mRNA Vaccines for Plasmodium: current and future prespective.

Hikmat Ullah[1], Sumaira Kanwal[2], Sundas Asghar[3], Bilal Ahmad Noor[4], Muhammad Subbayyal Akram[5], Muhammad Mobashar[6], Rasheed Ahmad[7], Asim Ejaz[8], Warda Qamar[5] ,Muhammad Adnan Sabir Mughal[5], Ghulam Murtaza[9], Muhammad Adil[10], Muhammad Abdullah Qureshi[4].

1 Department of Microbiology, Kohat University of Science and Technology, Pakistan.
2 Department of Biological Science, Feculty of Sciences, The Superior University, Lahore.
3 Department of Zoology, The University of Lahore, Sargodha Campus, Pakistan.
4 Feculty of Veterinary Science, University of Agriculture Faisalabad, 38040, Pakistan.
5 Department of Parasitology, University of Agriculture Faisalabad, 38040, Pakistan.
6 Department of Animal Nutrition, The University of Agriculture Peshawar-Pakistan.
7 Head of MEAL department, Pak Mission Society, Pakistan.
8 Assistant of MEAL department, Pak Mission Society, Pakistan.
9 Department of Anatomy, University of Agriculture Faisalabad, 38040, Pakistan.
10 Department of Clinical Medicine & Surgery, University of Agriculture, Faisalabad, 38040, Pakistan.

ABSTRACT

The complex landscape of mRNA vaccines is explored in this in-depth review, which focuses on the cutting edge of vaccine research against the deadly parasite Plasmodium falciparum. Parasite life cycle, significance, and host range are introduced, and then the importance of developing new vaccines is stressed. The report elucidates the context of vaccine development, exposing the merits of immunization and the difficulties faced by malaria vaccine efforts. Before diving into an in-depth investigation of new technologies, it is helpful to get a firm grounding in the history and current practices of vaccine development. In particular, the pros and cons of RNA vaccines for protecting against Plasmodium are discussed at length. This review concludes with an optimistic look into the future of mRNA vaccines, emphasizing their potential to treat not only malaria but also other infectious illnesses. The analysis highlights the speed and potential of mRNA vaccine development and tailored cancer vaccines at a time when global vaccination equality is of paramount importance. This voyage of evaluation spans the promise and limitations of mRNA vaccines, providing a complete picture of how they may or may not impact disease prevention and international health security.

KEYWORDS: Plasmodium falciparum, mRNA vaccines, Vaccine development, Malaria, Emerging technologies, Limitations, Global vaccine equity

I. INTRODUCTION

The parasitic protozoan genus Plasmodium is the source of malaria, one of the most serious infectious diseases afflicting people worldwide (Collins and Jeffery, 2007; Langford et al., 2015). There are many species in this genus, but P. falciparum and P. vivax are the most prevalent and harmful to human health (McKenzie et al., 2002; Mueller et al., 2007; Grande et al., 2019). These parasitic microbes, which are members of the phylum Apicomplexa, have an unusual and intricate life cycle (Yman et al., 2019; Akram et al., 2021). Once within the human host, they have the ability to infect and grow within red blood cells, resulting in the typical symptoms of malaria . They are transferred to humans through the bite of infected female Anopheles mosquitoes. Because different Plasmodium species can have a range of clinical symptoms and severity, they are a serious public health concern. In order to battle malaria and lessen its global impact on public health, effective measures, including potential mRNA vaccines, must be developed (Rutledge et al., 2017). For this to happen, it is imperative to understand the biology and genetics of Plasmodium parasites. Malaria is a severe illness that is transmitted to humans mostly through the bites of infected female Anopheles mosquitoes. Infected mosquitoes spread the disease by injecting sporozoites into a person's bloodstream when they bite. The sporozoites then go to the liver, where they multiply and change into merozoites (Hawadak et al., 2021).

Once the sporozoites reach the liver, they begin a lengthy period of growth that results in an increase in the number of merozoites (Yerlikaya et al., 2018). Malaria's merozoites are to blame for everything from the disease's classic fever and chills to more serious complications including anemia and organ failure. The

species of Plasmodium responsible for an infection can have a major impact on the severity and clinical presentation of malaria (Ansari et al., 2016). Malaria caused by Plasmodium falciparum is the most severe and potentially fatal form of the disease. The propensity of P. vivax to form latent liver stages that can reactivate and induce relapses long after the original infection is made is noteworthy, however, and can lead to recurring infections. Effective techniques for malaria prevention and treatment need an understanding of the complexities of the parasite's life cycle and the wide range of clinical symptoms it can cause (Cao et al., 2016). The importance of learning about the Plasmodium parasite and its complex life cycle in the context of international health cannot be overstated. Plasmodium infection, which causes malaria, is still a big problem in areas where it is widely spread (Rajahram et al., 2012). The life cycle of the parasite is quite intricate, requiring it to switch between human hosts and mosquito vectors. Because of its cyclical nature, understanding its nuances is crucial. Targeted therapies are significantly aided by in-depth knowledge of the life cycle. Researchers and public health officials can develop targeted strategies, such as vaccines, drugs, and mosquito control measures, to interrupt transmission and lessen the disease's burden by zeroing in on the most susceptible points in the cycle, such as sporozoite transmission or erythrocytic development. In addition, understanding the life cycle of Plasmodium helps guide the creation of vaccines, such as new mRNA vaccine candidates, that attempt to elicit immune responses against discrete parasitic life cycles (Mason et al., 1999; Ellis McKenzie et al., 2001). The development of effective antimalarial medications that can target and suppress parasite growth at crucial periods requires a knowledge of the various phases. A thorough understanding of the biology of the parasite, as depicted through its life cycle, remains central to strategic planning and the ongoing battle to lessen the global impact of malaria, especially among the most vulnerable populations, as efforts to control and eradicate the disease continue (Kotepui et al., 2020).

The development of new vaccination methods over time is a prime example of the role that scientific progress may play in ensuring the public's health (Vinetz et al., 1998). Major turning points in the history of vaccine creation include Edward Jenner's groundbreaking smallpox immunization work, the advent of polio vaccinations, and much more (Li et al., 2016; Jain et al., 2021). The historical context of malaria management exemplifies humanity's dogged search for answers to battle this lethal parasite ailment. Despite the fact that malaria vaccines have been studied and developed for decades, they have proven difficult to implement due to the complicated life cycle of Plasmodium parasites and the wide variety of species that may cause human infections. However, malaria vaccinations have the potential to have a significant effect and have worldwide relevance in reducing the global burden of this dreadful disease (Tsoumani et al., 2023). Modern initiatives, such as the investigation of novel mRNA vaccines, show promise in developing effective tools for malaria control and advancing the pursuit of global malaria eradication, building on the history of vaccine development (Hayashi et al., 2022). Vaccines protect against several infectious diseases, making them a vital tool in improving people's health and longevity all around the world. Vaccines not only decrease the spread of disease but also significantly lessen the burden of disease on the body, leading to less severe symptoms and, most importantly, fewer fatalities (Armbruster et al., 2019; Okamura and Ebina, 2021). The importance of vaccinations to the idea of herd immunity becomes obvious when considering their larger social ramifications. When a large enough proportion of a community acquires protection against a disease, this phenomenon is known as "herd immunity." To put it simply, it creates a buffer zone around persons who cannot get vaccinations due to age, health, or other factors. Vaccinations protect the most vulnerable members of society by lowering the disease's prevalence in the population as a whole (Versteeg et al., 2019; Gergen and Petsch, 2021).

