Overview of Epidemiological Study Designs

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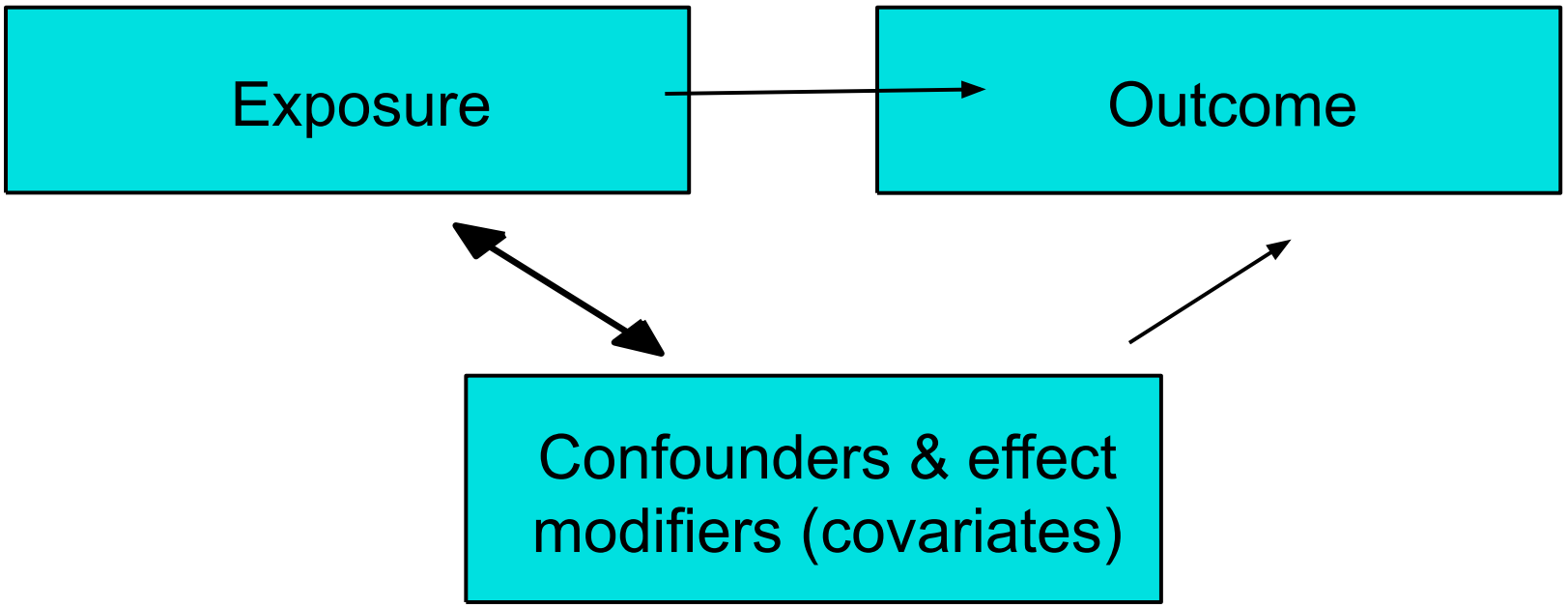
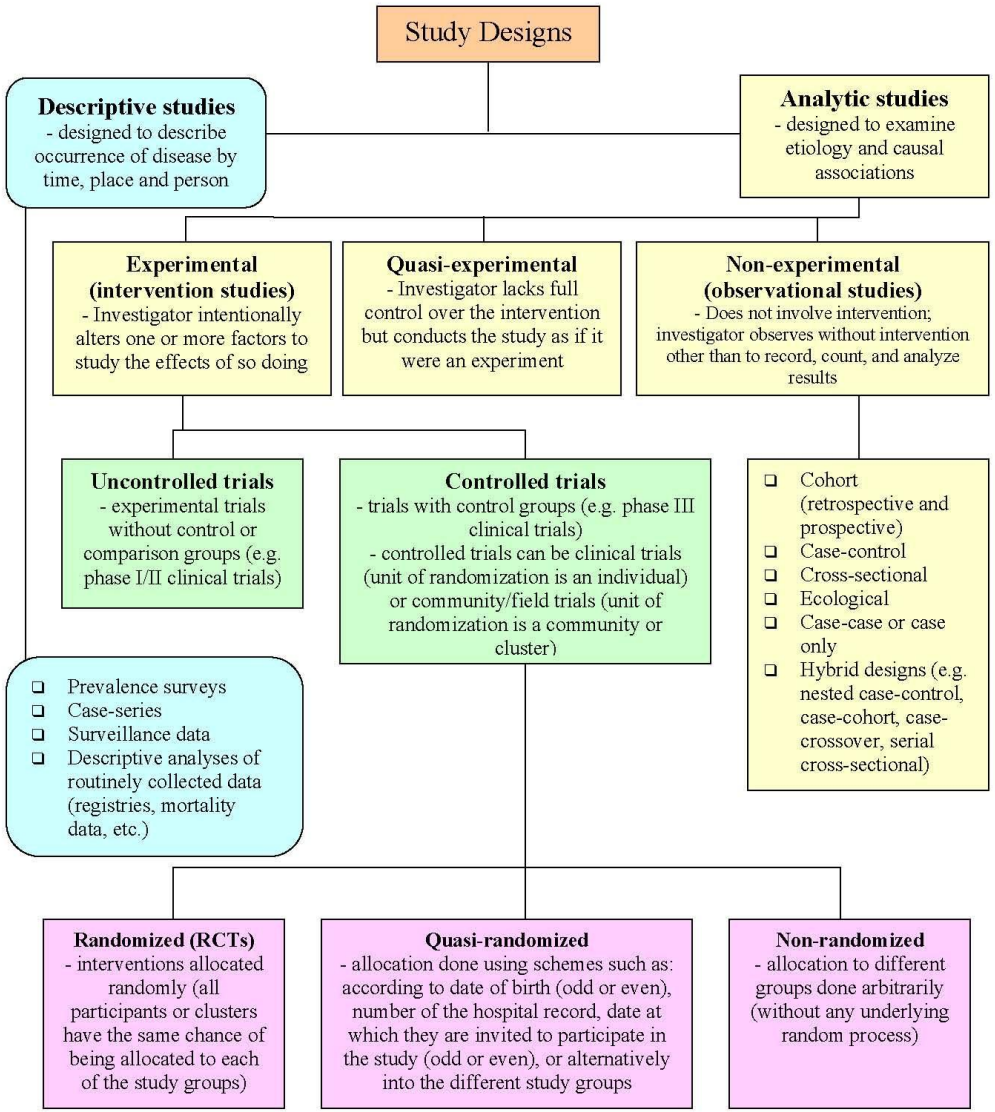
Exposures & Outcomes

