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REVIEW ARTICLE

The Impact of Genomic Variability on Vaccine Efficacy against Infectious Diseases in Sub-Saharan Africa

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Abstract

In Sub-Saharan Africa, an area with great genetic variation and a high prevalence of infectious diseases like HIV/AIDS, malaria, and tuberculosis, the study investigates the dramatic effects of genomic variability on vaccine efficacy against infectious diseases. Worldwide, vaccination is still a key component of controlling infectious diseases, but immune responses and vaccine efficacy are influenced by genetic variations in both pathogens and hosts. The unique genetic landscape of Sub-Saharan Africa, influenced by intricate demographic history and environmental factors, impacts disease susceptibility and vaccination reactions, necessitating customised immunisation regimens. The review emphasises that genetic polymorphisms, especially in immune-related genes such as HLA, cytokines, and innate immunity receptors, influence vaccine-induced immunity and disease consequences. Variations in the Plasmodium falciparum circumsporozoite protein gene and human immunological genes impact malaria vaccine efficacy, whereas host genetic variables also influence reactions to BCG and HIV vaccinations. The report emphasises the essential requirement for inclusive genomic research and clinical trials that accurately represent African populations to advance vaccine development and public health strategies, hence enhancing disease prevention and management in the region. Understanding the relationship between genomic variation and vaccine response is crucial for designing effective, long-lasting vaccines tailored to the specific genetic profiles of Sub-Saharan African populations.

Keywords: Genomic Variability, Vaccine Efficacy, Sub-Saharan Africa, Malaria, Host Genetic Polymorphisms.

1. Introduction

The English surgeon Edward Jenner created the foundation for modern vaccination by achieving protection against variola in the 18th century (1). For many years, vaccinations have been vital in managing and averting the spread of infectious diseases and globally they have stopped infectious disease epidemics and saved millions of lives (2). The ability to immunize individuals and populations against deadly and debilitating pathogens has had immeasurable benefits, including the global eradication of smallpox and the near elimination of poliomyelitis (3). The immunity imparted by vaccinations derives from a complex combination of innate, humoral, and cell-mediated immune responses (3, 4). Worldwide, vaccine lay an important role in reducing the burden of infectious diseases generating immunity against microbial infections (2), serving as a vital and cost-effective approach for protecting public health (3).

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COVID-19 vaccinations have showed successful immunity in managing the pandemic (5), leading to a large fall in case numbers in the nations that reached adequate vaccination coverage (1). These advancements are essential for responding to the constantly evolving trend of infections and ensuring public health.

The efficacy of vaccination is affected by multiple parameters relating to the vaccine, the pathogen, and the host (Figure 1). Numerous studies have shown that the host's genetic background (genotype) significantly affects the immunological response to vaccinations, such as those for influenza, Hepatitis B, or measles. In recent years, it has been widely suggested that genetic information may be utilised to forecast vaccine efficacy and assist in the development of more successful, personalised immunisation programs (6). This paper summarises the fundamental concepts of how host genetic differences can influence the diversity of vaccine-induced humoral immunity. Additionally, we examine significant clinical research and the use of mathematical, mechanistic models in identifying therapeutic targets for personalised vaccination techniques.

Pathogen genetic diversity affects vaccine immunogenicity and efficiency (7)(8). However, there is significant individual-to-individual variance in vaccination effectiveness due to host genetic factors (9). The genetic variety of viruses caused by mutations is of great medical and biological relevance, because it greatly influences future treatment options as well as the prevention and diagnosis of infectious diseases (10). Numerous genetic variations of SARS-CoV-2 have been observed to have emerged in different parts of the world (11), indicating that the virus is still evolving quickly (11). Current vaccines may become less effective as a result of this change, necessitating ongoing observation and potential vaccine formula modifications. Variability in immune responses have been documented among individuals despite the success of widespread vaccine administration (5). These variations can be explained by changes in individual genetic make variables (10). Developing effective immunizations that offer long-lasting defense requires knowledge of genetic variability. Within this multifaceted landscape, researchers tend to concentrate more on analysing the role of host genetic elements (5). In the face of developing disease pathogens, this ability to adapt is important to retaining vaccine effectiveness.

