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COVID-19 ARTICLE

The COVID-19 pandemic and a reflection on the conduct of clinical trials in times of war

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1. Commentary

Since the start of the pandemic, we are interested in the analogies to refer to the coronavirus disease 2019 (COVID-19) pandemic. The most common that we have found in news or journal articles is the ''war'' analogy.

We do not fully agree with this analogy. The SARS-CoV-2 did not declare war on anybody, and it will certainly not ''surrender'' anytime soon. Indeed, the only battles we are fighting are against our model of society and the way we provide health care at a population level. Other authors have already raised the discussion on why war analogies are probably not appropriate to be used in the pandemic context [1].

However, we understand where this analogy comes from. We are living unprecedented times that require unpreceded actions, but this does not mean we need to start taking rushed decisions, especially when we are deciding to give interventions to almost the entire population of a country.

Because of the ''war'' analogy, some people have argued that we may loosen the scientific procedures and rely on ''evidence of lower quality,'' as there is ''no time to lose.'' Well, again, it is hard to agree with this line of argument. If we are indeed in an unprecedented period, we should rely even more on sound scientific evidence.

Most of the precipitated recommendations made at the beginning of the pandemic and that are still being made happened because people relied on low-quality observational evidence under the argument that ''we do not have time to conduct randomized controlled trials.''

Even if we are at war against the severe acute respiratory syndrome coronavirus 2, it would still be better to rely on randomized controlled trials to confidently decide which interventions are effective and safe and which ones we should recommend as a routine measure.

Another concern is that some country's pandemic responses are being led by the military, in part based on the argument that this pandemic is somehow similar to a war period [2]. This may be additionally problematic if the technical perspective is put aside to base the strategic planning of a national response based on the ''war'' analogy.

2. What is it like to conduct a controlled trial during a war?

The sustained use of the war analogy reminds us of one piece of experience professor Archibald Cochrane shared with us in his article ''Sickness in Salonica: my first, worst, and most successful clinical trial'' [3].

In this small piece, Cochrane presents us his memories as a war prisoner in Salonica, Greece, in 1941. He tells us how he was led to being the medical in charge of 8,000 hungry prisoners, who were affected by several conditions, including diphtheria and typhoid fever.

The focus of the article is around the increasing incidence of ''ankle edema'' he observed after some period of imprisonment. As expected, the situation in the camp was very precarious. Cochrane mentions some occasions where the guards deliberately shot his staff and how devastating was the results of a grenade that was thrown in ''a crowded latrine.'' He even mentions a bullet that passed through his hair during clinical rounds after one unjustified shooting.

As the situation of the patients with edema was getting worse, Cochrane started to argue with the guards that action

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was required to treat the patients, but little was done as they attributed the edema to the lack of sunlight. Desperate, he designs an experiment to test his hypothesis that patients were suffering from vitamin deficiency.

The trial he describes next is straightforward. He acquired yeast from the prison's black market and divided 20 numbered patients into two equal-sized groups: the odd group received only two spoons full of yeast and the even group received a tablet of vitamin C he had from his reserve. After several measurements, Cochrane convinced himself that the patients from the yeast group were significantly better.

At that time, he seemed satisfied with the trial conduction, despite mentioning some challenges, such as having his staff "under frequent threat of being shot" or that he had to measure frequency urination, as he did not have "buckets" to measure volume.

Armed with the results from his experimentation, Cochrane tells us that he arranged a meeting with the officials, where he mentioned James Lind [4] and presented his hypothesis that patients were suffering from vitamin deficiency and that the administration of yeast was sufficient to reduce the occurrence of edema. In the article, there is still a graphical reproduction of the outcome annotation from the period [3].

After the meeting, for Cochrane's surprise, he was supplied yeast to treat the prisoners. At the end of the article, Cochrane makes a reflection that the trial was not that good, as he was testing the wrong hypothesis and that patients probably recovered from the small amount of proteins the yeast provided. In the last sentence, however, he states that "it was amazing what a little bit of science and a little bit of luck achieved."

3. What can we learn from Cochrane's trial?

Much can be learned from this brief report that Cochrane presents us about the trial he conducted at the prison camp during the war. Perhaps one of the most important is that even in the most horrifying and degrading situation, Cochrane was able to design and conduct a clinical trial using only his knowledge and ability.

Indeed, it is not reasonable to compare the scenario Cochrane lived from what we are now living during the COVID-19 pandemic almost 80 years after. Nonetheless, there is no arguing that the structure, conditions, financial, and any other aspect to conduct a clinical trial have significantly improved.

By no means, we are saying that it is easy to conduct clinical trials enrolling COVID-19 patients. However, after reading Cochrane's report, any justifications to not conduct them using the "war analogy" seems to us very vague, if not inappropriate.

With a simple experiment enrolling 20 patients, Cochrane retrieved enough evidence to convince the guards to make available an intervention that ultimately led to the general improvement of clinical conditions of the prisoners. Even if the experiment was testing the wrong hypothesis, this scientific piece was able to convince the guards that it was not the lack of sunlight that was causing the edema and that the yeast administration was associated with clinical improvement.

If we were "randomizing since the first patient" of the pandemic instead of using weak analogies [5], we would probably have substantial more reliable information about the effectiveness and safety of treatments proposed to treat COVID-19 patients. More importantly, we would be making decisions based on significantly less uncertainty.

The COVID-19 pandemic showed us some examples of astonishing success, such as the Recovery Trial that, to this date, managed to recruit more than 16,000 patients to address uncertainties in suggested COVID-19 treatments [6]. The Recovery Trial is an example from this pandemic that large randomized trials are feasible and that decision-making should consider more rigorously appraised evidence.

4. Conclusions

We do not agree with the use of "war" analogy to refer to the unprecedented challenges we are facing because of the COVID-19 pandemic, but in any case, the better way to act is based on the most robust level of evidence. When assessing the effects of interventions, we must rely on the results of clinical trials, as Cochrane did.

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