J Korean Med Sci. 2021 Dec 27;36(50):e338
https://doi.org/10.3346/jkms.2021.36.e338
eISSN 1598-6357·pISSN 1011-8934

JKMS

Review Article
Editing, Writing & Publishing

Check for updates

Formulating Hypotheses for Different Study Designs

Durga Prasanna Misra [1] **Armen Yuri Gasparyan** [2] **Olena Zimba** [3] **Marlen Yessirkepov** [4] **Vikas Agarwal** [1] **and George D. Kitas** [2,5]

[1]Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India
[2]Departments of Rheumatology and Research and Development, Dudley Group NHS Foundation Trust (Teaching Trust of the University of Birmingham, UK), Russells Hall Hospital, Dudley, UK
[3]Department of Internal Medicine #2, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine
[4]Department of Biology and Biochemistry, South Kazakhstan Medical Academy, Shymkent, Kazakhstan
[5]Centre for Epidemiology versus Arthritis, University of Manchester, Manchester, UK

Received: Oct 21, 2021
Accepted: Nov 11, 2021

Address for Correspondence:
Armen Yuri Gasparyan, MD, PhD
Departments of Rheumatology and Research and Development, Dudley Group NHS Foundation Trust (Teaching Trust of the University of Birmingham, UK), Russells Hall Hospital, Pensnett Road, Dudley DY1 2HQ, UK.
E-mail: a.gasparyan@gmail.com

ORCID iDs
Durga Prasanna Misra
https://orcid.org/0000-0002-5035-7396
Armen Yuri Gasparyan
https://orcid.org/0000-0001-8749-6018
Olena Zimba
https://orcid.org/0000-0002-4188-8486
Marlen Yessirkepov
https://orcid.org/0000-0003-2511-6918
Vikas Agarwal
https://orcid.org/0000-0002-4508-1233
George D. Kitas
https://orcid.org/0000-0002-0828-6176

Disclosure
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Generating a testable working hypothesis is the first step towards conducting original research. Such research may prove or disprove the proposed hypothesis. Case reports, case series, online surveys and other observational studies, clinical trials, and narrative reviews help to generate hypotheses. Observational and interventional studies help to test hypotheses. A good hypothesis is usually based on previous evidence-based reports. Hypotheses without evidence-based justification and a priori ideas are not received favourably by the scientific community. Original research to test a hypothesis should be carefully planned to ensure appropriate methodology and adequate statistical power. While hypotheses can challenge conventional thinking and may be controversial, they should not be destructive. A hypothesis should be tested by ethically sound experiments with meaningful ethical and clinical implications. The coronavirus disease 2019 pandemic has brought into sharp focus numerous hypotheses, some of which were proven (e.g. effectiveness of corticosteroids in those with hypoxia) while others were disproven (e.g. ineffectiveness of hydroxychloroquine and ivermectin).

Keywords: Hypotheses; Research Ethics; Study Design; Pandemic

DEFINING WORKING AND STANDALONE SCIENTIFIC HYPOTHESES

Science is the systematized description of natural truths and facts. Routine observations of existing life phenomena lead to the creative thinking and generation of ideas about mechanisms of such phenomena and related human interventions. Such ideas presented in a structured format can be viewed as hypotheses. After generating a hypothesis, it is necessary to test it to prove its validity. Thus, hypothesis can be defined as a proposed mechanism of a naturally occurring event or a proposed outcome of an intervention.[1,2]

Hypothesis testing requires choosing the most appropriate methodology and adequately powering statistically the study to be able to "prove" or "disprove" it within predetermined and widely accepted levels of certainty. This entails sample size calculation that often takes into account previously published observations and pilot studies.[2,3] In the era of digitization,

Author Contributions
Data curation: Gasparyan AY, Misra DP, Zimba O, Yessirkepov M, Agarwal V, Kitas GD.

hypothesis generation and testing may benefit from the availability of numerous platforms for data dissemination, social networking, and expert validation. Related expert evaluations may reveal strengths and limitations of proposed ideas at early stages of post-publication promotion, preventing the implementation of unsupported controversial points.[4]

Thus, hypothesis generation is an important initial step in the research workflow, reflecting accumulating evidence and experts' stance. In this article, we overview the genesis and importance of scientific hypotheses and their relevance in the era of the coronavirus disease 2019 (COVID-19) pandemic.

DO WE NEED HYPOTHESES FOR ALL STUDY DESIGNS?