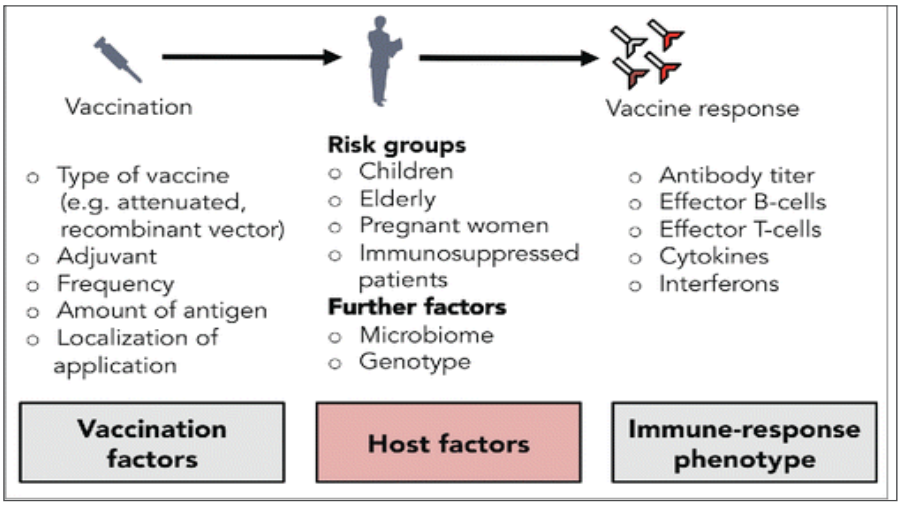

Figure 1. *Factors for successful vaccination (6)*

2. Importance of Studying this in the Context of Sub-Saharan Africa

In Sub-Saharan Africa, where infectious illnesses continue to be a major source of morbidity and mortality (7), investigations into vaccine development and genetic variability are especially crucial (4) as Sub-Saharan Africa is home to approximately 1.16 billion people, about 15% of the world's population (12). Africa is an important place to study human genetic diversity because of its population (13) (figure 2), and differences in climate (14), diet (15), and exposure to infectious disease (16). Clinical trials are essential for enhancing medical knowledge (17), formulating new treatments, and verifying the safety and efficacy of healthcare interventions (18). For these trials to be genuinely effective, diverse representation is required by adding individuals from other ethnicities and genetic lineages, especially those originating from Africa (14). A high illness burden, inadequate healthcare infrastructure, and uneven vaccine accessibility are some of the region's particular problems (19). Developing efficient vaccination plans suited to the unique requirements of the local population requires an understanding of pathogen variability and local epidemiology (7).

Furthermore, diseases like tuberculosis, HIV/AIDS, and malaria have had a major impact on Sub-Saharan Africa and call for focused vaccine development efforts (7). Research must take these aspects into account because the region's varied genetic landscape among populations might also affect vaccine reactions (20)(21). In Sub-Saharan Africa, researchers can improve public health outcomes and vaccine efficacy by concentrating on local settings and genomic heterogeneity. Individuals of African heritage exhibit a heightened prevalence and mortality associated with many specific disease types (13). This gap is particularly evident among persons residing in Africa (22), where the likelihood of mortality before age 75 following a disease diagnosis is approximately double that seen in high-income nations (23). Given the increasing incidence and mortality rates of diseases in Africa, this continent demands prioritization in clinical trial initiatives.

Figure 2. *Map of Africa showing Sub-Sahara Africa (countries below the grey area) (24)*

3. Genomic Diversity and Infectious Disease Burden in Sub-Saharan Africa

3.1 Overview of Genomic Diversity in Sub-Saharan African Populations

Africa, generally considered the cradle of humanity, possesses the greatest genetic variety among its populations compared to other continents (25). Genetic and archaeological evidence suggests that anatomically modern humans predominantly inhabited sub-Saharan Africa until the out-of-Africa migration approximately 75,000 years ago (26). Sub-Saharan Africa is known for having a high level of genetic diversity (22) due to the continent's diverse climatic conditions and complicated demographic history (27). This genetic variability poses high level of significance as it creates opportunities to improve pharmacogenomics (16), better understanding gene interactions and find new genetic variants presented by this diversity (25).

The genetic landscape of Sub-Saharan Africa illustrates a rich array of ancestral lineages and Studies have identified numerous distinct genetic clusters corresponding to different ethnic groups and geographic regions, highlighting the intricate population structure of the continent (28). Given the substantial genetic variation among African populations, there is a significant need for novel approaches to address different health concerns prevalent in Africa (25). For example, the distinct genetic composition of these groups may affect their vulnerability to certain illnesses as well as the effectiveness of medications and vaccinations. This is especially true for infectious diseases, where immune responses and disease outcomes can be impacted by genetic differences (29). Many prevalent diseases, such as malaria, HIV/AIDS, and sickle cell anemia, display varying prevalence and severity across African communities, impacted by both genetic and environmental factors (28). Additionally, identifying particular genetic markers linked to diseases that are common in different communities can result in better diagnosis and tailored treatments, bridging the gap in healthcare disparities that present globally (30).

