The Mechanism, Progress, and Potential Problems behind Different Types of COVID-19 Vaccines

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Keywords: Covid-19; Vaccine; Types; Accessibility.

Abstract: Ever since the smallpox vaccine was invented in 1976, vaccination has been a prominent way of helping humans against viruses. The killed or weakened version of the virus inside the vaccine will be recognized by the immune system inside the human body as foreign. In response, it creates memory cells and antibodies to protect humans against future infection. The ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses enormous threats to not only public health but also economic development globally and calls for effective cure. Miracle drugs for the COVID-19 have not been launched in large quantities. Under this circumstance, recovery is expected if there is no delay in developing vaccines against this fatal infectious disease. This article provides an overview of the different types of vaccines available and why they are so important for patients with COVID-19. Nevertheless, the vaccine is still in the clinical stage, and scientists cannot predict its after-effects or assess its resistance to the latest variants. When it comes to minimizing the negative impacts of the COVID-19 outbreak, there is no replacement for the role that immunizations play.

1. Introduction

Since the world health organization (WHO) declared the COVID-19 global pandemic on March 11, 2020, the pandemic has posed a devastating threat to public health and economic development globally. By July 24, 2021, the number of deaths from COVID-19 has reached 4.14 million [1]. In addition, most major economies were estimated to lose at least 4.5 per cent of their gross domestic product (GDP) over 2020. To put this number in perspective, global GDP was estimated at around 87.55 trillion U.S. dollars in 2019 – meaning that a 4.5 per cent drop in economic growth results in almost 3.94 trillion U.S. dollars of lost economic output [2]. Thus, we must develop some measures to hinder the spread of the disease and consequent loss to render our life back to normal. As is always the case, the most powerful weapon in control or even elimination of an infectious disease is the vaccination of the corresponding vaccines [3]. Looking back on human history, vaccines play an important role in eradicating some infectious diseases such as smallpox and rinderpest [4]. Similarly, in terms of coping with COVID-19, we are pinning our hopes on the rapid development of effective and safe vaccines and subsequent mass vaccination out of consideration for reducing the tragic loss of life and modulating the disease process. The introduction of a vaccine will prevent the loss of US$ 375 billion to the global economy every month, estimated by the Global Alliance for Vaccines and Immunisation (GAVI) [5]. To pick up the pace of development of COVID-19 vaccines, we need to figure out the research and development process of the COVID-19 vaccines and potential adverse effects that needs to be addressed. So, this paper is a review focused on the types of COVID-19 vaccines available, corresponding mechanism and follow-up immune response. Besides, it is estimated that at least 75% of the population should be vaccinated to stop spreading the virus for the

population's immunity. Consequently, the distribution of the vaccines is also noteworthy. In addition to the technical sides of the COVID-19 vaccines, distribution issue such as accessibility is also discussed in this paper.

2. Four main types of vaccines and their basics

2.1 Inactivated Vaccine

The inactivated vaccine is one of the most widely used and rapidly developed vaccines. Its lengthy history made it available for multiple viruses. Whole-cell inactivated vaccines have been developed for polio, hepatitis A and rabies; fractional inactivated vaccines can target hepatitis B, anthrax, and tetanus [6]. Live attenuated vaccine stands longer, but there was a record that oral polio vaccine arose an outbreak of paralytic poliomyelitis from 2000 to 2001 in the Dominican Republic [7]. Thus, the promotion had been made based on live counterpart and therefore inactivated vaccine established, which is comparably safer and more controllable because the pathogen has no risk of reverting back to a pathogenic state. The production procedure is stringent, sophisticated, accurate, and is continuously developing. Thus, the production required biosafety level 3 facilities. The classic steps include preparing the cell culture, inoculation with working seed, virus replication, harvest, frozen stage, purification, inactivation, and final sterile filtration [8]. When a person is vaccinated with inactivated virus, it will induce an immune response. However, because the virus is killed, it cannot replicate enough quantity and yield enough igGs. Thus, repeat injection is required to obtain a robust immunization.

