Overview of Epidemiological Study Designs

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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)

Study Designs

Descriptive studies
- designed to describe occurrence of disease by
time, place and person

Experimental (intervention studies)
- investigator intentionally alters one or more factors to
to study the effects of doing so

Quasi-experimental
- investigator lacks full control over the intervention
- but conducts the study as if were an experiment

Non-experimental (observational studies)
- does not involve intervention;
- investigator observes without intervention other than to record, count, and analyze
- results

Uncontrolled trials
- experimental trials without control or comparison groups (e.g.
- phase I/II clinical trials)

Controlled trials
- trials with control groups (e.g. phase III clinical trials)
- controlled trials can be clinical trials
- unit of randomization is an individual
- or community/field trials (unit of randomization is a community or
- cluster)

Randomized (RCTs)
- interventions allocated randomly (all
- participants or clusters have the same chance of
- being allocated to each of the study groups)

Quasi-randomized
- allocation done using schemes such as:
- according to date of birth (odd or even),
- number of the hospital record, date at
- which they are invited to participate in
- the study (odd or even), or alternatively
- into the different study groups

Non-randomized
- allocation to different groups done arbitrarily
- (without any underlying random process)

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

**Uncontrolled trials**
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**Controlled trials**
- trials with control groups (e.g. phase III clinical trials)
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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.
Compassionate Use of Remdesivir for Patients with Severe Covid-19


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.)
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
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.
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.
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.
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.
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
Case-control study

Schematic diagram of case-control study design
Case-control study on HCQ for prevention

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

Pranab Chatterjee\textsuperscript{1, a}, Tanu Anand\textsuperscript{2, a}, Kh. Jitenkumar Singh\textsuperscript{2}, Reeta Rasaily\textsuperscript{3}, Ravinder Singh\textsuperscript{4}, Santasabuj Das\textsuperscript{5}, Harpreet Singh\textsuperscript{6}, Ira Praharaj\textsuperscript{7}, Raman R. Gangakhedkar\textsuperscript{8}, Balram Bhargava\textsuperscript{1} & Samiran Panda\textsuperscript{9}

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

Eran Bendavid¹, Bianca Mulaney², Neeraj Sood³, Soleil Shah², Emilia Ling², Rebecca Bromley-Dulflano², Cara Lai², Zoe Weissberg², Rodrigo Saavedra-Walker⁴, Jim Tedrow⁵, Dona Tversky⁶, Andrew Bogan⁷, Thomas Kupiec⁸, Daniel Eichner⁹, Ribhav Gupta¹⁰, John P.A. Ioannidis¹¹, John Bhattacharya¹

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.

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

Petre Cristian Ilie¹ · Simina Stefănescu² · Lee Smith³

Fig. 1  Mean vitamin D levels per country 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’

<table>
<thead>
<tr>
<th></th>
<th>Disease +</th>
<th>Disease -</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test +</strong></td>
<td>True Positive</td>
<td>False Positive</td>
</tr>
<tr>
<td><strong>Test -</strong></td>
<td>False Negative</td>
<td>True Negative</td>
</tr>
</tbody>
</table>
Improved Molecular Diagnosis of COVID-19 by the Novel, Highly Sensitive and Specific COVID-19-RdRp/He1 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,f Vincent Chi-Chung Cheng,f Kwok-Hung Chan,a,c,d Owen Tak-Yin Tsang,f 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

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


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

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


On behalf of the Imperial College COVID-19 Response Team

Total deaths

131,967 COVID-19 deaths
projected by August 4, 2020

![Graph showing total deaths over time](image)