

Factors Causing COVID-19 Vaccine Hesitancy, A Global Perspective

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Abstract. At the end of the year 2019, all human beings experienced an unprecedented challenge. COVID-19, born in nowhere, has spread worldwide with a beast-like momentum. Surprisingly, scientists broke the record by creating vaccines within the shortest time after the pandemic was declared. Vaccines, commonly known to be an effective approach, not only offer great prevention to an individual but also promote the formation of herd immunity. However, people doubting the efficacy of vaccines hold divergent views toward vaccines made in a rush. In this essay, multiple types of vaccines are introduced, and numerous factors of hesitancy, including economy, education, and religiosity, are taken a closer look at. Following a grand view of worldwide research regarding vaccine efficacy, a specific recommendation, establishing trust publicly, is proposed as well.

Keywords: COVID-19, Vaccine, Hesitancy, Efficacy.

1. Introduction

It has been nearly three years since the pandemic commenced. Economic reduction, locomoting restriction, family devastation - these are all dilemma people encountered when the pandemic is the most serious. Nearly all the people on the planet anticipate an end to this pandemic, which myriad scientists are contributing to. When eventually vaccines broke through thousands of clinical trials and came into public sights, the situation does not seem to be optimistic: a high inoculation rate is not seen worldwide. People appear doubtful of whether to get vaccinated or not. Even though extensive research and essays associated with vaccine efficacy are present all over the internet, a poor connection and transmission of information to the general public is still a huge problem unsolved: the latest and valid experimental results proving an efficacious vaccine are not published effectively. Vaccines, for no matter what kind of diseases, are the primary, superior, and affordable option. While hesitancy remains in the world, bringing an intangible hurdle to the control of disease globally, acquiring positive solutions for the hesitancy becomes a priority. Analyzing the causes of vaccine hesitancy, scientists can get an outline of hesitancy as a result.

However, there still are challenges existing. Religiosity-related immobilized ideology of people toward vaccines, lack of education, spread of rumors about vaccines on the internet - all are potential barriers scientists are currently facing. Previously, a bunch of factors-of-hesitancy-centered essays have highlighted multiple valuable and feasible ideas, so a summary of the main aspects is included in the passage, rendering the vaccine administration more significant.

This essay utilized PubMed as a main source of information and extracted frequently-appeared information as core thoughts, attempting to grab attention to raise vaccination awareness. With a concentration on vaccine hesitancy, the essay included a rich array of cultural elements reflected in the grand social background.

2. Information About COVID-19

2.1. Epidemiology

In Wuhan, China, by the year of 2019's close, a viral outbreak went unanticipated. People reported cases displayed symptoms of pneumonia. The further survey pointed out that the majority of the cases were associated with a local seafood market. The virus, with its staggering infectivity, has expanded

its realm to all continents, with over 500 million cases worldwide. However, after numerous factors, for instance, the difference between previous exposure to COVID-19 and amount of cases reported or erroneous testing results, were taken into account, an estimation of over 3 billion people having been infected was concluded.

Scientists, bewildered and petrified by this unstoppable spread of disease, found its mode of transmission: person-to-person. When two people are in close contact, for example, at a distance less than two meters, the respiratory particles released by the host coughing or sneezing are possibly breathed in. Moreover, a pair of hands covered with viruses can infect an individual by touching organs like the nose, mouth, or eyes. The extent of airborne transmission for a distance over 2 meters was still unknown, but it was still worthy to be researched deeply. In a few studies, viruses were sampled in a closed space with bad ventilation where patients live.

Other transmission modes were accounted for as well. Viruses were discovered in fecates of patients, though no virus could be found in the upper respiratory systems. There were also cases where RNA of SARS-COV-2 was searched in blood samples. Nevertheless, with little evidence and research, they are not regarded as the main approaches to transmission.

A rich array of variants of COVID-19 has been declared in WHO: Alpha, Beta, Delta, Omicron, etc. Different variants seem to differ in their infectivity and morbidity. However, increasing infectivity was seen along its evolution route. The basic reproduction number (R_0), which states the average number of more cases caused by one reported patient, of Omicron BA.5 is around 18.3, about sixfold that of the primary types, which is about 3.0 to 3.3 [1].

