THE FORUM FOR COLLABORATIVE RESEARCH

TOWARDS ACCELERATING HBV CLINICAL RESEARCH IN AFRICA

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THE FORUM
For Collaborative Research℠

Berkeley Public Health

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SESSION I: INTRODUCTORY REMARKS AND PROGRAM OVERVIEW

Welcome, Introduction, Forum Updates, Program Overview, and Acknowledgement

I. INTRODUCTORY REMARKS AND SETTING THE STAGE

Presenter: Veronica Miller, Forum for Collaborative Research

Dr. Miller provided an overview of the Forum's operating principles, including HBV Forum's model of working with different stakeholder groups to facilitate HBV drug development. The Forum's role is to convene and facilitate a safe space for open discussion, through the active participation of all groups. This meeting's aim was to strengthen collaborations with the African networks to create a path towards conducting clinical trials of HBV diagnostics and novel therapeutics on the continent. Given the limited investment in HBV clinical research in Africa, the Forum aims to facilitate global health collaboration towards strengthening the HBV research infrastructure in Africa.

The Forum recognized the importance of paying equal attention to both the operational and clinical sides of research (Figure 1). Operational research ensures equitable access to new and current therapies, and the infrastructural development of care systems facilitates clinical research which ensures the development of new treatments and access to the latest diagnostic technology. Ultimately, the binding factor is community involvement and ownership which facilitates equitable access to the most effective treatments and helps elucidate host and virus-specific biomarkers that are specific to the phenotype of the disease in the African context.

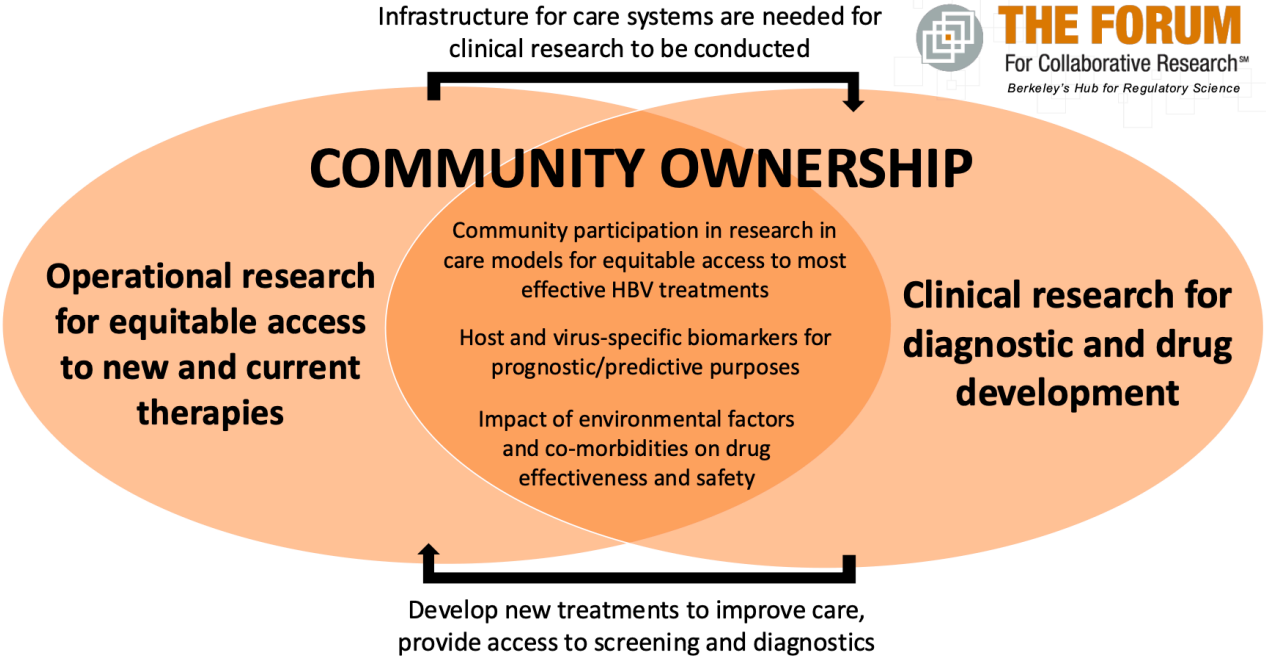


Figure 1. Bridging HBV operational and clinical research

II. WORLD HEALTH ORGANIZATION PERSPECTIVE

Presenters: Philippa Easterbrook, World Health Organization, Olufunmilayo (Funmi) Lesi, World Health Organization

