Controversy over ivermectin and COVID-19: Six blind men and an elephant

Gilbert Berdine MD

*T*here has been great disagreement among experts about everything related to COVID-19, including its origin, public health policy, and treatment of individual cases. Disagreement about the use of ivermectin is particularly intense. During a podcast with Joe Rogan, Dr. Robert Malone claimed that half-a-million excess deaths were caused by governments that suppressed the early treatment of COVID-19 with drugs including ivermectin and hydroxychloroquine.[1] The *Journal of the American Medical Association* (JAMA) recently suggested that anyone promoting ivermectin for the treatment of COVID-19 should be disciplined by state medical boards.[2] How can people who are educated and who have access to the same information reach such different conclusions about ivermectin and COVID-19?

THE PARABLE

The parable of the six blind men and the elephant is about tunnel vision, sampling bias, and the inability of a single person to know everything about a complex problem. In the parable, each blind man uses touch to carefully examine part of an elephant. Each blind man reaches a correct conclusion about what was observed. None of the blind men are guilty of fraud, dishonesty, or misinformation. However, none of the blind men reaches a correct conclusion about the totality of the elephant.

The parable of the six blind men and the elephant is applicable to uncertainty in medicine at many levels. At the broadest level, there can be too much information for one person to analyze. As discussed in a previous issue of *The Southwest Respiratory and Critical*

Corresponding author: **Gilbert Berdine**
Contact Information: Gilbert.Berdine@ttuhsc.edu
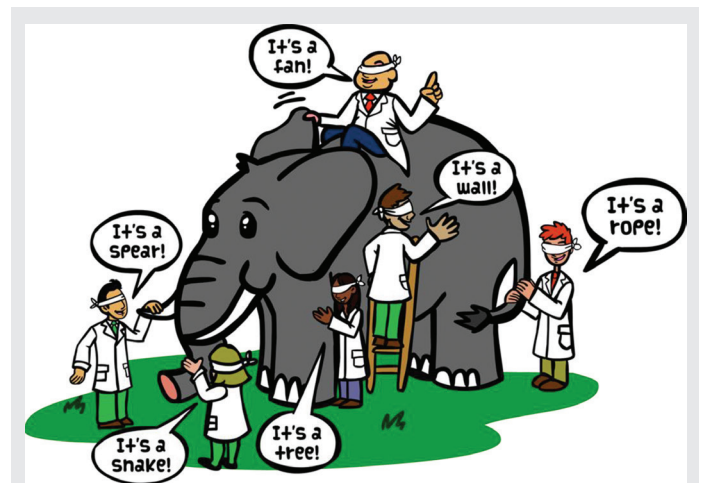***DOI:*** 10.12746/swrccc.v10i43.1027

Figure 1. The six blind men and the elephant.[3]

Care Chronicles, COVID-19 led to mass publication of ideas that sacrificed issues of quality in favor of brainstorming a critical public health crisis.[4] Large volumes of information create a demand for "experts" who distill the large volumes into summary statements or recommendations. There are important differences between "experts" whose recommendations are mere suggestions and government "experts" whose recommendations are mandates backed by the coercive power of the state. These differences will be discussed in greater detail below.

ALL STUDIES HAVE FLAWS

All studies do not have equal merit. Larger studies have greater statistical power compared to smaller studies. Blinded studies avoid biases introduced by either the subjects or the observers. Controlled studies avoid biases due to effects of extraneous variables. Choice of endpoints determine the ease of detecting significant differences due to interventions. Unfortunately, the merit or quality of a study cannot

be objectively assigned a score as it is impossible to compare differences of different types. At a fundamental level, human studies are never as reproducible as a physics experiment due to the variability among individual human beings. Medical studies necessarily introduce elements of tunnel vision and sampling bias seen in the parable of the six blind men and the elephant.

The National Library of Medicine includes reviews about efficacy of ivermectin for the treatment of COVID-19. One review supports the use of ivermectin.[5] Another review claims no benefit of ivermectin.[6] How do we determine which review reaches the correct conclusion? Perhaps, like the six blind men in the parable, the two reviews are observing fundamentally different aspects (tusk vs. leg) of a broader totality (elephant). Perhaps the devil is in the details of the studies. Perhaps there is no objectively correct answer as to which review conclusion is correct.

Even randomized controlled trials–the gold standard of clinical research trials–have limitations that prevent objectively correct conclusions. No two groups of people can possibly be equal due to the inherent variability among humans. Statistical methods are needed to determine the likelihood that differences in outcomes are due to interventions rather than random chance. Statistical methods are always subject to type I and type II errors. A type I error is a false positive conclusion by rejection of a true null hypothesis. Opponents of an intervention can claim that a study demonstrating a significant benefit of an intervention was a type I error. A type II error is a false negative conclusion due to random luck rather than a true null hypothesis. Advocates of an intervention can claim that a study showing no benefit of an intervention was a type II error.

