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Cross-sectional evaluation of medical reversals among National Institute of Health guideline practices implemented during the COVID-19 pandemic: how often did experts err in a time of crisis?

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ABSTRACT

Objective The COVID-19 pandemic required the rapid and often widespread implementation of medical practices without robust data. Many of these practices have since been tested in large, randomised trials and were found to be in error. We sought to identify incorrect recommendations, or reversals, among National Institute of Health COVID-19 guidelines and Food and Drug Administration (FDA) approvals and authorisations.

Design Retrospective cross-sectional study.

Participants Recommended medical practices and FDA authorisations or approvals for COVID-19 prevention, treatment and/or management.

Main outcome measures The frequency and characteristics of COVID-19 medical reversals, defined as practices that were implemented and/or recommended during the pandemic, but were later tested in randomised trials that failed to find benefit.

Results We found 332 COVID-19 recommendations. 85 (25.6%) opposed a medical practice, 23 (6.9%) were to continue a pre-COVID standard of care without deviation and 224 (67.5%) reccommended a new medical practice. We found randomised trials assessing 72 of these practices (32.1%), among which 25 (35%) were found to be in error and deemed medical reversals. Among medical reversals, 21 (84%) were prescription medications and 1 (4%) was convalescent plasma. 17 (68%) were repurposed medications. Two (8%) were procedures or mechanical interventions and one (4%) was a device. 16 (64%) reversals pertained to the hospital setting (4 to intensive care units), 4 (16%) were non-specific (ie, applicable to any setting), 4 (16%) pertained to a non-hospital setting and 1 pertained to healthcare workers.

Conclusion When faced with a novel pandemic, policymakers rapidly made hundreds of specific medical recommendations. More than two out of three were never robustly tested. Among practices tested in a randomised fashion, one in three was made in error. Pandemic recommendation errors were substantial. Early and coordinated efforts to initiate randomised trials, even during dire situations, may mitigate the perpetuation of ineffective practices.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We included recommendations and practices during the pandemic, which were made by the US public health agency.
⇒ We relied on high-quality randomised trials to determine whether interventions were effective or not.
⇒ The list of evaluated practices is not exhaustive of all practices during the COVID-19 pandemic, since many practices were used off-label.

INTRODUCTION

The COVID-19 pandemic was an unprecedented medical emergency. Globally, 7 million people died during the pandemic.[1] US expert groups, such as the National Institute of Health (NIH) and US Food and Drug Administration (FDA) issued medical practice recommendations, approvals and authorisations in the wake of the crisis. Over time, emerging evidence has found that some of these recommendations were made in error. Errors may have contributed to drug shortages (eg, hydroxychloroquine) or even iatrogenic harm to individuals undergoing interventions that did not help. As with practices implemented in prior pandemics,[2] many of the practices that were adopted early in the pandemic have been abandoned after trials showed that they were ineffective.

Previously, we and others have described the concept of medical reversal. A reversal occurs when medical providers adopt a practice without robust evidence of efficacy. Later, often after considerable time, robust studies are performed, and some practices are found to be in error. Previously, we have found that 40% of widely adopted medical practices were reversed.[3] A separate analysis revealed over 396 medical practices that were incorrect.[4] Notably, reversals are not merely

course corrections in medicine, where the evidence changed, but represent practices that were always incorrect. Reversals have spanned all domains, including drugs, devices, procedures, systems interventions and even screening campaigns. Large systematic analyses have revealed hundreds of reversals across general medicine, cardiology, oncology, cardiopulmonary resuscitation and gastroenterology.[3–8]

In this paper, we systematically review recommendations made in the USA by the NIH and FDA during the COVID-19 pandemic. We ask, what fraction of recommendations and authorisations is ultimately studied in randomised trials? Among those studied, we ask, how often are practices found to be in error? We provide a list of reversed COVID-19 practices and draw lessons for future crises.

METHODS

We sought to assemble a set of public health and medical recommendations made by the NIH and/or the US FDA (authorisations and approvals) during the COVID-19 pandemic. For these recommendations, we sought to describe the ultimate evidence base, and whether the recommendation was later tested or not tested in randomised fashion, and if tested, validated or contradicted. The latter we term medical reversal.

Dataset generation

We searched current and archived NIH COVID-19 Treatment Guidelines on 23 October 2023 to generate a list of current and formerly recommended therapies and interventions.[9] We extracted recommendations that were either for or against a medical practice (eg, drug, therapy or procedure).

We extracted the grade of evidence that was assigned to the recommendation. Recommendations extracted were either newly added, reversed or had changes that affected to whom the recommendations applied. We included recommendations for both inpatient and outpatient practices. We did not include NIH statements that indicated insufficient evidence, as per NIH, for making a recommendation for or against a practice (eg, 'There are insufficient data for the Panel to recommend for or against the use of sarilumab for the treatment of COVID-19'). We also did not include statements about populations that should be prioritised for treatment or therapy in settings where these were limited or recommendations that had changing evidence but without changes to the actual recommendation.

