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Data Integrity Analysis of the Dexamethasone Study in Hospitalized COVID-19 Patients

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Abstract. The paper entitled "Effect of Dexamethasone in hospitalized patients with COVID-19: Preliminary report" by Horby et al. and published in medRxiv was highly anticipated because it offered the only slim hope that the lives of individuals infected with SARS-COV-2 could be saved. Before the paper appeared in medRxiv which cautioned that it had not been peer-reviewed, the authors had already orchestrated a big fanfare in front of the world's press (it is the new way of disseminating scientific data now-days!). Horby et al. concluded that "Prior to the completion of this trial, many COVID-19 treatment guidelines have stated that corticosteroids are either contraindicated or not recommended in COVID-19. These should now be updated as has already happened with the UK. Dexamethasone provides an effective treatment for the sickest patients with COVID and given its low cost, well understood profile and widespread availability, is one that can be used world-wide". Because of the Hydroxychloroquine fiasco and Remdesivir uncertainties, it is legitimate to investigate if the conclusions of Horby et al. are borne out by the presented data. Here, it is shown that there have been instances of Dishonest Scientific Reporting, violation of scientific ethics rule and data anomaly that must be resolved before one can pronounce whether Dexamethasone had any effects, one way or another on the mortality of SARS-COV-2 infected patients who were admitted into hospital care. Data anomaly in the paper of Horby et al. include: (i) In Horby et al., the mortality rate of patients who did not require oxygen and invasive mechanical ventilation was ~25% whereas in other countries, including France, China and the United States, the mortality rate of patients is ~16% for all patients admitted to hospital care in the absence of Dexamethasone treatment, (ii) In Horby et al., the mortality rate of all patients admitted to hospital care requiring oxygen was ~25% whereas in a comparable study in France, the

mortality rate was ~9%, and (iii) In Horby et al., the mortality rate of patients who required oxygen and invasive mechanical ventilation was ~40% whereas in two comparable studies, the mortality rate was ~30%. It is not possible to explain the discrepancies of mortality rates reported in the study by Horby et al. and the other studies.

On or around June 22, 2020, a paper entitled "Effect of Dexamethasone in hospitalized patients with COVID-19: Preliminary report" by Horby et al. [1] was posted on medRxiv. The paper by Horby et al [1] was highly anticipated because the authors concerned had decided that their results were so good that they could not keep it under wrap and also because it offered the only hope that lives of individuals who became very ill as a result of SARS-COV-2 infections could be saved by a cheap drug. The paper carries a warning sign that it had not been peer-reviewed and that it should not be used to guide medical practice. However, everyone knows that Dexamethasone has been and will be offered for treating hospitalized patients who are infected with SARS-COV-2 even though there has been no peer-review of the paper (whatever peer-review means and is supposed to do). In view of the Hydroxychloroquine fiasco and the doubtful effectiveness of Remdesivir, it is legitimate to investigate the paper by Horby et al [1] in some details.

In their summary, Horby et al. [1] stated that "Dexamethasone reduced deaths by one third in patients receiving invasive mechanical ventilation (29% vs. 40.7%, RR. 0.65 [95 % Cl 0.51 to 0.82]; $p < 0.0001$), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5 % vs. 25.0%, RR. 0.80 [95% Cl 0.706 to 0.92]; $p= 0.0002$, but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95 Cl 0.93 to 1.61]; $p= 0.14$, and concluded that "in patients hospitalized with COVID-19, Dexamethasone reduces 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomization but not among patients not receiving respiratory support. In their paper, in Table 2, Horby et al. [1] showed that the over-all 28-day mortality rate for patients treated with Dexamethasone was 21.6% (454 deaths out of 2104 total patients) and for patients not treated with Dexamethasone and receiving usual care was 24.6% (1065 deaths out of 4321 total patients). In Figure 2, Horby

et al [1] showed that 85 out of 501 (17%) patients who did not receive oxygen but were treated with Dexamethasone had died on day 28 whereas 137 out of 1034 (13.2%) who did not receive oxygen or Dexamethasone had died died on day 28. (Nothing was said about any of the patients beyond day 28. Were they all discharged from hospital?) In contrast, the mortality rate for patients who received oxygen plus Dexamethasone and invasive mechanical ventilation plus Dexamethasone were shown to be 21.5% (275 out of 1279) and 29% (94 out of 324) compared to 25% (650 out of 2604) and 40.7% (278 out of 683) of patients who did not receive Dexamethasone respectively. Horby et al. [1] concluded that "1 death would be prevented by treatment of around 8 patients requiring mechanical ventilation or around 25 patients requiring oxygen",

