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# Different Types of Vaccine and Their Properties-taking Inactivated and mRNA Vaccines as Examples

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**Abstract.** In the background of COVID-19, vaccines have become the central point. Various countries and companies investigated vaccines against the virus in various forms, including inactivated, mRNA vaccines, and so on. However, they always talked independently and never compared with each other. The paper discussed their unique dominance and compared their contributions in the battle with COVID-19. In addition, some accessories for vaccines like carriers and adjuvants were also considered, although they may be special for one type of vaccine. The paper concludes that mRNA as a novel vaccine played a more determined role against COVID-19 than inactivated or other vaccines, but all approved drugs could trigger an immune response. Apart from viruses, mRNA is also a potential warrior against cancer. The investigation of inactivated vaccines is still at its recent pace.

**Keywords:** mRNA vaccine, inactivated vaccine, carrier, Covid-19, mRNA cancer treatment

## 1. Introduction

Vaccination began with the vaccination of cowpox in 1796 and the invention of smallpox in 1798. The next great innovation is a vaccine based on pathogens, including attenuated, killed, or parted pathogens. Recently, nucleic acid (DNA and mRNA) vaccines have been investigated. Normally, one proven vaccine is enough for the treatment or prevention of a type of disease, and there is no need to investigate numerous vaccines like other drugs. For example, rabies vaccine is an inactivated vaccine, but it has also been investigated as a recombinant vector recently. The yellow fever vaccine is live attenuated. Unexpectedly, the novel disease led by the SARS-CoV-2 virus swept the whole world and caused a serious pandemic. However, COVID-19 has triggered the appearance of distinct kinds of vaccines, including inactivated, subunit, and mRNA vaccines from different countries and companies. Not only do various vaccines reduce the death rate, but it also offers data and comparison among all the vaccines.

Through the method of literature review, this paper will illustrate the mechanisms, advantages, and disadvantages of inactivated and mRNA vaccines. Their mechanism and development will be discussed first, which correlates to their following properties. For some vaccines, like the subunit one, adjuvant is required, which is another essential process in the history of vaccines. Futural research about each vaccine is also considered, in carrier, efficiency, etc. Because of the invention of different types of vaccines against COVID-19, it is possible to compare the properties of each drug.

Besides, since the discovery of vaccine, it has prevented 103 million cases of childhood diseases between 1924 and 2010 in the US [1]. The eradication of smallpox was one of the miraculous

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successes that exhibited the potential capacity of vaccines. The paper will also summarize the development of vaccines and their future research and study. It hopes that the paper will give some opinions on the comparison between inactivated and mRNA vaccines in the area of COVID-19 and their unique advantages.

## 2. Mechanism and production

### *2.1. Inactivated vaccine (INV)*

The genes in the pathogen are destroyed by heating or chemicals, which ensures no replication after injection. At the same time, the appearance of the pathogen, like antigens, can still be recognized by the adaptive immune system. The antigen-presenting cells take the antigens or pieces by endocytosis and deliver them to the lymph node. The antigens are shown by the major histocompatibility complex (MHC) type I to activate T cells. In addition, the long-lived effector cells, called memory cells, have a long half-life and respond efficiently and quickly after the next infection by the same pathogen.

### *2.2. mRNA vaccine*

The mRNA vaccine is a novel platform for drug delivery, but it still utilizes the antigen of a pathogen to elicit an immune response. However, the antigens are translated from the injected vaccine instead of subunits directly. After understanding the genes encoding the interesting antigens, the mRNA is transcribed in vitro. Then, the molecules are injected intradermally, intramuscularly, or intravenously depending on the efficiency of the carriers. Since the translation happens in the cell but not in the nucleus, the vaccine will not affect the genome. The antigen will appear on the cell membrane and attract the immune system's contribution. In other words, the mRNA vaccine teaches the patien how to defend the pathogens.

## 3. Production

### *3.1. INV*

The industrial production of INV is composed of two parts: the growth of desired pathogens and inactivation methods. Any promotions in two bulks can improve the efficiency and safety of the vaccination manufacturing process. Because the INV is conventional, the platforms and industrial environment are already mature and the methods are varied.

The amount of pathogen that should reach the immune response threshold is the foundation of INV. A clone experiment was carried out in order to produce high-yield inactivated Zika vaccines. Their results demonstrated the faster viral replication of triple mutations than the wild types only in Vero and Huh7 cells. In addition, the properties, including viral thermostability, attachments, and maturation, did not change. Yang et al. gave a plausible explanation of the multifunctional protein flavivirus NS1, which switches the efficiency of replication [2].