Documents are available that describe the WHO research agenda priority lists and guidelines for advancing progress towards HBV and HCV elimination. There is an updated WHO Hepatitis B guideline which informs the WHO's process of establishing implementation considerations and research priorities. Four research gap areas that were emphasized are: who to treat, use of antiviral prophylaxis for PMTCT, treatment of adolescents and children, and simplified service delivery. Regarding "who to treat" the following research priorities for HBV research were outlined:

- Conducting long-term studies to understand the overall impact and effectiveness of expanding treatment eligibility. These studies are essential to determine how broader access to treatment can influence patient outcomes over time.
- Prioritizing studies for low- and middle-income countries and in under-searched populations such as, children, young adults, and pregnant women. These regions often face unique challenges in healthcare delivery, making it crucial to tailor research to their specific needs and conditions. Addressing these priorities can help improve HBV management in areas where the burden of the disease is often highest.
- Conducting Randomized Controlled Trials (RCTs) of antiviral therapies to establish treatment impact among people with low-level viremia and early fibrosis stages, especially in sub-Saharan Africa. These trials are necessary to rigorously evaluate the safety and efficacy of new treatments, providing the evidence needed to guide clinical practice and improve patient care.

- Prioritizing long-term prospective cohort studies to establish the minimum treatment duration required for effective disease management. Understanding the optimal duration of treatment can help prevent the development of drug resistance and improve long-term patient outcomes.
- Longitudinal studies are needed to evaluate the cut-offs for abnormal alanine aminotransferase (ALT) levels. These studies can help refine diagnostic criteria and treatment guidelines, ensuring that patients receive the most appropriate care based on accurate and reliable biomarkers.

Research priorities for PMTCT were outlined as follows:

- Evaluate feasibility, effectiveness, and cost-effectiveness of maternal peripartum antiviral prophylaxis +/- timely birth dose vaccine especially in settings where access is limited.
- Antiviral prophylaxis adherence studies to determine discontinuation rates, adverse outcomes, and uptake of onward referral.
- Follow-up studies to determine benefits and potential harm of discontinuing versus continuing antiviral therapy postpartum.
- Assessment of feasibility and effectiveness of different integrated and simplified antenatal HBV service delivery models and treatment.

Research priorities for adolescents and children were outlined as follows:

- Burden and routes of transmission in different regions, including among higher-risk groups.
- Prevalence and progression of liver fibrosis during childhood.
- Validating thresholds of non-invasive tests for liver fibrosis staging.
- Comparative trials and long-term follow-up studies assessing treatment impact on liver fibrosis
- Long-term prospective studies that assess potential adverse effects of long-term antiviral treatment on kidney and bone health.
- Optimal strategies to promote and maintain adherence.

Regarding service delivery, the HCV 2022 guideline recommendations encourage decentralization, integration, and task shifting to improve service delivery. It also recommends moving treatment and care out of specialty clinics. Research priorities for gaps in service delivery were outlined as follows:

- There is a need for more rigorous evaluation studies comparing packages of different service delivery interventions, including interventions already well established in HIV, especially in LMICs.
- Evaluation studies, assessing different service delivery models, including cost/cost-effectiveness data to capture outcome across the entire continuum of care.

SESSION II: OPERATIONAL RESEARCH PRIORITY: PREVENTING MOTHER-TO-CHILD TRANSMISSION (PMTCT)

CHGE Overview on PMTCT

Presenter: John Ward, Coalition for Global Hepatitis Elimination at the Task Force for Global Health

Africa has the highest global burden of chronic HBV, with most new infections occurring among children. Vertical (mother-to-child) transmission is responsible for the majority of HBV incidence in Africa. There is an opportunity to prevent 25.6M incident infections and avert 8.6M deaths, however investment in HBV research fairs poorly when compared to other infectious diseases such as HIV, malaria, and Zika. The CGHE's priority areas for operational research to expand access to HBV prevention include:

- Priority 1: Simplify delivery models to assure decentralized equitable access to hepatitis B testing and treatment.
- Priority 2: Improve interventions to eliminate MTCT of HBV that protect the health of mother and newborn, and their families.
- Priority 3: Develop and operationalize technologies for simplified hepatitis B diagnosis, treatment and monitoring.
- Priority 4: Detect persons living with Hepatitis B at highest risk for progression of fibrosis and development of HCC.

