Variety of Cancers.” Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan.
- 1/11 Cancer Center Grand Rounds, “Why is Pancreatic Cancer Less Frequent in Asia than in the US, in Spite of the Higher Prevalence of Risk Factors in Asia? Observations on the Etiology of Pancreatic Cancer.” Japan National Cancer Center, Tokyo, Japan.
- 11/10 Educational Session Seminar, “Gene, environment, and risk-factor interaction in pancreatic cancer.” AACR Frontiers in Cancer Prevention Annual International Meeting, Philadelphia PA.
- 11/10 Workshop Presentation: “*KRAS* variation and risk of ovarian cancer.” Biennial meeting of the Ovarian Cancer Association Consortium (OCAC), Bethesda, MD.
- 5/10 Cancer Center Retreat Seminar, “ABO blood group, *Helicobacter pylori* colonization and pancreatic cancer.” Yale University School of Medicine, New Haven, CT.
- 3/10 “*Helicobacter pylori* colonization, ABO blood group and risk of pancreatic cancer,” Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Bethesda, MD.
- 7/09 Epidemiology Grand Rounds: “Pancreas Cancer and *Helicobacter pylori* in the U.S. and China.” Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China.

- 3/09 Cancer Center Grand Rounds: “Inconsistencies in Pancreas-Cancer Risk Factors and Disease Incidence Between the U.S. and China: Observations on the Etiology of Pancreas Cancer.” Yale University School of Medicine, New Haven, CT.
- 11/08 Workshop Participant, Defining the Public Health Research Agenda for Ovarian Cancer, Centers for Disease Control, Atlanta, GA.
- 7/08 Workshop Presentation: “*Helicobacter pylori* and pancreas cancer.” Biological and Clinical Risks and Potential Benefits of *Helicobacter pylori* Colonization, Division of Microbiology and Infectious Diseases, NIAID, NIH, Bethesda, MD.
- 1/08 Research Seminar: “Smoking and lung cancer in women—yet again.” Program in Cancer Prevention and Control, Yale Cancer Center, New Haven, CT.
- 11/07 Workshop Presentation: “*BRCA1* and *BRCA2* Mutations: Frequencies in the General Population of North America and Associations with Breast, Ovary, Stomach, Pancreas and Other Cancers.” Nanjing International Symposium of New Frontiers in Cancer Research and Advanced Training Workshop of Cancer Molecular Epidemiology, Nanjing Medical University, Nanjing, China.
- 10/07 Workshop Presentation: “Why have epidemiology data and outcomes of clinical trials not correlated?” Third Haifa Cancer Prevention Workshop. CHS National Cancer Control Center, Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel.
- 6/07 Workshop: “Advanced Statistical Methods for Epidemiologic Studies”. Department of Community Medicine and Epidemiology, Technion Israel Institute of Technology Faculty of Medicine, Haifa, Israel.
- 3/07 Ruth and Bruce Rappaport Seminar: “Why Pancreas Cancer is Less Frequent in China than the US, in Spite of the Generally Higher Chinese Prevalence of Risk Factors: Insights on the Etiology of Pancreas Cancer.” Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel.
- 2/07 Seminar: “Smoking and lung cancer in women—yet again.” Department of Community Medicine and Epidemiology, Technion Israel Institute of Technology Faculty of Medicine, Haifa, Israel.
- 1/07 Seminar: “Etiologic theories for epithelial ovarian cancer.” Department of Community Medicine and Epidemiology, Technion Israel Institute of Technology Faculty of Medicine, Haifa, Israel.
- 11/06 Seminar: “*BRCA1* and *BRCA2* Mutations: Frequencies in the General Population and Associations with Breast, Ovary, Stomach, Pancreas and Other Cancers.” New York University Cancer Center, New York, NY.
- 2/06 Cancer Center Grand Rounds: “*BRCA1* and *BRCA2* Mutations: Their Frequencies in the General Population and Their Associations with

- Breast, Ovary, Stomach, Pancreas and Other Cancers," Yale University School of Medicine, New Haven, CT.
- 11/05 Symposium: "Why Pancreas Cancer is Less Frequent in China than the US, in spite of the Generally Higher Chinese Prevalence of Risk Factors: Insights on the Etiology of Pancreas Cancer." Clinical Oncological Society of Australia annual scientific meeting, Brisbane, Australia (Sponsored by the Queensland Cancer Fund).
- 11/05 Symposium: "Risks and penetrances of germline *BRCA1* and *BRCA2* mutations for ovarian, breast, stomach, pancreas and other cancers: updated results from the Ontario (Canada) ovarian cancer kin-cohort study." Clinical Oncological Society of Australia annual scientific meeting, Brisbane, Australia (Sponsored by the Queensland Cancer Fund).
- 6/05 Seminar: "Why Pancreas Cancer is Less Frequent in China than the US, in spite of the Generally Higher Chinese Prevalence of Risk Factors: Insights on the Etiology of Pancreas Cancer." Tumor Registrars Association of Connecticut Quarterly Meeting, Yale-New Haven Hospital, New Haven, CT.
- 5/05 Seminar: "Why Pancreas Cancer is Less Frequent in China than the US, in spite of the Higher Prevalence of Risk Factors There: Insights on the Etiology of Pancreas Cancer." Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL.
- 5/02 Symposium: "Genetic Epidemiology of Ovarian Cancer." Ovarian Cancer and High-Risk Women: Implications of Prevention, Screening and Early Detection. University of Pittsburgh, Pittsburgh, PA.
- 12/01 Seminar: "Prevalence and Penetrance of Germline *BRCA1* and *BRCA2* Mutations in Unselected Ovarian Cancer." Kaplan Cancer Center, NYU School of Medicine, New York, NY.
- 10/01 Research Seminar: "Prevalence and Penetrance of Germline *BRCA1* and *BRCA2* Mutations in Unselected Ovarian Cancer." Memorial Sloan Kettering Cancer Center, New York, NY.
- 6/01 Combined Monthly Research Seminar: "Prevalence and Penetrance of Germline *BRCA1* and *BRCA2* Mutations in Unselected Ovarian Cancer." Programs in Ovarian Cancer, Cancer Genetics and Cancer Prevention, Yale Cancer Center, New Haven, CT.
- 10/00 Departmental Seminar: "Etiology of Epithelial Ovarian Cancer." Department of Public Health Sciences, Fox Chase Cancer Center, Philadelphia, PA.
- 9/98 "Etiologic Mechanisms in Epithelial Ovarian Cancer," Third International Symposium on Hormonal Carcinogenesis, Seattle, WA.
- 5/98 Departmental Grand Rounds: "BRCA1 and BRCA2 Mutations in Unselected Ovarian Cancer," Department of Gynecologic Oncology, Yale University School of Medicine, New Haven, CT.

- 9/97 Departmental Seminar: "Etiologic Mechanisms in Epithelial Ovarian Cancer." Division of Epidemiology, Columbia University School of Public Health, New York, NY.
- 9/97 "Use of aspirin and other non-steroidal anti-inflammatory drugs and risk of esophageal and gastric cancer." American College of Epidemiology Annual Meetings, Cambridge, MA.
- 3/97 "Risk Factors for Familial and Hereditary Ovarian Cancer." American Cancer Society Science Writers Seminar, Reston, VA.
- 2/97 Departmental Grand Rounds: "Etiologic and Histologic Considerations in the Occurrence of Ovarian Cancer." Department of Pathology, Yale School of Medicine, New Haven, CT.
- 1/97 Departmental Seminar: "Ovarian Cancer Pathophysiology: Etiologic and Methodologic Issues." Department of Epidemiology, University of North Carolina School of Public Health, Chapel Hill, NC.
- 6/96 "Risk factors for BRCA1-associated ovarian cancer." NCI Extramural Genetic Epidemiology PIs Second Biennial Meetings, Frederick, MD.
- 6/96 "Estrogen replacement therapy and the risk of epithelial ovarian cancer." Society for Epidemiologic Research Annual Meetings, Boston, MA.
- 6/95 "Pelvic inflammatory disease and the risk of epithelial ovarian cancer." Society for Epidemiologic Research Annual Meetings, Snowbird, UT.
- 6/94 "Dietary fat intake and the risk of epithelial ovarian cancer." Society for Epidemiologic Research Annual Meetings, Miami, FL.
- 6/93 "A cohort study of menopausal hormone usage and breast cancer in Saskatchewan." Society for Epidemiologic Research Annual Meetings, Keystone, CO.
- 2/93 "A cohort study of menopausal hormone usage and breast cancer in the province of Saskatchewan, Canada." International Epidemiology Association Regional European Meeting, Jerusalem.
- 9/92 "A record-linkage cohort study of menopausal hormone usage and breast cancer in Saskatchewan." American College of Epidemiology Annual Meetings, Bethesda, MD.
- 9/92 "Record-linkage cohort study of menopausal hormone usage and breast cancer." Yale/Dana Farber Conference on Cancer Prevention and Control, Department of Epidemiology and Public Health, Yale University, New Haven, CT.
- 6/92 "Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type." Society for Epidemiologic Research Annual Meetings, Minneapolis, MN.
- 12/91 Departmental Seminar: "Some interesting results on lung cancer in women." Department of Epidemiology and Public Health, Yale University, New Haven, CT.