Appropriate inactivation methods are equally essential to the number of pathogens. Sabbaghi et al. separated the inactivation methods into chemical and radiation methods [3]. The common chemicals are formaldehyde and b-propiolactone. Both can inactivate the virulence of pathogens by the inhibition of genomic replication and gene degradation. However, the former one caused the protein cross-linking on the surface, and the latter retained the structure of pathogens and affected the genes more. The mechanism of INV is the structure of the pathogen, so the alternation in the outside protein may trigger undesired effects. Additionally, the chemical reagents utilized are toxic, so they must be removed from the drug, which is another cost. Therefore, methods without toxicity are preferred. Radiation such as UV light, gamma radiation, visible ultrashort pulsed laser, and low-energy electron irradiation have been discovered by industry and laboratories to kill pathogens. They rarely cause an unsatisfactory change in the structure, but the amount of radiation should be a concern for those low-penetrated powers. Their mechanism is still the degradation of genes, but the difference between them and chemical methods is the integrity of genes after reactions. Chemicals will change the structure of

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one base or connect them. Nevertheless, the radiation will break the genes into multiple segments by removing the covalent bonds. One disadvantage caused by radiation is the appearance of oxidative elements, which can be resolved by antioxidants or in a deeply frozen state.

### *3.2. mRNA vaccine*

The mRNA vaccine consists of four parts: target selection, the synthesis of DNA template, in vitro transcription, and purification [4]. Rosa et al. combined the first three steps into upstream processing [5]. A well-established manufacturing of mRNA vaccine is still lacking today, and all steps can be refined to increase efficiency and safety.

A target antigen and its complement-DNA should be confirmed first. Then, the 5 cap and poly-A tail should be added to the template, and in vitro transcription happens. In this phase, the mRNA is produced in a cell-free system, so no biochemical impurities or other contaminants are present. Indeed, it is time-saving to accomplish the reactions compared with conventional vaccines [5]. Nevertheless, the quality of reagents in the processes is difficult to reach and expensive. For example, the DNA should be transcribed in a linear fashion, so buffer and enzymes are concerned. Mostly, the cutting point is targeted, and restricted enzymes are necessary. After transcription, the DNA will be degraded by the DNase, which is terminated by EDTA. All chemicals mentioned came from different companies in Whitley research, which demonstrates the high criteria of mRNA manufacture [6]. On the other hand, scientists have attempted to reduce the cost. They invented a one-pot system with cap analogs that minimizes the precipitation and purification in the IVT [4].

The latter part is the purification, which is the biggest problem in large-scale production of mRNA vaccines. To meet the clinical requirements of vaccines, the product from IAV will be isolated and purified several times. In the manufacturing, chromatography techniques such as size exclusion, ion pair reverse-phase, ion exchange, and affinity-based separation are all used [5]. HPLC helps eliminate the double-strand RNA (dsRNA) from the mixture currently, but it seems that the cellulose removal will replace the HPLC. To expel the small impurities, industry has recently utilized tangential flow filtration, which was used in the production of the SARS-CoV-2 mRNA vaccine [4].

## 4. Adjuvant

After discovering the vaccine, people thought it could cure the disease in human beings like the cases in the animal models. The mere vaccine against diphtheria and tetanus only caused a weak and ineffective immune response, but the diphtheria toxoid with aluminum salts triggered the enhancement of immune response [1]. In some vaccines, like the attenuated vaccine, the manufacturer announced no adjuvant is not necessary. However, some chemicals or reactions after the inoculation of these vaccines replace the function of adjuvants. The adjuvant stimulated the innate immune system through pattern recognition receptors, which is the prerequisite for activation of the adaptive immune system [1].

The adjuvant is grouped into immune potentiators and delivery systems by [7]. The difference between the two groups is their methods of activating the innate immune system. The former one strengthens the immune response directly by simulating the particles like Toll-like receptor agonists. The other group is called delivery systems. Examples include alum and emulsion. Aluminum salt has been assigned as the only approved adjacent. In 2009, emulsion was used in the human papillomavirus types 16 and 18 vaccines. Some carriers can also be adjuvants. Lima et al. injected cationic liposomes with recombinant proteins that could not provide protection against Mycobacterium tuberculosis, and the mice developed immune responses [7].

Biological adjuvants, including microorganism-derived adjuvants, were also investigated. Because the whole killed pathogen is toxic for humans, its particles, like the proteins on the cell surface, can be adjuvants. Muramyl dipeptide (MDP) is the main part that can enhance the immune response to the inoculation [8]. The content of CpG motifs in bacterial nucleic acids can also be utilized as adjuvants. TLR9 CpG ligands are classified into three types. CpG 1018 is tested in the COVID-19 vaccines.

