The hydroxychloroquine controversy for COVID-19: A review of the statistical evidence

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Outline

- Brief background on the COVID-19 disease
- Early evidence for hydroxychloroquine, azithromycin, zinc triple therapy
- Hydroxychloroquine pre-exposure prophylaxis protocol
- Case series threshold analysis technique
- Analysis of Raoult's 30,423 patient public database
- Final Comments

The zinc/zinc ionophore concept

OPEN ACCESS Freely available online

PLoS PATHOGENS

Zn^{2+} Inhibits Coronavirus and Arterivirus RNA Polymerase Activity *In Vitro* and Zinc Ionophores Block the Replication of These Viruses in Cell Culture

Aartjan J. W. te Velthuis[1], Sjoerd H. E. van den Worm[1], Amy C. Sims[2], Ralph S. Baric[2], Eric J. Snijder[1]*, Martijn J. van Hemert[1]*

1 Molecular Virology Laboratory, Department of Medical Microbiology, Center of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands, **2** Departments of Epidemiology and Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America

- Confirmed *in vitro* in 2010: intracellular Zn^{+2} ions slow viral replication by interfering with RdRp (RNA dependent RNA polymerase), used by SARS-1 and EAV (Equine Arteritis Virus) to replicate.
- RdRp is also used by: the common cold, SARS-CoV-2, influenza viruses, RSV (Respiratory Syncytial Virus), Marburg, Ebola
- Zn^{+2} ions require a zinc ionophore to bring them inside the cell
- Known zinc ionophores: pyrithione, chloroquine, hydroxychloroquine, ivermectin, quercetin, EGCG (Epigallocatechin Gallate)

Spikeopathy: Spike protein causes the COVID-19 disease

biomedicines

MDPI

Review

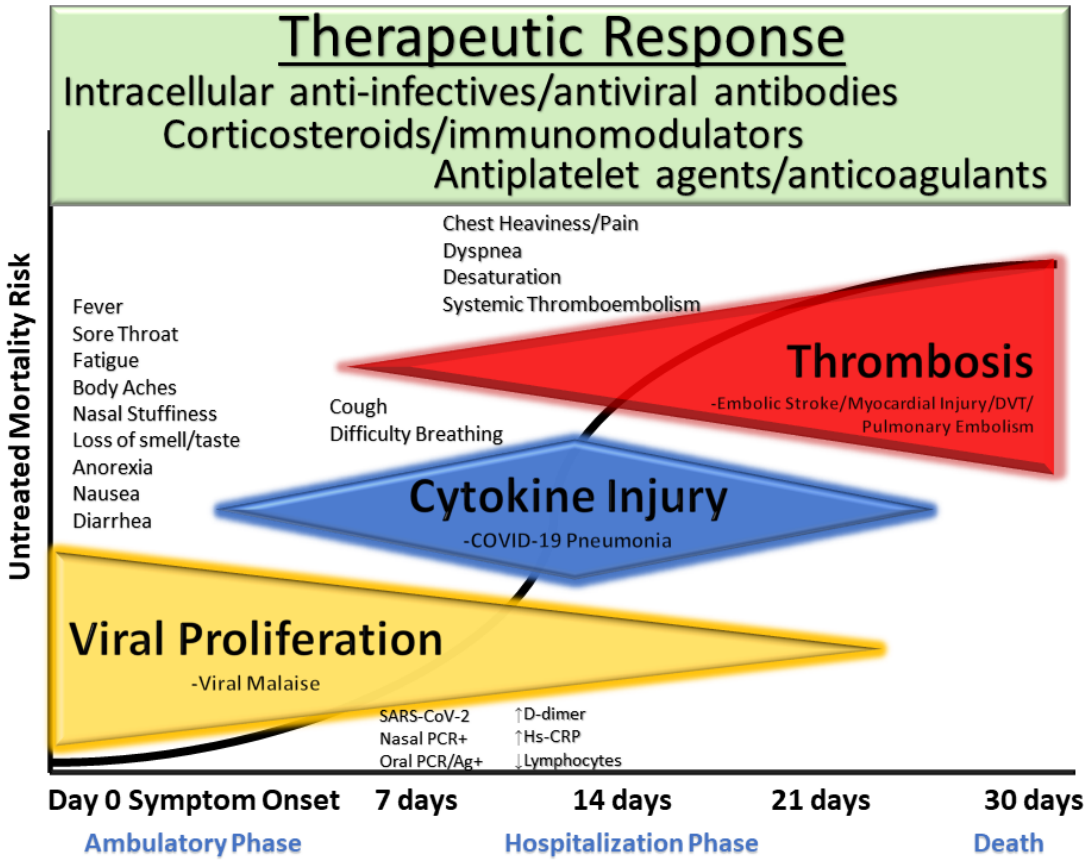
'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA

Peter I. Parry [1,2,*], Astrid Lefringhausen [3], Conny Turni [4], Christopher J. Neil [5], Robyn Cosford [3], Nicholas J. Hudson [6] and Julian Gillespie [3]

Biomedicines **2023**, *11*, 2287. https://doi.org/10.3390/biomedicines11082287 https://www.mdpi.com/journal/biomedicines

- The spike protein is used by the SARS-CoV-2 virus to dock with human cells and inject genetic material for replication.
- The spike protein causes the COVID-19 disease: hyperinflammation (coughing, difficulty breathing), microclots (oxygen desaturation, typically preceding death), immune suppression (difficulty implications for cancer elimination by the immune system)
- The spike protein may persist in the body for a very long period of time resulting in long-covid symptoms.
- Thus, a rational strategy is to minimize overall exposure to the SARS-CoV-2 spike protein.

Progression of COVID-19 disease



- A primarily anti-viral treatment may be effective only within the first few days of infection.
- **Cytokine Injury stage:** Corticosteroids, nebulized budesonide were suggested for treatment at this stage
- **Thrombosis phase:** Anti-coagulants, ivermectin, and nebulized nanosilver have been proposed.

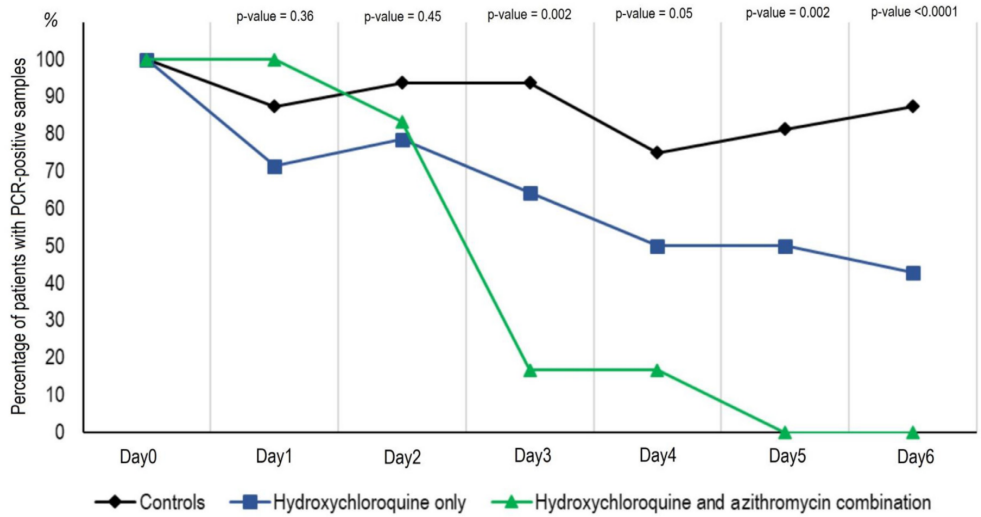
HCQ+AZ: Earliest evidence from IHU (Marseilles, France)

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial ☆

Philippe Gautret[a,b,$], Jean-Christophe Lagier[a,c,$], Philippe Parola[a,b], Van Thuan Hoang[a,b,d], Line Meddeb[a], Morgane Mailhe[a], Barbara Doudier[a], Johan Courjon[e,f,g], Valérie Giordanengo[h], Vera Esteves Vieira[a], Hervé Tissot Dupont[a,c], Stéphane Honoré[i,j], Philippe Colson[a,c], Eric Chabrière[a,c], Bernard La Scola[a,c], Jean-Marc Rolain[a,c],

International Journal of Antimicrobial Agents 56 (2020) 105949

- Treatment: HCQ (200 mg 3 times daily for 10 days), AZ (500 mg on day 1, 250mg on days 2-4; active for 10 days) within 2-6 days from onset of symptoms.