2.2 mRNA Vaccine

mRNA vaccine opens up a new era in vaccinology. Since the first report of successful in vitro mRNA transcription in animals, over two decades have past and innovations have been done to enable mRNA in vaccine development. Compared to other vaccines, it is safer and more efficient for mRNA to be non-infectious, more stable, and highly translatable. mRNA vaccines have been put into production target influenza virus, Zika virus, rabies virus, etc. The production of mRNA vaccine uses the feature that once the mRNA transits to the cytosol, the cellular translation machinery will produce a modified, properly folded, and fully functioned protein [9]. However, several technical difficulties need to be solved. First, linear plasmid DNA is required and transcribed into mRNA in a mixture of nucleoside and recombinant RNA polymerase. Then the desired mRNA should be separated from the mixture contain contaminants by precipitation and extraction steps such as the chromatographic method. mRNA vaccine does not trigger an immune response but teaches the vaccinator’s cells to make an integral or partial protein that triggers an immune response. Thus, several steps should be implemented to improve the translation and stability of synthetic mRNA once it entered human calls. Vaccinia virus capping complex and anti-reverse cap analogs should be used to avoid unmethylation. Lengthening the Poly(A) tail can enhance peak protein level. Combining the 5’-untranslated region (UTR) and 3’-UTR and inclusion of internal ribosomal entry site can stabilize RNA, enhance translation of mRNA and achieve expression of therapeutic proteins. Besides, appropriate control of calcium level, dose rate, and temperature can significantly increase the efficiency of this step. Also, some additional adjuvants in the vaccine can assist in delivering the mRNA into the plasma without being degraded. Electroporation and cationic lipofection can allow the cell generate protein by the usage of mRNA [10].

2.3 Adenovirus-based Vaccine

Adenovirus-based vaccines or recombinant adenovirus vaccines are augmented in immunity response to induce both innate and adaptive responses [11]. Though the technology is relatively new, several vaccines have been developed and put into trials, for instance, vaccines against HIV, Ebola virus, influenza virus, Mycobacterium tuberculosis, and Plasmodium falciparum. Adenoviruses were first isolated from adenoid tissues and cause a variety of mild respiratory infections [12]. The viruses are resistant to inactivation and degradation but allowing purification and molecular investigation.

Human Adenoviruses type 5 are perfect vaccine vectors because they are immunogenic, can easily be amplified, and can introduce heterologous DNA sequences [11]. Different gene regions in the virus can be engineered to delete unwanted features such as pathogenicity or confer the capacity to carry more extensive exogenous DNA sequences and give better vaccine performance [13]. The inserted gene will furtherly express the target antigen inside the human body and induce an immune response. Recombinant adenovirus vaccine with Human adenoviruses five vectors appears to produce a CD8+ T-cell with interesting features, elicit notably extended effector phase and the ability to respond in a secondary fashion independent of CD4+ T-cell help [13].

2.4 Recombinant Protein Subunits Vaccine

Recombinant protein subunits vaccine shares a similarity with the inactivated vaccine in that they both do not contain any living component of a pathogen. But the difference is that they only contain antigenic proteins of the pathogen that could elicit immune response instead of the whole cell [14]. The antigen gene is combined with a heterologous host cell gene and synthesized to produce recombinant protein [15]. The protein is well-defined in that it has no risk of pathogenicity but is purified for high effectiveness [16]. With this method, the hepatitis B vaccine came out as the first recombinant protein vaccine, where the pathogen gene was combined with the yeast cell gene to produce antigen [17]. Others like acellular pertussis vaccines, human papillomavirus vaccines are also used protein-based subunit vaccines. Though this type of vaccine's safety can be ensured, its cost is comparably high because the antigenic properties of the various subunits of the pathogen need to be examined in detail to determine the ones that can produce an effective immune response. What's more, even if an immune response is induced, it is no guarantee that memory will form for future responses [14].

3. Vaccine development of SARS-CoV-2

3.1 Basic Information about the Vaccine

As the COVID-19 outbreak rages worldwide, much of the world remains in the shadow of the epidemic. There are high hopes for a vaccine as the ultimate weapon against a global pandemic of the virus. It has attracted a great deal of attention [18]. The reason people may need a booster shot of the COVID-19 vaccine is to prevent the virus from infecting them and to reduce the side effects of an attack of the disease.