2.2. The Harmfulness and Structure of COVID-19

Symptoms are the most direct manifestations assessing viral harmfulness. Patients, ranging from mild to severe, may display divergent symptoms. These include but do not limit to fever, diarrhea, breathing difficulty, fatigue, coughing, headache, the disappearance of taste, sore throat, vomiting, and congestion. These symptoms can be seen within 2 to 14 days after a viral exposure. However, wondering about long-term effects on patients, scientists focused on potential sequelae. In a recent study, researchers looked at renal involvements in 430 patients age-stratified and noticed a significantly higher risk of renal burden in elderly people in comparison to people under or at the age of 18: a higher rate of proteinuria (28.1% vs. 8.0%), pathological tubular urine (42.2% vs. 19.6%) and a minute decline of estimated glomerular filtration rate (34.9% vs. 6.2%) [2]. Moreover, reflections of incidences of 'Post-Covid', or 'Long Covid', were present all around the world, mainly a prolonged symptom for months or longer. To be more specific, except for the general symptoms, some symptoms are difficult to explain: those symptoms hold great similarity with myalgic encephalomyelitis or chronic fatigue syndrome. In addition, the misery may foster the development of mental issues, for example, post-traumatic stress disorder (PTSD). Unfortunately, 'Post-Covid' cases are not detected via normal daily tests.

Brief recognition of the structure of the coronavirus is essential. Coronavirus generally consists of four structural proteins: Nucleocapsid protein, Envelope protein, Membrane protein, and most importantly, Spike protein, which is largely utilized in vaccine production and preventive mechanisms [3]. Those Spike proteins are usually used as antigens that trigger the immune system to work. However, all variants of the virus hold different versions of RNA coding for Spike proteins. It brings challenges for scientists to devise the latest effective vaccines as much as possible.

2.3. Possible Treatments of COVID-19

Currently, there have been two mainstream treatments available: antiviral treatment and monoclonal antibodies. Antiviral treatments usually exist in forms of prescription oral pills. These pills prevent viruses from duplicating in human bodies, leading to much milder symptoms [4]. Monoclonal antibodies are extracted from immune cells specifically targeting pathogens from cured patients. Usually, intravenous infusion or injection is needed in the therapy. Nevertheless, with regard to the duration of effects, an option of vaccination, an implementation reducing the probability of one

getting infected prior to exposure to viruses, is preferable: monoclonal antibodies crave for resistance to breakdown in cells for a prolonged circulation in bodies, whereas the effects of vaccines last for a much longer period. On the other hand, a large span and a great expense are needed for the development of monoclonal antibodies [5]. Consequently, vaccines are anticipated globally and are more achievable for the vast majority.

3. Types Of Vaccines

Having a fundamental knowledge of the basic types of the vaccines is a priority and necessity. It can be roughly classified into 7 major types: DNA vaccines, mRNA vaccines, non-replicating viral vector vaccines, inactivated vaccines, live attenuated vaccines, and subunit vaccines.

3.1. DNA vaccines

DNA vaccine does its job by triggering host cells to express viral gene segments to generate antigens, and as a result, stimulating the immune response to prevent it. When it is injected into the body, the plasmid with the antigen-coding gene is transfected in the host genome, utilizing the host protein translation system to express the target gene.

DNA vaccine utilizing virus DNA double helices rather than the virus itself guarantees safety. DNA vaccines are outstanding in terms of stability and allow freeze-drying for long-term storage. Nevertheless, DNA vaccine has downsides as far as their immunogenicity is concerned. DNA vaccines only work in intercellular space after administration, and they must enter the cell to induce immune responses; however, only a negligible amount can successfully penetrate the cells which leads to a few protein immunogens generated thus largely lessening the efficacy. In order to tackle this problem, electrodes are sometimes combined with DNA vaccines to ensure or improve efficacy by shortly opening the cell membrane and allowing the entrance of plasmids. Given this feasibility, its low application still brings obstacles to large-scale vaccination and affects the approval of human DNA vaccines [6].

3.2. mRNA vaccines

DNA vaccines must cross the cell membrane and enter the nucleus to integrate the gene into the host genome before translation, whereas mRNA vaccines can just reach the cytoplasm and participate in translation directly, which raises safety to a higher level. However, it still has defects when it comes to side effects. Headaches, fatigue, muscle pain - all are potential symptoms injecting mRNA vaccines can lead to. Moreover, the immunity remains approximately for only one year before its effects disappeared. To put it in a nutshell, the protection spans and its possible side effects are aspects scientists should improve on [6].

3.3. Non-replicating viral vector vaccines

It used proper viral vectors that can carry the gene and trigger immune responses without causing infections. Non-replicating viral vectors have the replicating genes knockout, such that they are rendered incapable of self-replication. The most researched vector is the Adenovirus with a DNA genome. Carrying genes expressing full-length S-protein (antigen), Adenovirus is engulfed by an antigen-presenting cell that displays parts of the virus (usually the antigen) which triggers helper T cells to bind those antigens and downstream immune response [6].

3.4. Inactivated vaccines

It kills the genetic material of the virus in various ways: formaldehyde, β -propiolactone, and ultraviolet. Akin to non-replicating viral vector vaccines, inactivated viruses do not replicate in host cells, and they are engulfed by antigen-presenting cells as well. The mechanism of triggering the immune system is the same. However, some studies have shown pathological reactions in experiments while using MERS-inactivated vaccines in mice. Moreover, since a high concentration

of live viruses is operated in the production of inactivated vaccines, they are likely to pose biological threats to humans as well [6].

