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A review of the use of persuasion and coercion to overcome COVID-19 vaccine hesitancy

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Abstract: Vaccines against COVID-19 have been available for about one year, but compliance with these vaccines has been less than expected. Vaccine hesitancy and refusal have limited vaccination rates, thus contributing to morbidity and mortality associated with COVID-19. This review explores the history of vaccines, beginning with their use in India over 3,500 years ago to prevent smallpox, and continuing through their current use to combat COVID-19. The past efforts of governments to compel individuals to get vaccinated are reviewed as well as the problems that resulted from such actions. Historical and contemporary factors that contribute to vaccine hesitancy are examined. One such factor is concern about the risks of the vaccines. Most adverse effects associated with the COVID-19 vaccines are mild. However, rare but serious adverse effects also occur including anaphylaxis, thrombosis, and myocarditis. Concerns about these potentially life-threatening complications contribute to vaccine hesitancy. The lack of an adequate system for reporting adverse events as well as the absence of an effective compensatory system to assist those who suffer untoward problems resulting from COVID-19 vaccines also contribute to vaccine hesitancy. Still another factor impeding vaccine compliance is lack of trust. This includes lack of trust in the vaccines, the pharmaceutical companies who manufacture the vaccines, the healthcare providers who recommend the vaccines, the governmental agencies who determine policies about the vaccines, and the media who report on the vaccines. The basis for mistrust in each of these areas is examined and includes a lack of transparency, ulterior financial motives, and suppression of alternative viewpoints. The effects of rumors and conspiracy theories on attitudes about vaccines are assessed as well. Finally, tactics utilized to increase vaccination rates are reviewed. These include education, persuasion, incentivization, and coercion. When education and persuasion fail, governments may turn to the use of coercive strategies, such as imposing vaccine mandates and implementing penalties and restrictions on those who fail to comply. The potential adverse consequences of these approaches are reviewed and include an unexpected decrease in vaccination rates, failure to protect individual autonomy, lack of informed consent associated with vaccinations, and polarization between the vaccinated and the unvaccinated leading to "vaccine tribalism." Evidence demonstrating the efficacy of these approaches for improving vaccination compliance is found to be lacking. Thus, further research is recommended to find improved methods for improving vaccination rates as well as exploring alternative strategies for ending the COVID-19 pandemic, such as the concurrent use of effective antiviral treatments.

Keywords: Vaccine hesitancy, vaccine refusal, persuasion, incentivization, mandates, coercion, natural immunity.

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I. INTRODUCTION

As of November 10, 2021, there have been more than 250 million confirmed cases and over 5 million reported deaths of COVID-19 worldwide. In addition, over 7 billion doses of COVID-19 vaccines have been administered [1]. However, despite growing evidence [2] and reassurance from the U. S. Centers for Disease Control and Prevention (CDC) [3] that vaccines are safe and effective at preventing severe illness and death, vaccine hesitancy continues to limit the use of vaccines [4-5].

Decisions about whether to get vaccinated exist on a spectrum ranging from total acceptance to outright refusal. This continuum has been referred to as "vaccine hesitancy." The World Health Organization (WHO) defines vaccine hesitancy as a "delay in acceptance or refusal of safe vaccines despite availability of vaccine services" [6]. The ongoing failure to vaccinate adequate numbers of people to achieve herd immunity raises the questions (1) What factors contribute to vaccine hesitancy? and (2) What methods are being used to overcome vaccine hesitancy? To answer these questions, we need to understand the history of vaccines as well as the responses they provoke in the general public. Vaccine hesitancy did not originate with the COVID-19 vaccines. In fact, vaccine hesitancy may be as old as vaccines themselves.

Inoculation originated in India more than 3500 years ago (see Table 1). Dhanwantari, the Vedic father of medicine and earliest known Hindu physician, recommended inoculating healthy individuals to prevent smallpox. From India, inoculation spread to the Far East

and Africa where it was used for protection against not only smallpox, but also syphilis and the bites of venomous snakes [7]. Eventually, inoculation was brought to England by Lady Mary Wortley Montagu, who was the wife of the English ambassador to Turkey. After witnessing the procedure being performed by old Greek women in Constantinople, Montagu had her 6-year-old son inoculated against smallpox in 1718. Three years later, she returned to London and had her 2½ year old daughter inoculated against smallpox after sharing the procedure with a group of royal physicians. The procedure came to be known as *variolation*, which this is derived from the name of the virus that causes smallpox (i.e. *variola*).

In the New World, variolation began in the early 1700's when Boston physician Zaddiel Bylston used a lancet to puncture boils from persons suffering from smallpox, then squeezed the fluid into a glass jar. A cut was then made in the patient's arm or leg, and the pus was applied to the cut. Bylston's method resulted in about 3% of his patients dying following variolation whereas 14% of the people who became ill from smallpox died.

Table 1: Timeline of Vaccine development:

Date	Event
1500 B.C.E	Inoculation originates in India to prevent smallpox.
1718	Lady Mary Wortley Montagu has her son variolated in Constantinople to prevent smallpox.
1721	Physician Zabdiel Boylston begins variolating patients in Boston to prevent smallpox.
1796	Edward Jenner inoculates an 8-year-old boy with cowpox and the boy does not get sick with smallpox.
1798	Jenner publishes *An Inquiry into the Causes and Effects of the Variolae Vaccinae*, using the Latin term that translates as "cow pustules,"thus launching the term "vaccine."
1801	Nearly 100,000 people get vaccinated in Europe.
1840	UK Parliament outlaws variolation and makes vaccination with cowpox the official UK strategy for controlling smallpox.
1853	Vaccination of all infants is made mandatory in England.
1871	Britain implements mandatory vaccine policy with refusers subjected to penalties that include fines and loss of property.
1873	Germany passes a compulsory vaccination law.
1898	Anti-vaccination movement in England resists mandatory vaccines through protests, demonstrations, and riots leading to the addition of a "conscience clause"that excused parents who believed vaccination would harm their children.
1900's	U.S. implements forced vaccination policies.
1948	Britain ends mandatory vaccination.
March 30, 2020	Operation Warp Speed announced in the U.S. to expedite development of vaccines for COVID-19.
December 2020	The first COVID-19 vaccine receives regulatory approval in the UK. Vaccines were also granted Emergency Use Authorization in the U.S. and several other countries.
2021	A growing list of vaccine mandates around the world is associated with penalties and restrictions.
November 2021	Cases of COVID-19 surge in Europe and the U.S. despite higher rates of vaccination for COVID-19 than many other countries around the world.

In 1796, a country physician named Edward Jenner from Gloucestershire tried a new approach to prevent smallpox. After hearing a legend that milk maids who milked cows infected with cowpox did not contract smallpox, he took the pus from a sore on one of these milk maids and dabbed it onto two small cuts he had made in the arm of an 8-year-old boy. The boy subsequently developed symptoms of cowpox. Then, 18 days later, Jenner variolated the boy with smallpox and waited to see what would happen. The boy never developed smallpox. Two years later, Jenner published his results with this technique in *An Inquiry into the Causes and Effects of the Variolae Vaccinae*. By using the Latin term *variolae vaccinae*, which translates as "cow pustules," Jenner launched the term "vaccine" [8]. Over time, the UK became divided into those who supported vaccination with cowpox and those who believed variolation was the only way to protect the populace from smallpox infection. Finally, in 1840, Parliament outlawed variolation and made vaccination with cowpox the official UK strategy for controlling smallpox [9].

Following the success of cowpox inoculation, vaccines became one of the most effective tools for combating vaccine-preventable diseases (VPDs) and

drastic declines in VPDs resulted from increasing numbers of individuals becoming vaccinated [10]. However, as infectious diseases declined, many people chose to forgo vaccinations and take their chances with the increasingly uncommon diseases rather than undergo what they perceived to be risky vaccinations. This reluctance or hesitancy to get vaccinated led governments to institute legal compulsions.

In 1853 the vaccination of all infants was mandated in England. However, many British citizens viewed such mandates as a violation of their bodies and resisted compulsory vaccinations. In 1871 Britain implemented a policy that subjected refusers to fines, loss of property, or a sentence to the workhouse [8] The legal compulsion to be vaccinated gave rise to a large and vocal anti-vaccination movement that resisted the law through protests, demonstrations, and riots. This public outcry influenced England to add a "conscience clause" in 1898 that excused parents who believed that vaccination would harm their children. Eventually, because of organized resistance, Britain ended mandatory vaccination in 1948 [8]. Several other countries similarly instituted compulsory vaccinations. For example, Germany passed a compulsory vaccination law in 1873 [11] and the U.S. implemented forced vaccination policies in the early 1900s [8]. However, despite vaccine mandates, some people remain hesitant to be vaccinated. This raises the question of how to deal with people who choose not to get vaccinated.

One recommendation is to understand that attitudes that contribute to vaccine hesitancy [12].Vaccine hesitancy can be polarizing as individuals who express reservations about vaccination may be labeled as "anti-vaxxers", a term that carries judgmental overtones [13]. Also, individuals who are hesitant to be vaccinated may be shamed or blamed for the COVID-19 pandemic. This was demonstrated by US President Joe Biden who labeled the current pandemic a "pandemic of the unvaccinated" [14]. Vaccine hesitancy is associated with additional risks. For example, vaccine hesitancy can disrupt the relationship between a patient and his/her provider. In a study involving members of the American Academy of Pediatrics, nearly 40% of respondents said they would not provide care to a family that refused all vaccines, and 28% said they would not provide care to a family that refused some vaccines. These responses are in direct opposition to the academy's Committee on Bioethics which advises against discontinuing care for families that decline vaccines [15]. Approaches to managing vaccine hesitancy range from various forms of persuasion, such as education and incentivization, to coercion through penalties and/or restrictions. This review examines factors contributing to vaccine hesitancy and examines the use of persuasion and coercion as strategies for influencing vaccine hesitancy.

