

Vaccine Mandates and Evidence-Based Medicine: A Narrative Review

Mitchell B. Liester¹

Abstract

Background: Evidence-based medicine (EBM), as defined by Sackett and colleagues, requires the integration of three equally necessary components: the best available research evidence, individual clinical expertise, and patient values and preferences. All three of these components are seriously compromised in current vaccination policy. Vaccine mandates, as implemented during the COVID-19 pandemic, explicitly eliminated the second and third components—clinical expertise and patient autonomy—while relying exclusively on published research evidence as justification. Yet that first component is itself deeply unreliable. Widespread reproducibility failures, systematic publication bias, selective outcome reporting, and pervasive industry conflicts of interest have so corrupted the published literature that editors of the world's most prestigious medical journals have declared that much of it cannot be trusted. The result is a policy framework in which none of EBM's three pillars is intact. This narrative review examines (1) the principles of EBM and how vaccine mandates deviate from them, (2) the documented unreliability of published medical research, (3) the ethical and legal frameworks governing informed consent, (4) the historical precedents of medical consensus errors, and (5) recommendations for restoring EBM principles to vac-

cination policy.

Methods: A narrative review of the peer-reviewed literature, regulatory documents, historical case studies, and editorials from high-impact medical journals was conducted. Sources were identified through PubMed, MEDLINE, and the Cochrane Library.

Results: The peer-reviewed literature documents: (a) unreliability in published clinical research, including problems of reproducibility, publication bias, and conflicts of interest, (b) significant individual variability in vaccine risk-benefit profiles based on age, sex, prior immunity, and comorbidities, (c) ethical and legal frameworks that recognize the sanctity of informed consent, and (d) historical examples of widespread medical harm resulting from consensus-driven interventions that bypassed individualized assessment.

Conclusions: Vaccine mandates, as currently implemented, are incompatible with EBM. A restoration of EBM's three-component model that includes the best available evidence, clinical judgment, and patient autonomy is necessary to ensure that vaccination policy meets the ethical and scientific standards of modern medicine.

Keywords: Evidence-based medicine, vaccine mandates, informed consent, clinical autonomy, medical ethics, patient autonomy

¹ University of Colorado School of Medicine, Colorado, USA

Corresponding author:

Mitchell B. Liester, MD, PC
University of Colorado School of Medicine
153 Washington St, Ste 103, Monument, CO 80132, USA
Tel: 719-488-0024
Fax: 719-488-6672
Email: mitchell.liester@cuanschutz.edu

Introduction

Evidence-based medicine (EBM) is widely regarded as the gold standard of clinical practice. From the time it was conceived in the early 1990s, it has changed how clinicians evaluate research, make treatment decisions, and communicate risks and benefits to patients. Yet despite the prominence of EBM rhetoric in medical education, public health communication, and pharmaceutical marketing, the basic principles underlying EBM are frequently misapplied, selectively invoked, or abandoned altogether.

Vaccine mandates represent one of the most conspicuous examples of how EBM principles are ignored in contemporary medicine. These mandates require individuals to receive specific vaccines as conditions of employment, school enrollment, military service, or participation in certain public activities, without individualized risk-benefit assessment and without informed consent. The term “evidence-based” is frequently used to justify these mandates. Yet, as this review demonstrates, mandates eliminate two of EBM’s three required components, and the third component involves well-documented reliability problems.

This article is not an argument against vaccines. Rather, this review argues that the mandatory administration of vaccines without individualized clinical assessment or respect for patient autonomy, violates the basic principles of EBM and poses risks that often are not adequately acknowledged in policy discussions.

The present narrative review examines: (1) the three-component model of EBM and how vaccine mandates deviate from it, (2) the documented problems with published medical research, (3) evidence for individual variability in vaccine risk-benefit ratios, (4) the ethical and legal frameworks governing informed consent, (5) historical examples of medical harm caused by enforcing consensus without individualized judgment, and (6) recommendations for restoring EBM principles to vaccination policy.