We also searched the US FDA's Emergency Use Authorization (EUA) page for drugs, vaccines and other biological products that had received COVID-19 EUA.[10]

After categorising each recommendation (eg, venous thromboembolism prophylaxis, remdesivir drug, prone positioning), we removed any duplicate recommendations, and subcategorised as a recommendation for a practice, recommendation against a practice or recommendation to continue standard, pre-COVID-19 care (eg, 'Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications').

For each of the practices that had a recommendation for it, we searched PubMed for randomised studies that tested the practice (30 October 2023–27 November 2023). Generally, our search strategy included the name of the drug, therapy or procedure 'and' (Boolean operator) covid. For relevant trials, we noted whether they were positive, negative or equivocal. If the trial was negative, it was considered as a potential reversal, as all of these had been included in guidelines or approvals that promoted its widespread use. The outcome to determine whether a trial was positive or negative was the pre-specified primary outcome of the trial, as specified by the study author, unless overall survival, as a secondary outcome, was significantly higher in one group. When multiple trials were relevant and had differing results, we searched for a meta-analysis using the same search strategy as randomised trials. If one could not be found, we considered the conclusion as equivocal (ie, not a reversal), unless one trial was a large and formative trial. For all interventions, we looked for patient outcomes rather than biological markers. For example, when looking at vaccine studies, we only looked at those reporting on infections or hospitalisations and not immunogenicity.

Once a list of potential reversals was developed, each one was reviewed by two practicing physicians (ASC and VP).

Statistical analysis

Descriptive statistics are reported. Data were analysed in R statistical software (V.4.2.1).

In accordance with 45 CFR §46.102(f), this study was not submitted for institutional review board approval because it involved publicly available data and did not involve individual patient data.

Patient and public involvement

This research is a comprehensive analysis of guidelines developed by NIH panellists, sometimes with comments from the public. Given that ours is a meta-research study, reviewing the level of evidence for numerous medical practices spanning many domains of medical expertise was needed to determine appropriateness and efficacy of medical interventions, and therefore, it was not feasible to have patient involvement in this part of the research.

RESULTS

We found 329 recommendations made in NIH COVID-19 Treatment Guidelines and 18 approvals and authorisations given by FDA. All but 3 of the FDA approvals or authorisations were integrated into recommendations by the NIH, for a total of 332 recommendations (including the 3 approvals) in our dataset. Of the 332 recommendations, 85 (26%) advocated against a practice, 23 (7%)

Table 1 Medical reversals in COVID-19 guidelines

Therapy	RCT/publication	Acuity of care	Number	Primary endpoint
Anticoagulation (therapeutic dosing for VTE prophylaxis or prevention of COVID-19 progression)	ACTIV-4a / ATTACC / REMAP-CAP[16]	Non-ICU	2244	Organ support-free days
		ICU	1098	Organ support-free days
	RAPID[24]	Non-ICU	465	Composite*
	INSPIRATION[25]	ICU	562	Composite*
	RECOVERY[26]	All	14 892	Mortality
	COVID-PACT[27]	ICU	582	Composite*
Azithromycin	RECOVERY[28]	All	7763	Mortality
Colchicine	RECOVERY[29]	All	11 340	Mortality
	COLCOVID[30]	All	1279	Composite*
	GRECCO-19[31]	All	105	Composite*
Hydroxy-chloroquine	WHO Solidarity[32]	All	1863	Mortality
	DisCoVeRy[33]	All	293	Composite*
Chloroquine	Axfors *et al* 2021[15 34]	All	357	Mix
Interferons	ACTT-3[35]	All	969	Composite (not mortality)
	WHO Solidarity[32]	All	4751	Mortality
	DisCoVeRy[33]	All	293	Composite*
Ivermectin	Abd-Elsalam *et al*, 2021[36]	All	164	Mortality
Lopinavir/ritonavir	RECOVERY[18]	All	5040	Mortality
	DisCoVeRy[33]	All	293	Composite*
Inhaled pulmonary vasodilator (mechanically ventilated)	Haeberle *et al*, 2023[37]	ICU	150	Mortality
	Di Fenza *et al*, 2023[38]	ICU	200	Mortality
Low-dose corticosteroid (refractory shock)	REMAP-CAP[39]	ICU	614	Organ support
Anakinra	ANA-COVID-GEAS[40]	All	179	Organ support
	SAVE-MORE[41]	All	606	Composite*
Convalescent plasma	Mihalek *et al*, 2023[42]	All	11 558	Mortality
Remdesivir (mechanically ventilated)	ACTT-1[43]	ICU	1062	Time to recovery
Remdesivir (non-intubated)	WHO Solidarity[44]	All	4751	Mortality
	CATCO[45]	All	1282	Mortality
	DisCoVeRy[32]	All	293	Composite*
Anticoagulation	OVID[46]	All	472	Composite*
	ETHIC[47]	All	219	Composite*
Azithromycin	PRINCIPLE[48]	All	1415	Composite*
Colchicine	COLCORONA[49]	All	4488	Composite*
	PRINCIPLE[50]	All	1301	Composite*
Hydroxychloroquine	Skipper *et al*, 2020[51]	All	491	Symptom change / resolution
Interferons	Jagannathan *et al*, 2021[52]	All	120	Resolution of viral shedding
	Feld *et al*, 2021[53]	All	60	Resolution of viral shedding
Ivermectin	TOGETHER[19]	All	1358	Composite (not mortality)
	IVERCOR-COVID19[54]	All	501	Hospitalisation
	I-TECH[55]	All	490	Development of hypoxia
	López-Medina *et al*, 2021[56]	All	400	Symptom change / resolution
	Ravikirti *et al*, 2021[57]	All	115	Resolution of viral shedding
	RIVET-COV[58]	All	157	Resolution of viral shedding
	COVER[59]	All	93	Resolution of viral shedding
Molnupiravir	PANORAMIC[60]	All	26 411	Composite (not mortality)