II. Results & Discussion

What is vaccine hesitancy?

In 2019, the WHO named vaccine hesitancy as one the ten gravest threats to global health [16]. But why would anyone question the use of vaccines as a useful tool in the COVID-19 pandemic? Haven't vaccines made an enormous contribution to global health by preventing infectious diseases? Haven't the CDC and U.S. Food and Drug Administration (FDA) said COVID-19 vaccines are safe and effective? These questions form the basis for understanding people's reactions to the COVID-19 vaccines as well as the various approaches being utilized to increase vaccination compliance. When trying to understand the reasons for vaccine hesitancy, it is important to understand that attitudes toward vaccination exist on a continuum ranging from active demand for vaccines to complete refusal of all vaccines. Vaccine-hesitant individuals are a heterogeneous group who lie in the middle of this continuum [17].

It is also important to understand that within this heterogeneous group of vaccine hesitant individuals there exists both *vaccination* hesitancy and *vaccine* hesitancy. The former refers to individuals who are hesitant to get any vaccine, whereas the latter refers to individuals who may get several vaccines but are reluctant to get a specific vaccine. For the purposes of this review, vaccine hesitancy is defined as a delay in getting a specific vaccine (e.g. a COVID-19 vaccine).

What are the reasons for vaccine hesitancy?

Myriad factors contribute to vaccine hesitancy and these factors vary by time and place [4]. Demographic factors include gender, religious, scientific, cultural, socioeconomic, and political beliefs [18]. Specific concerns that may contribute to vaccine hesitancy include apprehension about immediate and long-term adverse effects, previous side effects to other vaccines, unknown future effects of vaccine on health, concerns about the number of mandated vaccines, low confidence in vaccines, simultaneous administration of multiple vaccines, immune system intolerance, concerns about the speed of development of vaccines, the rapid approval of newer vaccines, lack of trust in the pharmaceutical companies that produced the vaccines due to perceived financial interests, lack of communication about side effects, perception of lower risk of COVID-19, apprehension surrounding fertility, pregnancy and breastfeeding, and previous COVID-19 infection [4,13,19-20]. Misinformation, confirmation bias, and conspiracy theories have also been reported to contribute

to vaccine hesitancy as well [4, 21]. Numerous models have been proposed to explain what causes vaccine hesitancy. Four of these models are summarized in Table 2.

Table 2: Causes of vaccine hesitancy:

- MacDonald [6]
  - Complacency
  - Convenience
  - Confidence
- Jacobson et al.[22]
  - Heuristic thinking
  - Success of vaccinations
  - Unnaturalness of vaccination
  - Nature of scientific evidence
  - Nature of pharmaceutical or biological materials
  - Presence of excipients
- Grzybowski et al. [23]
  - Philosophical
  - Naturalistic
  - Religious
  - Medical
- Dubé et al. [17]
  - Risk perception
  - Trust

Lucia et al. [20] and Razai et al. [5] examined factors contributing to vaccine hesitancy as it pertains to the COVID-19 vaccines. They found a number of factors contributed to vaccine hesitancy including concerns about adverse effects, lack of trust in information received from public health experts, politicization of the vaccine, need for transparency, concerns about the speed of vaccine development potentially impacting vaccine safety, rumors, and conspiracy theories. These factors share in common a heightened perception of risk following vaccination. A deeper exploration of factors contributing to risk perception follows.

Adverse events

Risk perception involves an assessment of the dangers associated with a particular intervention, such as getting a COVID-19 vaccine. Understanding these dangers requires an assessment of the vaccine-related adverse events. In the U.S., adverse events can be reported to the Vaccine Adverse Event Reporting System (VAERS), which is a passive national reporting system co-managed by the CDC and FDA. Anyone can submit a report to VAERS, including patients, family, and healthcare providers [24]. However, a Harvard study found dramatic underreporting of adverse events to VAERS, with fewer than 1% of AEs reported [25]. Acute adverse events following vaccination with the COVID-19 vaccines are generally mild and are more common in younger than older age groups [26]. However, serious adverse events such as anaphylaxis, thromboembolism, myocarditis, and pericarditis may contribute to vaccine hesitancy.

Anaphylaxis is a systemic, rapidly evolving, multisystem, life-threatening disorder that can lead to fatal airway obstruction and culminate in cardiopulmonary arrest [27]. The CDC reported anaphylaxis following COVID-19 vaccination is rare and occurs in approximately 2 to 5 people per million vaccinated in the United States [28]. Allergy to polyethylene glycol, one of the excipients in the Pfizer and Moderna vaccines, was described as the cause of anaphylaxis following vaccination for COVID-19 [29]. *Thrombosis* is the process of forming a blood clot (thrombus) in blood vessels. When the thrombus breaks off and travels to another area of the body, the clot is called an *embolus*. An embolus can lodge itself in a blood vessel thereby blocking the blood supply to an organ. This blockage of a blood vessel by an embolus is called an *embolism*. Collectively, this process is referred to as *thromboembolism*. Thromboembolic events have been reported following COVID-19 vaccines [30-31]. On April 7, 2021, the European Medical Agency (EMA) declared concerns about serious adverse events associated with the Astra-Zeneca vaccines were justified based on 62 cases of cerebral venous thrombosis (CVT) and 24 cases of splanchnic venous thrombosis among the nearly 25 million people vaccinated in the UK [32]. On April 23, 2021, the CDC and FDA recommended use of Johnson & Johnson's Janssen COVID-19 vaccine resume in the U.S. This followed a temporary pause after reports emerged showing that the J&J/Janssen COVID-19 vaccine was associated with an increased risk of an adverse event called *thrombosis with thrombocytopenia syndrome* (TTS), also known as *vaccine-induced thrombotic thrombocytopenia* (VITT). Most reports of this serious condition, which involves the formation of blood clots along with a decrease in platelets, occurred in adult women under the age of 50. The CDC determined that the benefits of the J&J/Janssen COVID-19 vaccine outweigh its risks [3]. A review by Cai et al. based upon adverse events reported to VAERS found the rate of thromboembolism following COVID-19 vaccines to be 21–75 cases per million doses [33]. An analysis of European data concluded the risk of developing thrombocytopenia in recipients of AstraZeneca vaccine was 151 per million doses [34].

Myocarditis, which involves inflammation of the heart muscle, and *pericarditis*, which involves inflammation of the pericardium, have been reported following COVID-19 vaccines[35-38]. These events are

reported to be more common in young males and more common after the second dose of a COVID-19 vaccine [39]. Høeg et al. found rates of 162.2 per million and 94 per million in boys 12-15 and 16-17 respectively following two doses of mRNA COVID-19 vaccines [40]. Rates of myocarditis in the 12-15-year-old age group are reported to be 19 times higher than the expected background rate [41]. On June 25, 2021, the FDA revised its patient and provider fact sheets for the Moderna and Pfizer COVID-19 vaccines to include a warning about increased risks of myocarditis and pericarditis following vaccination [42]. On October 6, 2021, Sweden and Denmark announced they were putting a temporary halt to the use of the Moderna COVID-19 vaccine for everyone born 1991 and after due to concerns about myocarditis and pericarditis. Both countries continue to use the Pfizer vaccine for this age group [43].

Reports of additional serious, but rare adverse events have occurred following COVID-19 vaccinations. These include encephalopathy [44], encephalopathy with seizures [45], and death [46]. Reports of rare but serious adverse events may contribute to vaccine hesitancy.

Trust

Risk perception is often closely linked with trust when determining vaccine acceptance or hesitancy. This includes trust in the healthcare provider who recommends the vaccines, the pharmaceutical companies who manufacture the vaccines, the governmental organizations who recommend the vaccines, and the media that dispenses information about COVID-19 and the vaccines.

Trust in the vaccines

Trust in the vaccines involves an assessment of their efficacy and safety. The initial Phase 3 trials evaluating the Pfizer and Moderna vaccines demonstrated they were 95% [47] and 94% [48] effective at preventing infection. With time, this efficacy waned for the Pfizer vaccine [49] whereas the Moderna vaccine maintained its initial efficacy [50]. However, a recent study found vaccinated individuals have peak viral loads similar to those of unvaccinated people and transmit infection just as readily as unvaccinated individuals [51].

A study from Harvard examined the relationship between vaccination and protection from COVID-19 in 68 countries around the world [52]. The authors found no relationship between the percentage of the population who were fully vaccinated and a reduction in new COVID-19 cases. In fact, they observed a trend suggesting a positive association. In other words, countries with a higher percentage of the population fully vaccinated had a higher rate of COVID-19 cases. Similarly, across the U.S. they found no evidence of COVID-19 cases decreasing in counties with higher percentages of the population fully vaccinated. The authors recommended that continuing efforts should be made to encourage populations to get vaccinated. However, they also recommended this should be done with humility and respect, as stigmatizing populations can do more harm than good. Furthermore, they suggested that the sole reliance on vaccination as a primary strategy to mitigate COVID-19 should be re-examined and that other pharmacological and non-pharmacological interventions need to be implemented.