Modern vaccines are generally made by artificial attenuated, inactivated, cleaved, recombinant or purified methods against pathogenic microorganisms or their proteins, polysaccharides or nucleic acids, which can induce the body to produce the corresponding protective immune substances. The following article will explain the various types of vaccines.

3.1.1 Inactivated Vaccine

Inactivated vaccines are made up of viral particles, bacteria, or other pathogens that have been grown in culture and then killed to eliminate their capacity to cause disease. Inactivated vaccines have pathogens that grow under controlled conditions and are killed to reduce infectivity, thereby preventing infection from the vaccine [19]. Inactivated vaccines can be classified as whole virus vaccines, split virus vaccines and subunit vaccines [20]. Inactivated vaccines use non-replicating antigens, which are safe but also become less immunogenic and often necessitate booster immunization [21]. Some partially inactivated vaccines are low in potency and require improved protection and duration of immunity, such as the traditional inactivated influenza and typhoid vaccines. Most of these low potency vaccines will be replaced by newer vaccines [22].

3.1.2 mRNA Vaccine

An mRNA vaccine is a type of vaccine that induces an immunological response by using a copy of a molecule called messenger RNA (mRNA) [23]. The vaccine works by transfecting immune cells with synthetic RNA molecules. The mRNA vaccine is a new type of vaccine to prevent infectious

diseases. To trigger an immune response, many vaccines inject a weakened or inactivated bacterium into our bodies. mRNA vaccines are not vaccines in which an inactivated or weakened bacterium is injected into the body. mRNA vaccines allow cells to make a protein or protein fragment that triggers an immune response in the body [24].

3.1.3 Adenovirus Vaccine

An adenovirus vaccination is a modified virus that cannot cause illness, cannot multiply, and cannot integrate into your DNA. Adenovirus vector vaccines are made from adenovirus that has been modified to be harmless and used as a vector to stimulate the production of antibodies in humans [11]. At the moment, adenovirus-based vaccinations are used to protect against a wide variety of infections, including Mycobacterium TB, HIV, and Plasmodium falciparum. Adenovirus vaccines for COVID are represented by the vaccine developed jointly by AstraZeneca Pharmaceuticals in the UK, the University of Oxford, and Johnson & Johnson.

3.1.4 Heavy Protein Subunits Vaccine

Protein subunit vaccines are created by putting the antigen's genetic coding into yeast cells, which are easy to cultivate and capable of producing vast amounts of protein. Subunit vaccinations stimulate the immune system with one or more antigens without introducing entire or fragmented pathogen particles [25]. A subunit vaccine utilizes only a single component (subunit) of a virus or bacteria that the immune system must recognize. It is not a complete microorganism and does not make use of a safety virus as a carrier. Proteins or carbohydrates may be used as subunits [26].

3.2 Follow-up and Timely Immune Response

Suspected abnormal reactions to vaccination (Adverse Event Following Immunization (AEFI) are reactions or events that occur in individuals after vaccination that are suspected to be related to vaccination. It can be divided into five categories: adverse reactions, vaccine quality incidents, vaccination accidents, comorbidities, and psychogenic reactions [18]. Adverse reactions are reactions caused by the characteristics of the vaccine itself, which are related to individual differences of the vaccine recipient and are not related to the purpose of vaccination or unexpected, including general reactions and abnormal reactions. Vaccine reactions mainly refer to adverse reactions that cause damage to the vaccine recipient's tissues, organs, or functions and rarely occur, such as acute severe allergic reactions [19].

Suppose you suspect an abnormal reaction after vaccination. In that case, you need to go to the hospital for consultation and treatment and consult and report to the vaccination clinic, medical institution or the CDC. For those requiring investigation, the vaccines should provide relevant information such as past medical history and medical records of the visit as required and cooperate with the relevant work [20].

