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Concerns About the Special Article on Hydroxychloroquine and Azithromycin in High Risk Outpatients with COVID-19 by Dr. Harvey Risch

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Conflicts of Interest: LDM has received consulting fees from Acelity and Sanofi in the past five years. EJM has received consulting fees from Blue Cross Blue Shield, MA in the past five years. BDJ has received consulting fees from the Alzheimer's Association in the past five years. SHM has received speaking fees from speaker fees from Gilead in the past five years. MPF has received speaking fees from Merk in the past five years.

Running Head: **Concerns About Special Article by Dr. Risch**

Abstract

In May, this journal published an opinion piece by one of the members of the Editorial Board, Dr. Harvey Risch, that reviewed several papers and argued that using hydroxychloroquine (HCQ) + azithromycin (AZ) early to treat symptomatic COVID-19 cases in high-risk patients should be broadly applied. As members of the journal's editorial board, we are strongly supportive of open debate in science, which is essential even on highly contentious issues. However, we must also be thorough in our examination of the facts and open to changing our minds when new information arises. In this commentary, we document several important errors in the manuscript by Dr. Risch, review the literature he presented and demonstrate why it is not of sufficient quality to support scale up of HCQ+AZ, and then discuss the literature that has been generated since his publication, which also does not support use of this therapy. Unfortunately, the current scientific evidence does not support HCQ+AZ as an effective treatment for COVID-19, if it ever did; and even suggests many risks. Continuing to push the view that it is an essential treatment in the face of this evidence is irresponsible and harmful to the many people already suffering from infection.

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Keywords: Hydroxychloroquine; Azithromycin; observational studies; randomized trials; bias; confounding

Abbreviations: Hydroxychloroquine (HCQ); Azithromycin (AZ)

In May, this journal published an opinion piece by one of the members of the Editorial Board, Dr. Harvey Risch, that reviewed several papers – published and unpublished – and argued that using hydroxychloroquine (HCQ) + azithromycin (AZ) early to treat symptomatic COVID-19 cases in high-risk patients early should be broadly applied[1]. This piece received little attention until the author wrote a similar piece for Newsweek[2] – followed by interviews on Fox News– implying that by publishing his opinion, the American Journal of Epidemiology Editorial Board agreed with his assessment. This is categorically not the case.

As members of the journal's editorial board, we are strongly supportive of open debate in science, which is essential even on highly contentious issues. However, we must also be thorough in our examination of the facts and open to changing our minds when new information arises. While the article in question is an opinion piece, not a systematic scientific review of the evidence, that does not excuse inaccurate reporting of the facts. This article contains numerous factual errors and ambiguous statements, that need to be corrected or clarified. These issues, detailed below, are not open to interpretation, but rather are a clear misstatement of the evidence from the cited materials or misstatements of epidemiologic

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principles. Furthermore, since then, new information has come to light that must be taken into consideration when formulating an opinion on the efficaciousness of a treatment, and Dr. Risch's position on use of HCQ+AZ must be evaluated in the context of this new, unfavorable, information.

This occurrence - like many others during this time of COVID-19 – has laid bare longstanding tensions between the scientific endeavor, medicine and public health practice, and between private and public goods. However, the urge for swift medical action and to do the best by patients does not give us license to ignore evidence or fail to update our views when that evidence changes, as doing so hurts both the patients themselves and public health as a whole.

Inaccuracies and Errors

Dr Risch identified five studies[3–8], which he used to argue that HCQ+AZ is an effective early treatment for COVID-19 in high-risk outpatients. We deal with the quality of the evidence in these studies in the next section, but first want to detail a number of inaccuracies in Dr. Risch's presentation of the evidence that we feel need to be corrected. This is not a comprehensive list, but rather some key points that we think are essential to his argument.