Long-term safety of the vaccines

The long-term safety of the COVID-19 vaccines will not be known for many years. We know this because previous vaccines were found to have adverse events years after the vaccines were first developed. For example, following the release of a vaccine for Human Papilloma Virus in 2006, it was 12 years before a study reported women who received the vaccine had a 56% increased risk of developing Celiac Disease [53]. Other studies have described an increased risk of adverse effects following vaccines including narcolepsy [54], Guillain-Barre syndrome [55], multiple sclerosis [56], and systemic lupus erythematosus [57].

Furthermore, as we can learn from studying medical history, treatments once considered safe and effective are now considered risky or even dangerous. For example, Portuguese neurologist Egas Moniz won the Nobel Prize for Medicine in 1949 for his discovery of the therapeutic value of prefrontal leukotomy. Moniz was lauded by the *New York Herald Tribune* and the scientific journal *Nature* [58]. Yet today a lobotomy is considered one of the most brutal and barbaric medical procedures of all time [59]. It may be years before we know if the long-term risks of the COVID-19 vaccines outweigh the benefits, and whether the creation of the COVID-19 vaccines is worthy of a Nobel Prize or was a huge mistake. In the meantime, we are faced with the question of who we can trust to advise us about the risks and benefits of the vaccines.

Trust in healthcare provider

An important factor that increases vaccination compliance is trust between a patient and their provider [60]. Trust is built when a provider spends time discussing vaccines, does not deride the patient's concerns, is knowledgeable, and provides satisfactory answers [61]. Physicians today are being offered instructions on how to convince their patients to get the vaccine. In the U.S., the American Medical Association offers doctors 10 tips for talking with patients about the vaccine. These include (1) tell patients they need to get

the vaccine and (2) focus the discussion on how getting a vaccine can help protect loved ones such as a grandparent or child, or someone who is immunocompromised [62]. The CDC recommends doctors use motivational interviewing techniques to encourage vaccine compliance [63].

Lim et al. [64] recommended psychiatrists use the skills of persuasion and become vaccine ambassadors for their patients by applying behavioral management techniques such as motivational interviewing and "nudging" to encourage their patients to get vaccinated. They point out that psychiatrists can contribute to the success of vaccination campaigns because of their frequent contact with patients, the high level of trust their patients have in them, and their expertise in behavioral management. Furthermore, they point out that psychiatrists are particularly able to help their patients with serious mental illness get vaccinated by using counter messages to common vaccine-related concerns and misinformation. For example, if a patient states "I am afraid of the serious side effects I heard from the media," the psychiatrist can respond "With millions of vaccinations, it is not surprising to hear a few people experienced side effects, including rare and serious ones" (21).

Trust in pharmaceutical companies

Another concern expressed by individuals who are hesitant to get a COVID-19 vaccine is mistrust of the pharmaceutical companies that developed the vaccines. This lack of trust is based in part on the criminal histories of pharmaceutical companies. In 2009, Pfizer agreed to pay $2.3 billion, which at that time was the largest health care fraud settlement in the history of the U.S. Department of Justice. Pfizer pleaded guilty to a felony violation for misbranding one of its products with the intent to defraud or mislead. The company agreed to pay a criminal fine of $1.195 billion, the largest criminal fine ever imposed in the U.S. for any matter. Pfizer also agreed to pay an additional $1 billion for illegally promoting four drugs and for paying kickbacks to healthcare providers to induce them to prescribe these drugs [65].

In 2013, Johnson & Johnson agreed to pay $2.2 billion for promoting uses of medication not approved as safe and effective by the FDA, and payment of kickbacks to physicians and to the nation's largest long-term care pharmacy provider [66]. In 2014, Pfizer settled another lawsuit in US District Court in Boston for $325 million to resolve claims it defrauded insurers and other healthcare benefit providers by marketing Neurontin for unapproved uses. Just six weeks earlier, Pfizer agreed to pay $190 million to settle separate litigation in a federal court in New Jersey in which consumers accused the company of taking steps to keep cheaper generic versions of Pfizer's drug off the market [67].

Prior to the COVID-19 pandemic, Moderna had never developed an approved drug or vaccine [68]. Yet, one of Moderna's Board of Directors and Chair of the Product Development Committee at Moderna, Dr. Moncef Slaoui, was appointed to oversee the White House's Operation Warp Speed in May 2020. Slaoui resigned in January 2021, at the request of President Biden [69]. As of April 2021, the U.S. Government had paid Moderna almost $6 billion to develop a vaccine for COVID-19 [70].

Now Moderna and the U.S. National Institutes of Health (NIH) are embroiled in a dispute over patent rights for the vaccine co-developed by Moderna and the NIH. Moderna contends they were solely responsible for creating a key component of the COVID-19 vaccine whereas the NIH claims three of their scientists worked on the genetic sequence for the spike protein that produces the immune response. Moderna's patent application filed in July 2021 did not include the 3 NIH scientists who were involved in the development of the N.I.H.-Moderna COVID-19 Vaccine. This fight involves more than notoriety, however, because if the NIH is listed as a co-creator of the vaccine, it would give them the right to license the technology, which could bring in millions of dollars to the federal treasury [71]. These criminal charges, lawsuits, and battles over patent rights contribute to a lack of trust in the pharmaceutical companies that produced the COVID-19 vaccines.

Trust in the U.S. governmental policymakers

Trust in governmental policymakers is another key factor in determining vaccine acceptance or hesitancy [72]. A June 2020 global survey of potential acceptance of a COVID-19 vaccine found the highest rate of vaccine acceptance in countries with a strong trust in central governments, such as China, South Korea, and Singapore [25]. In countries such as the U.S., where the COVID-19 vaccines have become highly politicized, levels of trust in the government are at a historic low [73]. Compounding this lack of trust has been a lack of transparency about these agencies' involvement in the development of the vaccines and mixed messages about the pandemic.

The NIH and the National Institute of Allergy and Infectious Diseases (NIAID) have been at the forefront of a controversy over funding of research involving coronavirus. In 2014, NIAID, which is a branch of the NIH, awarded a multimillion-dollar grant to Ecohealth Alliance to study coronaviruses. Co-investigators on this project included personnel from the Wuhan Institute of Virology [74]. This led some to claim

that NIH director, Francis Collins, and NIAID director, Anthony Fauci, made untruthful statements to the U.S. Congress when they denied funding gain of function research in Wuhan [75].

Further concerns relate to the NIAID's role in the development of the Moderna vaccine. As previously noted, the NIAID had been working with Moderna to develop vaccines for several viruses, including coronavirus, as early as 2015 [76]. In a research collaboration agreement, the NIAID acknowledged it had developed a coronavirus spike protein that is more immunogenic than wild-type or subunit proteins and Moderna had developed a proprietary mRNA vaccine platform. The NIAID and Moderna entered into a collaborative agreement to evaluate the immunogenicity of mRNA vaccines for coronaviruses [77]. Moderna agreed to pay the NIAID a royalty for the use of their modified spike protein in the development of vaccines. For reasons that are unclear, all reports required by this collaborative agreement were said to be not subject to disclosure under the Freedom of Information Act, which provides public access to such documents [78]. In 2020, Collins downplayed a financial motivation for the pharmaceutical companies involved in developing COVID-19 vaccines. During an Economic Club interview Collins related:

"Talking to the companies, I don't hear any of them say they think this (vaccine) is a money-maker...I think they want to recoup their costs and maybe make a tiny percentage of increase of profit over that, like single digits percentage wise, but that's it. Nobody sees this as a way to make billions of dollars" [79].

However, it turns out Collins misjudged the pharmaceutical companies' motives. Forbes list of America's wealthiest people for 2021 includes two of Moderna's founders and one of their investors. Moderna's co-founder and chairman Noubar Afeyan is listed as having a net worth of $5 billion, co-founder and board member Robert Langer has a net worth of $4.9 billion, and investor Timothy Springer's net worth is reported to be $5.9 billion [80].

In July 2021, Pfizer estimated its 2021 earning from the vaccine to be $33.5 billion [81], whereas Pfizer and Moderna together have received commitments of over $60 billion in sales of the vaccines for 2021 and 2022 [82]. On October 5, 2021, Collins announced he was resigning as Director of the CDC [83].

Repeated changes in the CDC's recommendations regarding the wearing of masks and their decision to stop reporting breakthrough cases of COVID-19 in vaccinated individuals unless they are hospitalized or die [84] have caused additional controversy [85].

Trust in the FDA has eroded following a series of controversial decisions. One involved a manuscript authored by 18 physicians and scientists published on September 13, 2021 in the Lancet which stated current evidence does not support booster doses of COVID-19 vaccines in the general public [86]. The lead author on the paper was Dr. Philip Krause, the Deputy Director of the FDA's Office of Vaccines Research and Review. However, just nine days later, the FDA approved a booster for people ages 65 and older and some high-risk Americans [87]. Dr. Marion Gruber, the director of the FDA's Office of Vaccines Research and Review along with Dr. Krause resigned from the FDA due to President Biden's insistence on moving ahead with COVID-19 boosters even before the FDA had ruled on their safety and efficacy [88].

Thus, questions about independence, potential ulterior motives, and respect for the scientific process have fueled distrust in the U.S. governmental agencies that are supposed to protect its citizens.

Trust in media

Distrust in the media is another area that contributes to vaccine hesitancy and the breakdown of trust. The dissemination of false information, the removal of dissenting opinions regarding the vaccines, and the suppression of information about treatments for COVID-19 contribute to the public's lack of trust in the media.