Malaria continues to be a significant concern among vector-borne infectious illnesses in sub-Saharan Africa, despite deliberate attempts to combat it and its curable and preventable nature (31). Studies

have shown that malaria vaccines may not protect all communities or individuals equally (31) due to different vaccine-specific parasite and human genetic polymorphisms such as the HLA type (32). Efforts have been made since 1940 to develop vaccine for malaria and (32). The current malaria vaccines RTS,S/AS01 (RTS,S) (33) that has been rolled out in Kenya, Malawi, and Ghana (31) only produces modest short lived protection (32). Specifically the response of individuals to RTS,S/AS01 vaccination may be influenced by genetic variations in genes that encode antigen presentation (33), cytokine generation (8), or immune cell activation and differentiation (32). These vaccines are made of *Plasmodium falciparum* circumsporozoite protein (PfCSP) (34), however, variations in the gene raise questions about strain-specific responses (8) and the long-term efficacy of these vaccinations (35). It has been demonstrated that the genetic diversity of the malaria vector, "Anopheles funestus", affects how well vector control techniques like indoor residual spraying (IRS) (29) and insecticide-treated nets (ITNs) work (29). According to recent genomic research, some genetic variations within "Anopheles" populations may impart pesticide resistance, making control efforts more difficult and perhaps compromising the efficacy of vaccines by changing the dynamics of transmission (36)(37). A comprehensive understanding of genetic variants affecting the presentation of P. falciparum antigens to the immune system and enhancing the efficacy of the RTS,S/AS01 malaria vaccine must be promptly established. (32).

Genomic diversity may also have an impact on the effectiveness of TB vaccinations. Different immunological reactions to the Bacillus Calmette-Guérin (BCG) vaccine may result from differences in host genetics between populations (20). According to studies, certain immune-related genes' single nucleotide polymorphisms (SNPs) may affect how well a vaccine protects against tuberculosis (30). Therefore, it is essential to comprehend the genomic makeup of African populations in order to create more potent TB vaccines that are suited to their distinct genetic makeup.

HIV presents another major challenge where genetic diversity affects vaccine development. HIV's high rate of mutation causes a variety of virus strains to circulate throughout Sub-Saharan Africa, which makes vaccine development more difficult (28). Furthermore, the course of the disease and vulnerability to HIV infection might be influenced by host genetic variables. Numerous genetic loci linked to HIV resistance have been found through research, highlighting the necessity of tailored vaccine development strategies that take into account each person's unique genetic background (38). In addition to HIV, TB, and malaria, genetic diversity may also have an impact on other infectious diseases that are common in Sub-Saharan Africa. For instance, differences in immune response-related genes can influence a person's vulnerability to illnesses including viral hepatitis and schistosomiasis (28). In order to detect these differences and their consequences for disease preventive and treatment techniques, it is imperative that genetic research be conducted continuously. The knowledge of the genetic variety found in Sub-Saharan African populations is essential for both evolutionary biology and the management of infectious disease-related public health issues. These obstacles have made it impossible to create vaccines against hypervariable and highly complex pathogens, including HIV, HCV, coronaviruses, malaria-causing Plasmodium, hookworm, and Mycobacterium tuberculosis, using the conventional empiric technique (39). Better interventions catered to the distinct genetic landscapes of these populations would be made possible by increased representation of African genomes in research.

3.2 Genomic Factors Influencing Vaccine Efficacy

3.2.1 Role of genetic polymorphisms in immune response to vaccines

Genetic polymorphisms are acknowledged to effect responses to both viral infections and vaccination (30). In reality, previous studies have demonstrated that with respect to conventional vaccines, such as Measles Mumps Rubella MMR, Hepatitis B Vaccine HBV, and influenza, the causes for individual variability in immune responses following immunisation can be significantly explained by changes in genetic variables (3,40). Vaccination effectiveness is influenced by various vaccine, pathogen, and host-related factors (19). Host genetic polymorphisms have been demonstrated to correlate with immune response post-vaccination (8), vaccine-related adverse events (30), and disease severity across diverse infectious illnesses (41). Notable occurrences encompassed the association of polymorphisms in the mannose-binding lectin (MBL)–2 gene (42), which encodes a calcium-dependent protein crucial for innate immunity and linked to heightened vulnerability to several infections (43). Multiple polymorphisms in the promoter regions of Interleukin (IL)–10 and change in the level of IL-10 production are linked to the control of cellular immune responses (44), while