Broadly, research can be categorized as primary or secondary. In the context of medicine, primary research may include real-life observations of disease presentations and outcomes. Single case descriptions, which often lead to new ideas and hypotheses, serve as important starting points or justifications for case series and cohort studies. The importance of case descriptions is particularly evident in the context of the COVID-19 pandemic when unique, educational case reports have heralded a new era in clinical medicine.[5]

Case series serve similar purpose to single case reports, but are based on a slightly larger quantum of information. Observational studies, including online surveys, describe the existing phenomena at a larger scale, often involving various control groups. Observational studies include variable-scale epidemiological investigations at different time points. Interventional studies detail the results of therapeutic interventions.

Secondary research is based on already published literature and does not directly involve human or animal subjects. Review articles are generated by secondary research. These could be systematic reviews which follow methods akin to primary research but with the unit of study being published papers rather than humans or animals. Systematic reviews have a rigid structure with a mandatory search strategy encompassing multiple databases, systematic screening of search results against pre-defined inclusion and exclusion criteria, critical appraisal of study quality and an optional component of collating results across studies quantitatively to derive summary estimates (meta-analysis).[6] Narrative reviews, on the other hand, have a more flexible structure. Systematic literature searches to minimise bias in selection of articles are highly recommended but not mandatory.[7] Narrative reviews are influenced by the authors' viewpoint who may preferentially analyse selected sets of articles.[8]

In relation to primary research, case studies and case series are generally not driven by a working hypothesis. Rather, they serve as a basis to generate a hypothesis. Observational or interventional studies should have a hypothesis for choosing research design and sample size. The results of observational and interventional studies further lead to the generation of new hypotheses, testing of which forms the basis of future studies. Review articles, on the other hand, may not be hypothesis-driven, but form fertile ground to generate future hypotheses for evaluation. **Fig. 1** summarizes which type of studies are hypothesis-driven and which lead on to hypothesis generation.

https://doi.org/10.3346/jkms.2021.36.e338

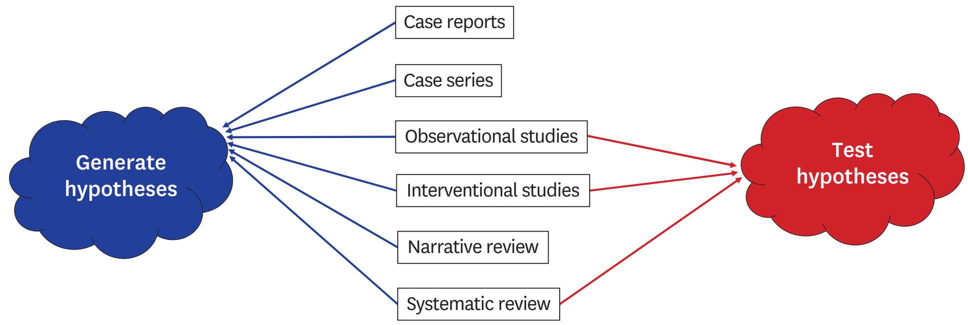

Fig. 1. Types of studies that help to generate and test hypotheses.

STANDARDS OF WORKING AND SCIENTIFIC HYPOTHESES

A review of the published literature did not enable the identification of clearly defined standards for working and scientific hypotheses. It is essential to distinguish influential versus not influential hypotheses, evidence-based hypotheses versus a priori statements and ideas, ethical versus unethical, or potentially harmful ideas. The following points are proposed for consideration while generating working and scientific hypotheses.[1,2] **Table 1** summarizes these points.

Evidence-based data

A scientific hypothesis should have a sound basis on previously published literature as well as the scientist's observations. Randomly generated (a priori) hypotheses are unlikely to be proven. A thorough literature search should form the basis of a hypothesis based on published evidence.[7]

Testable

Unless a scientific hypothesis can be tested, it can neither be proven nor be disproven. Therefore, a scientific hypothesis should be amenable to testing with the available technologies and the present understanding of science.

Supported by pilot studies

If a hypothesis is based purely on a novel observation by the scientist in question, it should be grounded on some preliminary studies to support it. For example, if a drug that targets a specific cell population is hypothesized to be useful in a particular disease setting, then there must be some preliminary evidence that the specific cell population plays a role in driving that disease process.