- 11/89 Departmental Seminar: "Occupational and dietary associations with bladder-cancer incidence." Department of Epidemiology and Public Health, Yale University, New Haven, CT.
- 8/89 "A demonstration of the GLIMP computer program for epidemiologic analysis." Canadian Epidemiology Research Conference Meetings, Ottawa.
- 4/89 "Nonlinear dose-response models with standard logistic regression." Upstate New York and Southern Ontario Epidemiology Group Meetings, Toronto.
- 6/88 "A unified framework for meta-analysis by maximum likelihood." Society for Epidemiologic Research Annual Meetings, Vancouver.
- 4/88 Departmental Seminar: "Occupational and dietary factors in the study of cancer of the bladder." Division of Epidemiology and Biostatistics, Graduate School of Public Health, San Diego State University, San Diego, CA.
- 3/88 Seminar: "Diet and occupation in the causation of bladder cancer." School of Public Health, New York State Department of Health, SUNY, Albany, NY.
- 12/87 Departmental Seminar: "Dietary and occupation factors in a case-control study of bladder cancer." Department of Epidemiology, Harvard School of Public Health, Boston, MA.
- 12/87 Departmental Seminar: "Risk factors for spontaneous abortion and its recurrence, and habitual abortion." Department of Medical Genetics, Hospital for Sick Children, Toronto.
- 11/87 Departmental Seminar: "Occupational and dietary factors in the causation of bladder cancer." Department of Social and Preventive Medicine, SUNY School of Medicine, Buffalo, NY.
- 11/87 Departmental Seminar: "Dietary and occupational factors in the study of bladder cancer." Department of Epidemiology and Biostatistics, University of Western Ontario, London.
- 9/87 Departmental Seminar: "Dietary and occupational factors in a case-control study of bladder cancer." Department of Epidemiology and Community Medicine, University of Ottawa.
- 11/86 Departmental Seminar: "Application of linear structural hypotheses in observational epidemiologic studies." Department of Environmental and Occupational Medicine, Mount Sinai School of Medicine, New York, NY.
- 9/86 Departmental Seminar: "Application of linear structural equations in observational epidemiologic studies." Department of Epidemiology and Public Health, Yale University, New Haven, CT.

- 6/86 "Measuring tumor induction period in case-control studies of chronic exposures." Society for Epidemiologic Research Annual Meetings, Pittsburgh, PA.
- 8/84 "Nitrate and ascorbate in a study of gastric cancer." International Epidemiology Association Meetings, Vancouver.
- 5/84 "An improved method for obtaining confidence intervals of the odds ratio in logistic regression." Epidemiologic Methods Workshop, Upstate New York and Southern Ontario Epidemiology Group Meetings, Toronto.

Item #5

Biosketch5Risch 2020-7

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Risch, Harvey A.

eRA COMMONS USER NAME (credential, e.g., agency login): hrisch

POSITION TITLE: Professor of Epidemiology

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|--|---------------------------|----------------------------|----------------------|
| California Institute of Technology, Pasadena, CA | B.S. | 06/1972 | Mathematics, Biology |
| UCSD School of Medicine, La Jolla, CA | M.D. | 06/1976 | Medicine |
| University of Chicago, Chicago, IL | Ph.D. | 06/1980 | Biomathematics |
| University of Washington, Seattle, WA | Postdoctoral | 12/1982 | Epidemiology |

A. Personal Statement

Harvey A. Risch, MD, PhD, Professor of Epidemiology at the Yale School of Public Health, Yale School of Medicine and the Yale Cancer Center; Director of the Molecular Cancer Epidemiology Laboratory and Shared Resource of the Yale Cancer Center and Yale School of Public Health. I am a medically trained epidemiologist with graduate training in biomathematics and postgraduate training in epidemiology and prevention. I have worked extensively as an investigator in the field of cancer epidemiology for more than 30 years. I have served on numerous national and international committees and review panels, as well as on various editorial boards, currently including the *Journal of the National Cancer Institute*, the *American Journal of Epidemiology*, and the *International Journal of Cancer*. Over my academic career, I have been PhD advisor to five students; PhD dissertation committee member for 11; MPH/MSc advisor for 39; Postdoctoral Fellow advisor for 16 fellows, and host to four visiting professors. My long-term research interests include dietary, hormonal, molecular and genetic factors and the etiology and prevention of neoplasms of various sites, particularly of the pancreas, and particularly involving *Helicobacter pylori*. I have been principal investigator of more than a half dozen large field studies of cancer. These projects include case-control studies of gastric cancer in Ontario, Canada; two of dietary and reproductive factors and ovarian cancer and one of *BRCA1* and *BRCA2* mutations in Ontario; and case-control studies in Connecticut of esophageal and gastric cancer and ovarian cancer. More recently, I have been principal investigator of two large population-based case-control studies of pancreatic cancer, one in the state of Connecticut and a second in Shanghai, China. I am also a co-investigator of a large population-based case-control study of pancreatic cancer in Queensland, Australia. I have also been the Yale Connecticut subcontract PI for the Connecticut-NJ Liver Cancer Study.

I am a founding member and steering committee member of the Pancreas Cancer Case-Control (PanC4) Consortium, have participated extensively in the PanScan (Pancreas Cancer Genome-wide Association Studies) Consortium and in four other international cancer research consortia. In my career to-date, I have received more than \$13 million in research funding. According to Google Scholar (<https://scholar.google.com/citations?user=E1US9ucAAAAJ&hl=en&oi=ao>), I have an h-index of **88** and more than 36,400 research citations to-date.

B. Positions and Honors

| | |
|--------------|--|
| 9/79-8/80 | Fellow, Department of Pathology, University of Chicago, Chicago, IL. |
| 9/80-12/82 | Postdoctoral Fellow, Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA. |
| 1/83-12/90 | Epidemiologist-Biostatistician, National Cancer Institute of Canada, Toronto, Ontario. |
| 1/83-6/90 | Assistant Professor, Dept. of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario (Concurrent Appointment). |
| 7/90-12/90 | Associate Professor, Dept. of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario (Concurrent Appointment). |
| 1/91-6/01 | Associate Professor, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT. |
| 9/06-8/07 | Lady Davis Visiting Professor, Department of Community Medicine and Epidemiology, Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel |
| 7/01-Present | Professor, Department of Chronic Disease Epidemiology, Yale School of Public Health. |
| 1/12-Present | Director, Molecular Cancer Epidemiology Laboratory and Shared Resource, Yale Cancer Center and Yale School of Public Health |
| 1982-Present | Member, Society for Epidemiologic Research |
| 1984-Present | American Society of Preventive Oncology |
| 1991-Present | Fellow, American College of Epidemiology (Member 1984-1990) |
| 1987-1991 | Health and Welfare Canada, National Health Research and Development Program Grant Review Panels 53, 58: Epidemiology, Occupational Health and Chronic Disease |
| 1995 | NIH External Site Reviewer |
| 1997-2002 | US Army MRMC Ovarian Cancer Research Program Advisory/Review Integration Panel |
| 1997; 2000 | NIH Study Section Member: Epidemiology (EDC2) |
| 1998 | American Cancer Society Extramural Grant Reviewer |
| 1998, 2001-3 | NIH Study Section Member: Special Emphasis (ZRG4/1) |
| 2000-2002 | Study Section Chair: National Cancer Institute of Canada Epidemiology Panel |
| 2000, 01, 08 | Dutch Cancer Society Extramural Research Grant Reviewer |