Toll-like receptor (TLR) genes are connected with the initiation of innate immune responses (4) and disease severity (41). The polymorphism of genes associated with membrane trafficking and antigen processing has been demonstrated to significantly affect human responses to influenza vaccination. The effect of genetic polymorphism in the major histocompatibility complex (MHC) region on the variety of immunological responses has been the subject of several studies (45). When people who failed not respond to the hepatitis B vaccine showed a significant excess of HLA-DR7 and a complete lack of HLA-DR1, the influence of MHC variations on the immune response to the vaccine was first demonstrated (46). The degree or kinetics of the HBV vaccine-induced antibody response or cell proliferation have been linked to polymorphisms in the IL1 gene family, IL2, IL4, IL6, IL10, IL12β, TNFα, GNB3 (47), and haptoglobin (47).

Human leucocyte antigens (HLA) genes have been found to be important determinants of adaptive immune responses to a range of vaccinations (48). The human leukocyte antigen (HLA) system on chromosome 6 constitutes the most polymorphic genes within the human genome (49) and is widely recognised for its possible pathological impact (50). The human leukocyte antigens (HLA) encoded by genes within the major histocompatibility complex display an impressive degree of variability (51). Most somatic cells exhibit HLA class I gene expression, however the expression levels differ across various tissues. HLA class II genes are generally expressed by a specific population of immune cells, such as B cells, activated T cells, thymic epithelial cells, dendritic cells, and macrophages (52). A review of studies from the previous decade identifying genetic differences as a cause of disparate vaccine reactions is offered in Table 1. Smatti *et.al*., (2022) demonstrated that about 30% of inter-individual variation in measles vaccine specific humoral immunity is due to genetic polymorphisms of the HLA cytokines, innate immunity, viral receptor and other genes (53). Nishida *et.al.,* (2018) reported that Individuals possessing specific HLA class II alleles (DRB1*01:01, DRB1*08:03, DQB1*05:01, and DPB1*04:02) have shown enhanced humoral immune responses following hepatitis B vaccination, this is in contrast to several HLA alleles, including HLA-DQB1*04:01 which have been linked to diminished vaccine induced antibody synthesis (49). An individual genetic factor can influence the susceptibility or disease progression to chronic infection (45).

Moreover, ABO, APOE, ACE2, and HLA are additional genetic factors that have been identified as significant moderators of IgG and neutralising antibody responses to SARS-CoV-2 vaccines (54). Changes in the strength or kinetics of the immune response to the vaccination have been associated with gene polymorphisms (55), including those in the IL-1 family, TNF-α, GNB3 (guanine nucleotide-binding protein) , haptoglobin, IL-2, IL-4, IL-6, IL-10, IL-12β, and interferon-γ (IFN-γ) (46). In previous research involving 346 people, Specific SLAM (rs3796504 and rs164288) and CD46 (rs11118580 and rs2724384) polymorphisms that showed an allele dose-related decrease in measles virus (Edmonston vaccine strain) antibody response were found (56). Both H and nucleocapsid (N) measles proteins' MHC class II antigen presentation is improved when human CD46 is expressed in murine B cells, suggesting that the CD46 receptor plays a crucial part in measles virus antigen presentation (57). Particularly, several amino acid residues, including Arg59 in the measles virus binding domain of the CD46 receptor and Asn481 in the H protein of the measles virus (40), are critical for viral fusion and host cell entrance (57). Consequently, genetic variations in the CD46 receptor may affect receptor kinetics and functionality, thereby impacting future immunological responses to viral vaccinations.

Table 1. *Demonstration of genetic variation as a factor in vaccine response (52)*

Type of vaccine	Main locus(i)/ gene(s) studied	Main conclusion
MMR-II	*TLR3|RIG-I*	A TLR3 polymorphism has functional effects on receptor expression and cytokine response.
MMR-II	*IL4|IL7R|IL18|IFNA1|IL6ST| IFNA21|TNF|IL6|IFNA8| IFNA10|IL1R2|CSF2RB|IL12B| IL1RN*	New plausible genetic determinants, including IL7R polymorphisms, regulate measles vaccine-induced immunity in a race-specific manner.
MMR-II	*CD46|IFI44L*	Common CD46 and IFI44L SNPs are associated with measles-specific humoral immunity.
HepB	*HLA-DPB1*	*HLA-DBP1* is significantly correlated with response to booster HepB vaccination in adolescent who had received postnatal active HepB vaccination.