When we evaluate the role vaccinations have played in the eradication and near-eradication of some ailments, we can see the significant influence they have had on infectious diseases (Sehrawat et al., 2022). The once-dreaded disease of smallpox was eradicated from the planet thanks to massive vaccination campaigns. Similarly, polio has been nearly eradicated over the world because of immunizations that protect against severe illness and stop transmission (Karam and Daoud, 2022). These outstanding results highlight the far-reaching consequences and unquestionable relevance of immunizations in the field of public health. Malaria is one of the most imminent threats in the ongoing fight against infectious illnesses. Researchers and medical professionals throughout the world are working tirelessly to create a malaria vaccine that will reduce the disease's terrible effects and boost herd immunity (Desmond and Offit, 2021). The objectives are quite clear: lessen the impact of malaria, stop serious sickness, and save lives. Finding an effective malaria vaccine would be a major step forward in the war against this tenacious and lethal disease (Piché-Renaud et al., 2023).

A successful malaria vaccination would have far-reaching consequences for malaria-endemic areas, and this fact should be kept in mind when we consider the revolutionary potential of vaccines. This has the potential to make malaria, a major source of death and misery in the past, a disease that can be avoided and controlled in the future. Vaccinations have the potential to greatly impact the future of public health throughout the world, and this possibility serves as a striking reminder of that potential. It's a tribute to human ingenuity and tenacity in the face of some of the gravest health crises our species has ever faced (Tsoumani et al., 2023).

The creation of a malaria vaccine is an enormous task fraught with difficult obstacles that require creative answers. The intricacy of the Plasmodium life cycle is the primary challenge. Challenges in efficiently targeting several stages of the parasite are posed by its adaptability to varied host conditions and the complexity of its transitions between mosquito vectors and human hosts (Ganley et al., 2023).

The genetic variety of Plasmodium species further complicates efforts to create a vaccine against the disease. The genetic heterogeneity of Plasmodium falciparum, the parasite responsible for most instances of malaria, makes it difficult to develop a vaccine that would protect everyone. Plasmodium strains vary genetically, therefore it's important for potential vaccines to account for that. The development of an effective vaccine against malaria is hampered by immunological obstacles. Because Plasmodium parasites use complex strategies to avoid being

attacked by the host's immune system, it might be difficult to provoke a helpful immune response. A thorough comprehension of the immunological landscape is also required due to the complexity of host-parasite interactions and the impact of host genetics in vaccination response (Borkens, 2023).

Despite these obstacles, the area of malaria immunization is progressing because to continued research, which includes the development of novel techniques such mRNA vaccines. The enormous public health effect of a successful malaria vaccine is a driving force behind these efforts, highlighting the resolve to overcome difficulties and go on in the fight to reduce and ultimately eliminate malaria (Versteeg et al., 2019).

Historical Vaccine Development Methods

There was a lot of bravery and uncertainty in the first stages of vaccine research (Plotkin and Plotkin, 2012). In an effort to save lives from deadly illnesses like smallpox and rabies, historical scientists undertook an amazing voyage (Lombard et al., 2007). They relied on empirical methods, which are founded on experimentation (Volpedo et al., 2021). The English physician Edward Jenner made one of the most significant contributions to immunization history when he successfully eradicated smallpox (Plotkin, 2014). In 1796, he experimented on the theory that cowpox, a milder relative of smallpox, may protect humans from being infected with the fatal smallpox virus. His ground-breaking experiment entailed inoculating a young kid called James Phipps with material taken from a cowpox sore (Plotkin, 2011). The key point is that the youngster contracted cowpox but did not catch smallpox when he was subsequently purposefully exposed to the virus (Taylor et al., 2006). This seminal event heralded the birth of the first vaccination, which had been developed experimentally using a procedure that anticipated the scientific method.Louis Pasteur, in the late 19th century, used a similar method of trial and error to produce a vaccine against rabies. To render the rabies virus safe for use in vaccinations, Pasteur experimented with a variety of techniques. As a result of his efforts, a vaccine against rabies was developed, which has saved countless lives and shown that empirical methods may be effective in the fight against infectious illnesses (Hilleman, 1998).

Safer vaccinations have been developed as vaccine technology has progressed. Strategies that inactivate or attenuate infections while yet allowing them to excite the immune system have gained prominence (Cha, 2012).Treatment with heat or chemicals renders the pathogen non-infectious while retaining its antigenic features; this process is known as inactivation. Inactivated polio vaccinations are possible because of this technique; with this vaccine, the poliovirus is treated to render it harmless while still triggering an immune response (Stern and Markel, 2005). In contrast, attenuation is the process of reducing a pathogen's strength via repeated passes in non-human hosts. Despite being less dangerous, the attenuated pathogen can still provoke an immune response. The use of live but attenuated viruses to provide immunity has led to the development of vaccinations like the measles, mumps, and rubella (MMR) vaccine (Mueller et al., 2007; Barberis et al., 2016).

Modern Vaccine Development Methods

Subunit Vaccines: The creation of vaccines has entered a new age of pinpoint accuracy because to developments in molecular biology and biotechnology (Liljeqvist and Ståhl, 1999). To induce immune responses, subunit vaccines employ solely isolated and purified pathogen components, such proteins or polysaccharides. Subunit vaccines provide a more secure and specific method of vaccination by excluding potentially dangerous non-essential components. A viral protein component is all that's needed for the human papillomavirus (HPV) vaccination, which protects against cervical cancer, to generate an immune response (Hansson et al., 2000; Moyle and Toth, 2013).

Recombinant DNA Technology: Recombinant DNA technology's precision in producing antigens has greatly aided vaccine development (Godse et al., 2023). In order to mass-produce some antigens, researchers are turning to genetic engineering to insert the necessary genes into host species like yeast or bacteria. Vaccines like the one for hepatitis B, which uses yeast cells modified to generate hepatitis B surface antigen, have been made possible using this method (Eun, 1996; Khan et al., 2016).

Vector-Based Vaccines: vaccinations that rely on live vectors, often viruses, to transport and deliver antigens into host cells, are called vector-based vaccinations (Chavda et al., 2023). These vectors have been engineered to transport the infectious disease-free genetic material required for antigen synthesis. Antigen delivery stimulates the host immune system, which then mounts an effective defense against the invading infection. Vaccines against infectious illnesses like Ebola and HIV employ this strategy (Ura et al., 2014; Zeedan et al., 2023).

mRNA Vaccines: The *Plasmodium* vaccinations are a striking example of the revolutionary breakthrough in vaccine science represented by the invention of mRNA vaccines (Chen et al., 2023). Vaccines of this type transmit, via mRNA, the genetic instructions necessary for the host cells to make a harmless fragment of the protein that is the target of the vaccination. By reacting strongly to this foreign protein fragment, the immune system trains itself to combat the full-fledged virus should it ever be met again (Makoni, 2023; Tsoumani et al., 2023).

Adjuvants: Adjuvants are chemicals added to vaccines to increase the body's protective reaction (Martinez et al., 2023). They boost the vaccine's effectiveness by stimulating the body's innate immune system to react more strongly (Hou et al., 2023). Adjuvants have been used to great effect in vaccines, particularly those containing subunit antigens, to increase their immunogenicity. Aluminum salts are used as an adjuvant in several vaccines, including those for hepatitis A and diphtheria-tetanus-pertussis (Rajneesh et al., 2023; Veiga et al., 2023).

