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PHARMACOLOGICAL OPTIONS FOR MANAGEMENT OF COVID-19: ISSUES CONCERNING ETHICS AND RATIONAL MEDICINE USE

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ABSTRACT: Coronavirus disease 2019 (COVID-19) pandemic has emerged as a major healthcare problem and has posed a great challenge to our existing healthcare facilities. Treatment of COVID-19 has been primarily based on repurposed drugs, drugs approved under emergency authorization or other options which are not thoroughly evaluated in patients with COVID-19, hence, lacking an adequate data on safety and efficacy. Public awareness and education regarding the potential benefits and safety concerns of the available therapeutic/prophylactic options are crucial to avoid ethical and medicolegal issues. Fundraising and global partnership are required to raise the research on potential older drugs likely to be repurposed, along with novel treatment options for COVID-19. A global effort is required to ensure the availability, distribution, and safer administration of COVID-19 vaccines. A rational and ethical approach is required to manage the patients with COVID-19. Equitable access to COVID-19 vaccines should be a priority to end this pandemic. In this review, we have focused on concerns regarding ethics and rational medicine use in view of the available and emerging therapeutic and prophylactic options for the management of COVID-19.

INTRODUCTION: On March 2020, the World Health Organization (WHO) announced that there were no safe and effective medicines to cure coronavirus disease-19 (COVID-19) at that time [1]. This led to a significant increase in the search for a cure for COVID-19. The most viable option at that time was off-label prescribing or repurposing of drugs based on preclinical reports or previously found promising in infectious disease [2]. Off-label drug use does not comply with the definition as advanced by the WHO 1985 for rational use of medicines which stated. "The patient is given right dose of medicine as per clinical requirement for right period of time at an affordable price" [3].

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The drug use for indications other than those approved by the national medicines regulatory authority is considered "off-label" use [3]. In times of a pandemic like COVID-19, where no effective treatment is available, it is ethical to offer medicine to patient case specific. With so much published literature, it becomes difficult to interpret which drug is to be used in which subtype of patients. So, when drugs are to be administered for a new disease with incomplete evidence, ethical concerns are likely to increase. Letting the patient follow the disease course without giving any available therapies is not justified.

However, at the same time, full autonomy should be given to the patient regarding the acceptance of therapy given and informed about (wherever deemed applicable) the risks associated with the same. Off-label use of drugs is not illegal or irrational, but it is often interpreted wrongly. However, the prescribing physician should take all

the responsibility, keep patient safety as the prime concern, and not neglect rare adverse effects, especially when alternative therapy is not available [4]. It is generally not advisable to accept the clinical research findings before large randomized controlled trials (RCTs) are carried out and their findings are available [5]. One of the false beliefs among patients and physicians is that the drug certainly has a benefit over harm. Also, too much of optimism about unproven drug such as hydroxychloroquine (HCQ) in the treatment of COVID-19, despite its already known side effects, leads to unethical practice and irrational medicine use [6]. Off-label use of drugs for treatment of disease not only compromises the safety and efficacy of drug but also gives opportunity to Pharma companies to bypass expensive RCTs and approve the drug for secondary indication [7].

In context of Ebola outbreak in 2014, numerous drugs were tested against virus including chloroquine, HCQ, favipiravir, brincidofovir, monoclonal antibodies, antisense RNA, convalescent plasma *etc*. to rule out an efficacious treatment against Ebola. However, all the efforts were in vain. One of the reasons for this failure was most of the studies did not have control groups [5]. A similar situation was seen during this pandemic (COVID-19), where most drugs were either started based on *in-vitro* data or studies carried with single treatment groups. In such situations, ethical issues will arise where there is no clear-cut answer, and one needs to choose a partially correct answer. Further, it is difficult to track whether the four principles of bioethics (beneficence, non-maleficence, respect for autonomy, and justice) are preserved while dealing with the treatment of patients with COVID-19 [8]. Evolving knowledge regarding the organism and possible therapeutic and preventive strategies demand a balanced approach to justify ethics and rational medicine use. In this review, we will focus on the concerns regarding ethics and rational medicine use linked with treatment of patients with COVID-19.

Current Evidence and Ethical Concerns of Drugs used for COVID-19 Treatment: Off label prescribing of antimalarial drugs such as HCQ and chloroquine was the first hope for the treatment of COVID-19, but later, it was over-hyped politically [9, 10].

This led to the shortage of drugs in the market, depriving the patients of the availability of drugs who were taking drugs for specific indications like rheumatoid arthritis and systemic lupus erythematosus, etc., and encouraging self-medication among asymptomatic patients [10]. Off-label use of antimalarial drugs chloroquine and HCQ has been associated with many controversies [9]. The United States Food and Drug Administration (US-FDA) issued Emergency Use Authorization (EUA) status to HCQ in March 2020 based on data available then. Still, it later revoked this EUA status based on safety concerns and incomplete trial results [9]. Further, the HCQ arm of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, which used high doses of HCQ, was stopped with preliminary results showing possible excess mortality with HCQ (25·7% with HCQ vs 23·5% with usual care).

In addition, HCQ was ineffective in reducing mortality among hospitalized patients due to COVID-19 [11]. The WHO-led SOLIDARITY Trial, which included over 12,000 patients in 500 hospitalsites in over 30 countries, for evaluating the efficacy of HCQ, remdesivir, lopinavir/ritonavir, and interferon in severely ill COVID-19 patients, also provided valuable clinical findings compared to standard of care (SOC) [12]. In addition, the current evidence and ethical concerns of drugs used for COVID-19 treatment are presented in **Table 1** [13-45].

