The immune divide: factors influencing immune variation and differences in vaccine responses

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Chapter 1

General introduction and thesis outline

Introduction

Vaccines represent a significant milestone in modern medicine, second only to clean water and sanitation for reducing morbidity and mortality from infectious diseases[1-3]. However, immune systems vary significantly across populations, resulting in variations in immune response to vaccines[4-8]. Understanding the factors associated with immune variability that led to differences in vaccine responses is critical to addressing poor vaccine efficacy in populations that need it the most. Leveraging advanced single-cell technologies such as Mass Cytometry (CyTOF)[9], conventional flow cytometry [10],16S rRNA Sequencing[11], other omics technologies[12-14], and advanced data analysis, researchers have been able to dissect the factors driving immune variability across different populations. These tools have also shed light on the underlying factors linked to variations in immune responses to vaccines as further demonstrated below.

Genetics, sex and age

Immune variability is partly driven by genetic background [4, 7, 15-18]. Human genetic factors such as HLA polymorphisms[19, 20], PRRs [21, 22], and cytokine production genes[21], are linked to vaccine response variability. For example, individuals with certain HLA haplotypes show higher immune responses to HIV [23] and malaria vaccines[24, 25]. Beyond genetics, sex differences significantly impacts immune variation [26, 27], with women typically generating higher antibody titers to most of the vaccines than men[28-30]. However, gender roles in low- and middle-income countries (LMICs) can confound these differences[33]. Age also modulates immune variability, especially at the extremes of life in infants[34], and the elderly due to less developed or reduced activity of the immune system[35-38]. This consequently causes poor vaccine responses in both age groups[39-42]. It is important to note that age is also influenced by extrinsic factors, including environmental influences, which play a role in immune-biological ageing.

Geographical location and seasons

Non-genetic factors often play a larger role, particularly in adaptive immunity, which is more susceptible to environmental influences[4, 7, 15-18]. Immune profiles vary between HICs and LMICs [43-45], and between rural and urban settings[44, 45]. Similarly, immunogenicity to

vaccines differs in similar patterns, for example, vaccine immunogenicity was higher in the UK and Switzerland compared to Senegal, Malawi, and Uganda[46, 47]. Higher immunogenicity to tetanus and influenza vaccines has been also observed in semi-urban compared to their rural counterparts[48, 49]. Evidence suggests that dry and wet seasons influence immunological differences[50], higher antibody levels have been observed for vaccines administered during wet seasons compared to dry seasons in some populations[51, 52].

Infections/Pathogen factors

Pathogens significantly shape immune system function, contributing to immune variation. For instance, cytomegalovirus (CMV), which infects over 90% of individuals in LMICs, is strongly linked to immune variation and impairs vaccine responses, such as those for Ebola[53-55]. Similarly, Schistosoma infection skews the immune system [44, 56] and is associated with reducing vaccine efficacy for hepatitis B[57], BCG [58], TT[59], and measles vaccines[60]. Furthermore, malaria, endemic in many tropical regions, is linked to immune variation [61-64] and is associated with lower antibody responses to vaccines like measles[65], tetanus[66], *Haemophilus influenzae* type B, *Salmonella typhi*, and *Neisseria meningitidis*[67]. Ectoparasites such as tsetse flies, kissing bugs, fleas, and ticks, can also drive immune variations through compounds they inject, though their impact on vaccines remains uncertain [68, 69]. Additionally, chronic infections such as HIV, tuberculosis, and hepatitis C virus (HCV) also contribute to immune variation and affect vaccine efficacy/immunogenicity [70].

Lifestyle and socioeconomic factors

Lifestyle factors such as smoking, exercise, sleeping and alcohol consumption are linked to immune variation[71]. Cigarette smoking is known to affect both innate- and adaptive immunity[72], leading to increased leukocytes and reduced NK cell numbers, serum immunoglobulin levels and poor vaccine efficacy/immunogenicity[73-75]. While socioeconomic status (SES) is complex and intertwined with other factors, making it difficult to isolate, low SES is linked to higher exposure to pathogens, poorer nutrition, and limited access to healthcare, all of which contribute to immune variation[76]. This, in turn, has been linked to reduced vaccine efficacy as seen with vaccines like polio [77] and oral rotavirus [78, 79]. Diet is vital for immune function, fueling both innate and adaptive systems[80, 81].

