Interdisciplinary symposium on challenges and opportunities for vaccines: a comprehensive approach of current and future vaccine strategies to improve vaccine effectiveness in complex chronic infectious contexts

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A B S T R A C T

Vaccination is a key public health intervention, but vaccine immunogenicity, efficacy, and effectiveness vary geographically. These variations are not yet fully understood but are likely influenced by factors such as chronic infections, environmental and genetic differences, social and behavioral factors, and operational challenges, particularly in low- and middle-income countries (LMICs). To address these issues, the "International Symposium on Global Challenges and Opportunities for Vaccines" was held in Kloster Bernried, Germany, bringing together international scientists and stakeholders. Key discussions included: (1) Compromised vaccine immunogenicity due to helminth infections, (2) new vaccine approaches in vaccine development, (3) new frontiers in therapeutic vaccination, (4) challenges of vaccine trials, especially in low-resource settings, and (5) conceptualizing vaccine confidence in low and high resource contexts. The symposium highlighted the challenges of conducting vaccine trials in LMICs, such as participant follow-up, logistics, resources, and building trust. The main recommendation was to improve future vaccine trial designs through a comprehensive, interdisciplinary approach, including tools to evaluate vaccine immunogenicity, efficacy, and effectiveness.

1. Introduction

Vaccination against diseases that cause significant morbidity and mortality remains a cornerstone of global public health [1]. It is crucial in reducing morbidity and mortality worldwide, particularly in low- and middle-income countries (LMICs), at relatively low costs [2–6]. Vaccines are estimated to save 3·5 to 5 million lives annually [7]. The World Health Organization's (WHO) Expanded Program on Immunization (EPI) and the Global Alliance for Vaccines and Immunization (GAVI) have played vital roles in delivering vaccines, especially in LMICs, protecting populations from a wide range of infectious diseases [8]. Immunization activates the innate and adaptive immune systems through live or dead organisms or subunit vaccines, leading to the production of antibodies and memory B and T lymphocytes crucial for long-term pathogen protection. The immunogenicity, safety, and efficacy of vaccines are evaluated in controlled clinical trials, while the real-world vaccine impact, termed effectiveness, may differ from clinical efficacy [7,8].

Vaccine efficacy and effectiveness often vary by population. For example, the rotavirus vaccine's efficacy is over 95 % in high-income countries (HICs) but less than 75 % in LMICs, with Mali reporting only 49·2 % efficacy [9–12]. The yellow fever vaccine demonstrated high efficacy in Europe and the USA (99 %), and Latin America (94 %) but is lower in Mali (91 %) and Ghana (63·8 %) [13–15]. Bacille Calmette-Guerin (BCG) vaccine efficacy ranged from 23 % to 69 %, increasing from southern to northern regions [16]. The unlicensed malaria vaccine *Plasmodium falciparum* sporozoite–chemoprophylaxis vaccine (PfSPZ–CVac) showed efficacy ranging from over 90 % in US and German participants to 55 % in Equatorial Guinea [17–19].

Several factors influence vaccine immunogenicity, efficacy, and effectiveness. These include (1) individual factors like age [20,21], concurrent infections [22,23], nutrients [24], microbiota [25], pollution, toxins [26], and genetics [27]; (2) vaccine-intrinsic factors include adjuvants, formulation [28,29], timing, schedule [30], and viral, parasitic or antigenic variation [31–33]. To address low immunogenicity, researchers are exploring interventions beyond conventional vaccination, such as micronutrient supplementation, probiotics [34], anthelmintic [35] and HIV treatments [36].

In recent years, growing awareness of interactions affecting vaccines has led to interdisciplinary collaborations aimed at identifying factors that reduce immunogenicity, efficacy, and effectiveness. These efforts, coupled with tailored interventions and effective stakeholder