TABLE 1: CURRENT EVIDENCE AND POTENTIAL ETHICAL CONCERNS OF DRUGS USED FOR COVID-19 TREATMENT

S. no.	Therapeutic options and rationale behind their use / Recommendations	Ethical concerns
1	**Corticosteroids:** -Corticosteroids are recommended for the specific stages of COVID-19 because the tissue injury is due to the dysregulation of immune and inflammatory response. Therefore, the use	Irrational and unsupervised use of corticosteroids may lead to flare up of infection, development of secondary infections and increased morbidity and mortality[15]. Recent example of irrational corticosteroids use is the higher incidence of mucormycosis reported during the second wave of COVID-19 in India[16]

	of corticosteroids is strongly recommended for treatment of patients with severe and critical COVID-19 illness [13, 14]. Conditional recommendation: For patients with non-severe COVID-19 infection (absence of criteria for severe or critical infection) [14]	
2	**Tocilizumab (TCZ):** -Pulmonary complications developing in the second week of illness have been linked to excessive inflammatory response in the form of massive cytokine and chemokine release called 'cytokine storm'. This is indicative of uncontrolled dysregulation of host immune response[17]. Interleukin (IL-6) is also released from bronchial epithelial cells during infection caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was hypothesized that IL-inhibitors could have a beneficial role in severe illness with COVID-19 suffering from ARDS and /or cytokine syndrome[18]. Treatment with IL-6 receptor blockers (tocilizumab or sarilumab) is recommended in patients with severe or critical COVID-19 infection [14]	Treatment outcomes reported in COVID-19 confirmed hospitalized patients were variable[19-27]. Increased risk of secondary infections [21, 27]. Addition of TCZ could increase the treatment cost; up to 93.1% of the total treatment cost has been reported [27].
3	**Remdesivir:** WHO provided the conditional recommendation on use of remdesivir in COVID-19 hospitalized patients irrespective of severity, as there was no evidence that remdesivir could improve survival and other outcomes[28].	Use as intravenous drug (remdesivir) with doubtful efficacy raises a question about remdesivir being a potential candidate for coronavirus. One cannot underestimate the role of commercial interests to promote any drug with partial results which creates unnecessary hope among people that a new potential treatment of COVID-19 has been found. As clearly highlighted in one editorial[29], results published by company sponsored trials were in preliminary stages with inadequate sample size, without peer review and favored use of remdesivir, whereas findings of independent trials in other parts of world had difference of opinion. Concerns related to availability and affordability of remdesivir; its use for COVID-19 treatment is relatively insignificant in low- and middle-income countries[30]
4	**Ivermectin:** Ivermectin was found to have anti-viral activity against SARS-CoV-2 in an invitro settings; where authors reported that ivermectin was able to achieve 5000 folds reduction in viral RNA at 48 h with the single addition (5 μM ivermectin) to Vero-hSLAM cells[31]. It has been recommended to not to use ivermectin in patients with COVID-19 except in the context of a clinical trial [14]	With regards to human equivalent dose, the results are much disappointing since the concentration required for 50 % inhibition (IC_{50}) of2 μM is 35 times greater than the plasma concentration of (0.05 μM) of approved dose (~200 μg/kg)32. Thus, the equivalent human dose that is required to attain the estimated plasma concentration required to inhibit the SARS-CoV-2 will be several times larger than the approved dose human dose. Based on the previous pharmacokinetic data of ivermectin, the concentration used for treatment of parasites are practically unattainable to inhibit the SARS-CoV-233. Previous preclinical studies found ivermectin as neurotoxic and as well as fetotoxic [3] The adverse events following inadvertent use of ivermectin in pregnant females remained inconclusive regarding the safety profile of ivermectin in pregnant females. However, it was suggested to avoid inadvertent use of ivermectin in pregnant women35. It was also reported that the metanalyses and other data in the case of ivermectin are misleading due to poorly designed studies and have a low level of certainty [36]
5	**Favipiravir:** Anti-viral drug (favipiravir) was approved in Japan for management of resistant cases of influenza and acts by inhibiting viral RNA dependent RNA polymerase[37]. Thus, based on anti-viral	The approval of favipiravir was surrounded with controversy, as scientific evidence regarding the efficacy, of favipiravir in COVID-19 patients, is weaker[39]. The dosing of Fabiflu tablet (Favipiravir, manufactured and marketed by pharma giant Glenmark) is1800 mg twice daily on first day, followed by 800mg twice daily up to day 14.

	properties this was repurposed to treat COVID-19 patients. In India, it has been granted permission by Drugs Controller General of India (DCGI) to be used in mild to moderate patients of COVID-19, with mandatory informed consent from patient / patient party before initiating the treatment[38].	Since, the dose used for the COVID-19 treatment is longer than used for treatment of influenza, (i.e., 1600 mg twice daily on day 1, followed by 600 mg twice daily for next 4 days) so, monitoring is required to prevent inadvertent adverse events [41]. Chen *et al.,* reported that the adverse event (raised serum uric acid) for favipiravir group (13.79%), was significantly more than control group[42]. Caution is required while using favipiravir since it is fetotoxic and teratogenic [41]. A Glenmark funded RCT carried out in 150 patients (mild to moderate RT-PCR confirmed COVID-19), failed to achieve the primary end point of time to RT-PCR negativity, though authors suggested the drug could be potential candidate in COVID-19 treatment as it was able to achieve significant improvement in time to clinical cure (secondary outcome).It is to be noted that this study also reported increased adverse events in favipiravir (35.6%) compared to treatment group (8.0%) [43]. Not only has the drug failed to prove the safety and efficacy in most of the studies, it is also costly[38,42, 43,44,45]