Reverse Vaccinology: As a result of the convergence of genetics and bioinformatics, reverse vaccinology has evolved as a very efficient method. Instead of extracting and identifying antigens in the usual way, reverse vaccinology uses computer methodologies to investigate disease genomes and locate potential vaccine candidates (All et al.; Srivastava and Jain, 2023). Vaccines have been developed using this strategy, protecting people from diseases caused by pathogens like Neisseria meningitidis (Goodswen et al., 2023). Vaccine research has gone a long way over the years, from the use of empirical approaches based on

trial and error to the use of cutting-edge technologies such as mRNA vaccines and reverse vaccinology. These advancements have increased the amount of diseases that might be prevented by immunization by making shots safer and more effective. As we face new infectious dangers to global health, the technology we have for generating vaccines will become increasingly crucial (Chou et al., 2023; Mariano et al., 2023).

RNA vaccines

DNA undergoes transcription into messenger RNA (mRNA), which is then translated into protein, according to the basic dogma of molecular biology (Hayashi et al., 2022). Complex regulatory systems direct the movement of genetic information over time and place. Gene therapy involves surgically implanting or injecting genetic material into a patient. In order to cure or significantly improve a patient's clinical state, scientists have turned to gene-correction techniques such as insertion, modification, and removal. Many different vectors, both viral and non-viral, have been used for gene therapy (Chen et al., 2022). Low host immunogenicity and the possibility for scale-up are two advantages of non-viral vectors over viral vectors. However, plasmid DNA (pDNA) delivery barriers, such as the need to cross the nuclear membrane prior to translation, the presence of antibiotic resistance genes in pDNA, and most importantly, the difficulty in controlling and regulating long-term expression, have severely limited the success of non-viral gene therapy in the past. The inability to immediately halt therapy with pDNA, in contrast to conventional medications, is a major drawback due to the treatment's length and potential adverse effects. These limitations of pDNA may be circumvented by use mRNA (Maruggi et al., 2021). The ribosomes in the cytosol use the genetic information stored in the DNA in the nucleus as a template to make proteins. In contrast to pDNA, mRNA is effective in both actively dividing and non-dividing cells because it exerts its role in the cytoplasm. Furthermore, mRNA is a safer vector than pDNA or viral vectors since it does not include any additional foreign genes. Since mRNA causes a quick, transitory expression of the encoded protein and the period of the synthesis is well-defined (typically a few days or weeks, depending on the individual mRNA platform), it may also be used to circumvent the barrier of long-term expression given by pDNA. In comparison to pDNA and viral vectors, mRNA expression may be more easily regulated. The absence of cells throughout the production process greatly lessens the likelihood of bacterial contamination during mRNA production. Under GMP conditions, mRNA production is simplified as compared to pDNA production. Unlike viral vectors or virus-like particles, which may produce a particular immune response against the exposed viral proteins, mRNA therapies do not suffer from vector-induced immunogenicity (Knapp et al., 1991; Fotoran et al., 2023). Particular medicinal uses of mRNA that are being investigated include

(i) Vaccination against cancer and infectious diseases

(ii) Protein-replacement therapy

(iii) Gene editing.

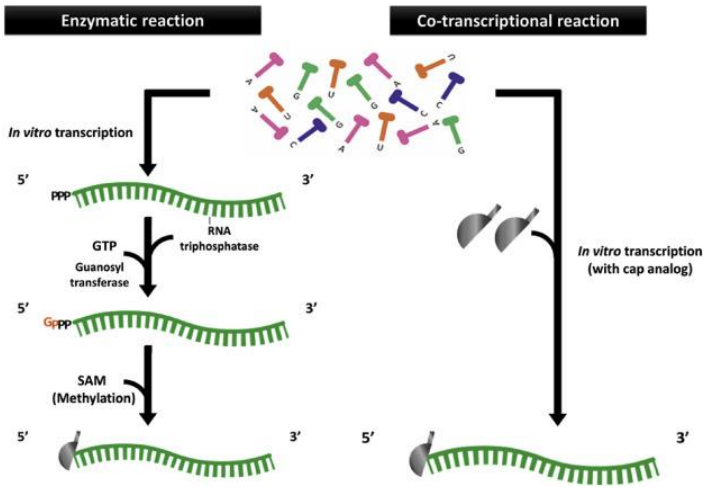
RNA vaccines are a game-changing innovation in the field of immunization that promises to usher in a new age of vaccine research and development. These cutting-edge vaccines use mRNA to direct the human body's cells to generate inert pathogen pieces, evoking a strong and targeted immune response (Rouf et al., 2022). RNA vaccines have been at the forefront of medical and scientific study because of their exceptional efficacy in battling the COVID-19 epidemic. From their theoretical foundations to their practical uses in preventing a wide range of infectious illnesses, RNA vaccines are explored in depth in this section. This article delves into how this game-changing technology has not only proven its incredible efficacy but also paved the way for a more rapid, flexible, and pinpoint method of vaccine creation (Alameh et al., 2020).

mRNA VACCINE AGAINST PLASMODIUM

The Plasmodium parasites that cause malaria are still a major public health problem across the world and novel techniques to vaccine development are needed to combat this disease. One innovative strategy that has showed promise in the battle against this pervasive illness is the use of mRNA vaccination technology. This section describes how mRNA vaccines are being developed for use against Plasmodium infections and highlights the critical importance of this novel approach (Li et al., 2022). Identifying appropriate antigens, proteins on the surface of the Plasmodium parasite that can elicit a strong and focused immune response, is a critical initial step in developing an mRNA vaccine against malaria. Initiating the immune system's defense mechanisms against the parasite, these chosen antigens are at the heart of the mRNA vaccination technique (Kairuz et al., 2022).

The production of messenger RNA (mRNA) is the next crucial step after identifying antigens, and it requires extreme care and accuracy. To produce the synthetic mRNA sequences encoding the established Plasmodium antigens, in vitro transcription is used as shown in **Figure 1**. The accuracy required to create synthetic mRNA templates that are biochemically and functionally similar to target antigens located on the surface of the parasite cannot be stressed. This rigorous laboratory method assures the mRNA vaccines are not only efficient, but also safe, and able to elicit a robust immune response against Plasmodium. Using mRNA vaccine technology to combat malaria is a novel strategy with exciting potential. Parasite genetics are being used to train the immune system to detect and destroy Plasmodium, opening a new door in the fight against malaria. The development of malaria vaccines might be greatly aided by this novel approach, raising the possibility that one day this devastating disease would be brought under control and eventually eradicated (Pardi et al., 2020).

