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A Critique of Recent Medical Research in JAMA on COVID-19*

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Abstract

The world community has been changed irrevocably by the highly infectious and mutating SARS-CoV-2 virus that causes the COVID-19 disease. The necessary research output on COVID-19 has been revolutionary, especially in the medical and biomedical sciences, where the search for a vaccine is essential for the world to have a semblance of normality in the era of COVID-19. Much of the advanced research has been distributed in the leading medical journals, including the *Journal of the American Medical Association (JAMA)*, where the latest medical research is distributed on a daily basis, and where comments can also be published. The purpose of this paper is to provide a critique of 110 interesting and highly topical research papers that have been published in *JAMA*, mostly within the past two months. The diverse topics include: treating influenza and COVID-19 simultaneously, dealing with a second wave of COVID-19 in Beijing, honesty is best for known and unknown GAWI and WIST, unreliability of asymptomatic COVID-19 testing outcomes for children, the effectiveness of flu vaccines, acute anxiety during COVID-19, MAID as an end of life option, longer-term effects of corticosteroids on the mortality of critically ill COVID-19 patients, isolation, loneliness and psychological distress during COVID-19, the selection of volunteers for COVID-19 vaccine trials, the mental health of children and adolescents during COVID-19, fertility preservation through hormonal intervention for transgender adolescents, safe, effective and affordable COVID-19 vaccines, essential requirements for acceptance of a COVID-19 vaccine, ischemic stroke rates from COVID-19 and influenza, mandatory COVID-19 vaccination of children, COVID-19 asymptomatic children and adults, Who Dares Wins (Qui Audet Adipiscitur), even against COVID-19, global health security index and responses to COVID-19, quality of life and dying, immunity from COVID-19, whom to trust or not to trust regarding COVID-19, the value of health care for cancer patients, previous medical research bodes well for a COVID-19 vaccine, you cannot fight COVID-19 alone, causality between hypertension and COVID-19, coffee consumption and metastatic colorectal cancer, improving statistical analysis of health policies on children and adolescents, COVID-19 does not respect anyone, politics diminishes the integrity and reputation of healthcare agencies, primary, secondary and tertiary cancers in the lung, health care should include everyone, especially for COVID-19, prioritizing access to COVID-19 vaccines, further questions about COVID-19 vaccines, estimating direct and indirect excess deaths from COVID-19, herd immunity for COVID-19, daily eyeglass

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COVID-19, COVID-19 mutations and vaccines, mandatory vaccinations against COVID-19, allergic reactions to the first dose of the Pfizer vaccine, neutralization of monoclonal antibodies for COVID-19, pricing tele dermatology during COVID-19, and SARS-CoV-2 COVID-19 are spreading virtually everywhere, transmission of SARS-CoV-2 and COVID-19 by children, addressing racial and ethnic health disparities during COVID-19, race and medical research during and after COVID-19, adherence to nonpharmaceutical interventions during COVID-19, further unanswered questions for cancer patients during COVID-19, how are children affected by COVID-19, is the California variant another COVID-19 escaped mutant?, tracking escaped mutants of SARS-CoV-2 and COVID-19, optimal timing separation and strength of prime and booster shots, confounding errors in response to COVID-19, durability and duration of approved vaccines against escaped mutants, and hospital mortality and hospice discharge of COVID-19 patients depend on population size.

Keywords: COVID-19, risk, influenza, asymptomatic, acute anxiety, corticosteroids, mortality, isolation, loneliness, psychological distress, vaccine trials, mental health, ischemic strokes, global health security index, quality of life and dying, hypertension, herd immunity, depression and suicide, science denial, conspiracy theories, masking, long haulers, reinfection, otolaryngology, herd immunity, psychological distress, sedentary behavior, cancer, cardiac arrests, fake news.

JEL: G32, H55, I12, I13, I18.

1. Introduction

The world community has been changed irrevocably by the highly infectious and mutating SARS-CoV-2 virus that causes the COVID-19 disease. The necessary research output on COVID-19 has been revolutionary, especially in the medical and biomedical sciences, where the search for a vaccine is essential for the world to have a semblance of normality in the era of COVID-19.

A substantial amount of the recent advanced research has been distributed in the leading medical journals, including the *Journal of the American Medical Association (JAMA)*, where the latest research is distributed on a daily basis, and where comments can also be published. In respect of critical evaluation of recent papers in *JAMA* on COVID-19, some of which are based on published Comments, McAleer (2020a) discusses one paper in general medicine, McAleer (2020b) evaluates 10 papers in general medicine, internal medicine, and oncology, Chang, McAleer and Wong (2020) examine 16 papers in general medicine, internal medicine and oncology, McAleer (2020c) analyses 15 papers in general medicine, internal medicine and oncology, McAleer (2020d) assesses 19 papers in general medicine, global health, healthcare, internal medicine, oncology, and pediatrics, and McAleer (2020e) evaluates 44 recent papers on general medicine, global health, oncology, internal medicine, pediatrics, geriatrics, and surgery.

In addition to medical research, Chang and McAleer (2020) estimate and evaluate alternative global health security indexes for risk analysis of COVID-19, Chang, McAleer and Ramos (2020a, b) present a charter for sustainable tourism after COVID-19, whenever that might occur, and discuss the future of tourism in the COVID-19 era, Chang, McAleer and Wong (2020) examine risk and financial management of COVID-19 in business, economics and finance, Wang, Cheng, Yue and McAleer (2020) analyse risk management of COVID-19 by universities in China, Chang, McAleer and Wang (2020) evaluate herding behaviour in energy stock markets during the global financial crisis, SARS, and COVID-19, and Magnus and McAleer (2020) discuss key issues and provide suggestions about the future of academic journals in a COVID-19 world.

As discussed in a number of research papers on COVID-19, many of these papers have been included in the World Health Organization's (2020) "WHO COVID-19 Global literature on coronavirus disease", which is intended to bring "the world's scientists and global health professionals together to accelerate the research and development process, and develop new norms

and standards to contain the spread of the coronavirus pandemic and help care for those affected.” The list currently has over one million entries.

The purpose of this paper is to supplement the previous reviews and perspectives discussed above by providing a critique of 110 interesting, informative, and highly topical research papers that have been published in *JAMA*, mostly within the past few months. The diverse topics in *JAMA* and its various specialty journals, include public health, general medicine, internal medicine, oncology, pediatrics, geriatrics, surgery, otolaryngology, neurology, psychiatry, ophthalmology, dermatology, public health, and biostatistics. *JAMA* has a specialty journal, *JAMA Cardiology*, which does not permit Comments to be submitted.

Each of the papers evaluated here is worth highlighting as they cover several highly topical medical issues in the COVID-19 era, including treating influenza and COVID-19 simultaneously, dealing with a second wave of COVID-19 in Beijing, honesty is best for known and unknown GAWI and WIST, unreliability of asymptomatic COVID-19 testing outcomes for children, the effectiveness of flu vaccines, acute anxiety during COVID-19, MAID as an end of life option, longer-term effects of corticosteroids on the mortality of critically ill COVID-19 patients, isolation, loneliness and psychological distress during COVID-19, the selection of volunteers for COVID-19 vaccine trials, the mental health of children and adolescents during COVID-19, fertility preservation through hormonal intervention for transgender adolescents, safe, effective and affordable COVID-19 vaccines, essential requirements for acceptance of a COVID-19 vaccine, ischemic stroke rates from COVID-19 and influenza, mandatory COVID-19 vaccination of children, COVID-19 asymptomatic children and adults, Who Dares Wins (Qui Audet Adipiscitur), even against COVID-19, global health security index and responses to COVID-19, quality of life and dying, immunity from COVID-19, whom to trust or not to trust regarding COVID-19, the value of health care for cancer patients, previous medical research bodes well for a COVID-19 vaccine, you cannot fight COVID-19 alone, causality between hypertension and COVID-19, coffee consumption and metastatic colorectal cancer, improving statistical analysis of health policies on children and adolescents, COVID-19 does not respect anyone, politics diminishes the integrity and reputation of healthcare agencies, primary, secondary and tertiary cancers in the lung, health care should include everyone, especially for COVID-19, prioritizing access to COVID-19 vaccines, further questions about COVID-19 vaccines, estimating direct and indirect excess deaths from COVID-19, herd immunity for COVID-19, daily eyeglass wear and COVID-19 infection,

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2. Treating Influenza and COVID-19 Simultaneously

The world listens when the US CDC (see Grohskopf, Liburd and Redfield, 2020) speaks, especially on influenza and COVID-19 as the flu season approaches.

Prioritizing vaccination against flu should increase protection for the population in the face of COVID-19 that does not seem to respect seasonal changes across different continents.

Important issues for interventionist healthcare policy for all gender, age, race, ethnic, and medically, physically, psychologically, economically, and financially disadvantaged cohorts in the population, might be to determine if:

- (1) flu precedes or follows COVID-19;
- (2) treatment for flu and COVID-19 simultaneously is feasible;
- (3) reinfection of flu and COVID-19 can occur contemporaneously;
- (4) sequential reinfection is possible;
- (5) the order can be determined if sequential reinfection occurs;
- (6) the duration between initial and repeat infection can be determined;
- (7) COVID-19 treatment is affected by flu;
- (8) vaccination against flu is affected by COVID-19.

The problematic issues are likely to be exacerbated with the onset of stress, anxiety, and mental illness arising from social distancing, self isolation, quarantining, and lockdowns.

3. Dealing with a Second Wave of COVID-19 in Beijing, China

In Wu et al. (2020), the clear explanation of the dynamic development of a second wave of COVID-19 in an agricultural wholesale market in Beijing from 11 June - 10 July 2020 provides helpful information, advice and a warning to every country that is experiencing a wave of whatever order after purported abatement, to prepare and plan public health policy in anticipation of a shock that is likely to occur.

For purposes of interpretation, a preliminary case study involving 33 asymptomatic positive infections were not recorded as part of the 335 confirmed cases until 5 July 2020, with no informed consent, but with immediate and aggressive contact tracing, self isolation, and quarantining.

In a stark warning to act quickly with a prepared plan of attack, the public health intervention led to a duration of 7 days from early symptom onset to confirmed case and outbreak alert, with rapid community containment imposed within 24 hours.

Further studies in dealing with second and subsequent waves would make the results of the present study more robust and widely applicable.

As the second wave was flattened quickly, a rapid response with strict isolation measures should be a cornerstone of public healthcare policy for any COVID-19 wave that might be churning.

4. Honesty Is Best for Known and Unknown GAWI and WIST

The honest and sensitive declaration by a caring pediatrician (Borowsky, 2020) on known and unknown “Got Away With It (GAWI)” and “Will I Sleep Tonight” (WIST) outcomes reflect on the issue that honesty is always the best policy for the physician and their patient.

In many countries, physicians will not always inform their patients of serious diagnoses that affect morbidity and mortality in order to “spare the patient unnecessary stress and anxiety”, which is a denial of informed consent.

GAWI might, in fact, be “Got Away With It Somehow” (GAWIS), but maybe only this time? If only all physicians could be so humble and compassionate.

5. Unreliability of Asymptomatic COVID-19 Testing Outcomes for Children

The analysis by a team of medical researchers (Sola et al., 2020) investigating the reliability of asymptomatic COVID-19 testing outcomes for children bears careful scrutiny because of the indicative prevalence of infection in children without symptoms that can have a significant effect on infection control policy.

The data and statistical analysis suggest that there is a strong correlation between disease prevalence in asymptomatic children and the weekly general incidence of COVID-19 in the population.

The estimated linear regression models in Figures 2A and 2B seem, at first glance, to support the inferences that are drawn, though the lack of statistical diagnostic checks raises serious questions relating to the robustness of the empirical analysis.

The estimated model in Figure 2A shows the linear relationship between prevalence and general incidence.

Two obvious outliers in the top and centre right in Figure 2A lead to a downward bias in the estimated linear model, with a concomitant flatter relationship between prevalence and general incidence.

Judicious removal of the two outliers would show a steeper and stronger relationship between the two variables.

The impact of outliers is even more pronounced in Figure 2B, where only one observation lies above the estimated linear regression, with 3 observations sitting on the estimated line, and 7 below, which indicates that the estimated model cannot possibly be the line of best fit.

Furthermore, deletion of the two outliers on the right would make the estimated line much steeper, but without going through the origin, which is logically problematic.

As the detailed study suggests, there is undoubtedly a strong correlation between disease prevalence in asymptomatic children and the weekly incidence of COVID-19 in the general population, with greater scrutiny of the data and alternative estimated models adding greater strength, reliability, and robustness to the important investigation.

6. How Effective Are Flu Vaccines?

The informative message about flu vaccines by Walter (2020) bears careful attention by medical practitioners and patients alike.

In addition to asthma sufferers, who are designated as high risk potential recipients of the flu shot, and how closely monitored are they in a clinic, hospital, or at home?

What are the major causes of suppressed immune systems and chronic medical conditions?

What are the potential morbidity and mortality side effects when a live attenuated vaccines are given to children aged 2-17 years and to adults aged 18-49 years, both with suppressed immune systems, and how does inactivated vaccines and recombinant vaccines are given to adults, presumably without suppressed immune systems?

What are the likely effects of flu vaccines on asymptomatic COVID-19 patients, and those who have purportedly recovered from the first bout of the disease?

Potentially catastrophic?

7. Acute Anxiety During COVID-19

As discussed in Ayers et al. (2020), stress and anxiety are clear indicators of mental distress due to the possibility of infection, seeing close relatives and friends infected, the likelihood of becoming unemployed with or without medical and employment insurance, and lack of social connections and cohesion through social distancing, self isolation, quarantining, and lockdowns.

The informative and helpful empirical analysis was conducted using US data from 13 March to 9 May 2020.

Recent research for the USA and UK through to August 2020 shows that stress, acute anxiety, mental distress, mental illness, and self harm, all of which are keywords in any internet search, are continuing to grow across all age cohorts, especially among the young, and young women, as the COVID-19 pandemic shows little indication of abatement.

8. MAID as an End of Life Option

The sensitive message from a caring neurologist (Kluger, 2020) on medical aid in living is reminiscent of the final words of *The Last Samurai*, where the Emperor Meiji asks Nathan Algren about the warrior Katsumoto: "Tell me how he died", to which the response is: "I will tell you how he lived".

The medical aid-in-dying (MAID) law enables terminally ill patients with a prognosis of six months or less to request medication to voluntarily end their lives as an end of life option.

Some terminal illnesses may provide clear indications of longevity, but others might be more opaque about the expected time to the end of life.

How accurate is the prognosis of six months for all illnesses and all patients, especially regarding the possible feedback effect of admission to a MAID program on the prognosis?

9. Longer-Term Effects of Corticosteroids on Mortality of Critical COVID-19 Patients

A striking finding in the important meta-analysis of clinical trials of systemic corticosteroids for critically ill COVID-19 patients, compared with usual care or placebo as the conditioning set, was associated with lower 28-day all-cause mortality.

Mortality and serious adverse effects of the corticosteroids were mentioned, but the latter was not explained critically as the definitions differed across the clinical trials.

As five of the seven randomized trials reported shorter-term mortality at 28 days, this time frame was chosen arbitrarily as the primary outcome.