Malnutrition is linked to poor disease control and reduced vaccine responses[82]. Additionally, essential nutrients like iron and vitamin D also influence immune variation and vaccine efficacy based on their availability.

Microbiome

The microbiome significantly influences immune system variation through interactions with immune cells, affecting their development and regulatory functions[83]. Variations in microbiome composition are linked to differences in immune profiles and immune response to vaccines [84, 85]. Additionally, specific microbial populations can induce distinct immune profiles, underscoring the role of personalized microbiota in shaping immune variation[86, 87]. Although not always the case, individuals with similar microbiomes, regardless of location, tend to have comparable vaccine responses, as seen in infants from Ghana, Pakistan, and the Netherlands[88, 89]. Certain bacteria, like *Bifidobacterium longum*, enhance vaccine responses to tetanus, BCG, and Hepatitis B[90], while others, like *Proteobacteria*, are negatively associated with vaccine efficacy[40]. Factors such as delivery method at birth, diet, infections, and medications also shape microbiomes[91].

Pre-existing immunity

Pre-existing immunity can reduce vaccine efficacy. For instance, exposure to non-tuberculous mycobacteria (NTM) has been linked to lower BCG efficacy against *Mycobacterium tuberculosis*[92], similarly, exposure to Malaria has been associated with reduced or no change in antibody levels after administration of malaria vaccines[93]. In the case of yellow fever, prior vaccination can impair the boosting effect of the Yellow Fever vaccine[94], though some flaviviruses, such as dengue, benefit from prior exposure to related viruses [95]. Also, the natural infections or previous vaccinations with Ebola [96] or COVID-19[97, 98] vaccines lead to higher antibody production after subsequent vaccinations. Possibly this is due to differences in vaccine type and mechanism of action of vaccines[99].

Vaccine-related factors

Vaccine factors, such as differences in Yellow Fever vaccine strains (17D-204, 17D-213, and 17DD) used by different countries, can cause variations in vaccine efficacy/immunogenicity[100]. Dosing and schedules vary and can be linked to variations in vaccine efficacy[101][103]. Additionally, adjuvants as seen with influenza[104] and hepatitis B vaccines[105].

Baseline immune status

Finally, baseline immune status is associated with variation in vaccine response. All host factors discussed above can potentially determine the status of baseline immune status(BIS)[106]. BIS has been linked to a diversity of vaccine responses [107-110]. Baseline immune status, both innate and adaptive level, if optimized before vaccination can help improve the vaccine responses.

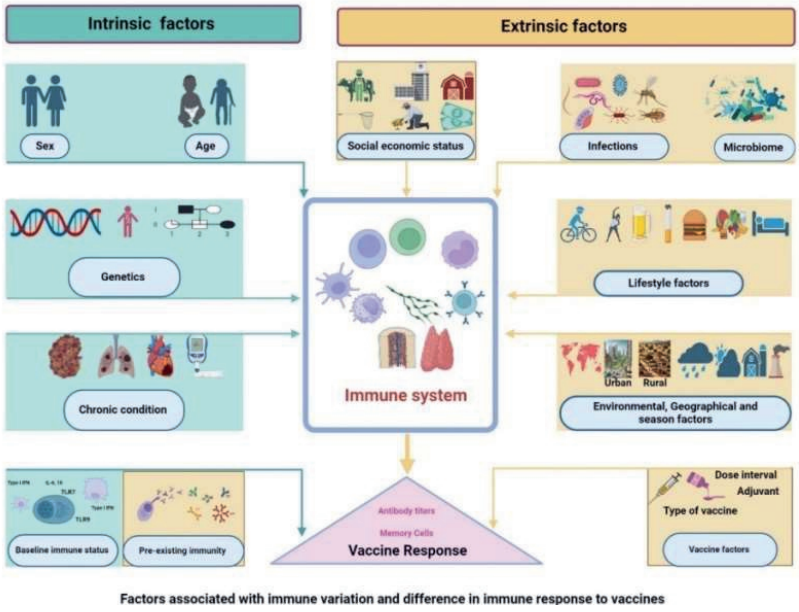

Figure 1: The factors associated with immune variation and differences in immune response to vaccines.