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Moreover, the CpG monomeric or multimeric molecules also trigger the immune response in different mechanisms [9].

## 5. Carriers

Unlike the inactivated vaccine, the mRNA vaccine needs the carriers normally to evade the degradation from enzymes like RNase during transition to the targeted cells. Although some physical methods like gene guns can also transfer the mRNA into the cell, inefficiency data has been shown in large animals [10]. Recently, lipid nanoparticles (LNPs) have been seen as a possible and potential carrier for the mRNA vaccine.

The LNP is like a liposome, but it has no lipid bilayer or is like a micelle, which encapsulates the delivery molecules in a non-aqueous environment. The ionizable lipid part generates a rigid morphology and kinetic stability. Also, the polyethylene glycol on the LNP decreases the nonspecific properties of proteins, which enhances their biological stability. Apart from that, the ionization state will change according to the pH environment, and the intracellular delivery is more efficient. Compared with liposomes, LNPs have low toxicity and elicit less immunogenicity [11].

Ren and colleagues designed a novel mRNA delivery carrier called vitamin E succinate modified polyethyleneimine copolymer (PVES). Polyethyleneimine (PEI) and Vitamin E (VE) can form amphiphilic and do self-assembly. The PVES exhibited high transfection efficiency without cytotoxicity. Additionally, the scientists stimulated the adaptive immune system to defend against SARS-CoV-2 RBD antigens. After observing the histopathology and injection sites, no adverse effects or pathological alternations were found. The results demonstrated such a carrier possesses the capacity to be a delivery vector [12].

## 6. Efficiency

### *6.1. Comparison of eliciting immune response against the severe symptoms from COVID-19*

As mentioned in the introduction, a type of vaccine is responsible for a disease, so which kind of vaccine is the most useful is unknown because of the lack of data on comparison of one disease. Unfortunately, but also fortunately, COVID-19, which claimed millions of lives and destroyed the global economy, provided a platform to compare most vaccines. The selective vaccines are inactivated vaccines from Sinopharm in China and mRNA vaccines from Pfizer in the United States and Germany. Notably, the contradiction can only illustrate these vaccines against COVID-19 in the current step. It will be so hard to give a thorough result of a comparison between inactivated and mRNA vaccines, or between the protein-based and virus-based subunit.

Safety is the priority for vaccines, so the adverse responses should be considered properly. All vaccines have common adverse effects like fever and pain at the injection site. However, if the patients have a history of allergies, BNT162b2 and mRNA-1273 could cause allergic reactions. The vaccine, on the other hand, resulted in fewer severe adverse cases; it was determined to be processed and proven by the FDA Emergency Use Authorization [13].

Before comparing the details, it is necessary to state that all the vaccines are functional after injection. They enhance the immune response, taking the richness of CD8+ and CD4+ T cells in Pfizer and the improvement of immunogenicity and neutralizing antibodies in Sinopharm as examples. The mean titre of anti-RBD IgG level illustrated the level of concentration of antibodies in the blood, and the value was taken after the two vaccine shots. The people with Pfizer reached 11,478 AU/mL, but Sinopharm could only generate 1385.9 AU/mL. The second test is about the sustainability of antibody titre. Both vaccines remain seropositive for four months after the inoculation. Nonetheless, Sinopharm's seropositive cases decreased by more than 50% six months after the second shot, whereas Pfizer maintained a steady state for six months. The final test from the research is the time that patients had COVID-19 after the completed injection. The mean value of Pfizer is 37 days, but the mean is over doubled in Sinopharm, at 78.5 days [14]. In contrast, the final test is not only affected by the type of vaccine but also by political and personal factors. Most of the people taking Sinopharm are

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Chinese, and China still insists on a law called Dynamic Clear, which reduces the flow of viruses. Countries occupied by Pfizer ceased isolation in 2020. Therefore, the possibility of people being exposed to the virus is incredibly different, which weakens the pertinence of the third test. As a result, although both vaccines can elicit an efficient immune response against the severe symptoms of COVID-19, the mRNA vaccines exhibit a strong and sustainable reaction.