1. In summarizing the study by Gautret et al[3], Dr. Risch refers to a 50-fold benefit of the HCQ+AZT vs control, but nowhere in the paper is a 50-fold increase reported. In the cited re-analysis[9] there is a reported odds ratio (OR) of 52 but given the outcome is so

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common, the odds ratio will be a markedly inflated version of the more relevant parameter, the risk ratio. Using the data from Gautret, we calculate a risk ratio (RR) of about 5. We further note no confidence intervals are presented in Dr. Risch's comment, so there is no way to see if the data are consistent with very large and very small associations. This is particularly important given the small size of this study (just 42 patients total, subdivided into 3 groups, some patients excluded). Small studies that find large effects, even if unbiased and from trials, tend to overstate effect sizes[10]. In the re-analysis[11] cited by Risch a risk ratio of 3.84 is reported for HCQ overall, and no results for the RR for HCQ+AZ due to model separation. When switching to the odds ratio, we see that the confidence interval for the 52-fold odds ratio goes from 1.95 to 1,399, an incredibly imprecise finding. Thus, even if the effect is real, it is very likely overstated.

2. Dr. Risch, in referring to the study by Gautret et al.[3] makes the argument that a large effect cannot be explained by confounding. This is incorrect. Large effects *can* be explained by confounding particularly when the relationships between the omitted variable and the variables of interest are strong (think of the classic example of the relationship between carrying matches and lung cancer) or the sample size is small. In addition, selection bias, measurement error, and other sources of bias mean it is very plausible that the observed association could be explained by bias and random error.

3. Referring to the Gautret et al. study[3], Dr. Risch then states "Further, the study showed a significant, 7-fold benefit of taking HCQ+AZ over HCQ alone, P-value=.035, which cannot

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be explained by differential characteristics of the controls, since it compares one treatment group to the other"[1, p 9]. This statement suffers from the same issues outlined in (1) and (2) (i.e. no description of the outcome or effect measure, lack of confidence interval, very small sample size). In addition, the statement that this cannot be explained by "differential characteristics of the controls" does not make sense, as with such a small (non-randomized) sample it is entirely plausible that there are differential characteristics between the 14 patients that received HCQ alone and the 6 who received HCQ+AZ. Furthermore, even in a large, non-randomized study, there can be important differential characteristics between those who received HCQ alone and those who received HCQ and AZ.

The evidence for this treatment, even in May, was weak and low quality

Leaving aside the issue of errors and inaccuracies in his opinion piece, we still strongly disagree with the position Dr. Risch has taken on HCQ+AZ. We believe that the evidence, even in May 2020 when the piece was written, did not support the use of these drugs , even for early outpatient treatment of Covid-19 for high risk patients. There have been many critiques of Dr. Risch's manuscript and the individual studies he cites; as an example, see comments by Rosendaal[12] and Machiels[13] among others on the Gautret study[3]. There have also been numerous letters published in response to Dr. Risch's comment which we support[14–16]. We do not wish to reproduce all of these critiques and restrict ourselves to some additional key points.

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As noted previously, Dr. Risch considers five studies in evaluating the evidence. Three of these have no control groups[5–8], and therefore cannot be used as evidence for estimating the causal effect of HCQ+AZ on COVID-19 outcomes. This leaves only two studies from which to draw conclusions about the risks or benefits of this treatment regime[3,4]. Both of these studies have serious limitations -- limitations which we consider so severe that they provide little evidence.

The Gautret *et al.* study[3] was a small study. The small sample size alone provides cause for concern despite Dr. Risch's assertion to the contrary. Even a *randomized* trial of 42 patients (6 of whom were lost to follow up) in which only 6 patients got the treatment of interest would provide very weak (if any) evidence for an effect. But this was not a randomized trial, yet it appears that no measures were taken to control for confounding at either the study design or the analysis phase. Little data on potential confounders are even reported to allow for such adjustment to be done. As such, this study could at best provide exploratory evidence suggesting this treatment should be examined further. It cannot provide sufficient evidence on which to base policy despite the urgency for action. This limitation becomes even more problematic when Dr. Risch attempts to stratify the already thin data into those who did and did not have "presentation with asymptomatic or upper respiratory tract infection[1 p 9], vs lower respiratory-tract infection" to make the case that the medication needs to be used as early as possible in treatment. Given the small sample size, the data cannot support stratified analysis.