For example, the New York Times printed a retraction [89] after running a story that falsely reported Sweden and Denmark had begun offering single doses of the Moderna vaccine to children, when in fact these countries had paused the use of the Moderna vaccine in people under 18 years of age due to concerns about myocarditis. Additionally, the original article misrepresented the number of COVID-19 hospitalizations in U.S. children since the start of the pandemic as 900,000, when in fact the correct number was 63,000 from August 2020 to October 2021.

FaceBook was criticized by U.S. President Biden who claimed the social media company was killing people by permitting misinformation to be spread on its platform [90]. FaceBook responded by removing over 18 million pieces of content from Facebook and Instagram that they claimed had been debunked by public health experts and could cause harm [91].

Twitter came under fire after they labeled the online obituary of a 37-year-old Seattle, Washington mother who died of Vaccine-Induced Thrombotic

Thrombocytopenia (VITT) as misleading. Jessica Berg Wilson died September 7, 2021 and an online obituary described her cause of death as VITT, which was diagnosed by her doctors. Twitter fact-checked the obituary, then labeled the tweet as misleading and added information on why health officials consider COVID-19 vaccines safe for most people. The fact-check warning was subsequently removed by Twitter [46].

Another example of censorship by the media involves the removal of information related to the use of chlorine dioxide (ClO_2) to treat COVID-19. Two in vitro studies have described how this oxidizing agent prevents the SARS-CoV-2 virus from attaching to ACE2 receptors, thereby blocking the virus from infecting human cells [92-93]. Additional published studies have reported the safe and effective use of ClO_2 as a treatment for COVID-19 in humans [94-95].

However, after Bolivia approved ClO_2 for the prevention and treatment of COVID-19 in August 2020, internet postings about this action were rapidly removed from the internet. The U.S. press decreed Bolivia's approval of chlorine dioxide as a dangerous move and claimed Bolivians were drinking a toxic bleach [96-97] or a toxic disinfectant [98]. These claims were made despite the fact that the U.S. Environmental Protection Agency has approved ClO_2 to purify drinking water and ClO_2 is used to purify water not only in the U.S [99], but also in Australia [100], numerous European countries, Sweden, [101], and Botswana[102]. Furthermore, the National Aeronautics and Space Administration (NASA) identified ClO_2 as "a universal antidote" [103].

Following Bolivia's approval of ClO_2 and the subsequent availability of this product at pharmacies as an over-the-counter product that did not require a prescription, cases of COVID-19 dropped 93% in 16 weeks and daily deaths decreased 82% [94]. Furthermore, as of September 28, 2021, despite having a vaccination rate less than half the U.S. rate, the case rate of COVID-19 in Bolivia is 94% lower and the death rate 92% lower than the rates in the U.S. (see Table 3) [104].

Table 3: COVID-19 Statistics USA versus Bolivia*

Country	Case Rate (per 100,000)	Death Rate (per 100,000)	Vaccination Rate
U.S.	36	0.62	55%
Bolivia	2	0.05	27%

*The New York Times. (September 28, 2021). Available at: https://www.nytimes.com/interactive/2021/world/covid-cases.html

Association does not prove causation, and thus these findings do not prove ClO_2 caused this dramatic improvement in COVID-19. However, it certainly suggests that hyperbolic press reports that fuel controversy about ClO_2 rather than supporting further research into a potentially safe, inexpensive, and effective treatment are not only unwarranted but are counterproductive [105]. The failure of the press to retract their previous inaccurate statements or to impartially investigate potentially effective treatments only exacerbates distrust in the media as a valid source of information. Furthermore, the suppression of content on social media platforms such as YouTube and Twitter raises questions about how dissenting opinions are to be managed. YouTube, which is owned by Google, is also banning channels associated with several prominent activists such as Robert F. Kennedy Jr. and Joseph Mercola [106]. Suppression of non-mainstream opinions exacerbates distrust in the media among individuals who trust or respect such individuals.

Rumors and conspiracy theories

Additional factors contributing to vaccine hesitancy include rumors, confirmation bias, and conspiracy theories [5,21]. As pertains to COVID-19 vaccines, Islam et al. [107] defined a *rumor* as "any unverified claims related to COVID-19 vaccine(s) or the process of immunization/vaccination circulating on the online platforms that could be classified as true, false, or misleading or exaggerated after verification by the fact-checking agencies" (3). One source of information for rumors is misinformation. *Misinformation* is defined as "inaccurate or false information shared by someone unwittingly and without any intention to cause harm" (Islam 3). This information is typically shared by people who don't realize the information they are sharing is false or misleading. For example, the CDC's reversal on the association between COVID-19 vaccines and myocarditis is not an example of misinformation. The CDC's initial claim that rates of myocarditis and pericarditis following the vaccines were no higher than the expected background rate was later followed by an acknowledgement of an increased risk. This change was the result of new information being obtained over time and is not an example of misinformation, because the initial reports failed to demonstrate an increased risk [108].

Confirmation bias can also contribute to vaccine hesitancy. This type of bias occurs when a person pays attention to evidence that supports their prior beliefs while disregarding evidence that conflicts with their prior beliefs [21]. Confirmation bias can work in opposite directions. For example, individuals who support vaccines and believe vaccines are the best way, or the

only way, to end the pandemic may disregard evidence that conflicts with their beliefs, such as reports of side effects or evidence supporting treatments for COVID-19. Individuals who do not support vaccines and believe the risks of the vaccines are greater than the risks associated with contracting COVID-19 may dismiss evidence that conflicts with their beliefs, such as reports of reduced severity of illness, hospitalization, and death following vaccination.

Conspiracy theories can contribute to vaccine hesitancy. Islam et al. [107] defined conspiracy theories as "any claims by an individual or group of people to reach malicious goals" (3). Conspiracy theories may result from the spread of *disinformation*, which has been defined as misinformation that is "spread intentionally to serve a malicious purpose, such as to trick people into believing something for financial gain or political advantage" [109]. A historical example of disinformation is the sugar industry's funding of research in the 1960s and 1970s that cast doubt on the role played by sucrose in coronary heart disease while promoting fat as the dietary culprit [110].

Jamieson describes numerous conspiracy theories related to the COVID-19 pandemic [111]. He points out that some individuals exploit the provisional and evolving nature of scientific knowledge as well as the funding structures that support scientific investigations to generate conspiracy theories. These conspiracy theories then cause some individuals to distrust public health authorities' recommendations about wearing a mask and vaccination.

Islam et al. [107] searched online platforms and found 637 rumors and conspiracy theories from 52 countries in 29 languages. Of these, 91% were classified as rumors and 9% as conspiracy theories. The authors concluded that rumors and conspiracy theories can negatively impact confidence towards COVID-19 vaccines. Several challenges exist when attempting to determine if information is factual. First, medical knowledge is turning over at an ever-accelerating rate. Densen reported the doubling time for medical knowledge increased from 50 years in 1950, to 7 years in 2010, and to just 73 days in 2020 [112]. Thus, medical knowledge that was believed to be factual just a few months ago may now be outdated or proven false.

Second, identifying whether something is a conspiracy theory has become more difficult in part due to the increased use of the term *conspiracy theory* as a label to persuade others that an opinion or story should be dismissed as irrational or paranoid rather than accepted as reasonable suspicion [113]. According to Rankin [114], this began with a Central Intelligence Agency (CIA) program designed to counteract questioning of the findings of the Warren Commission, which investigated the assassination of President John F. Kennedy [115]. Now the conspiracy theory meme has become entrenched as a pejorative label and is used to discredit opinions one wishes to discount [114].

The use of persuasion and coercion to overcome vaccine hesitancy

Amid rumors, confirmation bias, conspiracy theories, and questions about safety and efficacy of the COVID-19 vaccines, several strategies have been explored to combat vaccine hesitancy. The most frequently employed interventions are persuasion and coercion. Persuasion can take many forms, but three of the most common are education, psychological persuasion, and incentivization.

Education

Education is frequently recommended as a response to vaccine refusal [10]. Evidence-based counseling tips include: (1) start early - when striving to increase childhood vaccination rates, take advantage of prenatal appointments and the first few postnatal appointments to educate parents about vaccines, (2) present vaccines as the default approach - the CDC recommends a presumptive approach to discussions about vaccinations rather than a participatory approach [116], (3) be honest about side effects and reassure patients of a robust vaccine safety system, (4) tell stories in addition to providing scientific facts, (5) build trust with patients, and (6) use motivational interviewing to highlight the importance of individual protection [117].

Kata [10] and Callender [13] report individuals who refuse vaccinations are more likely to have garnered anti-vaccination information from the Internet, specifically from anti-vaccination websites. They point out that these individuals have been exposed to a variety of misinformation regarding vaccination which has influenced their attitude towards vaccinations.

Building trust in immunization as a social good is another method recommended to increase vaccine coverage [118]. Suggested methods for building trust include (1) accurately reporting adverse events, (2) having ways of reporting adverse events that are both user friendly and comprehensive, (3) be forthcoming with information regarding adverse events, and (4) educate physicians regarding how to counter arguments against vaccines [13].

Psychological persuasion

Psychological persuasion has been recommended to improve vaccination compliance. Chou and Budenz recommended leveraging patients' emotions to address

vaccine hesitancy. They suggested acknowledging fears, anger, and other similar emotions while emphasizing the safety and efficacy of COVID-19 vaccine development and fostering individuals' self-efficacy through vaccination [119].

Some writers have suggested using fear to motivate people to get vaccinated. Walker claims the main reason people get vaccinated is fear; they fear the disease more than the vaccine [121]. However, Fairchild and Bayersuggest using fear to motivate people to get vaccinated could backfire by further eroding trust in public health officials and scientists. Also, it could instill fear that the government will go too far and erode civil liberties [122].