Breakout Session

There was sample research questions drafted (based on Priority 2 listed above) for break-out groups to discuss, these were the questions:

1. How can maternal HBsAg screening be integrated into antenatal care and with other screening tests (i.e. triple elimination of HBV, HIV and syphilis)?
2. How can HBsAg+ women be routinely checked to identify those at high risk of HBV transmission to newborn?
3. How can uptake and adherence to antiviral prophylaxis be optimized in pregnant women?
4. How to implement maternal antiviral prophylaxis (universal or high HBV DNA driven) for HBsAg-positive pregnant women, also in the absence of timely birth dose, including home births?
5. How to study optimal timing of TDF initiation/duration during pregnancy and postpartum treatment including studies of benefits and potential harm of discontinuing versus continuing antiviral therapy.

Summary of Small Group Discussion:

The group raised several points regarding operational research priorities which include:

- Cost-effectiveness of potential solutions. By prioritizing the most cost-effective treatment methods, we can ensure that resources are used efficiently and that patients receive the best possible treatment without unnecessary expenditure.

- A thorough review of "existing context" when proposing solutions or conducting research. Often, new initiatives will build upon what is already in place, so integrating new research with current systems is vital. The findings from ongoing work must be published and shared with the wider community. This transparency allows for more informed decision-making regarding policies and research questions, fostering collaboration with communities.

- Ensuring mothers adhere to treatment. There is a major need to understand the best strategies for keeping mothers engaged with their treatment, which would improve outcomes for both mothers and their children. There was sentiment from the group that there must be bold recommendations. One of them being that testing for Hepatitis B in pregnant women is no longer a research question—it is an established necessity.

- Improving information technology infrastructure to collect real-time data as new HBV programs are rolled out. This infrastructure will enable continuous monitoring and adjustment, ensuring that the programs are responsive and effective. There is also merit for the role of social science in implementing these programs across different geographical regions that cannot be ignored. Understanding the local context and the social dynamics at play is crucial for successful implementation. By considering these factors, the field can ensure that research initiatives are both effective and culturally sensitive.

- Consideration of the feasibility of research programs within a country setting. The success of any program or research initiative depends on its adaptability to local conditions. Additionally, the outcomes from existing systems need to be clarified to identify what is working and what needs improvement.

Operational Research Priority: Simplifying Delivery Methods

Presenter: John Ward, Coalition for Global Hepatitis Elimination at the Task Force for Global Health

The WHO HCV 2022 guidelines recommend decentralization and integration of service delivery methods. China has its own recommendation that goes beyond the WHO guidelines where everyone over the age of 30 that has detectable DNA is treated for hepatitis B. The CGHE's research priority 1 is to simplify delivery models to assure decentralized, equitable access to hepatitis B testing and treatment.

Breakout Session

Sample research questions were drafted (based on Priority 1 mentioned above) for the break-out groups to discuss. They are listed below:

1. What recent studies are assessing the overall impact and effectiveness of updated and expanded treatment eligibility guidelines by WHO and national health ministries?
    a. Treatment impact among people with low-level viraemia and early fibrosis stages in Sub-Saharan Africa.
    b. Treatment impact among persons with certain co-morbidities (e.g. DM, HDV), and the intersection with social (e.g. migration) and genetic factors.

