Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Antimicrobial Agents 57 (2021) 106169

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Letter to the Editor

Uncertain effects of hydroxychloroquine and azithromycin on SARS-Cov-2 viral load

Dear Editor:

Gautret and colleagues [1] claim that hydroxychloroquine (HCQ) and azithromycin are efficacious in the treatment of patients infected with SARS-cov-2. However, their conclusion that hydroxychloroquine is associated with viral load reduction is not based on rigorous study design or analysis.

The authors tested whether there is a difference in the rate of negative RT-PCR tests in treated versus untreated patients in each day. This method is not optimal for the longitudinal study design, in which each patient has been repeatedly measured on multiple occasions. The serial measurements introduce the problem of intra-patient correlation in the outcome that can lead to biased estimate of treatment effect and incorrect P values [2]. Using the authors' data, I estimated that the intraclass correlation in the rate of negative tests was 0.37 (95% confidence interval: 0.22 to 0.52), suggesting a substantial within-patient correlation that needs to be accounted for.

The mixed-effects logistic regression model [3] can be used to model the change within each patient, and hence give an unbiased estimate of treatment effect. Using the authors' data in the appendix [1], I conducted a mixed-effects logistic regression analysis accounting for the interaction effects of HCQ and azithromycin and time (Table 1). While the rate of negative tests increased with time, the increase was not significantly different between those on HCQ and those not on HCQ (P = 0.355). Interestingly, patients on azithromycin had a significantly greater rate of negative tests compared to those not on azithromycin (P = 0.019; Figure 1). On the basis of the results presented, I propose an alternative interpreta-

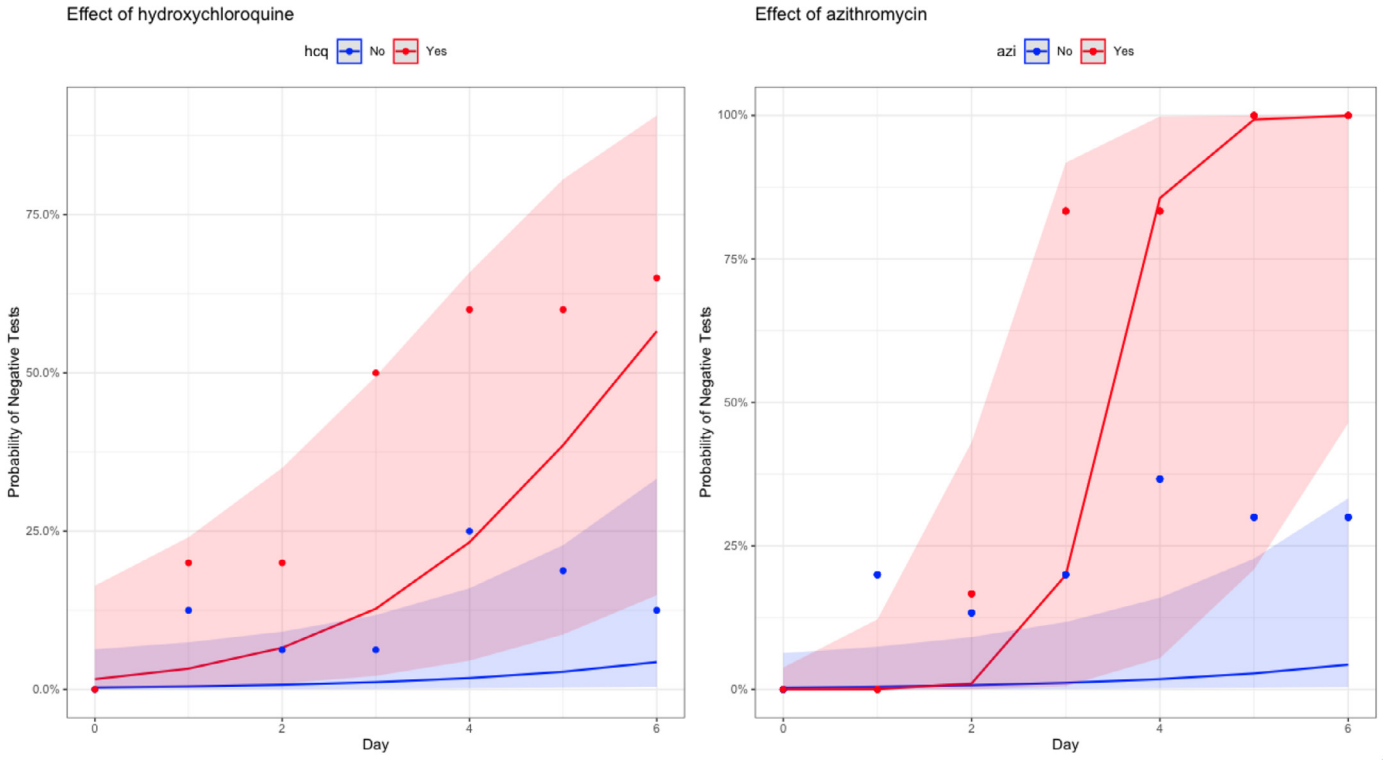

Figure 1. Predictive percent of negative tests by treatment group (HCQ or azithromycin) on each day. The interaction effect between HCQ and day was not statistically significant (P = 0.355), but the interaction effect between azithromycin and day was statistically significant (P = 0.019).

DOI of original article: 10.1016/j.ijantimicag.2020.105949

https://doi.org/10.1016/j.ijantimicag.2020.106169

Table 1
Effects of day, hydroxychloroquine (HCQ), and azithromycin on the rate of negative tests: result of a mixed-effects logistic regression model.

Parameter	Estimate (Standard error)	P-value
Day	0.45 (0.23)	0.047
HCQ	1.71 (1.73)	0.322
Azithromycin	-5.09 (3.43)	0.138
HCQ by Day	0.27 (0.30)	0.355
Azithromycin by Day	2.72 (1.16)	0.019

Note: Results were obtained from the model log(P / (1 - P)) = Day + HCQ + Azithromycin + HCQ x Day + Azithromycin x Day, where P is the probability of negative test.

tion that the effect of hydroxychloroquine and azithromycin on the elimination of viral load remains uncertain.

Declaration of Competing Interest

No conflict of interest

Funding

No funding

Ethical Approval obtained

NA

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