OPEN ACCESS
Research Journal of Veterinary Practitioners

Review Article

Advancements in Vaccination Strategies: From Historical Milestones to Modern Innovations in Viral Disease Prevention and Public Health

Kashif Abdaal, Aneeza Batool, Muhammad Tariq Navid*, Saeed Ahmed, Asma Saleem Qazi, Waseem Safdar, Haidar Ali, Mobeen Ur Rashid, Somia Rafaqat

Department of Biological Sciences, National University of Medical Sciences, Rawalpindi-46000, Pakistan.

Abstract | Vaccines have improved global health by eradicating infectious diseases. Yet ongoing research on vaccines is crucial for addressing persistent infections including the challenging ones like malaria and tuberculosis and exploring their potential applications in non-infectious conditions like Alzheimer's. Traditional vaccines such as: live attenuated and inactivated have long been treated as effective against infectious diseases. However, recent advancements in vaccine development strategies including mRNA- and recombinant DNA technologies along with viral vector-based vaccines containing specific DNA segment(s) of an infectious pathogen(s), nanoparticle-based and plant-based delivery mechanisms have proven as more targeted and adaptable approaches to boost immune responses. Hence, it proves the vaccines as a big breakthrough in preventive and therapeutic medicine over 200 years and named "Future Medicine". To assess vaccine safety and efficacy, scientists are now using various model animals like mice, ferrets, pigs, and nonhuman primates before using them for human trials. The other side of successful vaccine intervention, however, contains various issues that need to be rectified. These concerns primarily depend on target pathogen selection, novel vaccine efficacy, development, and duration of optimum immunological responses, selection of appropriate animal model, need for booster dose, route of administration, and post-administration safety and post-marketing analysis (social and economic concerns). All these steps are important for a vaccine that leads to its success in preventing infectious diseases. It is crucial to address these challenges to make safer vaccines for effective infectious disease control and prevention to save humanity. Addressing challenges in vaccination coverage and gaps is crucial for global health. Vaccines have played a crucial role in global health preventing diseases and saving lives as evident from the rapid development of COVID-19 vaccines in response to the SARS-CoV-2 virus.

Keywords | Vaccination, modern vaccination, failure in strategies, COVID-19, Vaccine development, Vaccine hesitancy

Received | December 28, 2023; **Accepted** | February 10, 2024; **Published** | February 20, 2024
***Correspondence** | Muhammad Tariq Naveed, Department of Biological Sciences, National University of Medical Sciences, Rawalpindi-46000, Pakistan; **Email:** tariq.navid@numspak.edu.pk
Citation | Abdaal K, Batool A, Navid MT, Ahmed S, Qazi AS, Safdar W, Ali H, Rashid M, Rafaqat S (2024). Advancements in vaccination strategies: from historical milestones to modern innovations in viral disease prevention and public health. Res J. Vet. Pract. 12(1): 11-21.
DOI | http://dx.doi.org/10.17582/journal.rjvp/2024/12.1.11.21
ISSN | 2308-2798

INTRODUCTION

Brief History of Vaccination

400 B.C., the vaccine's journey was initiated when Hippocrates first talked about mumps and diphtheria. Initially, the process was slow until the 18th century when vaccines for smallpox, cholera, and yellow fever were developed. Edward Jenner made a major contribution through his work on smallpox (Simon et al., 2006). The first method to prevent smallpox was called variolation that was originated possibly from China or India where skin tissue was smeared with smallpox pus pustules. However, in 1796, it was observed by English physician Edward A. Jenner that milkmaids who had been in contact with cowpox were immune to smallpox. He used pus from a cowpox blister to inoculate a boy proving the effectiveness of vaccination and leading to the global implementation of the smallpox vaccine. Later, this disease was eradicated in 1980 (Matić

& Šantak, 2022). In 1885 Louis Pasteur created the first successful rabies vaccine that was initially administered to a person bitten by a rabid animal. The vaccine was developed by the spinal cord of rabbits infected with rabies marking a significant advancement in the prevention of this deadly disease (Hicks et al., 2012). In 1923, Alexander Glenny discovered a way to neutralize the tetanus toxin by using formaldehyde. This breakthrough method was later applied in 1926 to create a vaccine for diphtheria. Additionally, the development of the pertussis vaccine took more time and the first licensed whole-cell vaccine was introduced in the United States in 1948 (*Brief History of Vaccines*, n.d.).

During the late 1800s and early 1900s, polio became the world's most dreaded disease due to its frequent outbreaks. In 1916, a severe outbreak of polio in New York City claimed the lives of over 2000 people, while the deadliest recorded U.S. outbreak in 1952 resulted in the deaths of more than 3000 individuals. In 1949 Enders, Weller, and Robbins cultivated the polioviruses in human tissue which led to winning a Nobel Prize in later stages. Shortly after this innovation, Jonas Salk developed the first successful polio vaccine which was tested on himself in 1953 and later on a wider scale on 1.6 million children in Canada, Finland, and the USA by 1954 (*History of Polio Vaccination*, n.d.). Immunization is a successful and cost-effective public health intervention that saves up to three million lives annually according to the United Nations (UN). The Expanded Program on Immunization (EPI) was launched in 1974 to universally vaccinate against six diseases resulting in a notable reduction in childhood illnesses and deaths from preventable causes (Mantel & Cherian, 2020). The Gardasil vaccine was developed by Merck and was the first HPV vaccine approved by the FDA in 2006. Meanwhile, the Cervarix® vaccine created by GSK received approval from the European Medicines Agency in 2007 and later from the FDA in 2009 (Cheng et al., 2020). In early 2020 scientists from worldwide raced to create safer and effective COVID-19 vaccine resulting in over 200 candidates. By December 2020, the Pfizer-BioNTech collaboration achieved a breakthrough developing the first approved COVID-19 vaccine marking one of the quickest successes in the history of vaccine development. (Saleh et al., 2021)

This data is taken from the WHO website (*World Health Organization (WHO)*, n.d.). The picture is generated through Bio render®.