Abbreviations: BCG, Bacille Calmette-Guerin; CSP, Circumsporozoite protein; CLR, C-type lectin receptor; DALYs, Disability-adjusted-life-years; DC, Dendritic cells; EPI, Expanded Program on Immunization; FGS, Female Genital Schistosomiasis; GAVI, Global Alliance for Vaccines and Immunization; GLOHRA, German Alliance for Global Health Research; GMZ2, Plasmodium falciparum recombinant protein vaccine consisting of conserved domains of GLURP and MSP3; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HBV, Hepatitis B virus; HelmSys, Impact of helminth infections on vaccine responses in humans: a systematic literature review; HICs, High-income countries; HPV, Human papillomavirus; IFN-γ, Interferon-gamma; IgG, Immunoglobulin G; LMICs, Low-and-middle-income-countries; MERS, Middle East respiratory syndrome; MMR, Measles, mumps and rubella vaccine; Mtb, *Mycobacterium tuberculosis*; MVA, Modified Vaccinia virus Ankara; MINCLE, Macrophage-Inducible C-Type Lectin; NTD, Neglected tropical diseases; PfSPZ–CVac, *Plasmodium falciparum* sporozoite–chemoprophylaxis vaccine; RTS,S, Malaria vaccine (Mosquirix); Sm, *Schistosoma mansoni*; Sh, *Schistosoma haematobium*; STIKO, Ständige Impfkommission (the German Standing Committee on Vaccination); TB, Tuberculosis; TDB, Trehalose-6,6-dibehenate; TDM, Trehalose-6,6-dimycolate; Th1, T helper cell type 1; TT, Tetanus toxoid; WHO, World Health Organization.

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communication, are essential for enhancing vaccine acceptance—shaped by trust in healthcare systems, beliefs, and cultural attitudes—which is crucial for achieving herd immunity through widespread vaccine coverage and ensuring immunization success.

To address these issues, the "Interdisciplinary Symposium on Global Challenges and Opportunities for Vaccines" was held from November 30 to December 1, 2023, in Bernried near Munich, Germany. This event brought together international scientists to discuss immunization challenges in LMICs, organized by the HelmSys consortium and funded by the German Alliance for Global Health Research (GLOHRA). The HelmSys consortium aimed to investigate the impact of helminth infections on vaccine outcomes in humans by conducting a systematic literature review with partners from the Technical University of Munich and the University of Tübingen since helminths are one of several potential drivers of impaired immunogenicity, impaired efficacy, and impaired effectiveness of vaccines as mentioned above.

During this symposium, the following topics were presented and discussed: (1) Compromised vaccine immunogenicity due to helminth infections; (2) New vaccine approaches in vaccine development; (3) New frontiers in therapeutic vaccination; (4) Challenges of vaccine trials, especially in low-resource settings; and (5) Conceptualizing vaccine confidence in low and high resource contexts.

2. Insights from the symposium

2.1. Compromised vaccine immunogenicity due to helminth infections

Helminths, affecting 1·5 billion people and associated with the loss of 1·9 million Disability-adjusted-life-years (DALYs) globally [37–40], are potent immune regulators, influencing concomitant infections, immune diseases, and vaccine outcomes [41–47].

Numerous studies in animals show that helminths strongly regulate the immune system. While suppressed vaccine responses in experimental animal models are clear [35,44], the situation in humans, particularly in LMICs like sub-Saharan Africa (SSA), remains unclear [35,42,48–56]. Additionally, previous human studies have not yet provided clear evidence on whether anthelminthic treatment offers significant benefit for improved vaccine outcomes.

Given these observations, symposium speakers presented their work on vaccine-induced immune responses and vaccines' efficacy, including underlying mechanisms potentially explaining this crosstalk.

Minka Breloer, Bernhard Nocht Institute of Tropical Medicine, Hamburg, Germany, presented results from an experimental helminth infection mouse model. Mice infected with *Litomosoides sigmodontis*, a parasitic nematode used as an accepted model for chronic human filariasis, showed diminished quantity and quality of antibody responses to vaccination against non-adjuvanted trivalent split subunit seasonal influenza A H1N1 A/HH/NY/1580/09 strain (2009 pH1N1) that is commonly known as "swine flu" (Bergripal, Sequirus). Moreover, protection against subsequent challenge infection with the human pathogenic 2009 pandemic H1N1 influenza A virus was impaired in vaccinated mice with underlying helminth infection. If vaccines were given after immune-driven or drug-induced clearance of a previous helminth infection, impaired responses were also observed. Mechanistically, the suppression was associated with a systemic and sustained expansion of IL-10-producing $CD4^{+}CD49b^{+}LAG\text{-}3^{+}$ type-1 regulatory T cells and partially abrogated by in vivo blockade of the IL-10 receptor [44,57–59].

