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Editorial

Understanding vaccination in the era of pandemic

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Vaccination is one of the most successful achievements in the health-care system and helped in eradicating various diseases from different parts of the world. The use of vaccination by humans can be traced back as early as 1500 AD when the Chinese used to treat smallpox by the inoculation of scratching matter from a smallpox sore into a healthy person's arm.[1] In 1796, Edward Jenner introduced the smallpox vaccine. The vaccine works on the principle of inducing immune responses in the human body by reacting to a less virulent form of pathogen or by imitating the actual pathogen infection. They are designed in such a way that they must elicit immune responses like a natural infection but of low intensity without causing the symptoms of the disease. Vaccine (antigen) is usually captured by APC for MHC presentation to activate T cells via TCR. Traditional vaccines are usually made from live attenuated pathogens, inactivated pathogens, or form part of the surface antigen of respective pathogens. The use of nucleic acid is a novel way of developing vaccines. A few years back nobody has ever thought of vaccinating populations with mRNA or DNA vaccines, but the COVID-19 pandemic has changed the scenario across the world. Now the mRNA-based Pfizer-BioNTech vaccine for COVID-19 has gained momentum so much so fore that the demand for this vaccine out showed other candidates in this arena.[2]

To understand, the mechanism of vaccination one should know the immune responses against foreign entities. The human immune system requires the interaction of innate and adaptive immune systems to help fight the infection or clear the pathogen. The innate system is the first line of defense any pathogen or foreign agent encounters and comprises cells such as neutrophils, monocytes, and eosinophils. Complement proteins also aid the innate immune response and help to recruit phagocytes and facilitate pathogenesis. The innate immune system lacks specificity and the pathogens have evolved to escape this pathway. The innate system itself induces an adaptive immune response. One of the ways to achieve this is by the help of immature dendritic cells (DCs). The immature DCs after ingesting the antigens convert into mature DCs or APCs. They convey the information to the adaptive immune system.[3] The adaptive immune system helps to compete for the elimination of pathogens and termination of the disease. The best feature of the adaptive immune response is the development of immunological memory and generation of antigen-specific memory cells which will trigger a much faster and efficient response when exposed to the same pathogen again.[3] The adaptive immune system is composed of B and T lymphocytes. Both B and T lymphocytes express a unique antigen-specific receptor, but these receptors differ in binding to the antigenic molecule. TCR requires antigens to be broken down into small fragments for recognition while BCR can recognize whole antigens. The activation of these cells also differs, the T cells require APCs to break down antigens into small fragments and then transport them to the cell surface which in association with MHC activates TCR. These T cells express CD4 cell surface protein and recognize antigen in MHC Class II molecule. These CD4+ T cells help to activate other T cell subsets which perform various functions. In BCR, the antigen-binding activates B cells, and they differentiate into plasma cells. These plasma cells secrete antibodies.

Many vaccines in the 20th century were developed empirically and the exact mechanism of how they activate the immune system and lead to immunity could only be studied after recent advances in molecular biology, immunology, and genetics. These advancements helped in understanding the biology of pathogens and how these foreign agents interact with the body's immune system.[3,4]

The impact of vaccination on human health cannot be explained in words, except safe water no other commodity has contributed to the reduction of death rate than vaccination.[5] In developing countries during 1960s, a large number of deaths and morbidities were occurring from infectious diseases and at that time the vaccine could reach <5% of the population. To overcome this, the WHO add

an Expanded Programme of Immunization on vaccination in 1974 to help vaccines to reach children of low- and middle-income countries. The success of vaccination could be explained by just one stats, in the United States alone, there was a decline of infectious diseases by 90% due to inoculation of diphtheria, tetanus, and acellular pertussis, Measles, Mumps, and Rubella and polio vaccines till 2017.[6] It has completely eradicated smallpox, polio, and measles too disappeared from most of the countries. The Polio vaccine once eradicated is expected to save around 1.5 billion USD every year and millions of lives. Having said that, still, vaccine-preventable diseases are prevalent in different parts of the world due to changing strains, unequal distribution of vaccines, immunocompromised individuals, and public concern regarding the safety of vaccines. It has also helped the government to save much cost on the health-care system as well as increased the working population of the countries, thus helping the economy. Scientists working on vaccine development focused on those diseases which are deadly and lead to high mortalities.[6]