- Control patients were younger on average (some declined treatment or were treated in another hospital not offering treatment)
- Historical control cited: about 20 days for viral clearance without treatment.

HCQ+AZ+Zinc: Earliest evidence from Dr. Vladimir Zelenko

Dr. Vladimir (Zev) Zelenko M.D.
Board Certified Family Practitioner
501 Rt 208, Monroe, NY 10950
845-782-0000

April 28, 2020

To all medical professionals around the world:

- Risk stratification: treatment was offered to high-risk patients (age $>$ 60 years or comorbidities $>$ 0) as follows:
  1. Any patient with shortness of breath was treated
  2. Any patient in the high-risk category even with mild symptoms was treated.
  3. Young, healthy, low-risk patients, even with symptoms, were not treated.
- Treatment:
  1. Hydroxychloroquine: 200 mg twice a day for 5 days
  2. Azithromycin: 500mg once a day for 5 days
  3. Zinc sulfate: 50 mg (elemental) once a day for 5 days.
- The following outcomes were communicated in 3 open letters:
  - March 23, 2020: 500 patients (low and high risk, 0 deaths, 0 hospitalizations)
  - April 28, 2020: 1,450 patients, 405 high risk patients, 2 deaths, 6 hospitalizations
  - June 14, 2020: 2,200 patients, 800 high-risk patients, 2 deaths, 12 hospitalizations

Pre-exposure prophylaxis with hydroxychloroquine and Zinc

Journal of Infection and Public Health 14 (2021) 1161–1163

Hydroxychloroquine Pre-Exposure Prophylaxis for COVID-19 in Healthcare Workers from India: A Meta-Analysis



Raphael B. Stricker*, Melissa C. Fesler

Union Square Medical Associates, San Francisco, CA, USA

- On March 23, 2020 The Indian Council of Medical Research (ICMR) adopted a modified version of Zelenko's HCQ PrEP protocol and recommended it for healthcare workers.
- **ICMR PrEP protocol:** 400 mg HCQ twice a day on Day 1, then 400 mg HCQ once a week.
- **Zelenko PrEP protocol:** 200 mg once a day for 5 days then 400 mg HCQ once a week; and zinc 25-50 mg per day
- **Underlying principle:** load at least 2400 mg HCQ over a 40-day window, keeping daily dosage below 600 mg, exploiting the long half-life of the molecule.
- Meta-analysis of 11 studies of HCQ PrEP in India:
  - **Endpoint:** Reduction in symptomatic infection rate.
  - For all 11 studies: RR $= 0.56$; $p = 0.004$ – **44% efficacy**
  - In 5 of 11 studies, health care workers had already 6 doses weekly HCQ
  - For these 5 studies: RR $= 0.25$; $p < 0.0001$ – **75% efficacy**
- Better efficacy is expected for non-healthcare workers with no excessive exposure to the virus.

HCQ+AZ+Zinc: Call for emergency adoption by Dr. Harvey Risch

American Journal of Epidemiology
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Advance Access publication:
May 27, 2020

Special Article

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*

* Correspondence to Dr. Harvey A. Risch, Department of Chronic Disease Epidemiology, Yale School of Public Health, P.O. Box 208034, New Haven, CT 06520-8034 (e-mail: harvey.risch@yale.edu).

- On May 22, 2020: Dr. Harvey Risch called for the emergency adoption of outpatient treatment of symptomatic high-risk COVID-19 patients using hydroxychloroquine-based treatment protocols.
- Cited studies from:
  1. IHU, Marseilles, France
  2. Case series data from Dr. Vladimir Zelenko (as of April 28, 2020)
  3. Unpublished study from Sao Paolo, Brasil, of 636 symptomatic high-risk patients.
- Risch also proposed that case series data could be compared against historical controls, but did not propose a mathematically rigorous method for doing so.