Choice of end point is a major difference in study design and has a big impact on the ability to detect efficacy or benefit. Choice of subjects is another aspect of study design that determines the ability to detect efficacy or benefit. There is also an effect on the magnitude of costs or side effects. A study on ICU patients requiring mechanical ventilation will require fewer subjects to detect deaths, but disease progression might be too great for intervention to change outcome. A study on patients with positive PCR tests for the COVID virus will require more subjects to detect deaths, but intervention is more likely to have a favorable impact on an outcome, and a large percentage of subjects are expected to survive without any intervention.

SAMPLING BIAS

In the parable of the six blind men and the elephant, there was sampling bias due to non-homogeneous features of the elephant. The front of the elephant has much different characteristics than the rear of the elephant. Human beings are not fungible commodities. For COVID-19, age is a major risk factor for poor outcome. Furthermore, the risk of age is not linear, so it is not sufficient that the mean age of the treatment group be equal to the mean age of the control group, but the distribution of age in the two groups can also affect outcome. Usual tests to ensure that the treatment group is comparable to the control group may not be adequate for the age variable in a study on COVID-19 due to the marked non-linearity of effect of age on outcome. If the distribution of age in a treatment group does not properly match the distribution of age in the control group, one could see either a false positive conclusion or a false negative conclusion.

Randomized control trials can be controlled only for variables that we know are important. It is not possible for the two groups of subjects to be precisely matched for all variables. We try to match the two groups of subjects for those variables known to be important to outcome. Even with the best of scientific intentions, it is not possible to control for variables not known to be important. It is possible for either a false positive conclusion or a false negative conclusion due to things we do not know. It is hubris to think we know everything that is important for something as complicated as COVID-19. We become one of the six blind men in the elephant parable. Humility requires us to consider that conclusions from the best randomized control trials might be wrong. Humility requires each of the six blind men to consider the opinions of the other blind men.

CONFIRMATION BIAS

All lies and jest
Still, a man hears what he wants to hear
And disregards the rest
The Boxer by Simon and Garfunkel

How do we resolve the conflicting information about ivermectin and COVID-19? It is easy to be a dispassionate observer before we reach any conclusion. As one reviews data, however, once one hypothesis seems more likely correct, subsequent observation becomes subject to confirmation bias. We all have limited time. Nobody has enough time to dispassionately weigh every study. If an observer finds evidence for fraud or plagiarism, the observer will likely dismiss the study and move on to the next one. Confirmation bias determines how much time and effort an observer will devote to an honest study. If the study conclusion agrees with the observer bias, there is little incentive to look for flaws. If the study conclusion disagrees with the observer bias, there is incentive to more carefully analyze methodology looking for flaws such as sampling bias. Both tendencies increase observer satisfaction that his or her bias is objectively correct. Prior to reaching a preliminary conclusion, it might take a feather weight of evidence to persuade an observer one way or another. Once a preliminary conclusion has been reached, however, it takes a sledgehammer of evidence to persuade an observer to switch sides. The more evidence has been analyzed, a larger and heavier sledgehammer is required to change observer conclusion. If the blind man observing the tail thinks his conclusion about the rope is correct, the blind man will dismiss alternative observations as incorrect over any flaw found in the observations of the other five blind men. As the confirmation bias of a single blind man becomes more deeply ingrained, smaller and smaller flaws become sufficient to dismiss the observations of the other five blind men.

TREATMENT OF DISSENT

As noted above, there are studies supporting the use of ivermectin in COVID-19 and other studies concluding that ivermectin has no benefit. During the preceding discussion, I have described how individuals decide which opinion to accept as correct. How does society make this decision? One method is to have one opinion declared as Truth and regard dissenting opinions as dangerous that need to be suppressed or purged. *The Journal of the American Medical Association* (JAMA) recently applied this method and suggested that anyone who promoted the use of ivermectin for the treatment of COVID-19 should be disciplined by the state medical board.[2] The elevation of an opinion to a Truth that cannot permit or tolerate any dissent has the character of a religious cult rather than a scientific organization. Frequently, this approach employs a logical fallacy known as Appeal to Authority.[7] An opinion is asserted to represent unassailable Truth based on the authority of the person or persons articulating the opinion. This elevates the authority as a divine source of infallible Truth. Dissent is treated as evil that should be suppressed and punished as either apostasy or heresy. The JAMA commentary suggested that any disagreement with CDC guidelines should be disciplined by the state medical board.[2] There can be serious problems for society even if the official Truth is, in fact, correct. By directing attention to dissenting opinions, the publicity may actually spread the dissent rather than suppress it. This is known as the Streisand Effect.[8] It is named after the entertainer Barbara Streisand who attempted to suppress a photograph but, instead, increased views of the photograph. Obviously, the greater danger to society is when the official Truth is, in fact, incorrect, which can lead to incorrect conclusions that are derived from the axiomatic assumption of the incorrect view. A famous example is the treatment of Galileo and Copernicus by the Catholic Church. This approach is characterized by hubris.