There are a number of important and disturbing issues that the paper by Horby et al. [1] revealed. While Horby et. al. [1] trumpeted the apparent beneficial effects of Dexamethasone on mortality in patients treated with oxygen and oxygen with invasive mechanical ventilation with data and analysis, they failed to do so with respect to the very serious and consequential finding that Dexamethasone caused deaths in patients who were not under oxygen and invasive mechanical ventilation: According to the data provided by Horby et al. [1] Dexamethasone caused ~4% more deaths in patients not receiving oxygen or invasive mechanical ventilation than in patients not receiving Dexamethasone. Treating patients who did not require Dexamethasone is derelict of duty and violation of scientific ethics [2].

Analysis of the number of patients infected with SARS-COV-2 who died following their hospitalization from a number of countries, including France, China and United States showed that the mortality rate is ~15 ± 5.3 [3-11] (See Figure 1).

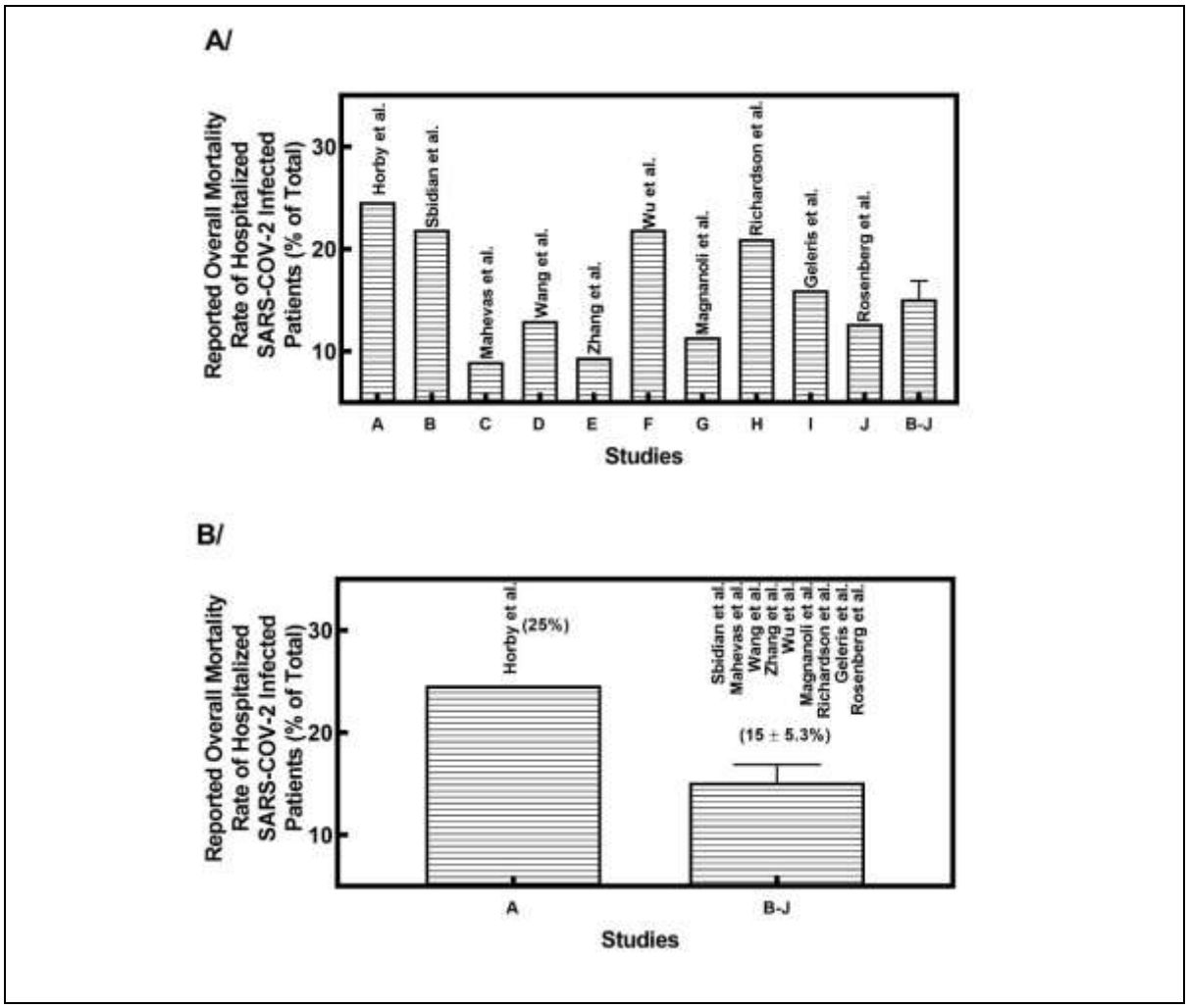

Figure 1: Comparison of Reported Overall Mortality Rate of Hospitalized SARS-COV-2 infected patients. Study is from Horby et al. [1]. Studies B to J are from [3-11]. B-J combines the studies of B to J.

Horby et al. [1] stated that the overall mortality rate in their study was ~24.6%. Quoting Docherty, A.B. et al [12], Horby et al. [1] stated that "Around 15% of all UK hospitalized patients with COVID-19 were enrolled in the trial and the control arm fatality rate is consistent with the overall hospitalized case fatality rate in the UK. However, it is not clear whether all the patients who died in the study of Docherty, A.B. et al. [6] and Horby et al. [1] were positive for SARS-COV-2. Indeed, in Table 1, Horby et al. [1] stated that ~10% of the total patients in their study were negative for SARS-COV-2 and test results of another ~9% of the total patients in their study were still missing. 19% of the total number of patients is too large to ignore in a clinical trial in which the overall mortality rates of patients treated