HCQ+AZ+Zinc: Derwand, Scholz, Zelenko (2020) study

International Journal of Antimicrobial Agents 56 (2020) 106214

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

Roland Derwand[a,1], Martin Scholz[b,1,*], Vladimir Zelenko[c]

[a] Alexion Pharma Germany GmbH, 80687, Munich, Germany
[b] Heinrich-Heine-University, Düsseldorf, Moorenstr. 5, 40225, Düsseldorf, Germany
[c] Medical Group Practice, Monroe, NY, 10950, USA

- Reported on 141 high-risk patients with PCR or antibody test confirmation (other patients who were clinically diagnosed were not included in this case series)
  - Patients were treated between March 18, 2020 and May 14, 2020 by Dr. Zelenko.
  - Outcomes: 4 hospitalizations (2.8%), 1 death (0.7%)
- Compared with outcomes in patients treated by other doctors in the same community:
  - 377 patients, both low-risk and high-risk
  - 58 hospitalizations (15.4%) and 13 deaths (3.4%)
  - Fatality rate is consistent with national CFR during the same time period.
- Hospitalization reduction: $OR = 0.16$ (CI: 0.05 – 0.45); $p = 0.02$ – **84% efficacy**
- Mortality reduction: $OR = 0.2$ (CI: 0.02 – 1.54); $p = 0.12$ – **not significant**
- However: improved results if complete April data set is used:
  - 405 treated high-risk patients; 6 hospitalizations (1.4%), 2 deaths (0.4%)
  - Hospitalization reduction: $OR = 0.08$ (CI: 0.03–0.19); $p = 10^{-11}$ – **92% efficacy**
  - Mortality reduction: $OR = 0.13$ (CI 0.03 – 0.61); $p = 0.0029$ – **87% efficacy**

Case series threshold analysis method.

COVID

MDPI

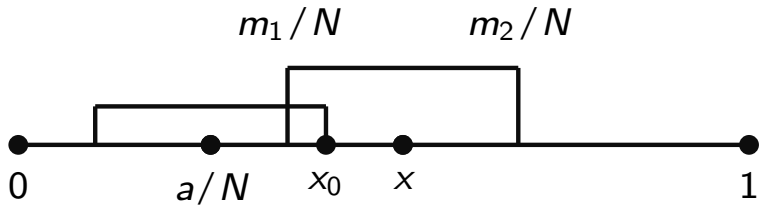
Article

Statistical Analysis Methods Applied to Early Outpatient COVID-19 Treatment Case Series Data

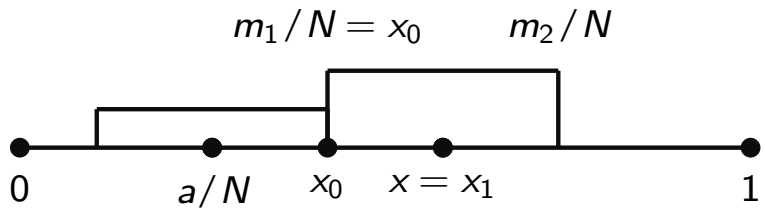
Eleftherios Gkioulekas [1,*], Peter A. McCullough [2] and Vladimir Zelenko [3,†]

COVID **2022**, *2*, 1139–1182. https://doi.org/10.3390/covid2080084 https://www.mdpi.com/journal/covid