2. What studies are assessing components of effective models of hepatitis B service delivery for decentralized and non-specialized settings for resource-constrained settings?
    a. Health promotion
    b. Community-based services
    c. Service integration
    d. Patient support for acceptance of testing, linkage to care and adherence to therapy.
    e. Technical tools to initiate and monitor response to therapy and disease progression.
3. What studies are assessing new technologies to facilitate clinical decisions regarding patient eligibility for treatment?
    a. Non-invasive test for liver fibrosis
    b. Virological tests, DNA, HBcrAg, quantitative HBsAg
    c. Other

Small Group Discussion

As the field explores the potential for a point of care test for Delta, it's crucial to consider whether this would be a valuable area of focus for future research. This question addresses a significant gap in our current knowledge, highlighting the need for targeted investments to secure the necessary data. Key areas to consider in advancing HBV research were identified as follows:

- Facilitating collaborations among education and multi-stakeholder teams to achieve integrated care. By presenting proposals that demonstrate the value of these partnerships, we can support efforts to secure proper funding for these initiatives. Understanding how effective collaborations contribute to better patient outcomes will be key in making a compelling case.

- Improving data flow with technological advancements. For instance, the use of smartphones and AI-based apps to collect data could revolutionize how we monitor and respond to health trends. Evaluating the feasibility and impact of these technologies is essential to harnessing their potential fully.

- Identifying and understanding bottlenecks in current HBV treatment systems. By pinpointing where delays or obstacles occur, we can develop strategies to streamline processes and improve efficiency. This understanding is vital for enhancing overall system performance.

- The introduction of new HBV policies must be carefully weighed against the impact on existing programs for other pathogens. Evaluating these impacts will help ensure that resources are allocated effectively, and that no area of healthcare is inadvertently neglected.

Funding remains a significant challenge in conducting these studies. Overcoming this roadblock will require innovative approaches to secure financial support and demonstrate the value of these research efforts. By addressing these various elements, we can create a robust framework for advancing HBV research and improving public health outcomes.

Cape Coast Teaching Hospital Experience

Presenter: Yvonne Nartey, Cape Coast Teaching Hospital, Ghana

The HBV clinic at the Cape Coast Teaching Hospital in Ghana, a 400-bed capacity tertiary referral center, operates once a week, treating 12-15 patients each open day. The clinic's services are structured according to the national guidelines of Ghana and the World Health Organization (WHO).

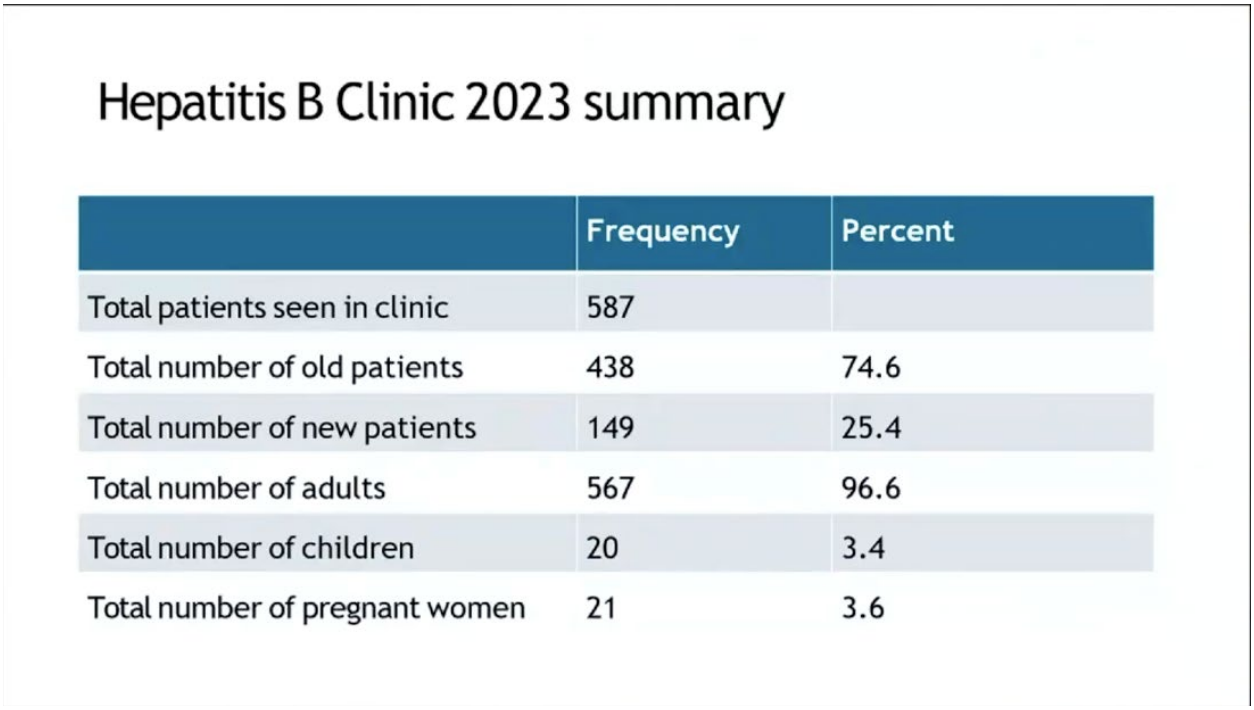
Cape Coast Teaching Hospital serves as an optimal model for decentralizing and expanding HBV services. Dr. Nartey discussed strategies for engaging more HBV patients in care. One approach featured a healthcare worker workshop to increase health care personnel knowledge of key issues in HBV clinical care.