Roland Lang, Institute of Clinical Microbiology, Immunology and Hygiene, FAU Erlangen-Nuremberg, Germany, explored consequences of helminth infection for the T cell response to vaccination. Immunization of mice with a recombinant fusion protein of *Mycobacterium tuberculosis,* adjuvanted with the synthetic analog of mycobacterial cord factor trehalose-6,6'dibehenate (TDB), induces strong antigen-specific Th1/Th17 immunity [60]. TDB is sensed by the myeloid C-type lectin receptor MINCLE [61], leading to macrophage activation and IL-1-dependent Th17 induction [62]. The Th2 cytokines IL-4/IL-13 inhibit MINCLE expression by murine and human macrophages and DC in vitro, and they inhibit the cytokine response to BCG [63]. The impact of concurrent helminth infection on MINCLE-dependent vaccination was investigated in mice infected with *Nippostrongylus brasiliensis* (a roundworm with a lifecycle similar to human hookworms) or with *Schistosoma mansoni* (Sm) [64]. Both helminths promoted T cell-derived IL-4 production and suppressed vaccine-induced Th1/Th17 responses. The use of mice genetically deficient in IL-4 and IL-13 showed that inhibition of Th1/Th17 responses by *N. brasiliensis* was dependent on these hallmark cytokines of helminth infection. Of interest, upon use of a TLR4-dependent adjuvant, helminth infection selectively impaired induction of Th1, but not Th17 cells. Together, the results from the mouse model suggest downregulation of MINCLE expression on myeloid cells by IL-4/IL-13 as a mechanism of thwarted Th17 vaccination responses by underlying helminth infection.

Justin Komguep Nono, Institute of Medical Research and Medicinal Plant studies, Ministry of Scientific Research and Innovation, Yaoundé, Cameroon investigated the impact of chronic *Schistosoma mansoni* (Sm) infection on the efficacy of vaccine-induced immunity by combining exploratory clinical observations in school-aged children with in-depth mechanistic experiments in laboratory mice. Results revealed impaired persistence of vaccine-specific antibodies in poliovirus-vaccinated subjects. Using a mouse model of anti-viral vaccination, mechanistic evaluations demonstrated that chronic schistosomiasis caused vaccine-elicited immunity impairment through reduced survival of plasmablasts and antibody-producing plasma B cells in the bone marrow. Effective annual treatment (status moving from infected to not infected) with 3 times 40 mg/kg antiparasitic drug praziquantel (PZQ), each year between 2016 and 2018, partially reversed the impact of chronic schistosomiasis on serological immunity of both vaccinated children and mice and restored the plasma B cell populations in the bone marrow of mice when compared to untreated hosts. These findings underscore the need for interventions to treat schistosomiasis to ensure optimal vaccination in endemic areas [43,50].

Taken together, these experimental studies provide mechanistic insights on vaccine immunogenicity differences between helminth-endemic and non-endemic areas, which might facilitate testing and optimal rollout of licensed vaccines in these affected areas.

3. New vaccine approaches in vaccine development

Advances in molecular biology, genomics, and immunology are driving innovation in vaccine research, leading to new targets against pathogens. At the symposium, novel vaccine approaches for hookworm, malaria, Middle East respiratory syndrome-related coronavirus (MERS-CoV), and *Shigella* were discussed, highlighting strategies to enhance efficacy, broaden coverage, and improve immune responses [65].

Ayola Akim Adegnika, Centre de Recherches Médicales de Lambaréné, Lambaréné, Gabon, presented a new vaccine candidate that targets hookworm infection caused by *Necator americanus* a soil-transmitted helminth (STH) which is a significant source of global morbidity including anemia, with a pronounced impact on the most economically disadvantaged populations worldwide. The transmission primarily occurs through larval invasion of exposed skin, and the mature worms reside in the host's small intestine, where they feed on the host's blood. The ensuing chronic iron deficiency anemia can result in growth stunting and cognitive impairments in children, decreased work capacity in adults, and various complications during pregnancy [66–69]. The urgent need for a hookworm vaccine, considering mass drug administration's suboptimal control, is emphasized. *N. americanus* antigens Na-APR-1 and Na-GST-1 are promising in animal models and are safe and immunogenic when administered to healthy children and adults. A phase I clinical trial co-administering Na-GST-1 and Na-APR-1 in Gabonese children [70] and adults [71] documented good safety and tolerability profiles, with induction of IgG to both antigens, indicating

good immunogenicity. Functional data that may support testing for efficacy in future studies are currently being obtained. This marks the first report of co-administered Na-APR-1 in an *N. americanus*-endemic area. Additionally, metabolomic profiling in a separate trial discerns differences in individuals and detects metabolic changes post-vaccination, offering insights into physiological responses.