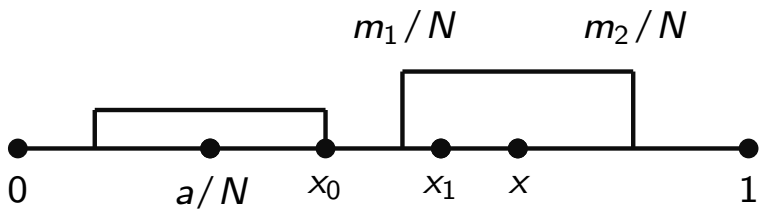
- **Preponderance of the evidence**



- **Crossover to clear and convincing**

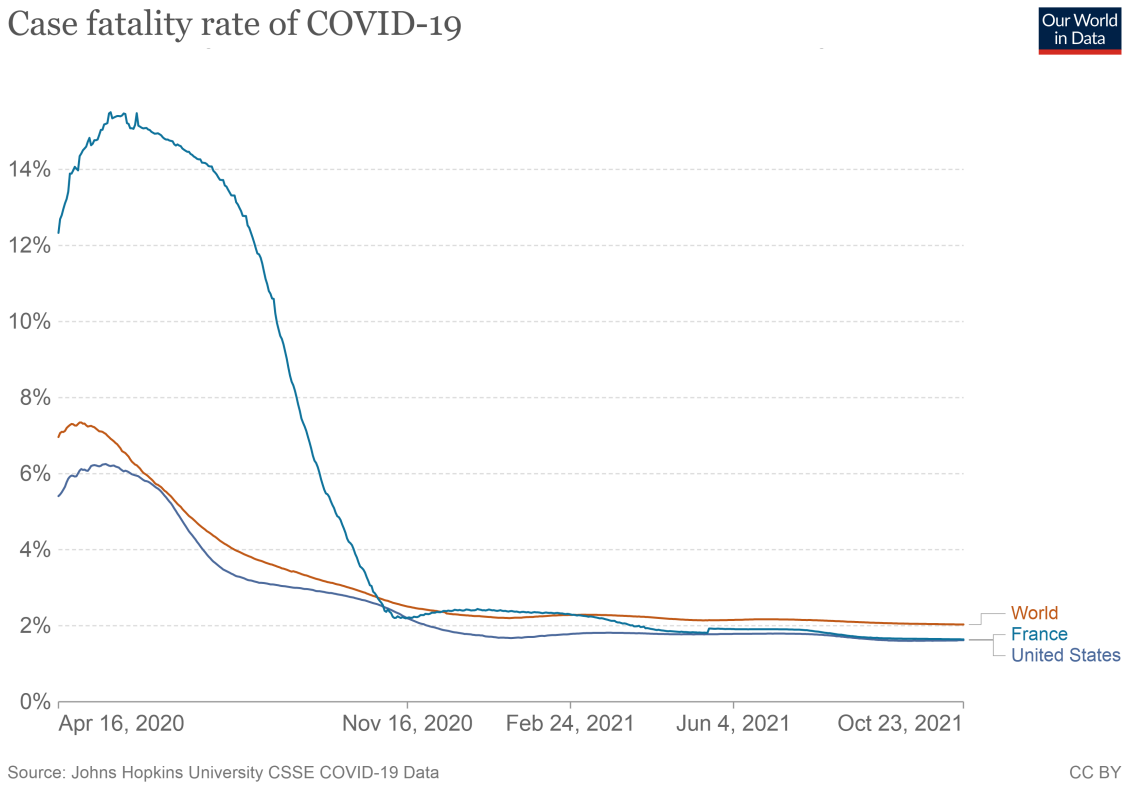


- **Clear and convincing**



- Efficacy threshold x_0 may be increased to adjusted efficacy threshold y_0 to control a Bayesian factor. Then y_0 is used to obtain x_1.

Case Fatality Rate in the US and France



- US CFR ranged from 2% to 6% in 2020 and converged to 1.7% in 2021
- France CFR ranged from 2% to 16% in 2020 and converged to 1.7% in 2021
- Comparison with Zelenko case series:
  - until April 28, 2020: **preponderance of the evidence** for mortality reduction
  - until June 15 2020: crossover to **clear and convincing evidence** for mortality reduction

Raoult's 10,429 patient study: early outpatient treatment

Early combination therapy with hydroxychloroquine and azithromycin reduces mortality in 10,429 COVID-19 outpatients