MenC	*CD44|TLR3*	Single Nucleotide Polymorphisms in the *TLR3* and *CD44* Genes Are Associated with Persistence of Vaccine-Induced Immunity to MenC vaccines.
MCV4	*TLR2|TLR4|TLR9|FCγRII*	For HIV-infected youth, the initial antibody response to MCV4 is associated with variants in *TLR2* and *TLR4* while the long-term response is associated with genetic polymorphisms in *TLR9* and *FCγRII.*
EV71	*EEA1|TRIM59|ABCA7|HLA-DRB1|HLA-DQA1| HLA-DQB1*	It is a meaningful attempt on the comparison of genomic profiles between potent and ineffective immune responders induced by EV71 vaccine, and several candidate potentially detrimental genes were identified.

3.3 Case Studies Where Vaccine Efficacy Varies across Populations Due to Genetic Diversity

Given the overall genetic diversity and data regarding susceptibility and resistance patterns among different human populations of various diseases, vaccine efficacy should differ among the specific human population targeted (58). According to the study by Cruz Cisneros *et al.,* Diverse Outbred DO mice inoculated against SARS-CoV-2 demonstrated large levels of variance in vaccine-induced neutralizing antibody responses. While the majority of the vaccinated mice were protected from virus-induced illness, similar to human populations, they detected vaccination breakthrough in a fraction of animals (59). A recent study analyzed the degree of polymorphism in 550 children were recruited and randomized to receive Trivalent Influenza Vaccine (TIV) (60), 376/535 (70.3%) of them were classified as responder based on having post-vaccination titer ≥40 for the three vaccine strains, 181/535 (33.8%) of them were classified as responder based on ≥4-fold rise (60). The variability in vaccine response among children is associated with genetic factors that may affect the degree of immune protection. Also, in a genome study done by Mentzer *et.al*., (2023), it was discovered that persons expressing HLA-DQB1*06 alleles exhibit greater antibody responses against SARS-CoV-2 spike protein and the RBD after immunisation with both ChAdOx1 nCoV-19 and BNT162b2 vaccines than individuals not carrying this allele (61). These variations in vaccination responses have an effect both protective efficacy and the longevity of protection (4). These diversities in Sub-Saharan Africa enables researchers to comprehend the effects of interventions on a wider range of people, which aids in identifying possible differences in treatment response, adverse effects, and overall efficacy (14). According to the study done by Ryu *et.al.,* (2024), HDAC9 gene's SNP rs7795433 was identified as the promising candidate gene influencing antibody production post SARA-CoV-2 vaccination (5). They also examined the allele frequency of HDAC9 SNP, the A allele and A allele carriers (AA + GA) were more likely to be in the high-antibody group, while the G allele and G allele carriers (GA + GG) were more likely to be in the low-antibody group, and after performing RT-PCR on three individuals from each AA, GA, GG genotype, and antibody group to confirm HDAC9 gene expression differences (5). The results show that in the high-antibody group, the AA genotype had the highest expression, while in the low-antibody group, the GG genotype had the highest expression.

3.4 Implications for Vaccine Development and Performance in Sub-Saharan Africa

In Sub-Saharan Africa COVID-19 vaccination efforts have faced significant challenges, resulting in the region lagging behind the rest of the world in achieving widespread coverage (12). Sub-Saharan Africa is a region that has been of particular concern in the quest for global vaccine coverage (13) despite being the world's poorest region where the pandemic impinged on already vulnerable livelihoods (62). Sub-Sahara Africa constitutes almost two-thirds of the global poorest population (63). Sub-Saharan Africa is home to 433 million people living below the international absolute poverty line (64). A work done by Kayanda *et.al.,* (2021) revealed high acceptance rate of COVID-19 vaccine with at least 4 in five respondents signaling their willingness to be vaccinated in all but one of the Sub-Sahara countries (65). A significant proportion **(**14–34%**)** of individuals of African descent were found to harbor a unique genetic variant in the CYP2D6 gene (66), which is responsible for liver metabolism of Tamoxifen, a common breast cancer treatment (66). This genetic difference reduces vaccine efficacy, meaning African patients may not receive the full therapeutic benefit, leading to poorer treatment outcomes. However, these acceptance rates sometimes do not translate into actual vaccination rates, with access to vaccines, rather than hesitancy, being a primary barrier (67). Also, while acceptance rates have generally been generally high, there have been instances of hesitance that are influenced by factors such as safety concerns about side effects (68).