The Three-Component Model of Evidence-Based Medicine

The term “evidence-based medicine” first appeared in the medical literature in 1991. (1) However, the standard definition was established in 1996 by David Sackett and colleagues in the *British Medical Journal*. (2) They defined EBM as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of indi-

vidual patients.” Their definition emphasized that EBM requires the integration of three components:

- The best available research evidence from systematic clinical investigation
- Individual clinical expertise: the proficiency and judgment that individual clinicians acquire through their clinical experience and practice, and
- Patient values and preferences: the unique preferences, concerns, and expectations that each patient brings to a clinical encounter (2)

Sackett and colleagues were explicit that neither the evidence alone, nor clinical expertise alone, nor patient preferences alone were sufficient:

“Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without current best evidence, practice risks becoming rapidly out of date, to the detriment of patients.” (2)

This framework was further elaborated in subsequent literature. (3,4) Straus and McAlister noted that critics had identified two persistent misunderstandings of EBM. First, the misapplication of EBM ignores individual clinical expertise and patient values, presenting a single strand of research data as if it constituted the complete EBM framework. Second, this misrepresentation produces “cookbook medicine,” that is applied uniformly across patient populations. (3) To be clear, these are not flaws of EBM itself but of its selective and incomplete application—a practice in which population-level research findings alone are mislabeled as “evidence-based” while the other two equally required components, clinical expertise and patient values, are discarded. Both misapplications are replicated by vaccine mandates: they remove individualized expertise and patient values, and apply a single protocol to entire populations. It is worth noting how the term “evidence-based medicine” itself has come to function as a rhetorical stop sign in contemporary medical discourse. Rather than serving as an invitation to rigorous inquiry, the phrase is frequently deployed by hospital systems, public health agencies, and policymakers to delegitimize critical thinking and suppress dissent. Clinicians who raise questions about a mandated intervention are dismissed with the assertion that “the science is settled” or that the intervention is simply “evidence-based.” This mis-

use of EBM terminology converts a sophisticated three-component framework into a blunt instrument of institutional conformity. In reality, the science is rarely if ever settled in medicine, and a genuine commitment to EBM demands that opposing viewpoints and heterodox data be examined rather than silenced. Cookbook medicine, which is the uniform application of population-level protocols to individual patients without clinical judgment, is precisely what Sackett's original framework was designed to prevent.

How Vaccine Mandates Deviate from the Three-Component Model

Vaccine mandates eliminate the second and third components of the EBM framework and rely exclusively on "the evidence." This deviation from EBM has three significant implications:

1. **Elimination of Individual Clinical Expertise**
A physician evaluating whether to recommend any medical intervention must assess whether the available evidence is applicable to their patient. This requires knowledge of the patient's medical history, current medications, immune status, prior adverse reactions, genetic predispositions, risk factors, and individual circumstances. (5) Under a mandate, this individualized assessment is eliminated. The clinician is reduced from a practicing physician exercising professional judgment to a policy enforcer administering a predetermined intervention.

Evidence-based medicine recognizes that population-level findings do not automatically translate to individual patients. Aggregate risk-benefit ratios can diverge substantially from those relevant to a specific clinical context, (6) and individual variability in treatment response carries significant clinical consequences. (7)
2. **Elimination of Patient Values and Preferences**
The right of competent individuals to make autonomous medical decisions is a cornerstone of both medical ethics and law. It is codified in multiple international declarations, national statutes, and professional codes of conduct. (8,9) When a vaccine is required as a condition of maintaining employment, attending school, or participating in public activities, the patient's ability to exercise autonomous choice is eliminated. Faden and Beauchamp's work on informed consent established that genuine consent requires:
 - a. disclosure of relevant information
 - b. comprehension of that information
 - c. voluntariness
 - d. capacity (8)

Coercion, whether it be explicit or structural, undermines voluntariness and therefore negates true informed consent.

Problems with the Evidence

If vaccine mandates are to be justified solely on the basis of the best available evidence, the quality of that evidence is critically important. Substantial evidence exists that documents widespread problems with published medical research.

The Reproducibility Crisis

In 2005, Stanford University epidemiologist John Ioannidis published what became the most downloaded article in the history of *PLOS Medicine*: "Why Most Published Research Findings Are False." (10) Using formal probability modeling, Ioannidis demonstrated that for most research designs and fields, it is more likely that a research claim is false than true, due to small sample sizes, low prior probabilities, high flexibility in data analysis, financial conflicts of interest, and publication bias.

In a companion study published in *JAMA*, Ioannidis examined 45 highly cited clinical research studies published between 1990 and 2003 and found that 16% were contradicted by subsequent research, 16% had effects shown to be stronger than they actually were, and 44% remained unchallenged after replication. (11) Taken together, only one-third of highly cited clinical studies could be reliably confirmed.