In summary, in this Phase 1b vaccine trial, the co-administration of Na-GST-1 and Na-APR-1 / Alhydrogel was safe, well-tolerated, and immunogenic in children and adults living in hookworm-endemic areas of Gabon. The vaccine elicited antigen-specific IgG antibodies with the peak of the antibody response two weeks after the third vaccine dose. Further studies in proof-of-concept efficacy phase 2 trials will be required to evaluate the vaccine's efficacy.

Benjamin Mordmüller, Radboud University Medical Center, Nijmegen, The Netherlands, stated that the quest for an effective malaria vaccine is pivotal for achieving better malaria control. Two vaccines are being implemented in Africa (RTS,S and R21). So far, their impact is restricted because efficacy is short-lived, the target group is limited to small children, and vaccine roll-out is slow. Nevertheless, they represent a milestone in vaccinology and malaria control. GMZ2, a recombinant protein targeting the asexual blood stage of malaria, showed good tolerability and immunogenicity, but its efficacy was low in phase II and controlled human infection trials, possibly due to parasite polymorphism [72–74].

The asexual blood stage vaccine Rh5 [75] and two placental malaria vaccines [76,77] are still in development. Rh5 is the first asexual blood stage candidate that showed clinically significant efficacy in African children [78]. *Plasmodium falciparum* sporozoite (PfSPZ) vaccines, consisting of attenuated, purified, cryopreserved sporozoites, demonstrate > 90 % efficacy against *P. falciparum* in clinical trials [79]. Distinct attenuation methods led to PfSPZ vaccines that are safe and highly efficacious and provide long-lasting protection, including against non-vaccine strains. It was shown that the later the parasite arrests its development due to the attenuation, the better the protection. A second generation of genetically attenuated, late-arresting PfSPZ is under development [80,81] and in a proof-of-efficacy trial, one candidate was highly efficacious [76]. PfSPZ vaccines also have to overcome challenges; most importantly, the efficacy of the current vaccines is significantly lower in lifelong malaria-exposed compared to malaria-naïve individuals.

Current research aims to improve PfSPZ vaccine efficacy for use in malaria-endemic regions through systems-immunology approaches. The development of PfSPZ vaccines is a notable example of community-driven, cooperative efforts to develop a highly effective malaria vaccine [77,82–89]. In addition to malaria vaccines to prevent infection or complications, proof-of-concept for transmission-blocking vaccines has been achieved [90,91]. This type of vaccine could play a role, e.g., in containment and eradication scenarios. For all types of malaria vaccines, proof of concept requires controlled human infections or large field trials. Immunological surrogate endpoints would reduce costs significantly and could streamline vaccine development [92–97].

The emergence of novel pathogens poses a constant threat to global health security. Viruses like MERS-CoV and bacteria like *Shigella* species represent formidable challenges with the potential for widespread outbreaks and severe morbidity. As these pathogens continue to evolve and adapt, the development of effective vaccines becomes imperative [98,99].

Anahita Fathi, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, discussed the opportunities and challenges that investigator-initiated clinical trials pose in the context of early-phase vaccine development. This research is focused on the clinical development of viral vector vaccines for pandemic preparedness. Early-phase clinical trials are characterized by several opportunities to study vaccine-induced immunity in detail: Study participants are well-defined, and a variety of immune responses (e.g., humoral, cellular, and innate) is studied at various time points throughout the trial. Due to a relatively small number of study participants (usually in the range of 10–100 per group), very close monitoring and detailed safety assessments are possible. However, implementing such trials in an academic environment can be challenging, as they are costly and require extensive collaborations. In addition, because of the small study size that usually only includes healthy and young (e.g., 18–55 years) volunteers, the assessment of differences in the immune response (e.g., sex, age, and regional differences) is limited. The poxviral vector Modified Vaccinia virus Ankara (MVA)-based vaccine is studied, and it is a well-established viral vector with an excellent safety profile. Preliminary results of a Phase Ib clinical trial of MVA-MERS-S were presented, an MVA vector vaccine expressing the spike glycoprotein of MERS-CoV. It is a highly virulent human coronavirus that has caused sporadic outbreaks since 2012 and has a reported case-fatality rate of around 35 % [100]. No licensed vaccines or specific treatments exist to date. Building on successful preclinical and first-in-human clinical studies, this Phase Ib trial was a randomized-controlled trial (NCT04119440) that assessed two different dose levels and two dosing regimens (four vs. eight-week interval between prime/boost intervals plus an additional booster dose at nine months after prime) [101].