- 2002-2003 NIH Study Section Member: Pancreas SPORE (ZCA1)
- 2003 NIH Study Section Member: Small Grants in Epidemiology (ZCA1)
- 2004 Cancer Council Australia Extramural Research Grant Reviewer
- 2004, 2006 NIH Study Section Member: Cancer Genetics (CG)
- 2005 NIH Study Section Member: Cancer Epidemiology, Prevention and Control (NCI-E X1)
- 2006-2008 Pancreatic Cancer Action Network-AACR Career Development Awards Scientific Review Cmte
- 2007 NIH Study Section Member: Gene-Environment Interactions (ZHL1 CSR-D S1 R)
- 2009, 2010 NIH Study Section Member: Epidemiology of Cancer Member Conflicts (ZRG1 HOP-Q, PSE-B)
- 2011 NIH Study Section Member: Barrett's Esophagus Translational Res. Network (ZCA1 SRLB-1)
- 2013-2015 NIH Study Section Member: Cancer Epidemiology Cohorts (ZCA1 SRLB-9 M2 B, TCRB-9 J2 R)
- 2013 NIH Study Section Member: Cancer Management and Epidemiology (ZCA1 SRLB-B (J1) S)
- 2016 NIH Study Section Member: Population Science (U01) (ZCA1 RTRB-Z M1 R)
- 2019 Medical Research Council UK External Reviewer
- 1997-2014 Associate Editor and Editor *pro tem*: *American Journal of Epidemiology*
- 2014-Present Member, Board of Editors: *American Journal of Epidemiology*
- 2000-Present Associate Editor: *Journal of the National Cancer Institute*
- 2008-Present Editor: *International Journal of Cancer*
- 2018 “Best of the AACR Journals” for “Aspirin Use and Reduced Risk of Pancreatic Cancer,” one of the most highly cited Cancer Epidemiology, Biomarkers & Prevention (CEBP) articles published in 2016 (April 2018) (<http://aacrjournals.org/h-a-risch-bio>)
- 2018 The Ruth Leff Siegel Award for Excellence in Pancreatic Cancer Research (2018), \$50,000 (<http://columbiasurgery.org/pancreas/ruth-leff-siegel-award>)
- 2019 Member, [Connecticut Academy of Science and Engineering](#)
- 2020 Highest attention-scoring paper ever published in the American Journal of Epidemiology (<https://oxfordjournals.altmetric.com/details/82900954>)

C. Contributions to Science (from more than 325 peer-reviewed scientific research publications to-date)

1. Etiology of Ovarian Cancer. Despite dozens of studies showing reduced risk of ovarian cancer with increasing parity and with increasing duration of oral contraceptive use, how these factors are involved in the etiologic process has remained obscure. Over the last three decades, two main theories have competed for scientific attention: the “incessant ovulation hypothesis,” and the “gonadotropin stimulation hypothesis.” Evidence bearing upon these theories does not distinguish them well. During my postdoctoral fellowship at the University of Washington, I worked on an ovarian cancer case-control study led by Dr. Noel Weiss. I developed a statistical approach that showed that the magnitudes of effects for age, parity, use of oral contraception and other factors contributing to duration of ovulation were substantially

inconsistent, and thus that these factors had to exert at least some of their effects on risk in a manner different from any effect on ovulation:

- a. **Risch HA**, Weiss NS, Lyon JL, Daling JR, Liff JM. Events of reproductive life and the incidence of epithelial ovarian cancer. *Am J Epidemiol* 1983;117:128-39.

In addition, whether the lower parity among women with ovarian cancer was a result of underlying conditions, or due to behavioral choices for having smaller families was unknown. These relations bear on the causal direction of the association between parity and ovarian cancer risk. In a case-control study of ovarian cancer that I carried out as PI in Ontario, Canada, 1989-1992, among other aspects, I examined episodes of unsuccessful pregnancy attempts, and found that for nulliparous women, later age at onset of the first unsuccessful attempt was significantly associated with risk ($p=.0016$); cases reported such infertility about 4.7 years later than controls. Over ages 15-45 years, more than 80% of the subjects were not prevented by infertility or hysterectomy from becoming pregnant. Thus, the relatively lower parity of cases compared to controls is likely due to voluntary choices for having fewer children:

- b. **Risch HA**, Marrett LD, Howe GR. Parity, contraception, infertility and the risk of epithelial ovarian cancer. *Am J Epidemiol* 1994;140:585-97.

Through the mid-1990s, epithelial ovarian cancer was considered largely one etiologic disease, with some different characteristics for endometrioid tumors. In evaluating data from my study and others, I realized that mucinous tumors also had substantially different etiologic characteristics. This work opened the field to recognizing that the main types of epithelial ovarian cancer have distinguishing etiologies:

- c. **Risch HA**, Marrett LD, Jain M, Howe GR. Differences in risk factors for epithelial ovarian cancer by histologic type: results of a case-control study. *Am J Epidemiol* 1996;144:363-72.

Finally, in considering my studies in the context of the literature on the etiology of ovarian cancer, I realized that appreciable evidence implicated the hormones progesterone and androgens in the etiology (decreasing and increasing risk, respectively). I proposed this theory in a review paper, and subsequent work by many individuals on this topic continues to-date:

- d. **Risch HA**. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. *J Natl Cancer Inst* 1998;90:1774-86.

2. *BRCA1* and *BRCA2* Mutations and Cancer. In the mid-1990s, it became apparent that high penetrance mutations were contributing to substantial fractions of familial ovarian cancer. Just before *BRCA1* and *BRCA2* were identified, as PI I carried out during 1994-2000 a population-based case-control study of high penetrance mutations in ovarian cancer, in Ontario, Canada. After the study began, the genes were identified and we used sequencing and related methods to identify mutations. This work was conducted with Dr. Steven Narod, who became PI of the study renewal after 2000. I developed statistical methods to estimate lifetime penetrance of the mutations for ovarian and other cancers, to estimate population prevalence of the mutations, and to examine differences in risk and penetrance according to locations of the mutations in the genes. This work has been a standard of reference for knowledge about *BRCA1/2* mutations in ovarian and other cancers:

- a. Narod SA, **Risch H**, Moslehi R, Dørum A, Neuhausen S, Olsson H, Provencher D, Radice P, Evans G, Bishop S, Brunet J-S, Ponder BAJ, Klijn JGM. Oral

contraceptives and the risk of hereditary ovarian cancer. The Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 1998;339:424-8.

- b. **Risch HA**, McLaughlin JR, Cole DEC, Rosen B, Bradley L, Kwan E, Jack E, Vesprini DJ, Kuperstein G, Abrahamson JLA, Fan I, Wong B, Narod SA. Prevalence and penetrance of germline *BRCA1* and *BRCA2* mutations in a population series of 649 women with ovarian cancer. *Am J Human Genet* 2001;68:700-10.
- c. **Risch HA**, McLaughlin JR, Cole DEC, Rosen B, Bradley L, Fan I, Tang J, Li S, Zhang S, Shaw PA, Narod SA. Population *BRCA1* and *BRCA2* mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. *J Natl Cancer Inst* 2006;98:1694-706.

Paper 2.c was among the first population-based studies to demonstrate a significant association of *BRCA2* mutations in pancreatic cancer, and helped to establish that *BRCA1* and *BRCA2* mutations (not just mutations in the gene regions) are involved in cancers other than breast and ovary.

3. Lung Cancer in Women. In the 1980s, it had become apparent that incidence rates of lung cancer in women in North America were rising dramatically. From a population-based case-control study of lung cancer in men and women in Ontario, Canada, led by Dr. Anthony Miller, I analyzed cigarette smoking differences and showed that at every level of smoking, female smokers had significantly greater risks than male smokers, and concluded that females had, dose-for-dose, greater susceptibility to cigarette smoking than males:

- a. **Risch HA**, Howe GR, Jain MJ, Burch JD, Holowaty EJ, Miller AB. Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type. *Am J Epidemiol* 1993;138:281-93.

This paper received substantial attention, as well as some criticism that absolute risks are not assessable in case-control studies. A few subsequent cohort analyses claimed to show no smoking-adjusted risk differences between males and females. I pointed out that ten cohort studies by that time had shown baseline lung-cancer risks for women at 75% of male risks, thus the huge smoking risks for women did indeed reflect higher absolute risks. Further, I showed that the cohort analyses had used erroneous statistical hypotheses, the correct one examining dose-response separately for males and females (i.e., interaction between sex and smoking dose):

- b. **Risch HA**, Howe GR, Jain MJ, Burch JD, Holowaty EJ, Miller AB. Lung cancer risk for female smokers. *Science* 1994;263:1206-8.
- c. **Risch HA**, Miller AB. Re: "Are Women More Susceptible to Lung Cancer?" *J Natl Cancer Inst* 2004;96:1560.

4. Etiology of Pancreatic Cancer. In 2001, a second report was published showing an association between colonization by *Helicobacter pylori* and risk of pancreatic cancer. After determining that *H. pylori* does not colonize the human pancreas, in reviewing the pathophysiology of the organism, I theorized that it was the bacterial effects on gastric acidity, risk up or down according to organism CagA negative or positive strain type, respectively, that modulates pancreatic cancer risk. This hypothesis has received a lot of scientific attention:

- a. **Risch HA**. Etiology of pancreatic cancer, with a hypothesis concerning the role of *N*-nitroso compounds and excess gastric acidity. *J Natl Cancer Inst* 2003;95(13):948-60.