Testable by ethical studies

The hypothesis should be testable by experiments that are ethically acceptable.[9] For example, a hypothesis that parachutes reduce mortality from falls from an airplane cannot be tested

Table 1. Points on valid hypotheses

Points to be considered while evaluating the validity of hypotheses
Backed by evidence-based data
Testable by relevant study designs
Supported by preliminary (pilot) studies
Testable by ethical studies
Maintaining a balance between scientific temper and controversy

https://doi.org/10.3346/jkms.2021.36.e338

using a randomized controlled trial.[10] This is because it is obvious that all those jumping from a flying plane without a parachute would likely die. Similarly, the hypothesis that smoking tobacco causes lung cancer cannot be tested by a clinical trial that makes people take up smoking (since there is considerable evidence for the health hazards associated with smoking). Instead, long-term observational studies comparing outcomes in those who smoke and those who do not, as was performed in the landmark epidemiological case control study by Doll and Hill,[11] are more ethical and practical.

Balance between scientific temper and controversy

Novel findings, including novel hypotheses, particularly those that challenge established norms, are bound to face resistance for their wider acceptance. Such resistance is inevitable until the time such findings are proven with appropriate scientific rigor. However, hypotheses that generate controversy are generally unwelcome. For example, at the time the pandemic of human immunodeficiency virus (HIV) and AIDS was taking foot, there were numerous deniers that refused to believe that HIV caused AIDS.[12,13] Similarly, at a time when climate change is causing catastrophic changes to weather patterns worldwide, denial that climate change is occurring and consequent attempts to block climate change are certainly unwelcome.[14] The denialism and misinformation during the COVID-19 pandemic, including unfortunate examples of vaccine hesitancy, are more recent examples of controversial hypotheses not backed by science.[15,16] An example of a controversial hypothesis that was a revolutionary scientific breakthrough was the hypothesis put forth by Warren and Marshall that *Helicobacter pylori* causes peptic ulcers. Initially, the hypothesis that a microorganism could cause gastritis and gastric ulcers faced immense resistance. When the scientists that proposed the hypothesis themselves ingested *H. pylori* to induce gastritis in themselves, only then could they convince the wider world about their hypothesis. Such was the impact of the hypothesis was that Barry Marshall and Robin Warren were awarded the Nobel Prize in Physiology or Medicine in 2005 for this discovery.[17,18]

DISTINGUISHING THE MOST INFLUENTIAL HYPOTHESES

Influential hypotheses are those that have stood the test of time. An archetype of an influential hypothesis is that proposed by Edward Jenner in the eighteenth century that cowpox infection protects against smallpox. While this observation had been reported for nearly a century before this time, it had not been suitably tested and publicised until Jenner conducted his experiments on a young boy by demonstrating protection against smallpox after inoculation with cowpox.[19] These experiments were the basis for widespread smallpox immunization strategies worldwide in the 20th century which resulted in the elimination of smallpox as a human disease today.[20]

Other influential hypotheses are those which have been read and cited widely. An example of this is the hygiene hypothesis proposing an inverse relationship between infections in early life and allergies or autoimmunity in adulthood. An analysis reported that this hypothesis had been cited more than 3,000 times on Scopus.[1]

LESSONS LEARNED FROM HYPOTHESES AMIDST THE COVID-19 PANDEMIC

The COVID-19 pandemic devastated the world like no other in recent memory. During this period, various hypotheses emerged, understandably so considering the public health emergency situation with innumerable deaths and suffering for humanity. Within weeks of the first reports of COVID-19, aberrant immune system activation was identified as a key driver of organ dysfunction and mortality in this disease.[21] Consequently, numerous drugs that suppress the immune system or abrogate the activation of the immune system were hypothesized to have a role in COVID-19.[22] One of the earliest drugs hypothesized to have a benefit was hydroxychloroquine. Hydroxychloroquine was proposed to interfere with Toll-like receptor activation and consequently ameliorate the aberrant immune system activation leading to pathology in COVID-19.[22] The drug was also hypothesized to have a prophylactic role in preventing infection or disease severity in COVID-19. It was also touted as a wonder drug for the disease by many prominent international figures. However, later studies which were well-designed randomized controlled trials failed to demonstrate any benefit of hydroxychloroquine in COVID-19.[23-26] Subsequently, azithromycin[27,28] and ivermectin[29] were hypothesized as potential therapies for COVID-19, but were not supported by evidence from randomized controlled trials. The role of vitamin D in preventing disease severity was also proposed, but has not been proven definitively until now.[30,31] On the other hand, randomized controlled trials identified the evidence supporting dexamethasone[32] and interleukin-6 pathway blockade with tocilizumab as effective therapies for COVID-19 in specific situations such as at the onset of hypoxia.[33,34] Clues towards the apparent effectiveness of various drugs against severe acute respiratory syndrome coronavirus 2 in vitro but their ineffectiveness in vivo have recently been identified. Many of these drugs are weak, lipophilic bases and some others induce phospholipidosis which results in apparent in vitro effectiveness due to non-specific off-target effects that are not replicated inside living systems.[35,36]