There are many questions that can be directed to the empirical findings of meta-analyses, with the following issues of paramount importance to the health care policies, treatment and outcomes of critically ill patients infected with COVID-19:

- (1) examining different age (median 60 years) and gender (29% women) cohorts;
- (2) using surveys of random trials that are representative of socio-economic, race and ethnicity, geographic, and environmental considerations;
- (3) analysing longer-term mortality beyond 28 days for post-discharge patients;
- (4) analysing longer-term mortality beyond 28 days for different age and gender cohorts;
- (5) explaining the more serious adverse effects, in addition to secondary infections and sepsis, across different intervention groups;

- (6) evaluating the potential corticosteroid-induced complications based on consistent definitions and methods of assessment for the clinical trials;
- (7) expanding the numbers of patients with serious adverse effects in each clinical trial;
- (8) extending the clinical trials data set for future meta-analyses beyond June 9, 2020;
- (9) performing follow-up analyses on all seven clinical trials for post-discharge patients;
- (10) preparing and analysing surveys of random trials that are representative of socio-economic, race and ethnicity, geographic, and environmental considerations.

Findings from future clinical trials and associated meta-analyses would add strength and robustness to the significant findings of the novel meta-analysis investigated by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group (2020).

10. Isolation, Loneliness and Psychological Distress During COVID-19

The invaluable and sensitive research letter by McGinty, Presskreischer, Han and Barry (2020) on psychological distress and loneliness will strike a touching chord with everyone who has experienced such symptoms, or knows someone who has, especially during the COVID-19 pandemic which shows little sign of abatement.

The important findings based on a comparison of national data from 2018 and an independent representative national survey in April 2020 for respondents aged 18 years or older would be enhanced considerably with further surveys and clinical analysis according to:

- (1) updating the findings from the early days of the pandemic in April 2020 through to August 2020;
- (2) expanding the analysis to include elementary school children and high school students;
- (3) using gradations of psychological distress from serious to medium and mild, together with degrees of loneliness, isolation, social distancing, quarantining, and lockdowns;
- (4) conditioning on a wider set of control variables, including race, ethnicity, and varying degrees of income and employment disparities;
- (5) including non-healthcare essential services providers who are faced with a higher likelihood of contracting the disease in the workplace;

- (6) conducting separate surveys for front line healthcare workers, who are known to suffer from both COVID-19 and acute mental health issues, ranging from medium through to extremely serious cases of morbidity and mortality.

It is not surprising that the symptoms of psychological distress and loneliness are greater in 2020 than in 2018, but this disparity will have increased substantially as the pandemic continues to grow exponentially rather than flattening.

11. Who Should be Selected as Volunteers for COVID-19 Vaccine Trials?

The insightful perspective by Jaclevic (2020) regarding the selection of recruits for COVID-19 vaccine clinical trials highlights key elements in convincing individuals that their safety can be guaranteed when they volunteer to be tested.

The temporary suspension on 9/9 of the Oxford University - AstraZeneca COVID-19 clinical trials due to an adverse reaction in a single patient emphasizes the need for care and caution, and the implementation of the most rigorous scientific safety standards in testing the efficacy of any proposed vaccines.

The enthusiasm of warp speed testing of clinical trials needs to be tempered with scientific wariness for all individuals, regardless of the severe and diverse imbalance in terms of the socioeconomic, geographic, gender, age, race, ethnicity, and income disparities of the members of minority communities who might be most heavily affected by the disease.

12. Mental Health of Children and Adolescents During COVID-19

There have been substantial anecdotal evidence and empirical studies regarding the greater stress, anxiety, mental illness, self harm, and worse, faced by various cohorts in the population, with an emphasis on gender issues and young adults, who are suffering from social distancing, self isolation, quarantining, and lock downs.

The fatigue associated with the temporary, though sustained, pressure on social relationships is a constant reminder of the mental strain that the COVID-19 pandemic is inflicting on all sectors of modern society.

The viewpoint by public health care experts Golberstein, Wen and Miller (2020) on the mental health of children and adolescents is a welcome and significant contribution, though data are not as widely or readily available as for young adults and older age cohorts, especially according to household income disparities.

The young in society have longer life expectancy, but this also results in a longer life with lingering mental health illnesses if such issues are not resolved at a tender age.

School closures have inflicted extreme social disruption on the young when learning with and from their peers is needed the most.

Extensive surveys on mental illness are required which, in many countries, are undertaken with adults in mind, albeit young adults and older age cohorts.

Domestic violence faced by the young is also frequently exacerbated during extended lockdowns when mental health care is required by all members of households.

If left untreated, the long term effects of mental illness, especially as an existing condition, may be as severe for children and adolescents as the unknown long term morbidities associated with the cause of the pandemic.

13. Preserving Fertility for Transgender Adolescents

The research in Pang et al. (2020) on fertility preservation through hormonal intervention for transgender adolescents 18 years or younger suggests that a significant proportion is in favour of the treatment.

What proportion of the sample was either intending to take or were undergoing sexual reassignment surgery or gender confirmation surgery?

Is fertility preservation reversible after prolonged hormonal intervention?

14. Safe, Effective and Affordable COVID-19 Vaccines

Any vaccine must be safe and effective and, in addition, should be affordable.

The first two essential requirements are based on medical science and extensive clinical trials that are not based on warp speed.

A key word is missing from an otherwise excellent Viewpoint in Persad, Peek and Emanuel (2020), namely “affordability”.

Ethical and equity considerations may be important in theory, but affordability is based on economics.

In some countries, national and state governments might be willing to subsidise the cost of vaccination, whereas in others it will be the user who pays.

In short, who is willing and able to pay the cost of safe and effective vaccines for COVID-19? Only time will tell.

15. Essential Requirements for Acceptance of a COVID-19 Vaccine

Bauchner, Malani and Sharfstein (2020) present an informative editorial on reassuring the public and clinical community about the scientific review and approval of a COVID-19 vaccine.

What seems to be missing about attracting support and acceptance are the essential requirements for a COVID-19 vaccine to be accepted by any community, namely safety, effectiveness, availability, affordability, and trust in the science of medical health experts regarding widespread vaccination.

Nothing else matters.

16. Ischemic Stroke Rates from COVID-19 and Influenza

The comprehensive investigation by expert neurologists in Merkler, Parikh, Mir et al. (2020), found that the likelihood of ischemic stroke was higher with COVID-19 infection than influenza infection.

Control, conditioning and adjustment factors included demographic variables (such as age, gender, race), and a variety of vascular risk factors, viral symptomatology, and intensive care unit admission.

The critical analysis did not seem to analyse the effects of:

- (1) simultaneous infection with COVID-19 and influenza;
- (2) duration of infections with COVID-19 and influenza;

- (3) one or more comorbidities, including mental illness;
- (4) younger cohorts of patients infected with COVID-19 and influenza;
- (5) geographic dispersion of COVID-19 and influenza across states and cities.

The significant findings suggest that healthcare policy should accommodate time-sensitive interventions to reduce the burden of long-term disability.

17. Mandatory COVID-19 Vaccination of Children

The questioning and challenging Viewpoint by expert pediatricians in Opel, Diekema and Ross (2020) is essential reading for parents, healthcare workers, and education and public policy authorities.

The existence of safe, effective, available, and affordable vaccines is moving inexorably from theory to practice, and is an issue that confronts every individual, not just children.

With the politicization of COVID-19 and the numerous vaccines that are in preparation, together with the questioning of trust in medical science and in leading administration officials at the national, state, and municipal levels, mandatory vaccinations will be fraught with civil unrest.

It is clear that COVID-19 is far more serious than the seasonal flu, in both the short and long run, and societal attitudes regarding vaccines for COVID-19 are correspondingly more strident

With the opening of schools, there will be more evidence as to how quickly children can spread the disease to their families and other members of society.

Parental attitudes cannot be ignored in considering mandatory vaccination of children, especially as the long hauler effects, including mental illness, after contracting and supposedly recovering from the disease, are not well established.

18. COVID-19 Asymptomatic Children and Adults

The percentage of individuals in society who are asymptomatic carriers of COVID-19 is important for efficient healthcare policy in monitoring and management the disease.

A significant finding in et al. (2020) is that children are not at higher risk than adults of asymptotically carrying the SARS-CoV-2 virus that causes COVID-19.

A threshold of 18 years is used to distinguish between children and adults, though the median ages of 5.3 and 77 years , respectively, tend to bias the results toward old-age adults who are more likely to be sensitive to the disease.

The significant findings would be further strengthened in future studies using more recent data with the addition of:

- (1) cohorts of adults for 18+ years with different median ages;
- (2) cohorts of children for 18- years with different median ages;
- (3) percentages of children and adults with comorbidities;
- (4) non-hospitalized children and adults;
- (5) accommodating geographic boundaries, racial and ethnic backgrounds, and socioeconomic and income disparities.

19. Who Dares Wins (Qui Audet Adipiscitur), Even Against COVID-19

Legal professionals use laws to govern behaviour, economists rely on the price mechanism, and medical and healthcare practitioners use clinical and empirical evidence.

As discussed in Gostin, Hodge Jr and Levin (2020), interventions are essential to modify and change behaviour, as in the case of the declining life expectancy in the USA and elsewhere.

The situation may well be magnified in a world that is presently being exacerbated by the COVID-19 pandemic.

The War on Drugs is being won by drugs, with similar sad outcomes for the War on Anything, including Sickness, Poverty, Ignorance, Human Trafficking, Domestic Violence, Child Abuse, and Reduced Life Expectancy, among many sad maladies that do not reflect well on society.

The War on COVID-19 will eventually be won by the combined global efforts of innovative medical researchers.

Lawyers will then determine regulations about discovery, ownership, patents, and legal liability, while economists will prognosticate about the prices of vaccines, and medical and health insurance premiums.

20. Global Health Security Index and Responses to COVID-19

There is no doubt that the USA has performed rather poorly in dealing with the COVID-19 pandemic (see Nuzzo, Bell and Cameron, 2020).

Although the USA was the highest ranked country in 5 of the 6 categories in the Global Health Security Index, it was ranked 19 in terms of the “Risk Environment: Overall risk environment and country vulnerability to biological threats”, a category in which Liechtenstein was ranked number 1, despite being ranked 71 overall (Chang and McAleer, 2020).

It is worth mentioning that, ignoring nations with small populations, Taiwan with a population of just under 24 million (2018 estimate) has been the most successful country in terms of dealing with COVID-19, with 509 total cases and 7 deaths (<https://www.worldometers.info/coronavirus/>).

It is also worth mentioning that Taiwan was not included in the Global Health Security Index.

21. Quality of Life and Dying

Further to the interesting perspective of Tang and Bruera (2020), the quality of life is important and essential for every individual, regardless of their health status.

Anyone who is approaching the end of their life wants to be surrounded by those who will miss them the most.

Dying at home is preferred by many terminally-ill patients, but when to move from a hospital to their home or to a hospice depends on just how close they are to the end.

22. Immunity from COVID-19?

Vaccine or no vaccine, immunity from COVID-19 in whatever form is the end game in the battle against COVID-19, so the Viewpoint from medical specialists (Stephens and McElrath, 2020) is encouraging in understanding and predicting the duration of protection.

Adaptive immunity within the first 7 to 10 days of infection would seem to be useful if the precise timing and degree of severity of infection were possible.

Virus neutralizing antibodies may be a viable path to immunity, but can the duration of protection be predicted with accuracy?

Key issues to consider in existing clinical trials to strengthen the important findings on establishing immunity from COVID-19 would be to consider the effects of :

- (1) precise timing and degree of severity of infection;
- (2) existing comorbidities, including COVID-19;
- (3) severely weakened immune systems, including cancer patients undergoing chemo and radio therapies;
- (4) differences in age, gender, and ethnicity;
- (5) duration and severity of COVID-19 infection;
- (6) duration of protection from COVID-19 infection;
- (7) duration since presumed recovery from COVID-19;
- (8) reinfection of COVID-19;
- (9) interaction with seasonal influenza;
- (10) half life of neutralizing antibodies.

Predicting the degree of immunity from COVID-19 might be as useful as determining whether sterilizing immunity exists.

23. To Trust or Not to Trust Regarding COVID-19

When leading healthcare agencies, including the US Centers for Disease Control and Prevention (CDC), are seemingly compromised after coming under immense political pressure, scientists need to step up.

This is where the Societal Experts Action Network (SEAN) (see Abbasi, 2020) is set to become a leading source of scientific and medical advice in dealing with the COVID-19 pandemic.

24. Value of Health Care for Cancer Patients

Further to the interesting viewpoint by Dietz and Pronovost (2020, cancer patients are concerned about their quality of life, as well as the quality, availability, and affordability of medical treatment.

Nothing else matters for cancer patients.

25. Previous Medical Research Bodes Well for a COVID-19 Vaccine

Excellence in medical research on viruses, and prevention of associated diseases through the discovery of safe, effective, affordable and available vaccines has been a hallmark of previous recipients of the Lasker Award.

The COVID-9 pandemic might have disrupted the award of a 2020 Lasker (see Goldstein, 2020), but this will also be associated with greater research intensity in the search for a workable vaccine, possibly at warp speed.

26. You Cannot Fight COVID-19 Alone

The personal and reflective perspective by Tisch (2020) regarding a panic attack highlights the issues of stress, anxiety, and mental illness associated with the COVID-19 pandemic.

COVID-19 has brought into sharp focus a number of long-term issues, including purportedly recovered long-haul patients whose ongoing or likely future diagnoses include mental health issues, Parkinson's disease symptoms, and chronic tiredness.

As COVID-19 is new and developing coronavirus, there are many unknowns that have not yet been transformed into knowns through recent factual experience.

Extrapolating from previous coronaviruses and pandemics can do little without facts, but anecdotal evidence suggests that long haulers might eventually experience chronic fatigue syndrome.

27. Causality Between Hypertension and COVID-19

It is disconcerting though not surprising that obesity and hypertension increase risks associated with COVID-19, regardless of age (see Katz, 2020a).

Hypertension as an existing condition may increase the risk of contracting COVID-19 and experiencing the more severe symptoms of the disease.

As social distancing, self isolation, quarantine, and lockdowns lead to increased stress, anxiety, and even more serious mental health issues, regardless of age, it would be useful to determine whether COVID-19 increases hypertension in a vicious and repeating cycle.

28. Coffee Consumption and Metastatic Colorectal Cancer

As in many things in life, there are costs and benefits to one's health in partaking in any food or beverage, especially when they involve stimulating compounds.

Although coffee consumption is often associated with chronic disease risk factors, it may also be associated with reduced risk of disease progression and death because of beneficial compounds.

In addition to the invaluable issues considered by Mackintosh, Yuan, Ou et al. (2020), the association of coffee consumption with metastatic colorectal cancer might also be evaluated in terms of:

- (1) extending the data set beyond the end-point of 18 January 2018;
- (2) the duration and cumulative effects over time of coffee drinking;
- (3) the benefits of coffee consumption on relaxation and improved mental health;
- (4) alternative drinks with caffeine, including tea, chocolate and energy drinks.

29. Improving Statistical Analysis of Health Policies on Children and Adolescents

Effective health policy for children and adolescents, as well as patients in all age cohorts, depends on rigorous scientific clinical trials, factually based evidence, accurate empirical analysis, and close collaboration between investigators and statisticians, which are presented in the excellent viewpoint by expert pediatricians and statisticians.

It is important to model the effects of healthcare policy arising from announcements versus implementation of public policy decisions, especially when the timing duration might be lengthy.

The critical analysis of estimated models in the invaluable presentation by French and Stuart (2020), concentrated on marijuana use by adolescents.