The Open Science Collaboration's large-scale replication effort, published in *Science* in 2015, attempted to replicate 100 psychological research findings and successfully reproduced only 36%–39% of them. (12) While psychology is not pharmacology, similar reproducibility concerns have been documented in preclinical biomedical research. (13)

Publication Bias and Selective Reporting

Publication bias has been extensively documented across medical specialties. (14) Systematic reviews of registered clinical trials have found that results favoring an experimental intervention are consistently more likely to be published than unfavorable results. (15)

Turner and colleagues conducted an analysis of FDA-registered antidepressant trials and found that 94% of trials with positive results were published,

compared with only 8% of trials with negative results. (16) When all registered trials were included in a meta-analysis, estimated effect sizes were reduced by approximately 32% compared to published-only meta-analyses.

Outcome switching, which involves changing pre-specified primary endpoints after data has been collected, has been documented in clinical trials. (17) A comparison of clinical trial registrations against published reports found that approximately half of all studies had at least one primary outcome that was changed, introduced, or omitted.

Industry Influence and Conflicts of Interest

A substantial body of evidence documents that industry sponsorship of clinical trials is associated with more favorable outcomes for sponsored products. (18) A Cochrane review by Lundh and colleagues found that industry-sponsored trials were more likely to report favorable efficacy results (relative risk 1.27) and favorable harm results (relative risk 1.37) compared to non-industry-sponsored trials. (18)

The former editors of two of medicine's highest-impact journals have made damning assessments of the state of published research. Richard Horton, editor-in-chief of *The Lancet*, wrote in a 2015 editorial:

Much of the scientific literature, perhaps half, may simply be untrue. Afflicted by studies with small sample sizes, tiny effects, invalid exploratory analyses, and flagrant conflicts of interest, together with an obsession for pursuing fashionable trends of dubious importance, science has taken a turn towards darkness. (19)

Similarly, Marcia Angell, former editor-in-chief of the *New England Journal of Medicine*, wrote:

It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of the New England Journal of Medicine. (20)

Peter Gøtzsche, co-founder of the Cochrane Collab-

oration which is an organization that was established to produce unbiased systematic reviews of medical evidence, documented in his peer-reviewed publications and in his 2013 book *Deadly Medicines and Organised Crime* that pharmaceutical industry misconduct, including research fraud, data manipulation, and illegal marketing, is widespread. (21) Gøtzsche's subsequent removal from the Cochrane governing board following his criticism of a Cochrane review of the HPV vaccine, was described by resigning board members as "an assault on scientific independence." (22)

Individual Variability in Vaccine Risk-Benefit Ratios

A central premise of vaccine mandates is that a given vaccine is appropriate for all members of a defined population. However, accumulating evidence demonstrates that significant individual variability exists in both vaccine benefits and risks, which suggests that individualized assessment is clinically justified.

Age-Stratified Risk-Benefit Analysis

Multiple studies have demonstrated that the risk-benefit profile of COVID-19 vaccination varies substantially by age. (23,24) Some analyses suggest that, in low-risk young adults, the number of serious adverse events may be non-trivial relative to hospitalizations prevented. (23)

Myocarditis following mRNA COVID-19 vaccination has been established as a genuine adverse event, with the highest incidence documented in young males aged 16–24 years following the second dose. (24,25) A large Nordic cohort study estimated that, among males aged 16–24 years, the second dose of mRNA vaccines was associated with approximately 4–7 excess myocarditis cases per 100,000 vaccines for BNT162b2 (Pfizer-BioNTech) and 9–28 per 100,000 for mRNA-1273 (Moderna), with the risk being highest after the second dose. (25)

The Role of Prior Immunity

The immunological significance of prior SARS-CoV-2 infection (i.e. natural immunity) has been a debated topic in vaccine mandate debates. (26,27) In a large retrospective cohort of Cleveland Clinic employees, Shrestha and colleagues found that both prior SARS-CoV-2 infection and COVID-19 vaccination were associated with substantial protection

against COVID-19, and that vaccination of previously infected individuals provided additional protection against symptomatic disease only after several months. (26)

Gazit and colleagues, in a large matched-cohort study, found that previously infected unvaccinated individuals had significantly lower rates of reinfection than the rates of breakthrough infection observed in previously uninfected vaccinated individuals. (27) These findings suggest that population-wide vaccination mandates that do not account for prior immunity status may impose unnecessary risks on individuals for whom the benefit is marginal.