Another hypothesis proposed was the association of the routine policy of vaccination with Bacillus Calmette-Guerin (BCG) with lower deaths due to COVID-19. This hypothesis emerged in the middle of 2020 when COVID-19 was still taking foot in many parts of the world.[37,38] Subsequently, many countries which had lower deaths at that time point went on to have higher numbers of mortality, comparable to other areas of the world. Furthermore, the hypothesis that BCG vaccination reduced COVID-19 mortality was a classic example of ecological fallacy. Associations between population level events (ecological studies; in this case, BCG vaccination and COVID-19 mortality) cannot be directly extrapolated to the individual level. Furthermore, such associations cannot per se be attributed as causal in nature, and can only serve to generate hypotheses that need to be tested at the individual level.[39]

IS TRADITIONAL PEER REVIEW EFFICIENT FOR EVALUATION OF WORKING AND SCIENTIFIC HYPOTHESES?

Traditionally, publication after peer review has been considered the gold standard before any new idea finds acceptability amongst the scientific community. Getting a work (including a working or scientific hypothesis) reviewed by experts in the field before experiments are conducted to prove or disprove it helps to refine the idea further as well as improve the experiments planned to test the hypothesis.[40] A route towards this has been the emergence of journals dedicated to publishing hypotheses such as the *Central Asian Journal of Medical Hypotheses and Ethics*.[41] Another means of publishing hypotheses is through registered research protocols detailing the background, hypothesis, and methodology of a particular study. If such protocols are published after peer review, then the journal commits to publishing the completed study irrespective of whether the study hypothesis is proven or disproven.[42] In the post-pandemic world, online research methods such as online surveys powered via social media channels such as Twitter and Instagram might serve as critical tools to generate as well as to preliminarily test the appropriateness of hypotheses for further evaluation.[43,44]

Some radical hypotheses might be difficult to publish after traditional peer review. These hypotheses might only be acceptable by the scientific community after they are tested in research studies. Preprints might be a way to disseminate such controversial and ground-breaking hypotheses.[45] However, scientists might prefer to keep their hypotheses confidential for the fear of plagiarism of ideas, avoiding online posting and publishing until they have tested the hypotheses.

SUGGESTIONS ON GENERATING AND PUBLISHING HYPOTHESES

Publication of hypotheses is important, however, a balance is required between scientific temper and controversy. Journal editors and reviewers might keep in mind these specific points, summarized in **Table 2** and detailed hereafter, while judging the merit of hypotheses for publication. Keeping in mind the ethical principle of primum non nocere, a hypothesis should be published only if it is testable in a manner that is ethically appropriate.[46] Such hypotheses should be grounded in reality and lend themselves to further testing to either prove or disprove them. It must be considered that subsequent experiments to prove or disprove a hypothesis have an equal chance of failing or succeeding, akin to tossing a coin. A pre-conceived belief that a hypothesis is unlikely to be proven correct should not form the basis of rejection of such a hypothesis for publication. In this context, hypotheses generated after a thorough literature search to identify knowledge gaps or based on concrete clinical observations on a considerable number of patients (as opposed to random observations on a few patients) are more likely to be acceptable for publication by peer-reviewed journals. Also, hypotheses should be considered for publication or rejection based on their implications for science at large rather than whether the subsequent experiments to test them end up with results in favour of or against the original hypothesis.

Table 2. Considerations for evaluating hypotheses for publication

Points to be considered before a hypothesis is acceptable for publication
Experiments required to test hypotheses should be ethically acceptable as per the World Medical Association declaration on ethics and related statements
Pilot studies support hypotheses
Single clinical observations and expert opinion surveys may support hypotheses
Testing hypotheses requires robust methodology and statistical power
Hypotheses that challenge established views and concepts require proper evidence-based justification

https://doi.org/10.3346/jkms.2021.36.e338

CONCLUSION

Hypotheses form an important part of the scientific literature. The COVID-19 pandemic has reiterated the importance and relevance of hypotheses for dealing with public health emergencies and highlighted the need for evidence-based and ethical hypotheses. A good hypothesis is testable in a relevant study design, backed by preliminary evidence, and has positive ethical and clinical implications. General medical journals might consider publishing hypotheses as a specific article type to enable more rapid advancement of science.