Incentivization

Another approach to improve vaccine compliance is incentivization in the way of payments to individuals who get vaccinated. Such payments may be monetary or non-monetary. As of mid-June 2021, twenty-two states in the U.S. and the District of Columbia offered some type of incentive to encourage people to get vaccinated. Ten states offer vaccine lotteries with winners receiving up to $1.588 million. Other incentives for getting a COVID-19 vaccine include discounts for food and beverage, paid time off for employees, discounts at grocery stores, free baseball tickets, college scholarships, and gift/debit cards [122]. President Biden called on state and local governments to pay $100 to every newly vaccinated American [123].

In Australia, the government employs financial incentives in the form of childcare payments as well as tax benefits to increase vaccination rates [124]. In Moscow, authorities held a weekly drawing for the vaccinated and gave away 5 cars each week. In London, the vaccinated were eligible to win tickets for the Euro 2020 Soccer Championship. Romanians were offered a barbecued sausage sandwich. Indonesians could win live chickens. In Lebanon, Uber offered free rides to and from vaccination centers. In the Philippines, a town mayor was planning to raffle off a cow while another community raffled off sacks of rice to the vaccinated. Additional incentives for the vaccinated include complimentary dessert in Malaysia, free beer in Israel, and raffle tickets for a $1.4 million apartment in Hong Kong [125].

Studies examining the success of incentivization programs demonstrate mixed results. Wong et al. reported a 42% increase in vaccination rate in four North Carolina counties when a $25 cash card was offered to adults who received or drove someone to receive their first dose of COVID-19 vaccine [126]. A study in Sweden found small cash incentives ($24 USD) resulted in an increase of 4.2% in vaccination rates [127].

However, an interview with vaccine experts found minimal success from incentives [128]. Chang et al. reported $10 or $50 financial incentives and other behavioral nudges did not significantly increase SARS-CoV-2 vaccination rates amongst the vaccine hesitant [129]. In Germany, a study found that payments of as much as €200 failed to increase vaccination rates [130]. Another study found no evidence that the Ohio vaccine lottery was associated with increased rates of adult vaccination against COVID-19 [131].

Thus, the effectiveness of incentives for increasing vaccination rates remains controversial and minimal evidence exists to support incentives as an effective tool for increasing COVID-19 vaccination rates.

Coercion

When persuasion is ineffective or insufficient, governments may turn to coercion as a means to improve vaccination compliance. Coercive policies to increase vaccination have a long history that predates the COVID-19 pandemic [132]. A large body of literature exists regarding the justification for the use of coercion in public health and infectious disease. Generally, such justification is based upon Millian grounds whereby the risk of an unvaccinated individual harming others is viewed as adequate to justify the use of coercion [133].

McCoy found that coercion has historically been utilized by the United Kingdom, the United States, and Australia at various times and to varying degrees to improve vaccination rates. However, the use of coercion has met with resistance, resulting in changes to vaccine policies in each of these countries [134]. The primary method of coercion involves compulsory vaccines via mandates, with consequences for non-compliance that include financial penalties/fines, loss of jobs, and restriction of freedoms [135].

Mandates

Vaccine mandates or compulsory vaccinations have been recommended by some authors. Comparing vaccine refusal to firing a weapon into the air and endangering innocent bystanders, Flanigan [136] wrote "Vaccine refusal harms and risks innocent bystanders. People are not entitled to harm innocents or to impose deadly risks on others, so in these cases there is nothing to be said for the right to refuse vaccination" (5).

Savulesco listed four conditions which he feels justify making vaccines mandatory or compulsory. These are: (1) if there is a grave threat to public health, (2) the vaccine is safe and effective, (3) mandatory vaccination

has a superior cost/benefit profile compared with other alternatives, (4) the level of coercion is proportionate [133].

When mandates are less effective than desirable, providing individuals with the option to opt-out has been shown to increase vaccine uptake [137]. Bester advocates vaccine mandates while also recommending an opt-out policy that encourages maximal vaccine uptake [132]. Vaccine mandates are being implemented around the world. More than 30 countries now require COVID-19 vaccination [138]. In the US, President Biden has ordered sweeping vaccine mandates that may affect up to 100 million citizens. The rules mandate all federal employees in the executive branch as well as all employees of contractors that do business with the federal government get vaccinated. Additionally, employers with more than 100 workers must require their employees to be vaccinated or undergo weekly testing for the virus. This affects about 80 million Americans. Approximately 17 million individuals who work at health facilities that receive federal Medicare or Medicaid also will have to be fully vaccinated [139]. On August 24th the U.S. Secretary of Defense required active duty, National Guard, and Reserve military members to get vaccinated [140].

In addition to mandates by the federal government, numerous non-governmental organizations have implemented vaccine mandates as well. A compilation of 100 large companies in the U.S. found nearly half (47%) have implemented a vaccine mandate for at least some of their employees and some say they will terminate employees who refuse to get vaccinated [141]. Many healthcare facilities are requiring their employees to get vaccinated or face termination as well [142]. Around the world, vaccine mandates are being implemented in a growing number of countries including Australia, the United Kingdom, as well as countries in North America, Central America, Europe, Asia, and Africa [138]. Individuals who refuse to comply with COVID-19 vaccine mandates face a range of potential consequences that include fines/penalties and various types of restrictions. While numerous studies discuss the ethics of vaccine mandates, data evaluating their effectiveness is lacking. Prospective studies are needed to evaluate the effectiveness of mandates for increasing vaccination rates.

Fines/penalties

Historically, fines/penalties have been imposed on individuals who refuse to comply with vaccine mandates [143] and fines are now being used to improve compliance with COVID-19 vaccinations. In Jakarta, Indonesia, fines up to 5 million rupiah ($350 USD) can be levied against people who refuse vaccination. In the U.S., employers who don't comply with the federal vaccination mandate can be fined up to $14,000 per violation [144]. Students at Quinnipiac University in the U.S. have been threatened with fines of $100 a week, to a maximum of $2,275 [145]. In Australia, individuals who refuse vaccination for coronavirus could be sentenced to five years imprisonment and/or a $66,600 fine under the Australian Biosecurity Act 2015 [146]. In British Columbia, Canadians who refuse to show proof of vaccination to businesses that require them could face fines of $575 per individual, and fines of $2,300 can be levied against owners, operators, and event organizers who host a non-compliant event. Furthermore, repeat offenders could face a $10,000 fine and/or one year in prison [147]. In France, businesses that fail to check if clients have a health pass will be fined up to 1,500 euros, and the fine will increase progressively for repeat offenders [148].

Despite the widespread use of financial penalties for not getting vaccinated, no studies could be found that examined the effectiveness of such penalties for increasing vaccine compliance. Thus the efficacy of financial penalties for increasing vaccine compliance remains unknown.

Restrictions

Unvaccinated individuals face a growing number of restrictions at their workplaces, entertainment venues, sporting events, and restaurants. Proof of vaccination is now required for employees and customers of indoor eateries, gyms, and entertainment centers in New York City, for patrons and employees at indoor bars, nightclubs, and breweries in Los Angeles County [149], at all restaurants, bars, clubs, gyms and large indoor events for patrons and employees in San Francisco [150], and at restaurants and gyms in New Orleans [148]. In Moscow, unvaccinated employees can be suspended without pay and businesses that fail to comply with vaccine requirements can be forced to close for up to 3 months [151]. In Fiji, unvaccinated public servants are forced to go on leave and those who remain unvaccinated starting in November will be fired. In Greece, only vaccinated customers are allowed in bars, movie theatres and other closed spaces. Malta has banned visitors from entering the country unless they are fully vaccinated, and in Saudi Arabia, vaccination is required to enter any government, private, or education establishment [148]. Officials in the town of Saifai, India advised liquor stores not to sell to anyone who is unvaccinated. Some countries restrict access to certain events or public spaces if people are not vaccinated. For example, the United Arab Emirates prohibits the unvaccinated from attending live sporting events as well as cultural or arts activities. Kazakhstan restricts access to bars, cinemas, and airports.

In Saudi Arabia, people are banned from shopping malls if they are unvaccinated. Other governments have threatened the unvaccinated with additional serious consequences. In Russia, the Kremlin decreed that the unvaccinated would be unable to work and could be discriminated against. Philippines's President Rodrigo Duterte told his citizens if they didn't get vaccinated, they would serve jail time [125].

Do restrictions work? No studies or data could be found regarding the effectiveness of restrictions to increase COVID-19 vaccination rates.

Arguments against using persuasion or coercion to overcome vaccine hesitancy

Not all agree with the use of persuasion or coercion to increase compliance with vaccines. In their discussion of ethical principles for immunization programs, Verweij and Dawson [152] suggested that participation in vaccination programs "should, generally, be voluntary unless compulsory vaccination is essential to prevent a concrete and serious harm".

Kata [10] found that educational interventions intended to increase vaccinations are often ineffective and rather than improving vaccination rates, can actually reduce vaccination rates. Furthermore, she reports labeling those on the other side of the pro-vaccine versus anti-vaccine debate as "wrong" is ineffectual.

Nyhan et al. conducted a survey experiment in which they sent pro-vaccine messages to parents via the internet. These messages were targeted at correcting misinformation about vaccines and were intended to increase vaccination rates. The authors found none of the interventions increased the intention of parents to vaccinate their children. In fact, among parents who had a negative view of vaccination prior to the educational interventions, their intent to vaccinate decreased after the intervention [153].