3.5 Challenges in Vaccine Development and Deployment

The availability of comprehensive genomic data is critical for vaccine development, especially for pathogens with high genetic variability. In a recent analysis of 1,091 high-coverage African genomes, 67,795 structural variations were found; 6,414 of them were unique when compared to databases already in existence (22). In the world's poorest region, Sub-Saharan Africa, the pandemic affected livelihoods that were already insecure (65). Furthermore, there is generally little reliable data available in Sub-Saharan Africa on topics like vaccine acceptance or access hurdles that can guide the implementation of vaccination campaigns (12). Due to the availability of genetic data from American, European, and Asian populations, Africa has been excluded from the majority of contemporary scientific advancements and judgements (69,70), particularly those pertaining to precision medicine and vaccine production (69). Insufficient African genetic data hampers researchers' ability to predict vaccination efficacy among various African ethnic groups, resulting in poor vaccine compositions. The vaccines developed may not be tailored to the distinct genetic variety of African populations, thereby diminishing their efficiency. According to the findings, more inclusive genomic research that includes African individuals is vital to enhancing our knowledge of genetic variation and how it affects health and disease (28). The absence of representation in population frequency databases considerably complicates the therapeutic interpretation of genetic data in Africa (55). Efforts to bridge this disparity are essential for enhancing health outcomes and ensuring equitable healthcare solutions throughout the continent.

A mere fraction of African genomic data is accessible to aid in global disease prevention and management efforts, resulting in a genomic data deficit (69), leading to biases in vaccination efficacy assessments (71). The under-representation continues to hinder several African nations from achieving the necessary vaccination coverage (72). These disparities in representation may hinder the generalisation of trial results to the full range of intended patient populations and could obstruct scientific progress for specific at-risk persons who would derive significant benefits from the trial outcomes. The unequal impact of infectious diseases on African American, Latin, and Native American populations renders it ethically unacceptable to perform or publish research that fail to specify whether the variables examined influence minorities differently (32). The design and successful conduct of worldwide standard Good Clinical Practice (GCP) vaccine trials in resource-constrained settings are challenging but crucial for generating effective vaccines for these populations (73). Early COVID-19 vaccination studies were criticised for inadequate representation of minority groups, even though these populations were disproportionately impacted by the disease (17). Given the pressing requirement for a safe and effective vaccination, COVID-19 vaccine clinical trials encountered significant challenges in efficiently enrolling patients while maintaining broad representation (74). Furthermore, political and economic impediments may abruptly disrupt critical vaccine studies in the area. In 2025, South African researchers were progressing with an HIV vaccine experiment utilising mRNA technology tailored to local HIV strains (75). The abrupt cessation of funding due to political decisions resulted in the indefinite suspension of this promising research, highlighting the vulnerability of vaccine development initiatives in Sub-Saharan Africa to foreign political influences (75). This may affect the generalizability of clinical trial outcomes, as the efficacy and safety of vaccines can vary by race or ethnicity, ultimately diminishing public confidence and vaccine acceptance (17). Initiatives to improve diversity in trials necessitate focused recruitment techniques and community involvement to mitigate past distrust and logistical obstacles.

Effective vaccine development relies on robust data collection systems, but these are often undermined by inadequate infrastructure, funding constraints, and ethical concerns. Additionally, logistical issues such as sample storage, transport, and processing further complicate data collection efforts (76). A major obstacle is the inadequate infrastructure for vaccine storage and distribution. The World Health Organization (WHO) assessed 34 African countries and found that around 30% have gaps in cold-chain refrigeration capacity in over half of their regions. Moreover, just 28% of health facilities in Sub-Saharan Africa have access to a stable power supply, providing considerable challenges for vaccine preservation and distribution (77). In many low- and middle-income countries (LMICs), poor data-sharing standards and fragmented health systems hinder the collection and integration of clinical trial data. Financial limitations adversely hinder vaccine research and development in the region (76). Although long-term investment is necessary for genomic research, many African nations devote less than 1% of their GDP to scientific research and development (78).

Research objectives are frequently determined by external agendas rather than the unique health requirement of local communities as a result of reliance on foreign grants and international finance. Establishing and sustaining large-scale genomic research projects becomes difficult in the absence of consistent domestic investment. The enormous expenses associated with vaccine research, coupled with the risk of failure, inhibit investment. Additionally, political decisions can unexpectedly end financing, as illustrated by the 2025 cessation of U.S. aid that halted HIV vaccine trials in South Africa. This sudden funding loss led to the indefinite halting of promising research endeavours (75).