I subsequently carried out two population-based case-control studies, one in Connecticut, where CagA positive and negative strains are both common, and a second in Shanghai, China, where CagA-positive strains predominate. These studies both showed that CagA-negative colonization is associated with increased risk, and CagA-positive colonization with decreased risk:

- b. **Risch HA**, Yu H, Lu L, Kidd MS. ABO blood group, *Helicobacter pylori* seropositivity, and risk of pancreatic cancer: a case-control study. *J Natl Cancer Inst* 2010;102(7):502-5. PMID: PMC2902822.
- c. **Risch HA**, Lu L, Kidd MS, Wang J, Zhang W, Ni Q, Gao Y-T, Yu H. *Helicobacter pylori* seropositivities and risk of pancreatic carcinoma. *Cancer Epidemiol Biomarkers Prev* 2014;23(1):172-8. PMID: PMC394715.

Meta-analysis suggests that this etiologic distinction by strain type may be real, and it has been moderately confirmed in studies in Poland and Australia, though other earlier studies are unclear. This theory needs to be resolved, as it has substantial bearing on possible prevention of pancreatic cancer. Finally, I have recently developed statistical models to show that the known risk factors, when accompanied by objective prodrome signs and symptoms of the disease, can be used to predict the diagnosis of pancreatic cancer over the subsequent 2-3 years:

- d. **Risch HA**, Yu H, Lu L, Kidd MS. Detectable symptomatology preceding the diagnosis of pancreatic cancer and absolute risk of pancreatic cancer diagnosis. *Am J Epidemiol* 2015;182(1):26-34. PMID: PMC Journal in Process.

My PhD dissertation in biomathematics involved development of quantitative stochastic differential equation models of infectious epidemic processes and advanced statistical analysis of data in these models. I completed substantial graduate coursework in measure-theoretic advanced probability theory and statistics in the department of statistics at the University of Chicago, under Patrick Billingsley, Ron Thisted and Paul Meier. This preparation, along with extensive undergraduate work in mathematics, computer programming and computation, made me highly suited for the development of the absolute-risk statistical models in the above work.

5. Genome-wide Association Studies of Ovarian, Endometrial, Esophageal and Pancreatic Cancer. I have been an active participant in the OCAC, iCOGS, E2C2, BEAGESS and PanScan consortial genome-wide association (GWAS) studies. I am also a co-investigator of the Johns Hopkins Pancreatic Cancer GWAS Study, led by Dr. Alison Klein, and Co-PI with her of the CIDR application that funded GWAS genotyping in that study. As part of my biomathematics PhD curriculum, I took coursework in human genetics, statistical genetics and theoretical population genetics. My involvements in the GWAS consortia, while not comprising leadership roles, have provided me with continuing and extensive experience with all of the methodologies employed to carry out and interpret GWAS studies of cancer. Data from my case-control studies have been included in all of these consortial analyses, and I have contributed substantial points of interpretation and discussion to the published manuscripts. To-date, I am a co-author on more than three dozen cancer GWAS publications, of which the following three serve as a representative sample among eight in pancreas cancer:

- a. Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, Arslan AA, Bueno-de-Mesquita HB, Gallinger S, Gross M, Helzlsouer K, Holly EA, Jacobs EJ, Klein AP, LaCroix A, Li D, Mandelson MT, Olson SH, **Risch HA**, Zheng W, Albanes D, Bamlet WR, Berg CD, Boutron-

Ruault M-C, Buring JE, Bracci PM, Canzian F, Clipp S, Cotterchio M, de Andrade M, Duell EJ, Gaziano JM, Giovannucci EL, Goggins M, Hallmans G, Hankinson SE, Hassan M, Howard B, Hunter DJ, Hutchinson A, Jenab M, Kaaks R, Kooperberg C, Krogh V, Kurtz RC, Lynch SM, McWilliams RR, Mendelsohn JB, Michaud DS, Parikh H, Patel AV, Peeters PHM, Rajkovic A, Riboli E, Rodriguez L, Seminara D, Shu X-O, Thomas G, Tjønneland A, Tobias GS, Trichopoulos D, Van Den Eeden SK, Virtamo J, Wactawski-Wende J, Wang Z, Wolpin B, Yu H, Yu K, Zeleniuch-Jacquotte A, Fraumeni JF Jr, Hoover RN, Hartge P, Chanock SJ. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. *Nat Genet* 2010;42:224-8. PMID: PMC28533179.

- b. Parikh H, Jia J, Zhang X, Chung C, Jacobs KB, Yeager M, Boland J, Hutchinson A, Burdett L, **Risch HA**, Jacobs EJ, Stolzenberg-Solomon RZ, Chanock SJ, Wolpin BM, Petersen GM, Fuchs CS, Hartge P, Amundadottir L. A re-sequencing analysis of genomic loci on chromosomes 1q32.1, 5p15.33 and 13q22.1 associated with pancreatic cancer risk. *Pancreas* 2013;42(2):209-215. PMID: PMC3618611.
- c. Tang H, Wei P, Duell EJ, **Risch HA**, Olson SH, Bueno-de-Mesquita HB, Gallinger S, Holly EA, Petersen GM, Bracci PM, McWilliams RR, Jenab M, Riboli E, Tjønneland A, Boutron-Ruault MC, Kaaks R, Trichopoulos D, Panico S, Sund M, Peeters PHM, Khaw K-T, Amos CI, Li D. Genes-environment interactions in obesity- and diabetes-associated pancreatic cancer: A GWAS data analysis. *Cancer Epidemiol Biomarkers Prev* 2014;23(1):98-106. PMID: PMC3947145.

A complete list of my published work is in MyBibliography (not including papers accepted for publication or in press):<https://www.ncbi.nlm.nih.gov/sites/myncbi/harvey.risch.1/bibliography/40494257/public/?sort=date&direction=descending>

D. Research Support

Ongoing Research Support

NIH/NCI: 1U01 CA247283 (AP Klein PI) 5/01/20-4/30/25

Multi-Ancestry Mapping of Pancreatic Cancer Susceptibility Loci

Collaborative multi-center study to validate and explore ancestry/ethnicity-specific genome-wide genetic associations in pancreatic cancer. Dr. Risch serves as epidemiology Co-Investigator and subsite PI in this study.

NIH/NCI: 2R01 CA154823 (AP Klein PI) 4/01/16-3/31/21

Validation and Fine-Scale Mapping of Pancreatic Cancer Susceptibility Loci

Collaborative multi-center study to validate and explore genome-wide genetic associations in pancreatic cancer. Dr. Risch serves as epidemiology Co-Investigator and subsite PI in this study.

Recently Completed Research Support

NIH/NCI: 1R21 CA220073 (C Jeon PI) 4/01/18-3/31/20

Predicting the Diagnosis of Pancreatic Cancer by Leveraging Big Data

Project to develop a prediction model that relies on multiple health indicators present in ongoing collections of electronic health data to identify people with a high probability of having undiagnosed pancreatic cancer. Dr. Risch serves as epidemiology Co-Investigator and subsite PI in this study

Item #6

Brazil Covid-19 Treatment Paper

Risk of Hospitalization for a New Covid-19 Outpatient Treatment Protocol in Brazil

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Abbreviations: ER, Emergency Room; HMO, Health Maintenance Organization; HCQ, hydroxychloroquine

Running Head: Covid-19 Outpatient-Treatment Hospitalization Risk in Brazil

Conflicts of Interest: Dr. Risch acknowledges past advisory consulting work with two of the more than 50 manufacturers of the various medications analyzed herein. This past work was not related to any of these medications and was completed more than two years ago. He has no ongoing, planned or projected relationships with any of these companies, nor any

other potential conflicts-of-interest to disclose. None of the other authors have any potential conflicts of interest to disclose.

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Abstract

For the past few months, HMOs have faced crowded emergency rooms and insufficient hospital and intensive-care-unit beds, all from the worst pandemic of this century, COVID-19. In a large HMO in Brazil, our approach was to allow treating physicians to prescribe antiviral medications immediately at presentation, and prednisone starting on day-6 of symptoms to treat pulmonary inflammation. We implemented this COVID-19 protocol for outpatients and studied 717 consecutive SARS-CoV-2-positive patients 40 years of age or older presenting at our emergency rooms. Use of hydroxychloroquine (HCQ), prednisone or both significantly reduced hospitalization risk by 50-60%. Ivermectin, azithromycin and oseltamivir did not reduce risk further. Hospitalization risk was doubled for people with diabetes or obesity, increased by two-thirds for people with heart disease, and by 75% for each decade of age over age 40. Similar magnitudes of reduced risk with HCQ and prednisone use were seen for mortality risk, though were not significant because of only 11 deaths among the 717 patients. This work adds to the growing literature of studies that have found substantial benefit for use of HCQ combined with other agents in the early outpatient treatment of COVID-19, and adds the possibility of steroid use to enhance treatment efficacy.