FIGURE 1: Synthetic mRNA Synthesis

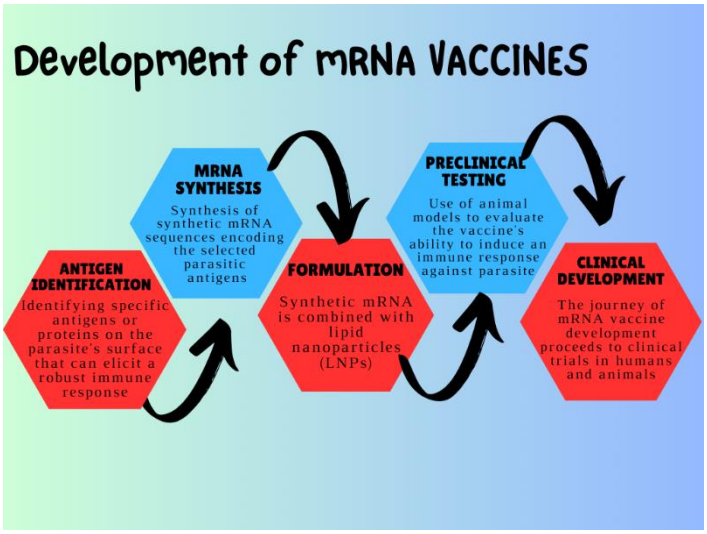


The production of mRNA vaccines that are unique to Plasmodium infections calls for a well-orchestrated set of procedures, each of which plays an important part in ensuring the safety and effectiveness of the vaccine candidate that is being considered (Tsoumani et al., 2023). After an antigen has been found and mRNA has been generated, the next critical stage in the process is formulation. In this case, the synthetic mRNA sequences are encapsulated inside of lipid nanoparticles, also known as LNPs. In two distinct ways, LNPs promote cellular absorption while also protecting the mRNA cargo. They prevent the mRNA from becoming destroyed while it is in route and make it possible for host cells to efficiently take it up. This brilliantly planned formulation has significantly improved the stability and bioavailability of the mRNA vaccine, turning it into a potent tool in the battle against malaria (Ganley et al., 2023).

Following this, the mRNA vaccine is put through rigorous testing using well-defined animal models before going on to clinical evaluation in humans. In order to determine whether or whether the immunization creates any unintended side effects, this step is very necessary. Simultaneously, the vaccine's immunogenicity is examined through preclinical testing by assessing its capacity to trigger an immune response against Plasmodium antigens. This evaluation determines the vaccine's potential to protect against malaria (Makoni, 2023).

Clinical development is a multi-stage process that is aimed to evaluate whether or not the vaccine is appropriate for general administration. Once it has been demonstrated that the mRNA vaccine is both safe and effective in preclinical tests, it will enter clinical development. A preliminary stage of testing on humans known as Phase I involves the participation of a limited number of volunteers who are in good health (Chuang et al., 2023). The primary objectives of this research are to identify the minimum risk associated with receiving the immunization and to evaluate the safety of the vaccine as a whole. In the second phase of the experiment, hundreds more participants will take part, and more in-depth safety assessments will be conducted. It is being determined whether or whether the vaccine is successful in preventing infection with Plasmodium, as well as the magnitude and duration of the immune response that it induces (Borkens, 2023). Phase III clinical trials are the most advanced kind of clinical testing, and they entail the participation of thousands upon thousands of people from a wide variety of backgrounds. During this stage, the vaccine is tested on a broader population to verify that it is both safe and effective, while also keeping a close look out for any unforeseen adverse effects. The conclusion of Phase III testing with favorable findings is a significant step forward in the fight against malaria since it provides the evidence required for regulatory approval and paves the way for the worldwide deployment of the vaccine (You et al., 2023). This is an important step in the struggle against malaria **Figure 2**. The evolution of Plasmodium-specific mRNA vaccines exemplifies the coming together of cutting-edge research with dogged will to address a prevalent global health problem. The revolutionary potential of this cutting-edge technology for malaria control and elimination becomes clearer with each passing day (Dickey and Tolia, 2023).

FIGURE 2: DEVELOPMENT OF mRNA VACCINE



Mode of Action

The complexity of the malaria parasite's life cycle and its genetic variety have made vaccine development difficult. The development of mRNA vaccines, however, shows promise for combating this serious health issue (Al Fayez et al., 2023). Now that the vaccine has been prepared, it may be administered to the host and the biochemical changes it induces in the host's immune system in order to combat the alien parasite can be seen **Figure 3**. The following sequence of events occurs: **Vaccine Administration:** Vaccine administration entails injecting the mRNA vaccine, which contains the genetic instructions for the chosen antigens, into muscle cells (Gergen and Petsch, 2021).

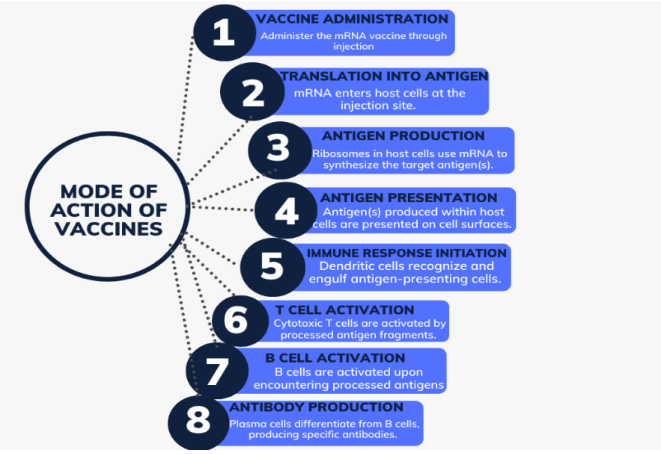


FIGURE 3: MODE OF ACTION OF VACCINES.

Translation into Antigen Production: Once the synthetic mRNA reaches the host cells at the injection site, the ribosomes in those cells use it as a blueprint to make the antigen (Pourseif et al., 2022). **Antigen Production:** The vaccine's mRNA is used by the host cells to produce the Plasmodium falciparum antigen(s) that are encoded by the vaccination. These antigens are generated by the host cells themselves (Maruggi et al., 2021). **Antigen Presentation:** The freshly generated Plasmodium falciparum antigen(s) are displayed on the surface of the host cells, a process known as ***antigen presentation***. This advertises the foreign antigens to the immune system in an efficient manner (Iavarone et al., 2017). **Immune Response Initiation:** The beginnings of an immune response are made possible by dendritic cells' recognizing the Plasmodium falciparum antigens that have been presented. Antigen-presenting cells are ingested and their antigens are processed before being presented to T cells and B cells (Turley and Lavelle, 2022). **T Cell Activation:** When cytotoxic T lymphocytes come into contact with the cleaved Plasmodium falciparum antigen fragments, they become activated. These newly activated T cells can detect and destroy malaria parasite-infected cells, stopping the spread of the disease (Kramps and Probst, 2013). **B Cell Activation and Antibody Production:** The processed Plasmodium falciparum antigens also activate B cells, which then produce antibodies. They undergo a process of terminal differentiation into plasma cells, which then secrete antibodies that bind to antigens on the malaria parasite (De Gregorio et al., 2013). **Memory Cell Formation:** Memory Cell Formation: Following the immune response, memory B cells and memory T cells are created, ready to kill the parasite if it infects the individual. To prepare for a prompt and efficient immune response in the event of future exposure to the malaria parasite, these memory cells "remember" the Plasmodium falciparum antigens (Gote et al., 2023). Plasmodium falciparum is the causative agent of malaria, and this technique might be used to create an mRNA vaccine that induces the host's cells to manufacture the parasite's antigens, so preparing the immune system to detect and destroy the parasite. Once exposed to the real parasite, the vaccine-generated immunological memory might give protection against malaria, lessening the severity of the sickness or avoiding it completely (Kowalczyk et al., 2016).

Limitations

Like any other medical intervention, mRNA vaccines have their own set of constraints and difficulties that must be overcome before they can be used effectively and safely. It is critical to be aware of and appreciate the limits of this novel method, despite the fact that mRNA vaccine technology has showed amazing promise, especially during the COVID-19 pandemic with vaccines like those developed by Pfizer-BioNTech and Moderna (Wang et al., 2023). Storage and stability requirements are major obstacles for mRNA vaccines. The need for ultra-cold temperatures to store these vaccinations is a logistical barrier, especially in areas where such facilities are scarce. Vaccine deployment is made more difficult by the need to keep the vaccines refrigerated throughout the whole distribution process (Jiménez-Díaz et al., 2023).