Vaccine(s) and Global Health; Empirical example(s)

Vaccines have made a big difference in global health by eliminating diseases like smallpox and rinderpest. The WHO has Expanded the Programs of Immunization and the Global Health Alliance for Vaccination and Immunization. The program is helping cover many of the major childhood diseases. Previously, we have done well in controlling many viral infections like measles and smallpox, and we are near to getting rid of polio, globally. It shows our strong commitment to preventing infectious diseases through vaccination strategy; however, a lot of kids still die from preventable infections like pneumonia and diarrhea. Making vaccines for relatively harsh diseases like malaria, tuberculosis, and HIV is hard, so more research is needed in this field. We might need to use a combination of vaccines to boost the immune system. Besides stopping infections, vaccines could also help with non-infectious diseases like cancer and Alzheimer's. Progress has already been made with cancer vaccines. (Greenwood, 2014).

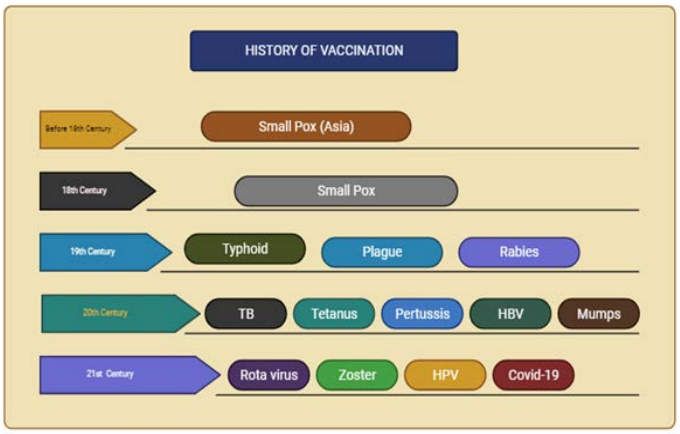

Figure 1: This picture shows the brief history of different vaccines that were developed.

COMPARISON OF OLD AND MODERN VACCINATION STRATEGIES

The main immunization methods used in the past were protein subunit and live attenuated inactivated vaccines. Live attenuated vaccines include weakened viral forms, such as rotavirus, varicella, and MMR (McLean et al., 2018), whereas inactivated vaccinations such as those for polio, hepatitis A, and rabies, contain viruses that have been killed or inactivated (van Walstijn et al., 2023). Like pneumococcal and influenza vaccinations, protein subunit vaccines include harmless viral fragments that the immune system targets (Song et al., 2017). For many years, these conventional vaccinations have been utilized and helped to manage and eradicate a wide range of infectious illnesses.

Recently, the art of vaccine development has been improved and their traditional rationale is updated on various basis vis. platforms containing the pathogen's mRNA the viral vectors containing recombinant immunological gene(s) the nanoparticles having complete or partial segments of the pathogen, or transgenic plants that contain genes of interest. These modern vaccines are more specific

Table 1: This table shows the difference between the old vaccination strategies and modern vaccination strategies.

Characteristics	Types of vaccines							
	Inactivated vaccines	Live-attenuated vaccines	Protein subunit vaccines	mRNA vaccines	Viral vector vaccines	DNA vaccines	Nanoparticle-based vaccines	Plant-based vaccines
Immune responses	Humoral immunity	Humoral and cellular immunity	Humoral immunity	Humoral immunity and stimulate T-cell immunity	Humoral and cellular immunity	Humoral and cellular immunity	Humoral and cellular immunity	Humoral and cellular immunity
Duration of immunity	Limited	Long-lasting	The duration of immunity is not constant	Long-lasting	The selection of a particular viral vector might influence the duration of immunity	Long-lasting	Long-lasting	Long-lasting
Booster doses	Required	Not frequently	Required	Maybe required	Maybe required	Required	Required	Required
For immuno-compromised person	Safe	Hazardous	Safe	Safe	Safe	Vary	Safe	Safe
Versatility to variation	The genetic variations between the original virus and the variant may impact the efficacy of vaccination against it	A certain level of cross-protection against variations	Show considerable flexibility variation, particularly if the targeted protein is conserved in all the variants	A high degree of adaptability	Varies	A high degree of adaptability	The features of the used antigens and their conservation will determine the variations	The features of the used antigens and their conservation will determine the variations
Cold chain	Refrigeration	refrigeration	refrigeration	Requires specific cold chain storage	Refrigeration	Varies	Refrigeration	Refrigeration
References	Ruan et al., 2020)	(Qi et al., 2019)	(Pandey et al., 2019)	(Hu et al., 2022)	Stuart et al., 2022)	Yassein et al., 2021)	(Bezbaruah et al., 2022)	Canada, 2022)

Table 2: This table shows how modern vaccine strategies work.

Modern vaccination strategies	Advancement	References
mRNA vaccines	A small portion of the virus genetic information is used in mRNA vaccines to elicit an immunological response	(Hu et al., 2022)
Viral vector vaccines	Vaccines against viral vectors work by modifying a virus to introduce genetic material from the specific pathogen into the body	(Stuart et al., 2022)
DNA vaccines	Genetically modified DNA is used in DNA vaccines to elicit an immunological response	(Yassein et al., 2021)
Nanoparticle-based vaccines	Vaccines based on nanoparticles work by delivering antigens to the immune system via nanoparticles	(Bezbaruah et al., 2022)
Plant-based vaccines	Plants are used as bioreactors to manufacture vaccine antigens in plant-based vaccination	(Canada, 2022)

to the individual pathogen/(s) and more sensitive to induce optimum immunological responses. Recently we learnt pleasant lessons from these novel technologies vis. mRNA vaccines for COVID-19 developed by Pfizer-BioNTech and Moderna (Kracalik et al., 2022), Viral vector vaccines developed by Oxford-AstraZeneca and Johnson & Johnson for COVID-19. Similarly, Many substances including lipids, metal and nonmetal inorganics, various polymers, and virus-like particles (VLPs) can be used to develop vaccines based on nanoparticles (Lu et al., 2023) and vaccines like Medicago Covifenz® COVID-19 vaccine have been developed using plant-based technologies (Phoolcharoen et al., 2023). This vaccine mimics the virus and stimulates the immune system without spreading illness by leveraging the plant's natural cell mechanism to create non-infectious VLPs (Ma et al., 2023; Trad & El Falou, 2022). Table 1 shows the comparison between old and modern vaccination strategies. Table 2 discusses the advancements that are made to develop modern vaccines.

PRINCIPLES OF VACCINE DEVELOPMENT

General principles of vaccine development

Vaccines are considered one of the major accomplishments in modern medicine. The fields of vaccinology and immunology have a shared history of over 200 years. Both fields are interlinked, and a successful vaccine needs a deeper understanding of the principles of immunology. However recent discoveries in the field of innate immunity have provided new knowledge about how vaccines work and create immunity (Brisse et al., 2020).