Extensive Literature and Therapeutic Dilemma: Published literature is extensive and largely differs in opinion. So, results seem inconclusive and make it difficult for physicians to follow any specific form of therapeutic measure. Also, guidelines are changing daily, making the situation and its management more confusing [46]. In certain situations, misinterpreting results obtained from poorly framed studies or being highlighted by eminent people can be misleading and lead to irrational drug use [47]. This could be more detrimental in certain developing countries where a stringent regulatory control is lacking. Huge number of research reports or another form of articles are being written on COVID-19 by the academicians/health professionals in different parts of the world. Considering the public emergency, they are being peer reviewed quickly and made available on the web, which is well in the public domain. Quality of the published literature cannot be understood by every person or health professional and many times it could be interpreted in an over-ambitious manner or wrongly [4]. Every effort should be put in disseminating strong evidence-based data so that the information is not misleading, and the generated data can be helpful in dealing the emergency situations like COVID-19 [4].

Potential Ethical Issues: In times of crisis like COVID-19, special attention must be given right from diagnosis to management of infection in pregnant females as they are among the vulnerable group who are more susceptible to infection due to the change in physiological state [48]. Due care should be given while treating female patients of reproductive age infected with COVID-19. Patient care should be based on a case-to-case basis approach and drugs likely to have fetal adverse effects, for instance, doxycycline and favipiravir, should beavoided [48]. A medicolegal issue can also arise if person tests COVID-19 positive or his underlying condition deteriorates after stopping the therapy.

It can also lead to an ethical dilemma about which patient should be given corticosteroids or not and who would take responsibility for any untoward incidence if it occurs. In the current scenario, what if you deny such people from taking drug and they become COVID-19 positive. Here also, the ethical concern may arise since principle of beneficence and non-maleficence are compromised. The principle of non-maleficence is violated in this situation. In such scenarios, the undertaking physician is expected to decide the patient's best interests. However, this may not apply if doctor's decision contradicts with the patient's advance directive regarding the therapy use [49]. Here, a question arises whether doctors should be granted immunity against civil and criminal negligence arising from treatment provided to patients during COVID-19 pandemic? There is a polarization in views on whether to provide criminal negligence immunity to doctors during pandemic [50, 51]. From the pandemic's beginning, the efforts of frontline Health Care Workers (HCWs) were well appreciated globally. The HCWs and their families were at a greater risk of developing COVID-19 since they were in close contact with the patients (symptomatic/asymptomatic). Further, such claims from patients regarding the negligence would

demotivate the doctors and other healthcare staff, leading to stress and anxiety among them [50].

In contrast, negligence claims would improve the standards and help us cope better in future pandemics. Also, the immunity to medical negligence would give a negative impression to the patients regarding their treatment [50]. If compensation is provided to the COVID-19 patients and their families, it would help to overcome negligence claims liability [50].

Informed Consent: In emergency and uncommon situations like infectious disease out-breaks, it is imperative to conduct research as soon as possible and provide feasible treatment options quickly. However, ethical issues, such as valid written informed consent may be needed from every patient while explaining all the pros and cons of such therapies. Informed consent is a process to educate a patient or patient party regarding the purpose, benefits, and potential risks of a medical or surgical intervention and then seek permission before conducting a healthcare intervention [52, 53]. It is basically taking a confirmation (signature/thumb impression) from the patient/patient party that they are aware of the health care intervention's possible consequences (risk and benefit). Further, it is the physician's responsibility to take informed consent from the patient and to assess the patient's comprehension to take the decision voluntarily regarding acceptance and denial of the medical intervention[52]. However, informing the patient regarding the unavailable treatment option will not provide the information for receiving or refusing the accessible treatment option[53]. The informed consent can be waived under special circumstances. For instances, public health emergency (pandemic / epidemic), a medical emergency, patient waiver, therapeutic privilege and when patient is incompetent [52].

Older and Potential Drugs:

Promising Role? Some older drugs like minocycline and doxycycline, with established safety profiles, strong preclinical evidence, and wide availability, are not being promoted to clinical trials [54, 55]. Despite the promising immunomodulatory, anti-viral and anti-inflammatory effects of tetracyclines (minocycline and doxycycline), have not been highlighted much among the potential repurposing drugs against COVID-19 [54, 55]. One of the advantages of using these drugs is that they are readily available at an affordable price, even in developing countries [55]. Further, using minocycline in COVID-19 patients could provide clinical benefits in cytokine-induced myocardial injury and life-threatening acute respiratory distress syndrome (ARDS) [55]. Purwati *et al.*, reported a significant decrease in viral load within 1 week of treatment of lopinavir/ritonavir plus doxycycline group (n=124) in mild to moderate patients with COVID-19. They also reported that C-reactive protein (CRP) and IL-6 were significantly lower as compared to control groups [56].