The shelf life of mRNA vaccines is often shorter than that of conventional vaccinations. Due to their short shelf life, vaccinations require meticulous planning and monitoring to ensure they are utilized before they expire (Hassert and Harty, 2023). Production of mRNA vaccines on a worldwide scale can be difficult. Synthetic messenger RNA (mRNA) and lipid nanoparticles are two of the many complex components of the manufacturing process. One of the biggest challenges is making sure there is enough vaccination to go around. There have been reports of adverse responses to mRNA vaccinations, which is cause for caution. Despite their rarity, these events underline the importance of closely monitoring vaccination recipients, especially those who have a history of severe allergies. To reduce exposure, rigorous screening and monitoring are required. A solid cold chain infrastructure is necessary for the deployment of mRNA vaccines due to their storage needs. Maintaining sufficient cold storage capacity is often difficult in many areas, especially in low-resource contexts. For vaccines to be distributed fairly, this infrastructure must be developed and strengthened (Hayashi et al., 2023).

It is still difficult to provide universally accessible mRNA vaccinations. These vaccinations have been more widely available in high-income countries, which might put at risk the more susceptible people in low-income countries. Coordination is essential for the success of initiatives like COVAX, which aim to improve vaccination fairness. Some viruses, including SARS-CoV-2, have the potential for mutations in their genetic material (Tan et al., 2023). The sustained efficiency of mRNA vaccines against new versions of these viruses requires constant monitoring, despite their proven usefulness. It's possible that mRNA vaccines will need to be modified to work against emerging strains (Gsell et al., 2023). Due to their intrinsic instability and susceptibility to fast degradation, mRNA molecules necessitate distribution through lipid nanoparticles. Because of this volatility, it is difficult to create vaccinations that will remain effective from creation through administration (Fotoran et al., 2023). Finally, mRNA vaccines have contributed significantly to the science of vaccinology by providing a novel, rapid-development platform for combating infectious illnesses. However, in order to optimize their influence on global health, challenges like as storage space, manufacturing scalability, and the necessity for cold chain infrastructure must be overcome. It is anticipated that these obstacles will be surmounted by creative ideas and ongoing research to make this game-changing method

of immunization even safer and more widely available (Nakamae et al., 2023).

Future Perspectives

mRNA vaccines have left an indelible impression on vaccinology, with Pfizer-BioNTech and Moderna's COVID-19 vaccines serving as especially shining examples of their quick development and effectiveness. These innovative vaccinations have not only helped in the fight against the epidemic, but they have also shown the way for future preventative medicine. The possibility for new advances in disease prevention, new difficulties, and new frontiers arise when we consider the future of mRNA vaccines (Satapathy et al., 2023). Because of their adaptability, mRNA vaccination systems can quickly respond to emerging infectious diseases. Vaccine research in the future will likely investigate a wide variety of pathogens, such as newly discovered viruses, bacteria, and parasites (You et al., 2023). It has long been a goal of the field of immunization to develop influenza vaccines that offer wide and long-lasting protection against many strains, and mRNA vaccines hold the potential to address these and other long-standing global health concerns. By zeroing down on the virus's conserved sections, mRNA technology provides hope for the creation of universal influenza vaccines that can be used against seasonal and pandemic flu. In the field of personalized medicine, mRNA vaccines show tremendous potential. The creation of individualized cancer vaccines that target a patient's unique tumor antigens is a promising new direction in cancer immunotherapy. The development of tailored cancer vaccinations using mRNA vaccines might significantly improve the current state of cancer treatment. The speed with which mRNA vaccines might be developed during the COVID-19 epidemic was astounding. In the future, the capacity to quickly respond to new infectious disease risks will be of paramount importance. Potentially ushering forth a new era of proactive pandemic preparedness, this might dramatically improve our ability to control outbreaks and stop pandemics (Kohli et al., 2023; Rajneesh et al., 2023).

Ongoing R&D initiatives aim to standardize and enhance the mRNA vaccine production procedure. Vaccine accessibility and response during global health crises will be improved by reducing production delays and expanding production capacity. There will soon be research on combination vaccines, wherein many vaccines are administered in a single dosage. This method has the potential to reduce the complexity of vaccination schedules while increasing immunization coverage and providing protection against numerous illnesses at once. Rare illnesses with limited patient populations are ideal candidates for mRNA vaccine development. People afflicted by diseases for which vaccines have been developed sparingly in the past owing to financial considerations should take heart from this. The efficacy and immunogenicity of mRNA vaccines can be improved by study of novel adjuvants and delivery mechanisms. Improved vaccination responses are expected as a result of these developments, which might eventually reduce the frequency of booster shots (Hotez, 2023). The necessity of establishing worldwide vaccination equality is highlighted in the context of the future. Guaranteeing that people in countries with low and intermediate incomes have access to vaccinations is dependent on efforts to spread mRNA vaccine technology and encourage local vaccine manufacturing. Long-term research and safety monitoring are essential as mRNA vaccines are widely distributed over the world. The stability and safety characteristics of vaccines will be monitored on an ongoing basis to identify and resolve any new issues as they arise (Gross, 2023; You et al., 2023).

In conclusion, the advent of mRNA vaccines heralds a new age in both vaccination research and public health. Their achievements during the COVID-19 pandemic have shed light on a future with huge promise for tackling a variety of infectious illnesses, malignancies, and global health concerns. The future of mRNA vaccines is marked by flexibility, the capacity to respond quickly, and a dedication to achieving health equity on a global scale. mRNA vaccines have the potential to herald in a new age of disease prevention and global health security, but only if scientists, governments, and healthcare systems work together to fully realize their promise (Ye et al., 2023).

Conclusion

The advent of mRNA vaccines heralds a new age in disease prevention, marking a watershed milestone in the history of contemporary medicine. Due to their novel design, these vaccines have quickly become effective weapons in the war against infectious illnesses and beyond. In addition to providing hope during the worst of the pandemic, the rapid development and remarkable efficacy of COVID-19 vaccines from companies like Pfizer-BioNTech and Moderna have revealed a promising path forward for addressing a wide range of global health challenges (Alhajjat et al., 2023; Komori et al., 2023).

Many more potential vaccination targets are now within reach because to the adaptability of mRNA vaccine systems. mRNA vaccines have the potential to radically alter the way infectious diseases are prevented and treated, including for both new and old threats like HIV, malaria and TB. An answer to a persistent global health problem, universal influenza vaccinations are on the horizon and can provide wide and lasting protection against ever-evolving strains (Matarazzo and Bettencourt, 2023).

mRNA-based cancer vaccines are a prime example of the potential of customized treatment. These vaccinations have the potential to transform cancer therapy by activating the immune system to specifically target and kill cancer cells based on their specific genetic markers. It exemplifies how mRNA technology may be rapidly adapted to solve different medical problems. The importance of quick reaction skills was highlighted as a key takeaway from the COVID-19 pandemic (Ye et al., 2023). Safe and effective vaccinations may be developed quickly, as demonstrated by mRNA vaccines. This increased nimbleness allows us to be more proactive in our pandemic preparations and respond more quickly to any new infectious disease risks that may arise. We are all committed to maximizing production efficiency and decreasing lead times in the future to make vaccines more widely available around the world. The potential for combination vaccines to streamline immunization regimens and increase coverage is exciting and within reach (Tsoumani et al., 2023). Transferring mRNA vaccine technology and enabling local manufacturing in resource-limited contexts exemplifies the commitment to vaccination equality on a global scale. Such efforts are crucial in reducing vaccination inequalities and bolstering our common defense against global health threats

(You et al., 2023). Finally, mRNA vaccines have opened up a whole new era in preventative medicine. The potential of a better and healthier future for all lies in their flexibility, responsiveness, and adaptability. The development and widespread use of mRNA vaccines is a triumph of human intellect, teamwork, and dedication to the highest ideals of scientific inquiry. As we move through this changing landscape, the international community is committed to using mRNA vaccines to their full potential so that future generations can enjoy better health, more resilience, and greater equality (Ye et al., 2023).