or not with Dexamethasone differed by ~ 5% (21.6% v. 24.6%). If the value of ~16% is taken as the average mortality rate for hospitalized patients that are tested positive, it can be argued that Dexamethasone actually caused as many as 113 (~5.6% of 2014) unnecessary deaths. According to a study by Mahon et al [13], on or around April 2, 2020, the mortality rate of all patients hospitalized because of SARS-COV-2 infection and COVID-19 in the United Kingdom was 6% (644 out of 10734) and that on or around June 15, 2020, the mortality rate had dropped to 1.5% (50 out of 3270). It is possible that there may have been careless recording of data, analysis of data and literature search (The paper of Horby et al [1] does not document the findings of Mahon et al. [13] and the reporting of the results of Mahon et al. [15]. Not reporting results that may have an impact of one's paper is called Dishonest Scientific Report, a form of Scientific Misconduct [2,14]).

According to a study in France by Mahevas et al [4], the mortality rate for patients who required oxygen treatment was 9% (8 out of 89) in the absence of treatment with corticosteroids. Mahevas et al. [4] also reported that at day 21, 80% of the patients were discharged to home or rehabilitation and the overall survival rate was 91% without treatment with corticosteroids. The results of Mahevas et al. [4] are in stark contrast and cannot be reconciled with the results of Horby et al. [1] which showed that the mortality rate of patients who required oxygen treatment was 25% and Dexamethasone reduced the mortality rate to 21.5%. It is difficult to explain the huge difference in the mortality rates of patients receiving oxygen treatment (9% v. 25%) (Figure 2) in the two studies unless one invokes the idea that the level of care in the United Kingdom is worse than in France.