The analysis would be strengthened by considering some of the following extensions regarding empirical public policy analysis for a broader range of cohorts:

- (1) panel data with fixed or random effects versus time series analysis;
- (2) dynamic models, including dynamic panel data, versus static models;
- (3) single equation versus multivariate models;
- (4) event study analysis, which evaluates the impact of significant policy announcements;
- (5) modelling structural change arising from public policy announcements;
- (6) modelling levels and higher moments of the distribution;
- (7) evaluating appropriate conditioning factors;
- (8) diagnostic checks of the underlying assumptions;
- (9) tests of model functional form misspecification;
- (10) tests of possible outliers and extreme observations;
- (11) tests of directional causality;
- (12) generating accurate forecasts and predictions.

30. COVID-19 Does Not Respect Anyone

Stephenson (2020) states that the informative findings of the US Centers for Disease Control and Prevention (CDC) that young children in care centers can spread COVID-19 is further evidence that the disease does not respect anyone or anything.

Eternal vigilance is essential as COVID-19 can and does strike when it is unexpected, and when it is not.

Respecting COVID-9 does not mean that the respect will be returned, because it will not be.

31. Politics Diminishes the Integrity and Reputation of Healthcare Agencies

International politics diminished the reputation of the World Health Organization, especially its mishandling of the COVID-19 pandemic.

Shah and Forman 92020) argue that domestic politics is affecting the independence of the US CDC, and its integrity and reputation to dispense the best scientific healthcare advice, including how best to deal with COVID-19.

Critical assessments of healthcare advice should be based on provable facts and remain independent of politics.

32. Primary, Secondary and Tertiary Cancers in the Lung

The novel and informative research findings by Elkrief, Kazandjian and Bouganim (2020) on treatment of lung cancer during the COVID-19 pandemic is beneficial to specialists and patients.

The focus is on lung cancer patients without COVID-19 during the period 26 April 26 to 19 May 2020, because lung cancer has high mortality rates from COVID-19 as a serious pre-existing condition.

The exclusion of 14 of a total of 289 patients “owing to the presence of other tumor histology” presumably refers to non-lung cancer that has secondaried or tertiaried to the lungs, such as from the colon or liver.

It would be beneficial to examine if cancer in the lungs leads to different cancer treatments and outcomes as there are many cancer patients who have experienced transition from the original source to the lungs, which would qualify as advanced or extensive, especially as cancer patients might have experienced extended duration of chemo, radio and palliative care therapies since the original diagnoses.

33. Health Care Should Include Everyone, Especially For COVID-19

The incisive and challenging editorial by Miller and Mukherjee (2020) on healthcare rights for all, regardless of undocumented immigrant status, asylum seekers, refugees, age, gender, socioeconomic status, race, ethnicity, politics, religion, geography, incarceration, or for any other reason, was most welcome when it was published toward the end of 2019.

Such a morally and legally supportive is even more important now in the new normal world of COVID-19, where reductions in national income, employment opportunities, increasing medical

and insurance costs, and access to quality healthcare, and restrictions on migration, among others, are being felt around the globe.

Prognostications one-year ahead can be dramatically and directionally incorrect, especially when a Presidential Election is fast approaching, with unexpected daily shocks becoming regular and unpredictable events.

Deaths of children in custody reflects on the society that enables it, though what is almost as heinous is having children incarcerated at all, with the attendant human misery, stress, anxiety, self harm, and worse.

Access to healthcare in a country as wealthy as the USA should be a right for all, especially when human lives are at stake.

34. Prioritizing Access to COVID-19 Vaccines

As presented in the balanced and Viewpoint by Schmidt, Gostin and Williams (2020), legal and ethical issues abound in distributing a safe, effective and affordable vaccine to protect individuals against COVID-19.

Primary healthcare workers and severely ill patients would likely be at the head of the queue, after which important legal and ethical issues have to be accommodated in prioritizing the allocation of limited quantities of vaccines.

Racial and ethnic minorities need to be supported in access to healthcare, though this involves a strategy that favours individuals and groups in society while postponing treatment of others.

Economists tend to favour the price mechanism for optimal allocation of scarce resources, but vaccines are not a typical product for sale at market prices.

Allocation of scarce resources requires important choices to be made, which depend on non-price mechanisms that include legal and ethical prioritization.

35. Further Questions About COVID-19 Vaccines

The instructive and informative Viewpoint by Goodman, Grabenstein and Braun (2020) regarding answerable questions about COVID-19 vaccines is welcome for everyone, especially

non-specialists who seek reassurance from specialists about the discovery of a safe and effective vaccine.

Further questions that deserve attention include:

- (1) Can a 50% success rate, or even an asymmetric confidence interval with endpoints (30%, 80%) in reducing the risk of COVID-19 and its complications be regarded as effective?
- (2) Why are children and pregnant women omitted from clinical trials at any stage when they will eventually require vaccination?
- (3) What is the likelihood of severe reactions to a COVID-19 vaccine by different age cohorts, gender, race, ethnicity, and socioeconomic circumstances?
- (4) What is the duration of effectiveness of a COVID-19 vaccine, on average, as well as for different age cohorts, gender, race, ethnicity, and socioeconomic circumstances?
- (5) If different vaccines are based on different clinical trials and patients, how should they be compared in terms of relative safety and efficacy?
- (6) Does a vaccine eliminate the virus and disease, the symptoms, or both?
- (7) What is the likelihood of recurrence of COVID-19 for a vaccinated patient?
- (8) Should testing for COVID-19 continue after vaccination and, if so, for what duration?
- (9) Can a patient become infected after the first dose of a 2-dose regimen?
- (10) Will a vaccine likely be safe and effective for any mutations of the SARS-CoV-2 virus?

36. Estimating Direct and Indirect Excess Deaths from COVID-19

The detailed statistical analysis by Woolf, Chapman, Sabo et al. (2020) of excess deaths from COVID-19 and other causes leads to questions for which answers might be discernible from the data set used in the empirical analysis.

As the pandemic has traversed the northern hemisphere's late-winter, spring and summer months, and is now heading from early-fall into winter, is it possible to:

- (1) decompose excess deaths into those directly and indirectly associated with community spread of COVID-19;

- (2) estimate the number of lives that were saved because of self isolation, quarantining, lockdowns, and substantially reduced domestic travel by motor vehicles?
- (3) calculate the direct and indirect excess deaths according to the season;
- (4) compare excess deaths directly and indirectly from COVID-19 with changes in seasonal influenza?

37. Herd Immunity for COVID-19

The informative and insightful analyses by Omer, Yildirim and Forman (2020) and Desai and Majumder (2020) on vaccine-induced herd immunity is a welcome and reassuring indicator of how society might be protected against the COVID-19 pandemic.

The eradication of smallpox is frequently cited as a vaccination success, but the prevalence of seasonal flu makes it clear that safe and effective vaccines are not a panacea.

The figure on "Herd Immunity Thresholds by Disease" lists 5 thresholds that are greater than for the SARS-CoV-2 virus, but the most recent is from the SARS epidemic of 2002-2003 that has seemingly disappeared.

The herd immunity threshold argument depends on a proportion of individuals in the population who have acquired immunity, which depends on a wide range of assumed factors, including:

- (1) genuine immunity for individuals in the herd, which is difficult to assess;
- (2) estimation of the herd immunity threshold, which is a point estimate that requires confidence intervals for any meaningful analysis;
- (3) estimation of the effective reproduction number, which is also a point estimate;
- (4) estimation of the dynamic process underlying the effective reproduction number, which involves a series of point estimates;
- (5) the duration of immunity through vaccination, which is also a point estimate;
- (6) the key model assumption that “all individuals are equally susceptible and equally infectious”, which is questionable;

- (7) another important assumption regarding “random mixing between individuals in a population”, namely the effect of heterogeneity in social mixing on herd immunity, which is problematic;
- (8) the possibility of “cross-reactivity with other coronaviruses”, for which there is presently no empirical evidence;
- (9) the likely effectiveness of any vaccine in the presence of a mutating SARS-CoV-2 virus;
- (10) the practical effectiveness of acquiring herd immunity in an internationalized world community.

38. Daily Eyeglass Wear and COVID-19 Infection

The interesting and novel report by Zeng, Wang, Li et al. (2020), suggests that daily wearers of eyeglasses for more than 8 hours may be less likely to be infected with COVID-19, based on 276 patients in Suizhou, Hubei province, China, for the period 27 January to 13 March 2020.

Droplets near the eyes are viewed as an important route of infection, which is a prescient observation based on data that ended in mid-March 2020.

Comprehensive discussions since the end of the sample data in the study of the transmission of COVID-19 by droplets and, more worryingly, by lighter evaporating aerosols, are given in Klompas, Baker and Rhee (2020) and Jayaweera, Perera, Gunawardana and Manatunge (2020).

The wearing of eyeglasses may have a noticeable effect on the spread of COVID-19 against droplets, as shown in the report.

However, as the SARS-CoV-2 virus can be carried by aerosols that remain suspended in the air and are carried by currents, medical masks, face shields, social distancing, the wearing of eyeglasses might not provide adequate protection against infection in the COVID-19 pandemic, especially as second or possibly third waves are hitting much of Europe and the USA as the northern hemisphere moves towards winter.

39. Use Anything That Prevents the Spread of COVID-19

The helpful and informative expert advice provided by Lerner, Folkers and Fauci (2020) at the National Institute of Allergy and Infectious Diseases regarding prevention of the spread of the

virus that causes COVID-19 using anything, including "low tech" interventions, should be heeded by everyone everywhere, irrespective of the economic and financial status of society

The timeliness of the warning is apropos, given the second or even third waves that are swamping many countries that might have become complacent against a pandemic that seems to be accelerating.

Such prescient advice is crucial in the absence of a safe, effective, affordable, and societal-embraced vaccine, and is likely to remain so for some time to come in many international communities that have less than ideal and affordable medical facilities and healthcare.

The universal wearing of masks both inside and outside the family home and any other buildings is standard in many countries, even when it is not mandated.

Social distancing and regular washing of hands are low tech and achievable strategies which, together with frequent testing and contact tracing, can significantly limit the spread of the infectious disease that can easily be transmitted through droplets and aerosols.

One does not need to be a medical expert to realize that the wearing of masks should be mandated everywhere.

40. Deferral of Care for Serious Non-COVID-19 Conditions

Further to the cautious warning in the editorial by DeJong, Katz and Covinsky (2020), the research letter by DeJong, Katz and Covinsky (2020) on the observed significant deferral of care patterns, as evidenced in non-COVID-19 hospitalizations for chronic disease and acute conditions in 4 hospitals in the NYU Langone Health system from 1 March 1 to 9 May for each of the years 2018, 2019, and 2020, is givend by one or more of the following seven alternative explanations:

- (1) lost health insurance;
- (2) increased threshold for hospitalization by clinicians;
- (3) changes in patient lifestyle;
- (4) self-management in the context of social distancing;
- (5) prior overuse of hospitalization;
- (6) improved self-management;
- (7) imperfect capture of COVID-19 and other diagnoses.

Additional reasons include:

- (8) lack of trust in the healthcare system with the onset of COVID-19;
- (9) negative social media pronouncements regarding hospitalization and surgery;
- (10) decreased threshold for hospitalization by patients;
- (11) increased health insurance costs;
- (12) changes in coverage for pre-existing conditions.

Disentangling the alternative explanations would assist hospitalization and healthcare policy regarding the effect of COVID-19 on the best possible treatment of chronically ill non-COVID-19 patients.

41. Society's United Fight Against Depression and Suicide

As highlighted in Gallagher and Taylor (2020), the medical community has a key role and shared burden in dealing with depression and suicide in the military, which seem to be common denominators in both dignified professions.

The recognition by the community that such thoughts and acts by patients in the military and medical professions need a united response are also paramount to the gatekeeper's role as a shared burden.

Society needs to appreciate, respect, and accept the stress that is associated with military action, especially in terms of entering, after a life of service, the broader community that has little understanding of the pressures and primary threats that are faced in serving their country, especially when their lives are threatened on a daily basis.

42. The Positive Outcomes in Delaying Low-Risk Thyroid Cancer Treatment During COVID-19

The intriguing viewpoint by surgeons and medical experts in Nickel, Glover and Miller (2020) critically analyses the key issues associated with delays in the treatment of low-risk thyroid cancer treatment during COVID-19, and what might be assimilated.

In addition to the detailed examples of potential critical research questions given in the viewpoint, the following queries might also be considered as to what might be learned and gained from delaying treatment:

- (1) What is the definition of low-risk thyroid cancer?
- (2) Is the level of risk similar across different types of cancer?
- (3) What is the degree of over-diagnosis of small, low-risk papillary thyroid cancers?
- (4) For what duration might a low-risk cancer treatment be delayed before it changes to a higher level of risk?
- (5) Is thyroid cancer a primary or secondary cancer?
- (6) Have alternative diagnostic treatments for thyroid cancer, such as active surveillance, also been delayed?
- (7) How is psychological harm to patients determined as a result of delayed treatment?
- (8) What information have patients received from their endocrinologist to regard immediate surgery as essential for low-risk thyroid cancer?
- (9) Why have not all thyroid clinical specialists received training in active surveillance management for patients with low-risk thyroid cancer?
- (10) How might delayed treatment affect healthcare and medical insurance premiums after an extended duration that might lead to the assessment that low-risk thyroid cancer is a preexisting condition?

43. The Likely Future Toll from COVID-19

The detailed and encompassing editorial by Fineberg (2020) on the toll of COVID-19 begs the question as to the likely future toll arising from COVID-19.

General acceptance and understanding of social measures include the wearing of masks and possibly specialist eyeglasses, hand hygiene, social distancing, self isolation, quarantining, and lockdowns.

When a safe, effective, affordable, and widely available vaccine is discovered, protection against the spread of the disease will be mitigated, though not eliminated.

As of 6 November 2020, there were almost 50 million COVID-19 cases worldwide, and almost 10 million in the USA, with over 1.245 million and 241,100 deaths worldwide and in the USA, respectively.

The fact that the USA comprises approximately 20% of both cases and deaths is an alarming statistic.

With respect, including all pneumonia deaths together with influenza and COVID-19 deaths leads to a numerical measure that is speculative, at best, as is stated in the editorial.

Pre-existing conditions, reduced immunity through a range of illnesses, age, socio-economic condition, gender, race, and ethnicity are likely to increase the future toll from COVID-19, especially if there is an extended period until a vaccine can be made widely available.

Fake news on social media and academic social media can lead to criticism of medical science, and science in general, which makes it difficult for even (non-medically) educated members of society to separate the wheat from the chaff.

What is important for public policy considerations is to distinguish between the empirical correlations among the numbers of cases and deaths from both COVID-19 and the seasonal flu, especially whether it is positive or negative.

Mental healthcare is also likely to be accorded high priority, especially in the medical healthcare and military professions.

What is beyond likely, and almost certain, are the continuing waves of the disease across the globe.

44. Excluding Older Persons From Vaccine and Clinical Trials for COVID-19

The research provided by experts from a wide range of medical disciplines in Helfand, Webb, Gartaganis et al. (2020), on the exclusion of older persons from vaccine and clinical trials for COVID-19 begs the question as to whether such practice is intended, necessary, and efficacious.

It is well known that persons older than 65 years of age are highly susceptible to contracting the disease, and dying from it even more so, though they do not figure highly in terms of the problematic herd immunity requirement of at least 65% of the population.