Informed Consent: Ethical and Legal Frameworks

International Declarations

The Nuremberg Code of 1947 was established in response to the medical atrocities of the Nazi regime. This code provides the international framework for medical consent. (28) Its first principle states: “The voluntary consent of the human subject is absolutely essential.” The Code explicitly specifies that consent must be given without “any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion.”

The Declaration of Helsinki, adopted by the World Medical Association in 1964 and subsequently revised, extends informed consent requirements to all medical research and practice. (29) It states that “Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary” and “each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study.”

Legal Frameworks

The legal right to refuse medical treatment, even life-saving treatment, has been affirmed by courts across multiple jurisdictions. (30) In the United States, the Supreme Court has recognized that a competent adult has a constitutionally protected liberty interest, under the 14th Amendment’s Due Process Clause, in refusing unwanted medical treatment, as articulated in *Cruzan v. Director, Missouri Department of Health* (30) and reaffirmed in *Washington v. Glucksberg*. (31)

The U.S. Supreme Court’s 1905 decision in *Jacobson v. Massachusetts* (32) is frequently cited in support of vaccine mandates. This decision, however, was rendered over 120 years ago — long before the development of modern informed consent policy or contemporary vaccine technology. The ruling also included provisions that courts have since interpreted as requiring that any mandate must not be unreasonable, arbitrary, or oppressive. (33) The prevailing legal view holds that *Jacobson* cannot be interpreted to override the more developed informed consent frameworks that have emerged over the subsequent century.

Coercion and the Invalidation of Consent

The bioethics literature has long recognized that structural coercion can be just as consent-invalidating as direct physical coercion. (34) When individuals face the loss of employment, educational access, or the ability to participate in public activities as a consequence of vaccine refusal, the voluntariness required for genuine consent is compromised.

Bioethics and policy analyses note that COVID-19 vaccine mandates involve significant coercive pressure, particularly when framed as ‘get vaccinated or get fired,’ raising concerns about the voluntariness of consent. (35–38) A qualitative study of nurses in Italy described them as feeling forced or ‘blackmailed’ into accepting COVID-19 vaccination, rather than seeing their decision as fully autonomous. (39)

Historical Precedents: When Medical Consensus Was Wrong

Throughout the history of medicine, a recurring theme is that the prevailing consensus and the actual evidence do not always agree. This pattern relates directly to the question of vaccine mandates because it illustrates the cost of removing clinical judgment and patient autonomy from medical decision-making.

Thalidomide

Examples of this recurring theme include the approval of thalidomide as a sedative and antiemetic based on short-term safety data. (40) Subsequently, the use of this medicine to treat morning sickness in pregnant women resulted in the birth of over ten thousand children with severe limb malformations and other birth defects between 1957 and 1962. The thalidomide disaster prompted the modern regulatory requirement for rigorous pre-approval clinical

testing and demonstrated the catastrophic consequences of inadequate safety monitoring. (41)

Diethylstilbestrol (DES)

Diethylstilbestrol (DES) was prescribed to millions of pregnant women between 1940 and 1971 to prevent miscarriage, despite the absence of evidence for its efficacy. A 1953 randomized controlled trial found no benefit over placebo, yet prescribing continued for nearly two decades. (42,43) Subsequent research established that DES caused vaginal clear cell adenocarcinoma in daughters of exposed women, as well as reproductive tract abnormalities in both sons and daughters. (44,45)

Frontal Lobotomy

Prefrontal leucotomy (lobotomy) was performed on an estimated 40,000 to 50,000 patients in the United States from the late 1930s through the 1950s. Its inventor, António Egas Moniz, received the Nobel Prize in Physiology or Medicine in 1949. The procedure was promoted and endorsed by leading psychiatric authorities of the era on the basis of uncontrolled case series and impressionistic outcome reports. However, the long-term consequences, including severe personality changes, cognitive impairment, incontinence, and death, were widely underreported and not fully recognized for many years. (46)

Rofecoxib (Vioxx)

Rofecoxib (Vioxx) was approved by the FDA in 1999 and was marketed as a safer alternative to traditional NSAIDs. (47) Evidence of cardiovascular risk was present in early trials but was not adequately communicated to clinicians or patients. (48) Based on a large, nested case-control study of US Kaiser Permanente members, Graham and colleagues estimated that 88,000 to 140,000 excess cases of serious coronary heart disease occurred in the United States that were attributable to rofecoxib before this medicine was withdrawn from the market in 2004. (49) Internal Merck documents that were later revealed through litigation showed the cardiovascular risk had been recognized within the company years before the drug's withdrawal. (48)

These historical cases share a common feature: interventions were administered on the basis of inadequate evidence, without sufficient individualized clinical assessment or genuine informed consent. The patients suffered as a result.