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The second study, by Barbosa et al.[4], was an observational study conducted in Brazil. It was larger than the previously described study, having 412 patients who got the treatment. However, in this case, the authors used the 224 patients who refused treatment as controls. In such a case confounding is all but assured. It is very likely the groups differed with respect to the risk for outcomes. This confounding, if not corrected for, means we cannot learn much from the study. Without detailed information about the participants of the trial, it is impossible to determine the impact of this confounding on the results. For example, if the sickest patients agreed to take HCQ+AZ, then confounding by indication could make this treatment regimen look less beneficial. However, it's important to remember that this study (and Dr. Risch's recommendations) focus on outpatient treatment of early COVID-19 patients with mild symptoms. Therefore, Dr. Risch's argument that those who chose to try the experimental treatment were sicker (and thus presumably desperate to try anything) seems unsupported. A plausible alternative is that the sicker patients decided to decline this treatment in favor of seeking more intensive care elsewhere. This would supplement the control group with individuals who were the most likely to die and overinflate the observed benefits of the treatment regimen. Further there appears to have been no confirmation of infection with SARS-CoV-2 in this study, making it impossible to determine effectiveness of the treatment for the condition specified. The direction of confounding by indication can be difficult to predict and can go in either direction.

The final three studies included by Dr. Risch[5–8] are case series with no control group. Such studies can be useful for prompting new research questions and guiding future research. They

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cannot be used to support a causal conclusion about the efficacy of a treatment. While universally fatal conditions such as rabies and some cancers represent a rare exception to this rule, COVID-19 in no way meets this criterion. Hence, these studies do nothing to support Dr. Risch's argument.

Given these severe limitations, we do not consider any of these studies useful for policy making.

The evidence has moved on

Dr. Risch notes that "Each piece of evidence, contained in each study, must be carefully considered and not dismissed because in an ideal world such evidence would fall in a lower part of the evidence-quality triangle."[1, p 8]. We agree with this, but that is also not a reason to accept flawed research and use it to make strong statements that the evidence cannot support (see the title of Dr. Risch's article which calls for "ramping up" this treatment – see the title[1, p 1]). As Dr. Risch notes, all treatments have risks[1] (he falsely notes that they all have benefits, which is not the case) and as such, using bad evidence can lead to harm. Additionally, if one is going to act on such evidence, it is critical that they continue to collect additional information and reevaluate their conclusions as more evidence is generated. In this case, since the publication of his article, stronger randomized trial evidence has emerged. Dr. Risch has dismissed these studies because he does not believe RCT evidence is *de facto* more valuable than observational data—this is a straw man argument; we as fellow epidemiologists also believe strongly that

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observational evidence should be given due consideration, but as a general rule, well-conducted randomized controlled trials give a more accurate estimate of a causal effect than poorly designed, small observational studies. In fact, a large observational study of hydroxychloroquine alone or with zinc compared to neither did find a protective association with mortality for each treatment (interestingly finding about the same association for both), but rightly concluded, "Prospective trials are needed to examine this impact."[17, p 396]

We note that Dr. Risch, in his own response to letters of concern, presents 7 additional studies that had been published since his May letter[11]. Four of the seven, again, have no control population and cannot be regarded as evidence. The remaining studies, except for one are listed as personal communication and as such cannot be evaluated and the remaining has no control group and is a media report. None are randomized controlled trials, which would provide much stronger evidence as they are better able to limit the impact of confounding.