Matthieu MILLION[1,*], Jean-Christophe LAGIER[1], Hervé TISSOT-DUPONT[1], Isabelle RAVAUX[1], Catherine DHIVER[1], Christelle TOMEI[1], Nadim CASSIR[1], Léa DELORME[2], Sébastien CORTAREDONA[2], Sophie AMRANE[2], Camille AUBRY[2], Karim BENDAMARDJI[1], Cyril BERENGER[2], Barbara DOUDIER[1], Sophie EDOUARD[1], Marie HOCQUART[2], Morgane MAILHE[1], Coralie PORCHETO[1], Piseth SENG[1], Catherine TRIQUET[1], Stéphanie GENTILE[3], Elisabeth JOUVE[3], Audrey GIRAUD-GATINEAU[2], Herve CHAUDET[2], Laurence CAMOIN-JAU[4], Philippe COLSON[1], Philippe GAUTRET[2], Pierre-Edouard FOURNIER[2], Baptiste MAILLE[5], Jean-Claude DEHARO[5], Paul HABERT[6], Jean-Yves GAUBERT[6], Alexis JACQUIER[6], Stéphane HONORE[7], Katell GUILLON-LORVELLEC[1], Yolande OBADIA[2], Philippe PAROLA[2], Philippe BROUQUI[1], Didier RAOULT[1]

Rev. Cardiovasc. Med. 2021 vol. 22(3), 1063-1072

- **Treatment period:** between March 17, 2020 and December 31, 2020
- **Treatment:** 200 mg hydroxychloroquine 3 times a day for 10 days, azithromycin 500 mg on day 1 and 250 mg on days 2-5, zinc, enoxaparin (if age $>$ 70 years or comorbidities $>$ 0), dexamethasone (case by case basis)
- **treatment group:** 8315 patients received treatment as outpatients; **control group:** 2114 patients did not consent to treatment or had contraindications.
- No deaths for patients with age $<$ 60 years in the treatment group.
- For high-risk patients with age $>$ 60 years:
  - **treatment group:** 1495 patients, 5 deaths; **control group:** 520 patients, 11 deaths
  - adjusted OR $= 0.17$ (CI: 0.06 – 0.48), $p = 0.0007$ – **83% efficacy**
  - Compared with population level CFR ($\approx$ 2%) of *both low-risk and high-risk patients*: **clear and convincing** mortality rate reduction

Raoult/IHU database of 30,423 patients treated during 2020-2021

Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241 DOI: 10.26717/BJSTR.2023.52.008265

Construction, Quality Control and Regulatory Aspect of a Database of 30,423 COVID-19 Patients Cared for at the IHU Méditerranée Infection France

Philippe Brouqui* and Didier Raoult

MEPHI, Aix Marseille Université, 19-21 Boulevard Jean Moulin, 13005 Marseille, France

- Database includes 30,423 treated in IHU (Marseilles, France) between March 2, 2020 and December 31, 2021 and was made publicly available as a community resource.
- The database includes the following information:
  1. age and sex of patient
  2. Epidemic wave time period
  3. Outpatient treatment (yes/no), inpatient treatment (yes/no)
  4. Medications used: Hydroxychloroquine, azithromycin, ivermectin
  5. ICU admission (yes/no), ICU start time, ICU end time (in days)
  6. Death time (in days)
  7. Vaccination status (yes/no)
  8. Comorbidities (yes/no): diabetes, asthma, COPD, cancer, immunodeficiency, chronic cardiac disease, autoimmune disease.
- The construction of the database and the quality controls were verified by a bailiff.

Independent analysis of the Raoult/IHU database of 30,423 patients

An Independent Analysis of a Retrospective Cohort of 30,423 Covid-19 Patients Treated at IHU-Mediterranean in Marseille, France: Part 1, Efficacy of early Treatment with Hydroxychloroquine and Azithromycin

Valere Lounnas[*,1], Eleftherios Gkioulekas[2], Marc Rendell[3], Alexis Lacout[4], Xavier Azalbert[5], Christian Perronne [6]

Citation: Valere Lounnas, Eleftherios Gkioulekas, Marc Rendell Alexis Lacout, Xavier Azalbert, Christian Perronne. An Independent Analysis of a Retrospective Cohort of 30,423 Covid-19 Patients Treated at IHU- Mediterranean in Marseille, France: Part 1, Efficacy of early Treatment with Hydroxychloroquine and Azithromycin. Archives of Microbiology and Immunology. 8 (2024): 51-66.