Another observational study reported that a combination of HCQ and doxycycline showed a promising effect on the treatment of mild to moderate COVID-19 patients. Here, number of patients was less though (n=32); out of which 9 patients also took favipiravir. All patients' symptoms improved and they tested negative for COVID-19 at the time of discharge (range 8-21 days) [57]. Yates et al., reported significant improvement in the patients' symptoms with doxycycline treatment in a case series of four COVID-19 patients with comorbid pulmonary disease. An important thing to note in this study is that all four patients did not administer any other concomitant medication along with doxycycline; their ages ranged from 40 to 88 years [54]. Also, a drug like budesonide, which is widely available and listed in WHO essential list of medicines [58], can be a viable option in the future to treat mild and moderate COVID-19 patients at home and can decrease hospital overload in such emergency situations. Government and other funding authorities should support and encourage research activities so that larger clinical studies can be planned and conducted to reach a meaningful conclusion.

Emergency Vaccine Approval:

Vaccine trial Designs and Approval Issues: Since, the beginning of January 2020, before COVID-19 was declared a pandemic, the race for the vaccine had already begun. Under normal circumstances, it can take more than a decade for vaccine approval (for instance, polio vaccine took nearly 40 years and Ebola vaccine took nearly 5

years) [59]. Though the WHO took one year to provide the emergency use validation to the first COVID-19 vaccine (i.e., Comirnaty COVID-19 mRNA vaccine) [60], many vaccine candidates have already got approval from the regulatory authority and a number of potential vaccine candidates are in phase 1 to phase 3 clinical trials [61].

Generally, these vaccines have been given emergency approval based on data available from phase I and phase II data on a limited number of subjects. Phase I and phase II trials in the case of vaccines are not enough to give robust data about the efficacy and safety of a vaccine, rather they are more directed towards capturing the information on immunogenicity and reactogenicity [62, 63]. In this case, investigators, sponsors, and regulators depend on the extrapolation of data to provide some information on safety and efficacy. Sometimes, it is the post-hoc analysis or analysis with respect to secondary objectives which tells about the likely beneficial effects of a vaccine. There was a transformation of outcomes of vaccine trial from evaluating vaccine efficacy in preventing the COVID-19 in the vaccinated subjects to preventing the disease severity in terms of hospitalizations and deaths [64, 65]. This information should be clearly provided to the different stakeholders.

Issues Regarding Public Acceptance of Vaccines and their Availability: Obviously, the vaccine development has marked a sign of relief for the global population, as COVID-19 has not only claimed millions of lives but also brutally affected the global economy. Nearly two dozen COVID-19 vaccines have got authorization, and many more are at different stages of development [61].

Vaccine hesitancy is defined as the delay in acceptance or refusal of vaccination despite availability of vaccination services. This is influenced by factors such as complacency, convenience, and confidence[66]. A global survey reported that the most common reason for vaccine hesitancy was risk-benefit (scientific evidence e.g., vaccine safety concerns), which accounted for nearly 22 %. Further, vaccine hesitancy (unrelated to the COVID-19 vaccine) was reported in more than 90 % of countries globally [67]. In June 2020, a global online survey conducted in 19 countries regarding COVID-19 vaccine acceptance ranged from 55% (in Russia) to almost 90% (in China) [68]. A recently published study reported that the people of low-and middle-income countries (LMICs) have more willingness (mean 80.3%) to take a COVID-19 vaccine as compared to the United States (mean 64.6%) and Russia (mean 30.4%) [69].

Even though vaccine acceptance is more in LMICs than developed countries like the United States, the availability of COVID-19 vaccines in LMICs remains a hurdle to end the pandemic. Globally, 38.02 million people are being administered COVID-19 vaccines each day, though only 1.6% of people from low-income countries have received at least one dose [70].

The pace at which the vaccination is proceeding in LMICs, it will be around 2023 when the world gets vaccinated. Thus, the emergence of a highly contagious delta variant remains a threat to a larger unvaccinated population [71]. Even if the vaccination drive has tremendously increased in the past few months, there are still reports of subjects missing the second dose of the vaccine within the stipulated time interval. Currently, India is among the top nations for vaccinating the maximum number of people against COVID-19 [70]. The incidence of missing second doses remains a concern in some parts of India, which reported nearly 1.3 million doses (Odisha) and 0.394 million doses (Tamil Nadu) [72, 73].

One of the reasons for this was the unavailability of COVID-19 vaccines and overcrowding in vaccination centers[73]. Missing the second dose of COVID-19 vaccines has also been reported in developed countries like the US. Here, nearly 15 million people missed taking their second dose of vaccine within the ideal window period, which showed an increase from the previous year's missing rate [74]. Another major ethical issue is that even after vaccination, there is no permanent protection against COVID-19 and its spread. If a patient develops a life-threatening adverse event after vaccination, it can lead to medicolegal issues. Proper history from participants should be taken before vaccinating people. A very important aspect that anyone can miss at a busy vaccine clinic is the possibility of current COVID-19 infection, which is asymptomatic in most cases, and exposure of the subjects to a person who is positive for COVID-19.

This demands a robust standard operating procedure (SOPs) before vaccinating people. For instance, every person should be tested for COVID-19 before vaccination; this will ensure that a positive person does not get vaccinated, as the interplay of concomitant COVID-19 infection and vaccine can lead to an exaggerated immune reaction and may lead to excessive cytokine release [75]. At the same time, if any positive person comes for vaccination, it should be deferred for at least 2 weeks [76].