Some authors argue against the use of coercion. For example, Pennings and Symons, who argue that persuasion is preferable to coercion, recommend evidence-based public health measures to build public trust in vaccination rather than resorting to coercion [154]. Other authors, such as Chantler et al., prefer one type of coercion over another. They suggest mandating vaccines as an entrance requirement to educational establishments as opposed to imposing fines or requiring intermediaries to report vaccine refusers to authorities [118].

Another problem with coerced or mandated vaccines is the conflict between protecting individual autonomy (i.e. informed consent) and protecting the common good of society (i.e. public health protection). Zagaja and colleagues point out that consent presupposes a consciousness and will of the person concerned to undergo a certain medical procedure [143]. The WHO emphasizes that one of the premises for informed consent is voluntariness [155], "For consent to be valid, it must be informed, understood and voluntary, and the person consenting must have the capacity to make the decision" (2).

The U.S. Justice Department [156] has stated that the emergency use authorizations for the COVID-19 vaccines require that vaccine recipients "are informed...of the option to accept or refuse administration of the product" (7). Furthermore, public or private entities are permitted to impose vaccination requirements for vaccines that are subject to EUAs.

However, Zagaja et al. pointed out that when vaccines are obligatory, voluntariness is lacking, and thus from an ethical and legal perspective, the whole informed consent is invalid. They recommend replacing the informed consent form with a simple signature on a document confirming that vaccination occurred. On such a document, they recommend including information on the obligation to vaccinate and the sanctions for failing to do so [143].

Coercing individuals based on the premise that vaccine refusal risks harming innocent bystanders assumes that the unvaccinated pose a risk to the vaccinated. But the CDC has reported that vaccines are effective at preventing infection, reducing severity of illness [157], and reducing the likelihood of hospitalization and death [158]. Thus, according to the CDC, individuals who have already been vaccinated are at decreased risk of harm from the SARS-CoV-2 virus whether it comes from unvaccinated or vaccinated individuals. Also, vaccinated individuals with breakthrough cases and unvaccinated individuals who contract COVID-19 carry equal viral lodes and are equally efficient at spreading COVID-19 [51].

Other authors argue against compulsory vaccinations based on their finding that they simply don't work. Sadaf et al. conducted a systematic review and found no convincing evidence for effective interventions that directly address vaccine hesitancy and refusal [159]. Additionally, coercion can sometimes have the unintended effect of galvanizing resistance to vaccination [132]. Britain abandoned its policy of mandatory vaccinations in 1948 due to organized resistance, and in the U.S. resistance to compulsory vaccinations has shifted from passive to active resistance over the years [8]. Chantler et al. suggested introducing a coercive policy can undermine the public trust necessary to ensure high vaccination rates [118].

Another consequence of vaccine mandates and the resultant polarization between the vaccinated and the unvaccinated is the shaming and blaming of the latter [160-161]. Dr. Eric Topol at Scripps Research pointed out that blaming the unvaccinated is neither accurate nor helpful. He explained, "The pandemic clearly involves all people, not just the unvaccinated" [14]. Blaming the unvaccinated can lead to vaccine shaming and stigmatization. Hoetez suggests the unvaccinated should not be blamed. Instead, he suggested pursuing those who disseminate disinformation while recognizing that the unvaccinated are victims of disinformation. Robert Blendon, of the Harvard T.H. Chan School of Public Health, says calling the pandemic a "pandemic of the unvaccinated" is provocative [14].

Some countries have introduced COVID vaccine passes or passports which have triggered protests against what some perceive as restrictions on their civil liberties [162]. In Australia, unintended consequences of vaccine restrictions include encouraging healthcare providers who disagree with vaccine mandates to commit fraud by signing medical ineligibility forms, cementing a politicized collective identity for people who are opposed to vaccines, and failing to increase vaccination uptake [124].

Natural immunity vs. vaccine-induced immunity

Another issue that contributes to vaccine hesitancy is the question of whether people who have already recovered from COVID-19 need to get vaccinated. Several studies have examined the efficacy of natural immunity at preventing reinfection.

A study in Qatar compared reinfection rates in 43,044 antibody-positive individuals who were followed for a median of 16.3 weeks with an antibody-negative cohort of 149,923 individuals who were followed for a median of 17.0 weeks. The efficacy of natural immunity against reinfection was found to be 95.2% [163]. Additional evidence for the robustness of natural immunity comes from a study in Geneva, Switzerland that demonstrated natural immunity reduced the risk of infection 94% compared with seronegative controls >8 months after initial serology assessment [164]. Still another study supporting the superiority of natural immunity found that neutralizing antibodies to COVID-19 persist in most individuals for at least one year following SARS-CoV-2 infection [165].

A study from Israel matched 16,215 persons who were previously infected with COVID-19 and 16,215 individuals who had been fully vaccinated. During the follow-up period, the authors found a statistically significant 13-fold increased risk of infection in individuals with vaccine-immunity versus natural immunity [166].

A study of 52,238 employees at the Cleveland Clinic found individuals who previously had SARS-CoV-2 infection were unlikely to benefit from COVID-19 vaccination. This was based on the finding that the cumulative incidence of SARS-CoV-2 infection did not differ among previously infected unvaccinated subjects, previously infected vaccinated subjects, and previously uninfected subjects who were vaccinated [167].

The findings of these studies may be explained by the finding that vaccine efficacy against infection diminishes over time. Puranik et al. studied the effectiveness of the Moderna and Pfizer vaccines against infection at the Mayo Clinic Health System [168]. They found that effectiveness against infection dropped after six months to 76% for Moderna and 42% for Pfizer. However, effectiveness against hospitalization remained high at 81% for Moderna and 75% for Pfizer.

However, not all studies find natural immunity to be superior to vaccine-induced immunity. A CDC study retrospectively examined the risk of reinfection in 246 individuals who previously contracted COVID-19 and were either vaccinated or not vaccinated. They found that previously infected individuals who were unvaccinated were 2.34 times more likely to become reinfected than those who were previously infected and were fully vaccinated [169]. Another CDC study of 72 individuals who had a previous positive RT-PCR test for SARS-CoV-2 found 26 participants (36%) were serological nonresponders (i.e. they did not produce anti-SARS-CoV-2 antibodies). It is unknown if these same individuals would produce antibodies if they received a COVID-19 vaccine [170]. A third CDC study examined data from 187 hospitals across 9 states in the U.S.from January-September 2021. They looked at patients who were hospitalized with COVID-19-like illness and found that of the 7,348 patients who met their inclusion criteria, 1,020 hospitalizations were among previously infected and unvaccinated persons (i.e. natural immunity breakthrough cases) and 6,328 hospitalizations were among fully vaccinated and previously uninfected persons (i.e. vaccination breakthrough cases). Laboratory-confirmed SARS-CoV-2 infection was identified in 324 (5.1%) of the fully vaccinated and 89 (8.7%) of the unvaccinated, previously infected individuals. Thus, previously vaccinated individuals made up a higher percentage of hospitalizations for COVID-19-like illness, but were less likely to test positive for SARS-CoV-2 infection [171].

At this time, conflicting evidence exists regarding whether individuals who have recovered from COVID-19

should get vaccinated. However, the CDC continues to recommend they get vaccinated [172].

Lack of compensation for adverse events

In the U.S., individuals who are injured by the COVID-19 vaccine are referred to the Countermeasures Injury Compensation Program (CICP) which covers serious injuries or death only. However, this program does not cover attorneys' fees and costs. Also, requesters must prove to the Department of Health and Human Services (HHS) that the COVID-19 vaccine caused their serious injury or death [173].

How effective is this program? The program has been described as a "black hole" by Peter Meyers, an emeritus professor at George Washington University School of Law [174]. Meyers explains the process of filing claims is handled entirely within the HHS without fees for attorneys or expert witnesses and a short one-year window to file claims. Since this program's inception in 2010, only 29 claims have been paid. The other 452 claims (91.4%) were denied [175].

The World Health Organisation has a no-fault compensation program for 92 low- and middle-income countries that can help with rare but serious adverse events that are related to COVID-19 vaccines. However, this program is only applicable until June 2022 [176]. In March 2020, the U.S. Secretary of HHS issued a PREP Act Declaration covering COVID-19 vaccines providing liability protections to manufacturers, distributors, states, localities, and licensed healthcare professionals. This declaration grants indemnity to the pharmaceutical companies who produce the COVID-19 vaccines. Thus, they are immune from lawsuits and liability under federal and state law with respect to all claims for loss resulting from the administration or use of a COVID-19 vaccine [177]. In other words, the vaccine manufacturers cannot be sued or held liable for any harm resulting from the vaccines.

Breakthrough cases

Reports of breakthrough cases of COVID-19 in individuals who had received at least 2 doses of the Pfizer and Moderna vaccines began to appear in the scientific literature within months of the vaccines' release [178]. Investigators initially found such breakthrough cases to be rare, but also found that nearly half (46%) of people who were hospitalized with breakthrough cases had moderate, severe, or critical illness [179]. With time, breakthrough cases became more common.

In March 2021, breakthrough cases accounted for only 2% of all COVID-19 cases in Los Angeles. By June this number had risen to 20% and by July breakthrough cases constituted 30% of all COVID-19 cases [180]. In July 2021, the CDC reported an outbreak of 469 cases in Massachusetts. The vaccination coverage rate of eligible Massachusetts residents at that time was 69%. Approximately three quarters (346;74%) of cases occurred in fully vaccinated persons and 79% of vaccinated persons with breakthrough infection were symptomatic. Of the five individuals with COVID-19 who required hospitalization, four were fully vaccinated [181].