In May, around the time of Dr. Risch's comment, a randomized controlled trial was published in the BMJ[18] which did compare HCQ (not with AZ) with standard of care in adults in China. These were hospitalized patients but almost all (148 of 150) had mild to moderate coronavirus and the outcome was negative conversion between 2 and 28 days. Perhaps a small benefit was seen, but with very poor precision (risk difference 4.1%; 95% CI: -10.3% to 18.5%, the authors concluded no benefit based on the p-value). Dr. Risch has argued that we cannot use studies that did not use HCQ and AZ as evidence and as noted, this study did not include azithromycin. However, it does provide more evidence against any large benefits such as those seen in the

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Gautret study. A similar result was found in a trial of HCQ (again not with AZ) by Skipper et al.[19] in 423 adult outpatients in the US with early, mild disease, 341 of whom had lab confirmed infection, and found very little difference in symptom severity compared to placebo at day 14 (−0.27 points, 95% CI: −0.61 to 0.07 on a 10 point scale). A third trial of HCQ alone in Spain by Mitjà et al.[20] of early treatment among 293 patients with mild disease found no differences in mean reduction of viral load at day 3. There was some reduction in risk of hospitalization (RR 0.75; 95% CI: 0.32;1.77) but the authors concluded no difference based on the lack of significance.

A more relevant study was recently published, a randomized trial from a group in Brazil[21]. Cavalcanti et al. randomized 667 patients with mild to moderate disease to either HCQ+AZ, HCQ alone or standard of care. Of those, 504 were then confirmed to have had COVID-19 and among those, there was no benefit to HCQ+AZ on clinical status at 15 days (odds ratio 0.99; 95% CI: 0.57 - 1.73). Dr. Risch has argued that the treatment is only effective in high-risk patients including those over 60 and those with comorbidities. While this study was not limited to those over 60, the mean age was about 50, about 39% had hypertension, about 16% were obese and about 19% had diabetes. A subgroup analysis shown in the appendix limited to those over 60 also showed no benefit (odds ratio 0.95; 95% CI: 0.37 - 2.43). Thus, while not limited to high-risk patients, clearly the high-risk patients Dr. Risch says are the ones that need to be studied make up a strong proportion of this study population.

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No doubt these studies too have limitations such as lack of blinding, but the evidence they provide is still much stronger than that presented by Dr. Risch. And certainly, the result of one trial is not enough to draw strong conclusions either, but to date, this is the best evidence we have, and it does not support use of HCQ+AZ in early disease. Given this new randomized controlled trial evidence, there is no way to continue to support the position that HCQ+AZ use is beneficial, nor that it will save a hundred thousand lives unless some new evidence were to emerge that would support such a statement.

Conclusion

We believe that Dr. Risch's summary of the evidence in May contained factual errors, and that the evidence presented, even at the time of publication, was weak at best. Since then, stronger evidence has demonstrated no benefit for early treatment of high-risk patients with mild COVID-19 patients with HCQ+AZ. Disagreement and opposing points of view are welcome in science, and there is some subjectivity in deciding when a study's flaws are sufficient enough to invalidate its conclusions. However, we do not believe that Dr. Risch provides a sound basis to refuting the scientific evidence against a benefit for early treatment with HCQ+AZ in high-risk patients with mild COVID-19, and he certainly does not provide evidence to support policy claims such as "ramping up" this treatment.

Dr. Risch makes the comment that "In this context, we cannot afford the luxury of perfect knowledge"[1, p 8]. We wholeheartedly share Dr. Risch's desire for an effective treatment in the

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face of this pandemic and we would be ecstatic if the evidence supported HCQ+AZ or any other treatment. However, when acting on limited evidence we must be careful not to view the data with rose-colored glasses, and we must be quick to adjust our views, abandoning positions as the evidence changes. Unfortunately, the current scientific evidence does not support HCQ+AZ as an effective treatment for COVID-19, if it ever did. Continuing to push the view that it is an essential treatment in the face of this evidence is irresponsible and harmful to the many people already suffering from infection.

REFERENCES

1 Risch HA. Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis. *Am J Epidemiol* 2020; published online May 27. DOI:10.1093/aje/kwaa093.