- A major goal of epi research is causality
- Epi studies measure 3 things: exposures, confounders & outcomes
- Once quantified, the association between exposure and outcome is the central focus
- There are many ways of evaluating the association between an exposure and an outcome: these are the different study designs



Classification of study designs (Version 8)

(Qualitative studies are not included in this scheme; categories shown are not necessarily mutually exclusive, hybrid and mixed designs are possible)



Note: Systematic reviews and meta-analyses involve the secondary analysis and synthesis of original studies and are not considered in this classification system

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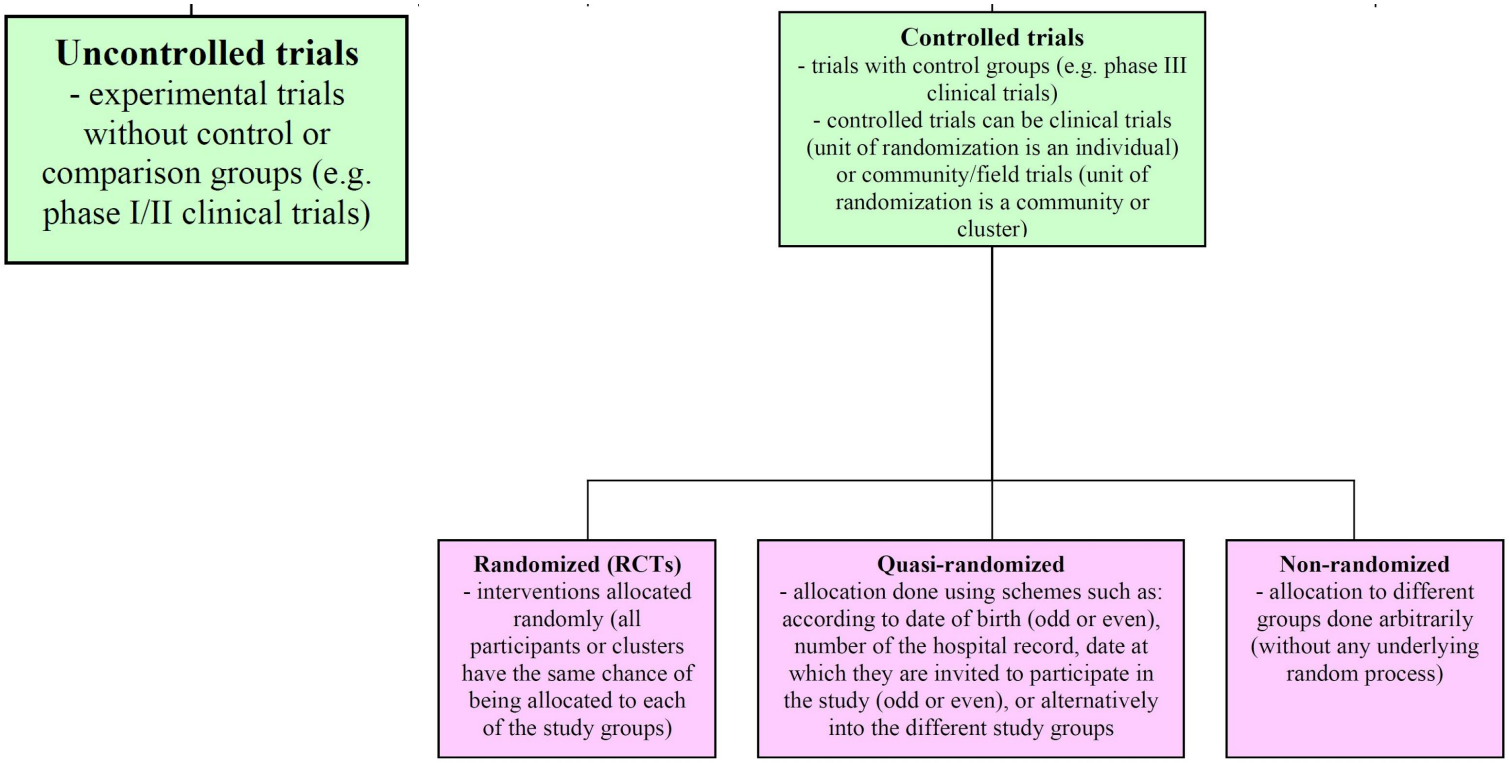
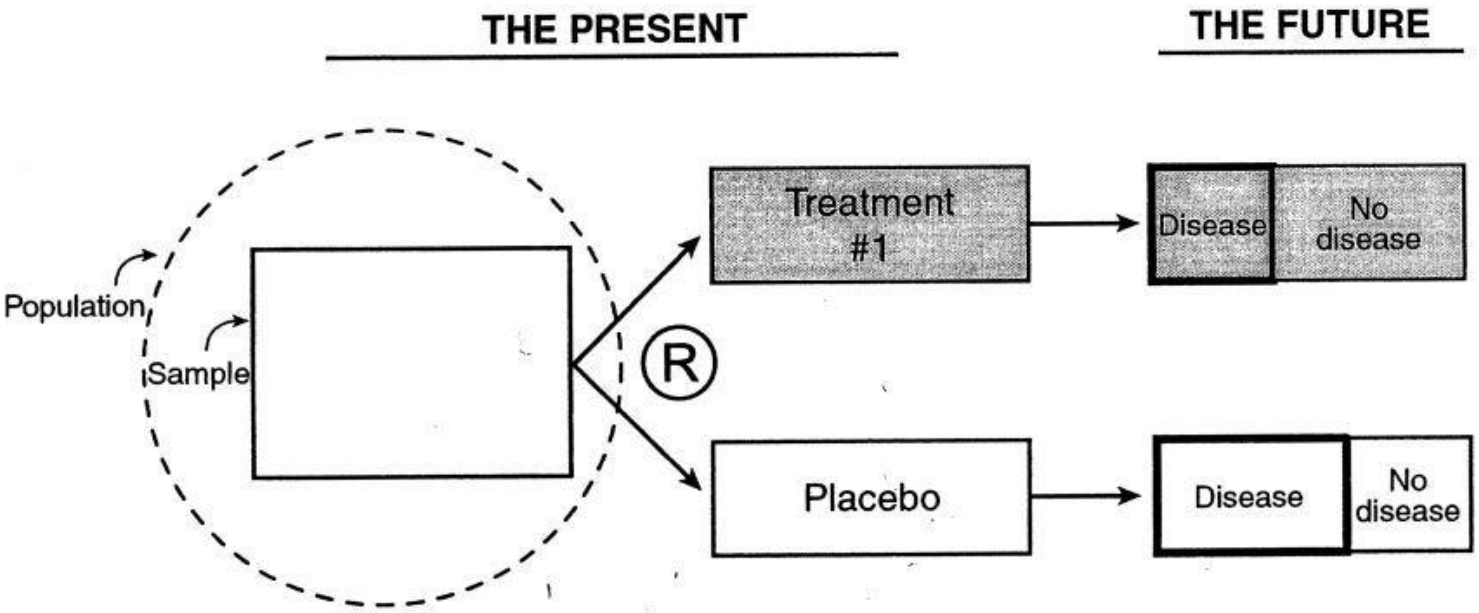
Experimental designs