3.5. Live attenuated vaccines

Live attenuated virus vaccines contain certain virulent but weakened parts (through point mutation or deletion). However, their immunogenicity and ability to replicate is not affected. Even though they are shown to be extraordinarily effective in terms of their immunogenicity, whether they will regain virulence for a continuous period lacks scientific evidence. Moreover, patients with compromised immune systems may have the risk to be infected by the weakened virus [6].

3.6. Subunit vaccines

Subunit vaccines include antigenic proteins without genetic material, so they are generally considered to be the safest. Nevertheless, by using subunit vaccines sensitized cytotoxic T cells are not effectively produced. The response induced is not equally strong as other vaccines. Therefore, it is usually used in combination with other vaccines or adjuvants [6].

4. Factors of Hesitancy

With a general outline of current COVID-19 vaccines, epidemiologists are attempting to acquire more understanding of factors causing vaccination hesitancy.

4.1. Level of Economic Development

People in different regions or countries appear to have different vaccine acceptance, especially between developing and developed countries. Due to some research, surveys on vaccine acceptability were distributed among 15 distinct geographic areas, including 10 low and middle income countries (LMICs) in Asia, Africa, South America, Russia, and the US. According to the data, a significantly higher willingness for vaccination is seen in LMIC samples (mean 80.3%) in comparison to the high-income countries. This study confirmed that while vaccination acceptance is often higher in low-middle-income nations, vaccine hesitancy is generally higher in high-income or upper-middle-income countries. Researchers attributed these phenomena to individuals' interests in COVID-19 personal protection [7].

4.2. Students' Age and Parental Level of Education

Along with the increasing number of studies on COVID-19 vaccines, those vaccines on the market are gradually transforming from being incompatible with the young to higher compatibility for a wide range of ages. Nevertheless, there has been debate on the vaccination acceptance of children and adolescents, even though some European countries have approved vaccination for children over twelve years old. Related studies were done to find the association between some factors and vaccine acceptance, and they mainly focused on children's age and their parent's level of education. The investigation involved 903 students aged from 9 to 20 in a cohort of German secondary school. The results showed that 89 students were vaccinated, and the rest 735 students were not. Among vaccinated students, those who were between 16 to 19 years old occupied a staggeringly high proportion of 90%. Among unvaccinated students, approximately 68.3% reported intentions to be vaccinated. Holistically, less educated groups show more reluctance to get vaccinated [8].

4.3. Religiosity

In some cases, religiosity does play a role in increasing vaccine hesitancy. A recent study showed that religious teachings prioritize beliefs over scientific medication: they tend to have a higher preference for holy water or other alternative approaches to vaccines. Moreover, other beliefs, for example, even prohibit the usage of pork derivatives in vaccine production in Islam [9]. Conclusively, religiosity seems to influence the decision to inoculate with the vaccine to some extent.

4.4. Ethnicity

With data showing a significantly higher level of hesitancy among Black/African American respondents, researchers begin to pay attention to race/ethnicity. Black and African American respondents showed two times as much COVID-19 vaccine reluctance (50.00%) as White respondents in a July and August 2020 online survey. This could relate to their larger burden of hospitalizations and mortality. A long-term hesitancy could foster health disparities. The distrust of Black/African Americans can be traced back to racist exploitation by medical workers [10].

4.5. Personal Belief

There also exists personal objections or hesitancy aiming at the vaccine itself: people innately reject vaccination due to a series of doubts. Some commonly regard all kinds of vaccines as detrimental. As for the efficacy of vaccines, such vaccines developed in a rush was doubted; on the contrary, those who look down on the morbidity of the virus tend to overlook the vaccine as well. With little to no consciousness of searching for information or reports on the internet, people find it easy to question the provenience of vaccines [11].

To conclude, with the data shown above, the economy of a country, parental education and ages, religions, and races, along with individual thoughts toward vaccines are likely to affect the extent of vaccine hesitancy. Still, all of these phenomena seem to point to the origin of low education and few campaigns of information on vaccines. A widespread advertisement is thought to raise public awareness.

5. Worldwide study of Vaccine Efficacy

Despite existing hesitancy everywhere for any reason, vaccines still display great efficacy around the world. Multiple countries, having implemented the study of vaccine efficacy, achieved fantastic and visible results in experimental environments. By comparing the reported cases of the experimental group (vaccine group) and control group respectively, researchers can get a profile of vaccine efficacy.