REFERENCES

1. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. Scientific hypotheses: writing, promoting, and predicting implications. *J Korean Med Sci* 2019;34(45):e300.
   PUBMED | CROSSREF
2. Misra DP, Agarwal V. Generating working hypotheses for original research studies. *Cent Asian J Med Hypotheses Ethics* 2020;1(1):14-9.
   CROSSREF
3. Misra DP, Zimba O, Gasparyan AY. Statistical data presentation: a primer for rheumatology researchers. *Rheumatol Int* 2021;41(1):43-55.
   PUBMED | CROSSREF
4. Yessirkepov M, Gasparyan AY. Embracing social media for generating and testing hypotheses. *Cent Asian J Med Hypotheses Ethics* 2021;2(3):133-6.
   CROSSREF
5. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020;382(10):929-36.
   PUBMED | CROSSREF
6. Misra DP, Agarwal V. Systematic reviews: challenges for their justification, related comprehensive searches, and implications. *J Korean Med Sci* 2018;33(12):e92.
   PUBMED | CROSSREF
7. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. *Rheumatol Int* 2011;31(11):1409-17.
   PUBMED | CROSSREF
8. Röhrig B, du Prel JB, Wachtlin D, Blettner M. Types of study in medical research: part 3 of a series on evaluation of scientific publications. *Dtsch Arztebl Int* 2009;106(15):262-8.
   PUBMED | CROSSREF
9. Misra DP, Agarwal V. Integrity of clinical research conduct, reporting, publishing, and post-publication promotion in rheumatology. *Clin Rheumatol* 2020;39(4):1049-60.
   PUBMED | CROSSREF
10. Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003;327(7429):1459-61.
    PUBMED | CROSSREF
11. Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. *BMJ* 1950;2(4682):739-48.
    PUBMED | CROSSREF
12. Goudsmit J. Alternative view on AIDS. *Lancet* 1992;339(8804):1289-90.
    PUBMED | CROSSREF
13. Duesberg P. Infectious AIDS--stretching the germ theory beyond its limits. *Int Arch Allergy Immunol* 1994;103(2):118-27.
    PUBMED | CROSSREF
14. Dunlap RE, Jacques PJ. Climate change denial books and conservative think tanks: exploring the connection. *Am Behav Sci* 2013;57(6):699-731.
    PUBMED | CROSSREF
15. Gupta L, Gasparyan AY, Misra DP, Agarwal V, Zimba O, Yessirkepov M. Information and misinformation on COVID-19: a cross-sectional survey study. *J Korean Med Sci* 2020;35(27):e256.
    PUBMED | CROSSREF