Simple, two-arm (parallel) RCT



■ **FIGURE 10.1**

In a randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions (one should be a blinded placebo, if possible), (e) follows up the cohort, (f) measures outcome variables (blindly, if possible) and analyzes the results.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

Compassionate Use of Remdesivir for Patients with Severe Covid-19

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, and T. Flanigan

ABSTRACT

BACKGROUND

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

METHODS

We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

RESULTS

Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

CONCLUSIONS

In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Brainard at Gilead Sciences, 333 Lakeside Dr., Foster City, CA 94404, or at diana.brainard@gilead.com.

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DOI: 10.1056/NEJMoa2007016

Uncontrolled trial on Remdesivir

NEJM 2020

Controlled trial on Remdesivir

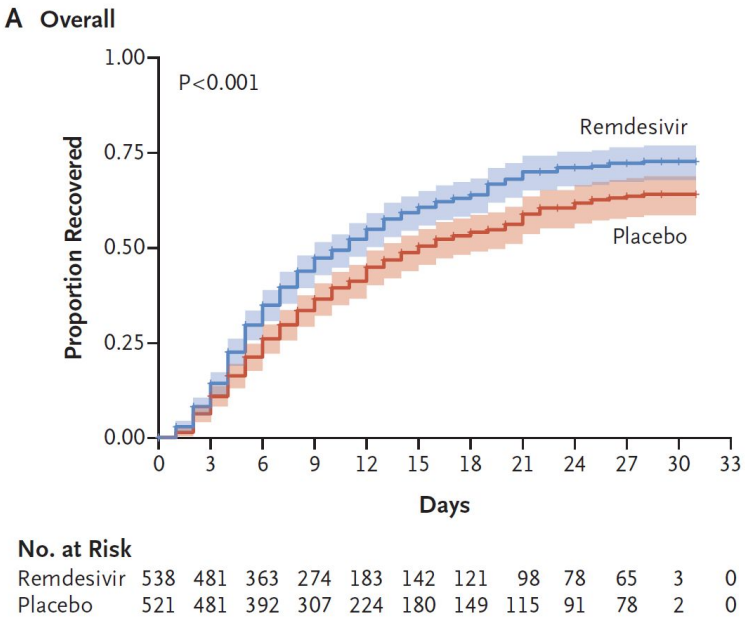
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 11 days, as compared with 15 days; rate ratio for recovery, 1.32; 95% CI 1.12 to 1.55; P<0.001



NEJM 2020

Uncontrolled trial on HCQ

ELSEVIER

International Journal of Antimicrobial Agents

Available online 20 March 2020, 105949

In Press, Journal Pre-proof

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], Philippe Brouqui [a, c], Didier Raoult [a, c]

Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.

Int J Antimicro Agents 2020

Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial

Wei Tang,[1,2] Zhujun Cao,[3] Mingfeng Han,[4] Zhengyan Wang,[5] Junwen Chen,[6] Wenjin Sun,[7] Yaojie Wu,[8] Wei Xiao,[9] Shengyong Liu,[10] Erzhen Chen,[11] Wei Chen,[1,2] Xiongbiao Wang,[12] Jiuyong Yang,[13] Jun Lin,[14] Qingxia Zhao,[15] Youqin Yan,[16] Zhibin Xie,[17] Dan Li,[18] Yaofeng Yang,[19] Leshan Liu,[20] Jieming Qu,[1,2] Guang Ning,[21] Guochao Shi,[1,2] Qing Xie[3]

DESIGN
Multicentre, open label, randomised controlled trial.