Healthcare workers (HCWs) receive training through polyclinics held weekly or monthly at the clinic, focusing on best practices to prevent mother-to-child transmission (MTCT) of Hepatitis B. Communication among staff is prominently facilitated through WhatsApp, which facilitates patient engagement in rural areas

The clinic is also a hub for HBV research. Moving forward, the clinic aims to expand its research efforts to:

- Identify optimal models for decentralized Hepatitis B services in Ghana.
- Pinpoint potential barriers and facilitators to treatment access in decentralized care settings.
- Evaluate the impact and implications of new, expanded treatment guidelines on e-health and patient services.
- Develop tools for following up and monitoring patients across different levels of the healthcare system.

These research initiatives are crucial for enhancing HBV clinical care and ensuring effective treatment and management for patients in Ghana.



Hepatitis B Clinic 2023 summary

	Frequency	Percent
Total patients seen in clinic	587	
Total number of old patients	438	74.6
Total number of new patients	149	25.4
Total number of adults	567	96.6
Total number of children	20	3.4
Total number of pregnant women	21	3.6

Figure 2. Summary of the outputs from the hepatitis B clinic at the Cape Coast Teaching Hospital, Ghana

SESSION III: COLLABORATION TO STRENGTHEN DIAGNOSTIC AND RESEARCH CAPACITY IN AFRICA

"We don't have any data from Africa" - true or false?

Presenter: Asgeir Johannessen, Hepatitis B in Africa Collaborative Network (HEPSANET)

HEPSANET is a collaborative research network with the goal of improving policy and clinical care for patients living with hepatitis B in Africa. This research network has active sites in West, Central, East, and Southern Africa. As Steering Committee Chair of HEPSANET, Dr. Johannessen focused his talk on the need to leverage African HBV data in support of HBV elimination across the continent.

African data have historically been excluded from HBV guidelines development, with HBV guidelines for African populations being based off data from Taiwan. Dr. Johannessen emphasized that this was unacceptable. For one, it is well understood that disease progression for chronic hepatitis B depends on:

1. Host factors: age, sex, co-morbidities, co-infections, lifestyle
2. Viral factors: genotype

3. Environmental factors: aflatoxin
4. Societal factors: access to diagnosis and treatment

As such, these factors are different in Africa compared to in Taiwan.

Smaller, inconclusive studies do not provide the same level of insight as large, collaborative studies that gather data from multiple sources. To address this, the Africa CDC is working on generating guidelines specifically tailored for African Union countries, based on data collected within the continent.

In this effort, HEPSANET is envisioned as a crucial platform for HBV research studies. This initiative aims to facilitate comprehensive research that can inform effective, region-specific implementation strategies and improve HBV disease management across Africa.

HBV genotypes in sub-Saharan Africa and clinical outcomes

Presenter: Professor Emerita Anna Kramvis, University of Witwatersrand

Hepatitis B virus (HBV) encompasses 9 genotypes (A to I) and over 35 sub-genotypes (including A-D, F, H, and I). In different regions, specific genotypes are more prevalent: Genotype D is common in the North, Genotype E in the West, and Genotype A in the Southwest. Within Africa, sub-genotype A1 is a notable variant of Genotype A.

