COVID-19 CADTH HEALTH TECHNOLOGY REVIEW

Chloroquine and Hydroxychloroquine, With or Without Azithromycin, for COVID-19: An Addendum to the April 20, 2020 Brief Overview (Update)

This report was published on June 5, 2020 at 4:00 p.m.

This report includes a recent clarification regarding the content of the Addendum to the Brief Overview published on May 29 at 3:00 p.m. The Lancet has since retracted an article that had significant impact on the conduct of clinical trials of hydroxychloroquine in the treatment of COVID-19. Note: CADTH used a modified approach to the selection and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.
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Cite As: Chloroquine and Hydroxychloroquine, With or Without Azithromycin, for COVID-19: An Addendum to the April 20, 2020 Brief Overview.

Ottawa: CADTH; 2020 June. (CADTH health technology review).

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Funding: CADTH receives funding from Canada’s federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to requests@cadth.ca.
Introduction

Since the CADTH posting of Chloroquine and Hydroxychloroquine, With or Without Azithromycin, for COVID-19: A Brief Overview on April 20, 2020, the Institute nationale d’excellence en santé et en services sociaux (INESSS) has updated its report on May 1.

Accounting for 11 new studies reported in the INESSS updated report, as well as two others retrieved separately, at least 13 new studies were published since the release of the CADTH report. Overall, findings from these studies do not fundamentally change the conclusions of the April 20, 2020 CADTH Brief Overview, with the caveat that potential safety concerns regarding the use of these drugs have augmented. Of note, on May 25, WHO decided to temporarily suspend the hydroxychloroquine arm of its Solidarity trial. This decision was based on the May 22 online publication of a multinational registry analysis in The Lancet. The findings of this analysis suggested that chloroquine and hydroxychloroquine, either used alone or in combination with a macrolide antibiotic, were associated with an absence of therapeutic benefit (i.e., decreased in-hospital survival) and potential harm (i.e., increased frequency of ventricular arrhythmias) when used for the treatment of patients with COVID-19 (see STUDY # 2 that follows). On June 4, 2020, The Lancet retracted this article due to concerns regarding the veracity of the data used in the analysis. Also, after having reviewed the safety concerns related to the use of hydroxychloroquine, WHO decided to resume the hydroxychloroquine arm of its Solidarity trial. In Canada, a decision had been made on May 28 to also pause the hydroxychloroquine trial conducted in Alberta (ALBERTA HOPE COVID-19) to verify the safety data. After reviewing these data, the HOPE trial safety committee approved resuming the trial. However, given that the number of active COVID-19 cases has decreased in Alberta, the trial will not resume immediately due to limited enrolment.

A brief description of the 13 new trials is subsequently provided (see New Studies). Also, an interesting editorial (entitled The Lack of efficacy of hydroxychloroquine in covid-19) was published on May 19, 2020 in the BMJ. This article is based on the most recent studies and supports both the INESSS and the CADTH reports. In addition, a quick assessment of the number of ongoing trials assessing chloroquine or hydroxychloroquine, either used alone or in combination with azithromycin, for the treatment of COVID-19 indicates the following:

Table 1: Ongoing Trials for Chloroquine or Hydroxychloroquine and/or Azithromycin for COVID-19

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Number of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine for the prophylaxis of COVID-19</td>
<td>7</td>
</tr>
<tr>
<td>Chloroquine for the treatment of COVID-19</td>
<td>15\textsuperscript{a}</td>
</tr>
<tr>
<td>Hydroxychloroquine for the prophylaxis of COVID-19</td>
<td>43</td>
</tr>
<tr>
<td>Hydroxychloroquine for the treatment of COVID-19</td>
<td>73\textsuperscript{b}</td>
</tr>
<tr>
<td>Chloroquine + azithromycin for the treatment of COVID-19</td>
<td>2</td>
</tr>
<tr>
<td>Hydroxychloroquine + azithromycin for the prophylaxis of COVID-19</td>
<td>1</td>
</tr>
<tr>
<td>Hydroxychloroquine + azithromycin for the treatment of COVID-19</td>
<td>39</td>
</tr>
<tr>
<td>Azithromycin for the treatment of COVID-19</td>
<td>13</td>
</tr>
<tr>
<td>Chloroquine combined with other drugs for the treatment of COVID-19</td>
<td>2</td>
</tr>
<tr>
<td>Hydroxychloroquine combined with other drugs for the treatment of COVID-19</td>
<td>37</td>
</tr>
<tr>
<td>Azithromycin combined with other drugs for the treatment of COVID-19</td>
<td>3</td>
</tr>
</tbody>
</table>


\textsuperscript{a} One of these studies assesses chloroquine analogue GNS651.