The Public Health Argument and Its Limitations

Proponents of vaccine mandates frequently argue that public health benefits justify overriding individual autonomy.

The Distinction Between Public Health and Evidence-Based Medicine

Public health and clinical medicine operate under different frameworks. (50) Clinical medicine focuses on the welfare of the individual patient whereas public health focuses on the health of populations. Population-level interventions necessarily involve trade-offs in which some individuals bear risks or harms for the collective benefit.

This distinction was recognized by Sackett and colleagues, who defined EBM explicitly in terms of “the care of individual patients” rather than populations. (2) When public health justifications are used to mandate medical interventions in individual people, two distinct frameworks are being confused, and the result is that the protections EBM provides to individuals are eliminated.

The Principle of Proportionality

Even within public health ethics, interventions that restrict individual liberties must satisfy the principle of proportionality. This principle states that the restriction imposed on individual autonomy must be proportionate to the public health benefit achieved. (51) Gostin and Wiley's text on public health law identifies proportionality as a limit on the legitimate use of state power to mandate health interventions. (52)

The proportionality of any specific vaccine mandate depends on multiple scientific issues, for example the degree of individual protection a vaccine provides and how quickly that protection wanes over time. (53,54) These issues cannot be resolved by a government invoking its authority over the populace. They require transparent, ongoing scientific inquiry.

The Slippery Slope of Compelled Medical Intervention

Concerns have been raised about the precedent established by permitting governments or institutions to invoke mandates for specific medical interventions, warning that such mandates may set a dangerous precedent for future government interventions in private healthcare decisions. (55) If the collective

benefit justifies overriding individual autonomy for vaccines, then the same logic could theoretically be applied to other interventions where individual choices or behaviors affect population health outcomes such as lifestyle modifications, dietary changes, or organ donation. These ethical limits are important because they protect the physician-patient relationship and ensure that individual patients are treated as persons, not as instruments of a collective policy. (51,56)

Effects of Mandates on Public Trust

Public trust in medicine, medical institutions and public health agencies declined substantially during the COVID-19 pandemic. (57) Large surveys in the United States show that trust in physicians and hospitals fell from around 70% in early 2020 to about 40% by 2024, (58) and confidence in federal public health agencies such as the CDC and NIH also dropped markedly between 2020 and 2022. (59)

Several bioethicists have argued that highly coercive COVID-19 vaccine mandates risk undermining trust by conveying that institutions do not respect individual autonomy and conscience, potentially provoking resentment and further loss of trust. (60,61)

Research in behavioral science suggests that perceived mandates and restrictions can trigger psychological reactance which may paradoxically reduce vaccination among vaccine-hesitant populations. (62)

Toward Evidence-Based Vaccination Policy

This review has argued that vaccine mandates, as they have been historically implemented, are incompatible with EBM principles. A policy that is consistent with EBM would preserve all three of Sackett's components while promoting high vaccine uptake through education, access, and genuine informed consent. The following recommendations are proposed:

1. Full Data Transparency

Several authors have pointed out the need for broad public access to complete clinical trial data. This includes patient-level data, which should be required as part of the regulatory approval process for new drugs and vaccines. (63) The principle of 'AllTrials'—that all clinical trials should be registered and all results reported—has been advocated as a standard that regulators and funders should require. It is par-

ticularly important for vaccines used in public health programs. (64)

2. Independent Safety and Efficacy Evaluation

Authors have also pointed out that pre-licensure trials are typically underpowered to detect rare adverse events and therefore they advocate for independent post-marketing surveillance systems with sufficient statistical power. They also recommend studies should be supported by public or non-industry funding rather than relying solely on pharmaceutical manufacturers. (65) This could help insulate regulatory agencies from the influence of the pharmaceutical industry, permitting them to conduct genuinely independent risk-benefit assessments.

3. Individualized Risk-Benefit Assessment

Clinical guidelines should reflect age-, sex-, and risk-stratified data on vaccine benefits and harms. Clinicians should be supported in conducting individualized assessments rather than being pressured to function as policy enforcers.

4. Genuine Informed Consent

Informed consent processes should present known and unknown risks, evidence of efficacy, and available alternatives without coercive language. (66) Individuals should be free to decline vaccination without penalty. Where public health justifications for vaccination are compelling, they should be communicated honestly rather than enforced coercively.