3.6 Ethical and Social Considerations

Issues of consent, privacy, and data sovereignty.

Ethical considerations linked to privacy and informed permission may arise when gathering sensitive health data. For instance, during the COVID-19 pandemic, ethical permissions for accessing clinical metadata slowed genetic surveillance efforts in numerous regions (79). The lack of adequate ethical norms and legislation can lead to exploitation and mistrust among the locals. Ensuring informed consent, preserving participant rights, and maintaining transparency are vital to establish community confidence and encourage participation in clinical studies (80). Obtaining genuine informed consent in Sub-Saharan Africa is hard due to cultural, language, and educational variables (81,82). In many communities, decisions are made collectively, and the concept of individual consent may be unfamiliar. For instance, in a rural community in Senegal, it was discovered by researchers conducting a pertussis vaccine experiment that consent was usually obtained from community leaders on behalf of all eligible members, rather than from individuals themselves (83). Additionally, challenges of data sovereignty particularly in LMICs arise when genomic or clinical data collected locally are held by external companies or exploited without sufficient benefit-sharing agreements (84). These ethical challenges underline the necessity for transparent governance structures that stress justice and respect for individual rights

Sub-Saharan African countries comprises 48 countries of which 22 are low income, 19 are lower middle and 6 upper middle-income, with only one which is high-income country (15). Vaccine inequity is a pressing issue in the Sub-Saharan Africa region (69). They may encounter uncertainties in acquiring vaccines due to diminished purchasing power relative to high-income countries (HIC) during negotiations with vaccine makers (85) as vaccine nationalism from high-income countries results in restricted access to essential vaccines required to eradicate pandemic in low-income countries (86). Low and middle-income countries (LMIC) encounter distinct obstacles in vaccine acquisition due to limited financial resources and a lack of expertise and technological capability for domestic vaccine production (85). They may confront problems in getting vaccines due to lower purchasing power relative to high-income countries (HIC) during talks with vaccine makers (85). Consequently, they depend more on multilaterally negotiated frameworks or bilateral funding to obtain new technologies.

3.7 Future Directions and Opportunities

3.7.1 Personalized Vaccine Approaches

Potential for vaccines tailored to genetic profiles.

Personalized vaccination has the potential to modify the effectiveness of vaccines as it accounts for genetic variations by tailoring vaccines to individual genetic makeup, variations in immune response and environmental factors (87). Genetic markers predict how well an individual will respond to a particular vaccine, predict vaccine efficacy and adverse reactions, and this promotes the production of vaccines that are more effective for specific genetic subgroups, minimizing adverse reactions and enhancing overall vaccine efficacy (88). Vaccines designed with genetic specificity may elicit stronger immune response given the significant genetic divert in immune-related genes (such as HLA and TLR variants) in the Sub-Saharan African population (32). Personalized vaccination program could guarantee greater levels of immunity for illnesses like influenza, for which the available vaccinations have differing degrees of efficacy, especially in children who are most at risk. A shortage of information on how the immune response develops, genetic variability in both pathogens and hosts that affects the immune response, environmental factors like obesity, geographic factors like the difficulty of maintaining a cold chain in tropical climates that could lower vaccine usage or efficacy, and licensing or regulatory issues are just a few of the barriers to the development of personalized vaccines (39,89). Humans can be susceptible to infectious diseases in different ways dependent on their immune system, genetic background, and underlying medical concerns (22). By creating immune responses that are particular to each patient and more effective, personalized vaccinations seek to address these differences (87). Also referred to as high-throughput sequencing (HTS), this technique allows for a thorough examination of a person's genetic composition, enabling scientists

to find genetic variants that could affect the safety or effectiveness of vaccines (90). NGS generates millions of sequencing reads in a single run at a reasonable cost. Personalized vaccinations that target particular genetic alterations linked to therapy response or disease susceptibility can be created by utilizing NGS data (91). NGS helps determine who is likely to benefit from particular vaccines or need alternate immunization techniques by enabling patient stratification based on genetic profiles (92). Through the discovery of single nucleotide polymorphisms (SNPs) linked to immunological diseases (91), NGS can direct the creation of customized vaccinations that are safer and more efficient for sub-Saharan diverse population. Furthermore, by identifying genetic markers that predict vaccine efficacy and adverse reactions, and by examining how genetic variations across diverse populations influence vaccine responses and disease susceptibility (27), it is feasible to develop vaccines that are more effective for particular genetic subgroups. This strategy seeks to reduce adverse effects and improve the overall effectiveness of immunization programs by considering genetic diversity.