5.1. Turkey

In the trial inactivated whole-virion SARS-COV-2 vaccine was used for testing efficacy. Subjects aged from 18 to 59 with no COVID-19 infection history (tested negative for both PCR and antibody test). In advance, participants who were in immunosuppressive medicine, had bleeding disorders, asplenia, or had recently received blood products or immunoglobulins were disqualified. Among the rest 10214 participants (6646 in the vaccine group and 3568 in the placebo group), only 9 of the vaccine group and 32 of the control group reported cases. Moreover, the frequency of any adverse events, for example, fatigue or injection-site pain, in the two groups displayed no significant difference. According to the findings, PCR-confirmed symptomatic COVID-19 can be prevented by the inactivated whole-vision SARS-COV-2 vaccine which not only guaranteed safety but high tolerability as well [12].

5.2. Indonesia

Likewise, inactivated SARS-COV-2 vaccine was as well tested in a study held in Indonesia, and participants were chosen from the same range of ages (18 - 59) followed by the exclusion of unqualified people. Following the first dosage of the vaccine or placebo, the researchers observed the volunteers, and those who reported symptoms for consecutive two days were sent to test for COVID-19. After a maximum of three months, the study confirmed seven instances in the vaccine group and 18 cases in the control group, indicating a 65.30% vaccine efficacy.[13].

5.3. the UK, Brazil, and South Africa

Excellent and fruitful results were obtained through the analysis of various studies conducted in those countries. A brief summary of the first trial is discussed here. Vaccine ChAdOx1 (developed at Oxford University, the composition of a non-replicating chimpanzee adenoviral vector) was specifically tested in this trial. In analyzing primary efficacy, 30 cases were found among the 5807 participants in the vaccine group and 101 cases were found among the 5829 participants in the control group, stating an efficacy of 70.4%. Overall, an acceptable safety profile was seen in ChAdOx1, and its efficacy against COVID-19 symptoms was demonstrated [14].

6. Ways to Lessen Hesitancy-Caused Effects

Having known the objective existence of hesitancy, people aim to seek possible approaches to minimize the effect brought by it. Looking at the previous studies associated with vaccine efficacy, citizens should form a basic ideology toward vaccination and acknowledge its benefits. Nevertheless, with regional unadvanced popularization of education or literacy, people living in rural areas may be convoluted by the latest information and news. Scientists, having done a lot of research, cognize a need to conquer those challenges. Another study regarding methods to alleviate hesitancy-caused burdens underscored the significance of building up public trust.

Among all the factors contributing to vaccine hesitancy, a salient one deals with ethnicity. This may partially originate from the infamous Tuskegee syphilis study, where mistrust formed between Black/African Americans and the medical community. In the study, participants from Long Island mentioned a dark history almost inscribed in Black/African Americans' minds: numerous slaves were unjustly sent and made use of in an experiment, the Tuskegee experiment. As a result, they remain skeptical or feel an inherent hostility whenever they hear things about getting vaccinated. Moreover, contemporary inequities among black people exist in terms of accessing healthcare as well, negatively maintaining or stimulating the mistrust. On the other hand, the lack of campaigns in marginalized communities is a problem. Citizens do not get vaccinated, do not get to know vaccines, or do not hear of them.

Aiming at those phenomena, researchers found trust-building to be effective implementation. Roughly three points were taken into account. First, the significance of task forces should be seen. When processing works, especially those that have been insufficient, task forces are in charge of declaring specific doctrines and rules to enhance efficiency. More interrelated task forces can also collaborate on developing buildings of health equity, for example, convening a meeting and legislating associated laws. Second, subsidizing community organizations is seen as a priority. Enduring the burden of continuously subsisting the communities, community structures face hurdles themselves in terms of funds. Timely support for those structures can guarantee a healthy and normal working status and put more effort into addressing vaccine equity. Last but not least, a lack of vaccine supply and shifting eligibility not only brings marginalized communities more barriers to vaccines but also makes campaigns look unrealistic and preposterous. As a result, while guaranteeing vaccine supply can assuage the current situation, establishing partnerships and enhancing informing tactics offering culturally sensitive information in terms of vaccine supply and eligibility earn the same importance [15].

7. Conclusion

Vaccines as an essential approach to controlling the disease are overlooked to a great extent. With the prior fixed and erroneous ideology of vaccines, with little possibility will the pandemic be eradicated. While a portion of people manifests hesitancy for various reasons, investigators try their best to magnify details and summarize. Worldwide and local organizations seek ways to enhance education about vaccines and their associated knowledge in a way of building up public trust. Problems are present in this essay as well. Detailed instruction to lessen or obliterate the hesitancy

does not appear, and some clear graphs or tables are lacking. Future prospect of having a more comprehensive and structural summary of factors of hesitancy is anticipated, with expectations of a surge in vaccination rate and consciousness.

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