5. Restoration of Clinical Discretion

Physicians should retain the authority to grant medical exemptions based on their individualized clinical assessment. The bureaucratic burden of exemption processes should not function as a mechanism for denying legitimate medical exemptions. (23)

Conclusions

Evidence-based medicine, as it is defined and broadly accepted in contemporary clinical practice, requires the integration of three components: the best available evidence, individual clinical expertise, and patient values and preferences. Vaccine mandates eliminate the second and third of these components.

The component that mandates retain (i.e. the evidence base) is subject to reliability problems, including research irreproducibility, publication bias, selective outcome reporting, and pharmaceutical in-

dustry influence. These problems have been documented not by critics of medicine but rather by the editors of the most prestigious medical journals and the founder of one of its most important evidence-synthesis institutions.

Individual variability in vaccine risk-benefit ratios is established and is clinically significant. The ethical and legal frameworks governing informed consent, which were developed over seven decades in response to the consequences of coerced medicine, are violated by mandates that impose medical interventions as conditions of employment, education, or social participation.

Historical examples demonstrate the costs of removing individual physician's clinical judgment and patient autonomy from medical decision-making. These costs have been borne largely by patients. The appropriate response to these concerns is not to

reject vaccinations, but rather to apply EBM's three-component model to vaccination policy: evidence, clinical expertise, and patient autonomy. These three elements were not designed to obstruct good medicine. They were designed to protect patients from well-intentioned policies that are based on incomplete, biased, or prematurely "settled" evidence. Vaccination policy will be more effective, more ethically sound, and more successful if it is built on a genuine commitment to evidence-based medicine in its complete form.

Declarations

Conflict of Interest: The author declares no conflicts of interest relevant to this manuscript.

Funding: No external funding was received for this work.

References

- Guyatt GH. Evidence-based medicine. ACP J Club. 1991;114(2):A-16.
- Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312(7023):71-72. doi:10.1136/bmj.312.7023.71
- Straus SE, McAlister FA. Evidence-based medicine: a commentary on common criticisms. *CMAJ*. 2000;163(7):837-841.
- Greenhalgh T, Howick J, Maskrey N; Evidence Based Medicine Renaissance Group. Evidence based medicine: a movement in crisis? *BMJ*. 2014;348:g3725. doi:10.1136/bmj.g3725
- Guyatt GH, Haynes RB, Jaeschke R, Cook DJ, Greenhalgh T, Meade MO, et al. Introduction: the philosophy of evidence-based medicine. In: Guyatt GH, Rennie D, Meade MO, Cook DJ, editors. *Users' Guides to the Medical Literature*. 2nd ed. New York: McGraw-Hill; 2008. p. 3-12.
- Kent DM, Rothwell PM, Ioannidis JPA, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials*. 2010;11:85. doi:10.1186/1745-6215-11-85
- Rothwell PM. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet*. 2005;365(9454):176-186. doi:10.1016/S0140-6736(05)17709-5
- Faden RR, Beauchamp TL. *A History and Theory of Informed Consent*. Oxford University Press; 1986.
- Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 8th ed. Oxford University Press; 2019.
- Ioannidis JPA. Why most published research findings are false. *PLoS Med*. 2005;2(8):e124. doi:10.1371/journal.pmed.0020124
- Ioannidis JPA. Contradicted and initially stronger effects in highly cited clinical research. *JAMA*. 2005;294(2):218-228. doi:10.1001/jama.294.2.218
- Open Science Collaboration. Estimating the reproducibility of psychological science. *Science*. 2015;349(6251):aac4716. doi:10.1126/science.aac4716
- Begley CG, Ellis LM. Drug development: raise standards for preclinical cancer research. *Nature*. 2012;483(7391):531-533. doi:10.1038/483531a
- Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet*. 1991;337(8746):867-872. doi:10.1016/0140-6736(91)90201-y
- Dwan K, Altman DG, Arnaiz JA, et al. Systematic review of the empirical evidence of study publication bias. *PLoS One*. 2008;3(8):e3081. doi:10.1371/journal.pone.0003081
- Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008;358(3):252-260. doi:10.1056/NEJMs065779
- Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA*. 2004;291(20):2457-2465. doi:10.1001/jama.291.20.2457
- Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*. 2017;2(2):MR000033. doi:10.1002/14651858.MR000033.pub3
- Horton R. Offline: What is medicine's 5 sigma? *Lancet*. 2015;385(9976):1380. doi:10.1016/S0140-6736(15)60696-1. Available at: [https://doi.org/10.1016/S0140-6736\(15\)60696-1](https://doi.org/10.1016/S0140-6736(15)60696-1)
- Angell M. *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*. Random House; 2004. Available at: <https://www.nybooks.com/articles/2004/07/15/the-truth-about-the-drug-companies/>
- Gøtzsche PC. *Deadly Medicines and Organised Crime: How Big Pharma Has Corrupted Healthcare*. Radcliffe Publishing; 2013.
- Boodman, E. "'Evidence-Based Medicine' and the Expulsion of Peter Gøtzsche." *Undark*. December 29, 2019. Available at: <https://undark.org/2019/12/30/peter-gotzsche-cochrane/>
- Bardosh K, et al. COVID-19 vaccine boosters for young adults: a risk-benefit assessment and ethical analysis. *J Med Ethics*. 2024;50:126-138
- Li M, Yuan J, Lv G, Brown J, Jiang X, Lu ZK. Myocarditis and pericarditis following COVID-19 vaccination: inequalities in age and vaccine types. *Journal of personalized medicine*. 2021 Oct 28;11(11):1106.
- Karlstad Ø, Hovi P, Husby A, et al. SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. *JAMA*