Despite significant progress in molecular virology and vaccine development, influenza remainsa major public health concern. Vaccinations have been the primary strategy for preventing influenza infection live attenuated influenza vaccines (LAIVs) gaining popularity due to their advantages over inactivated vaccines. One classic method for at-

tenuating viral virulence is cold- adaptation which has been successfully used to create safe and effective donor strains of LAIVs for seasonal epidemics and pandemics. Recent advances in reverse genetics have enabled the development of a broader range of LAIVs. The diversity of influenza antigens suggests that this expanded pool of LAIVs may provide better options for controlling pandemics (Jang & Seong, 2012).

Generally, inactivated viral vaccines are produced by cultivating the virus on a substrate to generate large quantities of antigens. Previously primary cells, tissues, fertilized eggs, and whole organisms have been utilized as substrates for virus growth. However, nowadays manufacturers are increasingly using continuous cell lines for virus growth which reduces production costs, increases vaccine safety, and simplifies upscaling. After the virus is propagated, it is purified and concentrated before being inactivated by using chemical or physical methods or a combination of both. Several inactivation agents or methods have been developed and used successfully for inactivating viruses for vaccine production. Despite this, formaldehyde and β-Propiolactone (BPL)are the most used inactivation agents for producing licensed human viral vaccines (Nunnally et al., n.d.).

The main approach for preventing infectious diseases involves the development of subunit vaccines. Recombinant DNA techniques have made it possible to design and produce subunit vaccines by improving the properties of targeted protein immunogens. The immunogenic properties of subunit vaccines can be enhanced by adding immuno-potentiation tags or targeting immunoreactivesites. Gene-fusion technology can also be used to efficiently incorporate the recombinant subunitinto adjuvant systems that boost the immune responses. Recombinant strategies have also become important in passive vaccination strategies which involve using antibodies or antibody fragments to prevent infectious diseases. Humanized antibodies and antibody fusion proteins are commonly used to combat infectious diseases. These examples demonstrate that recombinant technology will significantly impact the design, selection, and production of recombinant proteins for preventing infectious diseases (Hansson et al., 2000).

Nucleic acid-based vaccines are a new approach to immunization that can stimulate immune responses like those produced by live, weakened vaccines. These vaccines work by producing viral proteins that naturally similar structure to those produced during an actual viral infection. Nucleic acid vaccines have been demonstrated to elicit both antibody and cytotoxic T-cell responses to a variety of protein antigens. One of the main advantages of these vaccines is that they have a simple vector and are easy to administer with theexpression of antigen lasting for a significant period (Vogel & Sarver, 1995).

The role of animal models in vaccine development and pre-clinical testing

Scientists often use animals to check if vaccines are safe and effective in specific infections and to figure out the right amount and the right type of vaccine. They also study the appropriate method to deliver the vaccine, to assess how strong the immune response is, what kind of immunity it provides, and what factors support protection against the infection. Animal models help researchers understand and improve vaccines before they are tested on human subjects (Gerdts et al., 2015). Vaccines are essential in controlling and preventing the spread of infectious diseases. The development of new vaccine products generally requires conferring protection against the relevant infectious agent immunogenicity, efficacy, and safety profiles in pre-clinicalstudies. These studies are important for selecting candidate antigens, delivery systems, and vaccine formulation. Therefore, pre-clinical studies in animal models are critical for generating a strong pre-clinical package that is required for clinical trials (Riese et al., n.d.). The seriousness of the sickness caused by the influenza virus and how well a person's immune system works decide how bad the illness gets, ranging from mild symptoms to severe pneumonia that can be fatal. Even though the first flu vaccine was approved more than 60 years ago, scientists are still working on creating better vaccines with stronger protection. Animal models, like mice, ferrets, pigs, and nonhuman primates, have been crucial in helping researchers understand how the virus works and testing new vaccines before they're used in people. Each animal model has its pros and cons (Margine & Krammer, 2014). While many countries encourage minimizing animal experiments in research, the development of vaccines still relies on them due to the lack of alternative methods to test immune responses. Selecting the right animal model is vital for project success, aiming to save both animals and research resources in the long term (Kiros et al., 2012).

CURRENT VACCINES FOR VIRAL DISEASES

View of Viral Vaccines in practice including their composition, safety, and efficacy

There are two kinds of flu vaccines: one is called inactivated influenza vaccine (IIV), and the other is live attenuated influenza vaccine (LAIV). The IIV is given as a shot and is approved for people aged six months and older, including pregnant women and those with weak health conditions. On the other hand, LAIV is a weakened virus given as a nasal spray and is approved for healthy individuals aged 2 to 49 years in the US and 2 to 18 years in Europe. Pregnant women should not get LAIV. The good thing about LAIV is that it's given as a nasal spray, which can be helpful for

Table 3: Different viral diseases, their approved vaccines and their manufacturing companies.

Serial No	Viral Diseases	Vaccine type	Clinically Approved Vaccine	Manufacturer
1	Hepatitis B	Recombinant protein	1.Engerix-B 2. Twinrix 3. Recombivax	1,2. GlaxoSmithKline 3. Merck
2	Polio	Inactivated, live attenuated	1.IPOL (Inactivated Poliovirus Vaccine) 2.Poliovax (IPOL)	1. Sanofi Pasteur 2. Pfizer
3	Chickenpox	Live attenuated	Varivax	1. Merck
4	Dengue	Live attenuated	1.Dengvaxia 2. Qdenga	1. Sanofi Pasteur 2. TAK-003
5	Measles	Live attenuated	1.MMR 2.ProQuad	1,2 Merck
6	Mumps	Live attenuated	1.MMR 2.ProQuad	1,2 Merck
7	Rubella	Live attenuated	1.MMR 2.ProQuad	1,2Merck
8	Rabies	Inactivated	Imovax Rabies RabAvert	Sanofi Pasteur GlaxoSmithKline GmbH
9	Yellow Fever	Live attenuated	1.YF-VAX	1.Sanofi
10	COVID-19	1.mRNA 2. viral vector 3. protein subunit	Moderna, Pfizer-BioNTech Johnson & Johnson's Janssen	1.Moderna, Pfizer-BioNTech 2. Johnson & Johnson's Janssen
11	Flu (Influenza	Live attenuated, Inactivated, Subunit.	1.Fluzone (live attenuated) 2. Fluarix (inactivated (killed) 3. Flulaval (inactivated (killed) 4. Afluria (killed virus) 5.Flucelvax (inactivated)	1. Sanofi Pasteur 2,3 GlaxoSmithKline 4. Seqirus 5. Seqirus
12	Rotavirus	Live attenuated	1.RotaTeq 2. Rotarix	1. Merck & Co., Inc 2. GlaxoSmithKline (GSK)
13	Typhoid fever	1.Conjugated vaccine 2.Live Attenuated	1. Vi capsular polysaccharide vaccine (or ViCPS) 2. Ty21a	1. Bio-Med Pvt. Ltd. And Sanofi Pasteur. 2. PaxVax
14	Tetanus	Inactivated	1.DTaP (diphtheria, tetanus, and acellular pertussis). 2. Tdap	1,2. Sanofi Pasteur and GlaxoSmithKline
15	Shingles	1.Live attenuated. 2.Rrecombinant	1. Zostavax 2. Recombinant Zoster	1. Merck 2. GlaxoSmithKline
16	Tick-Borne Encephalitis (TBE)	Inactivated and Recombinant	TicoVac	1.Encepur, FSME-IMMUN
17	Respiratory Syncytial Virus (RSV)	1.Monoclonal antibody	Nirsevimab	Beyfortus, Sanofi and AstraZeneca