A high proportion of vaccine and clinical trials exhibits high risk for excluding older adults, specifically 50% of COVID-19 clinical trials and 100% of vaccine trials, thereby restricting relevance and inclusion to detect safety and effectiveness against adverse effects.

Including older persons in vaccine and clinical trials presumes that they will receive vaccinations when they are discovered, though the timing of any vaccine discoveries is as yet unknown.

If most older persons are restricted to aged care facilities and are not considered as essential inclusion in herd immunity policy considerations, it may not be necessary to include them in vaccine and clinical trials, though the healthcare staff and visitors should be inoculated when a COVID-19 vaccine becomes available.

45. Peaceful Miracles Make the Moment

The delightfully heartfelt and moving capture of an everlasting memory by Torres (2020) is what makes such moments miraculous.

The significant efforts of the caring pediatrician in balancing ethics approval and risk management to seek and obtain hyper-speed approval for an experimental remedy, if only to ease the minds of the distraught parents whose 15-year old child was receiving palliative care, are to be commended.

Medical health practitioners do everything to care for their patients, including doing their best to “do no harm”.

What more could any patient and their family ask for, other than for their caring pediatrician to share such priceless memories?

46. Dealing with COVID-19 Science Denial and Conspiracy Theories

Repeating consistent and easy to understand (simple, not simplistic) scientific statements in the media, social media, and scientific social media is essential in working to convince members of society about the most efficient methods for dealing with the COVID-pandemic.

As explained carefully and informatively in the viewpoint by Miller (2020), conspiracy theories are widespread, but trying to deny their legitimacy will see science descending to the same abysmally low level.

Science deniers and advocates of fake news are not likely ever to be convinced, but the only workable response is to repeat consistent and interpretable recommendations in a calm manner, including the wearing of masks and widely accepted social measures.

This is what scientists do in their professional lives, but the need to act more frequently and convincingly has never been more urgent for the international community.

47. Masking and Testing Should be Mandatory for COVID-19

The informative perspective by Rubin (2020a) on the wearing of masks and testing for the SARS-CoV-2 virus that causes the COVID-19 disease leads to questions of how this is even worth discussing.

Any cities, regions, states, and countries where the wearing of masks is standard, whether through society's acceptance with or without a government's mandatory legal enforcement, has a significantly higher chance of mitigating the spread of the virus.

In addition to the wearing of masks, high testing rates for any symptoms associated with possible infection, whether through COVID-9 or any other virus, should be strongly encouraged, for purposes of contact tracing, together with self isolation at home, if at all possible.

In a number of countries, local governments have made accommodation available for compulsory communal quarantining.

Refusal to self isolate or quarantine is not a matter for discussion, and will lead to fines if official orders are flagrantly disregarded.

The same condition should be mandated for the wearing of masks, which is essential to protect any individuals in society who might come into contact with asymptomatic carriers.

The degree of positivity rates should be calculated for at least 14 days, as in many countries, and retested in the period before the end of the 14-day period, rather than for 7 days, which does not allow accurate identification of infection or retesting.

It is difficult to understand the irresponsible and ignorant position of senior administrators in states and countries who argue that increased testing leads to more cases being reported, with the

ridiculous false causality that decreased testing will lead to fewer realized cases of COVID-19 rather than fewer reported cases.

Health departments and governments need to know how many individuals have been tested for COVID-19, and how many positive outcomes can be reported, for effective public policy considerations.

Failure to wear masks and refusal to be tested for a disease that kills susceptible and immune compromised and aged members of society, as well as infecting healthcare workers, should not be an optional or purported unconditional right, but a requirement to behave as a responsible member of a caring society.

48. Journal Reputation is Established by Scientific Creativity and Destroyed by Political Interference

It is difficult to disagree with the commanding viewpoint written by experts and former Editors-in-Chief in Rasmussen, Ward and Goodman (2020), of a leading journal in epidemiology that is published by the CDC, Morbidity and Mortality Weekly Report (MMWR).

If and when political appointees within the US Department of Health and Human Services (HHS), or anywhere else interfere in the editorial process, it should be made clear in the lead footnote and throughout each and every article that is published in the journal, with names wherever appropriate.

A journal's reputation can take many years to be established through innovative scientific creativity, but it can easily be destroyed, even with a hint of non-scientific interference.

Nothing does this more easily and speedily than political interference, which is anathema to scientific progress and creativity, especially when accurate information is essential during the COVID-19 pandemic.

49. Impact and Importance of Medical Research on COVID-19

There is no doubt that there have been many papers that have been published on COVID-19 in medical science research and cognate disciplines, including many in the sciences and

social sciences, especially in the search for a safe and effective vaccine, much of which has been presented since 10 July 2020, the end of the sample period for the research analysis.

How can the impact and importance of such (presumably published) be measured?

Publication in the leading medical journals provides a stamp of approval, including views, citations, altmetric attention score, social media and academic social media, and published comments, as appropriate, and is relatively free of the "fake news" criticism that is frequently directed toward scientific and medically-based information available in peer-reviewed journals.

Reads and uploading posts on to widely accessible preprint servers, such as *medRxiv.org*, is also useful and, in this content, listing on the **World Health Organization (WHO) COVID-19 Global literature on coronavirus disease (2020)**, which now lists almost one million papers, is a source of (possibly) too much information.

UNICEF (2020) and many other international organizations also have the latest information, but no references are more informative and rigorously peer reviewed than the leading medical journals.

50. Support for COVID-19 Long Haulers

The candid reflections of a long hauler, Siegelman (2020), who has lived with some of the varied prolonged after-effects of COVID-19, is very helpful to those who seemingly do not have continuing symptoms and also to those who have.

It is also a reminder that medical specialists can and do contract the virus and disease, whether through dealing with infected patients or with asymptomatic individuals in society, and can learn to be even more empathetic and comforting than they already are.

Self isolation can have severe negative effects because of significant shocks to what has been regarded as standard societal practice pre-COVID-19, but which no longer rings true.

Structural shocks include the isolation from family, friends, and colleagues, and the possibility of mental healthcare issues to patients and their carers arising from the illness and job losses, and persistent damage to hearing, taste, smell, and memory, among many others.

The reflective and instructive views of a long hauler are admirable and reassuring in that long haul need not mean forever, but that it is not possible to survive and recuperate on one's own.

51. Possible Reinfection and Long Term Recovery from COVID-19

The editorial by Katz (2020b) raises several intriguing and challenging concerns about testing for SARS-CoV-2 and possible recovery from COVID-19 infection, which are essential for determining public and private decisions regarding self isolation and quarantining for recovered patients.

The important editorial recommendations can be supplemented with further difficulties in determining:

- (1) correct interpretation of positive test results from previously recovered patients;
- (2) whether such results might be indicative of false negatives;
- (3) the lack of a viable test for viral reproduction and transmission of infection;
- (4) the optimal duration between tests for the virus after recovery;
- (5) the duration between episodes of recovery and possible reinfection;
- (6) tests for the reproductive capability of the virus;
- (7) tests for genetic differences in viruses between the first infection and reinfection;
- (8) tests for mutated viruses that are significantly different from the original infection.

52. Wabi-Sabi and the Beauty of Imperfection

The pursuit of perfection by Watson (2020) may be an ideal, but in reality it can lead to stress, anxiety, and worse.

The Japanese philosophy or mindset of Wabi-Sabi focuses on imperfection as an asset by making the most of daily life through concentrating on authenticity, simplicity, and transience.

The cracked, repaired, and imperfect tile is beautiful, as appreciated by the tiler, the repairer, the recipient, and all who have read the delightfully moving chronicle

53. Good, Better and Best Testing for COVID-19

There cannot be any argument against the salutary lesson from medical specialists in Manabe, Sharfstein and Armstrong (2020) regarding the need for more and better testing for COVID-19 to limit its spread through mitigation and prevention strategies.

The community needs to be informed clearly and frequently by medical specialists, public healthcare authorities, and city, state, regional, and federal government leaders about the good, better and best available tests for the virus and disease.

Best practice, where social distancing, mask wearing, and personal hygiene are widely practiced, would involve the rapid use of safe, effective, affordable, widely distributed, free, and robust to false outcome tests, and vaccines when they are discovered, for a high proportion of the population, whether done voluntarily or mandated by state and federal governments.

Guarding against presymptomatic and asymptomatic patients who may infect others relies as much on individual vigilance and caring for family and community members, as it does on education through the news media and social media.

The best tests are those that are widely respected and accepted, with prospective carriers voluntarily seeking testing when they suspect they might be infected.

State and federal government support for testing and supporting those with limited or no insurance coverage for medical expenses, and unemployment insurance for those who cannot work from home during self quarantining.

The experts end with the prescient warning: “Even the perfect test cannot go it alone”, which could be coupled with: “No individual can go it alone.”

54. Surgical Technical Skill and Long-Term Cancer Survival

As discussed in Brajcich, Stulberg, Palis et al. (2020), technical skills are a minimal expectation and requirement of any surgeon, whether it be for cancer or any other illness.

Postoperative treatment moves the patient from the operating theatre to ICU and then to the recovery room, the duration of recovery depending on the illness.

Probabilities or percentages are available for survival rates for a given number of years, such as the five-year survival rate, for many illnesses

Skill scores for colon surgeons can be evaluated through the use of video assessment tools, which gives a professional and technical analysis, although a single video and a small sample of surgeons necessarily raises issues of small sample bias.

Patients can also contribute to an evaluation of the colon surgeon's skills through aftercare over a number of years, including dealing with any postoperative complications that may arise.

Kaplan-Meier survival rates are easily calculated, and hazard ratios for deaths can be estimated using the multivariate Cox proportional hazards regression model, which provides the technical side of the analysis, although the small sample can distort the point estimates and confidence intervals.

The authors found that the 5-year survival rate was highest at 79% for highly-skilled surgeons, but what was not mentioned or explained is that the survival rate was also higher for lowly-skilled surgeons at 60% than for medium-skilled surgeons at 55%.

The differences in survival rates between highly-skilled and lowly-skilled surgeons are abundantly clear, though any statistical differences between medium-skilled and lowly-skilled surgeons are not.

Extensions of the innovative research for a larger sample of surgeons based on multiple videos to evaluate surgical technical skill would prove invaluable.

55. Prior Negative Recovery from RT-PCR Test Results for COVID-19

A team of medical experts in Liotti, Menchinelli, Marchetti, Posteraro, Landi, Sanguinetti and Cattani (2020) analysed patients who have purportedly recovered from COVID-19 with negative real-time polymerase chain reaction (RT-PCR) results have had positive follow-up RT-PCR test results, which indicates that such patients may still be positive at lower levels.

The absence of any symptoms of a recurrent infection or reinfection, which are impossible to separate, is not indicative of the viability or transmissibility of the SARS-CoV-2 RNA (ribonucleic acid).

The empirical analysis was conducted for 176 recovered patients, based on 2 negative RT-PCR results, from 21 April to 18 June 2020 for a subsequent COVID-19 follow up.

Of the 32 samples which tested positive for SARS-CoV-2 RNA, one with preexisting conditions was replicative, as either a recurrent infection or reinfection, while samples from the 32 were also replicative.

The mean time from COVID-19 diagnosis to follow-up was 48.6 days in 32 patients and 57.7 days in 144 patients, which are unlikely to be statistically different, despite the substantial differences in sample sizes.

As positivity in the patients did not necessarily capture viral carriage, replicative SARS-CoV-2 RNA detection was used as a proxy for virus replication, with inherent sampling bias, especially in small samples.

Sub-sampling, such as bootstrapping, from the replicative SARS-CoV-2 RNA detection would improve robustness of the proxy variable for virus replication.

Of the 31 remaining asymptomatic patients with positive results, the inference that this indicated either low level recurrent or resolving infection is problematic without additional data.

56. Age, Frailty, and Postoperative Surgical Outcomes

The important discovery by Anderson and Wick (2020) that frailty affects postoperative mortality across multiple surgical specialties is critical for decision making and planning, not only for surgeons, but also for patients.

The question remains as to the specific definition and measurement of frailty, and whether “one size fits all” is suitable for all major surgery and risk frameworks.

It is essential to determine the correlations across age, alternative frailty measures, and stress levels across surgical specialties, and to incorporate such measures into standard work flows to improve morbidity and mortality.

57. All Journals Should Have Diversity in the Editorial and Peer Review Process

Congratulations on an editorial by Kibbe and Freischlag (2020) that is long overdue.

Two powerful challenges are the first and last statements:

(1) “There is a great need for diversity and inclusion throughout the editorial and peer review process.”

This prescient opening statement should apply unconditionally to all journals in all disciplines.

(2) “Only when we achieve diversity and inclusion throughout the editorial and peer review process will we appreciate a heightened level of [understanding] that reflects the views and values all people. True diversity will also result in better and more innovative ... science [and social science] that can change practice and improve the health and lives of all people ...”

This prescient closing statement should apply unconditionally to all journals in all disciplines.

58. An Encompassing Digital Open Access Journal - JAMA Health Forum

In less than one year since its inception, which has coincided closely with the discovery and awareness of the COVID-19 pandemic, senior academic researchers and managers in Bauchner, Ayanian, Buntin, Flanagin and Shields (2020) have contributed to and encouraged innovative, informative, and challenging scientific research output, commentary, and directives on global and domestic public health care policy in the JAMA Health Forum.

The highly readable, suggestive, and significant contributions to and content of the Health Forum, frequently by prominent international and national health care and policy experts, have led to the welcome creation of a new specialty digital online open access journal under the same title, to commence in 2021.

Topical issues that overlap several disciplines and sub-disciplines in the medical profession, especially related to health care issues which include health care economics and finance, lend themselves naturally to a broad, inclusive, and multidisciplinary outlet.

The costs of hospitalization and public health care costs require informed input from a range of disciplines and sub-disciplines, including economics, finance, industrial organization, corporate finance, and health care insurance, which are closely related to and overlap significantly with medical and health economics.

Industrial Organization examines the strategic behaviour of industrial firms in competitive markets to maximize industrial corporate profits by applying the economic theory of prices to firms and industries.

Corporate Finance is closely related to industrial organization by examining how corporations maximize shareholder stock values through strategies to accommodate funding, financial planning and capital, and investment decisions.

Medical and Health Economics is closely related to industrial organization, corporate finance, and health care insurance by examining a variety of issues related to the strategic and efficient allocation of financial and physical capital resources associated with medicine, health, and health care by maximizing corporate profits and shareholder stock values of private hospital and health care organizations that operate in both the private and public sector, and the provision of accessible and affordable private and public health care insurance.

Researchers in the medical sciences, and the in the broader sciences and social sciences, including public health policymakers in economics, industrial organization, investment finance, corporate finance, and health economics, will view the new specialty JAMA Health Forum journal as an invaluable, timely, and propitious outlet for important international and national health and health care issues that impact everyone, especially in a COVID-19 normal world.

59. Righting Inequities Through Otolaryngology in a COVID-19 Normal America

The informative and challenging viewpoint by experienced surgeons and ENT (ear, nose, and throat) specialists, Burks, Ortega and Bergmark (2020), is a timely call for righting unfair inequities and disparities through Otolaryngology to try to achieve balanced economic, physical, and emotional health in a COVID-19 normal world.