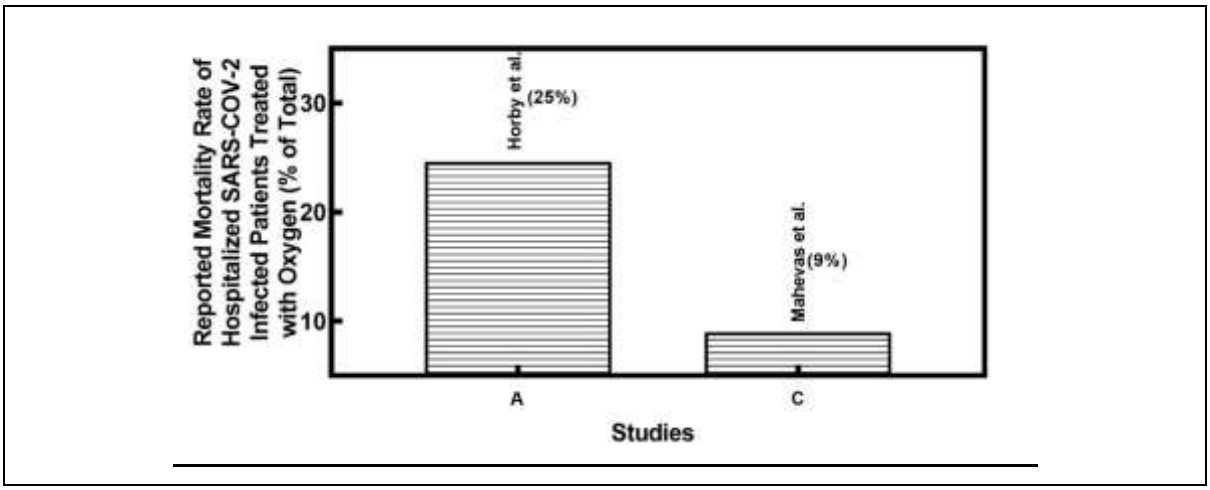

Figure 2: Comparison of Reported Overall Mortality Rate of Hospitalized SARS-COV-2 infected patients under oxygen treatment. Studies are from Horby et al. [1](A) and Mahevas et al. [4] (C).

It is fair to say that health care provision and the level of competence of health care providers are very similar in France and United Kingdom. It is not clear whether there was a justification to do clinical testing of the effect of Dexamethasone on the mortality rate of patients receiving oxygen treatment. Treatment of patients with drugs unnecessarily constitutes violation of scientific ethics. A detailed comparison of two similar studies would show that in the study of Horby et al. [1], there may have been as many as 11 (12.5% of 89) unnecessary deaths due to Dexamethasone treatment.

The results of Horby et al. [1] showing that the mortality rate of patients receiving invasive mechanical ventilation in the absence of Dexamethasone treatment was 40% compared to 29% for patients who received Dexamethasone are difficult to reconcile with those of Richardson et al. [11] and Auld et al. [16] which showed that the mortality rate of patients on invasive mechanical ventilation in the absence of Dexamethasone treatment were 25.5% (282 out of 1151) [11], and 35.7 % (59 out of 165) [16] respectively (Figure 3).

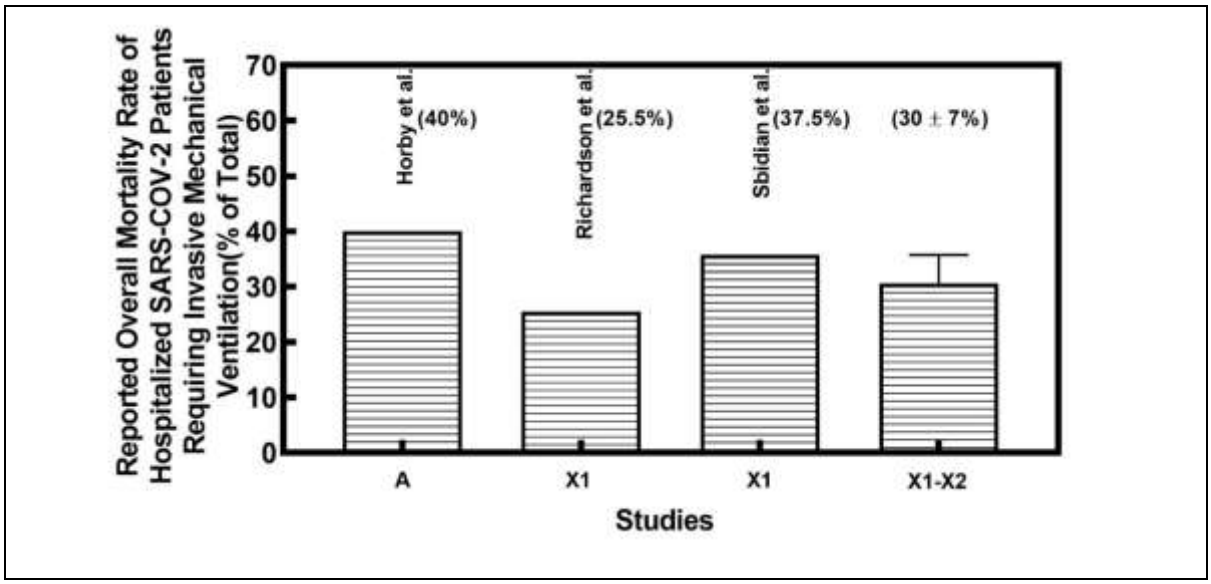

Figure 3: Comparison of Reported Overall Mortality Rate of Hospitalized SARS-COV-2 infected patients under invasive mechanical ventilation treatment. Studies are from Horby et al. [1](A), Richardson et al. [11] (X1), and Auld et al. [16] (X1).