mass immunization, especially during pandemics as it provides mucosal immunity and imitates natural infection (Perego et al., 2021).

Influenza virus vaccines stand out among currently approved viral vaccines due to the ongoing changes in the antigenic composition of the influenza virus surface glycoproteins, specifically hemagglutinin (HA) and neuraminidase (NA). To combat the constant antigenic drift in these proteins, influenza vaccines must undergo periodic updates to align with the prevalent wild-type viruses in each season. In the United States, inactivated influenza vaccines have been accessible since 1945, while a live attenuated influenza vaccine has been in use since its licensure in 2003

(Weir & Gruber, 2016).

COVID-19 vaccines, like BNT162b2, mRNA-1273, and Sputnik V, have been good at stopping the virus and its different forms. After two doses in the final testing phase, these vaccines showed more than 90% effectiveness in preventing sickness. mRNA vaccines, AZD1222, and CoronaVac also worked well against the Alpha, Beta, Gamma, and Delta variants, keeping people safe from getting sick or having severe COVID-19. In real life, these vaccines, especially mRNA and AZD1222, were good at preventing the original virus and the Alpha and Beta variants, but their ability to fight the Delta variant was a bit lower. After about 6 months, the protection from BNT162b2 and AZD1222 decreased. Luckily, serious problems from these vaccines were rare, like a few cases of severe allergic reactions and heart inflammation for every million doses given, and other vaccines were similarly safe (Fiolet et al., 2022). Since 1978, Oral Rabies Vaccines (ORVs) have effectively controlled rabies in wildlife in Europe and the USA. This article highlights the need and potential use of ORVs in free-roaming dogs to curb dog-transmitted rabies in India. Over 40 years, these vaccines have undergone continuous development ensuring consistent protection with high safety. Global health institutions support ORVs in dogs, giving confidence to countries like India, where rabies is a significant public health problem. Despite progress in human rabies prevention, mass dog vaccination campaigns are rare in India. Catching many stray dogs is challenging, especially in urban areas, where skilled teams face financial and logistical hurdles to achieve the required 70% vaccination coverage swiftly (Yale et al., 2022).

Different vaccines have been approved for different viral diseases. Some of their examples are given in Table No. 3 (Policy (OIDP), 2021; *Vaccines and Preventable Diseases | CDC*, 2022).

Successful vaccination campaigns reduced the incidence and /or severity of viral diseases.

Vaccines have had a remarkable impact on public health. A study found that in 2001, childhood vaccines saved 33,000 lives and prevented 14 million cases of disease in the US. Another study projected that between 2011 and 2020, vaccines would prevent 23.3 million deaths in 73 countries supported by the GAVI alliance (Amanna & Slifka, 2020).

FAILURE STRATEGIES OF VACCINE

Primary vaccine failure

When the first doses of a vaccination regimen do not produce virus-specific antibodies, it is called primary vaccine failure. The phenomenon of primary vaccine failure affects roughly 2-10% of vaccinated healthy individuals. The two key causes of vaccination failures are host-related and vaccine-related variables. Vaccine-related issues or failed vaccination regimens include delivery techniques or vaccine attenuation. Several host-related variables, such as host genetics, immunological state, age, health, or nutritional condition, have been linked to primary vaccination failures. The incapacity to react to the first immunization is the hallmark of primary vaccine failure (Wiedermann et al., 2016).

The causes of primary vaccine failure include host immune factors, such as immunosuppressive therapies and recognized immune deficiency illnesses, but can occur in a small proportion of otherwise immunocompetent individuals. Primary vaccination failure can occur, for example, in people receiving immunosuppressive therapy, in people with known immune deficiency disorders, or in those who have recently received blood products containing antibodies. Furthermore, children's immune responses may be weakened by the persistence of maternal antibodies that were passively acquired, which might result in a primary vaccination failure. Although primary vaccination failure is uncommon, it can have detrimental effects. This emphasizes how crucial it is to monitor to guarantee the efficacy of immunization programs. (Mohd Rahim et al., 2020).

Secondary vaccination failure

When immunity to the targeted pathogen diminishes over time because of the first vaccination, it is referred to as secondary vaccine failure. The hallmark of secondary vaccination failure is a reduction in protection post-initial efficacy. Certain vaccinations have a higher risk of secondary vaccine failure due to the nature of the immunological response they elicit. The longer the time elapsed from vaccination, the higher the probability of secondary vaccine failure, since the post-vaccination immune response may gradually diminish, particularly if boosting from exposure to a natural illness does not occur. There is a chance that some vaccinations can cause secondary vaccine failure, and the length of protection varies based on the vaccine and personal characteristics including age, health, and immunological status. Secondary vaccine failure can have two main causes: host-related factors like host genetics, immunological state, age, health, or nutritional status, or vaccine-related factors such as vaccine attenuation, immunization regimens, or administration errors (Kurata et al., 2020).

A major contributing factor to the spread of measles is secondary vaccine failure, which highlights the importance of routine booster injections and further study to better understand the immune traits of those who have had vaccinations. The significance of comprehending the dynamics of measles transmission in areas with high vaccination rates and the necessity of ongoing study and surveillance to guide public health initiatives and immunization plans

(Iwamoto et al., 2021, pp. 2018–19).