\textsuperscript{b} Three of these studies include a prophylaxis arm.
New Studies

Prophylaxis

There is one new study on the use of hydroxychloroquine for the prevention of COVID-19.


**Summary:** This observational study was conducted in a long-term care facility in South Korea. The purpose was to evaluate the effect of hydroxychloroquine for post-exposure prophylaxis following an outbreak of COVID-19. Hydroxychloroquine was administered to 211 persons; these included 189 patients and 22 health care staff members. The baseline polymerase chain reaction test for COVID-19 was negative for all individuals. Post-exposure prophylaxis was completed in 184 (97.4%) patients and 21 (95.5%) staff members. There were no serious adverse events. All tests were negative at the end of the 14-day quarantine.

**Comment from INESSS:** There are limitations with this study, leading to uncertainty in the results. This study was non-comparative; 92 staff members who were also exposed to the virus but who did not receive hydroxychloroquine as post-exposure prophylaxis also had negative test results after 12 to 13 days. There was no follow-up after the 14-day quarantine, which prevented the identification of positive cases after this time period. The evidence therefore remains insufficient to conclude the efficacy of hydroxychloroquine for the prevention of COVID-19.

Treatment — Non-Hospitalized Patients

No new studies were published that assessed the efficacy of chloroquine or hydroxychloroquine for the treatment of non-hospitalized patients with COVID-19. There remains insufficient evidence to determine the efficacy of these drugs for the treatment of COVID-19 in the community outpatient setting.

Treatment — Hospitalized Patients

There are 12 new studies assessing either chloroquine or hydroxychloroquine, used with or without azithromycin, for the treatment of hospitalized patients with COVID-19. The first study (Mehra MR et al) subsequently described was retrieved through searching the web, whereas the second one (Geleris J et al) was retrieved with the assistance of the Information Services officer who worked on the original version of the CADTH Brief Overview. The others were identified in the INESSS report updated on May 1. As no systematic literature search was conducted, it is possible that other new studies may not have been identified.

**Hydroxychloroquine**

**STUDY # 2:** Mehra MR et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Results were published online in *The Lancet* on May 22 (see: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31180-6/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31180-6/fulltext)).

**Note:** This study was retracted by *The Lancet* on June 4, 2020, due to concerns regarding the veracity of the data. These concerns were based on Surgisphere Corporation (the company that had provided the data to the researchers) declining to transfer the full dataset.
for an independent peer review. The authors of the study therefore requested to The Lancet that their paper be retracted.

Summary: This study was funded by the William Harvey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women’s Hospital. It was a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide (clarithromycin or azithromycin) for the treatment of patients with COVID-19. The registry included data from 671 hospitals located across the world. Patients were hospitalized between December 20, 2019, and April 14, 2020; they were admitted with a positive test for SARS-CoV-2. Drug therapy with one of four treatments of interest (i.e., chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide) was initiated within 48 hours of diagnosis. The control group was formed of patients who did not receive one of the four treatments. The main outcomes of interest were in-hospital mortality and new onset of ventricular arrhythmias (i.e., ventricular tachycardia or ventricular fibrillation). Overall, 96,032 patients met the inclusion criteria. Their mean age was 53.8 years; 46.3% were women. Treatment groups were composed of 14,888 patients (1,868 received chloroquine; 3,783 received chloroquine with a macrolide; 3,016 received hydroxychloroquine; and 6,221 received hydroxychloroquine with a macrolide). The control group included 81,144 patients. A total of 10,698 (11.1%) patients died while hospitalized. After controlling for several confounding factors (such as age, sex, body mass index, diabetes, and so forth), authors reported that the use of hydroxychloroquine (mortality of 18.0%; hazard ratio [HR] 1.335, 95% confidence interval [CI] 1.223 to 1.457), or hydroxychloroquine with a macrolide (23.8%; HR 1.447, 95% CI 1.368 to 1.531), or chloroquine (16.4%; HR 1.365, 95% CI 1.218 to 1.531), or chloroquine with a macrolide (22.2%; HR 1.368, 95% CI 1.273 to 1.469) was associated with an increased risk of mortality for all four drug regimens, compared with mortality observed in the control group (9.3%). Authors concluded that there was no benefit associated with the use of hydroxychloroquine or chloroquine, with or without a macrolide, on in-hospital outcomes of patients with COVID-19. Each of these drug regimens was associated with decreased in-hospital survival and increased harm in the form of ventricular arrhythmias.