Mankind has been facing one of the greatest challenges of the XXI century: a pandemic (1) caused by a new virus, SARS-CoV-2, thought to be transmitted by droplets and contact with contaminated surfaces or objects (2). Clinical manifestations of coronavirus disease 2019 (COVID-19) patients range from asymptomatic to mild non-specific signs and symptoms to severe pneumonia with organ function damage and eventually mortality (3, 4). There is a clear need to try to stop disease progression as early in the disease process as possible. Infected patients with comorbidities such as heart failure, diabetes, asthma or chronic obstructive pulmonary disease and obesity, and patients over sixty years of age are at substantially higher risk to develop severe disease and tend to have higher risks of death (5-7). Many drugs have been tried in hospitalized patients, with largely discordant results (8-11). Randomized double-blind controlled trials demonstrating benefit or lack of benefit of drugs will not be available any time soon, as many clinical sites are still recruiting patients (12). Early outpatient illness is very different than hospitalized severe disease and treatment therefore will differ between these two distinct groups. Relatively little is established about utility of medications in early outpatient treatment. Currently (13) it is understood that COVID-19 is a four-phase illness: phase 1 is viral replication, followed by pulmonary inflammation in phase 2, “cytokine storm” and acute respiratory distress in phase 3, and disseminated multi-organ involvement in phase 4. For treatment at the beginning of the illness, there are indications that chloroquine and especially hydroxychloroquine (HCQ) may be beneficial, but no specific antiviral medications have demonstrated proven efficacy as yet (14, 15). Recently, the Brazil Federal Committee for Medicine has approved the prescription of chloroquine and HCQ for clinically suspected COVID-19 patients at the physician’s discretion with informed consent (16) and the Health Ministry has

also endorsed the use of these medications (17). Brazil has the highest rate in South America in the ranking of COVID-19 deaths, with more than 1 million people infected in the country (18) in circumstances of a large population still to be affected and with economic difficulties resulting in inadequate social distancing. Data over March-May from the Federal Health Ministry (19) show that more than 90% of hospitalized patients with severe respiratory distress who were tested were positive for SARS-CoV-2, with less than 5% detected with influenza. Therefore we assumed in clinical practice that most patients coming to the emergency room with flu-like symptoms would have COVID-19. With all that, we developed a protocol for early recognition and treatment of high-risk patients (in our population, age greater than 40 years because of generally poorer health standards, or with comorbidities) who would come to our outpatient network of emergency rooms with flu-like symptoms: fever, cough, myalgia and headache, among others, and receive early treatment, provided to patients at the first doctor visit, using physician discretion from among HCQ, ivermectin, oseltamivir, zinc sulfate, nitazoxanide and prednisone (the last starting on day-6 of symptoms). We evaluate here risks of subsequent hospitalization based upon outpatient use of these various medications.

Methods: Patient data from electronic charts of health maintenance organization (HMO) Hapvida Saúde, the largest Brazilian HMO with 6 million members spread over five regions of the country, were analyzed. Data were collected after informed consent and Institutional Ethics Committee (4.087.824 CEP-University Fortaleza UNIFOR) approval for this study. To-date, during the pandemic, more than 300,000 monthly emergency room (ER) consults have occurred. Patients were all seen at the ERs of the widespread country hospital network and admitted if indicated. At the beginning of the pandemic in Brazil, late March-April 2020, the north and northeast

cities were more affected, with a great number of ER consults and hospital and intensive-care-unit admissions. A protocol for early treatment of COVID-19 was developed by a team of senior HMO medical staff and started in early May; it included clinical recognition of the commonly described main COVID-19 signs and symptoms, and protocol criteria assessment for hospital admission vs outpatient care. Patients coming with flu-like symptoms such as fever, sore throat, myalgia, arthralgia or coryza would enter the COVID-19 protocol. Patients presenting with hypoxia, defined as the need of oxygen to maintain an oxygen saturation greater than 92%, respiratory rate of or greater than 24 respirations/minute, hypotension defined as systolic pressure less than 90 mm Hg or diastolic pressure less than 60 mm Hg, or with confusion or extreme lethargy were immediately admitted to the hospital. The remaining patients over age 40 or with comorbidities were treated as outpatients. The protocol specifics were chosen by the attending physician, and all of its steps were monitored for quality assurance. The protocol was largely automated through on-screen suggestions and physician choice boxes leading to successive screens, medication prescription choices, etc. After discharge from the ER, patients received paper charts instructing them on isolation, symptoms to expect and medications to use, and QR codes for telemedicine, chat or phone consults. Telemedicine was also always available to HMO patients on the HMO website. For discharged patients, the COVID-19 protocol included (all as oral medications), as chosen by doctors and patients: HCQ as first-line treatment, if used (400 mg bid day 1, 400 mg qd days 2-5), prednisone (1 mg/kg qd x 5 days, no taper), azithromycin (500 mg qd x 5 days), ivermectin (12 mg qd x 2 days), plus symptom relievers. Zinc sulfate and nitazoxanide were also available to be prescribed but were used infrequently. As doctors quickly found that most of the prescribed HCQ was not

arrhythmia events requiring medication termination for any of the medications used in the 717 patients that we analyzed, and no deaths attributable to such arrhythmias.

Discussion SARS CoV2 will cause greater mortality than any recent contemporary pandemic; only when the pandemic ends it will be possible to assess the full health, social and economic impact of this global disaster (21-23). Preliminary data show that in developed countries, the impact will be huge. But in developing countries, where public health systems already face great challenges to provide basic health care to all in need, the impact will be several times greater (21-23). These problems will not be solved anytime soon. In the midst of the SARS-CoV-2 pandemic, a feasible approach, with inexpensive drugs, relying on syndromic signs and symptoms rather than scarce laboratory tests may help many patients and will be even more important in developing countries. Around the world there are already over 8 million confirmed COVID-19 cases (24). Brazil has the second-largest number, with 1 million cases and 47,000 deaths as of June 18th (24). If this trend continues, in about four months, Brazil will have the worldwide largest number of cases of any country.

In March 2020, the World Health Organization recommended the use of medications oseltamivir and antibiotics (25). On March 28, 2020, the FDA issued an emergency use authorization for remdesivir and HCQ for patients in both clinical trials and with severe hospitalized disease (26). Since then, pharmacological treatments have been controversial, and on June 15 the FDA retracted its earlier authorization, allowing general access to the US national strategic stockpile of HCQ and leaving its outpatient use available but not explicitly supported (27). Countries such as China and India have issued guidelines allowing for the use of chloroquine or HCQ in

COVID-19 (28, 29). Evidence of the real-world unimportance of arrhythmia and other cardiovascular adverse-event endpoints of HCQ and HCQ+AZ use is given in the large Oxford-based record-linkage study (30). Understanding the pathophysiology of COVID-19 in the different clinical stages of the disease is important, as treatments will change according to progression of the disease (13). Our study showed that HCQ alone, prednisone alone, and HCQ plus prednisone did better than standard treatment for early stage COVID-19. It may be that the corticosteroid benefit involves low levels of type I and III interferons juxtaposed to elevated chemokines and high expressions of IL-6. Reduced initial innate antiviral defenses allow the virus to multiply, followed after a few days by relatively excess inflammatory cytokine production, allowing for steroids to reduce the latter in the early features of COVID-19, before appreciable pneumonia has occurred (31).

Because all treatments have costs and benefits, treating all high-risk patients early would take a major effort from Brazil's Universal Public System (SUS) and its private HMOs, but would be much less expensive than hospital-based inpatient treatment, which would probably be impossible on the scale needed. Our study showed that about 10% of high-risk outpatients over age 40 treated with prednisone still required hospitalization, which is substantially better than the 24% among untreated patients, thus even this treatment plan could create a large hospital-bed demand. However, we found that even in hospital, these treated patients do better and their mortality is much lower.

In an ideal world, large randomized double-blinded controlled clinical trials establish evidence, but take time to complete and many are not large enough for the randomization to be sufficiently effective in reducing biases. To-date, treatment protocols have proposed drugs with antiviral activity, and with anti-inflammatory

responses, such as therapeutic regimens of IFN- α +lopinavir/ritonavir and IFN- α +lopinavir/ritonavir+ribavirin, among others. While cost-effectiveness of these regimens have been challenged, HCQ is generic and has been prescribed for malaria for decades, as it has antiviral and anti-inflammatory properties. On March 27th, 2020 the Brazilian Federal Health Authority issued a note saying that it would treat severely ill patients in the Public System with HCQ (32). On May 20th, the same authority issued another note that HCQ would be available for physicians to prescribe for outpatients and mild cases, according to symptoms and severity (17). Prednisone is also generic and inexpensive and has been used for many decades and does not interact adversely with HCQ.