Caution is also important in the case of people who are exposed to COVID-19-positive subjects. In this case, the vaccination may be deferred for a week or so, and after that, COVID-19 testing should be done, and if negative, the vaccine should be given. Reports have been obtained regarding the troublesome adverse effects [77]of COVID-19 vaccines and they further need to be addressed to avoid ethical and legal glitches. In addition to the above, no specific guidelines are in place to address the issues of medical and financial compensation to be awarded to individuals experiencing serious AEFI (since vaccines are given emergency authorization and are still undergoing late phases of clinical trial). All these issues demand a high level of SOPs and risk evaluation and mitigation plans so that this herculean task could be achieved smoothly.

COVID-19 Vaccines:

The Last Resort to End the Pandemic: COVID-19 vaccines are the last resort to end the pandemic since most drugs failed to show significant benefit to COVID-19 patients. A surge in hospitalization admission has recently been reported in unvaccinated pregnant women. In addition, the women admitted during the delta variant period were found to be at a greater risk than those admitted in the alpha variant period, with a greater proportion having pneumonia [78].

A recently published study has shown that the COVID-19 vaccines (BNT162b2 or ChAdOx1 nCoV-19) have a modest difference in effectiveness in the delta variant as compared with the alpha variant after two doses [79]. Even if someone is fully vaccinated, breakthrough infections are expected since no vaccine is 100% effective. Fully vaccinated individuals are less likely to develop severe illness or get COVID-19 as compared to unvaccinated [80]. Thus, public awareness is of utmost importance. At the same time, the government and health providers must educate and inform the public regarding the potential benefits of the vaccine and all minor and major safety issues, precautions, and contraindications.

All mild, moderate, and severe adverse events following immunization (AEFI) should be recorded and reported to gain confidence in the vaccine's potential beneficiaries. The stronger the confidence, the larger the population gets vaccinated and fewer cases of severe COVID-19 illness, hospitalization, and death [81]. A global effort is required to ensure the availability, distribution and safer administration of COVID-19 vaccines.

CONCLUSION: In a scenario like the COVID-19 pandemic, choosing off-label drugs becomes more complicated when there is no substantial evidence of their safety and efficacy. Even though off-label prescribing is legal and is practiced in the absence of adequate data but it should also be kept in mind that the clinical evidence in one subject (case specific) may not apply to others. Under normal circumstances and in times of crisis, it is to be noted that the four principles of bioethics (beneficence, non-maleficence, respect for autonomy, and justice) and rational medicine use should always be preserved. Emphasis should be given to promoting research on promising-looking older drugs apart from developing novel therapies. One cannot undermine the role of commercial interests to promote any drug with partial results, creating unnecessary hope among people.

All efforts should be made to provide public education and awareness regarding the risk-benefit profiles of the different therapies so that a rational and shared decision can be made. Over time, the number of COVID-19 cases has decreased, however, the new variant remains a concern for vaccine efficacy. Vaccines are expected to end the pandemic, but vaccine safety, efficacy, availability, and hesitancy among the public are some of the important hurdles. A global effort is required to ensure the availability, distribution, and safer administration of COVID-19 vaccines. Thus, public awareness is of utmost importance, and at

the same time it is the duty of the government and healthcare providers to educate and inform the public regarding the potential benefits of the vaccine and all minor and major safety issues, precautions, and contraindications.

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REFERENCES:

1. Off-label use of medicines for COVID-19. World Health Organization[Internet]. 2020 Mar 31 [cited 2021 Jul 15]. Available from: https://www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19.
2. Yousefi B, Valizadeh S, Ghaffari H, Vahedi A, Karbalaei M and Eslami M: A global treatments for coronaviruses including COVID-19. J Cell Physiol 2020; 235(12): 9133-9142.
3. Promoting rational use of medicines: core components. WHO policy perspectives on medicines. World Health Organization[Internet]. 2002 [cited 2021 Jul 15]. Available from: https://apps.who.int/iris/bitstream/handle/10665/67438/WHO_EDM_2002.3.pdf
4. Allen C, Heaven Taylor B and Winchester C: COVID-19 - Where should we go now?. Integr Med Res 2020; 9(3): 100468.
5. Kalil AC: Treating COVID-19-Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. JAMA 2020; 323(19): 1897-1898.
6. Alfandre DJ: Ethical Considerations in Prescribing Unproven Therapies for COVID-19. Renal & Urology News [Internet]. 2020 Sep 01 [cited 2021 Jul 15]. Available from: https://www.renalandurologynews.com/home/news/ethical-issues-in-medicine/covid-19-pandemic-off-label-prescribing-trade-offs/
7. Stafford RS: Regulating off-label drug use--rethinking the role of the FDA. N Engl J Med 2008; 358(14): 1427-1429.
8. Boyd KM: Medical ethics: principles, persons, and perspectives: from controversy to conversation. J Med Ethics 2005; 31(8): 481-486.
9. Singh H, Chauhan P and Kakkar AK: Hydroxychloroquine for the treatment and prophylaxis of COVID-19: The Journey so far and the road ahead. Eur J Pharmacol 2021; 890: 173717.
10. Narea N: Trump's reckless promotion of hydroxychloroquine to fight coronavirus, explained: it might not be the ''game changer'' Covid-19 treatment the president promised. Vox [Internet]. 2020 Mar 26 [cited 2021 Jul 15]. Available from: https://www.vox.com/2020/3/26/21193912/trump-hydroxychloroquine-coronavirus-treatment
11. No clinical benefit from use of hydroxychloroquine in hospitalized patients with COVID-19. Randomised Evaluation of COVid-19 thERapY (RECOVERY)[Internet]. 2020 Jun 05 [cited 2021 Jul 18]. Available from: https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19
12. Solidarity Therapeutics Trial produces conclusive evidence on the effectiveness of repurposed drugs for COVID-19 in record time. World Health Organization[Internet]. 2020 Oct 15 [cited 2021 Jul 18]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
13. Therapeutic Management of Hospitalized Adults With COVID-19. COVID-19 Treatment Guidelines. National Institutes of Health [Internet]. 2021[updated2021 Aug 21; cited 2021 Aug 30]. Available from: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/
14. Therapeutics and COVID-19: living guideline.World Health Organization [Internet]. 2021 Jul 07 [cited 2021 Aug 30] Available from: https://app.magicapp.org/#/guideline/5486
15. Ni YN, Chen G, Sun J, Liang BM and Liang ZA: Correction to: The effect of corticosteroids on the mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care 2020; 24(1): 376.
16. Rocha CN, Goyal S, Patel T, Jain S and Ghosh A: COVID-19 and mucormycosissyndemic: double health threat to a collapsing healthcare system in India. Trop Med Int Health 2021; 26(9): 1016-1018.
17. Shi Y, Wang Y, Shao C, Huang J, Gan J and Huang X: COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020; 27(5): 1451-1454.
18. Interleukin-6 Inhibitors. COVID-19 Treatment Guidelines. National Institutes of Health [Internet]. 2021 [updated 2021 Apr 21; cited 2021 Aug 25]. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/
19. Klopfenstein T, Zayet S, Lohse A, Balblanc JC, Badie J and Royer PY: Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Med Mal Infect 2020; 50(5): 397-400.
20. Lan SH, Lai CC, Huang HT, Chang SP, Lu LC and Hsueh PR: Tocilizumab for severe COVID-19: a systematic review and meta-analysis. Int J Antimicrob Agents 2020; 56(3): 106103.
21. Jain S and Sharma SK: Rational use of tocilizumab in COVID-19Annals of the Rheumatic Diseases Published Online First: 31 July 2020. doi: 10.1136/annrheumdis-2020-218519.
22. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L and Foulkes AS: Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med 2020; 383(24): 2333-2344.
23. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD and Bhagani S: Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med 2021; 384(16): 1503-1516.
24. Veiga VC, Prats JA, Farias DL, Rosa RG, Dourado LK and Zampieri FG: Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021; 372: 84.
25. Salama C, Han J, Yau L, Reiss WG, Kramer B and Neidhart JD: Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021; 384(1): 20-30.