The study of Richardson et al. [11] concerned patients who were admitted to ICU from March 1, 2020 to April 4, 2020 while the study of Auld et al [16] concerned patients who were admitted to ICU between March 6, 2020 and April 17, 2020. The 2 studies are comparable to the study of Horby et al. [1] which involved patients who were hospitalized between March 19, 2020 and June 8, 2020. The only difference is that the studies of Richardson et al. [1] and Auld et al [16] were conducted in the United States. It is reasonable to assume that the level of health care provision and competence of health care providers in the United States and United Kingdom are relative similar.

A number of questions that need to be answered with respect to the paper by Horby et al. [1] include: (i) What constitutes usual care. Did usual care consist of treatment with Hydroxychloroquine and Hydroxychlorine plus Azithromycin. It is hard to believe that patients who received invasive mechanical ventilation would be treated similarly as patients who did not receive oxygen or oxygen only treatment. (ii) Can Horby et al [1] explain why in a study in France by Mahevas et al. [4], it was reported that the mortality rate of patients requiring oxygen was 9% (8 out of 89) in the absence of treatment with corticosteroids. Significantly, at day 21, 80% of the patients were discharged to home or rehabilitation and

the overall survival rate was 91% without treatment with corticosteroids. Does this not mean that if the patients in Mahevas et al. [4] were treated with Dexamethasone as insistently advocated by Horby et al [1], there would have been 11 unnecessary deaths (12.5% of 89). Does this not also mean that that patients who receive oxygen treatment in Horby et al. [1] did not need to be treated with Dexamethasone and that treating patients with Dexamethasone who did not require it is a violation of scientific ethics. In France, corticosteroids are contra-indicated for COVID-19 and the patients in the study by Mahevas et al. [4] were not treated with Dexamethasone or other corticosteroids. (iii) Can Horby et al. [1] explain why studies in several countries, including France, China, United States and United Kingdom [3-11,13,15] reported that the mortality rate of hospitalized patients ranged from a low of 6% to a high of 21.9% and in view of the fact that Horby et al. [1] have forcefully advocated treating SARS-COV-2 infected patients requiring oxygen or invasive mechanical ventilation with Dexamethasone throughout the entire world in their paper (praised by the Director General of the World Health Organization!) at their triumphal and presumptuous press conference, why they did not referenced these papers that contradicted their results. (iv) Can Horby et al [1] explain why in a study by Beigel et al. [17], it was reported that the mortality rates at day 14 were 2.1% for patients who were not on oxygen treatment, 14.8% for patients who were on oxygen treatment, and 12.9% for patients who were on invasive mechanical ventilation. (v) Can Horby et al. [1] explain why their results showing that the mortality rate of patients receiving invasive mechanical ventilation in the absence of Dexamethasone treatment was 40% compared to 29% for patients who received Dexamethasone are different from the results of Richardson et al. [11] and Auld et al. [16] which showed that the mortality rate of patients on invasive mechanical ventilation in the absence of Dexamethasone treatment were 25.5% (282 out of 1151) and 35.7 % (59 out of 165) respectively.

Until the above questions are addressed by Horby et al. [1], the forceful advocation of Dexamethasone for the treatment of hospitalized patients infected with SARS-COV-2 and undergoing oxygen or invasive mechanical ventilation is unwarranted, can be dangerous and can cause unnecessary deaths. A comment by Russel et al. [18] in Lancet stated that "Overall, no unique reason exists to expect that patients with 2019-nCoV infection will benefit from

corticosteroids, and they might be more likely to be harmed with such treatment. We conclude that corticosteroid treatment should not be used for the treatment of 2019-nCoV-induced lung injury or shock outside of a clinical trial".

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