Immunization gaps and coverage issues

It is difficult to eradicate immunization gaps because of a lack of data, problems with operations, access to healthcare being restricted, and vaccine administration costs. The COVID-19 pandemic has led to a 40% rise in zero-dose children and a drop in measles vaccinations, increasing the danger of vaccine-preventable illness outbreaks. The goal of the Immunization Agenda 2030, one of the World Health Organization's programs to increase vaccine coverage worldwide, is to reach children who have not received all recommended doses of vaccinations (Fan et al., 2022). In low-income nations in particular, poor vaccination rates have raised the risk of vaccine-preventable illnesses, increased healthcare expenses, and reduced productivity. Low vaccination rates are caused by several factors, including distrust, disinformation, and vaccine reluctance. It will need specialized approaches, improved health systems, and more funding for immunization campaigns to address these problems and guarantee that everyone has access to immunizations that can save lives (Mantel & Cherian, 2020).

Achieving high vaccination coverage rates is hampered by vaccination gaps and coverage issues. There are some variables, such as vaccination costs, lack of health insurance coverage, insufficient vaccine supply and distribution, and logistical challenges experienced by healthcare professionals, that lead to immunization gaps and coverage concerns. Children's immunization status can be adversely affected by even brief interruptions in health insurance coverage, which can cause delays in receiving necessary medical attention and taking care of health concerns (Wallender et al., 2023). The necessity of ongoing vaccination effectiveness monitoring and the significance of routine booster doses for maintaining long-term protection against illnesses. Differences in vaccination status by state of residency, insurance status, race/ethnicity, and poverty, highlight the need for focused initiatives to lower the risk of serious consequences for vulnerable groups (Hamson et al., n.d.).

Antigenic variation and its impact

The term "antigen-variation" in vaccines describes a pathogen's capacity to alter its antigenic characteristics, making it more challenging for the immune system to identify and react to them efficiently. For those creating vaccines to combat infections with changeable antigens, this phenomenon presents a serious issue since it can result in vaccination failure. Low vaccination rates can lead to several negative effects, such as an elevated risk of vaccine-preventable disease outbreaks, increased healthcare expenses, and lower productivity (Servín-Blanco et al., 2016). The degree of antigenic variety varies significantly, with certain infections (e.g., HIV and HCV) having very high degrees of variability. Alternative strategies have been investigated to address the problems caused by antigenic diversity. These strategies include the use of DNA or RNA vaccines or multivalent vaccinations, which target many antigens (Servín-Blanco et al., 2016).

There are two main factors via through which antigenic variation can arise: genetic and epigenetic. Pathogens' antigenic qualities are altered by genetic processes like mutation and recombination, yet they can express distinct antigenic variations within a clonal population because of epigenetic mechanisms like phase variation. Because they may change their antigenic characteristics, viruses can elude immune system recognition and the effects of vaccinations and antimicrobial treatments (Singh et al., 2020).

For instance, antigenic drift, a process in which the virus's genes change slightly to alter its antigenic characteristics, is a process that influenza viruses undergo. To guarantee their efficacy against this phenomenon, flu shots must be updated annually (Verhagen et al., 2020). However, because the virus's antigenic characteristics vary and become less identifiable to an individual's current antibodies, antigenic drift might occasionally cause an individual to become vulnerable to flu virus infection again (Wang et al., 2022).

PUBLIC HEALTH STRATEGIES FOR VACCINATION

Role of vaccination in public health and the importance of high vaccine coverage

In the 1900s, vaccines were developed to be used for a larger portion of the human population to help everyone stay healthy. Even though we tried hard not everyone everywhere has the same access to life-saving vaccines. For a longer period, the practitioners, and scientists who investigated vaccines about how vaccines stop sickness and save lives. But later, researchers came to know that other factors are also considerable to assess a successful vaccination strategy like political will, vaccine cost and its availability, and societal approach and response. When the new virus, SARS-CoV-2 came in 2019, we needed vaccines as fast to fight COVID-19. This showed how important vaccines are for everyone around the world. It's important to tell everyone, including leaders, about how good vaccines are to fight different diseases (Rodrigues & Plotkin, 2020).

Scientists are investigating how certain vaccines, such as those for influenza, pneumonia, and tuberculosis, might help prevent or improve the outcome of COVID-19. These vaccines could work directly by boosting the immune system's response or indirectly by reducing the impact of other respiratory illnesses making it easier to diagnose COVID-19. Additionally, several vaccines for the viruses causing COVID-19 are currently in clinical trials

and are expected to be available soon with accelerated approval processes. To safeguard public health, it is crucial to monitor vaccine safety (vaccine vigilance) and carefully plan effective vaccination campaigns. This approach aims to ensure widespread protection against COVID-19 and related respiratory diseases (Sultana et al., 2020).

Vaccine hesitancy and strategies addressing it

Over the years, the widespread reluctance to get vaccinated has become a significant global health concern, prompting the World Health Organization to classify it as one of the top 10 threats in 2019 (Nuwarda et al., 2022). Vaccine hesitancy refers to a situation where people either delay or refuse to get vaccinated, even when vaccines are accessible. (Tolley et al., 2023). There's a limited amount of research on strategies to combat vaccine hesitancy with a focus on influenza, HPV, childhood vaccines, diphtheria, tetanus, pertussis, and polio in the Americas. The studies mostly look at multi-component approaches aiming to increase knowledge and awareness. Out of the evaluated strategies, thirteen studies showed moderate-quality evidence supporting the effectiveness of certain interventions. These include social mobilization, mass media campaigns, training healthcare workers using communication tools, offering non-financial incentives, and using reminder/recall systems. However, it's important to note that only a small percentage of both peer-reviewed and grey literature has explored and evaluated these strategies (Jarrett et al., 2015).

Childhood vaccination is widely recognized as an important step in keeping communities healthy. However, national vaccination strategy estimates might not capture differences within a country. When groups of people aren't fully vaccinated, diseases can spread more easily. Vaccine hesitancy, or people being unsure about vaccines, is a reason why some places don't have enough vaccinated individuals. Even parents who have been vaccinated earlier may have worried. Efforts to boost vaccine confidence should consider emotional, cultural, social, spiritual, and political factors, making tailored strategies crucial (Dubé et al., 2015).