Our results demonstrate a positive benefit of HCQ and prednisone in decreasing hospital admissions in a high-risk population over 40 years of age with RT-PCR-positive SARS-CoV-2 infection when started at first doctor visit. An outpatient benefit of HCQ use has been summarized elsewhere (30) but to our knowledge this is the first time that efficacy of outpatient prednisone use has been reported. Use of these medications also showed some evidence of reduced mortality in the study group, and larger studies of mortality will be needed to validate this finding. We observed that outpatient hospitalizations of the larger group of suspected COVID-19 ER patients, from the same HMO database before vs after the protocol started, March-April vs May, decreased significantly, 23% vs 9%, and mortality declined from 1.75% to 1.39%. For May, our HMO data also show that the mortality was less than COVID-19 mortality for Brazil as a whole.

Our study has several limitations. This is a retrospective, chart-based study, and even though our initial sample of patients was large, with almost 25,000 patients, few of these patients were tested due to the scarcity of RT-PCR tests. Then, we chose to

study only tested-positive SARS-CoV-2 patients to make sure we were dealing with confirmed cases of COVID-19. Limiting analyses to patients greater than 40 years of age further reduced our sample size. Nevertheless, our experience of approaching and treating patients with flu-like symptoms in this era of pandemic SARS-CoV-2 is useful and more generally applicable. In one State Hospital Network of the cohort this spring, more than 90% of patients admitted to the hospital with appreciable respiratory distress had positive RT-PCR for SARS-CoV-2 (33), so it seems reasonable to infer that it would be similar for patients with influenza-like illness presenting at the emergency room. Also, our study involved a range of treatment medications assigned by HMO physicians using their clinical judgements, rather than mandated by study design. Clinical treatment decisions allow for the possibility that sicker patients get more or more aggressive treatments, creating the potential of confounding by indication. The comorbidity distributions of the various treatments as shown in Table 1 suggest that except for shortness of breath, patients not treated with HCQ or prednisone may have been slightly less symptomatic than treated patients. However, this would if anything have tended to reduce the magnitude of risk lowering that we found for these medications toward the null. A pattern of chronic comorbidity differences is not apparent in the table; nevertheless, our results were adjusted for those comorbidities where associations with risk of hospitalization were observed (Table 2). In spite of the aforementioned, our study was large enough to have observed statistically significant results and was based on actual clinical conditions and data recorded in active clinical charts, to enable reasonable inference about lack of reporting biases in the analyzed data.

Our analyses thus show that it is possible to give HCQ with companion medications in an early stage protocol that proves to be safe, and warnings about cardiac

arrhythmia adverse events are unnecessary unless significant contraindications are known. Treatment-failure mortality, while small, is still the major concern of patient management. Our new protocol is continuing in clinical practice in our HMO, and we hope for it to be more generally applied across the rest of Brazil as quickly as possible.

Conclusion: We found early outpatient use of HCQ and prednisone, both as individual prescriptions and used together, to lower the risk of hospitalization in symptomatic high-risk COVID-19 patients presenting for primary care at the emergency rooms of our large HMO in Brazil. Other than the small numbers of treatment failure, no potentially life-threatening adverse events were recorded with medication treatment. These medications were found to be safe and beneficial for the early outpatient treatment of COVID-19.

Table 1. Characteristics of Tested-positive Covid-19 Patients Treated Under the New Hapvida Brazil HMO Protocol

| | Given neither HCQ nor Prednisone (n=244) | Given both HCQ and Prednisone (n=159) | Given HCQ Only (n=175) | Given Prednisone Only (n=139) | All Patients (n=717) |
|----------------------------------|--|---------------------------------------|------------------------|-------------------------------|----------------------|
| Age (mean, years) | 52.0 | 50.4 | 50.3 | 48.8 | 50.6 |
| Presentation delay* (mean, days) | 4.2 | 4.5 | 4.4 | 5.6 | 4.6 |
| Sex (% Female) | 54.5 | 45.9 | 48.0 | 59.0 | 51.9 |
| Hospitalized (%) | 24.2 | 10.1 | 14.3 | 10.1 | 15.9 |
| Ventilated (%) | 3.3 | 2.5 | 1.1 | 3.6 | 2.6 |
| Died (%) | 2.9 | 0.6 | 0.6 | 1.4 | 1.5 |
| Cough (%) | 67.2 | 73.0 | 74.9 | 66.9 | 70.3 |
| Fever (%) | 59.4 | 66.7 | 65.7 | 61.9 | 63.0 |
| Myalgia (%) | 37.7 | 44.7 | 53.1 | 36.0 | 42.7 |
| Sore Throat (%) | 19.3 | 23.9 | 29.1 | 26.6 | 24.1 |
| Headache (%) | 35.7 | 41.5 | 39.4 | 41.0 | 38.9 |
| Diarrhea (%) | 7.4 | 8.2 | 11.4 | 11.5 | 9.3 |
| Shortness of Breath (%) | 30.3 | 28.9 | 28.0 | 20.9 | 27.6 |
| Type 2 Diabetes Mellitus (%) | 18.4 | 15.1 | 21.7 | 11.5 | 17.2 |
| Obesity (BMI>30, %) | 7.8 | 6.9 | 20.6 | 5.0 | 10.2 |
| Heart Disease (%) | 29.9 | 31.4 | 41.1 | 18.8 | 30.8 |
| Pulmonary Disease (%) | 4.5 | 1.3 | 4.0 | 3.6 | 3.5 |
| Given Azithromycin (%) | 43.4 | 50.3 | 65.7 | 58.3 | 53.3 |
| Given Ivermectin (%) | 24.2 | 77.4 | 42.9 | 59.7 | 47.4 |
| Given Oseltamivir (%) | 9.0 | 7.5 | 26.3 | 7.9 | 12.7 |

* Number of patients with data on date of start of symptoms, 222, 152, 168, 134 and 676 in the respective columns.

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Item #7

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GAGNEZ UNE MAISON GRACE A L'EXPERT FRANCESOIR !

Covid-19: l'hydroxychloroquine marche, une preuve irréfutable

Publié le 13/07/2020 à 08:51 - Mise à jour à 12:56



Covid-19: l'hydroxychloroquine marche, une preuve irréfutable
Unsplash

PARTAGER :    

Auteur(s): Michel Jullian et Xavier Azalbert pour FranceSoir A⁺ A⁻

De longs échanges ont enflammé la toile et les réseaux sociaux sur le rôle de l'hydroxychloroquine comme traitement contre la Covid-19. Ces échanges se résument souvent à se jeter à la figure les résultats d'études diverses et variées. Il s'ensuit un débat d'experts sur la validité de l'étude et des divers protocoles, permettant de donner à chacun l'opportunité d'avancer, avec une certaine mauvaise foi, ses arguments orientés. En effet, **il est toujours possible de trouver un argument en faveur du résultat** d'une étude si elle tend à démontrer l'inefficacité de l'hydroxychloroquine, et inversement.

Quand son efficacité n'est pas en question, on parle de ses effets secondaires. La réalité est que ce médicament est prescrit depuis 65 ans (1955). Ses effets secondaires et précautions d'usage sont