The health and health care inequities and outcomes faced by vulnerable, socio-economically distressed, disadvantaged, poor, hospital and health care insurance deprived, geographically distanced, comorbidity enhanced, minority-serving hospitals, and racial and ethnicity minorities are well documented, as has the disproportionate representation in confirmed COVID-19 cases and deaths.

The lack of ENT treatment in the early stages of the pandemic led unavoidably to serious backlogs in all forms of treatment of afflicted patients, including diagnosis and treatment of ENT cancer, and related complications, especially to the disadvantaged who need care the most.

The courage and insistence by otolaryngologists to assist the disadvantaged in society through righting inequities as standard operating procedure in health and health care risk monitoring and management, including quality of life and mortality rate considerations, is timely and needs to be supported strongly by all in the medical profession and in the international community.

60. Resilient Mental Health in Older Adults Under COVID-19

The clear, informative, and helpful viewpoint by experts on mental health of older adults, aged variously 60 years or more, is a wake-up call for medical health researchers, policy makers, carers, and all individuals, irrespective of age (see Vahia, Jeste and Reynolds III, 2020).

It was found that: “counter to expectation, older adults as a group may be more resilient to the anxiety, depression, and stress-related mental health disorders characteristic of younger populations during the initial phase of the COVID-19 pandemic.”

With respect, it is arguable that the interesting findings are not necessarily “counter to expectations”, especially given the experience and wisdom of older adults in dealing with confronting situations, including economic, physical, and mental health issues.

Pierce et al. (2020) found that, by late April 2020, mental health in the UK had deteriorated compared with pre-COVID-19 levels, especially for women, teenagers 16 years and above, young adults, and parents with preschool aged children.

The reasons can be diverse, but obvious explanations are:

(1) difficulties in finding gainful employment as the economy shuts down in many countries where there are national, regional, state, and provincial lockdowns;

(2) lack of experience and patience in dealing with new social norms that include observing, respecting, and practising social distancing, self isolation, quarantining, and mandated lockdowns.

The behaviour of older teenagers, young adults and parents with young children, in particular, is of concern as they are in the highly stressed cohort.

Experiencing stress and incessant anxiety about issues that are difficult to experience and control is a recipe for mental health issues.

Further to the above, young adults tend to have greater energy levels and robust physical health compared with older adults, but the latter have a lifetime of experience to calibrate their psychological and mental health risk.

Older adults who live in assisted living and aged care nursing facilities have seen many cases of COVID-19 infections, as well as associated deaths, so they may be partly inured or resilient to such mental health outcomes, including self harm and suicide.

Such results seem to predominate in high income countries, where older adults may have access to hospital and healthcare insurance, and retirement incomes, while younger adults are finding it difficult to be gainfully employed during the pandemic.

Consequently, it would be useful to consider a broad cross-section of countries according to a variety of socio-economic considerations to gauge the differences across income and financial levels, in particular.

The effects of long haul COVID-19 symptoms across cohorts remains largely unknown, despite several long haul effects being known.

Loneliness can be a serious problem for every individual but, despite possibly having greater wisdom, older adults tend to have a smaller group of friends and relatives, and tend to socialize less than their younger counterparts.

Aging seemed to be a natural world order pre-pandemic, but COVID-19 has threatened every individual's future and healthcare, especially those who need it most.

61. Preventing Suicides in a COVID-19 Normal World

As communicated sensitively and cogently by Moutier (2020), the protection of individuals, provision of mental healthcare, and prevention of self harm, including suicides, would seem to be minimal requirements of a caring society, especially during and after the COVID-19 pandemic.

Acceptance of mental healthcare as a serious health problem that needs to be addressed and accepted by the wider community is essential for mental health to be mitigated and controlled.

COVID-19 imposes additional stress, anxiety and overall mental health issues on society, and especially on those who are already suffering.

Counsellors, psychologists, and psychiatrists lead the charge, but society needs to strongly and urgently support mental healthcare front line workers and patients in order to mitigate the suffering and costs inflicted on those who need care the most.

62. COVID-19 and Voluntary Participation in Cancer Clinical Trials

The informative research letter by cancer specialists, namely Fleury, Farner and Unger (2020), touches upon the important issue of how the COVID-19 pandemic has led to a substantial reduction in cancer clinical trials, and whether voluntary participation in cancer clinical trials will return to pre-pandemic levels.

A large group of 3054 cancer survivors, aged 18 years or older, diagnosed and treated for cancer within the last 5 years, was surveyed between May 27 and June 17, 2020 about their participation in cancer clinical trials during the ongoing pandemic.

There were 933 responses, with 73.1% female, 33.9% were offered trial participation, of whom 78.1% agreed to participate.

It is understandable that participants might be less willing to participate in cancer clinical trials during the pandemic because of the possibility of having a negative effect on the cancer treatment, and also the possibility of being infected in hospital and laboratory environments through increased exposure, especially in the absence of a safe, effective, and durable vaccine.

Voluntary participants in cancer clinical trials are not necessarily representative of all cancer patients, and might be distinguished according to:

- (1) different types of cancer;
- (2) different stages of cancer;
- (3) primary, secondary, and tertiary cancers;
- (4) duration of the existing cancer;
- (5) existing comorbidities;
- (6) prior successful treatment of cancer;
- (7) participants exposed to COVID-19 through family and social networks;
- (8) chemotherapy, radiotherapy, both, or alternative treatments.

63. Herd Immunity and COVID-19

The detailed commentary by Spellberg, Nielsen and Casadevall (2020) on antibodies and naturally acquired immunity for populations in the COVID-19 era begs the question as to whether herd immunity to control the spread of the virus and disease is possible.

The research study examines updated information on SARS-CoV-2 seroprevalence in the USA, with recognition of serum containing antibodies that recognize the virus at below 20% in Spain and Italy.

The latest information as of 28 November 2020 ranks India, Brazil, Russia and France ahead of Spain, with the UK between Spain and Italy (<https://www.worldometers.info/coronavirus/>).

A striking finding is that there is little evidence in the USA of prior COVID-19 infection by antibodies to SARS-CoV-2, with the seroprevalence of antibodies declining over time.

The primary goal of herd immunity involves inducing long-term protective natural immunity against reinfection following natural infection, although eradication of a disease requires a safe, effective, and durable vaccine that induces protective immunity.

Herd immunity can be attained when a “significant proportion” (aka “threshold”) of the population is protected through infection and recovery, or by a program of vaccinations, with or without previous infection, to mitigate the spread of COVID-19 transmission.

Vaccines must be approved by leading disease control institutions, and should be safe, effective, durable, affordable, and available.

Modelling and extrapolated empirical analysis from related diseases, as distinct from laboratory clinical trials, would seem to suggest that a threshold of 60% - 80% is required to develop adequate herd immunity at the population level to halt the continuing cycles of infection and disease, as distinct from eliminating the disease.

Although Sweden is not mentioned, the attempted herd immunity in the country has sadly been a failed experiment, with an estimated threshold of less than 20% in Stockholm, the largest city with around 22% of the population.

A vaccine may mitigate the spread of the virus and disease through protective immunity, but herd immunity is a Plan B that will likely lead to disastrous outcomes.

The unknown, through “reasonably high”, threshold for herd immunity depends on a multitude of factors, including the disease itself, which are themselves unknown, though they can be tested as important in affecting the threshold.

The duration of immunity from prior infection is unknown, and similarly for the effect of vaccination.

The discovery of several virulent mutant strains of the original wild-type coronavirus, such as those from the UK and South Africa, and possibly Spain, will affect infection rates and associated deaths, as well as the effectiveness and duration of existing approved vaccines, so the threshold for herd immunity will likely need to be increased.

64. Psychological Distress of US Adults Under COVID-19

The informative and helpful research letter on psychological distress and COVID-19 - related stressors in an expanded longitudinal cohort of US adults aged 18 years and older in April and July 2020 by McGinty, Presskreischer, Anderson, Han and Barry (2020), updates and provides dynamic analysis during COVID-19 of an earlier research study by McGinty, Presskreischer, Han and Barry (2020) on psychological distress and loneliness of US adults in 2018 and April 2020.

Psychological distress in the past 30 days was based on the Kessler 6 scale, with a score of 13 or more indicating serious distress, and a wide range of control variables.

It was instructive that the reported serious distress did not change significantly for any sub-groups in the three months between April 2020 and July 2020.

It was not surprising that the reported prevalence was highest for younger adults (aged 18-29 years), for those with lower incomes, and Hispanic individuals, as age, incomes, and ethnicity increase the likelihood of mental health disorders.

If the data permitted, it would be useful to examine, for the benefit of individuals with different socio-economic situations, of any changes between April and July 2020 based on the following:

- (1) updating the data to the second and higher waves of the pandemic in November 2020;
- (2) secondary school students;
- (3) separating older adults for those aged 65 years or older, and 75 years or older;
- (4) older adults in nursing homes and aged care facilities;

- (5) frontline healthcare workers, especially those in hospitals and who care for the aged;
- (6) young adults with pre-kindergarten infants;
- (7) gender;
- (8) pregnancy;
- (9) access to affordable healthcare insurance and healthcare facilities;
- (10) presence of preexisting comorbidities.

65. Repurposing Drugs for COVID-19

The informative, timely, and challenging health update by Rubin (2020b) is concerned with currently available drugs that might be safe, effective, and durable as promising treatments for COVID-19, which continues to spread across the globe.

The hospitalized adult volunteers with COVID-19 might be evaluated according to the following:

- (1) Are the 100 patients experiencing mild or severe effects of the SARS-CoV-2 virus?
- (2) Do the patients have any existing comorbidities?
- (3) Do the patients represent a cross-section of the population in terms of age, gender, race, ethnicity, and socio-economic circumstances?
- (4) Is the testing of up to 3 drugs at a time determined randomly or arbitrarily?
- (5) How effective is the antiviral remdesivir for mild and severe COVID-19 patients?
- (6) How effective is the monoclonal antibody risankizumab in treating mild and severe plaque psoriasis?
- (7) How effective is the investigational monoclonal antibody lenzilumab in treating mild and severe cytokinestorm, a hyperimmune response?
- (8) Is Day 8 a standard primary endpoint to determine the clinical efficacy of the investigational treatments?
- (9) Are the study visits on the secondary endpoints on days 15, 22, and 29 indicative of the expected recovery from COVID-19?
- (10) Is non-recovery after Day 29 indicative of long haul COVID-19?

66. Same Data + Different Models = Different Results : Statistical Research Using Improved Surgical Databases

The pointed, challenging, and informative viewpoint by Childers and Maggard-Gibbons (2020) on improving research on surgical databases is highly topical.

However, the viewpoint is not particularly different from valid critiques of empirical research in many disciplines in the sciences or social sciences.

Moreover, there is little point in improving any databases if the statistical analysis has flaws that can easily be eliminated.

It is well known that estimating different models on the same data set can lead to different results, regardless of whether one model is a special case of the other or not. Different results based on the same data set are extremely likely to arise when the models are non-nested, that is, when neither model is a special case of the other.

This is illustrated perfectly in the Table, where two sets of variables are used, with neither being a special case of the other. The paper by Fields, Lu, Palenzuela et al. (2019) uses many more variables than those in Turner, Jung and Scarborough (2019).

Nevertheless, Turner, Jung and Scarborough (2019) use some variables that are not used in the paper by Fields, Lu, Palenzuela et al. (2019).

For example, Age is continuous in Fields, Lu, Palenzuela et al. (2019), but it is dichotomous at 65 years in Turner, Jung and Scarborough (2019); BMI is continuous in Fields, Lu, Palenzuela et al. (2019), but categorical in Turner, Jung and Scarborough (2019); Complicated appendicitis is dichotomized in Fields, Lu, Palenzuela et al. (2019), but is based on two indicator variables in Turner, Jung and Scarborough (2019); and Operative time is continuous in Fields, Lu, Palenzuela et al. (2019), but is dichotomized at the 75th percentile in Turner, Jung and Scarborough (2019).

Moreover, with different sample sizes, 11475 versus 10357, and different primary outcomes, namely postoperative intra-abdominal abscess versus any SSI (superficial, deep, organ space) in Fields, Lu, Palenzuela et al. (2019) and Turner, Jung and Scarborough (2019), respectively, the outcomes are virtually guaranteed to be different, quantitatively and statistically significant.

Furthermore, the lack of any diagnostic checks makes it impossible to determine the robustness of the empirical results.

Critical analysis of surgical databases is important, as is critical analysis of empirical analysis, especially when improvements and simple explanations are readily available.

67. How Do Surges in COVID-19 Affect Healthcare Spending?

The analysis of the relationship between reductions in early healthcare spending and expected spending on COVID-19 by McWilliams, Mehrotra and Russo, A. (2020) is a welcome, critical, and informative public and private healthcare policy issue, which depends on a number of important assumptions and interpretations, including:

- (1) use of 2019 data to correct for unreported claims may be problematic as it presumes that the health insurance industry was the same in 2019 as it is during the COVID-19 pandemic;
- (2) inclusion of COVID-19 inpatient spending in 2019 and 2020 cannot be compared as the pandemic started in 2020, although it was notified to the WHO in 2019;
- (3) sample of changes in spending is from 3 March 2020 to 7 April 2020, which leads to a relatively small sample;
- (4) aggregate medical spending decreased across virtually every category considered, including elective procedures and age, though not necessarily gender, race, ethnicity, and socio-economic circumstances;
- (5) COVID-19 had a significant effect on medical spending, especially in the early phase;
- (6) massive reductions in non-COVID-19 healthcare expenses, especially for the aged, offset those on COVID-19 cases;
- (7) negative correlations between reductions in early healthcare spending and expected spending on COVID-19 might continue as the pandemic unfolds, though they need not remain below the levels observed before COVID-19, especially as the winter season approaches in the northern hemisphere;
- (8) net gains to commercial insurers in 2020 need not continue as extended waves of COVID-19 continue to expand exponentially.

68. Causality Between Sedentary Behavior and Cancer Mortality

Rezende, Lee and Giovannucci (2020) ask the important question: Does sedentary behavior cause cancer mortality, or the reverse, in which case unidirectional causality is examined, or both, whereby bidirectional causality is deemed to exist?

Reverse causation is such that latent or actively treated cancer can cause disability and illness, which can lead to sedentary behavior, and death, which is unidirectional reverse causation.

With 8002 observations on middle-aged adults, it would be possible to test for unidirectional and bidirectional causality.

If additional age cohorts were available beyond middle-aged males, thereby increasing the sample size, a powerful test of causality could be constructed.

69. Overdose Cardiac Arrests and Emergency Medicine During COVID-19

The research conducted by medical and health science experts, Friedman, Beletsky and Schriger (2020), highlights the heavy duties placed on emergency medical services that are faced with the demanding combination of an overdose crisis and the COVID-19 pandemic.

Flattening both the overdose mortality curve and the COVID-19 confirmed cases and mortality curves simultaneously is a monumental task, especially in view of the causal effect that is accelerating from COVID-19 to overdose mortality.

The empirical analysis of overdoses was based on comparing 2020 values for weeks 1-10, to accommodate potential decreases in overdose call volumes, with weekly averages in the 2018 and 2019 values, for adults aged 61 years and older.

For healthcare policy purposes, it would be informative to compare the changes in overdose mortality during the initial months of the pandemic, which was double in May 2020 and around 50% higher overall than the averages from 2018 and 2019, with the second wave in COVID-19 confirmed cases and mortality from mid-November 2020.