CONCLUSION

In conclusion, effective vaccination strategies play a crucial role in controlling and preventing viral outbreaks. Past viral outbreaks have provided valuable insights into the development of current vaccination strategies. The Ebola outbreak in West Africa from 2014 to 2016, for instance, demonstrated the importance of early and coordinated efforts in vaccine development. Despite the availability of effective vaccines, vaccine distribution and uptake remain a significant challenge. Addressing vaccine hesitancy, improving access and delivery, and ensuring equitable distribution of vaccines worldwide are necessary steps to enhance vaccine distribution and uptake. Ongoing research and development are needed to address emerging viruses and new challenges in vaccine distribution and uptake. By prioritizing vaccine development and distribution, we can work toward a healthier and more resilient world.

ACKNOWLEDGMENTS

We express our heartfelt gratitude to Dr. Muhammad Tariq Navid for his invaluable guidance and support in completing this review article. His expertise and insights have greatly enriched the content, contributing to the overall quality of work.

CONFLICT OF INTEREST

Regarding the publishing of this work, the author(s) state that they have no conflict interests.

FUNDING SOURCE

The paper was written without the assistance of any grants, funding, or other sources, as declared by the authors.

NOVELTY STATEMENT

The article explores the evolution of different vaccination strategies from traditional methods to modern advancements in vaccines, highlighting the role of vaccines in global health. It discusses the principles of vaccine development, the importance of animal models in pre-clinical testing, and current vaccines for various viral diseases. Additionally, it addresses challenges such as vaccine failure, immunization gaps, and vaccine hesitancy. It emphasizes the significance of high vaccine coverage in public. Novel approaches and strategies to address these challenges are proposed to ensure a healthier and more resilient world.

AUTHORS CONTRIBUTIONS

Every author made an equal contribution to the writing, editing, and study design. After reviewing the final draft of the article, all writers gave their approval.

REFERENCES

Amanna I. J., Slifka M. K. (2020). Successful vaccines. In Curr. Top. Microbiol. Immunol. (Vol. 428, pp. 1–30). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/82_2018_102

Bezbaruah R., Chavda V. P., Nongrang L., Alom S., Deka K., Kalita T., Ali F., Bhattacharjee B., Vora L. (2022). Nanoparticle-Based Delivery Systems for Vaccines. Vaccines., 10(11):

1946.

Brisse M., Vrba S. M., Kirk N., Liang Y., Ly H. (2020). Emerging Concepts and Technologies in Vaccine Development. In Front. Immunol. (Vol. 11). Frontiers Media S.A. https://doi.org/10.3389/fimmu.2020.583077

Canada H. (2022, February 24). COVID-19 plant-based vaccines: About, how they work, safety [Education and awareness]. https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines/plant-based.html

Cheng L., Wang Y., Du J. (2020). Human papillomavirus vaccines: An updated review. In Vaccines (Vol. 8, Issue 3, pp. 1–15). MDPI AG. https://doi.org/10.3390/vaccines8030391

Dubé E., Gagnon D., MacDonald N. E., Eskola J., Liang X., Chaudhuri M., Dube E., Gellin B., Goldstein S., Larson H., Manzo M. L., Reingold A., Tshering K., Zhou Y., Duclos P., Guirguis S., Hickler B., Schuster M. (2015). Strategies intended to address vaccine hesitancy: Review of published reviews. Vaccine., 33(34): 4191–4203. https://doi.org/10.1016/j.vaccine.2015.04.041

Fan G., Song H., Yip S., Zhang T., He D. (2022). Impact of low vaccine coverage on the resurgence of COVID-19 in Central and Eastern Europe. One Health., 14: 100402. https://doi.org/10.1016/j.onehlt.2022.100402

Fiolet T., Kherabi, Y., MacDonald C. J., Ghosn J., Peiffer-Smadja N. (2022). Comparing COVID-19 vaccines for their characteristics, efficacy, and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. In Clin. Microbiol Infect. (Vol. 28, Issue 2, pp. 202–221). Elsevier B.V. https://doi.org/10.1016/j.cmi.2021.10.005

Gerdts V., Wilson H. L., Meurens F., Van den Hurk S. van D. L., Wilson D., Walker S., Wheler C., Townsend H., Potter A. A. (2015). Large animal models for vaccine development and testing. ILAR J., 56(1): 53–62. https://doi.org/10.1093/ilar/ilv009

Greenwood B. (2014). The contribution of vaccination to global health: Past, present, and future. In Philosophical Transactions of the Royal Society B: Biological Sciences (Vol. 369, Issue 1645). Royal Society of London. https://doi.org/10.1098/rstb.2013.0433

Hamson E., Forbes C., Wittkopf P., Pandey A., Mendes D., Kowalik J., Czudek C., Mugwagwa T. (n.d.). Impact of pandemics and disruptions to vaccination on infectious diseases epidemiology past and present. Human Vacc. Immunotherapeut., 19(2): 2219577. https://doi.org/10.1080/21645515.2023.2219577

Hansson M., Nygren P., Sta¨hl S. (2000). Design and production of recombinant subunit vaccines. Biotechnol. Appl. Biochem/, 32(2). https://doi.org/10.1042/ba20000034

Hicks D. J., Fooks A. R., Johnson N. (2012). Developments in rabies vaccines. In Clin. Exper. Immunol. (Vol. 169, Issue 3, pp. 199–204). https://doi.org/10.1111/j.1365-2249.2012.04592.x

Hu Q., Zhao Y., Shaabani N., Lyu X., Powers C., Sun H., Cruz V., Stegman K., Xu J., Fossier A., Huang Y., Ho G., Kao Y., Wang Z., Wang Z., Hu Y., Zheng Y., Kyaw L., Zuluaga C., Chen R. (2022). Chimeric mRNA-based COVID-19 vaccine induces protective immunity against Omicron and Delta variants. Molecul. Ther. - Nucleic Acids., 30: 465–476. https://doi.org/10.1016/j.omtn.2022.10.021

Iwamoto M., Hickman C. J., Colley H., Arciuolo R. J., Mahle C. E., Deocharan B., Siemetzki-Kapoor U., Zucker J. R., Rosen J. B. (2021). Measles infection in persons with secondary vaccine failure, New York City, 2018–19. Vaccine., 39(38): 5346–5350. https://doi.org/10.1016/j.vaccine.2021.07.07

Jang Y. H., Seong B.-L. (2012). Principles underlying rational design of live attenuated influenza vaccines. Clin. Exper. Vacc. Res., 1(1): 35. https://doi.org/10.7774/cevr.2012.1.1.35