The weak immune responses triggered by inactivated vaccines are inevitable. The viruses are killed by physical or chemical processes like formalin, which ensures the safety of the vaccine. Nonetheless, the appearance of the viruses, especially the antigens like spike proteins, will also be changed, which may affect their immunogenicity [15]. IAV is not like the attenuated vaccine, which can still produce antigens, so the alternation is always irreversible. Formalin is a common inactivating agent in IAV manufacture, but it is shown that irreversible changes happen in numerous antigens. -propiolactone, which does not destroy the proteins, has been used in some rabies vaccines, and the agents will be hydrolyzed soon [15].

### *6.2. Factors affecting the efficiency of mRNA vaccine*

From the previous discussion, mRNA exhibited elegant success in the battle with COVID-19, but most of the vaccines are still in trials and have considerable potential for improvement. The factors affecting the efficiency of mRNA vaccines are stability and translation rate. First, the untranslated regions (UTRs) in the 5’ and 3’ affect the rate of translation and the half-life of mRNA [16]. Because the occurrence of translation is determined by the 5' site, the appropriate 5' cap is in charge of protein production. The poly (A) tail regulates the termination of translation and protects the integrity of mRNA [10]. Apart from the UTRs, the modifications to the nucleosides can also affect the mRNA. Karikó et al. discovered superior translation capacity in all tested mammalian systems and enhanced biological stability if they modified uridine into pseudouridine [17]. They reported the modified mRNA could resist the phosphodiesterase, which may be an assumption of its stability. Furthermore, the modified mRNA reduces mRNA immunogenicity due to a lack of IFN-and TNF-after injection. Similar cases occurred with 1-methylpseudouridine, which inhibits innate immune sensors such as Toll-like receptors 7 and 8 [10].

In addition to the mRNA modification, the manufacturing process in each step can also improve mRNA properties. Normally, there is precipitation and removement of reactants after each step in the manufacture of mRNA, causing loss of sample and high cost. In addition, HPLC is needed in the purification step, which is inaccessible to mass production. Therefore, new technologies, including CleanCap and cellulose absorption, were invented, which reduce the sample loss and make the production scalable [16].

### *6.3. INV efficiency*

Although the INV is weaker than the mRNA vaccines during the pandemic, However, it has had numerous performances against other pathogens in the past hundreds of years. Indeed, the INV is still polished and becoming as powerful as novel vaccines.

The INV is famous for its efficient protection. In Kim et al.'s research about the Zika virus purified inactivated virus (ZPIV) against Zika virus (ZIKV) [18], they described the efficiency of ZPIV in mice and marmosets. The experiments show that mice infected with ZK-PR and ZK-BR after two doses of ZPIV (a cross strain of ZPIV) have a high level of protection (84.9% and 89.7%, respectively). Moreover, marmosets injected with ZPIV elicited a high neutralizing antibody titer, and the protection could be passed on to the fetuses. Furthermore, people tried new technology on conventional vaccines. Ma et al. utilized X-ray to produce a novel whole-cell Pseudomonas aeruginosa vaccine against the Pseudomonas aeruginosa infection [19]. Their product acted on the cGAS-STING pathway and dendritic cells to prevent inflammation. Also, the INV can make the DCs mature and let them transfer the antigens to the T cells, which is used to evade the immunity of the diseases.

However, the protection offered by INV is still weaker than the live attenuated vaccines, so the safety and efficiency should be considered. In Li et al.'s research about the contrast between INV, live

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attenuated vaccine (LAV), and DNA vaccine against Japanese encephalitis virus, the latter two displayed nearly thorough protection (survival: 100% and 90%, neutralizing antibody titers: 1:1159, 1:2298). INV, on the other hand, provided disappointing protection (survival: 30%, neutralizing antibody titers: 1:80) [20]. Their hypothesis for this phenomenon is the generation of regulatory T cells.

## 7. The unique advantage of mRNA: therapy on cancer

The most impressive discovery of mRNA was for cancer treatment. The treatments can be divided into two groups: mRNA encoding antigens of tumors or signal proteins for activating the immune system.

### *7.1. mRNA encoding antigens*

In 1996, Boczkowski and colleagues first announced the DC mRNA cancer vaccines. The mRNA encoding tumor associated antigens (TAA) can be injected into DCs by electroporating and eliciting immune reactions against tumors. Multiple clinical trials and experiments have been tried, and multiple cancers, including metastatic prostate cancer, melanoma, and brain cancers, have been cured [10]. The main mechanism behind this method is the difference in expression between normal and cancer cells. For example, tyrosinase and gp100 are identified in melanoma [21]. As a result, this method is similar to the treatment of pathogens in that both vaccines elicit an immune response by exhibiting the special proteins of unwanted cells or viruses.