- Cardiol. 2022;7(6):600-612.
doi:10.1001/jamacardio.2022.0583
26. Shrestha NK, Burke PC, Nowacki AS, Terpeluk P, Gordon SM. Necessity of coronavirus disease 2019 (COVID-19) vaccination in persons who have already had COVID-19. *Clinical Infectious Diseases*. 2022 Jul 1;75(1):e662-71.
 27. Gazit S, Shlezinger R, Perez G, et al. Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections. *Science Immunol*. 2022;7(73):eabq1823.
doi:10.1126/sciimmunol.abq1823
 28. Nuremberg Code. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Vol. 2. US Government Printing Office; 1949:181-182.
 29. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
doi:10.1001/jama.2013.281053
 30. *Cruzan v. Director, Missouri Department of Health*. 497 US 261 (1990). Available at: <https://supreme.justia.com/cases/federal/us/497/261/>
 31. *Washington v. Glucksberg*. 521 US 702 (1997). Available at: <https://supreme.justia.com/cases/federal/us/521/702/>
 32. *Jacobson v. Massachusetts*. 197 US 11 (1905). Available at: <https://supreme.justia.com/cases/federal/us/197/11/>
 33. Gostin LO. *Jacobson v Massachusetts* at 100 years: police power and civil liberties in tension. *Am J Public Health*. 2005;95(4):576-581.
doi:10.2105/AJPH.2004.055152
 34. Wertheimer A. *Coercion*. Princeton University Press; 1987.
 35. Williams BM. The ethics of selective mandatory vaccination for COVID-19. *Public Health Ethics*. 2022 Apr 1;15(1):74-86.
 36. Smith MJ, Mackie E. Do vaccine mandates impair the voluntariness of informed consent?. *Journal of Medical Ethics*. 2026 Apr;52(4):215-9.
 37. Giubilini A, Savulescu J, Pugh J, Wilkinson D. Vaccine mandates for healthcare workers beyond COVID-19. *Journal of Medical Ethics*. 2023 Mar 1;49(3):211-20.
 38. Olick RS, Shaw J, Yang YT. Ethical issues in mandating COVID-19 vaccination for health care personnel. *Mayo Clinic Proceedings* 2021 Dec 1;96(12):2958-62.
 39. Ottonello G, Pesenti S, Napolitano F, Calzolari M, Pagnucci N, Aleo G, Zanini M, Catania G, Hayter M, Sasso L, Bagnasco A. Nurses' attitudes towards COVID-19 vaccines: A qualitative study (PROACTIVE-study). *Journal of Clinical Nursing*. 2024 Oct;33(10):4024-33.
 40. McBride WG. Thalidomide and congenital abnormalities. *Lancet*. 1961;278(7216):1358.
doi:10.1016/S0140-6736(61)90927-8
 41. Vargesson N. Thalidomide-induced teratogenesis: History and mechanisms. *Birth Defects Research Part C: Embryo Today: Reviews*. 2015 Jun;105(2):140-56.
 42. Dieckmann WJ, Davis ME, Rynkiewicz LM, Pottinger RE. Does the administration of diethylstilbestrol during pregnancy have therapeutic value?. *American journal of obstetrics and gynecology*. 1953 Nov 1;66(5):1062-81.
 43. Troisi R, Hatch EE, Titus L. The diethylstilbestrol legacy: a powerful case against intervention in uncomplicated pregnancy. *Pediatrics*. 2016 Nov 1;138(Supplement 1):S42-4.
 44. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *New England journal of medicine*. 1971 Apr 22;284(16):878-81.
 45. Wilcox AJ, Baird DD, Weinberg CR, Hornsby PP, Herbst AL. Fertility in men exposed prenatally to diethylstilbestrol. *New England Journal of Medicine*. 1995 May 25;332(21):1411-6.
 46. Pressman JD. *Last Resort: Psychosurgery and the Limits of Medicine*. Cambridge University Press; 1998.
 47. Cairns JA. The coxibs and traditional nonsteroidal anti-inflammatory drugs: a current perspective on cardiovascular risks. *Canadian Journal of Cardiology*. 2007 Feb 1;23(2):125-31.
 48. Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. *JAMA*. 2008;299(15):1813-1817.
doi:10.1001/jama.299.15.1813
 49. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet*. 2005;365(9458):475-481.
doi:10.1016/S0140-6736(05)17864-7
 50. Gostin LO. *Public Health Law: Power, Duty, Restraint*. 3rd ed. University of California Press; 2016.
 51. Childress JF, Faden RR, Gaare RD, et al. Public health ethics: mapping the terrain. *J Law Med Ethics*. 2002;30(2):170-178.