Comment from INESSS: None, as findings from this study were published after the updated INESSS report was posted.


Summary: This observational study was funded by the National Institutes of Health. It aimed to assess the association between hydroxychloroquine use and intubation or death. The study was conducted in a large medical centre in New York City. Authors collected data from consecutive patients hospitalized with COVID-19. Patients who were intubated, died, or discharged within 24 hours after presentation to the emergency were excluded. The primary outcome was a composite of intubation or death; these were evaluated in patients who received hydroxychloroquine and compared with those in patients who did not. This time-to-event analysis used a multivariable Cox model with inverse probability weighting according to the propensity score. Of 1,446 consecutive patients, 1,376 patients were included; the median follow-up period was 22.5 days. A total of 811 (58.9%) received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of five days); those patients were more severely ill at baseline compared with those in the control group. Overall, 346 patients (25.1%) had a primary end-point event. Of those, 180 patients were intubated (66
subsequently died); 166 died without intubation. There was no between-group difference in the primary outcome (HR 1.04, 95% CI 0.82 to 1.32). Authors concluded that hydroxychloroquine administration was not associated with either a decreased or an increased risk of the composite end point of intubation or death.

Comment from INESSS: None, as findings from this study were published after the updated INESSS report was posted.

STUDY # 4 : Tang W et al. Hydroxychloroquine in patients with mild to moderate COVID-19: Open label randomised clinical trial (see: https://www.bmj.com/content/369/bmj.m1849.full).

Summary: This multi-centre, open-label, randomized controlled trial aimed to compare the efficacy and safety of hydroxychloroquine plus standard of care with standard of care alone in adults with COVID-19. The study was conducted in 16 government-designated COVID-19 treatment centres in China in February 2020. A total of 150 hospitalized patients with confirmed COVID-19 were included (75 patients were assigned to the hydroxychloroquine plus standard of care group, while 75 others were assigned to the control group). Hydroxychloroquine was administered at a loading dose of 1,200 mg daily for three days followed by a maintenance dose of 800 mg daily. Treatment regimens were administered for two weeks in patients mild to moderate disease and for three weeks in patients with severe disease. The main outcome was negative test conversion at day 28. Overall, 148 patients had mild to moderate disease and two had severe disease. The probability of negative test conversion at day 28 was similar for both groups; i.e., 85.4% (95% CI, 73.8% to 93.8%) in the hydroxychloroquine with standard of care group and 81.3%, (95% CI, 71.2% to 89.6%) in the control group; the difference was 4.1% (95% CI, −10.3% to 18.5%). The most common adverse event reported by patients in the hydroxychloroquine group was diarrhea (10%); two patients in this group reported serious adverse events. Authors concluded that the use of hydroxychloroquine did not significantly increase the probability of negative test conversion, compared to standard of care, in hospitalized patients with COVID-19. There were more adverse events in patients who received hydroxychloroquine compared to those who did not.

Comment from INESSS: INESSS mainly commented on the secondary outcomes; i.e., the alleviation of symptoms. In the study, the probability of alleviation of symptoms by 28 days was similar in patients receiving standard of care with hydroxychloroquine (59.9%, 95% CI, 45.0% to 75.3%) and without hydroxychloroquine (66.6%, 95% CI, 39.5% to 90.9%). The difference between groups was −6.6% (−41.3% to 28.0%). Referring to the post-hoc analysis on the effect of hydroxychloroquine on symptom alleviation, which suggested that the addition of hydroxychloroquine to standard treatment may provide some potential effect of the drug in patients who did not receive antiviral therapy, INESSS commented that this analysis was not planned, was limited to 14 patients per group (after removing those who had received antivirals), and that there was no correction for confounding factors. Therefore, the impact of the drug on symptoms alleviation remains uncertain.