SETTING
16 government designated covid-19 treatment centres in China, 11 to 29 February 2020.

PARTICIPANTS
150 patients admitted to hospital with laboratory confirmed covid-19 were included in the intention to treat analysis (75 patients assigned to hydroxychloroquine plus standard of care, 75 to standard of care alone).

INTERVENTIONS
Hydroxychloroquine administrated at a loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily (total treatment duration: two or three weeks for patients with mild to moderate or severe disease, respectively).

MAIN OUTCOME MEASURE
Negative conversion of severe acute respiratory syndrome coronavirus 2 by 28 days, analysed according to the intention to treat principle. Adverse events were analysed in the safety population in which hydroxychloroquine recipients were

Controlled trial on HCQ

Administration of hydroxychloroquine did not result in a significantly higher probability of negative conversion than standard of care alone in patients admitted to hospital with mainly persistent mild to moderate covid-19.

BMJ 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

D.R. Boulware, M.F. Pullen, A.S. Bangdiwala, K.A. Pastick, S.M. Lofgren, E.C. Okafor, C.P. Skipper, A.A. Nascene, M.R. Nicol, M. Abassi, N.W. Engen, M.P. Cheng, D. LaBar, S.A. Lother, L.J. MacKenzie, G. Drobot, N. Marten, R. Zarychanski, L.E. Kelly, I.S. Schwartz, E.G. McDonald, R. Rajasingham, T.C. Lee, and K.H. Hullsiek

Controlled trial on HCQ for prevention

After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not
prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure.

NEJM 2020

Non-experimental (observational) designs

- Cohort studies
- Case-control studies
- Cross-sectional studies
- Ecologic studies
- Diagnostic accuracy studies

Cohort study

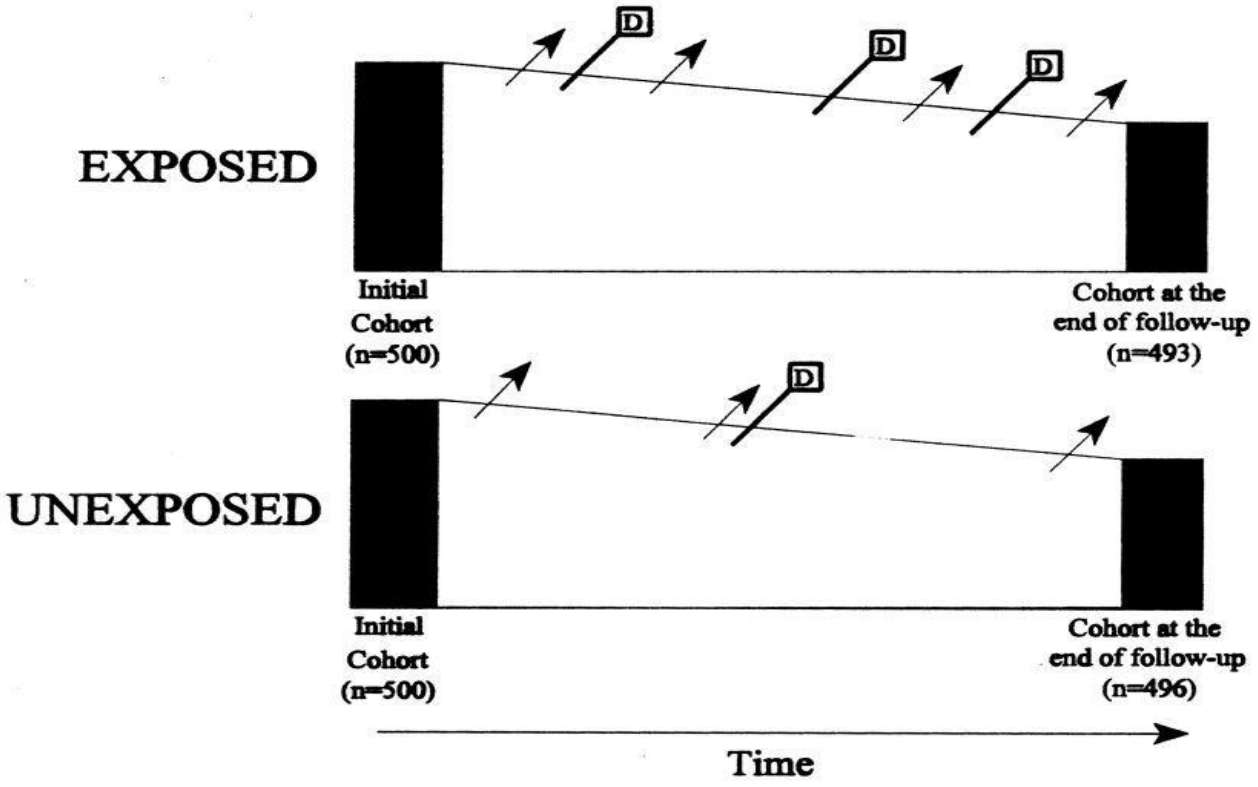


Figure 1–15 Same cohort study as in Figure 1–13, but the ascertainment of events and losses to follow-up is done separately among those exposed and unexposed.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Observational, cohort study on HCQ (retracted!)