Considering the number of patients who are likely to be younger than 61 years of age, examining overdose cardiac arrests requiring emergency medical services by age cohorts would also provide important information to healthcare providers, especially as overdose risk has not been mitigated during the pandemic.

The connection between overdose mortality and mental health issues by age cohort, data permitting, would also be invaluable for front line healthcare workers and patients who need them most.

70. COVID-19 Asymptomatic Children Versus Adults

Whether children have a higher risk of being COVID-19 asymptomatic carriers than adults is an empirical issue, as stated in Milani, Bottino, Rocchi et al. (2020), so the research findings from Milan, Italy for the 2-month period, 1 March to 30 April 2020, are highly informative.

The comparison was made between a sample of 83 children, with a mean age of 5.3 years, versus 131 adults, with a mean age of 77 years.

Given the age gap of almost three generations, conditioning on factors such as neurological or cardiac disease hardly seems necessary.

The striking primary finding that children are at not at a higher risk than adults of carrying being asymptomatic carriers would be strengthened significantly by:

- (1) follow-up analysis of the patients in the sample;
- (2) extending the sample period beyond 30 April 2020;
- (3) using data from a wide range of countries with varying stages of COVID-19 infections;
- (4) using age cohorts that are much narrower, including teenagers, and young, medium aged and older adults;
- (5) extending psychiatric disorders to include information on stress, anxiety, and mental health issues from prolonged and sustained social distancing, isolation, quarantining and lock downs;
- (6) decomposing "other conditions" into drug taking and self harm.

71. Why is Care for Serious Non-COVID-19 Conditions Seemingly Deferred?

The observed significant deferral of care patterns, as evidenced in Goodman, Grabenstein and Braun (2020), for non-COVID-19 hospitalizations for chronic disease and acute conditions

in 4 hospitals in the NYU Langone Health system from 1 March 1 to 9 May for each of the years 2018, 2019, and 2020, is explained by one or more of the following seven alternative explanations:

- (1) lost health insurance;
- (2) increased threshold for hospitalization by clinicians;
- (3) changes in patient lifestyle;
- (4) self-management in the context of social distancing'
- (5) prior overuse of hospitalization;
- (6) improved self-management;
- (7) imperfect capture of COVID-19 and other diagnoses.

Additional reasons include:

- (8) lack of trust in the healthcare system with the onset of COVID-19;
- (9) negative social media pronouncements regarding hospitalization and surgery;
- (10) increased threshold for hospitalization by patients;
- (11) increased health insurance costs;
- (12) changes in coverage for pre-existing conditions.

72. Confidentiality in a World of COVID-19 and Fake News

Public officials seek election by voters, who are entitled to have accurate information on the officials for whom they might be voting (see Klitzman (2020)).

In a world of fake news, which President Trump did not invent but rather popularized to great effect, it would be useful to know what kinds of steroids and other chemical ingredients were used in the cocktail of untested drugs to treat his COVID-19 infection.

Confidentiality is expected for anyone who does not seek public office, but accurate information rather than fake news is expected when the leader of a country and his medical team refuse to divulge information to inform everyone about what might be expected from the President, other than tweeting more fake news.

73. Mental Healthcare Data Disrupted by COVID-19

The informative viewpoint offered by medical experts in Shioda, Weinberger and Mori (2020) concentrates on research on physical ailments that have been impacted during COVID-19, including emergency cardiovascular conditions, worsening outcomes of cancer, and reserving surgical procedures for emergencies.

Modelling and forecasting of healthcare outcomes depend on critical assumptions, including that the structure of conditioning factors, such as hospitalization and healthcare availability, socio-economic demographics, among others, remain unchanged, which is unlikely during the pandemic.

The comprehensive empirical analysis in the viewpoint could be made even stronger and more encompassing if any disruption to the data during COVID-19 were to include mental healthcare outcomes, ranging from stress and anxiety through to more extreme measures

74. Do N95 Face Masks Protect Against COVID-19?

The filtration efficiency, effectiveness, and availability of N95 face masks for preventing the spread of COVID-19 in August 2020 (see Dugdale and Walensky (2020)) is a very different situation from mid-December 2020, where the USA is arguably experiencing the third wave of the pandemic.

The availability of a variety of purportedly safe and effective vaccines for COVID-19 may mitigate the spread of the virus and disease, and may also have the undesirable effect of increasing COVID-19 fatigue, both in terms of the long lasting effects in recovering from infection and also in response to having to deal with the pandemic.

Although not mentioned extensively in the commentary, aerosols seem to be more dangerous than droplets as the former can be spread widely after lingering in the air for hours, including outdoors where wind can transmit the airborne virus widely.

Masks, face shields, screens, and social distancing do not seem to provide adequate protection against aerosols, although they can provide much needed protection against droplets.

75. The Necessity of Face Masks During COVID-19

It would seem utterly obvious that paying careful attention to the best medical and healthcare advice during the debilitating COVID-19 pandemic, as stated powerfully by Steinbrook (2020), would be understood, respected, and accepted by every responsible individual who cares about their own health and life, as well as those of every other person with whom they might conceivably come into contact.

Social distancing, masking, and screens, as well as protective shields and goggles to protect the eyes, are mandatory protective equipment against droplets and aerosols, although aerosols would seem to be more difficult to contain in its spreading of the virus, whether indoors or outdoors.

COVID-19 fatigue is a reality, but it is unacceptable as an excuse for anyone to disregard sensible scientific advice, as compared with paying any attention to provably false fake news that is a danger to the health and life of every individual in society.

76. Nurses in COVID-19 Vaccine Trials

The enticing perspective by Choi (2020) confronts us with whether nurses or frontline healthcare workers should participate voluntarily in COVID-19 vaccine trials, especially with the possibility of a reactogenic response?

How does one know if the experimental result for a patient is based on a vaccine or a placebo, and should that matter in a random selection 50-50 process?

Extreme reactions, however common, after a second injection might be accommodated by a volunteer nurse, but would be far less likely for the majority of volunteers who have less experience with high quality hospital and medical standards.

It would be useful to know the duration of effectiveness of a vaccine, as well as the possible long hauler effects, for which evidence would seem to be lacking.

With respect, there would also seem to be little evidence that the extreme adverse effects of the vaccine are "transient and a normal sign of reactogenicity signaling an effective immune response".

The informative perspective is the right message to send about the COVID-19 vaccine, and deserves to go viral for the right reasons.

77. Eye Protection for COVID-19 Ventilated Patients

The medical experts, Sun, Hymowitz and Pomeranz (2020), provide an informative report regarding ophthalmic abnormalities of COVID-19 ventilated patients in ICU who are exposed to prolonged prone positioning.

Evaluating the effects of prolonged prone-positioned and ventilated patients with COVID-19 is innovative and important, but there did not seem to be any mention of the effect of aerosols or aerosol therapy on the COVID-19 patients in ICUs.

78. Healthcare Access, Social Needs, and Unemployment Insurance During COVID-19

The interesting and encompassing research reported by medical experts in Berkowitz and Basu (2020) covers broad ground in insurance, social needs in healthcare access, and mental health issues during COVID-19.

Although a wide range of unemployment insurance schemes has existed before and during the pandemic, the insurance benefits (or coverage) have been varied and expansive across the various schemes, and access to such schemes has tended to improve physical and mental healthcare access.

The cross-section data of continuous and categorical variables from 11 June to 21 July 2020 of working-age adults aged between 18 and 63 years, with median age of 39.5 years, led to a relatively low response rate of 3%.

Not surprisingly, receiving unemployment benefits led to mental healthcare issues associated with lack of affordability of food, housing, and access to appropriate healthcare.

The arbitrary use of log-Poisson regression models to estimate adjusted relative risks, which were not defined, multiple imputation of missing data, and estimated false discovery rates to control type I error probabilities, would lead to combined selection biases of unknown direction.

As the direction of causality was presumed throughout to be from unemployment insurance to healthcare access, and physical and mental healthcare issues, this critical assumption might be

examined statistically using bi-directional causality with time series data, if available, in combination with the cross-sectional data to enable estimation and testing of panel data models.

This would be especially important if any unemployment insurance reforms were presumed to affect healthcare access and benefits, and social needs, during and beyond the COVID-19 pandemic.

79. Pre-eminent Experts Evaluate the Distribution of COVID-19 Vaccines

The perceptive and prescient medical news and perspectives on JAMA Live Highlights relating to various critical issues surrounding COVID-19 vaccines, and more, by Foege, Offit, Gostin, Williams and Slavitt (2020) is a genuine pleasure to read and digest, especially for non-medical specialists.

Professor William H. Foege emphasizes prioritizing allocation of COVID-19 vaccines on the basis of science, ethics and equity, highlighting the risks of infection, becoming sicker, being hospitalized, and dying, based on racism and socio-economic inequities and vulnerabilities, among other factors.

Although these issues are bound to have been discussed in committees, along with contact tracing and seeking wisdom rather than relying on fake news, there does not seem to have been any direct mention of durability, affordability, or wide distribution, in any of the perspectives.

Professor Paul A. Offit critically discusses vaccinating placebo groups, and vaccine distribution to non-healthcare workers.

On the former issue, if all volunteers in placebo groups are to be vaccinated, might there be a tendency for individuals to volunteer to participate, guaranteeing they will receive the vaccine or placebo, which will eventually lead to early vaccination.

On the second issue, non-healthcare providers who are regarded as "essential care workers" are treated alongside healthcare workers in terms of reduced restrictions as the pandemic is tackled. These issues notwithstanding, who might be regarded as essential, and who decides?

Professor Lawrence O. Gostin evaluates race-based and non-race-based vaccine distribution, though not distribution based on ethnicity, the effect of litigation all the way to the Supreme Court, socio-economically disadvantaged and cultural groups, and the impacts of economics, political power, and celebrity.

The directional effects are conjectured, but they would seem to require empirical evidence before asymmetric effects could be tested.

Professor Michelle A. Williams examines the CDC's Social Vulnerability Index (SVI) to respond to natural disasters that impact communities that are vulnerable with respect to incomes, race, and ethnicity, especially during a pandemic. There is acceptance of the SVI as an adequate index of vulnerability, without comparing it to the Area Deprivation index, and Global Health Security Index.

Prevention of disparities is concerned with access to testing, and hospital and medical facilities, which relies on incomes, political power and influence, and celebrity status, that are difficult to control through political or judicial instructions. Moreover, what can be done about anti-maskers and anti-vaxxers, who affect those who are pro-masking and pro-vaccination?

Professor Andy Slavitt discusses the progress in ending the pandemic on the basis of the known knowns and known unknowns, which include critical side-effects on internal organs, though there is little or no discussion about reinfections, and purportedly recovered long-haul COVID-19 patients.

The aged in all societies seem to be dying at a far greater rate than younger and even mature aged adults. Even younger adults are facing reduced life expectancy, and teenagers and children are facing a far less reassuring future than their parents did at the same stage in their respective life cycles.

Distribution of the first available vaccines to healthcare and essential service workers might encourage and reassure all members of society to accept vaccines, but this may be unlikely in a world of fake news and committed anti-vaxxers.

80. The Effects of Current Vaccines Against SARS-CoV-2 and COVID-19 Mutations

Berkwits, Flanagan, Bauchner and Fontanarosa (2020) discuss the COVID-19 pandemic in the context of the JAMA Network.

The numerous authorized vaccines against COVID-19 are a small victory in the seemingly never ending war against the insidious pandemic.

Have any mutations of SARS-CoV-2 and COVID-19 been tested in the numerous clinical laboratory trials?

In particular, what are the likely effects of the VUI2020/12/01 mutant strain on the success of the current vaccines that are being distributed?

81. Unbearable Suffering Needs to be Respected

As portrayed sensitively in Meier (2020), only those who have suffered unbearably, or are caring for someone in such a situation, can fully comprehend the physical and/or mental health pain they are experiencing.

Medical advances do not necessarily cure or alleviate unbearable suffering, whether in aged care homes or in palliative care.

The only individuals who can truly understand and appreciate the unbearable suffering are the sufferers themselves, and their suffering carers.

Their needs and intentions must be respected.

82. Varied Public Attitudes Toward COVID-19 Vaccine Mandates

The detailed and informative research report by Largent, Persad, Sangenito et al. (2020) emphasizes public attitudes toward mandating of COVID-19 vaccines in the USA to stem transmission of the infectious and contagious virus and disease.

Anti-vaxxers, anti-maskers, those who do not like to be told what is in society's and their own best interests, individuals who are concerned about the numerous mutated strains of the wild-type SARS-CoV-2 virus, individuals with medically-approved dispensations, and those who need time to elapse to discover as yet unknown side effects of the various approved vaccines, will be difficult to persuade to be vaccinated, whether mandatory or not.

The Gallup-type probability-based panel surveys were undertaken between 14-27 September 2020, which is quite different from late-December 2020, when second and possibly third waves have been observed, with several approved vaccines being distributed.

States generally have the authority to issue mandates, but a concerted national approach would be more likely to succeed than face a backlash, something that has been lacking under current circumstances.

83. Enanthems, Exanthems, and COVID-19

Considerable time has passed since the prescient research findings in Jimenez-Cauhe, Ortega-Quijano, de Perosanz-Lobo et al. (2020) on enanthem in patients with COVID-19 and skin rash were published in July 2020, with the study conducted between 30 March and 8 April 2020, in the very early stages of the pandemic.

Possibly infectious skin rashes and disorders can be highly correlated with a range of diseases, including COVID-19, and can also be closely associated with drug reactions.

As skin disorders, diseases, and drug reactions can be highly correlated, it is crucial to determine the viral etiological (or causal) relationships among these variables.

Such a determination should be very helpful to healthcare specialists in dealing with exanthems and drug reactions, both of which are correlated with COVID-19, especially if a follow up clinical study could be extended to the end of 2020.

The invaluable study was conducted in the very early stages of the COVID-19 pandemic, when little was known about the original wild-strain SARS-CoV-2 virus, and without any knowledge as to when approved vaccines might be discovered, as well as the many mutated strains of the virus that are being observed globally.

84. A Wish List for a COVID-19 New Year

A wish list is a combination of needs and aspirations, without which the future can be even more confusing and disturbing than it already is.

The reassuring and carefully considered editorial wish list in Bauchner (2020) that is presented might consider:

- (1) adding mental healthcare;
- (2) evaluating the long haul symptoms of patients who have purportedly recovered from COVID-19 infection;
- (3) diagnosing the short and long term effects of the various mutations of COVID-19 that are being discovered globally;
- (4) evaluating how private and public hospital and health care insurance might be financed;

- (5) balancing care for COVID-19 patients with existing comorbidities;
- (6) strengthening the news and social media contributions from the medical fraternity;
- (7) greater inclusivity in encouraging non-medical specialists and academics from the social science disciplines to contribute to broad medical and healthcare goals;
- (8) improving the healthcare protection of those who are most vulnerable during COVID-19, especially front line healthcare workers, the young, the aged, and those with preexisting medical conditions;
- (9) evaluating the numerous alternative vaccines that are available in terms of their safety, effectiveness, durability, affordability, and availability;
- (10) strengthening the authority of the leading medical and academic institutions, and emphasizing science as the major source of public policy decision making.

85. Critical Statistical Rigour Before and During COVID-19

Critical scientific rigour might be argued to be more difficult in the COVID-19 world, as in Shyr, Berry and Hsu (2020), but the important concerns raised in the viewpoint exist regardless of the sample period and structural changes, such as before and during the pandemic.