The other approach is to let dissenting opinions compete for acceptance. This is the basis of trial by jury. The goal of the opposing attorneys is not to discover Truth. Nor is the goal of the opposing attorneys to compel a jury to accept one side as Truth. Rather the goal of the opposing attorneys is to convince the jury that their argument is more credible and has greater merit. This approach is part of the Scientific Method. The merit of a scientific hypothesis is based on the ability to make successful predictions of future observations and the ability to defend itself against dissent. Successful defense against dissent is based on the merits of the hypothesis rather than the reputations of those who articulate the hypothesis. With

respect to the parable of the six blind men and the elephant, this approach listens to the reports of all six blind men and permits hypotheses to consider that all six blind men are reporting part of the total picture. In terms of the debate about ivermectin, it is possible that ivermectin offers benefit when used early, but has no benefit for advanced disease. It is possible that ivermectin may offer greater or lesser benefit to young people rather than old people. The hypothesis that ivermectin is effective for treating COVID-19 and the hypothesis that ivermectin is not effective for treating COVID-19 may both be correct for certain subgroups of people. By allowing the free discussion of competing ideas, hypotheses can be refined in order to become a self-correcting search for truth. This approach is characterized by humility.

HUMILITY AND THE USE OF IVERMECTIN TO TREAT COVID-19

We recognize that we do not fully understand the utility of ivermectin for COVID-19. There are studies reaching different conclusions. All of the studies have flaws. None of the studies represent absolute proof. We cannot be certain about the best recommendation for a given situation. The best we can do is fairly explain the uncertainty about outcome to our patients and let patients make informed decisions. Experts can provide recommendations, but patients remain free to accept or decline the recommendations. No provider should be forced to recommend ivermectin in any given case of COVID-19. No provider should be prevented from recommending ivermectin in any given case of COVID-19. Patients should be free to seek providers who recommend ivermectin for the treatment of COVID-19. Patients should be free to avoid providers who recommend ivermectin for the treatment of COVID-19. By maximizing individual choice, we will gain more experience about what works and what does not work. As we gain experience, decision making will evolve. Like the non-homogeneity of the appearance of the elephant in our parable, the best choice in a given situation will depend on the individual circumstances. The humility of free choice recognizes that we cannot possibly be correct all the time, but that errors will self-correct over time. The hubris of

mandates guarantees that systematic errors will persist without hope for correction.

REFERENCES

1. The Joe Rogan Experience. Episode #1757 – Dr. Robert Malone, MD. https://open.spotify.com/episode/3SCsueX2b-ZdbEzRtKOCEyT. Accessed 3/26/2022.
2. Rubin R. When physicians spread unscientific information about COVID-19. JAMA 2022;327(10):904–906.
3. Blind men and an elephant parable. FavPNG. https://favpng.com/png_view/directional-church-board-members-blind-men-and-an-elephant-parable-point-of-view-fable-png/ybPVwsfs. Accessed 3/26/2022.
4. Anderson C, Peterson C, Dennis J. Mass publication during the COVID-19 pandemic: too much of a good thing? The Southwest Respiratory and Critical Care Chronicles 2022;10(42):22–24.
5. Hariyanto TI, Halim DA, Rosalind J, et al. Ivermectin and outcomes from Covid 19 pneumonia: A systematic review and meta analysis of randomized clinical trial studies. Rev Med Virol 2021;e2265.
6. Roman YM, Burela PA, Pasupuleti V, et al. Ivermectin for the treatment of coronavirus disease 2019: A systematic review and meta-analysis of randomized controlled trials. Clin Infect Dis 2022;74(6):1022–1029.
7. Cline A. Fallacies of relevance: Appeal to authority. ThoughtCo. https://www.thoughtco.com/logical-fallacies-appeal-to-authority-250336. Accessed 3/26/2022.
8. Wikipedia contributors. Streisand effect. Wikipedia. https://en.wikipedia.org/w/index.php?title=Streisand_effect&oldid=1079400054. Accessed 3/26/2022.