Additional reports of breakthrough cases in France [182], Israel [183], and Singapore [184] have occurred despite high rates of vaccination and boosters. Breakthrough cases are often associated with the Delta variant, which has a higher rate of breakthrough than the Alpha variant [185-186]. Also, fully vaccinated individuals have lower rates of severe COVID-19 disease, hospitalization, and death associated with the Delta variant than unvaccinated individuals [185]. In addition to the variant involved, demographic factors can also influence the outcome of breakthrough cases. A nosocomial outbreak of 42 cases at a hospital in Israel involved infection with the SARS-CoV-2 Delta variant. Of the 42 cases, 38 were fully vaccinated with the Pfizer vaccine, 1individual had received just 1 vaccination, and 3 were unvaccinated. In this study, the index case was a fully vaccinated hemodialysis patient in his 70s who was admitted to the hospital and four days later was diagnosed with COVID-19. This index case spread to others in the hospital and resulted in a total of 42 cases including 23 patients, 16 staff members, and 3 family members. Every transmissions that occurred between patients and staff involved transmission between masked and vaccinated individuals. The 23 patients had a mean age of 77 years, all had comorbidities, and 8 were immunocompromised. The severity of illness in the 23 patients included 8 patients who became severely ill, 6 critically ill, and 5 of the critically ill died. All 16 staff, whose median age was 33 years, remained asymptomatic or had only mild disease. Of the 3 unvaccinated individuals, 2 had only mild symptoms. In summary, this study found that the individuals who had the worst outcomes were older and had comorbidities [187].

As of May 1, 2021, the CDC chose to stop reporting breakthrough cases of COVID-19 in the U.S. in individuals who already received a COVID-19 vaccine [188]. Why? Their reported reason was to focus on the more serious cases (i.e. those involving hospitalization or death). But this contradicts medical and scientific logic. We don't ignore data that might help us better understand the risks and benefits of a therapeutic intervention. Would we ignore cases of cancer recurrence if we were studying a new chemotherapeutic agent to focus only on those individuals who were hospitalized or died? What about a

study exploring a new intervention designed to prevent cardiovascular disease? Would we ignore all cardiovascular events that occurred following the intervention unless the patients were hospitalized or died? Such an approach would be a travesty that would produce an outcry in the scientific community. So why is the CDC ignoring data about breakthrough cases? Their reasons remain unknown.

Risk of infecting others

Reports in the lay press have claimed vaccinated people are not as likely to spread the SARS-CoV-2 virus as the unvaccinated [189] and as a result declared that the unvaccinated pose a risk to everyone [190]. Some studies have suggested breakthrough infections, particularly among vaccinated individuals, have a lower viral load and therefore may be less likely to result in transmission [191-192]. However, other studies have shown that the vaccinated and unvaccinated carry similar viral loads and therefore are equally likely to spread the virus to others. These include a CDC report describing an outbreak of COVID-19 in Massachusetts [181] and a California study that found equal viral loads in vaccinated and unvaccinated individuals, as well as in symptomatic and asymptomatic individuals [193]. Several other studies found no difference in viral load between vaccinated and unvaccinated individuals [51, 194-196].

The fallacy of bifurcation

Another argument levied against compulsory vaccination is the focus on vaccines as the only solution to the COVID-19 pandemic. This is an example of the *fallacy of limited options* or more specifically, the *fallacy of bifurcation*. This fallacy is a false dilemma which results from the erroneous limitation of options to only two alternatives. If presented only with the option of getting COVID-19, with the inherent risks and sequelae of this disease, or with the option of getting the vaccine, assuming it is relatively effective and safe, most people would likely get the vaccine. However, a third option exists - using one of the numerous potential treatments that exist for COVID-19 (see Table 4).

Table 4: Potential treatments for COVID-19:

Treatment	Reference
Molnupiravir	[197]
Convalescent plasma	[198-200]
Remdesivir	[201-202]
Casirivimab & Imdevimab (monoclonal antibodies)	[203]
Fluvoxamine	[204-205]
Ivermectin	[206-210]
Chlorine dioxide	[92-94, 211]
Artemisia annua (wormwood)	[212]
Nigella sativa and honey	[213]
propolis	[214]
Uncaria tomentosa	[215]
N-acetylcysteine	[216]
Azadirachta Indica A. Juss (Neem)	[217]
Curcumin and Piperine	[218]
Taraxacum officinale (dandelion)	[219]
zinc	[220-222]
Vitamin D	[223-224]
Vitamin C	[225]
Cinnamaldehyde	[226]
Allicin	[226]
Selenium	[226]
Probiotics	[226]
Lactoferrin	[226]
Quercetin	[226]
Tea polyphenols [e.g. epigallocatechin-3-gallate (EGCG) from green tea and theaflavin-3,3′-digallate (TF3) from black tea]	[227-229]
Melatonin	[230-231]

Numerous therapeutic agents are being used to treat COVID-19 in countries throughout the world. In August 2020, the FDA granted an EUA for the use of convalescent plasma to treat hospitalized patients with COVID-19 [232]. Convalescent plasma is plasma donated by individuals who have recovered from COVID-19 infection that contains antibodies that may help patients with COVID-19 infections. Studies examining the use of convalescent plasma in individuals hospitalized with COVID-19 found this treatment to be safe and effective at improving clinical symptoms and reducing mortality [198-200]. However, not all studies have found benefits from convalescent plasma [233].

In May 2020 the FDA granted an EUA for Remdesivir for patients hospitalized with severe COVID-19. Remdesivir is an adenosine analogue which incorporates into nascent viral RNA chains and inhibits the viral RNA-dependent RNA polymerase [234]. Initial studies with Remdesivir produced mixed results regarding the drug's efficacy as a treatment for COVID-19 [201-202]. However, on October 22, 2020, the FDA approved Remdesivir for use in adult and pediatric patients 12 years of age and older weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization [235].

Casirivimab and Imdevimab are monoclonal antibodies that received an EUA from the FDA in November 2020. Casirivimab and Imdevimab are administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19 [203].

On November 4, 2021, Merck and Ridgeback Biotherapeutics received authorization from the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) for Molnupiravir, the first oral antiviral medication authorized to treat COVID-19. Molnupiravir has been approved for use in individuals who have mild to moderate COVID-19 and one or more risk factors for developing severe illness, such as obesity, older age (>60 years), diabetes mellitus, or heart disease [197].

The selective serotonin reuptake inhibitor Fluvoxamine has shown promise as a treatment for COVID-19. In a small study of 152 adult outpatients with COVID-19, Fluvoxamine was found to reduce the likelihood of clinical deterioration over 15 days [204]. In a larger study, 739 patients received Fluvoxamine while 733 controls received placebo. Fluvoxamine was found to reduce the need for extended emergency room observation or hospitalization in SARS-CoV-2 positive patients [205].

In addition, in vitro studies and clinical trials have identified multiple safe, inexpensive, non-prescription preventions and treatments for COVID-19 including Artemisia annua [212], Nigella sativa and honey [213], propolis [214,236], Uncaria tomentosa [215], N-acetylcysteine [216], Azadirachta Indica A. Juss (Neem) [217], curcumin and piperine [218], Taraxacum officinale (dandelion) [219], and chlorine dioxide [94, 211]. Nutritional supplements have also been suggested to boost the immune response and reduce the risk and/or severity of viral infection. Potential therapies include zinc [220-222], vitamin D [223-224], Vitamin C [225], cinnamaldehyde, allicin, selenium, probiotics, lactoferrin, and quercetin [226]. Ivermectin , a medicine with potent antiparasitic properties, has been used safely for over 35 years. This medicine dramatically lowered the incidence of river blindness, and its developers were awarded the Nobel Prize in Physiology and Medicine in 2015 [237]. Ivermectin also exhibits powerful antiviral and anticancer effects [238-239].

Currently, Ivermectin is being used effectively in countries throughout the world to treat COVID-19. Recent clinical trials in the U.S. [206], Brazil [207], Turkey [208], and Bangladesh [209], as well as a meta-analysis based on 18 randomized controlled treatment trials of Ivermectin in the treatment of COVID-19 [210] have found enhanced viral clearance, increased rate of clinical improvement, improvement in prognostic laboratory parameters, and reduced mortality following treatment with Ivermectin in patients with COVID-19. Additional systematic reviews and meta-analyses by Padhy et al. [240] and Kow et al. [241] showed statistically significant reductions in all-cause mortality. Another meta-analysis of 55 studies found 100% of 36 early treatment and prophylaxis studies reported positive effects. Statistically significant improvements were seen for mortality, ventilation, hospitalization, cases, and viral clearance. The probability that an ineffective treatment generated results as positive for the 71 studies examined was estimated to be 1 in 195 billion [242]. Over 20 countries have adopted Ivermectin and many of these countries have COVID-19 case rates and death rates that are only a fraction of the U.S. rate. These include India [243], Mexico [244], and Peru [245].

However, not all studies report positive findings. A preprint of an unpublished systematic review and meta-analysis by Roman et al. [246] of 10 randomized controlled trials found Ivermectin did not reduce all-cause mortality vs. controls, length of stay, or viral clearance in COVID-19 patients. These authors reviewed studies that involved only mild to moderate cases of COVID-19 and three of the RCTs were conducted in non-hospitalized patients. They also reported Ivermectin was not associated with adverse events or severe adverse events.