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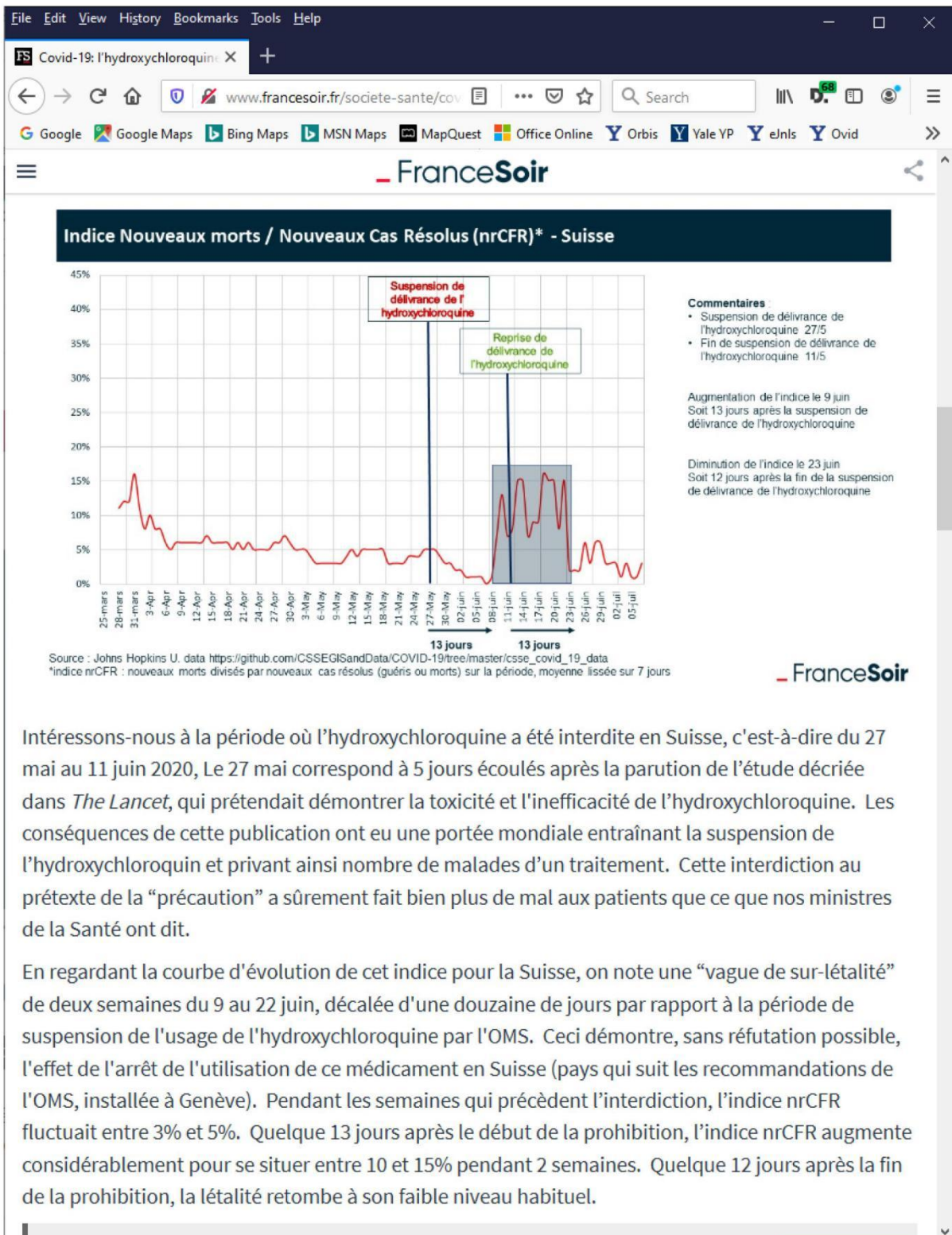
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Une différence statistiquement significative

Pour ceux qui ne seraient pas convaincus du résultat observationnel, nous avons conduit un test de différence statistique en comparant les trois périodes : 28 mai - 8 juin, 9 - 22 juin, 23 juin - 6 juillet. La période du 9 au 22 juin est celle où l'indice a augmenté quelque 13 jours après la suspension de l'hydroxychloroquine. Il y a bien entendu un effet de retard entre l'arrêt de la prescription du médicament et les décès éventuels, ce qui explique le décalage de 13 jours.

Test de différence statistique

| Période | Décès | Cas résolus (guéris ou morts) | Indice nrCFR |
|---------------------|-------|-------------------------------|--------------|
| 28 mai - 8 juin | 13 | 543 | 2.39% |
| 9 - 22 juin | 35 | 300 | 11.52% |
| 23 juin - 6 juillet | 9 | 300 | 3.00% |

Commentaires :

- Test statistique période 28 mai au 8 juin versus 9 juin au 22 juin statistiquement différent à 99% avec $p < 0.001$
- Test statistique période 9 au 22 juin versus période du 23 juin au 6 juillet statistiquement différent à 99% avec $p < 0.001$

Source : Johns Hopkins U. data https://github.com/CSSEGISandData/COVID-19/tree/master/csse_covid_19_data
 *indice nrCFR : nouveaux morts divisés par nouveaux cas résolus (guéris ou morts) sur la période, moyenne lissée sur 7 jours

FranceSoir

Nous observons donc que pour la période du 28 mai au 8 juin l'indice est de 2,39% puis passe à 11,52% soit 4,8 fois plus pour redescendre ensuite à 3%.

En faisant le test de significativité statistique entre les diverses observations, **la différence est significative à 99% avec un $p < 0.0001$** . 13 jours après la reprise de la prescription de l'HCQ l'indice redescend à 3% et c'est de nouveau un effet **significatif**.

Et pour la France

Cet indice pour la France sur la même période se trouve dans le graphe ci-dessous. On note que dans la période de prohibition de l'hydroxychloroquine en Suisse, l'indice nrCFR était à peu près identique entre la France et la Suisse.

Section 3

George C. Fareed, M.D.

Item #1

Letter to Member of Congress Juan Vargas

July 11, 2020

Dear Member of Congress, Juan Vargas:

My name is Dr. George Fareed. I am a physician in Imperial County, California, that has been hit hard by the COVID-19 pandemic. I take care of patients on both an outpatient and inpatient basis, as well as nursing home patients, the most vulnerable among us.

In this letter, I am proposing a medical strategy that can help us not only through this current crisis, but also that will enable us to approach outbreaks of COVID-19 that may occur in the future.

In my attempts to keep people alive, I have had an opportunity to use many different types of treatments- remdesivir, dexamethasone, convalescent plasma replacement, etc. Yet, by far the best tool beyond supportive care with oxygen has been the combination of hydroxychloroquine (HCQ), with either azithromycin or doxycycline, and zinc. This "HCQ cocktail" (that costs less than \$100) has enabled me to prevent patients from being admitted to the hospital, as well as help those patients that are hospitalized. The key is giving the HCQ cocktail early, within the first five days of the disease.

Not only have I seen outstanding results with this approach, I have not seen any patient exhibit serious side-effects. To be clear- this drug has been used as an anti-malarial and to treat systemic lupus erythematosus as well as rheumatoid arthritis, and has over a 50-year track record for safety. It is shocking that it only now is being characterized as a dangerous drug.

Moreover, I am in my seventies, and I (as well as some other older physicians in the hospital) use hydroxychloroquine and zinc as prophylaxis. None of us have contracted the disease despite our high exposure to COVID patients nor have we experienced any side-effects.

Despite the characterization in the mainstream media as the drug being "ineffective" and "dangerous", the evidence in the literature tells a different story. I am not only an "MD", but a former Harvard Medical School assistant professor and UCLA School of Medicine associate professor as well and am very competent at evaluating studies. There is ample evidence now that the HCQ cocktail is effective, and there is no good evidence that there are significant side effects.

Yet, like many of my colleagues in the trenches treating COVID, I find myself being obstructed on different levels from treating my patients with hydroxychloroquine. The

next option is remdesivir, which in my opinion is inferior and very expensive. Moreover, that drug is not readily available, and is rationed by hospitals. Despite the representations by Dr. Fauci and others, there is less evidence supporting the use of remdesivir than hydroxychloroquine.

To be clear- hydroxychloroquine is normally not helpful when given to very ill patients. Unfortunately, most of the studies have evaluated this drug only in that context. The HCQ cocktail is best used to *prevent* patients from getting to that dire stage.

This is all so tragic because the use of HCQ cocktail would solve some of the very basic problems we are now facing:

#1 The HCQ cocktail can be used for outpatients to prevent hospitalizations and thus keep our hospitals and ICUs from being overrun with COVID patients.

#2 The HCQ cocktail can be used early on in hospitalization to prevent patients from requiring mechanical ventilation and reducing the length of hospital stay.

#3 HCQ/zinc can be used for prophylaxis for high risk individuals including front line health providers, first responders, and even teachers who are at high risk for COVID.

As a physician, I am committed to my patients as well as doing my part to solve the COVID crisis. It has been deflating to see how the "science" has been corrupted and manipulated in an effort to disparage hydroxychloroquine. The fact that both Lancet and the New England Journal of Medicine had to retract articles relevant to hydroxychloroquine due to gross manipulation and mischaracterization of data goes to the heart of what is best characterized as a smear campaign.

As an example of the faulty science- one study (University of Minnesota) was cited in the mainstream media as disproving the effectiveness of hydroxychloroquine as "prophylaxis"- yet the patients received the drug 1 to 4 days AFTER exposure. That is not prophylaxis at all—the drug must be taken PRIOR to exposure. This is just one example of the non-scientific way the drug has been evaluated and the subsequent mainstream media mischaracterizations.