The primary topics considered briefly are generally unarguable, but the following deserve greater attention:

- (1) If the likelihood of missing data is high, insistence on the use of imputed data in place of the missing data will lead to biased estimates and biased standard errors, thereby leading to biased and invalid statistical inference.
- (2) The statements that “confining analysis to complete cases can be a source of bias” and “including all cases, with multiple imputation for missing data, generates more reliable and less biased results”, are problematic at best, and misleading at worst.
- (3) There are several alternative solutions to dealing with missing observations, but these typically rely on missing at random and a relatively small percentage of the total sample data, which does not seem to be the case based on medical records.

- (4) The selection of variables in a regression model needs to be done prior to estimation of the unknown parameters and/or distribution, based on known factors that have been discovered using prior independent data sets.
- (5) In order to conduct a serious sensitivity analysis, the underlying assumptions of the model need to be tested using regression-based or statistical diagnostics to evaluate the robustness of the empirical results.
- (6) Causality is difficult without extensive time series data or dynamic panel data models, as causality is synonymous with predictability.

86. Accepting Vaccines Is Essential Against COVID-19

History will tell in the long run if safe, effective, durable, affordable, and available vaccines helped to turn the tide against the COVID-19 pandemic.

In the meantime, as discussed in Szilagyi, Thomas, Shah et al. (2020), the short and medium term outcomes will need approved vaccines to be widely accepted in the community, without which any purported move toward herd immunity will be defeated.

The interesting and informative research outcomes by a team of medical experts used four cross-sectional internet surveys in April and May 2020, which occurred in the early months of the pandemic, and a robust Poisson regression approach to estimate adjusted risk ratios, as well as cluster-robust linear regression models.

Alternative models with associated diagnostic checks would be able to determine the robustness of the empirical estimates, standard errors, and valid confidence intervals.

The empirical findings across all cohorts based on socio-economic and demographic characteristics, between early April (74%) and November-December 2020 (56%), showed a dismaying reduction in the percentage of survey respondents who were likely to be vaccinated.

These results were obtained before the distribution of several vaccines globally, not all of which have passed stringent clinical trials, as well as in the USA, where two approved vaccines are presently being distributed, which are likely to affect the public's willingness to accept vaccination, especially as the second and higher waves of infections continue to escalate.

87. Social Distancing, Health Behaviour, and Cancer Outcomes During COVID-19

The penetrating and comprehensive viewpoint by medical experts, Ferrer, Acevedo and Agurs-Collins (2020), on the effects of social distancing, health behaviour, and cancer outcomes during COVID-19 is an eye-opener for every individual in society, especially regarding mental health, social support, and recurrent risk infection.

This is especially important in light of the continuing waves of infection spikes, and discovery of several mutations of the original wild-type form of the virus and associated disease.

Patients who have cancer with ongoing chemotherapy, radiotherapy, or other proven treatments, know intimately that it is not possible to survive, both physically and mentally, without substantial assistance from frontline healthcare workers, carers, relatives, and friends.

Social distancing can affect how cancer patients interact with other individuals in society, with associated effects on their recovery and rehabilitation, which are likely to be influenced by how society responds during the pandemic, and thereafter when the disease is mitigated through the discovery of safe, effective, durable, affordable, and available vaccines.

88. Readmission and Death From COVID-19 After Hospital Discharge

The sensitive and caring letter by an expert medical team, Donnelly, Wang, Iwashyna and Prescott (2020), on readmission and death from COVID-19 after initial hospital discharge elevates the pain and discomfort of patients, frontline health workers, carers, family, and friends when an initial purported recovery proves to be fatefully incorrect.

Readmission after initial discharge was examined among veterans at Veterans Affairs (VA) hospitals, with admission between 1 March and 1 June 2020, and discharge between 1 March and 1 July 2020, with numerous medical and demographic conditioning factors, and determination of the most common readmission diagnoses.

The data were used to estimate readmission or death after the initial hospital discharge, as well as hazard ratios based on the piecewise Cox proportional hazards regression.

The proportions of readmissions were 19.9%, deaths were 9.1%, and 27.0% were readmitted or died, within 60 days of discharge, with COVID-19 being the most common readmission diagnosis, and ICU being the most common treatment.

In the context of the empirical analysis, it would have been useful to present the piecewise Cox proportional hazard regressions, with an explanation of the piecewise breakdown, and regression diagnostic checks to determine the robustness of the empirical results.

An examination of existing comorbidities, and the severity of COVID-19 infection before discharge, together with the inclusion of socio-economic conditioning factors, would add even greater depth to the excellent empirical analysis.

A dynamic interactive study of COVID-19, heart failure, and COVID-19 would also enable an empirical evaluation of causality among these interrelated illnesses.

89. Beneficial Lessons From COVID-19

Every cloud has a silver lining, and the same could be said of the beneficial lessons that can be learnt from the emergence of COVID-19, as presented in the reassuring and optimistic commentary by Boudourakis and Uppal (2020).

The pros and cons of social distancing are well known, among which are reductions in transmissions, on the one hand, and mental health concerns, such as loneliness and anxiety, on the other.

However, the issue of increased masking and social distancing is questionable as there seems to be little empirical evidence as to the proportion of the population that actually engages in socially acceptable, recommended and, in some cases, mandated behaviour.

This is in contrast to surveys that ask interviewees how they might support social measures that are intended to mitigate the spread of COVID-19.

The medical advances at warp speed have hardly been seen in recent memory, and similarly for risk-adjusted mortality, but these advances show what can be done when the dire need arises.

Nevertheless, a reduction in the risk-adjusted mortality from January - April 2020, as compared with May - June 2020, bears little resemblance to what is happening in the USA with the second and higher waves from November 2020 onward.

Approved vaccines are presently being distributed in many countries, so the fight against COVID-19 is being strengthened.

The discovery of various more highly infectious mutated strains is an additional cause of concern, especially when hospitals become overwhelmed.

The need for universal healthcare is also being highlighted as beneficial for the entire community, as well as globally, when vaccines and herd immunity increase to the high levels that are required.

90. Estimating Racial Disparities in COVID-19 Testing

The interesting and informative research by Mody, Pfeifauf and Geng (2021) reported the cross-sectional estimation of racial inequalities in testing for COVID-19, for the period 14 March to 10 August 2020.

The Gini coefficient is the most widely used measure of economic inequality or disparity, based on economic measures such as income and wealth.

It can also be estimated based on other factors that are related to economic measures, including gender, ethnic background, and preexisting comorbidities.

Race, specifically individuals who are Black, is considered in the report, together with age, race, zip code, and dates, at the individual level, but the other important factors were not mentioned in the report.

It was reported that Black residents had consistently lower rates of tests per hospitalization compared with White residents.

The clear and important empirical evidence could be strengthened by:

- (1) extending the data set to incorporate the second and higher waves of the pandemic;
- (2) examining the production and distribution of approved vaccines;
- (3) analyzing the discovery of more highly infection mutated strains of the virus, such as from the UK and South Africa;
- (4) evaluating the safety, effectiveness, and duration of the vaccines against the viral mutations;
- (5) reporting diagnostic checks to evaluate the robustness of the empirical results.

91. Paying People to be Vaccinated Against COVID-19

If anyone is paid to be vaccinated against COVID-19, as in Largent and Miller (2021), how does this affect the random distribution of volunteers to those receiving the vaccinations against those receiving placebos?

What is the benefit for volunteers if they do not receive the vaccine?

92. COVID-19 Mutations and Vaccines

Lauring and Hodcroft (2021) examine the meaning of genetic variants of the SARS-CoV-2 virus that causes the COVID-19 disease.

The increasing number of highly transmissible and infectious mutated strains of the original wild-type coronavirus, aka COVID-19, have not yet been tested in clinical trials against the several approved vaccines that are presently being distributed.

The situation is becoming more precarious as the viral genetic strains seem to be exploding wherever they have been discovered globally.

If patients are not protected by current vaccines against the mutations, is there any point in the present global distribution of the vaccines?

Moreover, if additional mutated strains are discovered to be widespread, how will clinical laboratories determine the specific mutated strains that should be selected for the development of newer vaccines?

93. Mandatory Vaccinations Against COVID-19

As discussed in Gostin, Salmon and Larson (2020), mandatory vaccinations require simple and clear explanations from State healthcare officials, and an understanding and acceptance of the need for such actions.

Despite the precise threshold levels being unknown, a high proportion of the population needs to be infected and recover from the disease, or needs to be vaccinated, together with other social mitigation strategies, in order to attain herd immunity.

The informative viewpoint investigates whether mandating vaccines are lawful and ethical, and whether this would increase the willingness of individuals to be vaccinated, as distinct from deterring them as participating in ongoing, and as yet unproven, medical research.

In the absence of clear evidence regarding the safety, efficacy, and duration of the presently approved vaccines for the original wild-type virus, and the lack of evidence regarding any similar properties against the mutated strains from the UK and South Africa, mandated vaccines for adults is based on incomplete information.

The mental healthcare concerns about the stressful work environment during a pandemic, and requiring frontline healthcare workers to accept a mandated vaccine, adds further stress and anxiety.

There will always be objections to mandatory vaccination, including access to domestic and international air travel, when that becomes available again.

Without broad-based community support about the benefits of vaccines, mandated rather than voluntary vaccinations will face countless hurdles regarding agreement at a time of great need for all.

94. Allergic Reactions to the First Dose of the Pfizer Vaccine

In the detailed and informative insight by Shimabukuro and Nair (2021), the experts provide a clinical update on the range of allergic reactions and adverse effects after receiving the first dose of the Pfizer vaccine, to be followed by the second dose 21 days later.

If anaphylaxis typically occurs within minutes or hours after the first dose, what might be any secondary effects before the second dose?

What are the likely allergic reactions and adverse effects after the first dose of:

- (1) existing comorbidities;
- (2) previous allergic reactions to any other non-COVID-19 vaccine;
- (3) any allergic reaction after the second dose;
- (4) escaped mutants;
- (5) non-reporting of the onset of allergic reactions hours after discharge;
- (6) patients with undocumented histories of allergic reactions?

95. Neutralization of Monoclonal Antibodies for COVID-19

The informative editorial by leading experts in Malani and Golub (2021) addresses the neutralization of monoclonal antibodies for COVID-19 in mild and moderate cases.

It would be beneficial to researchers and healthcare policy makers if the ongoing clinical trials were to consider:

- (1) polyvalent antibodies,
- (2) severe cases of COVID-19;
- (3) the effect of escaped mutants;
- (4) the number of days to determine early intervention;
- (5) a wider range of combination therapies;
- (6) risk factors for progression to severe disease that include gender, race, ethnic and socioeconomic factors;
- (7) extending the database beyond 6 October 2020;
- (8) the effect of the second and higher waves of COVID-19 infection.

96. Pricing Teledermatology During COVID-19

Microeconomics 101 is concerned with prices that lead to equilibrium supply and demand.

As considered in Armstrong and Singh (2021), the mathematics cannot add up if none of these terms is specified for the viability of teledermatology, however useful and convenient it might be for treating patients, especially during COVID-19 when social distancing, quarantining, and lockdowns have been imposed, and online treatment has been accelerated.

Although revenues, costs, savings, fees, and reimbursement, each of which is indirectly associated with prices, are mentioned, no functional specifications are presented, so no equilibrium can be achieved.

Every aspect of anticipated and unexpected difficulties in teledermatology, both in terms of additional costs against cost savings for the dermatologist and their patient, need to be priced according to market supply and demand to determine if the sums add up.

97. SARS-CoV-2 and COVID-19 Are Spreading Virtually Everywhere

With the exception of a few countries and territories, the answer to the challenging question in the title of the editorial by O’Leary (2021) is that SARS-CoV-2 and COVID-19 are spreading virtually everywhere, and across all age cohorts.

Herd immunity requires an unknown high proportion of the population to be infected and to recover, or an unknown high proportion of the population to be protected through vaccination.

Contrary to the studies that are highlighted in the editorial, other studies have found that children may be more likely to transmit the disease and to infect others, in which case they should be vaccinated if the healthcare policy is to reduce transmission and infection.

Omissions in the editorial include:

- (1) the virtual absence of any mention of the aged, who may be more likely to die from the disease, so they should be vaccinated if the purpose is to reduce deaths;
- (2) the distribution of a range of approved vaccines, which can have a significant impact on herd immunity.

98. Transmission of SARS-CoV-2 and COVID-19 by Children

The original investigation in Tönshoff, Müller, Elling et al. (2021), based on data for children and their parents in southwest Germany, is important for its research findings and implications for education for children and public healthcare policy for all age cohorts.

The report was cited in an editorial by O’Leary (2021) to support the claim that:

“children 10 years and younger, as in the study by Tönshoff et al, are both less likely to acquire SARS-CoV-2 infection and less likely to transmit it to others.”

Although the review and meta-analysis by Viner, Mytton, Bonell et al. (2020), which could not find a clear role played by children in transmitting the SARS-CoV-2 virus, is cited in O’Leary (2021), it is not cited in Tönshoff, Müller, Elling et al. (2021), which is based on a more restricted data set that suggested that children did not play a key role in transmission.

Although it is generally agreed that children are less likely than adults to be infected by COVID-19, an updated meta-analysis would contribute greatly to determine if children are less likely to transmit the virus and associated disease than adults.

99. Addressing Racial and Ethnic Health Disparities During COVID-19

As discussed in Lopez III, L., L.H. Hart III and M.H. Katz (2021), addressing socioeconomic disparities that affect the marginalized members of society, including immigrants, and those in racial and ethnic groups, is difficult at the best of times, and are exacerbated during the COVID-19 norm.

The difficulties in increasing unemployment benefits and welfare payments, as well as significant contributions by the federal and state governments to healthcare access, when there is substantial public debate about how and what financial measures should be taken by an incoming administration, will be magnified.

Existing supply chain and production bottlenecks can be gauged with reference to the problematic distribution of approved vaccines for COVID-19.

Eliminating the inequalities faced by marginalized members of society will require a strong will that needs to be sustained during and beyond COVID-19.

100. Race and Medical Research During and After COVID-19

As presented in Ioannidis, Powe and Yancy (2021), socio-economic inequality is a thorny issue to address, is difficult to correct and eliminate, is visible according to gender and age cohorts, and even more so when race and ethnicity are considered, including for healthcare access and affordability, both before and during COVID-19.

The reasons why this might be an issue in medical research is confounding to those who are not trained as medical researchers or biologists, as equality is seen by many as a societal goal, regardless of the checkered history in medicine.

As the outcome of any empirical analysis, whether based on specific algebraic models or data constructs, depends on how and where the data were obtained, random sampling of volunteers for any clinical trial should eliminate some cultural and historical biases.

Alternative definitions of race and ethnicity could be analyzed, as socio-economic disparities cover the disadvantaged and marginalized across all racial and ethnic groups in society.

Qualitative factors can be included in models, whether then be so-called dummy variables, geographic zip codes, or differentiating by average incomes in different districts, to distinguish racial and ethnic effects, without choosing, say, "white males" as the standardizing factor.

Using appropriate definitions and analyses from the social sciences, where substantial empirical research has been published on racial and ethnic issues, would also contribute to the discussion.

With respect, contrary to the discussion in the informative and sensitive viewpoint of the scientific analysis of race and ethnicity in any discipline, it should be understood that the topic is an empirical rather than a theoretical issue, especially when there is so much at stake in a COVID-19 world.