Studies conducted outside Africa cannot be directly applied to the African context due to the unique genetic characteristics of HBV found on the continent. For instance, patients infected with Genotype A respond better to interferon-based therapy compared to those infected with Genotype D.

Moreover, sub-genotype A1 and Genotype E circulating in Africa differ molecularly and functionally both from each other and from the genotypes prevalent outside Africa. This genetic heterogeneity can significantly influence the natural history of HBV infection. Therefore, it's crucial to consider these differences when designing and testing various preventative, diagnostic, and antiviral strategies to ensure they are effective for the specific genotypes found in Africa.

Panel Discussion:

- Clinical practice guidelines provide structure, but one must consider the local requirements when drafting local policies.
- Retaining health care personnel to ensure a sustainable workforce is of utmost importance for ensuring strong research systems.
- Data integrity is something that needs to be championed otherwise it will be difficult to draw conclusions. However, on the flip side there is a challenge when patients do not have enough data to be enrolled in programs like HEPSANET.

SESSION IV: TRAINING, CAPACITY BUILDING, AND AFRICAN OWNERSHIP OF RESEARCH ENTERPRISE

Global Health EDCTP3 Joint Undertaking

Presenter: Michael Makanga, European & Developing Countries Clinical Trials Partnerships (EDCTP)

The Global Health European & Developing Countries Clinical Trials Partnership (EDCTP)3 Joint Undertaking (Global Health EDCTP3) was established in 2021 to support global collaborative research, capacity strengthening, and international initiatives to accelerate the development, evaluation, and implementation of interventions to prevent, identify, and treat infectious diseases and emerging/re-emerging infections in sub-Saharan Africa to reduce overall mortality and morbidity. A partnership between the European Commission, representing the European Union, and the EDCTP Association, representing the governments of 16 European and 29 sub-Saharan African countries, the Global Health EDCTP3 has five specific objectives:

1. advance biomedical interventions towards improved overall health
2. research capacity development
3. enhance coordination and alignment of countries around a common Strategic Research and Innovation Agenda (SRIA)
4. strengthen capacity for outbreaks/epidemic/pandemic preparedness
5. networking, building partnerships and strategic alliances.

EDCTP establishes its strategy and scope by identifying critical areas of unmet medical needs in sub-Saharan Africa. Priority infections are identified based on factors such as disease burden, patterns, co-morbidities, co-infections, and the potential for public health crises. These target diseases include human immunodeficiency virus (HIV), tuberculosis (TB), malaria, neglected infectious diseases, diarrheal diseases, lower respiratory tract infections, and emerging and re-emerging infections, with special reference to antimicrobial resistance, and the impact of the climate crisis on infectious diseases.

The goal is to contribute to the reduction of the social and economic burden of infectious diseases through strategic funding and research initiatives. To prioritize funding effectively, several criteria are considered:

- First, a comprehensive analysis of the product development landscape is conducted. This involves examining the current clinical development status of medical interventions and innovations relevant to Global Health, particularly within the scope of EDTCP3.
- Global and regional priorities are also considered. This involves identifying research and development priorities and capacity-building needs, addressing policy and knowledge gaps to support evidence-based policy and practice.

- Funding is directed towards effectiveness studies, pharmacovigilance, and product-focused implementation research to overcome translational bottlenecks. These efforts aim to address barriers that hinder the clinical development and adoption of novel interventions.
- Strategic partnerships play a crucial role in this approach. By collaborating with like-minded partners, regional and global alignment is enhanced, enabling coordinated responses to policy and public health challenges. Leveraging EU initiatives and previous EDCTP investments further strengthens these efforts.
- Finally, a balanced portfolio of grants ensures that resources are allocated effectively across various disease areas, interventions, and study designs. This balanced approach maximizes impact and addresses diverse health needs, contributing significantly to the reduction of the social and economic burden of infectious diseases.

One major point of discussion was EDCTP's role in funding research on HBV mono-infection vs. HBV co-infection with a priority disease area. Given that HBV mono-infection is not listed in EDCTP's priority disease areas, funding for HBV research would have to be in the context of co-infection. Mechanisms exist which facilitate EDCTP's classification of HBV as a disease of unmet medical need eligible for funding. This includes leveraging existing epidemiological data to demonstrate the potential for public health crisis and encourage its prioritization for funding.