Despite what appears to be strong evidence for the safety and efficacy of Ivermectin as a treatment for COVID-19, the FDA has blocked the use of Ivermectin to treat COVID-19 in the U.S. [247] and a physician in Arkansas is under investigation by the state's medical board for administering Ivermectin to inmates who contracted COVID-19 [248]. Following a review of the scientific literature regarding the use of Ivermectin as a treatment for COVID-19, the NIH upgraded the status of Ivermectin from "against" to "neither for nor against", which is the same recommendation given to monoclonal antibodies and convalescent plasma [249]. However, for reasons that remain unclear, the FDA continues to speak out against the off label use of Ivermectin to treat COVID-19, offering only vague rationale that states: (1) taking large doses of the medicine can be dangerous (which is true for all medicines), (2) Ivermectin can interact with other medicines (also true for many medicines), and (3)taking a drug for an unapproved use can be very dangerous [247]. The FDA's stance is particularly confusing when the FDA has stated elsewhere: From the FDA perspective, once the FDA approves a drug, healthcare providers generally may

prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient [250].

However, hyperbolic press reports that focus on the use of Ivermectin to deworm horses or associate it with fake cures [251] ignore the numerous studies demonstrating this medicine's safety and efficacy. They do not mention that 3.7 billion doses of Ivermectin have been distributed worldwide in the last 30 years [206]. At some point, the question needs to be asked, has the criticism of Ivermectin crossed the line from scientific critique to propaganda? Where is the science to back up the claims of dangerousness and ineffectiveness?

The Biden Administration announced on June 17, 2021 that the U.S. will invest $3 billion to accelerate the discovery, development, and manufacturing of antiviral medicines. The plan, called the Antiviral Program for Pandemics, is described as a response to the urgent need for antiviral medications to treat COVID-19 [252]. At this time, it is unknown if any of the aforementioned treatments will be included in this plan, however one treatment that is already being touted is an experimental new drug produced by Merck. In June 2021, Merck announced the U.S. government agreed to pay $1.2 billion for 1.7 million courses of its experimental COVID-19 treatment, Molnupiravir, if it is demonstrated to be effective. Also, the government has the option to purchase up to 3.5 million additional treatment courses. Merck expects to produce more than 10 million courses of the drug by the end of this year and hopes to sell the drug to other countries as well. The cost of a course of treatment in the U.S. is $700 USD, although Merck said it plans a tiered pricing scheme based on country income criteria [253-254]. The cost of the drug in the U.S. is reported to be 40 times the cost of manufacturing the drug [255].

Regardless of which treatment is investigated or utilized, the use of treatments for COVID-19 creates a 3rd option for individuals besides getting vaccinated or remaining unvaccinated.

Discussion

The effectiveness of persuasion and coercion to increase vaccination rates for COVID-19 remain unknown. Despite the widespread use of such strategies, studies examining their efficacy and drawbacks are needed to determine the effectives of these methods. Other strategies that may increase compliance and maintain relationships between providers and their patients need to be studied as well. Compassion, tolerance, and a willingness to consider alternative viewpoints are essential to the development of a trusting relationship. How can this be achieved in the contentious environment regarding COVID-19 vaccines? One place to start is with the recognition of how consensus reality affects our thoughts and behaviors. Consensus reality is an agreed-upon concept of reality which people in the world, a culture, or a group believe is real or treat as real. In other words, if enough people agree that something is real, then it becomes their reality.

Throughout history, consensus reality has shaped our beliefs, attitudes, behaviors, and laws. Examples include the beliefs that the world is flat, the earth is the center of the universe, women shouldn't vote because they could become infertile if they do too much thinking [256], black men should be denied education because they don't care about education [257], neurons communicate via electricity rather than chemicals [258], and bacteria do not cause ulcers [259]. Today, our consensus reality includes the concept that vaccines are the best way to end the COVID-19 pandemic [260-261] and the concept that vaccines are not safe because they are associated with potentially severe adverse effects and have not undergone sufficient time-proven testing [262]. Which reality is true? Only time will tell. Flexibility and openness to change are essential when determining our approach to vaccines and to the COVID-19 pandemic. Correcting course and allowing for change is not a sign of failure but rather demonstrates an open-minded willingness to adapt to changing conditions and newly acquired knowledge. However, the coexistence of the two aforementioned consensus realities regarding COVID-19 vaccines (i.e. pro-vaccine and anti-vaccine) is creating a deepening chasm that Prasad [263] has labeled *vaccine tribalism*. This tribalism leads to polarization and the demonizing of people with opinions different from our own. It also discourages open discussion of scientific findings.

We must guard against the pitfall of descending into an *us versus them* mentality whereby individuals who choose not to be vaccinated are viewed as ignorant, immoral, dangerous, and anti-vaxxers and instead recognize that differing opinions, while frustrating and sometimes frightening, are necessary if we are to continue learning. We must work to better understand the viewpoints of those who hold opinions different from our own, recognizing these as opportunities to expand our knowledge rather than as threats or dangers. We must seek to understand these differing perspectives to unite behind a common goal; the goal of overcoming the COVID-19 pandemic.

We must not fall prey to the trap of generalizing, lumping, and labeling all who choose not to be vaccinated as "anti-vaxxers" or other judgmental, pejorative, or derogatory terms that divide us rather than unite us. Intolerance, labeling, and vaccine shaming create deep splits within our families, communities, and countries.

Ultimately, we are all seeking the same goals - health and safety - but we differ in our beliefs about how best to achieve these goals. Respectful dialogue and tolerance of differing perspectives provide the best opportunity to build consensus regarding the optimal means to survive this pandemic while maintaining healthy, respectful, compassionate relationships post-pandemic.

III. Conclusions

Vaccines have been used safely for over 200 years to protect against infectious diseases. However, vaccines also can produce adverse events. The COVID-19 pandemic has generated intense controversy regarding vaccines against the SARS-CoV-2 virus, and this controversy has contributed to vaccine hesitancy. Efforts to increase vaccination rates, including education, persuasion, incentivization, and coercion have been only partially effective and may be contributing to a backlash against the vaccines. Further exploration of the risks and benefits of the vaccines are needed along with increased transparency about these risks and benefits. Additionally, research examining options for the prevention and treatment of COVID-19 must also be supported to help manage breakthrough cases and treatments for individuals who refuse vaccination or cannot mount an adequate immune response.

IV. Materials & Methods

This is a narrative review exploring vaccine hesitancy and strategies that are currently being used to increase vaccine compliance. Thus, strict selection criteria were not applied for the selection of articles included in this manuscript. Rather, articles were chosen based upon how informative, comprehensive, and relevant they were to the theme of this article. Topics explored in this article include: the history of vaccinations, reasons for vaccine hesitancy, adverse events that may contribute to vaccine hesitancy, the role of trust in vaccine hesitancy, approaches to combating vaccine hesitancy, and arguments against these same approaches. Results of evidence-based research articles, preprints, government documents, and online media reports were reviewed for inclusion in this review.

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Abbreviations:

CIA - Central Intelligence Agency

CDC - Centers for Disease Control and Prevention

ClO2 - Chlorine dioxide

CICP - Countermeasures Injury Compensation Program

COVID-19 - Coronavirus Disease 2019

CVT - cerebral venous thrombosis

HHS - U. S. Department of Health and Human Services
J&J - Johnson & Johnson

MHRA -United Kingdom Medicines and Healthcare products Regulatory Agency

NASA - National Aeronautics and Space Administration

NIAID - National Institute of Allergy and Infectious Diseases

NIH - National Institutes of Health

SAGE - Strategic Advisory Group of Experts on immunization

SARS-COV-2 - severe acute respiratory syndrome coronavirus 2

TTS - thrombosis with thrombocytopenia syndrome

VAERS - Vaccine Adverse Event Reporting System

VITT – Vaccine-Induced Thrombotic Thrombocytopenia

VPD - Vaccine Preventable Disease

WHO - World Health Organization

Definitions:

Compulsory vaccination - a vaccination required by a governmental body

Immunity - protection from an infectious disease. If you are immune to a disease, you can be exposed to it without becoming infected

Immunization - A process by which a person becomes protected against a disease through vaccination. This term is often used interchangeably with vaccination or inoculation

Inoculation - the introduction of a pathogen or antigen into a living organism to stimulate the production of antibodies

Vaccination - the act of introducing a vaccine into the body to produce immunity to a specific disease

Vaccination hesitancy - a delay in acceptance of getting vaccinated with any vaccines despite the availability of the vaccines

Vaccination refusal - refusal to get vaccinated with any vaccines. Vaccination refusers may refuse to get

vaccinations for any of a variety of reasons including medical, religious, or others.

Vaccine(historical) - an antigenic preparation of a typically inactivated or attenuated pathogenic agent (such as a bacterium or virus) or one of its components or products; (contemporary) - a preparation that is used to stimulate the body's immune response against diseases

Vaccine coercion - the use of coercion by medical, governmental, employer, or others in a position of power to use their power to attempt to force individuals to get vaccinated against their will

Vaccine hesitancy - a delay in getting a specific vaccine. Individuals who are vaccine hesitant may get many other vaccines, but be hesitant to get a specific vaccine

Vaccine incentivization - payment (either money or non-monetary) for getting vaccinated with a vaccine

Vaccine mandate - A requirement that an individual get vaccinated, or face adverse consequences, such as being restricted from entering a business, school, etc.

Vaccine refusal - refusal to get a specific vaccine. Vaccine refusers may get many vaccinations but refuse to get a specific vaccine.

Variolation - the deliberate inoculation of an uninfected person with the smallpox virus.

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