In summary, both dose intervals and dosing regimens were safe and well-tolerated and induced significant and durable binding and neutralizing antibody titers irrespective of pre-existing MVA-vector immunity. Three vaccinations with MVA-MERS-S additionally induced mpox cross-neutralizing antibodies [102].

Esther Ndungo, University of Maryland School of Medicine, Baltimore, USA, discussed vaccine approaches against *Shigella* spp., which causes a substantial global health burden of severe diarrhea, primarily affecting children under 5 years of age [103,104]. The rise of antibiotic-resistant strains poses a significant public health threat [105–109], but currently, no approved vaccines or immune therapies against shigellosis exist. Two vaccine approaches were presented: *Shigella* O-polysaccharide conjugated to a *Shigella*-relevant carrier protein, invasion plasmid protein B (IpaB), and vaccines based on conserved proteins, such as the type III secretion system proteins IpaB and IpaH, and the virulence gene, VirG. These approaches aim to overcome the limitation of clinically advanced vaccine candidates that rely only on immunity targeting the bacterial lipopolysaccharide, which is serotype-specific, as there are multiple disease-causing serotypes [110]. Preclinical testing of both vaccine approaches was promising, showing robust immune responses in mice and protection against two serotypes, *Shigella flexneri* 2a and *Shigella sonnei* [111,112]. These data present these approaches as viable candidates for evaluation in vulnerable populations.

Knowledge of the diversity of immune responses following vaccination or *Shigella* infection would assist in identifying relevant target antigens for future vaccine development. To this end, tools to evaluate protective *Shigella* immunity were discussed, including the development of a multiplex assay using Meso Scale Discovery (MSD) technology [113] and the bead-based systems serology [114] platforms, both of which interrogate immune responses to multiple antigens at once. These assays can be exploratory, e.g., for conducting serosurveys in endemic regions or contribute to identifying correlates of immune protection, as was previously performed on samples from controlled human *Shigella* infection models [114]. Lastly, an in vitro human enteroid/colonoid model [115] was presented as a useful tool for dissecting mucosal immune components against *Shigella* infection.

4. New frontiers in therapeutic vaccination

Therapeutic vaccines show promise for treating chronic infections, cancer, and autoimmune diseases by targeting infected cells or pathogens [116] and dendritic cells (DCs), crucial for antigen presentation and T cell activation, are central to developing effective preventive and therapeutic vaccines [117,118].

Ulrike Protzer, Technical University of Munich (TUM), and Helmholtz Munich, Munich, Germany, gave an overview of immunotherapies

against the Hepatitis B virus (HBV), which causes chronic and potentially fatal liver disease. Existing treatments control but do not cure infection. HBV's persistence relies on covalently closed circular DNA (cccDNA) in the nucleus of infected cells that is not targeted by current antivirals [119–124]. Curative strategies are under investigation emphasizing the necessity of targeting cccDNA for successful HBV eradication. Immunotherapy, on top of a therapy with directly acting antivirals, emerges as a potential solution to achieve immune recovery. The heterologous TherVacB prime-boost vaccination scheme proved most suitable for this. Based on studies in preclinical mouse models, the combination of recombinant, particulate HBsAg and HBcoreAg for prime vaccination with an adjuvant that activates a balanced Th1/Th2-type helper T cell response is promising. To boost effector T cell responses, a vaccine vector based on modified vaccinia virus Ankara (MVA) inducing a broad T cell response by covering several antigens of the five most prevalent HBV genotypes, A-E, covering 95 % of the circulating isolates globally, and named it MVA-HBVac was designed (WO 2017/121791 (PCT/EP2017/050553: Means and methods to treat HBV)). (Manuscript in preparation) Application of the TherVacB vaccination scheme in HBV-carrier mice resulted in HBsAg seroconversion and induction of a strong and HBV-specific CD4+ and CD8+ T cell response resulting in sustained reduction or elimination of HBeAg and HBV-DNA from the serum. Moreover, the TherVacB regimen could reliably overcome the virus-mediated immune tolerance and induce a therapeutic anti-viral effect against persistent HBV infection in mice with several HBV genotypes such as A, B, C, and D as well as HBeAg-negative HBV infection that is clinically most relevant. As a reason for the success of the heterologous prime-boost vaccination scheme, the group identified CD4 T cell activation to be crucial, providing insights into the design of effective treatments for chronic hepatitis B [125–127].