16. Gupta L, Gasparyan AY, Zimba O, Misra DP. Scholarly publishing and journal targeting in the time of the coronavirus disease 2019 (COVID-19) pandemic: a cross-sectional survey of rheumatologists and other specialists. *Rheumatol Int* 2020;40(12):2023-30.
PUBMED | CROSSREF
17. Parsonnet J. Clinician-discoverers--Marshall, Warren, and *H. pylori*. *N Engl J Med* 2005;353(23):2421-3.
PUBMED | CROSSREF
18. Marshall B. *Helicobacter pylori*--a Nobel pursuit? *Can J Gastroenterol* 2008;22(11):895-6.
PUBMED | CROSSREF
19. Riedel S. Edward Jenner and the history of smallpox and vaccination. *Proc Bayl Univ Med Cent* 2005;18(1):21-5.
PUBMED | CROSSREF
20. Heymann DL, Wilder-Smith A. Successful smallpox eradication: what can we learn to control COVID-19? *J Travel Med* 2020;27(4):taaa090.
PUBMED | CROSSREF
21. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395(10229):1033-4.
PUBMED | CROSSREF
22. Misra DP, Agarwal V, Gasparyan AY, Zimba O. Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. *Clin Rheumatol* 2020;39(7):2055-62.
PUBMED | CROSSREF
23. Misra DP, Gasparyan AY, Zimba O. Benefits and adverse effects of hydroxychloroquine, methotrexate and colchicine: searching for repurposable drug candidates. *Rheumatol Int* 2020;40(11):1741-51.
PUBMED | CROSSREF
24. Shah S, Das S, Jain A, Misra DP, Negi VS. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). *Int J Rheum Dis* 2020;23(5):613-9.
PUBMED | CROSSREF
25. Kim AHJ, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-García A, et al. A rush to judgment? Rapid reporting and dissemination of results and its consequences regarding the use of hydroxychloroquine for COVID-19. *Ann Intern Med* 2020;172(12):819-21.
PUBMED | CROSSREF
26. Sattui SE, Liew JW, Graef ER, Coler-Reilly A, Berenbaum F, Duarte-García A, et al. Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19. *Expert Rev Clin Immunol* 2020;16(7):659-66.
PUBMED | CROSSREF
27. PRINCIPLE Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* 2021;397(10279):1063-74.
PUBMED | CROSSREF
28. Echeverría-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, De-Antonio Cuscó M, Ferrández O, Horcajada JP, et al. Azithromycin in the treatment of COVID-19: a review. *Expert Rev Anti Infect Ther* 2021;19(2):147-63.
PUBMED | CROSSREF
29. Reardon S. Flawed ivermectin preprint highlights challenges of COVID drug studies. *Nature* 2021;596(7871):173-4.
PUBMED | CROSSREF
30. Butler-Laporte G, Nakanishi T, Mooser V, Morrison DR, Abdullah T, Adeleye O, et al. Vitamin D and COVID-19 susceptibility and severity in the COVID-19 host genetics initiative: a Mendelian randomization study. *PLoS Med* 2021;18(6):e1003605.
PUBMED | CROSSREF
31. The Lancet Diabetes Endocrinology. Vitamin D and COVID-19: why the controversy? *Lancet Diabetes Endocrinol* 2021;9(2):53.
PUBMED | CROSSREF
32. RECOVERY Collaborative GroupHorby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021;384(8):693-704.
PUBMED | CROSSREF
33. Khan FA, Stewart I, Fabbri L, Moss S, Robinson K, Smyth AR, et al. Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19. *Thorax* 2021;76(9):907-19.
PUBMED | CROSSREF
34. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397(10285):1637-45.
PUBMED | CROSSREF

35. Sauvat A, Ciccosanti F, Colavita F, Di Rienzo M, Castilletti C, Capobianchi MR, et al. On-target versus off-target effects of drugs inhibiting the replication of SARS-CoV-2. *Cell Death Dis* 2020;11(8):656.
PUBMED | CROSSREF

36. Tummino TA, Rezelj VV, Fischer B, Fischer A, O'Meara MJ, Monel B, et al. Drug-induced phospholipidosis confounds drug repurposing for SARS-CoV-2. *Science* 2021;373(6554):541-7.
PUBMED | CROSSREF

37. Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). *Proc Natl Acad Sci U S A* 2020;117(30):17720-6.
PUBMED | CROSSREF

38. Gasparyan AY, Misra DP, Yessirkepov M, Zimba O. Perspectives of immune therapy in coronavirus disease 2019. *J Korean Med Sci* 2020;35(18):e176.
PUBMED | CROSSREF

39. Portnov BA, Dubnov J, Barchana M. On ecological fallacy, assessment errors stemming from misguided variable selection, and the effect of aggregation on the outcome of epidemiological study. *J Expo Sci Environ Epidemiol* 2007;17(1):106-21.
PUBMED | CROSSREF

40. Zimba O, Gasparyan AY. Peer review guidance: a primer for researchers. *Reumatologia* 2021;59(1):3-8.
PUBMED | CROSSREF

41. Yessirkepov M, Gasparyan AY. From testable hypotheses to ethical papers and improved health service. *Cent Asian J Med Hypotheses Ethics* 2020;1(1):10-3.
CROSSREF

42. Wiseman R, Watt C, Kornbrot D. Registered reports: an early example and analysis. *PeerJ* 2019;7:e6232.
PUBMED | CROSSREF

43. Gaur PS, Zimba O, Agarwal V, Gupta L. Reporting survey based studies - a primer for authors. *J Korean Med Sci* 2020;35(45):e398.
PUBMED | CROSSREF

44. Zimba O, Radchenko O, Strilchuk L. Social media for research, education and practice in rheumatology. *Rheumatol Int* 2020;40(2):183-90.
PUBMED | CROSSREF

45. Ng W. Preprints as medium for communicating new ideas, hypotheses, data, analysis and beyond. *PeerJ Prepr* 2017;5:e3154v1.
CROSSREF

46. Smith CM. Origin and uses of primum non nocere--above all, do no harm! *J Clin Pharmacol* 2005;45(4):371-7.
PUBMED | CROSSREF