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

We were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19

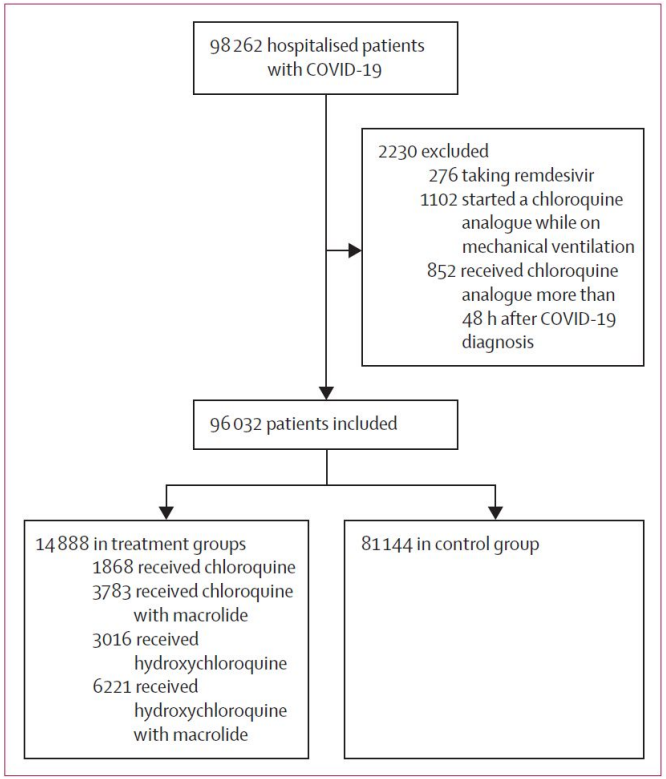
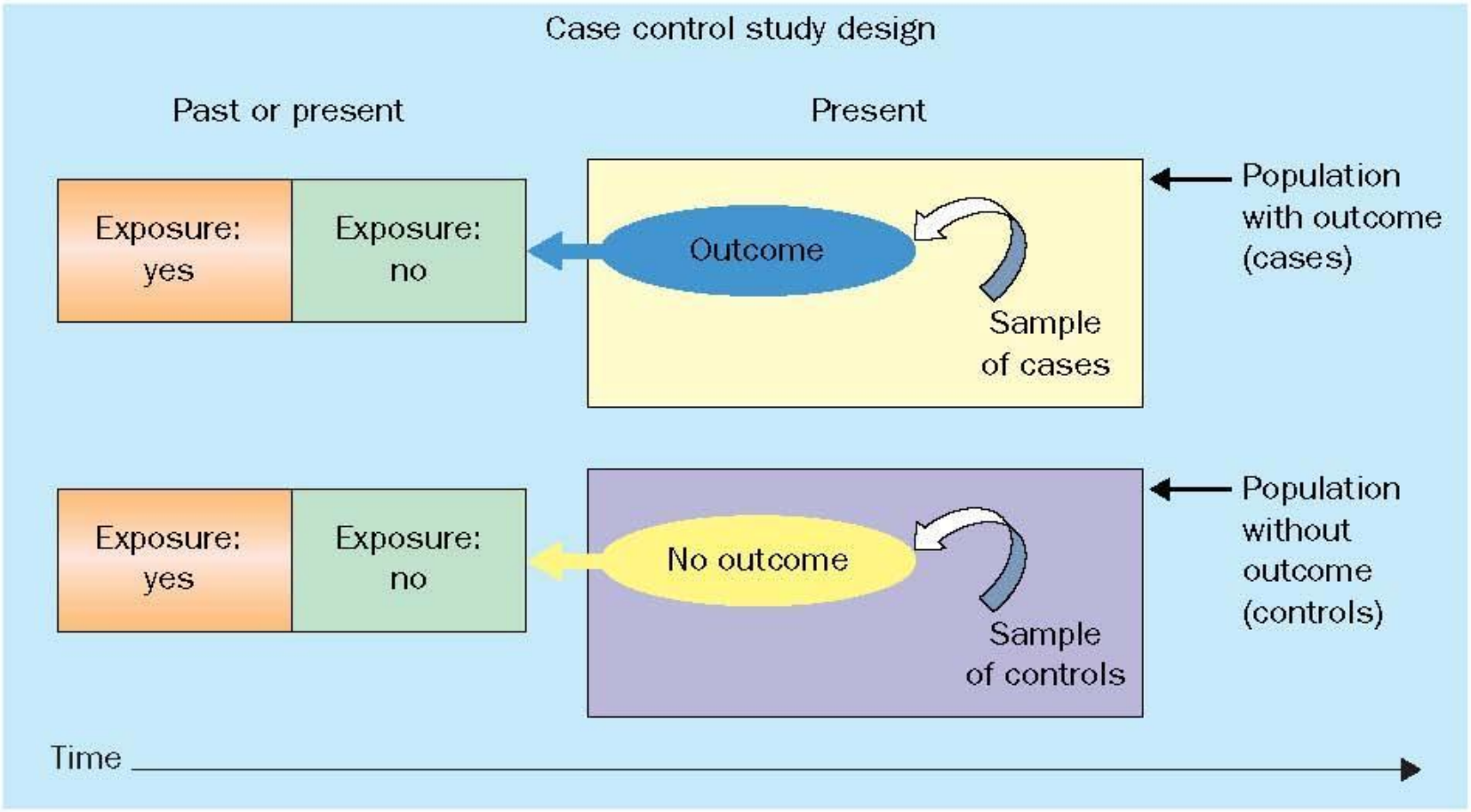


Figure 1: Study profile

Lancet 2020

Case-control study



Schematic diagram of case-control study design

Grimes et al. Lancet 2002;359:431-34

Case-control study on HCQ for prevention

Indian J Med Res, Epub ahead of print
DOI: 10.4103/ijmr.IJMR_2234_20

Quick Response Code:

Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19

Pranab Chatterjee[1,#], Tanu Anand[7,#], Kh. Jitenkumar Singh[2], Reeta Rasaily[3], Ravinder Singh[4], Santasabuj Das[8], Harpreet Singh[5], Ira Praharaj[6], Raman R. Gangakhedkar[6], Balram Bhargava[†] & Samiran Panda[9]