Summary: This study compared the efficacy of hydroxychloroquine with supportive care alone in hospitalized adults. Patients with a diagnosis of COVID-19 pneumonia were consecutively admitted during the month of March 2020. The primary outcomes were the need to escalate respiratory support, change in lymphocyte count, and change in neutrophil-
to-lymphocyte ratio. A total of 63 patients were included; 32 were in the hydroxychloroquine group. Compared to supportive care alone, the use of hydroxychloroquine was associated with a need for escalation of respiratory support level at day 5 (P = 0.013). There was no between-group difference in absolute lymphocyte change (P = 0.413); authors commented that, compared to supportive care alone, the use of hydroxychloroquine trended toward a worsening neutrophil-to-lymphocyte ratio (P = 0.51), as well as a higher risk for intubation (P = 0.051). They concluded that the administration of hydroxychloroquine to hospitalized adults with COVID-19 was associated with an increased need for the escalation of respiratory support and that there were no benefits of this drug with respect to mortality, lymphopenia, or neutrophil-to-lymphocyte ratio improvement.

Comment from INESSS: Results from this retrospective cohort study also reported that the mortality rate was higher in the hydroxychloroquine group, versus control, although this finding was not statistically significant (4/31 [12.90%] versus 1/32 [3.13%] P = 0.196).


Summary: This comparative observational study collected data in March 2020 from four French tertiary care centres providing care to patients with COVID-19. It aimed to assess the effectiveness of hydroxychloroquine in patients requiring oxygen but not intensive care. It compared the use of hydroxychloroquine (600 mg per day) with standard care (control group). The primary outcome was survival without transfer to the intensive care unit. The secondary outcomes included overall survival, survival without acute respiratory distress syndrome, weaning from oxygen, and discharge from the hospital; outcomes were measured at day 21. A total of 181 patients (aged 18 years to 80 years) were included. The overall survival rate was 89% in the treatment group compared with 91% in the control group (HR 1.2; 95% CI, 0.4 to 3.3). With respect to survival without acute respiratory distress syndrome, 69% of patients in the treatment group survived compared with 74% in the control group (HR 1.3; 95% CI, 0.7 to 2.6). Also, 82% of patients in the treatment group were weaned from oxygen compared with 76% in the control group (weighted risk ratio 1.1; 95% CI, 0.9 to 1.3). Electrocardiographic changes were observed in eight patients in the treatment group (10%); hydroxychloroquine was discontinued in these patients. The authors concluded that the results of their study do not support the use of hydroxychloroquine in patients admitted to hospital with COVID-19 who require oxygen.

Comment from INESSS: The higher risk of cardiovascular adverse events was noted by INESSS. It mentioned that among the 84 patients who had received hydroxychloroquine, eight had to discontinue therapy because of electrocardiogram changes after a median time of four days. Seven had QT interval prolongation. One patient developed first-degree atrioventricular block after two days of therapy.

STUDY # 7: Magagnoli et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Findings from this study were made available online prior to peer review on the medRxiv platform (see: https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2.full.pdf).

Summary: This retrospective study analyzed data from patients hospitalized with COVID-19 in all U.S. Department of Veterans Affairs medical centres; data were collected until April 11, 2020. Analysis compared patients treated with hydroxychloroquine monotherapy with those treated with hydroxychloroquine and azithromycin combination therapy, and those treated
with standard care without hydroxychloroquine. Death and the need for mechanical ventilation were the primary outcomes. Association between treatment and the primary outcomes was analyzed using competing risk hazard regression adjusted for clinical characteristics via propensity scores. Overall, 368 patients were evaluated (97 in the hydroxychloroquine monotherapy group, 113 in the hydroxychloroquine and azithromycin combination therapy group, and 158 in the no hydroxychloroquine/standard care group). The death rates in these groups were 27.8%, 22.1%, 11.4%, while rates of ventilation were 13.3%, 6.9%, and 14.1%, respectively. Compared with the standard care group, the risk of death from any cause was increased in the hydroxychloroquine group (adjusted HR, 2.61; 95% CI, 1.10 to 6.17; P = 0.03) but not in the combination drug therapy group (adjusted HR, 1.14; 95% CI, 0.56 to 2.32; P = 0.72). The risk of ventilation was similar in the hydroxychloroquine group (adjusted HR, 1.43; 95% CI, 0.53 to 3.79; P = 0.48) and in the combination drug therapy group (adjusted HR, 0.43; 95% CI, 0.16 to 1.12; P = 0.09) compared to the standard care group. The authors concluded that they did not observe evidence that the use of hydroxychloroquine, with or without azithromycin, reduces the risk of mechanical ventilation in patients hospitalized with COVID-19. They also reported an association of increased overall mortality in the patients who used hydroxychloroquine monotherapy.