4. Analysis of different epidemic economics

An epidemic is never a matter for one country but for humanity as a whole [21]. Restrictions on people's movement have negatively hit the economy from both the supply and demand sides. To address the imbalance in the global economic recovery, we must first promote international cooperation on vaccines [22].

4.1 Accessibility and availability of COVID-19 vaccines Follow-up and Timely Immune Response

4.1.1 Necessity of Reasonable Distribution of COVID-19 Vaccines

Vaccination against COVID-19 makes a difference to both individuals and countries. For individuals, vaccination can protect their own health and protect the health of their families and the people around them. For countries, vaccination helps reduce the rate of infection and resulting death, effectively block the spread of the pandemic and ensure the health of the majority of people, which

enables every country and eventually the world to achieve herd immunity against this contagious and potentially lethal disease.

Herd immunity occurs when a large portion of a community becomes immune to a disease, making the spread of disease from person to person unlikely. Consequently, the whole community become protected — not just those who are immune. If the proportion of the population that is immune to the disease is greater than the herd immunity threshold, the spread of the disease will decline. There are two main paths to reaching the herd immunity threshold — natural infection method and vaccination method [6]. Shao Yiming Shao, an adviser to the WHO's committee on vaccine development, pointed out that the herd immunity threshold is about 75% to 85% [7].

Waiting for herd immunity to occur naturally will increase morbidity and mortality, which will be time-consuming and costly. Comparatively, vaccines help build herd immunity quickly, rarely causing illness or resulting complications, and significantly reduce the socio-economic costs of the pandemic [6]. This gives a sound economic rationale for fast-tracking COVID-19 vaccine trials and ongoing vaccination programs worldwide. In conclusion, the only viable and cost-effective way to reach the herd immunity threshold is to promptly get the vaccination rate up to that level.

However, there is still an enormous gap between the current vaccination rate and the target. According to the data released by Our World in Data, by the end of July 18, 2021, only 13% of the worldwide population have been fully vaccinated, and merely 1% of people in low-income countries have received at least one dose [8]. To fill in that gap, on the one hand, vaccine discovery and production process should be hastened to boost the supply. On the other hand, careful consideration should be taken regarding the distributional issue when the vaccines are available but relatively scarce. The latter point is grounded in that the distributional aspect of the vaccines is the primary determinant of the accessibility and availability of vaccines across and within countries.

4.1.2 Inequitable Distribution of COVID-19 Vaccines among Countries

The basic attribute of COVID-19 vaccines is global public goods purchased by the government from those pharma companies and then provided to the public free of charge. Actually, those mentioned above global public good attribute is not 100% precise, since public goods must be non-rivalrous – meaning that using it doesn't reduce the amount for anyone else and also be non-excludable, meaning that it should be impossible to prevent anyone else from getting the benefits, while vaccines are often both rivalrous and excludable – for example if prices are set so high that low- and middle-income countries can't afford to buy them [9]. As shown in Fig.1, the number of doses administered per 100 people in relatively developing regions like Africa is only 4.3, less than one-tenth of that in developed regions like Europe and North America. A higher GDP per Capita is positively related to higher COVID-19 vaccine distribution [10]. 85 per cent of shots that have gone into arms worldwide have been administered in high- and upper-middle-income countries. Only 0.3 per cent of doses have been administered in low-income countries [11]. In summary, given that low-income countries are exposed to the risk of vaccine inaccessibility, COVID-19 vaccine distribution has been uneven and inequitable [12].

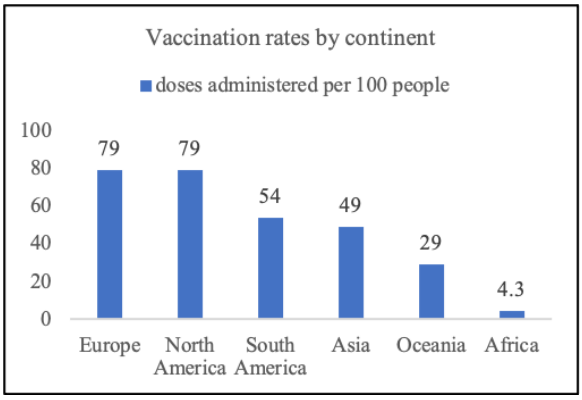

Figure 1. COVID-19 vaccine doses administered per 100 people by continent

source: https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html, up to July 20, 2021

4.1.3 Causes of Vaccine Distribution Inequity across Countries

To come up with solutions to distribution inequity worldwide and equitable, we need to figure out the underlying reasons why there is an uneven vaccine distribution between rich and poor countries.