Table III. Patterns of hydroxychloroquine (HCQ) prophylaxis in healthcare workers

Parameters	Cases (n_1=378) (%)	Controls (n_2=373) (%)	OR	95% CI of OR	*P*
HCQ prophylaxis					
No	206 (54.5)	180 (48.26)	1.28	0.96-1.71	0.087
Yes	172 (45.50)	193 (51.74)	Ref		
Number of maintenance doses of HCQ prophylaxis taken					
>6	12 (3.17)	56 (15.01)	0.19	0.1-0.36	<0.001
4-5	42 (11.11)	67 (17.96)	0.55	0.35-0.84	
2-3	70 (18.52)	37 (9.92)	1.65	1.06-2.58	
HCQ loading dose and irregular recall of maintenance	48 (12.7)	33 (8.85)	1.27	0.78-2.07	
None	206 (54.5)	180 (48.26)	Ref		
Combination prophylaxis					
HCQ only	130 (34.39)	133 (35.66)	0.85	0.62-1.17	0.002
HCQ+azithromycin+vitamins	25 (6.61)	16 (4.29)	1.36	0.71-2.64	
HCQ+vitamins	6 (1.59)	25 (6.70)	0.21	0.08-0.52	
HCQ+non-allopathic systems of medicines or others	11 (2.91)	19 (5.09)	0.51	0.23-1.09	
No HCQ	206 (54.5)	180 (48.26)	Ref		

Cross-sectional study

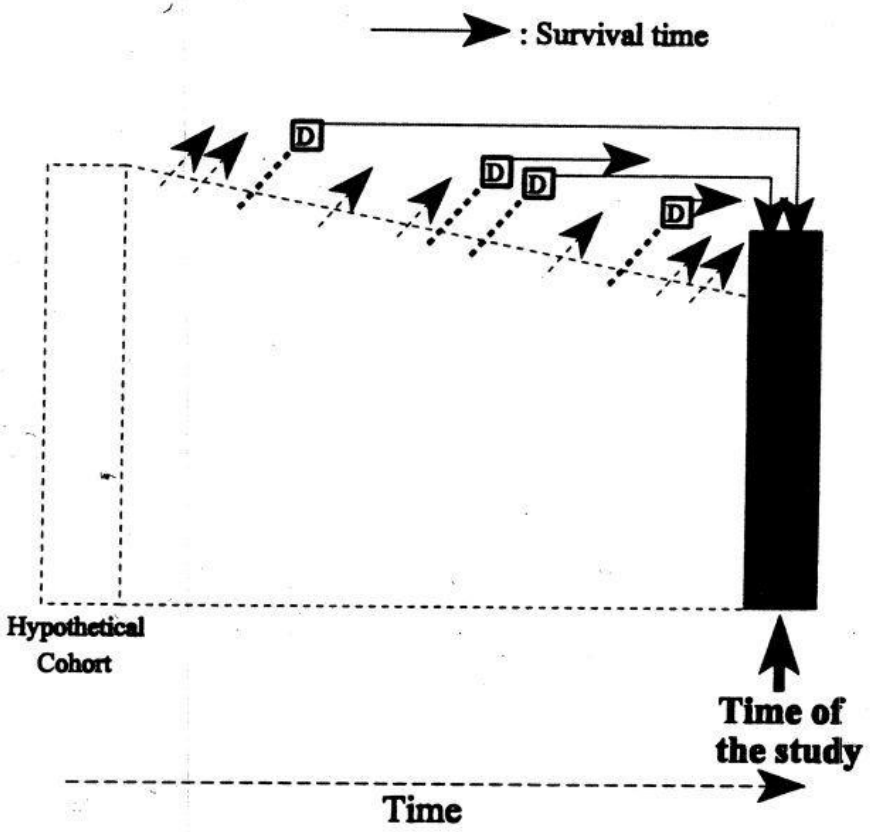


Figure 1–22 Schematic representation of a cross-sectional study, conceptually and methodologically analogous to the case-based case-control study represented in Figure 1–19, except that instead of explicitly selecting cases and controls, it selects a sample of the entire population. Broken diagonal lines with arrows represent losses to follow-up. Cases are represented by "D" boxes.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

COVID-19 Antibody Seroprevalence in Santa Clara County, California

Eran Bendavid[1], Bianca Mulaney[2], Neeraj Sood[3], Soleil Shah[2], Emilia Ling[2], Rebecca Bromley-Dulfano[2], Cara Lai[2], Zoe Weissberg[2], Rodrigo Saavedra-Walker[4], Jim Tedrow[5], Dona Tversky[6], Andrew Bogan[7], Thomas Kupiec[8], Daniel Eichner[9], Ribhav Gupta[10], John P.A. Ioannidis[1,10], Jay Bhattacharya[1]

Methods

On April 3-4, 2020, we tested county residents for antibodies to SARS-CoV-2 using a lateral flow immunoassay. Participants were recruited using Facebook ads targeting a sample of individuals living within the county by demographic and geographic characteristics. We estimate weights to adjust our sample to match the zip code, sex, and race/ethnicity distribution within the county. We report both the weighted and unweighted prevalence of antibodies to SARS-CoV-2. We also adjust for test performance characteristics by combining data from 16 independent samples obtained from manufacturer's data, regulatory submissions, and independent evaluations: 13 samples for specificity (3,324 specimens) and 3 samples for sensitivity (157 specimens).