Jarrett C., Wilson R., O'Leary M., Eckersberger E., Larson H. J., Eskola J., Liang X., Chaudhuri M., Dube E., Gellin B., Goldstein S., Larson H., MacDonald N., Manzo M. L., Reingold A., Tshering K., Zhou Y., Duclos P., Guirguis S., Schuster M. (2015). Strategies for addressing vaccine hesitancy - A systematic review. In Vaccine (Vol. 33, Issue 34, pp. 4180–4190). Elsevier Ltd. https://doi.org/10.1016/j.vaccine.2015.04.040

Kiros T. G., Levast B., Auray G., Strom S., Van Kessel J., Gerdts V. (2012). The importance of animal models in the development of vaccines. In Innovat. Vaccinol. Desig. Throu. Deliv. Testing. (Vol. 9789400745438, pp. 251–264). Springer Netherlands. https://doi.org/10.1007/978-94-007-4543-8_11

Kracalik I., Oster M. E., Broder K. R., Cortese M. M., Glover M., Shields K., Creech C. B., Romanson B., Novosad S., Soslow J., Walter E. B., Marquez P., Dendy J. M., Woo J., Valderrama A. L., Ramirez-Cardenas A., Assefa A., Campbell M. J., Su J. R., Works K. (2022). Outcomes at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults in the USA: A follow-up surveillance study. Lancet Child Adolescent Health., 6(11): 788–798. https://doi.org/10.1016/S2352-4642(22)00244-9

Kurata T., Kanbayashi D., Egawa K., Kinoshita M., Yoshida H., Miyazono M., Motomura K. (2020). A measles outbreak from an index case with immunologically confirmed secondary vaccine failure. Vaccine., 38(6): 1467–1475. https://doi.org/10.1016/j.vaccine.2019.11.075

Lu J., Wei W., He W. (2023). Regulatory perspective for quality evaluation of lipid nanoparticle-based mRNA vaccines in China. Biologicals., 84: 101700. https://doi.org/10.1016/j.biologicals.2023.101700

Ma M., Shi L., Liu M., Yang J., Xie W., Sun G. (2023). Comparison of COVID-19 vaccine policies and their effectiveness in Korea, Japan, and Singapore. Int. J. Equity in Health., 22(1): 224. https://doi.org/10.1186/s12939-023-02034-

Mantel C., Cherian T. (2020). New immunization strategies: adapting to global challenges. In Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz (Vol. 63, Issue 1, pp. 25–31). Springer. https://doi.org/10.1007/s00103-019-03066-x

Mohd Rahim S., Ezrin Ilham N., Norbaya Masri S., Seka Margine I., Krammer F. (2014). Animal models for influenza viruses: Implications for universal vaccine development. In Pathogens (Vol. 3, Issue 4, pp. 846–874). MDPI AG. https://doi.org/10.3390/pathogens3040845

Matić Z., Šantak M. (2022). Current view on novel vaccine technologies to combat human infectious diseases. In Applied Microbiology and Biotechnology (Vol. 106, Issue 1, pp. 25–56). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s00253-021-11713-0

McLean H. Q., Fiebelkorn A. P., Ogee-Nwankwo A., Hao L., Coleman L. A., Adebayo A., Icenogle J. P. (2018). Rubella virus neutralizing antibody response after a third dose of measles-mumps-rubella vaccine in young adults. Vaccine., 36(38): 5732–5737. https://doi.org/10.1016/j.vaccine.2018.08.010

Nuwarda R. F., Ramzan I., Weekes L., Kayser V. (2022). Vaccine Hesitancy: Contemporary Issues and Historical Background. In Vaccines. (Vol. 10, Issue 10). MDPI. https://doi.org/10.3390/vaccines10101595

Nunnally B. K., Turula V. E., Sitrin R. D. (n.d.). ().

Nuwarda R. F., Ramzan I., Weekes L., Kayser V. (2022). Vaccine Hesitancy: Contemporary Issues and Historical Background. In Vaccines. (Vol. 10, Issue 10). MDPI. https://doi.org/10.3390/vaccines10101595

Pandey R. K., Dahiya S., Mahita J., Sowdhamini R., Prajapati V. K. (2019). Vaccination and immunization strategies to design Aedes aegypti salivary protein-based subunit vaccine tackling Flavivirus infection. Int. J. Biolog. Macromolecul., 122: 1203–1211. https://doi.org/10.1016/j.ijbiomac.2018.09.071

Perego G., Vigezzi G. Pietro, Cocciolo G., Chiappa F., Salvati S., Balzarini F., Odone A., Signorelli C., Gianfredi V. (2021). Safety and efficacy of spray intranasal live attenuated influenza vaccine: Systematic review and meta-analysis. In Vaccines (Vol. 9, Issue 9). MDPI. https://doi.org/10.3390/vaccines9090998

Phoolcharoen W., Shanmugaraj B., Khorattanakulchai N., Sunyakumthorn P., Pichyangkul S., Taepavarapruk P., Praserthsee W., Malaivijitnond S., Manopwisedjaroen S., Thitithanyanont A., Srisutthisamphan K., Jongkaewwattana A., Tomai M., Fox C. B., Taychakhoonavudh S. (2023). Preclinical evaluation of immunogenicity, efficacy, and safety of a recombinant plant-based SARS-CoV-2 RBD vaccine formulated with 3M-052-Alum adjuvant. Vaccine., 41(17): 2781–2792. https://doi.org/10.1016/j.vaccine.2023.03.027

Qi W., Xu W., Zhao L., Xu X., Luo Z., Huang L., Yan Q. (2019). Protection against Pseudomonas plecoglossicida in Epinephelus coioides immunized with a cspA1-knock-down live attenuated vaccine. Fish Shellfish Immunol., 89: 498–504. https://doi.org/10.1016/j.fsi.2019.04.029

Rodrigues C. M. C., Plotkin S. A. (2020). Impact of Vaccines; Health, Economic and Social Perspectives. In Front. Microbiol. (Vol. 11). Frontiers Media S.A. https://doi.org/10.3389/fmicb.2020.01526

Riese P., Trittel S., Schulze K., Guzmán C. A. (n.d.). Rodents as pre-clinical models for predicting vaccine performance in humans. Item Type Article. http://hdl.handle.net/10033/579626