I am writing to you out of the frustration of knowing that there is a solution, but watching as our country flounders in dealing with COVID-19. In my opinion, tens of thousands are dying unnecessarily. Our current approach of waiting for these high-risk patients to become ill and then hospitalizing them is failing. The answer is early diagnosis of the high-risk individuals, and then treating them as outpatients with the

HCQ cocktail to prevent hospitalization.

So, what I am proposing is a drastic shift from our current approach: we need to ramp up our *outpatient* efforts of treating COVID-19 to decrease the burden on hospitals and save lives. Such an approach requires an effective outpatient treatment- we have that in the HCQ cocktail.

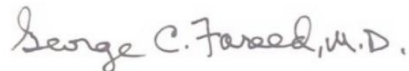
How do we get there? I propose a Congressional hearing in which our elected representatives could listen to clinicians like myself and researchers specifically regarding the HCQ cocktail (as well as the HCQ/zinc prophylaxis treatment), and how it can help us change to a model focused on outpatient treatment and prevention as opposed to a hospital-based approach only treating patients when they become ill. The FDA and CDC should be there as well given that they are the agencies that formulate the drug policies.

We need a medical strategy, not only for now while we are in a crisis, but for the future. There is no guarantee that a vaccine will rid us of COVID-19. If we had a strategy, we would not have to shut down American life, especially schools, every time there is an outbreak.

We should be seeking a solution that will save as many lives as possible, and the outpatient-based approach that I and some other doctors have been advocating will best accomplish that goal.

I hope you consider my proposal, and I look forward to hearing from you.

Sincerely yours,



George C. Fareed, M.D.
CMA Rural Physician of the Year 2015

Brawley, CA 92227
Mobile phone: 760-554-2244

Item #2

Article:

**“Local doctor pushing proven treatment of
COVID into national debate”**

Local Physician Proposes Medical Strategy Using ‘HCQ’

July 16, 2020 Dr. George Fareed



Dr. George Fareed

(EDITOR'S NOTE: The following is a July 11 letter Fareed penned to Congressman Juan Vargas and others in the federal government, including President Donald Trump. Fareed submitted it as an op-ed to be run in its entirety.)

My name is Dr. George Fareed. I am a physician in Imperial County, California, that has been hit hard by the COVID-19 pandemic. I take care of patients on both an outpatient and inpatient basis, as well as nursing home patients, the most vulnerable among us.

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I hope you consider my proposal, and I look forward to hearing from you.

Sincerely yours, George C. Fareed, M.D.

CMA Rural Physician of the Year 2015 Brawley, CA 92227

Item #3

Resume CV

CURRICULUM VITAE

GEORGE CARR FAREED, M.D.

PERSONAL:

Date of Birth August 31, 1944
Chicago, IL

Family Status Divorced with three children

EDUCATION:

June 1966 Bachelor of Arts -University of California, Berkley, CA

June 11, 1970 Doctor of Medicine - Harvard Medical School, Boston, MA (Received Soma Weiss Award for medical student research identified gene for key enzyme for recombinant technology.)

Medical Internship Peter Bent Brigham Hospital Boston, MA
1970 - 1971

LICENSURE

June 21, 1976 State of California G-31850
original date of issuance

HOSPITAL AFFILIATIONS

1988 - 1990 UCL A Medical Center, Los Angeles, CA

1992 - Present Pioneers Memorial Hospital, Brawley, CA

1996 - 1998 Pioneers Memorial Hospital Chief of Medicine

1995 - 1997 Chairman of Infection Control Committee

1993 - Present Current El Centro Regional Medical Center, El Centro, CA

1997 - 2002 Appointed Medical Director, AIDS Research Alliance, West Hollywood, CA

ACADEMIC APPOINTMENTS

1973 - 1976 Assistant Professor Harvard Medical School
Department of Biological Chemistry
Boston, MA

1979 - 1980 Visiting Professor University of Nice
Centre De Biochemie
Nice, France

Collaborative project developing one of the early vectors for gene transfer into animal and human cells.

1976 - 1983 Associate Professor UCLA School of Medicine
Los Angeles, CA
Microbiology and Immunology - developed new information on mutants in animal tumor viruses

1983 - 1990 Adjunct Associate Professor UCLA School of Medicine
Los Angeles, CA

MEMBERSHIP / APPOINTMENTS

1971 - 1973 Commissioned Officer (USPIIS)
National Institute of Allergy and Infectious Diseases, NIH

1976 - 1983 American Society for Biological Chemists

1984 - Present American Medical Association

1991 - 2013 Medical Director: The Carr Foundation (a non-profit medical research foundation)

1992 - 1995 Board of Directors: Arthur Ashe Foundation for the Defeat of AIDS

1995 - 1998 Campaign Committee, Arthur Ashe Wellness Center, UCLA

1993 - Present California Medical Association

1993 - Present Imperial Valley Medical Association

1993 - Present Physicians for Better Care, Imperial Valley, CA and Imperial Valley
Medical Group IPA (1995-Present)

1996 - Present Executive Committee member, Scripps Imperial Valley
Medical Associates IPA (Blue Shield/Secure Horizons / PacifiCare HMO Contracts)

1996 - 1997 Favorite Family Physician of employees of El Centro Regional Medical Center

2009 - 2017 Board of Director for Imperial County Physician Medical Group

2004 ITA Intercollegiate Tennis Association) Career Achievement Award Recipient

2007 Holtville High School Hall of fame Inductee

2008 AIDS Border Hero Award
(Presented at UBAST International AIDS conference,
Mexico City, MX August 2008)

2010 HIV Community Service Award, Imperial County CA

2010 Voted Best Physician of Imperial County CA

2013 - Present Imperial County Air Pollution Control District Board

MEDICAL PRACTICE

Practice in General Family Medicine

1984 - Practice in General Family Medicine
Los Angeles, CA

1991- Present Practice in General Family Medicine
Brawley and El Centro, CA

1996 - 2010 Occupational Medicine Program
Brawley and El Centro,

2012 - Present Hyperbaric Therapy and Wound Management Clinic
Pioneers Memorial Healthcare District Hospital
Brawley, CA

Practice in Sports Medicine

1984 L.A. ATP Tennis Tournament Doctor

1984 - 1991 Newsweek Grand Champions Tennis Tournament
Director, Special infection (HIV) Clinic

1995 - 1996 AIDS RESEARCH ALLIANCE
West Hollywood, CA

BIOMEDICAL RESEARCH ENTERPRISES:

1980 Founded International Genetic Engineering, Inc
(INGENE) Santa Monica, CA
(Developing products for the treatment of infections, cancer, and bone disease)

1980 - 1986 Director, Scientific Planning (INGENE)

1986 - 1989 Vice-President , Scientific Planning (INGENE)

1986 - 1989 Director of Cancer Biotherapy (INGENE)

1990 - 1991 Director, New Product Development XOMA Corp. (merged with
INGENE) Santa Monica, CA

1991 - 1994 Founder /President Advanced Antigens, Inc Santa Monica, CA
(Biotechnology Company developing immunization and gene
therapy products based on novel antigenic epitopes)

PATENTS

Inventor of three U.S. patents: two pertaining to cancer
regression antigens and one for the synthetic peptides for
arthrosclerosis.

PUBLICATIONS: 1983 "Molecular Biology of Polyomaviruses and Herpes
viruses."
New York: J.Wiley and Sons

Over 60 scientific articles published.

SPECIAL SKILLS

Fluency in French, written and spoken: Fluency in Spanish, written and spoken.

Experience with a variety of Macintosh and IBM- compatible software
applications

including: QD Clinical, NexGen EMR, eClinical Works, QCPR hospital charting,
Solarian Clinical hospital charting

CLINICAL RESEARCH EXPERIENCE

- 1986 - 1990 Adjunct Associate Professor, UCLA School of Medicine
Clinical Investigator, UCLA (Investigation Review
Committee Approval)
Trial: Active Specific Immunotherapy of Patients w/ Advanced
Solid Tumors: Intralymphatic Immunization with Irradiated
Human Tumor Cell
- 1988 - 1991 Regional Director (Los Angeles) and Investigator
Biological Therapy Trials Program **11-2/LAK** cell therapy trial,
Intralymphatic IL-2 infusion in solid tumor patients
(Sponsor: Biotherapies, Inc., Franklin TN)
- 1998 Investigator: 3TC Open Label Protocol NUCA3004 sponsored by
Glaxo Research Institute
- 1995 - 2000 Director of Clinical Research, AIDS Research Alliance
West Hollywood, CA
- 2008 POEM study of Maraviroc in advanced AIDS patients
Clinicas De Salud Del Pueblo, Brawley, CA
1988 -
1991 Regional Director (Los Angeles) and
Investigator
Biological Therapy Trials Program **11-2/LAK** cell therapy trial,
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