26. Antony SJ, Davis MA, Davis MG, Almaghlouth NK, Guevara R and Omar F: Early use of tocilizumab in the prevention of adult respiratory failure in SARS-CoV-2 infections and the utilization of interleukin-6 levels in the management. J Med Virol 2021; 93(1): 491-498.
27. Chamorro-de-Vega E, Rodriguez-Gonzalez CG, Manrique-Rodríguez S, Lobato-Matilla E, García-Moreno F and Olmedo M: Clinical course of severe patients with COVID-19 treated with tocilizumab: report from a cohort study in Spain. Expert Rev Clin Pharmacol 2021; 14(2): 249-260.
28. WHO recommends against the use of remdesivir in COVID-19 patients. World Health Organization [Internet]. 2020 Nov 20 [cited 2021 Aug 25]. Available from: https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients
29. Moynihan R, Macdonald H, Bero L and Godlee F: Commercial influence and covid-19. BMJ 2020; 369: 2456.
30. Adhikari S, Khadka S, Dahal S, Shrestha DB, Shahi J and Bajgain Y: Remdesivir in COVID-19 management: availability and relevance to low- and middle-income countries. Drugs Ther Perspect 2020; 1-3.
31. Caly L, Druce JD, Catton MG, Jans DA and Wagstaff KM: The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in-vitro*. Antiviral Res 2020; 178: 104787.
32. Schmith VD, Zhou JJ and Lohmer LRL: The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. Clin Pharmacol Ther 2020; 108(4): 762-765.
33. Momekov G and Momekova D: Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. Biotechnology & Biotechnological Equipment 2020: 34(1): 469-74.
34. Center for drug evaluation and research: approval package for Mectizan. Food and Drug Administration [Internet]. 1996 Nov 22 [cited 2021 Aug 25]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/96/050742ap.pdf
35. Nicolas P, Maia MF, Bassat Q, Kobylinski KC, Monteiro W and Rabinovich NR: Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis. Lancet Glob Health 2020; 8(1): 92-e100.
36. Garegnani LI, Madrid E and Meza N: Misleading clinical evidence and systematic reviews on ivermectin for COVID-19. BMJ Evid Based Med 2021; bmjebm-2021-111678.
37. Shiraki K and Daikoku T: Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther 2020; 209: 107512.
38. Approval of Favipiravir Tablets to Glenmark Pharmaceuticals and Remdesivir Injection to Cipla Ltd, Hetero Drugs and Mylan Labs. Central Drugs Standard Control Organization[Internet]. 2020 Jul 02 [cited 2021 Aug 20]. Available from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NjIxMw==
39. Pulla P: Covid-19: India's slow moving treatment guidelines are misleading and harming patients. BMJ 2021; 372: 278.
40. Glenmark becomes the first pharmaceutical company in India to receive regulatory approval for oral antiviral Favipiravir, for the treatment of mild to moderate COVID-19 Labs. GLENMARK[Internet]. 2020 Jun 20 [cited 2021 Aug 20]. Available from: https://www.glenmarkpharma.com/sites/default/files/Glenmark-becomes-the-first-pharmaceut-cal-company-in-India-to-receive.pdf
41. Report on the Deliberation Results of Avigan Tablet 200 mg. Pharmaceuticals and Medical Devices Agency[Internet]. 2014 Mar 4 [cited 2021 Aug 20]. Available from: https://www.pmda.go.jp/files/000210319.pdf
42. Cai Q, Yang M, Liu D, Chen J, Shu D and Xia J: Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing) 2020; 6(10): 1192-1198.
43. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S and Pendse A: Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infect Dis 2021; 103: 62-71.
44. Chen PJ, Chao CM and Lai CC: Clinical efficacy and safety of favipiravir in the treatment of COVID-19 patients. J Infect 2021; 82(5): 186-230.
45. Khamis F, Al Naabi H, Al Lawati A, Ambusaidi Z, Al Sharji M and Al Barwani U: Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia. Int J Infect Dis 2021; 102: 538-543.
46. Saperstein Y, Ong SY, Al-Bermani T, Park J, Saperstein Y and Olayinka J: COVID-19 Guidelines Changing Faster than the Virus: Implications of a Clinical Decision Support App. Int J Clin Res Trials 2020; 5(2): 148.
47. Gonsalves G and Yamey G: Political interference in public health science during covid-19. BMJ 2020; 371: 3878.
48. Manchanda K, Singh J, Bhagat R, Tiwana IK and Singh H: Safety of pharmacological options for the management of COVID-19 in pregnant women: An Indian perspective. Int J Risk Saf Med 2021; 32(1): 3-17.
49. Ethics - Definitions and approaches - The four common bioethical principles - Beneficence and non-maleficence. Alzheimer Europe[Internet]. 2009 Oct 09 [cited 2021 Aug 15]. Available from: https://www.alzheimer-europe.org/Ethics/Definitions-and-approaches/The-four-common-bioethical-principles/Beneficence-and-non-maleficence
50. Tomkins C, Purshouse C, Heywood R, Miola J, Cave E and Devaney S: Should doctors tackling covid-19 be immune from negligence liability claims. BMJ 2020; 370: 2487.
51. MDU calls for national debate over protecting NHS from COVID-19 clinical negligence claims - The MDU[Internet]. 2020 Apr 20 [cited 2021 Aug 15]. Available from: https://www.themdu.com/press-centre/press-releases/mdu-calls-for-national-debate-over-protecting-nhs-from-covid-19-clinical-negligence-claims
52. Cocanour CS: Informed consent-It's more than a signature on a piece of paper. Am J Surg 2017; 214(6): 993-997.
53. Turnham HL, Dunn M, Hill E, Thornburn GT and Wilkinson D: Consent in the time of COVID-19. J Med Ethics 2020; 46(9): 565-568.
54. Yates PA, Newman SA, Oshry LJ, Glassman RH, Leone AM and Reichel E: Doxycycline treatment of high-risk COVID-19-positive patients with comorbid pulmonary disease. Ther Adv Respir Dis 2020; 14: 1753466620951053.