First, many low-income countries with low socioeconomic status tend to lack the purchasing power to procure enough vaccines. According to Nature news, the leading vaccine developers once estimated that they could make sufficient doses of vaccine for at least one-third of the world's population by the end of 2021. Half of this capacity was pre-ordered by developed rich countries, accounting for approximately 13% of the global population. And low-income countries might have to be waitlisted until 2023 [14]. The wide disparity between the rich and the poor is one cause of the unfairness of vaccine allocation when supply remains much below the demand at the current pandemic stage.

Second, the disadvantageous geographical landscape of many low-income countries also brings about a challenge to vaccine distribution. Countries lying in high altitudinal landscapes such as Nepal, Pakistan, and Afghanistan, are relatively more difficult for the vaccine distributors to arrive [13]. And what's worse is that some remote militancy-wracked areas are even caught in instability and conflict. Under this circumstance, more than 160 million people are at risk of not receiving COVID-19 vaccines in places including Yemen, Syria, South Sudan, and Ethiopia, Yemen, Syria, South Sudan, and Ethiopia [14].

Third, specific storage conditions of COVID-19 vaccines can be problematic. Most of the available vaccines should be transported and stored at refrigerating to freezing temperatures, for instance, the Oxford-AstraZeneca COVID-19 vaccine at 2–8 °C and the Pfizer mRNA vaccine BNT162b2 at −70 °C, Moderna vaccine mRNA-1273 at −20 °C, and AstraZeneca vaccine at 2–8 °C [12-15]. Since temperature maintenance is crucial to the stability and efficacy of the vaccines, those low-income countries which are quite short of cold chain infrastructures need to tackle the storage temperature issue. Surveys from Cameroon report high failure levels in cold chain supply and monitoring in a number of vaccine delivery health centers, with an adverse impact on vaccine delivery, which further hinders coverage of the national immunization program [16]. Similarly, a shortage of cold chain infrastructures and technology to monitor the cold supply chain of COVID-19 vaccines may result in a low vaccination rate in the low-income countries, and consequently, the continuous COVID-19 endemicity.

There is a lot of further work to be done to mitigate or even eliminate the inequality of vaccine distribution. Fortunately, we have already seen some initiatives. Gavi is coordinating the development and implementation of the COVAX AMC. This financing instrument will support the participation of 92 low-income economies in the COVAX Facility, a global risk-sharing mechanism for pooled procurement and equitable distribution of COVID-19 vaccines. Gavi is also working with Alliance partners UNICEF and WHO to make sure that the immunization infrastructure is in place, and the technical support like cold chain available, to make sure COVID-19 vaccines can be safely delivered to all those who need them [5].

5. Conclusion

There are still many risks to national and regional economic recovery, such as the longer than expected duration and severity of the epidemic's impact, escalating global trade tensions, existing debt crises in some countries, fiscal deficits, and heavy reliance on capital flow. A substantial impact on vaccinations can be had by public trust in health services and the experience of health workers, both of which are crucial to the amount of trust in vaccines. Getting the general population to accept new vaccines will take some time. Maintaining open lines of communication between researchers and the public can help establish trust in new vaccines right from the start. It is also critical that public concerns are addressed and that plans for responding to adverse events are in place. Compared to

other aspects of human health and safety, the huge contribution that immunization coverage makes is rarely acknowledged. However, what worries the public most in the current grim situation is that the current vaccine does not do a good job of protecting against the virus in the face of the mutant strain. A large number of people begin to relax after receiving the vaccine; such an atmosphere will lead to the rapid spread of the new mutant strain and delay the second wave of infections.

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