Comment from INESSS: In addition to the results presented in this abstract, the INESSS report also mentioned results for a secondary outcome, which aimed to assess the effect of these therapies on death among patients who required mechanical ventilation. No significant difference was observed in the risk of death after ventilation in the HC group (adjusted hazard ratio [HR], 4.08; 95% CI, 0.77 to 21.70; P = 0.10) compared to the control group.

Note: With respect to the effect of hydroxychloroquine in the treatment of hospitalized patients with COVID-19, accounting for all studies reviewed in its updated report, INESSS indicated that there is currently weak evidence that this drug may provide some benefits in symptom alleviation and the improvement of radiological imaging. There is currently insufficient evidence to determine the effect of hydroxychloroquine on the clinical progression and prognosis of hospitalized patients with COVID-19.

Hydroxychloroquine + Azithromycin


Summary: Presented in the previous Hydroxychloroquine section.

Comment from INESSS: In addition to the lack of difference in the need for ventilation between the hydroxychloroquine + azithromycin group and the control group (adjusted HR, 0.43; 95% CI, 0.16 to 1.12; P = 0.09), there was also no difference between these groups for the secondary outcome of risk of death after ventilation (adjusted HR, 1.20; 95% CI, 0.25 to 5.77; P = 0.82).


Summary: This retrospective observational study evaluated the use of hydroxychloroquine (administered at a dose of 200 mg three times daily for ten days) combined with azithromycin (administered at a dose of 500 mg on the first day, followed by 250 mg daily for...
four days) in hospitalized patients with COVID-19. A total of 1,061 patients who tested positive for SARS-CoV-2 were included. The outcomes of interest were death, clinical worsening (defined as transfer to the intensive care unit, and hospitalization beyond 10 days), as well as viral shedding persistence (the latter defined as greater than 10 days). Authors indicated that therapeutic response (reported as good outcome) and virologic cure were observed in 973 patients (91.7%), whereas 46 patients (4.3%) had a poor clinical outcome; eight patients died (0.75%). These deaths were due to respiratory failure. Poor clinical outcome was associated with older age, severity of illness at admission, and low hydroxychloroquine blood level. Mild adverse events were reported by 2.3% of patients; these events included gastrointestinal or cutaneous events, headache, insomnia, and transient blurred vision. The authors concluded that the use of hydroxychloroquine and azithromycin combination therapy early in the course of the disease (i.e., before complications occur) is safe and associated with low mortality in patients with COVID-19.

Comment from INESSS: This study is the extension of one of the observational studies (Gautret et al 2020a) conducted in Marseille (France) and captured in the original INESSS report.

Note: With respect to the effect of hydroxychloroquine + azithromycin in the treatment of hospitalized patients with COVID-19, accounting for all the studies reviewed in its updated report, INESSS indicated that there is currently insufficient evidence to determine the effect of this drug combination on symptom alleviation, improvement of radiological imaging, clinical progression, and prognosis of hospitalized patients with COVID-19.

Chloroquine

STUDY # 9: Huang et al. Treating COVID-19 with chloroquine. Findings from this study were published online on April 1 in the Journal of Molecular Cell Biology in the form of an Application Note (https://academic.oup.com/jmcb/article/12/4/322/5814655).