Conventional protein vaccines helped in preventing various diseases, but they have some limitations which lead to the need for developing novel vaccine formats. For instance, they do not provide immunity against various subtypes of the same pathogen and less effective in non-infectious diseases like cancer. Furthermore, there are a large number of emerging viruses, for them; there is a need for developing rapid and large-scale vaccines. Nucleic acid vaccines have emerged in the past 2–3 decades and promise to be an alternative to conventional vaccines in near future.[7] The potential of DNA vaccines to elicit both humoral and cell mediated immune response has gathered the interest of scientists worldwide. In this type of vaccination, the immune system is stimulated by a gene from bacteria or virus. The immune system remembers the foreign entity and prevents the infection when it detects later. At present, DNA vaccines are in clinical trials phase (1–4) for various infectious diseases such as influenza, HIV, and Zika in human and some vaccines are already approved for veterinary uses.[7]

The limitation of DNA vaccines has led to the development of RNA vaccines. A blend of molecular biology and immunology resulted in the development of a new vaccine named mRNA. RNA became a promising alternative to conventional vaccines enabled by recent technological innovations. Nucleoside modification, stringent purification, and optimization of the coding and untranslated regions of RNA were illustrated to drastically refine in vivo translatability by allowing synthetic RNA to elude toll-like receptors and a variety of other RNA sensors that precipitate inflammatory reactions and consequently block mRNA translation.[8] The safety profile is the first significant advantage of mRNA vaccines. A unique benefit to mRNA vaccines is they do not lead to a risk of genomic integration and insertional mutagenesis as they do not require nuclear entry for their activity unlike DNA vaccines and viral based vaccines. mRNA vaccines, unlike live-attenuated vaccines, they ignore any concern linked with endotoxin and infections. The changing nature of mRNA activity is beneficial in the avoidance of over-expression of antigen protein, producing better temporal control of their activity.[9] A third advantage of the mRNA vaccine is its synthesis procedure as well as the flexibility in producing such vaccines. This flexibility in the manufacture of mRNA is remarkably beneficial to produce mRNA vaccines against rapidly spreading infectious agents. One example illustrating the rapid and flexible advantage of the synthesis of mRNA vaccines Is the National Institute of Allergy and Infectious Diseases of the US in concurrent efforts with Moderna, produced SARS-CoV-2 vaccines within 27 days after the release of the sequence of the virus.[9] This rapid enabling and bypassing of clinical trial Phases I, II, and II: Within 66 days, 140 days, and 199 days, respectively, (NCT04283461, NCT04405076, and NCT04470427). This, in turn, allowed the emergency use of authorization (EUA) of their mRNA vaccine in the US within a year.[10]

Vaccination leads to economic productivity, reduced burden on the health-care system, and increasing life expectancy. Undoubtedly, nucleic acid vaccines offer a more convincing option than conventional vaccines. Although mRNA vaccines in tumors and viruses have numerous advantages, they are still in the initial stage. Clinical trials would turn basic research into mRNA therapeutics in medical practicalities. In conclusion, the COVID-19 pandemic led to the rapid deployment of mRNA vaccines. Pfizer/BioNTech and Moderna vaccines which are mRNA based and completed Phase III clinical studies but their miraculous efficacy resulted in their acceptance worldwide. In the future, the mRNA vaccine is even expected to treat non-infectious diseases such as cancer and Alzheimer's. The development of vaccines against some complex infections such as HIV, Malaria, and TB is still a challenge for researchers. The success of vaccination requires an interdisciplinary approach and requires a sync among scientists, industries and governments for proper distribution to the public and hope to save millions of human lives in future.

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