Results

The raw prevalence of antibodies to SARS-CoV-2 in our sample was 1.5% (exact binomial 95CI 1.1-2.0%). Test performance specificity in our data was 99.5% (95CI 99.2-99.7%) and sensitivity was 82.8% (95CI 76.0-88.4%). The unweighted prevalence adjusted for test performance characteristics was 1.2% (95CI 0.7-1.8%). After weighting for population demographics of Santa Clara County, the prevalence was 2.8% (95CI 1.3-4.7%), using bootstrap to estimate confidence bounds. These prevalence point estimates imply that 54,000 (95CI 25,000 to 91,000 using weighted prevalence; 23,000 with 95CI 14,000-35,000 using unweighted prevalence) people were infected in Santa Clara County by early April, many more than the approximately 1,000 confirmed cases at the time of the survey.

https://www.medrxiv.org/content/10.1101/2020.04.14.20062463v2.full.pdf

Ecologic Studies

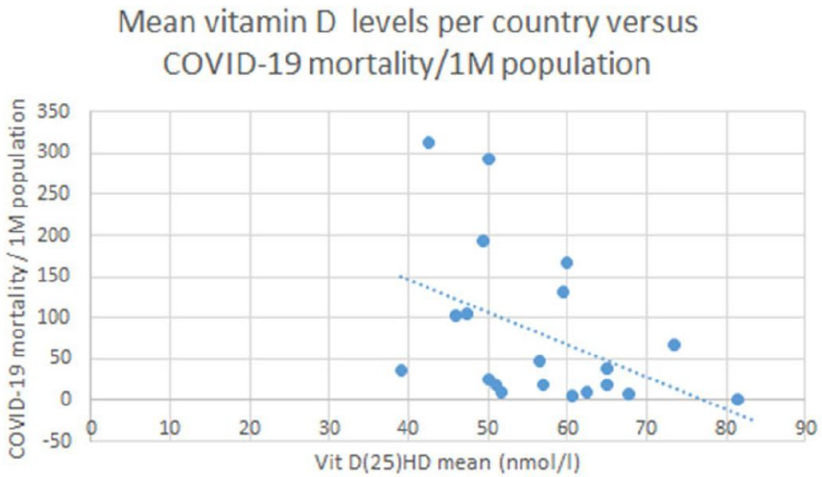
- Explores correlations between aggregate (group level) exposure and outcomes
- Unit of analysis: not individual, but clusters (e.g. countries, counties, schools)
- Useful for generating hypothesis
- Prone to “ecological fallacy”
- Cannot adjust well for confounding due to lack of comparability (due to lack of data on all potential covariates)

Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-020-01570-8

SHORT COMMUNICATION

The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality

Petre Cristian Ilie[1] · Simina Stefanescu[2] · Lee Smith[3]



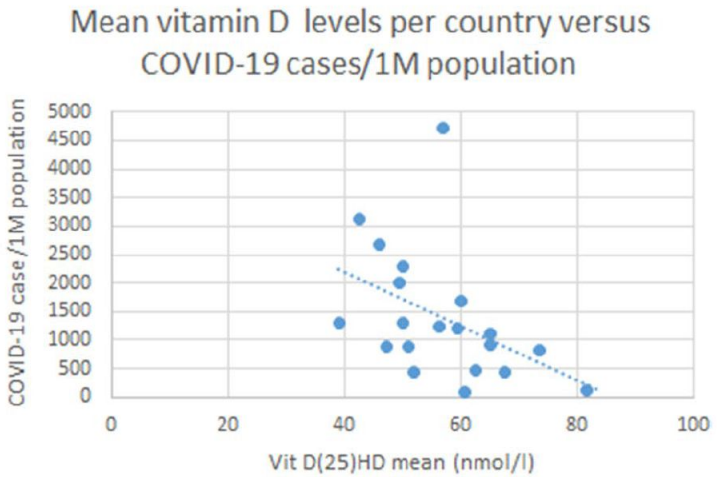


Fig. 1 Mean vitamin D levels per courtry versus COVID-19 cases and mortality/1M population

Diagnostic accuracy studies

- Goal is to estimate the accuracy of the new test, compared to an established 'gold standard'

	Disease +	Disease -
Test +	True Positive	False Positive
Test -	False Negative	True Negative