AUTHORS

First Author – Hikmat Ullah, Department of Microbiology, Kohat University of Science and Technology, Pakistan,
Equal First Author – Bilal Ahmad Noor, Feculty of Veterinary Science, University of Agriculture Faisalabad, 38040, Pakistan,

Second Author – Muhammad Subbayyal Akram, Department of Parasitology, University of Agriculture Faisalabad, 38040, Pakistan,
Correspondence Author – Muhammad Subbayyal Akram,
Acknowledgements: Authors acknowledge the financial support of MEAL Department, Pak Mission Society, Pakistan.

Biblioghraphy

Akram MS, Abbas RZ and Martinez JL, 2021. Antiprotozoal Effects of Wild Plants, Ethnopharmacology of Wild Plants. CRC Press.pp:129-147

Al Fayez N, Nassar MS, Alshehri AA, Alnefaie MK, Almughem FA, Alshehri BY, Alawad AO and Tawfik EA, 2023. Recent Advancement in mRNA Vaccine Development and Applications. Pharmaceutics, 15(7):1972.

Alameh M-G, Weissman D and Pardi N, 2020. Messenger RNA-based vaccines against infectious diseases. mRNA Vaccines:111-145.

Alhajjat AM, Redden CR, Langereis M, Papastefan ST, Ito JAS, Ott KC, Turner LE, Kang HK and Shaaban AF, 2023. CD4 and IL-2 mediated NK cell responses after COVID-19 infection and mRNA vaccination in adults. Immunobiology, 228(1):152304.

All IT, Would P, Chance S and Up TG, HOW 'REVERSE VACCINOLOGY'IS IDENTIFYING TARGETS FOR A NEW MALARIA VACCINE.

Ansari HR, Templeton TJ, Subudhi AK, Ramaprasad A, Tang J, Lu F, Naeem R, Hashish Y, Oguike MC and Benavente ED, 2016. Genome-scale comparison of expanded gene families in Plasmodium ovale wallikeri and Plasmodium ovale curtisi with Plasmodium malariae and with other Plasmodium species. International journal for parasitology, 46(11):685-696.

Armbruster N, Jasny E and Petsch B, 2019. Advances in RNA vaccines for preventive indications: a case study of a vaccine against rabies. Vaccines, 7(4):132.

Barberis I, Myles P, Ault SK, Bragazzi NL and Martini M, 2016. History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. Journal of preventive medicine and hygiene, 57(3):E115.

Borkens Y, 2023. Malaria & mRNA Vaccines: A Possible Salvation from One of the Most Relevant Infectious Diseases of the Global South. Acta Parasitologica:1-13.

Cao Y, Wang W, Liu Y, Cotter C, Zhou H, Zhu G, Tang J, Tang F, Lu F and Xu S, 2016. The increasing importance of Plasmodium ovale and Plasmodium malariae in a malaria elimination setting: an observational study of imported cases in Jiangsu Province, China, 2011–2014. Malaria journal, 15:1-9.

Cha S-H, 2012. The history of vaccination and current vaccination policies in Korea. Clinical and Experimental Vaccine Research, 1(1):3-8.

Chavda VP, Bezbaruah R, Valu D, Patel B, Kumar A, Prasad S, Kakoti BB, Kaushik A and Jesawadawala M, 2023. Adenoviral vector-based vaccine platform for COVID-19: Current status. Vaccines, 11(2):432.

Chen J, Chen J and Xu Q, 2022. Current developments and challenges of mRNA vaccines. Annual Review of Biomedical Engineering, 24:85-109.

Chen S, Huang X, Xue Y, Álvarez-Benedicto E, Shi Y, Chen W, Koo S, Siegwart DJ, Dong Y and Tao W, 2023. Nanotechnology-based mRNA vaccines. Nature Reviews Methods Primers, 3(1):63.

Chou RT, Ouattara A, Adams M, Berry AA and Takala-Harrison S, 2023. Supplementary materials for positive-unlabeled learning identifies vaccine candidate antigens in the malaria parasite Plasmodium falciparum.

Chuang Y-M, Alameh M-G, Abouneameh S, Raduwan H, Ledizet M, Weissman D and Fikrig E, 2023. A mosquito AgTRIO mRNA vaccine contributes to immunity against malaria. npj Vaccines, 8(1):88.

Collins WE and Jeffery GM, 2007. Plasmodium malariae: parasite and disease. Clinical microbiology reviews, 20(4):579-592.

De Gregorio E, Caproni E and Ulmer JB, 2013. Vaccine adjuvants: mode of action. Frontiers in Immunology, 4:214.

Desmond A and Offit PA, 2021. On the shoulders of giants—from Jenner's cowpox to mRNA Covid vaccines. New England Journal of Medicine, 384(12):1081-1083.

Dickey TH and Tolia NH, 2023. Designing an effective malaria vaccine targeting Plasmodium vivax duffy-binding protein. Trends in parasitology,

Ellis McKenzie F, Jeffery GM and Collins WE, 2001. Plasmodium malariae blood-stage dynamics. Journal of Parasitology, 87(3):626-637.

Eun H-M, 1996. Enzymology primer for recombinant DNA technology. Elsevier.

Fotoran WL, Silva JRd, Glitz C, Ferreira LCdS and Wunderlich G, 2023. Establishment of an Antiplasmodial Vaccine

Based on PfRH5-Encoding RNA Replicons Stabilized by Cationic Liposomes. Pharmaceutics, 15(4):1223.

Ganley M, Holz LE, Minnell JJ, de Menezes MN, Burn OK, Poa KCY, Draper SL, English K, Chan STS and Anderson RJ, 2023. mRNA vaccine against malaria tailored for liver-resident memory T cells. Nature Immunology, 24(9):1487-1498.

Gergen J and Petsch B, 2021. mRNA-based vaccines and mode of action. mRNA Vaccines:1-30.

Godse SA, Patil SM, Itape PT and Sarjerao V, 2023. Recombinant DNA technology.

Goodswen SJ, Kennedy PJ and Ellis JT, 2023. A guide to current methodology and usage of reverse vaccinology towards in silico vaccine discovery. FEMS Microbiology Reviews, 47(2):fuad004.

Gote V, Bolla PK, Kommineni N, Butreddy A, Nukala PK, Palakurthi SS and Khan W, 2023. A comprehensive Review of mRNA vaccines. International journal of molecular sciences, 24(3):2700.

Grande R, Antinori S, Meroni L, Menegon M and Severini C, 2019. A case of Plasmodium malariae recurrence: recrudescence or reinfection? Malaria journal, 18(1):1-9.

Gross M, 2023. New beginnings for malaria research. Current Biology, 33(6):R203-R205.