Continued

Table 1 Continued

Therapy	RCT/publication	Acuity of care	Number	Primary endpoint
Intravenous immunoglobulin	Lai *et al*, 2022 (meta-analysis)[61]	All	472	Mix
Prone positioning in awake, non-mechanically ventilated patients	Qin *et al*, 2023[62]	Non-ICU	2324	Mix
N-95 masks for healthcare workers (usual care)	Loeb *et al*, 2022[63]	All	1009	Virus detection
High-flow oxygen in respiratory failure	SOHO-COVID[64]	All	711	Mortality
	RECOVERY-RS[65]	All	1273	Composite*

*Composite endpoint includes mortality.
ICU, intensive care unit; RCT, randomised control trial; VTE, venous thrombus embolism.

advocated to continue pre-COVID standard of care and 224 (67%) were recommendations for a novel practice. We found randomised studies testing the novel practice for 72 of 224 (32%) recommendations. Among these, 25 (35%) were found to be contradicted—recommendations made in error, or what we term 'medical reversals'.

In table 1, we highlight the characteristics of the identified medical reversals. 21 (84%) were prescription medications and 1 (4%) was convalescent plasma. 17 (68%) were re-purposed medications. Two (8%) were procedures or mechanical interventions and one (4%) was a device. 16 (64%) reversals were specific to the hospital setting (4 specific to intensive care units), 4 (16%) were for any setting (ie, non-specific), 4 (16%) were specific to a non-hospital setting and 1 (4%) was specific to healthcare workers.

Each of the 25 reversals was confirmed as an error by 1–7 unique randomised studies, for a total of 50 randomised trials. Randomised control trials (RCT) supporting the reversals had a median sample size of 582 (IQR: 293–1401). RCTs were double blinded in 12 (24%) instances, single blinded in 3 (6%) instances and unblinded in 33 (66%). Two instances were a mix of blinded and unblinded studies. The primary endpoint was a composite endpoint including mortality in 17 (34%) studies, mortality in 13 (26%) instances, viral detection in 6 (12%) studies, organ support-free days in 4 (8%) studies, symptom change/resolution in 3 (6%) studies and another outcome in 4 studies (8%). Randomisation was 1:1 in 39 (78%) studies, skewed in 9 (18%) and a mix for 2 (4%) studies. 35 (70%) trials were funded by a governmental organisation, 17 (34%) by philanthropic organisations, 12 (24%) by universities/hospitals, 9 (18%) by industry and 2 (4%) with no or unknown funding sources.

DISCUSSION

During the COVID-19 pandemic, policymakers deployed a breadth of treatment and practice recommendations. These spanned many domains, including pharmacological, non-pharmacological, and inpatient and outpatient settings. We found over 332 recommendations—some for or against medical practices—made by US expert bodies and US drug regulators. Of these, 224 were positive recommendations. Most were never robustly studied in randomised trials. Just 72 (33%) underwent testing in randomised studies. When tested, over one in three (35%) recommendations were found to be in error. We call these medical reversals.

In our table, we detail and catalogue COVID-19 medical reversals. Many refer to specific and costly medical products, such as anakinra and remdesivir. Others pertain to pooled haematopoietic products that are laboriously collected, for example, convalescent plasma. Other examples refer to drugs with serious risks and narrow therapeutic windows, such as full dose anticoagulation. In at least one case, a reversal pertained to non-pharmacologic intervention. What lessons can we learn?