101. Adherence to Nonpharmaceutical Interventions During COVID-19

As reported in Crane, Shermock and Omer (2021), COVID-19 fatigue toward nonpharmaceutical interventions (NPIs), which provide a degree of protection against SARS-CoV-2, was observed for the USA between 1 April 2020 and 24 November 2020.

The time period for the survey responses, which has different numbers of responses to the first and second waves of the survey, ended just as the second wave was exponentiating globally, before the distribution of approved vaccines, and before the number of escaped mutants was widely known.

In the absence of clinical laboratory trials that might be able to report the safety, efficacy, and duration of existing vaccines against the mutated strains and variants, adherence to NPIs is an essential protective measure.

Despite an increase in masking, there was a reduction in the reported adherence to NPIs, despite the adherence measure not yet having been validated.

These issues lead to the following queries:

(1) Was there a decomposition of NPIs in terms of masking, social distancing, self isolation, quarantining, and lockdowns?

(2) Is there any relationship between pandemic fatigue and mental health illnesses?

(3) Has the need to wait for vaccines, despite the warp speed creation, approval, and distribution of vaccines in many countries, contributed to pandemic fatigue?

(4) Have the mixed messages arising from a heated Presidential election campaign contributed to pandemic fatigue?

Given the prevalence of escaped mutants, and the supply chain problems in the production and distribution of approved vaccines, public healthcare policy should be directed toward encouraging rather than mandating strict adherence to NCIs, as well as extending the data analysis in the informative report to capture important factors that have changed in the interim.

102. Further Unanswered Questions For Cancer Patients During COVID-19

The experts in Virnig and Nikpay (2020) evaluate sensitively and analytically a number of unanswered questions, or known unknowns, regarding cancer patients during the COVID-19 pandemic.

Although the list will be extended as additional known unknowns come to light in the future, further unanswered questions for cancer patients include:

(1) Is it safe to be vaccinated against COVID-19?

(2) Should there be prioritization or deprioritization for vaccination?

(3) Is vaccination against COVID-19 regarded as aggressive or less aggressive critical care?

(4) Should residents in palliative care be vaccinated?

(5) Does vaccination add to the quality of life?

(6) What are the effects of mutated strains and variants of the original wild type coronavirus?

(7) Should nonpharmaceutical interventions be considered in critical care?

(8) What are the effects of mild, medium or severe COVID-19?

(9) Should all types of cancer be considered in combination with vaccination?

(10) Is the cancer primary or secondary?

(11) What are the likely additional long haul effects from COVID-19?

(12) Should mental healthcare for COVID-19 be expanded?

- (13) What are the effects of the second and higher waves of COVID-19 infections?
- (14) Should overlapping responsibilities between the federal and state governments for COVID-19 be extended?
- (15) How will healthcare access, hospitalization, and healthcare insurance premiums change to cover protect against COVID-19 and cancer?

103. How are Children Affected by COVID-19?

As discussed in Thompson and Rasmussen (2021), personal hygiene, social distancing, and masking are essential to mitigate the effects of COVID-19, regardless of the availability of several approved vaccines.

As children are not included in clinical trials, the question remains whether the approved vaccines are safe, effective, and durable, especially for children who are immunocompromised from preexisting conditions.

In the month since the informative guide was reported, the escaped mutants from the UK, South Africa, Brazil, and possibly the USA, have established themselves globally, with the UK now dealing with the mutated domestic strain and also from South Africa.

Even if safe flu shots are given to children, how will this provide any protection against the original wild-type coronavirus, or any of its mutations?

It is essential to provide clear answers to the following additional questions as to whether children are more or less likely to:

- (1) become infected by COVID-19?
- (2) transmit and infect others?
- (3) be protected through vaccination?

104. Is the California Variant Another COVID-19 Escaped Mutant?

As discussed in Zhang, Davis, Chen, Sincuir Martinez et al. (2021), if the mutant variants from the UK, South Africa, Brazil, and possibly Spain, were not sufficiently disconcerting, the

USA might have another escaped mutant that could be more transmissible, infectious, and contagious than the original wild-type coronavirus (COVID-19).

Clear and informative responses to the following queries regarding the California variant would be helpful to healthcare authorities:

- (1) How virulent is it compared with the other known mutations?
- (2) How easily is it spread through aerosols?
- (3) Will infection with the original strain provide protection against recurrence against any variants?
- (4) How are safety, efficacy, and durability of the approved vaccines affected?
- (5) Which vaccines are most likely to retain potency?
- (6) Is it likely to replace the original strain of SARS-CoV-2 as the dominant strain in the USA?
- (7) How will a combination with one or more other variants affect the spread and severity of COVID-19 in the USA?
- (8) How likely is it to mutate again, and where might this occur?

105. Tracking Escaped Mutants of SARS-CoV-2 and COVID-19

The emergence and detection of viral variants to the original wild-type coronavirus that led to COVID-19 raises a number of troubling issues in addition to those discussed in the editorial by Mascola, Graham and Fauci (2021), including:

- (1) How does any shift from variant to strain to lineage of a virus affect its transmissible, infectious, contagious, and virulent nature?
- (2) Can mutant variants be predicted on the basis of the receptors and RNA loads of the original virus and its several mutations, such as those from the UK, South Africa, Brazil, and possibly Spain?
- (3) Can the safety, efficacy, and durability of the currently approved vaccines be determined against the viral variants?
- (4) Can the dominance and durability of specific viral variants be predicted?

- (5) How do such shifts affect the herd immunity strategy of a high threshold of the population being vaccinated or recovering from prior infection of the disease?
- (6) How many viral mutations are required for substantive immune resistance to approved vaccines?
- (7) Are there any clinical trials that have tested the approved vaccines against the viral variants?
- (8) How likely is infection from any viral variants between the first and second jabs of the prime and booster shots from the two-shot vaccines?
- (9) What is the optimal timing between the first and second shots against the viral variants?
- (10) What characteristics in Southern California have led to a possible viral variant, as compared with other nearby and distant States?

106. Optimal Timing Separation and Strength of Prime and Booster Shots

Although mentioned in Livingston (2021), for vaccines that require a prime shot followed by a booster, where is the clinical evidence that the optimal timing separation between the shots is 3 weeks for Pfizer, 4 weeks for Moderna, and between one and three months for AstraZeneca?

Moreover, what was the strength of the prime shot when only one jab was given, and what were the strengths of the prime and booster shots when two shots were given?

107. Confounding Errors in Response to COVID-19

In addition to the prescient information in Gostin (2021) as to what went wrong in dealing with the COVID-19 pandemic might be added:

- (1) the scientific community, especially the medical discipline, did not push back sufficiently hard against the fake news nonsense that was being distributed in Twitter feeds and other social media;
- (2) the reliance on a China-centric WHO that did not act sufficiently fast or pro-actively in response to the initial information about an unknown form of pneumonia that was wreaking havoc in Wuhan, China.

108. Durability and Duration of Approved Vaccines Against Escaped Mutants

The informative viewpoint by experts from the CDC and NIH in Walensky, Walke and Fauci (2021) discusses the challenges and opportunities of the escaped mutants of SARS-CoV-2 that are of concern in the USA, primarily from the UK, South Africa, and Brazil.

Since the research findings were published, several additional strains have also emerged in the USA.

These mutated variants are generally more highly transmissible, infectious, and contagious, reduce the potency of the approved vaccines, including reinfection, and increase the severity of infection from the disease.

The challenges and opportunities in the title of the viewpoint include responding to the following unasked and/or unanswered queries:

- (1) The report does not mention the durability of efficacy of the approved vaccines against the escaped mutants after the prime and booster shots at 21 days (for Pfizer) and at 28 days (for Moderna).
- (2) Neither Pfizer nor Moderna has provided clinical evidence regarding the optimality of the arbitrarily chosen temporal duration between the two shots at 21 and 28 days, respectively.

109. Hospital Mortality and Hospice Discharge of COVID-19 Patients Depend on Population Size

The research letter by Raschke, Agarwal, Rangan, Heise and Curry (2021) found that, based on 20 unique COVID-19 triage policies, the SOFA score was not sufficiently accurate in determining the probable mortality of COVID-19 patients

Regardless of whether mechanical ventilation was required for the seriously ill COVID-19 patients, the reported small variation in SOFA scores for 2546 COVID -19 patients between 1 March and 31 August 2020 led to insignificant results of SOFA in predicting the main outcome variables of hospital mortality and hospice discharge.

The prescient report ends with the caveat: “A better option is needed that incorporates variables specifically related to mortality in patients with COVID-19 pneumonia requiring mechanical ventilation.”

This is perfectly correct, and is straightforward to rectify.

The numbers of cases of COVID-19, admission to ICUs, and probable mortality are all directly related to the city, state, regional, or national population sizes, which were not considered as conditioning factors in the empirical analysis.

Conditioning on the population size would significantly improve the predictive ability of any empirical model, either by normalizing the hospital mortality and hospice discharge variables by population size, or by adding the missing population size variable to the models explaining hospital mortality and hospice discharge.

110. Concluding Remarks

The world community has been changed irrevocably by the highly infectious and mutating SARS-CoV-2 virus that causes the COVID-19 disease. Significant changes are being made to every aspect of society and the economy, including healthcare policy, treatment, and outcomes, including physical and mental health, opening up of the economy, restrictions on tourism, travel, and hospitality, employment, unemployment insurance, education, schooling, social distancing, self isolation, quarantining, and lockdowns, among many others.

The necessary research output on COVID-19 has been revolutionary, especially in the medical and biomedical sciences, where the search for a vaccine is essential for the world to have a semblance of normality in the era of COVID-19. A substantial amount of the recent advanced research has been distributed in the leading medical journals, including the *Journal of the American Medical Association (JAMA)*, where the latest research is distributed on a daily basis, and where comments can also be published. The COVID-19 pandemic has also highlighted the lack of preparation by the World Health Organization (WHO) and every national government worldwide to deal with such unpredictable structural changes in an increasingly volatile world.

The paper provided a critique of 109 interesting and highly topical research papers that have been published in the *Journal of the American Medical Association (JAMA)*. The diverse topics, which include treating influenza and COVID-19 simultaneously, dealing with a second wave of

COVID-19 in Beijing, honesty is best for known and unknown GAWI and WIST, unreliability of asymptomatic COVID-19 testing outcomes for children, the effectiveness of flu vaccines, acute anxiety during COVID-19, MAID as an end of life option, longer-term effects of corticosteroids on the mortality of critically ill COVID-19 patients, isolation, loneliness and psychological distress during COVID-19, the selection of volunteers for COVID-19 vaccine trials, the mental health of children and adolescents during COVID-19, fertility preservation through hormonal intervention for transgender adolescents, safe, effective and affordable COVID-19 vaccines, essential requirements for acceptance of a COVID-19 vaccine, ischemic stroke rates from COVID-19 and influenza, mandatory COVID-19 vaccination of children, COVID-19 asymptomatic children and adults, Who Dares Wins (Qui Audet Adipiscitur), even against COVID-19, global health security index and responses to COVID-19, quality of life and dying, immunity from COVID-19, whom to trust or not to trust regarding COVID-19, the value of health care for cancer patients, you cannot fight COVID-19 alone, previous medical research bodes well for a COVID-19 vaccine, causality between hypertension and COVID-19, coffee consumption and metastatic colorectal cancer, improving statistical analysis of health policies on children and adolescents, COVID-19 does not respect anyone, politics diminishes the integrity and reputation of healthcare agencies, primary, secondary and tertiary cancers in the lung, health care should include everyone, especially for COVID-19, prioritizing access to COVID-19 vaccines, further questions about COVID-19 vaccines, estimating direct and indirect excess deaths from COVID-19, herd immunity for COVID-19, daily eyeglass wear and COVID-19 infection, using anything that prevents the spread of COVID-19, deferral of care for serious non-COVID-19 conditions, society's united fight against depression and suicide, the positive outcomes in delaying low-risk thyroid cancer treatment during COVID-19, the likely future toll from COVID-19, excluding older persons from vaccine and clinical trials for COVID-19, peaceful miracles make the moment, dealing with COVID-19 science denial and conspiracy theories, masking and testing should be mandatory for COVID-19, journal reputation is established by scientific creativity and destroyed by political interference, impact and importance of medical research on COVID-19, support for COVID-19 long haulers, possible reinfection and long term recovery from COVID-19, Wabi-Sabi and the beauty of imperfection, good, better and best testing for COVID-19, surgical technical skill and long-term cancer survival, and prior negative recovery from RT-PCR test results for COVID-19, age, frailty, and postoperative surgical outcomes, and all journals should have diversity in the

editorial and peer review process, an encompassing digital open access journal - JAMA Health Forum, righting inequities through otolaryngology in a COVID-19 normal America, resilient mental health in older adults under COVID-19, preventing suicides in a COVID-19 normal world, COVID-19 and voluntary participation in cancer clinical trials, herd immunity and COVID-19, psychological distress of US adults under COVID-19, repurposing drugs for COVID-19, same data + different models = different results, how do surges in COVID-19 affect healthcare spending?, causality between sedentary behavior and cancer mortality, overdose cardiac arrests and emergency medicine during COVID-19, COVID-19 asymptomatic children versus adults, why is care for serious non-COVID-19 conditions seemingly deferred?, confidentiality in a world of COVID-19 and fake news, mental healthcare data disrupted by COVID-19, do N95 face masks protect against COVID-19?, the necessity of face masks during COVID-19, nurses in COVID-19 vaccine trials, eye protection for COVID-19 ventilated patients, and healthcare access, social needs, unemployment insurance during COVID-19, pre-eminent experts evaluate the distribution of COVID-19 vaccines, and the effects of current vaccines against SARS-CoV-2 and COVID-19 mutations, unbearable suffering needs to be respected, varied public attitudes toward COVID-19 vaccine mandates, enanthems, exanthems, and COVID-19, a wish list for a COVID-19 new year, critical statistical rigour before and during COVID-19, accepting vaccines is essential against COVID-19, and social distancing, health behaviour, cancer outcomes during COVID-19, readmission and death from COVID-19 after hospital discharge, beneficial lessons from COVID-19, estimating racial disparities in COVID-19 testing, paying people to be vaccinated against COVID-19, COVID-19 mutations and vaccines, mandatory vaccinations against COVID-19, allergic reactions to the first dose of the Pfizer vaccine, neutralization of monoclonal antibodies for COVID-19, pricing teledermatology during COVID-19, SARS-CoV-2 and COVID-19 are spreading virtually everywhere, transmission of SARS-CoV-2 and COVID-19 by children, addressing racial and ethnic health disparities during COVID-19, race and medical research during and after COVID-19, adherence to nonpharmaceutical interventions during COVID-19, further unanswered questions for cancer patients during COVID-19, how are children affected by COVID-19?, is the California variant another COVID-19 escaped mutant?, tracking escaped mutants of SARS-CoV-2 and COVID-19, optimal timing separation and strength of prime and booster shots, confounding errors in response to COVID-19, durability and duration of approved vaccines against escaped mutants, and hospital mortality and hospice discharge of COVID-19 patients depend on

population size, demonstrate that there are still many unanswered questions regarding the impact of COVID-19 on the international community.

As COVID-19 is exploding on a daily basis, the number of total cases continues to expand exponentially rather than flattening, and as mutations are being detected, eternal vigilance is essential as the increasing higher waves keep churning.

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