55. Singh H, Kakkar AK and Chauhan P: Repurposing minocycline for COVID-19 management: mechanisms, opportunities, and challenges. Expert Rev Anti Infect Ther 2020; 18(10): 997-1003.
56. Purwati, B, Rachman, BE, Yulistiani, M, Andang, N, Lardo S and Purnama: A Randomized, Double-Blind, Multicenter Clinical Study Comparing the Efficacy and Safety of a Drug Combination of Lopinavir/Ritonavir-Azithromycin, Lopinavir/Ritonavir-Doxycycline, and Azithromycin-Hydroxychloroquine for Patients Diagnosed with Mild to Moderate COVID-19 Infections. Biochem Res Int 2021; 2021: 6685921.
57. Huq AF, Rahman MF, Islam MA, Iqbal SA, Rahman A and Abdullah SA: Real-life Management Strategy of COVID-19 Patients in Bangladesh with No Death: An Observational and Cohort Study. Euroasian J Hepatogastroenterol 2020; 10(1): 31-35.
58. World Health Organization model list of essential medicines: 21st list 2019. World Health Organization[Internet]. 2019 [cited 2021 Aug 15]. Available from: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf
59. Wibawa T: COVID-19 vaccine research and development: ethical issues. Trop Med Int Health 2021; 26(1): 14-19.
60. WHO issues its first emergency use validation for a COVID-19 vaccine and emphasizes need for equitable global access. World Health Organization[Internet]. 2020 Dec 31 [cited 2021 Aug 10]. Available from: https://www.who.int/news/item/31-12-2020-who-issues-its-first-emergency-use-validation-for-a-covid-19-vaccine-and-emphasizes-need-for-equitable-global-access
61. Craven J: COVID-19 vaccine tracker. Regulatory Focus[Internet]. 2021 [updated 2021 Aug 23; cited 2021 Aug 23]. Available from: https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker
62. Biswas S: Covaxin: What was the rush to approve India's homegrown vaccine? BBC NEWS [Internet]. 2021 Jan 05 [cited 2021 Aug 10]. Available from: https://www.bbc.com/news/world-asia-india-55534902
63. Callaway E: Russia's fast-track coronavirus vaccine draws outrage over safety. Nature [Internet]. 2020 Aug 11 [cited 2021 Aug 10]. Available from: https://www.nature.com/articles/d41586-020-02386-2
64. Clinical Trials Registry- India [Internet]. New Delhi: ICMR National Institute of Medical. 2007 Jun 20-. Identifier CTRI/2020/08/027170, study to check the safety and immune response of a COVID-19 vaccine in healthy Indian adults; 2020 Aug 15 [cited 2021 Apr 12]; [about 6 screens]. Available from: http://ctri.nic.in/Clinicaltrials/advsearch.php
65. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT04641481, The BBV152 vaccine is being developed to prevent COVID-19, the disease resulting from Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) infection. The study is designed to primarily evaluate the efficacy, safety, and immunogenicity of BBV152 to prevent COVID-19 for up to 1 year after the second dose of BBV152. 2020 Nov 20 [cited 2021 Apr 12]; [about 10 screens]. Available from: https://clinicaltrials.gov/ct2/show/NCT04641481
66. MacDonald NE; SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: Definition, scope and determinants. Vaccine 2015; 33(34): 4161-4164.
67. Lane S, MacDonald NE, Marti M and Dumolard L: Vaccine hesitancy around the globe: Analysis of three years of WHO/UNICEF Joint Reporting Form data-2015-2017. Vaccine 2018; 36(26): 3861-3867.
68. Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ and Rabin K: A global survey of potential acceptance of a COVID-19 vaccine. Nat Med 2021; 27(2): 225-228.
69. Solís Arce JS, Warren SS, Meriggi NF, Scacco A, McMurry N and Voors M: COVID-19 vaccine acceptance and hesitancy in low- and middle-income countries. Nat Med 2021; 27(8): 1385-1394.
70. Hannah R, Edouard M, Lucas RG, Cameron A, Charlie G and Esteban OO: Coronavirus (COVID-19) Vaccinations. Our World in Data [Internet]. 2021 [updated 2021 Aug 29; cited 2021 Aug 29]. Available from: https://ourworldindata.org/covid-vaccinations
71. Padma TV: COVID vaccines to reach poorest countries in 2023 — despite recent pledges. Nature[Internet]. 2021 Jul 05 [cited 2021 Aug 30]. Available from: https://www.nature.com/articles/d41586-021-01762-w
72. Pon Vasanth BA: At least 3.94 lakh missed Covaxin 2nd dose within 6-week window. The Hindu[Internet]. 2021 Aug 17 [cited 2021 Aug 28]. Available from: https://www.thehindu.com/news/national/tamil-nadu/at-least-394-lakh-missed-covaxin-2nd-dose-within-6-week-window/article35948360.ece
73. Mohanty D: Around 13 lakh people in Odisha missed their 2nd dose of Covid vaccines. The Hindustan Times[Internet]. 2021 [updated 2021 Aug 28; cited 2021 Aug 28]. Available from: https://www.hindustantimes.com/cities/others/around-13-lakh-people-in-odisha-missed-their-2nd-dose-of-covid-vaccines-101630127494683.html
74. Anders C: 15 million people in the U.S. have missed their second dose of the coronavirus vaccine, CDC says. Health[Internet]. 2021 Jul 02 [cited 2021 Aug 28]. Available from: https://www.washingtonpost.com/health/2021/07/02/missed-second-dose-covid19-vaccine/
75. Farshi E: Cytokine Storm Response to COVID-19 Vaccinations. J Cytokine Biol. 2020;5(1000125):2.
76. Frequently Asked Questions on COVID-19 Vaccine. Ministry of Health and Family Welfare (MoHFW), Government of India [Internet]. 2020 [cited 2021 Aug 25]. Available from: https://www.mohfw.gov.in/pdf/FAQsonCOVID19VaccineDecember2020.pdf
77. AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. European Medicines Agency [Internet]. 2021 Apr 07 [cited 2021 Aug 25]. Available from: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood
78. New data show rise in hospital admissions for unvaccinated pregnant women. University of Oxford [Internet]. 2021 Jul 30 [cited 2021 Aug 25]. Available from: https://www.ox.ac.uk/news/2021-07-30-new-data-show-rise-hospital-admissions-unvaccinated-pregnant-women
79. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R and Thelwall S: Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med 2021; 385(7): 585-594.
80. The Possibility of COVID-19 after Vaccination: Breakthrough Infections. Centers for Disease Control and Prevention [Internet]. 2021 [updated 2021 Aug 23; cited 2021 Aug 25]. Available from: https://www.cdc.gov/coronavirus/2019-

ncov/vaccines/effectiveness/why-measure-effectiveness/breakthrough-cases.html

81. Vaccinate with Confidence Strategy to reinforce Confidence in COVID-19 Vaccines. Centers for Disease Control and Prevention [Internet]. 2021 Jun 03 [cited 2021 Aug 25]. Available from: https://www.cdc.gov/vaccines/covid-19/vaccinate-with-confidence.html

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