Although the upper method is successful and influential in cancer treatment, there are negligible problems that a few TAAs are found and there would be mutations in these antigens. Different patients probably have distinct mutations, so a common mRNA encoding TAAs may not stimulate the activation of the immune system. Therefore, if the mutated antigens are investigated, the most appropriate mRNA sequence will be found, and it is called mRNA encoding neoantigen. In a recent clinical trial, melanoma patients all acquired T cell responses against neoantigens after mRNA-encoding neoantigen injection [22].

### *7.2. mRNA encoding signal proteins*

Apart from utilizing the antigens to activate the immune system, scientists explore the immunogenicity in a more direct way by using mRNA-encoding immunostimulants. There are lots of proteins in the pathway of activating T cells. If these cells acquire these proteins directly, they are able to defend the tumor. Normally, the mRNA-encoding immunostimulants, like CD70, are injected into the tumor, so the surrounded T cells will be activated. eTheRNA immunotherapies developed TriMix, an mRNA vaccine that encodes CD70 and CD40 to activate CD8+ and CD4+ T cells [23].

## 8. Discussion

From the contrast between INV and mRNA vaccines, the latter seems to have more potential in the scientific and commercial areas, but it cannot replace the INV recently, although many vaccines in the INV have been investigated to see if they can be produced in the mRNA form. In the background of pandemics around the world, vaccines can be seen as an essential step in the success of this battle, but their disadvantages in different forms also appear.

The mRNA showed perfect efficiency of immune response against COVID-19, and it is being investigated in the treatment of cancer. However, it still has three negligible problems: immaturity, large-scale production, and safety. Not only is mRNA immature against pathogens, but it is also immature in cancer treatment. Compared with the INV, with hundreds of years of investigation, the technology of mRNA vaccines was prospected decades ago. Carriers, adjuvants, and undesirable immunogenicity are all currently under consideration. The purpose of the mRNA vaccine against cancer is to treat cancer instead of prevent it, and most of the technologies are still in trials. The second problem is how to transfer the vaccine from the laboratory into industry. Although many new, efficient, and low-cost steps, like TFF and cellulose, were invented, the cost is still high. Indeed, good manufacturing practice is complicated and incredible for most industries. Finally, the product from the

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machine will be checked by the gel electrophoresis or sequencing technology, but there are also adverse effects that appear after inoculation [5]. As a result, the potential and efficiency of mRNA vaccines cannot be denied, but we still have a long path to success.

Unlike the mRNA vaccine, the INV did not display desirable results in the pandemic, which is the flaw of this conventional vaccine. It can be seen as an option to the live attenuated vaccine if the latter is too toxic to utilize. However, the processes, especially inactivation methods, will diminish the efficiency. In addition, the safety of the patients and workers is equally important. Nevertheless, Wood and Robertson described the reassortants between viruses and human strains, which can eliminate the virulence of pathogens during the manufacture of vaccines [24]. Lothert designed a two-cellulose membrane technology that can help the recovery of proteins and degradation of DNA in the downstream purification of INV [25]. Subsequently, the invention of INV prevented billions of deaths, but its defect has been enlarged by the novel vaccines. If the vaccines are not investigated or polished in the future, they will be substituted by other novel vaccines.

## 9. Conclusion

After the discovery of vaccines, scientists paid enormous attention to the invention of compelling vaccines. Afterwards, adjuvants and carriers were also acknowledged and researched. Through the review of recent research, the paper concludes that mRNA as a novel vaccine played a more determined role against COVID-19 than inactivated or other vaccines, but all approved drugs could trigger an immune response. Apart from viruses, mRNA is also a potential warrior against cancer. The investigation of inactivated vaccines is still at its recent pace.

Many lives and the economy have been saved thanks to the invention of corresponding vaccines against COVID-19. All the vaccines can be discussed together and compared to their properties in this battle. mRNA displayed elegant protection compared with INV in many aspects. Furthermore, mRNA is a novel technology, so it possesses incredible potential for improvements, including the carriers, adjuvants, and structural modification. The utilization of chemotherapy in the treatment of cancer can also be improved in the future. Although INV is an old technology, it is still efficient and safe. It can also be polished by novel methods to become a cutting-edge treatment.

As for the shortcomings of this paper, less data was applied in the paper because there was less paper with data comparison between disparate vaccines. Additionally, some countries stopped recording the data, so the amount of accessible data is low. Besides, the author cannot acquire the secretory data related to the COVID-19 vaccines in different countries and companies because the vaccines are still being investigated. Producing and inventing vaccines is serious and rigorous, so many experiments were stopped in the early trials, and fewer details were shown in public.

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