3.8 Genomics-Guided Vaccine Development

Genomics informed vaccine development utilizes genomic epidemiology to improve vaccination efficacy by analyzing the genetic diversity of pathogens and populations. There is an urgent need to modernize and strengthen health services and public health surveillance as it has been demonstrated by researchers that epidemic response systems are a key aspect of health systems resilience. This approach has been crucial in directing public health interventions, especially during the COVID-19 pandemic, where whole genome sequencing (WGS) of SARS-CoV-2 variants facilitated vaccine development and risk evaluation (93). Mapping the pathogen evolution and identifying genetic markers associated with vaccine resistance aid researches to develop broad spectrum vaccines that target conserved antigens across multiple strains (94). The integration of genomic data into vaccine development also facilitates the identification of potential immune escape variants, ensuring that vaccines remain effective against evolving pathogens (84). The high genetic diversity in pathogens like Plasmodium falciparum and Mycobacterium tuberculosis complicates high vaccine development efforts in Sub-Saharan Africa (7). Genomic surveillance of P. falciparum has uncovered significant genetic diversity, complicating the development of universally effective malaria vaccines (94). The genetic flexibility of M. tuberculosis strains in the region requires vaccines capable of targeting varied bacterial populations (7). The integration of pan-genome analysis with reverse vaccinology enables scientists to develop next-generation vaccinations that preemptively address genetic variations in pathogens, so ensuring sustained efficacy. Reverse vaccinology relies on the combined use of immunological and genomic information to identify relevant protein antigens for diagnostic or vaccine purposes (95). The combination of artificial intelligence, artificial neural networks and other bioinformatics tools can other bioinformatics tools can be combined with reverse technology to generate accurate results leading to the generation of potential subunit vaccine (96). Facilitating universal access to real time whole genome sequencing data can enhance the efficacy of public health policy and vaccine development, hence improving preparedness for future pandemics (84)

3.9 Inclusive Clinical Trials: Strategies for Increasing African Representation in Trials

Enhancing African representation in clinical trials is crucial for guaranteeing the efficacy and safety of vaccinations and treatments across varied populations. Africa, home to approximately 17.7% of the global population, accounts for less than 2% of registered clinical studies worldwide (14). The under-representation presents considerable issues, since it restricts the availability of evidence regarding treatment efficacy in African populations, potentially resulting in diminished effectiveness or heightened adverse effects. The amount of African genomic data can be increased by making consent to share aggregate frequency data a crucial part of the research toolkit (97), encouraging researchers who have African data to share their data using public resources like ClinVar, DECIPHER, gnomAD, and AVGD, and encouraging them to use MatchMaker Exchange (55). Increase in funding to scale up the production of African genomic data that will be more representative of the continent's geographical and ethnolinguistic variation (55). To guarantee that vaccines are safe and effective for a variety of people, inclusive clinical trials are crucial. African groups have in the past been marginalized in clinical trials, which could result in differences in the safety and effectiveness of vaccines. Scaling up clinical trials in Africa is a public health priority, according to a 2024 World Health Organization (WHO) article, because it improves access to life-saving medications and vaccinations and strengthens healthcare interventions (98). Clinical studies conducted in Sub-Saharan Africa enable

the evaluation of vaccinations in light of regional epidemiological, genetic, and environmental factors. This strategy not only increases the applicability of study results but also promotes vaccine uptake and public trust in African communities. Additionally, empowering regional scientists and institutions and enhancing local research capacity through inclusive trials help to enhance healthcare in a sustainable way.

4. Conclusion

In conclusion, the considerable genomic variability within Sub-Saharan African populations significantly influences vaccine efficacy against prevalent infectious diseases such as malaria, tuberculosis, and HIV/AIDS. This genetic diversity affects both pathogen characteristics and host immune responses, leading to variable vaccine outcomes across different communities and individuals. Understanding the complex interplay between host genetic polymorphisms particularly within immune-related genes like HLA, cytokines, and innate immunity receptors and pathogen variability is crucial for developing more effective, tailored vaccines. Enhancing representation of African genomes in research and clinical trials is imperative to address the unique genetic landscape and disease burden in the region. Such efforts will facilitate the design of vaccines and immunization strategies that are better suited to the genetic profiles of Sub-Saharan African populations, ultimately improving public health outcomes and controlling infectious diseases more effectively in this high-need region.

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