Gsell P-S, Giersing B, Gottlieb S, Wilder-Smith A, Wu L and Friede M, 2023. Key considerations for the development of novel mRNA candidate vaccines in LMICs: A WHO/MPP mRNA Technology Transfer Programme meeting report. Vaccine,

Hansson M, Nygren PAk and Sta˚ hl S, 2000. Design and production of recombinant subunit vaccines. Biotechnology and applied biochemistry, 32(2):95-107.

Hassert M and Harty JT, 2023. Alt-RNAtive vaccines elicit anti-malarial TRM cells. Nature Immunology, 24(9):1397-1398.

Hawadak J, Dongang Nana RR and Singh V, 2021. Global trend of Plasmodium malariae and Plasmodium ovale spp. malaria infections in the last two decades (2000–2020): a systematic review and meta-analysis. Parasites & vectors, 14(1):297.

Hayashi CTH, Cao Y, Clark LC, Tripathi AK, Zavala F, Dwivedi G, Knox J, Alameh M-G, Lin PJC and Tam YK, 2022. mRNA-LNP expressing PfCSP and Pfs25 vaccine candidates targeting infection and transmission of Plasmodium falciparum. npj Vaccines, 7(1):155.

Hayashi CTH, Cao Y, Clark LC, Tripathi AK, Zavala F, Dwivedi G, Knox J, Alameh M-G, Lin PJC and Tam YK, 2023. Author Correction: mRNA-LNP expressing PfCSP and Pfs25 vaccine candidates targeting infection and transmission of Plasmodium falciparum. npj Vaccines, 8

Hilleman MR, 1998. Six decades of vaccine development—a personal history. Nature medicine, 4(Suppl 5):507-514.

Hotez PJ, 2023. Vaccine Preventable Disease and Vaccine Hesitancy. Medical Clinics, 107(6):979-987.

Hou MM, Barrett JR, Themistocleous Y, Rawlinson TA, Diouf A, Martinez FJ, Nielsen CM, Lias AM, King LDW and Edwards NJ, 2023. Vaccination with Plasmodium vivax Duffy-binding protein inhibits parasite growth during controlled human malaria infection. Science translational medicine, 15(704):eadf1782.

Iavarone C, O'hagan DT, Yu D, Delahaye NF and Ulmer JB, 2017. Mechanism of action of mRNA-based vaccines. Expert Review of Vaccines, 16(9):871-881.

Jain S, Venkataraman A, Wechsler ME and Peppas NA, 2021. Messenger RNA-based vaccines: Past, present, and future directions in the context of the COVID-19 pandemic. Advanced drug delivery reviews, 179:114000.

Jiménez-Díaz M-B, Möhrle JJ, Angulo-Barturen I and Demarta-Gatsi C, 2023. Using Cryopreserved Plasmodium falciparum Sporozoites in a Humanized Mouse Model to Study Early Malaria Infection Processes and Test Prophylactic Treatments. Microorganisms, 11(9):2209.

Kairuz D, Samudh N, Ely A, Arbuthnot P and Bloom K, 2022. Advancing mRNA technologies for therapies and vaccines: An African context. Frontiers in Immunology, 13:1018961.

Karam M and Daoud G, 2022. mRNA vaccines: Past, present, future. Asian journal of pharmaceutical sciences,

Khan S, Ullah MW, Siddique R, Nabi G, Manan S, Yousaf M and Hou H, 2016. Role of recombinant DNA technology to improve life. International journal of genomics, 2016

Knapp B, Nau U, Hundt E and Küpper HA, 1991. Demonstration of alternative splicing of a pre-mRNA expressed in the blood stage form of Plasmodium falciparum. Journal of Biological Chemistry, 266(11):7148-7154.

Kohli MA, Maschio M, Joshi K, Lee A, Fust K, Beck E, Van de Velde N and Weinstein MC, 2023. The potential clinical impact and cost-effectiveness of the updated COVID-19 mRNA Fall 2023 vaccines in the United States. Journal of Medical Economics, (just-accepted):1-22.

Komori M, Morey AL, Quinones-Molina AA, Fofana J, Romero L, Peters E, Matsuda K, Gummuluru S, Smith JF and Akahata W, 2023. Incorporation of 5 methylcytidine alleviates innate immune response to self-amplifying RNA vaccine. bioRxiv:2023-2011.

Kotepui M, Kotepui KU, Milanez GD and Masangkay FRJMJ, 2020. Global prevalence and mortality of severe Plasmodium malariae infection: A systematic review and meta-analysis. 19(1):1-13.

Kowalczyk A, Doener F, Zanzinger K, Noth J, Baumhof P, Fotin-Mleczek M and Heidenreich R, 2016. Self-adjuvanted mRNA vaccines induce local innate immune responses that lead to a potent and boostable adaptive immunity. Vaccine, 34(33):3882-3893.

Kramps T and Probst J, 2013. Messenger RNA-based vaccines: progress, challenges, applications. Wiley interdisciplinary reviews: RNA, 4(6):737-749.

Langford S, Douglas NM, Lampah DA, Simpson JA, Kenangalem E, Sugiarto P, Anstey NM, Poespoprodjo JR and Price RN, 2015. Plasmodium malariae infection associated with a high burden of anemia: a hospital-based surveillance study. PLoS neglected tropical diseases, 9(12):e0004195.

Li M, Wang Z, Xie C and Xia X, 2022. Advances in mRNA vaccines, International Review of Cell and Molecular Biology No. 372. Elsevier.pp:295-316

Li P, Zhao Z, Xing H, Li W, Zhu X, Cao Y, Yang Z, Sattabongkot J, Yan G and Fan Q, 2016. Plasmodium malariae and Plasmodium ovale infections in the China–Myanmar border area. Malaria journal, 15:1-10.

Liljeqvist S and Ståhl S, 1999. Production of recombinant subunit vaccines: protein immunogens, live delivery systems and nucleic acid vaccines. Journal of biotechnology, 73(1):1-33.

Lombard M, Pastoret P-P and Moulin AM, 2007. A brief history of vaccines and vaccination. Revue Scientifique et Technique-Office International des Epizooties, 26(1):29-48.

Makoni M, 2023. mRNA vaccine against malaria effective in preclinical model. The Lancet Microbe,

Mariano RMdS, Gonçalves AAM, Oliveira DSd, Ribeiro HS, Pereira DFS, Santos IS, Lair DF, Silva AVd, Galdino AS and Chávez-Fumagalli MA, 2023. A Review of Major Patents on Potential Malaria Vaccine Targets. Pathogens, 12(2):247.

Martinez FJ, Guillotte-Blisnick M, Huon C, England P, Popovici J, Laude H, Arowas L, Ungeheuer M-N, Reimer JM and Carter D, 2023. Immunogenicity of a Plasmodium vivax vaccine based on the duffy binding protein formulated using adjuvants compatible for use in humans. Scientific Reports, 13(1):13904.

Maruggi G, Ulmer JB, Rappuoli R and Yu D, 2021. Self-amplifying mRNA-based vaccine technology and its mode of action, mRNA Vaccines. Springer.pp:31-70

Mason DP, McKenzie FE and Bossert WH, 1999. The blood-stage dynamics of mixed Plasmodium malariae–Plasmodium falciparum infections. Journal of theoretical biology, 198(4):549-566.

Matarazzo L and Bettencourt PJJFiI, 2023. mRNA vaccines: a new opportunity for malaria, tuberculosis and HIV. 14:1172691.

McKenzie FE, Jeffery GM and Collins WE, 2002. Plasmodium malariae infection boosts Plasmodium falciparum gametocyte production. The American journal of tropical medicine and hygiene, 67(4):411.