Ruan B.-Y., Yao Y., Wang S.-Y., Gong X.-Q., Liu X.-M., Wang Q., Yu L.-X., Zhu S.-Q., Wang J., Shan T.-L., Zhou Y.-J., Tong W., Zheng H., Li G.-X., Gao F., Kong N., Yu H., Tong G.-Z. (2020). Protective efficacy of a bivalent inactivated reassortant H1N1 influenza virus vaccine against European avian-like and classical swine influenza H1N1 viruses in mice. Vet. Microbiol., 246: 108724. https://doi.org/10.1016/j.vetmic.2020.108724

Saleh A., Qamar S., Tekin A., Singh R., Kashyap R. (2021). Vaccine Development Throughout History. Cureus. https://doi.org/10.7759/cureus.16635

Servín-Blanco R., Zamora-Alvarado R., Gevorkian G., Manoutcharian K. (2016). Antigenic variability: Obstacles on the road to vaccines against traditionally difficult targets. Human Vacc. Immunotherapeut., 12(10): 2640–2648. https://doi.org/10.1080/21645515.2016.1191718

Simon V., Ho D. D., Abdool Karim Q. (2006). HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. In Lancet (Vol. 368, Issue 9534, pp. 489–504). Elsevier B.V. https://doi.org/10.1016/S0140-6736(06)69157-5

Singh P. K., Kulsum U., Rufai S. B., Mudliar S. R., Singh S. (2020). Mutations in SARS-CoV-2 Leading to Antigenic Variations in Spike Protein: A Challenge in Vaccine Development. J. Laborat. Physic., 12(2), 154–160. https://doi.org/10.1055/s-0040-1715790

Song J. Y., Cheong H. J., Hyun H. J., Seo Y. B., Lee J., Wie S.-H., Choi M. J., Choi W. S., Noh J. Y., Yun J. W., Yun J. G., Kim W. J. (2017). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine and an MF59-adjuvanted influenza vaccine after concomitant vaccination in 60-year-old adults. Vaccine., 35(2): 313–320. https://doi.org/10.1016/j.vaccine.2016.11.047

Stuart A. S. V., Shaw R. H., Liu X., Greenland M., Aley P. K., Andrews N. J., Cameron J. C., Charlton S., Clutterbuck E. A., Collins A. M., Darton T., Dinesh T., Duncan C. J. A., England A., Faust S. N., Ferreira D. M., Finn A., Goodman A. L., Green C. A., Snape M. D. (2022). Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): A single-blind, randomised, phase 2, non-inferiority trial. *Lancet.*, *399*(10319): 36–49. https://doi.org/10.1016/S0140-6736(21)02718-5

Sultana J., Mazzaglia G., Luxi N., Cancellieri A., Capuano A., Ferrajolo C., de Waure C., Ferlazzo G., Trifirò G. (2020). Potential effects of vaccinations on the prevention of COVID-19: rationale, clinical evidence, risks, and public health considerations. In Expert Rev. Vacc. (Vol. 19, Issue 10, pp. 919–936). Taylor and Francis Ltd. https://doi.org/10.1080/14760584.2020.1825951

Tolley A. J., Scott V. C., Mitsdarffer M. L., Scaccia J. P. (2023). The Moderating Effect of Vaccine Hesitancy on the Relationship between the COVID-19 Vaccine Coverage Index and Vaccine Coverage. Vaccines., 11(7). https://doi.org/10.3390/vaccines11071231

Trad F., El Falou, S. (2022). Testing Different COVID-19 Vaccination Strategies Using an Agent-Based Modeling Approach. Sn Comp. Sci., 3(4): 307. https://doi.org/10.1007/s42979-022-01199-6

van Walstijn C., Verweij S., Care R., Rigsby P., Clapper E.-B., Markey K., Vandebriel R. J., Stickings P., amp; Hoefnagel M. H. N. (2023). Variability of in vivo potency assays of whole-cell pertussis, inactivated polio, and meningococcal B vaccines. Vaccine., 41(38): 5603–5613. https://doi.org/10.1016/j.vaccine.2023.07.054

Verhagen J. H., Poen M., Stallknecht D. E., van der Vliet S., Lexmond P., Sreevatsan S., Poulson R. L., Fouchier R. A. M., Lebarbenchon C. (2020). Phylogeography and Antigenic Diversity of Low-Pathogenic Avian Influenza H13 and H16 Viruses. J. Virol., 94(13): 10.1128/jvi.00537-20. https://doi.org/10.1128/jvi.00537-20

Vogel F. R., Sarver N. (1995). Nucleic Acid Vaccines. In CLIN. MICROBIOl. REV. (Vol. 8, Issue 3).

Wallender E., Peacock G., Wharton M., Walensky R. P. (2023). Uninsured and Not Immune—Closing the Vaccine-Coverage Gap for Adults. New England J. Med., 389(3): 193–195. https://doi.org/10.1056/NEJMp2306200

Wang Y., Tang C. Y., Wan X.-F. (2022). Antigenic characterization of influenza and SARS-CoV-2 viruses. Analyt. Bioanaly. Chem., 414(9): 2841–2881. https://doi.org/10.1007/s00216-021-03806-6

Weir J. P., Gruber M. F. (2016). An overview of the regulation of influenza vaccines in the United States. Influen. Other Respirat. Virus., 10(5): 354–360. https://doi.org/10.1111/

irv.12383

Wiedermann U., Garner-Spitzer E., Wagner A. (2016). Primary vaccine failure to routine vaccines: Why and what to do? Human Vacc. Immunotherapeut., 12(1): 239–243. https://doi.org/10.1080/21645515.2015.1093263

Wi Z. (2020). Severe measles infection due to primary vaccine failure in vaccinated children – A case report. Int. J. Infect. Dis., 101: 476. https://doi.org/10.1016/j.ijid.2020.09.1247

Yale G., Lopes M., Isloor S., Head J. R., Mazeri S., Gamble L., Dukpa K., Gongal G., Gibson A. D. (2022). Review of Oral Rabies Vaccination of Dogs and Its Application in India. In Viruses (Vol. 14, Issue 1). MDPI. https://doi.org/10.3390/v14010155

Yassein A. A. M., Teleb A. A., Hassan G. M., El Fiky Z. A. (2021). The immune response and protective efficacy of a potential DNA vaccine against virulent Pasteurella multocida. *J. Genet. Engineer. Biotechnol.*, *19*(1): 81. https://doi.org/10.1186/s43141-021-00180-9