Therapeutic hepatitis B vaccines, such as TherVacB, provide an interesting approach to restoring and replenishing exhausted, sparse or dysfunctional HBV-specific T and B cell responses and are currently evaluated in clinical trials with the goal to cure chronic HBV infection [128].

Johannes U. Mayer, University Medical Center of the Johannes Gutenberg-University Mainz, Germany, illustrated that DCs are pivotal in orchestrating adaptive immune responses, serving as sophisticated antigen-presenting cells found throughout the body. However, tissue-specific DC subsets exhibit significant heterogeneity, influencing adaptive immunity. Lung, skin, and intestinal DCs display distinct signatures regulated by local immune networks that lead to the preferred induction of Th17, Th2, and regulatory T cell immunity, respectively [129–132].

Advancements in single-cell OMICS further enhance our understanding of DC diversity. Targeting functionally specialized, tissue-specific DC subsets holds promise for localized and targeted immune responses, aiming to improve tissue-specific vaccine efficacy, minimize off-target effects, and provide new opportunities in leveraging DC heterogeneity to enhance vaccine precision and effectiveness in specific tissues [133–135].

Summarized, combining specific DC subsets targeting with existing vaccine strategies to present dominant antigens to DCs and modulating their activity through subset-specific adjuvants or immunomodulatory agents also holds promise to enhance antigen-specific immune responses and overcome tolerance mechanisms in chronic infections and cancer [136,137].

5. Challenges of vaccine trials, especially in low-resource settings

Navigating vaccine responses and immunological diversity across populations is crucial. Discrepancies in efficacy are evident between HICs and LMICs, as well as in urban versus rural areas [138]. Recent findings highlight distinct immune cell profiles and Th2 skewing in geographically rural settings, emphasizing the need for a nuanced understanding of vaccine responses [138].

Marrium Habib and Vanesa Osmani, Technical University of Munich (TUM), Munich, Germany, presented the first results of an evidence-based systematic literature review on immunogenicity, efficacy, and effectiveness for different vaccines in humans infected with helminths. The systematic literature search, which included studies published from 1970 to 2024 covering indexed and non-indexed databases, resulted in 8575 citations. Of these, 39 publications (10 randomized controled trials (RCTs), 31 observational studies) were included, and study quality was assessed using standardized tools. The initial analysis focused on 10 RCTs, exploring the impact of anthelmintic treatment on specific BCG and cholera vaccine responses in study participants with helminth infections [139]. The preliminary results of the HelmSys project showed that only 4 out of 10 RCTs reported positive effects of the anthelminthic treatment for the investigated vaccine outcomes. Analyses of the included observational studies will be available soon. Challenges in conducting the systematic literature review were the various immunogenicity outcomes (humoral and cellular) and the heterogeneity of study designs.

Alison Elliott, London School of Hygiene and Tropical Medicine, London & Entebbe, UK & Uganda gave an overview and presented preliminary results of the "POPulation differences in VACcine responses" (POPVAC) program which undertook three harmonized trials (A, B, and C) to investigate the impact of individually randomized interventions against schistosomiasis (A) and malaria (B), as well as BCG revaccination (C), on a common set of vaccine responses, while struggling with low follow-up rates, capacity building in LMICs, and participants who are difficult to reach in rural areas. Adolescents from Ugandan schools in high-schistosomiasis (A), high-malaria (B), and (C) an urban birth cohort received BCG, yellow fever, oral typhoid, human papilloma virus (HPV) and tetanus/diphtheria vaccines. Primary outcomes include BCG-specific IFN-γ responses and antibody responses to key vaccine antigens. Secondary analyses explored protective immunity correlates, vaccine response dynamics, and parasite infection status (Trial registration numbers: ISRCTN60517191, ISRCTN62041885, ISRCTN10482904.) [51,140–142]. POPVAC A showed evidence of a benefit of treating schistosomiasis on the response to BCG and possibly typhoid responses and an adverse effect on HPV16-specific IgG response [143,144]. POPVAC B showed no evidence of a benefit of treating malaria on peak responses but possible benefit for waning of Yellow Fewer responses [145], and POPVAC C showed no evidence of a benefit for giving BCG ahead of other vaccines [146]. The result of the secondary analysis of the POPVAC A study is the inverse relationship between *Schistosoma mansoni* (Sm) infection and immune responses to *Salmonella typhi* O:LPS, while hookworm infections showed a positive correlation with diphtheria-specific IgG levels [147].