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VIROLOGY

Check for updates

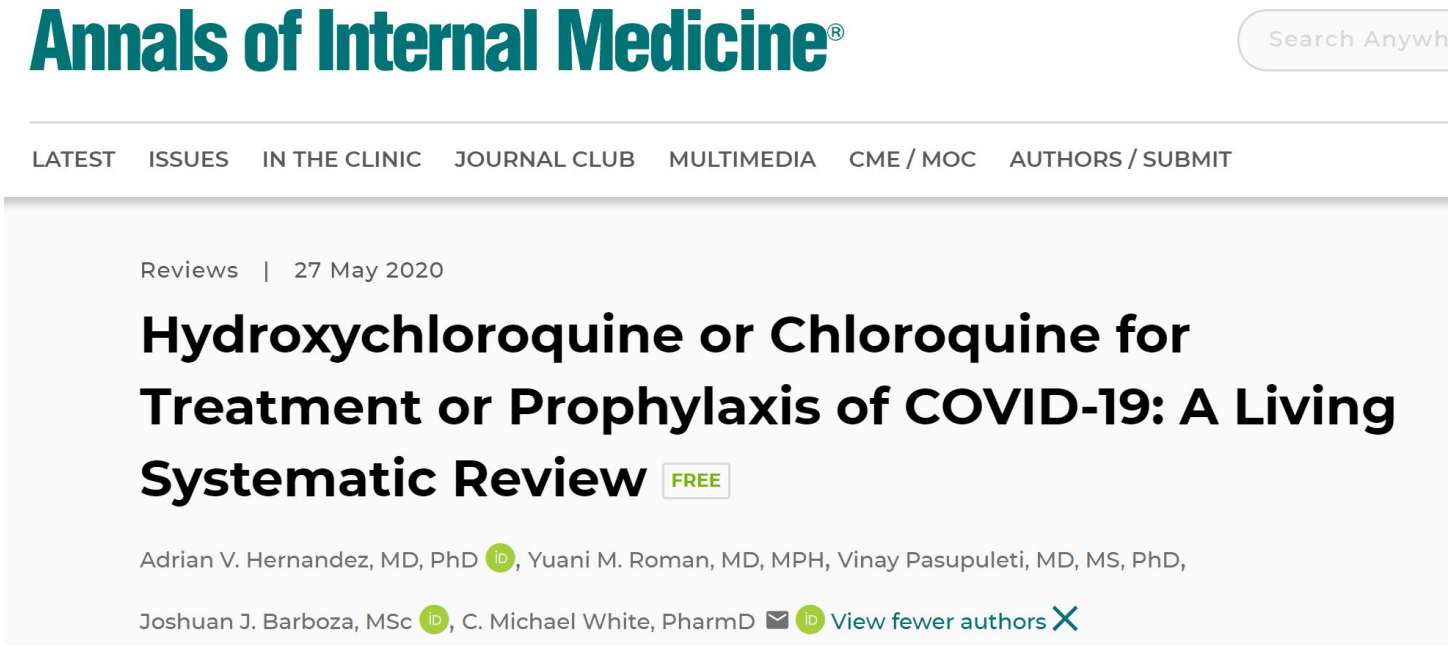
Improved Molecular Diagnosis of COVID-19 by the Novel, Highly Sensitive and Specific COVID-19-RdRp/Hel Real-Time Reverse Transcription-PCR Assay Validated *In Vitro* and with Clinical Specimens

Jasper Fuk-Woo Chan,[a,b,c,d,e] Cyril Chik-Yan Yip,[f] Kelvin Kai-Wang To,[a,b,c,d] Tommy Hing-Cheung Tang,[g] Sally Cheuk-Ying Wong,[h] Kit-Hang Leung,[c] Agnes Yim-Fong Fung,[c] Anthony Chin-Ki Ng,[c] Zijiao Zou,[c] Hoi-Wah Tsoi,[c] Garnet Kwan-Yue Choi,[f] Anthony Raymond Tam,[i] Vincent Chi-Chung Cheng,[f] Kwok-Hung Chan,[a,c,d] Owen Tak-Yin Tsang,[j] Kwok-Yung Yuen[b,c,d,e]

Systematic reviews & meta-analyses

"A systematic review is a review in which there is a comprehensive search for relevant studies on a specific topic, and those identified are then appraised and synthesized according to a predetermined and explicit method."

"A meta-analysis is the statistical combination of at least 2 studies to produce a single estimate of the effect of the healthcare intervention under consideration."



Evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19 is very weak and conflicting.

https://www.acpjournals.org/doi/10.7326/M20-2496

Mathematic modeling analyses

Science

RESEARCH ARTICLES

Cite as: P. G. T. Walker *et al.*, *Science* 10.1126/science.abc0035 (2020).

The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries

Patrick G. T. Walker[1*†], Charles Whittaker[1†], Oliver J Watson[1,2†], Marc Baguelin[1,3], Peter Winskill[1], Arran Hamlet[1], Bimandra A. Djafaara[1], Zulma Cucunubá[1], Daniela Olivera Mesa[1], Will Green[1], Hayley Thompson[1], Shevanthi Nayagam[1], Kylie E. C. Ainslie[1], Sangeeta Bhatia[1], Samir Bhatt[1], Adhiratha Boonyasiri[1], Olivia Boyd[1], Nicholas F. Brazeau[1], Lorenzo Cattarino[1], Gina Cuomo-Dannenburg[1], Amy Dighe[1], Christl A. Donnelly[1,4], Ilaria Dorigatti[1], Sabine L. van Elsland[1], Rich FitzJohn[1], Han Fu[1], Katy A.M. Gaythorpe[1], Lily Geidelberg[1], Nicholas Grassly[1], David Haw[1], Sarah Hayes[1], Wes Hinsley[1], Natsuko Imai[1], David Jorgensen[1], Edward Knock[1], Daniel Laydon[1], Swapnil Mishra[1], Gemma Nedjati-Gilani[1], Lucy C. Okell[1], H. Juliette Unwin[1], Robert Verity[1], Michaela Vollmer[1], Caroline E. Walters[1], Haowei Wang[1], Yuanrong Wang[1], Xiaoyue Xi[1], David G Lalloo[5], Neil M. Ferguson[1*], Azra C. Ghani[1*]

[1]MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, Imperial College London, London, UK. [2]Pathology and Laboratory Medicine, Warren Alpert Medical School, Brown University, Providence, RI, USA. [3]Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. [4]Department of Statistics, University of Oxford, Oxford, UK. [5]Liverpool School of Tropical Medicine, Liverpool, UK.

16 March 2020

Imperial College COVID-19 Response Team

Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand

Neil M Ferguson, Daniel Laydon, Gemma Nedjati-Gilani, Natsuko Imai, Kylie Ainslie, Marc Baguelin, Sangeeta Bhatia, Adhiratha Boonyasiri, Zulma Cucunubá, Gina Cuomo-Dannenburg, Amy Dighe, Ilaria Dorigatti, Han Fu, Katy Gaythorpe, Will Green, Arran Hamlet, Wes Hinsley, Lucy C Okell, Sabine van Elsland, Hayley Thompson, Robert Verity, Erik Volz, Haowei Wang, Yuanrong Wang, Patrick GT Walker, Caroline Walters, Peter Winskill, Charles Whittaker, Christl A Donnelly, Steven Riley, Azra C Ghani.

On behalf of the Imperial College COVID-19 Response Team