Potential mechanisms of pathogen-driven vaccine hypo-responsiveness

To move beyond observed associations and understand why vaccines underperform in certain populations, it is essential to explore the underlying immunological mechanisms. While this section enumerates pathogen-associated variations in vaccine efficacy, the mechanistic underpinnings such as immune exhaustion (characterized by sustained expression of PD1, TIM3, CTLA4, and diminished effector function), chronic immune activation marked by CD38+HLA-DR+ cell profiles, skewed T helper cell polarization (favoring regulatory or TH2 over TH1 responses), and structural alterations in lymphoid tissues are further dissected in **Chapter 2**. These immune dysregulations emerge in response to persistent exposure to environmental antigens, microbiome-derived metabolites, and chronic infections, particularly in low-resource settings. **Chapter 2** builds on these observations by examining how these contexts reshape the immune landscape, ultimately compromising vaccine responsiveness through exhaustion, immunosenescence, regulatory dominance, and disrupted antigen presentation.

The scope and aims of this thesis

The overarching aim of this thesis is to investigate how factors such as the microbiota, environment, lifestyle, and baseline immune profiles contribute to variations in vaccine immunogenicity. Focusing on healthy Tanzanian adults, we explore the rural–urban immune divide using high-resolution immune profiling tools such as mass cytometry, conventional flow cytometry and microbiome sequencing(16S rRNA sequencing). To achieve this, we conducted three distinct studies: two cross-sectional studies and one longitudinal cohort study. To ensure methodological rigor and minimize selection and measurement biases, all three studies employed standardized recruitment procedures, eligibility screening, and validated data collection tools. A school based approach, and community-based sensitization campaigns facilitated participant enrollment, and structured questionnaires adapted from previously validated studies used were administered by trained personnel. In the longitudinal study, participants were randomly assigned to vaccinated and control groups to reduce selection bias. In summary the first cross-sectional study focused on evaluating the prevalence and diagnostic accuracy of tools used for diagnosing schistosomiasis in a rural setting. This study involved over 500 school-aged children, providing critical insights into the prevalence and effectiveness of diagnostic methods in resource-limited environments. The second cross-sectional study aimed to compare the immunological profiles of individuals from rural and urban areas, while

identifying factors contributing to these variations. Participants were recruited from four distinct study sites, two rural and two urban, where blood, stool, and urine samples were collected. Detailed questionnaires were used to capture individual lifestyle factors such as socioeconomic status, diet, and environmental exposures, helping to elucidate the intrinsic and extrinsic drivers of immune variation.

The third study, a longitudinal cohort study, followed individuals from two of the selected study sites one rural and one urban. A total of 185 participants were recruited, with an even distribution between rural and urban settings. To examine the factors influencing vaccine response, both groups were administered the yellow fever vaccine. Biological samples (blood, stool, urine) were collected at multiple time points before vaccination, and on days 2, 7, 14, 28, 56, 90, and 178 post-vaccination. Additionally, detailed lifestyle information was gathered through questionnaires, capturing data on socio-economic factors, diet, and other relevant variables. Advanced single-cell technology, such as mass cytometry, helped in dissecting the immune cell profiles at high resolution, while 16S rRNA sequencing provided insights into microbiome composition. This integrative approach allowed for a comprehensive analysis of the intrinsic and extrinsic factors shaping immune variation and vaccine response in Tanzanian adults.

Thesis outline

This thesis is divided into seven chapters, each addressing key aspects of factors shaping immune variation and vaccine response.

The **first chapter serves** as an introduction, we provide an overview of various factors influencing immune system variation and vaccine responses, setting the foundation for this thesis.

In the **second chapter**, we conduct a comprehensive review of immunological factors linked to geographical variations in vaccine response, delving into the mechanisms behind vaccine hypo-responsiveness and global disparities in vaccine efficacy.

In the **third chapter**, we present field and laboratory-based findings on the prevalence of Schistosomiasis among school-aged children in Mwanga District, Tanzania, providing insight into the prevalence of schistosomiasis.

In the **fourth chapter**, we explore the impact of lifestyle factors on cellular immune profiles, focusing on differences between rural and urban populations in Tanzania, and analyze the factors associated with immune profile variations.

In the **fifth chapter**, we examine the association between the innate immune state at baseline and vaccine responses, aiming to gain a deeper understanding of the immunological mechanisms underlying variations in vaccine efficacy.
In the **sixth chapter**, we examine differences in gut microbiome composition between rural and urban settings and investigate the associations between gut microbiota and vaccine responses. We also compare vaccine responses between these populations.

In the **final chapter**, we discuss the key findings, synthesize the results, and propose future research directions based on the implications of the study.

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