doi:10.1111/j.1748-720X.2002.tb00384.x

52. Gostin LO, Wiley LF. *Public Health Law: Power, Duty, Restraint*. 3rd ed. Berkeley: University of California Press; 2016. Ch. 3: Constitutional Limits on Public Health Powers.
53. Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. *N Engl J Med*. 2021;385(24):e85. doi:10.1056/NEJMoa2114228
54. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N Engl J Med*. 2021;385(24):e83. doi:10.1056/NEJMoa2114114
55. Choti S. Vaccination Mandates and Civil Liberties. *Florida Atlantic University Undergraduate Law Journal*. 2025;12(1):8.
56. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 8th ed. Oxford University Press; 2019.
57. Blendon RJ, Benson JM. The public's views on COVID-19 vaccine mandates. *Prev Med*. 2022;162:107175. doi:10.1016/j.ypmed.2022.107175
58. Perlis RH, Ognyanova K, Uslu A, Lunz Trujillo K, Santillana M, Druckman JN, Baum MA, Lazer D. Trust in physicians and hospitals during the COVID-19 pandemic in a 50-state survey of US adults. *JAMA network open*. 2024 Jul 31;7(7):e2424984.
59. Melchinger H, Omer SB, Malik AA. Change in confidence in public health entities among US adults between 2020–2024. *PLOS Global Public Health*. 2025 Jun 26;5(6):e0004747.
60. Olick RS, Shaw J, Yang YT. Ethical issues in mandating COVID-19 vaccination for health care personnel. *Mayo Clinic Proceedings* 2021 Dec 1;96(12):2958-62
61. Riva MA, Paladino ME, Paleari A, Belingheri M. Workplace COVID-19 vaccination, challenges and opportunities. *Occupational Medicine*. 2022 May 1;72(4):235-7.
62. Huang L, Huschka TR, Barwise AK, Allen JS, Wolfersteig W, Hamm K, Cardenas LD, Phelan SM, Allyse MA. Psychological reactance, misinformation, and distrust: A mixed methods analysis of COVID-19 vaccine uptake. *Journal of clinical and translational science*. 2024 Jan;8(1):e48.
63. Doshi P, Goodman SN, Ioannidis JPA. Raw data from clinical trials: within reach? *Lancet*. 2013;381(9867):616-617. doi:10.1016/S0140-6736(13)60231-8
64. Brown T. It's time for AllTrials registered and reported. *The Cochrane database of systematic reviews*. 2013 Apr 30;2013(4):ED000057.
65. Dhanda S, Osborne V, Lynn E, Shakir S. Post-marketing studies: can they provide a safety net for COVID-19 vaccines in the UK?. *BMJ evidence-based medicine*. 2022 Feb 1;27(1):1-6.
66. Barstow, C., Shahan, B. and Roberts, M., 2018. Evaluating medical decision-making capacity in practice. *American family physician*, 98(1):40-46.

This page is intentionally left blank