Maria Yazdanbakhsh, Department of Parasitology, Leiden University Medical Center, The Netherlands, presented varying immunogenicity and efficacy data of vaccines across populations in HICs versus LMICs and urban versus rural areas within a country, challenging to predict immunogenicity and efficacy. Examples include attenuated malaria vaccines showing 100 % protection in Europe but dropping to 29 % in Africa. Similar trends are observed with rotavirus, BCG, Yellow fever, and Ebola vaccines. Advanced immune system characterization, by high dimensional omics analysis, reveals distinct profiles in rural LMIC populations marked by highly activated immune cell subsets and increased regulatory T and B cell frequencies, that might underlie poor vaccine performance. Identifying immunological pathways involved in vaccine hyporesponsiveness is crucial for effective interventions [45,138]. Controlled human infection trials while invasive accelerate drug and vaccine development for global infectious diseases. With ethical considerations and safety data being essential for progress.

Summarized, the subsequent review by Van Dorst et al. [138] presented the rising evidence of geographical differences in vaccine immunogenicity, efficacy and effectiveness. This leads to the discussion of the importance of "complementary study designs" across clinical trials and their trial arms to assess standardized data which can be

compared statistically and at meta level to provide more detailed data for vaccine efficacy and effectiveness in LMICs.

6. Conceptualizing vaccine confidence in low and high resource contexts

The success of vaccination campaigns depends on the confidence and acceptance of the target population. It scrutinizes the complex dynamics of vaccine confidence in both low and high-resource contexts, offering insights into the psychosocial factors influencing public perception [148–150].

Christian Bogdan, Institute of Clinical Microbiology, Immunology and Hygiene, FAU Erlangen-Nürnberg, Germany, who has served as a member of the German Standing Committee on Vaccination (STIKO) from 2011 until March 2024, provided an overview on the STIKO and its standard operating procedures. The STIKO is a group of currently 19 experts covering diverse fields of experimental and clinical medicine, who are appointed by the German Federal Ministry of Health and regularly issues recommendations on the use of all vaccines authorized by the European Commission. Working on an honorary and transparent basis, which entails the disclosure of conflicts of interest, the STIKO members are bound to follow strictly the principles of scientific evidence-based medicine and GRADE. They build their vaccination recommendations on the careful assessment of published basic research and clinical studies, which usually requires systematic reviews to be carried out (e.g. [151,152],), unless up-to-date meta-analyses are already available. The STIKO's rigorous approach, implemented since 2011, ensures robust decision-making processes during the initiation of new vaccination guidelines [153]. Bogdan outlined that the evaluation of the clinical efficacy, immunogenicity and safety of a vaccine, its benefit/risk ratio, the definition of the target population, and the formulation of the vaccination goal are essential components of the STIKO's work. The STIKO recommendations are always accompanied by detailed scientific justifications, which are published in the Epidemiological Bulletin of the Robert Koch Institute (RKI). Thereafter, the STIKO closely follows the results of the post-marketing surveillance of vaccines and regularly adapts its recommendations, which provides an additional level of vaccine safety for the German population.