First, while it was natural in an unprecedented emergency to make recommendations and provide guidelines even when evidence is uncertain, our study highlights that too often evidence generation never occurs. Two out of three recommendations were never studied in randomised fashion. Given the cost and time required of medical practices, persistent uncertainty is undesirable and untenable.

Second, the use of repurposed medications is reasonable in a time of crisis. However, we found many did not work. This is particularly problematic for costly drugs, and those that may cause harm. The suspected utility of hydroxychloroquine was first elevated by members of the scientific community, and deployed at top US hospitals, and then subsequently by the US president.[11] The drug was initially given EUA on 28 March 2020.[12] Later, the FDA revoked hydroxychloroquine's EUA in June of 2020, followed by the results of several notable trials failing to find clinical benefit for hydroxychloroquine's use in patients with COVID-19.[12–14] Ultimately, a meta-analysis of hydroxychloroquine showed an increased risk of death.[15]

Third, changing well-established guidelines for inpatient and outpatient anticoagulation entails significant risk. Anticoagulants were studied in hospitalised patients because of the suspected morbidity and mortality associated with COVID-19-related pro-thrombotic states. In an RCT jointly conducted by REMAP-CAP, ACTIV-4a and ATTACC, investigators failed to demonstrate that therapeutic-dose anticoagulation improved

survival or independence from cardiovascular or respiratory organ support.[16] We found that many recommendations to intensify anticoagulation were made in error, and ultimately reversed. It is possible that excess bleeding events occurred because of this error.

Fourth, although our study focused on the USA, other reversals occurred globally. For example, ivermectin was widely distributed by eight Latin American countries,[17] but the ACTIV-6 and TOGETHER trials failed to show this practice as being effective.[18 19]

Fifth, our work suggests the pressing need for a US-based system to iteratively assess novel recommendations in real-time, randomised studies. The UK rapidly deployed the RECOVERY platform. RECOVERY is a multiplatform, adaptive randomised trial designed to test treatments of COVID-19 with rapid uptake, some of which were unorthodox and were being debated in the medical community.[20] A similar system, if in place in the USA, could have settled many persistent debates, including the appropriate role of nirmatrelvir/ritonavir.[21]

Sixth, the overall rate of reversal of 35% is broadly consistent with our prior empirical work in medicine. It may be seen by some as reassuring that the rate of error in a time of crisis is broadly similar to the rate of error across medicine. Perhaps this figure reflects the general appetite to accept medical practice based on bioplausibility may be fairly stable across situation and time. On the other hand, it may be concerning that the rate of reversal is as high in a pandemic situation where the resources and ability of many more experts may be marshalled as it is in routine practice, which faces greater financial and work force constraints.

Prior work has sought to compile current COVID-19 recommendations, and some have provided limited evidence of the quality of guidelines, but our work is the first, to our knowledge, to systematically review COVID-19 recommendations and drug approvals that have been implemented or approved, but studies later showed a lack of benefit from these practices.[22] These situations, which we call 'medical reversals', are not unique to the COVID-19 pandemic, as they have been shown to occur in many medical specialties.[3 4 23]

There are several limitations to our analysis. First, the number of unique recommendations could be subjective since wording for the recommendations sometimes changed. Sometimes, these changes led to notably different recommendations such as clarifying whether the recommendation was for hospitalised versus non-hospitalised. If there was a question, we kept the recommendations as separate, which likely resulted in a greater number of total recommendations, thus underestimating the percentage of recommendations reversed. Second, we did not do an exhaustive search of trials testing each intervention. We used PubMed, which would identify the landmark trials for interventions (if any), and our methods again likely resulted in an underestimation of practices considered reversals. However, to be fair to the guidelines, we wanted to make sure that only high-quality studies with meaningful clinical outcomes were used to determine practices that were ineffective, and these would have been most likely captured on PubMed. Because COVID-19 is a fairly novel condition, some of these therapies have yet to be tested, and future testing during follow-up years may reveal other practices that are ineffective against the virus. Finally, our findings are not generalisable to all countries, as different countries may have different guidelines and healthcare systems, which may result in different effects of therapies.

CONCLUSION

During the COVID-19 pandemic, the US NIH and FDA made hundreds of medical practice recommendations, authorisations and approvals. Two of three were never studied in randomised trials, and when tested, one of three was found to be in error. These reversals spanned all domains of medicine—inpatient and outpatient—pharmacological and non-pharmacological. Future research structures should be developed to rapidly test recommendations and practices in times of crisis and course correct when initial impressions are incorrect. Medical reversals frequently plagued the COVID-19 pandemic response.

Contributors ASC, VP and AJK conceptualised the study; AJK and AH abstracted data and conducted data analysis; AJK wrote first drat, and all other authors approved final draft. AH and VP take full responsibility for the data and are responsible for the overall content as guarantor. VP provided funding.

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