2 Risch HA. The Key to Defeating COVID-19 Already Exists. We Need to Start Using It | Opinion. *Newsweek* 2020. https://www.newsweek.com/key-defeating-covid-19-already-exists-we-need-start-using-it-opinion-1519535.

3 Gautret P, Lagier JC, Parola P, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; **56**: 105949.

4 Barbosa Esper R, Souza da Silva R, Costa Oikawa FT, *et al.* Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine. https://pgibertie.files.wordpress.com/2020/04/2020.04.15-%0Ajournal-

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manuscript-final.pdf.

5 Million M, Lagier JC, Gautret P, *et al.* Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis* 2020; **35**: 101738.

6 Zelenko V. To all medical professionals around the world. https://docs.google.com/document/d/1pjgHlqIZuKOziN3txQsN5zz62v3K043pR3DdhEmcos/.

7 ABC Eyewitness News. Coronavirus News: Long Island doctors embrace combination drug therapy in fighting COVID-19. *April 13, 2020* https://abc7ny.com/coronavirustreatment-%0Along-island-news-nassau-county/6093072/.

8 Ahmad I, Alam M, Saadi R, Mahmud S, Saadi E. Doxycycline and Hydroxychloroquine as Treatment for High-Risk COVID-19 Patients: Experience from Case Series of 54 Patients in Long-Term Care Facilities. *medRxiv* 2020; 2020.05.18.20066902.

9 Lover AA. Quantifying Treatment Effects of Hydroxychloroquine and Azithromycin for COVID-19: A Secondary Analysis of an Open Label Non-randomized Clinical Trial: A Preprint. *medrxiv.org* 2020; doi: https://doi.org/10.1101/2020.03.22.20040949 https://www.medrxiv.org/content/10.1101/2020.03.22.20040949v2: Accessed August 7, 2020.

10 Ioannidis J. Why most discovered true associations are inflated. *Epidemiology* 2008; **19**: 640–8.

11 Risch HA. Response to: 'Early Outpatient Treatment of Symptomatic, High-Risk Covid-19

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Patients' and 'Re: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis'. *Am J Epidemiol* 2020; published online July 20. DOI:10.1093/aje/kwaa152. https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwaa152/5873640

12 Rosendaal FR. Review of: "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial Gautret et al 2010, DOI:10.1016/j.ijantimicag.2020.105949. Int. J. Antimicrob. Agents. 2020; **56**: 106063.

13 Machiels JD, Bleeker-Rovers CP, ter Heine R, *et al.* Reply to Gautret et al: hydroxychloroquine sulfate and azithromycin for COVID-19: what is the evidence and what are the risks? Int. J. Antimicrob. Agents. 2020; **56**: 106056.

14 Fleury V. Commentary: Comment on "Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis". *Am J Epidemiol* 2020; published online July 20. DOI:10.1093/aje/kwaa155.

15 Peiffer-Smadja N, Costagliola D. RE: Ealry Outpatient Treatment of Symptomatic, High-Risk COVID-19 Patients That Should Be Ramped-Up Immediatley As Key to the Pandemic Crisis *Am J Epidemiol* 2020; published online July 20. DOI:10.1093/aje/kwaa151.

16 Korman TM. Early outpatient treatment of symptomatic, high-risk Covid-19 patients. *Am J Epidemiol* 2020; kwaa154, https://doi.org/10.1093

17 Arshad S, Kilgore P, Chaudhry ZS, *et al.* Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis* 2020; **97**: 396–403.

18 Tang W, Cao Z, Han M, *et al.* Hydroxychloroquine in patients with mainly mild to

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moderate coronavirus disease 2019: Open label, randomised controlled trial. *BMJ* 2020; **369**.

19 Skipper CP, Pastick KA, Engen NW, *et al.* Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19. *Ann Intern Med* 2020; m20-4207.

20 Mitjà O, Corbacho-Monné M, Ubals M, *et al.* Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial. *Clin Infect Dis* 2020; ciaa1009.

21 Cavalcanti AB, Zampieri FG, Rosa RG, *et al.* Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med* 2020; nejmoa2019014.

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