Summary: This randomized clinical trial compared chloroquine to the antiviral combination drug lopinavir/ritonavir in hospitalized patients with COVID-19 in China. Outcomes of interest were real-time polymerase chain reaction for detecting COVID-19 viral ribonucleic acids, lung computerized tomography for assessing improvement in pneumonia severity, and hospital length of stay. A total of 82 patients were screened in January and February 2020; 22 patients met the inclusion criteria. These patients were randomized in two groups; i.e., chloroquine 500 mg orally twice daily for 10 days (n = 10, including three patients with severe disease and seven with moderate disease) and lopinavir/ritonavir 400/100 mg orally twice daily for 10 days (n = 12, including five patients with severe disease and seven with moderate disease). All 10 patients (100%) on chloroquine had SARS-CoV-2 negative as of day 13, whereas 11 out of 12 patients (91.7%) had negative test at day 14. Computerized tomography imaging was improved in twice as many patients in the chloroquine group at day 14 compared with patients in the lopinavir/ritonavir group (rate ratio 2.21; 95% CI, 0.81 to 6.62). By day 14, all 10 patients (100%) in the chloroquine group were discharged from the hospital compared to six patients (50%) in the lopinavir/ritonavir group. With respect to adverse events, all occurred in patients using chloroquine. Five patients reported a total of nine adverse events; these included vomiting, abdominal pain, nausea, diarrhea, rash, cough, and shortness of breath.

Comment from INESSS: This randomized clinical trial conducted in China compared chloroquine with lopinavir/ritonavir in 22 hospitalized patients. After 14 days, patients on chloroquine had a higher probability of improved lung radiological imaging compared with
patients on antiviral therapy (relative risk [RR] 1.33 [95 % CI 1.00 to 2.00]). Patients on chloroquine were also more likely to be discharged from the hospital within 14 days compared to patients on antiviral therapy (RR 2.00 [95 % CI 1.33 to 4.00]).

STUDY # 10: Feng et al. The use of adjuvant therapy in preventing progression to severe pneumonia in patients with coronavirus disease 2019: a multicenter data analysis. Findings of this study were made available online prior to peer review on the medRxiv platform (see: https://www.medrxiv.org/content/10.1101/2020.04.08.20057539v1).

Summary: This multi-centre, retrospective cohort study evaluated data from 564 patients (median age of 47 years; 50.4% of patients were men) with confirmed COVID-19. These were consecutively admitted between January 17 and February 28, 2020 in nine hospitals in China. Development of severe COVID-19 pneumonia was the main outcome of interest. Sixty-nine patients (12.2%) developed pneumonia. Patients who developed severe pneumonia were older; more patients had comorbidities (including hypertension, diabetes, and cardiovascular disease). Further analyses found that no patients treated with chloroquine had developed severe pneumonia. The authors, however, indicated that propensity score matching did not lead to a statistically significant difference (12.0%; 95% CI, −3.5% to 30.0%). Additional analyses were conducted with respect to the impact on pneumonia severity of antiviral therapy, as well as use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers in patients with hypertension. Authors concluded that the use of chloroquine should be further studied as a potential treatment for COVID-19.

Comment from INESSS: Results from this study on chloroquine are those from 25 patients admitted to the only centre that used chloroquine as part of a larger multi-centre study that included nine centres in China. The INESSS report noted that although none of these patients developed severe pneumonia, the propensity score-based adjustment of the different variables that can impact the evolution of COVID-19 did not reveal statistically significant results (difference of 12.0%; [95 % CI, −3.5% to 30.0%]; P = 0.074).

Note: With respect to the effect of chloroquine for the treatment of hospitalized patients with COVID-19, accounting for all studies included in its updated report, INESSS indicated that:

- There is currently weak evidence that the use of chloroquine may improve lung radiological imaging compared with the use of lopinavir/ritonavir.
- There is currently insufficient evidence to determine whether the use of chloroquine may prevent the development of severe pneumonia.
- There is currently weak evidence that the use of chloroquine may allow for earlier hospital discharge compared with the use of lopinavir/ritonavir.

Chloroquine + Azithromycin

No studies were identified. The INESSS report therefore stated that there is currently insufficient evidence to determine the effect of chloroquine + azithromycin in the treatment of hospitalized patients with COVID-19.