Greet Hendrickx from CONFiVAX, University of Antwerp, Belgium, discussed the role of healthcare providers (HCPs) as the most trusted source of vaccination information. According to the 2022 vaccine confidence survey in 27 European countries [154], between 67·3 % (France) and 99·2 % (Estonia) of HCPs believe vaccines are important, safe, and effective. However, even though HCPs are confident in vaccines, they don't always feel prepared to answer patients' vaccination-related questions. The Vaccine Training Barometer, a survey tool assessing HCPs' confidence in responding to vaccination queries, revealed when tested among HCP in Flanders, Belgium and in the Barcelona region in Spain, that less than half of HCPs felt confident in doing so. This highlights the need for further training of HCPs [155]. A survey of pre-medical and medical students revealed that half of them need an extended module on vaccination since their curriculum currently lacks practical skills, communication training, and knowledge on current and future developments in vaccinology.

Hendrickx presented the commonly used definition of vaccine hesitancy and emphasized that vaccine hesitancy exists on a continuum, from those who accept all vaccines to "anti-vaxxers" who reject them. Importantly, not everyone who has questions about vaccines should be labelled as an "anti-vaxxer".

In conclusion, vaccine confidence is influenced by multiple factors, including the vaccine itself, social and individual contexts, and other determinants. Recently, there has been a decline in public confidence, with a widening gap between younger and older age groups, especially for vaccines like HPV. While HCPs are the most trusted sources of vaccine information, many lack the confidence [156] to effectively address patients' concerns. Therefore, it is essential to invest in tailored training for HCPs, both in-service and pre-service, as well as involving local social scientists to improve understanding of the behavioral and social determinants of the vaccine decision can further enhance vaccine confidence.

7. Learnings from the symposium

During the two-day workshop, 14 presentations (table 1) and two round table discussions addressed key issues in vaccine studies. The first roundtable dealt with methodological challenges, such as the need for study designs that account for variations in population and vulnerability. It emphasized the importance of integrating social sciences early in the process to understand diverse perceptions and foster community engagement. Regulatory challenges, such as delays in approvals, and planning complexities, particularly with long-term studies and declining follow-up rates, were highlighted. Adequate healthcare personnel and public trust are crucial, especially for studies on vaccine immunogenicity and efficacy. Despite some progress, uncertainty remains about the reliability of immunological tests as surrogates for vaccine efficacy. Coordinated efforts are needed to validate markers of protection, like vaccine-specific antibodies and T cell responses. Additionally, tools for microbiological diagnosis, especially those considered gold standards, are debated for their accuracy in distinguishing between infection types. For the second roundtable, participants were asked to propose solutions and ways to address the challenges discussed in the first roundtable. It was recommended that interdisciplinary teams, including anthropologists and geoscientists, are formed to address geographic and demographic variations in study areas. Evaluating vaccine efficacy is challenging in areas with low disease incidence, underscoring the need for better biomarkers and models to reliably indicate vaccine protection across diverse populations and regions. New trial designs that address past drawbacks were also discussed.

8. Key Messages/Learnings

The symposium brought together experts to address vaccination challenges in LMICs, particularly SSA. Consensus emerged on the need for advanced studies on vaccine immunogenicity, efficacy, and effectiveness in these regions. The discussion marked the beginning of a new era dedicated at improving future research and grant applications. We are aware that this topic is extremely broad and multi-faceted, and therefore requires many more perspectives as well as in depth discussion. As a limitation, not all regions of the world, such as Asia, were represented in the discussion.

Key points included:

1. Understanding immunological changes in LMIC populations requires expertise from various fields, including microbiology, virology, molecular biology, immunology, and biochemistry.
2. Knowledge of infectious disease epidemiology in LMICs is crucial for designing effective vaccine studies.
3. Public health attitudes, education, and knowledge significantly impact on vaccine effectiveness and acceptance, highlighting the need for input from ethicists, social scientists, and communication experts.
4. High-quality RCTs and observational studies in LMICs are essential for generating reliable evidence. Proper study design, robust sample sizes, and sound statistical analysis are critical to addressing biases and confounding factors.
5. Multidisciplinary collaboration fosters innovative solutions to complex vaccine efficacy and effectiveness issues in LMICs.
6. Vaccine development, particularly with emerging mRNA technologies, is complex and lengthy, involving preclinical studies, clinical trials, regulatory approvals, and real-world implementation.

Contributors

ASS, MH, CDC and ME conceptualized and wrote the manuscript. ASS, MH, VO, SJK, CDC and ME organized the workshop. AAA, MB, CB, AE, AF, MH, GH, SJK, RL, JUM, BM, EN, JKN, VO, UP and MY wrote, edited and reviewed the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2025.100615.

Data availability

Data will be made available on request.

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