Moyle PM and Toth I, 2013. Modern subunit vaccines: development, components, and research opportunities. ChemMedChem, 8(3):360-376.

Mueller I, Zimmerman PA and Reeder JC, 2007. Plasmodium malariae and Plasmodium ovale–the 'bashful'malaria parasites. Trends in parasitology, 23(6):278-283.

Nakamae S, Miyagawa S, Ogawa K, Kamiya M, Taniguchi M, Ono A, Kawaguchi M, Teklemichael AA, Jian J-Y and Araki T, 2023. Induction of liver-resident memory T cells and protection at liver-stage malaria by mRNA-containing lipid nanoparticles. Frontiers in Immunology, 14

Okamura S and Ebina H, 2021. Could live attenuated vaccines better control COVID-19? Vaccine, 39(39):5719-5726.

Pardi N, Hogan MJ and Weissman D, 2020. Recent advances in mRNA vaccine technology. Current opinion in immunology, 65:14-20.

Piché-Renaud PP, Morris SK and Top KA, 2023. A narrative review of vaccine pharmacovigilance during mass vaccination campaigns: Focus on myocarditis and pericarditis after COVID-19 mRNA vaccination. British Journal of Clinical Pharmacology, 89(3):967-981.

Plotkin S, 2014. History of vaccination. Proceedings of the National Academy of Sciences, 111(34):12283-12287.

Plotkin SA, 2011. History of vaccine development. Springer Science & Business Media.

Plotkin SL and Plotkin SA, 2012. A short history of vaccination. Vaccines, 4

Pourseif MM, Masoudi-Sobhanzadeh Y, Azari E, Parvizpour S, Barar J, Ansari R and Omidi Y, 2022. Self-amplifying mRNA vaccines: mode of action, design, development and optimization. Drug Discovery Today:103341.

Rajahram GS, Barber BE, William T, Menon J, Anstey NM and Yeo TW, 2012. Deaths due to Plasmodium knowlesi malaria in Sabah, Malaysia: association with reporting as Plasmodium malariae and delayed parenteral artesunate. Malaria journal, 11(1):1-7.

Rajneesh, Tiwari R, Singh VK, Kumar A, Gupta RP, Singh AK, Gautam V and Kumar R, 2023. Advancements and Challenges in Developing Malaria Vaccines: Targeting Multiple Stages of the Parasite Life Cycle. ACS Infectious Diseases, 9(10):1795-1814.

Rouf NZ, Biswas S, Tarannum N, Oishee LM and Muna MM, 2022. Demystifying mRNA vaccines: an emerging platform at the forefront of cryptic diseases. RNA biology, 19(1):386-410.

Rutledge GG, Böhme U, Sanders M, Reid AJ, Cotton JA, Maiga-Ascofare O, Djimdé AA, Apinjoh TO, Amenga-Etego L and Manske M, 2017. Plasmodium malariae and P. ovale genomes provide insights into malaria parasite evolution. Nature, 542(7639):101-104.

Satapathy BS, Pattnaik G, Sahoo RN, Pattanaik S, Sarangi AK, Kandi V, Mishra S, Rabaan AA, Mohanty A and Sah R, 2023. COVID-19 vaccines and their underbelly: Are we going the right way? Health Science Reports, 6(9):e1540.

Sehrawat S, Osterrieder N, Schmid DS and Rouse BT, 2022. Can the triumph of mRNA vaccines against COVID-19 be extended to other viral infections of humans and domesticated animals? Microbes and Infection:105078.

Srivastava P and Jain CK, 2023. Computer Aided Reverse Vaccinology: A Game-changer Approach for Vaccine Development. Combinatorial Chemistry & High Throughput Screening, 26(10):1813-1821.

Stern AM and Markel H, 2005. The history of vaccines and immunization: familiar patterns, new challenges. Health affairs, 24(3):611-621.

Tan S, Alameh M-G, Renn JP, Allen JN, Pichugin AV, Duffy PE, Weissman D and Krzych U, 2023. Plasmodium falciparummRNA liver stage antigens induce antibody and liver CD8 TRM and CD8 T Ecell responses in mice. The Journal of Immunology, 210(1_Supplement):241-204.

Taylor WP, Roeder PL and Rweyemamu MM, 2006. History of vaccines and vaccination, Rinderpest and peste des petits ruminants. Elsevier.pp:222-246

Tsoumani ME, Voyiatzaki C and Efstathiou A, 2023. Malaria Vaccines: From the Past towards the mRNA Vaccine Era. Vaccines, 11(9):1452.

Turley JL and Lavelle EC, 2022. Resolving adjuvant mode of action to enhance vaccine efficacy. Current opinion in immunology, 77:102229.

Ura T, Okuda K and Shimada M, 2014. Developments in viral vector-based vaccines. Vaccines, 2(3):624-641.

Veiga GTSd, Moriggi MR, Vettorazzi JF, Müller-Santos M and Albrecht LJFiI, 2023. Plasmodium vivax vaccine: What is the best way to go? 13:910236.

Versteeg L, Almutairi MM, Hotez PJ and Pollet J, 2019. Enlisting the mRNA vaccine platform to combat parasitic infections. Vaccines, 7(4):122.

Vinetz JM, Li J, McCutchan TF and Kaslow DC, 1998. Plasmodium malariae infection in an asymptomatic 74-year-old Greek woman with splenomegaly. New England Journal of Medicine, 338(6):367-371.

Volpedo G, Huston RH, Holcomb EA, Pacheco-Fernandez T, Gannavaram S, Bhattacharya P, Nakhasi HL and Satoskar AR, 2021. From infection to vaccination: Reviewing the global burden, history of vaccine development, and recurring challenges in global leishmaniasis protection. Expert Review of Vaccines, 20(11):1431-1446.

Wang Y, Zhang Q, Zhang W, Chen J, Dai J and Zhou X, 2023. A conserved protein of Babesia microti elicits partial protection against Babesia and Plasmodium infection. Parasites & vectors, 16(1):306.

Ye Z, Harmon J, Ni W, Li Y, Wich D and Xu Q, 2023. The mRNA Vaccine Revolution: COVID-19 has launched the future of Vaccinology. ACS nano, 17(16):15231-15253.

Yerlikaya S, Campillo A and Gonzalez IJ, 2018. A systematic review: performance of rapid diagnostic tests for the detection of Plasmodium knowlesi, Plasmodium malariae, and Plasmodium ovale monoinfections in human blood. The Journal of Infectious Diseases, 218(2):265-276.

Yman V, Wandell G, Mutemi DD, Miglar A, Asghar M, Hammar U, Karlsson M, Lind I, Nordfjell C and Rooth I, 2019. Persistent transmission of Plasmodium malariae and Plasmodium ovale species in an area of declining Plasmodium falciparum transmission in eastern Tanzania. PLoS neglected tropical diseases, 13(5):e0007414.

You H, Jones MK, Gordon CA, Arganda AE, Cai P, Al-Wassiti H, Pouton CW and McManus DP, 2023. The mRNA Vaccine Technology Era and the Future Control of Parasitic Infections. Clinical microbiology reviews, 36(1):e00241-00221.

Zeedan GSG, Abdalhamed AM, Naguib AM, Shalaby SIA, Awad MAM and El Moniem MIA, 2023. An Overview of Adenovirus Vector-based Vaccines against SARS-CoV-2. World's Veterinary Journal:12-25.