Safety of the Use of Chloroquine or Hydroxychloroquine, With or Without Azithromycin

In addition to the 10 studies described in the preceding sections, three other new studies (Chorin E et al., Ramireddy A et al., and Borba et al.) were identified in the INESSS report. These were only described in the Safety section of the latter report. Authors of these studies
were interested in assessing the effect of chloroquine or hydroxychloroquine, with or without azithromycin, on the risk of cardiac arrhythmia.

**STUDY # 11:** Chorin E et al. The QT interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin. Findings of this study were made available online prior to peer review on the medRxiv platform (see: https://www.medrxiv.org/content/10.1101/2020.04.02.20047050v1).

*Summary:* The authors of this study reported on 84 consecutive patients with COVID-19 admitted to their institution and who were treated with a hydroxychloroquine and azithromycin combination. They found that the QTc interval was prolonged by greater than 40 milliseconds (ms) in 30% of these patients; severe QTc prolongation (i.e., greater than 500 ms) was observed in 11% patients. These patients were considered at high risk for arrhythmia.

*Comment from INESSS:* In addition to these results, INESSS mentioned that four patients died of multisystem failure; there were no cardiac arrhythmias. There were also no torsades de pointes reported, including in higher-risk patients (i.e., QT of greater than 500 milliseconds). Results of this study, posted prior to its review by peers, are associated with some limitations including the lack of information on doses used and the health status of patients.

**STUDY # 12:** Ramireddy A et al. Experience with hydroxychloroquine and azithromycin in the COVID-19 pandemic: implications for QT interval monitoring. Results of this study were made available online prior to peer review on the medRxiv platform (see: https://www.medrxiv.org/content/10.1101/2020.04.22.20075671v1).

*Summary:* This case series analyzed the QTc interval from the electrocardiographic readings of patients with (confirmed or suspected) COVID-19 admitted at the Cedars-Sinai Medical Center in Los Angeles, California (US) between early February and early April 2020. These patients were treated with azithromycin, hydroxychloroquine, or a combination of these drugs. The authors observed the most changes in QTc in patients using the hydroxychloroquine and azithromycin combination therapy compared to patients using one of these drugs alone. QTc prolongation was also greater in patients using combination therapy compared to those using azithromycin monotherapy (17 ms ± 39 ms versus. 0.5 ms ± 40 ms, P = 0.07). Authors reported that 12% of patients manifested critical QTc interval prolongation; there was no torsades de pointes. Authors concluded that clinicians should carefully assess the balance between uncertain benefit and potential risk when treating COVID-19 patients with either azithromycin, hydroxychloroquine, or a combination of these drugs.

*Comment from INESSS:* In addition to these results, INESSS mentioned that the number of patients with critical QTc prolongation was similar between the hydroxychloroquine + azithromycin group (N = 7) group and the azithromycin group (N = 5). No patients enrolled in the study had a cardiac event (syncope, torsades de pointes, fatal arrhythmia).
STUDY # 13: Borba MGS et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). Findings from this study were initially made available online prior to peer review on the medRxiv platform (see: https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v2). Findings were then published online in JAMA Network Open (see: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765499).

Summary: This study was funded by the Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, Manaus (Brazil). It was a parallel, double-blinded, randomized, phase IIb clinical trial, which aimed to evaluate the safety and efficacy of two different doses of chloroquine in patients with COVID-19 hospitalized for severe respiratory syndrome in Brazil. Dosage regimens evaluated were higher-dose chloroquine — defined as 600 mg twice daily for 10 days (total dose = 12 g) — and lower-dose chloroquine — defined as 450 mg for five days, twice daily only on the first day (total dose = 2.7 g). All patients also received ceftriaxone and azithromycin. A total of 81 patients were enrolled (out of 440 patients). QTc intervals greater than 500 ms were observed more frequently in patients using the higher dose of chloroquine (7 of 37 [18.9%]) compared to patients using the lower dose of chloroquine (4 of 36 [11.1%]). The authors cautioned against the use of higher-dose chloroquine in patients with COVID-19 presenting with severe respiratory syndrome.

Comment from INESSS: INESSS noted that a higher proportion of patients (18.9%) using higher-dose hydroxychloroquine had QTc of greater than 500 milliseconds compared with those (11.1%) who received a lower dose.