- **Endpoint:** combination of ICU admission and/or all-cause mortality within 56 days
- **HCQ+AZ group:** All patients treated with hydroxychloroquine, azithromycin, and standard of care
- **AZ group:** All patients treated with azithromycin and standard of care
- **Control group:** All patients treated only with standard of care. ($N = 1711$)
- **Standard of care:** zinc, dexamethasone (if clinically indicated), enoxaparin (if clinically indicated)
- Comparisons against control group used logistic regression with propensity score matching (full optimal matching)

Model	**adjusted OR**	**95% CI**	p-value
HCQ+AZ ($N = 24,943$)	0.419	$(0.327, 0.539)$	< 0.001
HCQ+AZ and age > 50 years ($N = 10,891$)	0.379	$(0.274, 0.582)$	< 0.001
AZ ($N = 6349$)	0.727	$(0.608, 0.870)$	< 0.001

Analysis of Raoult/IHU database of 30,423 patients by Raoult and colleagues

New Microbes and New Infections 55 (2023) 101188

Outcomes after early treatment with hydroxychloroquine and azithromycin: An analysis of a database of 30,423 COVID-19 patients

Philippe Brouqui [a], Matthieu Million [a], Philippe Parola [a], Peter A. Mccullough [b], Didier Raoult [a,*]

[a] *Aix-Marseille Université, Marseille, France*
[b] *Internal Medicine, Truth for Health Foundation, Tucson, USA*

- **Endpoint:** all-cause mortality within 42 days
- Comparisons against control group used logistic regression and three models:
  1. Model A: adjusted for sex, age, period, outpatient (yes/no)
  2. Model B: all Model A covariates and also adjusted for virus variant
  3. Model C: all Model B covariates and also adjusted for vaccination status and comorbidities
- Propensity score matching was not used

Model	**adjusted OR**	**95% CI**	p-value
Model A ($N = 30,202$)	0.55	$(0.45, 0.68)$	< 0.001
Model B ($N = 21,664$)	0.55	$(0.44, 0.69)$	< 0.001
Model C ($N = 16,063$)	0.47	$(0.29, 0.75)$	0.002

Controversy: HCQ+AZ effective primarily for early outpatient treatment

Hydroxychloroquine is effective, and consistently so when provided early, for COVID-19: a systematic review

C. Prodromos[1] and T. Rumschlag[2]

1) *Illinois Sports Medicine and Orthopaedic Center and* 2) *Foundation for Orthopaedics and Regenerative Medicine, Glenview, IL, USA*

New Microbe and New Infect 2020; **38:** 100776

https://doi.org/10.1016/j.nmni.2020.100776

- As of September 2020, it was already clear that hydroxychloroquine-based treatment was optimally effective for early outpatient treatment but not consistently effective for hospitalized patients.
- Out of 42 studies, all 11 outpatient studies showed clinical improvement
- Out of 42 reviewed studies, 7 were RCTs:
  - 2 RCTs on outpatients: both showed clinical improvement, however they were underpowered and did not reach statistical significance.
  - 5 RCTs on hospitalized patients: 1 showed clinical improvement, 3 showed no effect, 1 showed negative effect.
  - The 1 RCT, showing negative effect, used a toxic overdose of HCQ (a total of dose 2400mg of HCQ in day 1): REVOVERY trial (Oxford University)
- Out of 42 studies, all 3 studies showing worse results with HCQ were on hospitalized patients. Of those 3 studies, only 1 study was an RCT.

Conclusion

- Controversy: Didier Raoult and colleagues were targetted with orchestrated predatory retractions, however the RECOVERY trial paper, documenting use of an unethical toxic dose of 2400 mg of HCQ in 24 hours, remains in print in a high impact journal.
- Main findings:
  - Evidence from the Raoult and Zelenko data supports the efficacy of hydroxychloroquine-based treatments for high-risk outpatients, when initiated early.
  - Prophylactic use of hydroxychloroquine for 6 weeks is equivalent to pre-emptive treatment. Thus, for breakthrough infections, symptoms are expected to be very mild and there is an increased time window for initiating treatment.
  - Combining prophylaxis and treatment minimizes exposure to the viral spike protein, which is expected to reduce the likelihood of long covid symptoms.
- Ivermectin-based combination treatment plays a more important role for late treatment.