African Vaccine Regulatory Forum (AVAREF): Role in Research and Innovation

Presenter: Chinwe Iwu-Jaja**,** AVAREF

AVAREF is a network of 55 member countries with a vision of facilitating timely access to safe and efficacious products of assured quality. Dr. Iwu-Jaja indicated that biomedical research in Africah has surged in the past decade. Given this development, a regulatory platform is needed to improve expertise, access to therapies, and regulatory efficiency.

The level and extent of research and innovation in Africa is currently significantly lower than what is required, yet there are tremendous opportunities for growth. To capitalize on these opportunities, it is crucial for all parties to enhance their activities and approaches. This includes harnessing untapped resources such as the talent of African scientists and the continent's rich genetic diversity to produce innovative products for global use.

Capacity-building is a major focus for AVAREF. Establishing a platform for global research, where African researchers can effectively contribute, has the potential to be a game changer on the global stage. This is especially true when researchers collaborate with industry and the users of their research results. Such a platform would enable African researchers to make significant contributions to global scientific advancements.

A life cycle approach is necessary to ensure the viability of the vaccine research ecosystem in Africa. This approach entails efforts along the entire innovation life cycle, from design and development to product licensing, use, and disposal. By adopting this comprehensive strategy, the sustainability and impact of vaccine research can be ensured. The WHO and AVAREF are

committed to using their network approach, experience, and ability to bring multiple stakeholders together. Their goal is to strengthen the technical capacity needed for this initiative, ultimately fostering a robust and innovative research environment in Africa.

Panel Discussion

The panel discussed the delivery techniques for vaccines. One method that was discussed was the UNI Jack method which is used to administer vaccines to babies that are born outside of health facilities.

Dr. Heba Khalil of the Egyptian Drug Authority provided regulatory perspectives on drug development in Egypt. The country has gradually built its capacity to now have a Maturity Level 3. In addition, they have used support & funding from the WHO to conduct clinical trials within the country for polio vaccines. One of the factors that influenced this was the Cairo Declaration, which is a government measure to ensure that vaccines are developed in Egypt and supplied to various countries on the continent. For this mechanism to be effective, governments need to take the first step by asking their embassies in Egypt to approach the government and ensure that there is a clear pathway for the drugs/vaccines to be approved by the relevant regulatory authorities. This ensures that the customs protocols are established, and that there is a partnership mentality that is embraced.

The panel also highlighted the impact of the Africa Medicines Agency (AMA), which will be a specialized agency of the African Union dedicated to improving equitable access to quality, safe, and effective medical products in Africa. Successful regulatory harmonization across the continent will rely on strengthening of information and data systems such that data can collectively be collected and categorized for various development needs. Panel discussants emphasized that logistics are a major challenge to conducting clinical trials in Africa. Ensuring proper follow-up for trial participants is difficult given suboptimal or lack of infrastructure. These considerations must be addressed to conduct clinical trials in Africa.

Closing Remarks: Where Do We Go from Here?

The paradox that the WHO African region accounts for a significant global burden of HBV morbidity and mortality but only 1% of clinical trials is alarming. Given this glaring underinvestment, enhanced HBV clinical trial activity must be done in partnership with local scientists, health systems, civil societies, and people with lived experience of HBV. Embedding HBV clinical research into African communities is a key and necessary step to transition from research to practical implementation of screening, diagnosis, and linkage to care. To address these gaps, a coordinated and sustainable international response involving local and regional governments, industry, global health funders and donors, and increased community advocacy is urgently needed. Any externally funded research by international organizations, governments, and other funding entities should also ensure that research is African owned. These efforts will benefit all HBV stakeholders and would especially elevate the HBV community's voice in balancing benefits and risks as finite curative therapies progress through clinical development. By generating region-specific data and providing critical

scientific insights on safety and efficacy, including diverse African participants in HBV clinical trials would optimize progress towards achieving global HBV elimination targets. Through continued global collaboration that strongly emphasizes capacity building, ethical considerations, and equitable partnerships, we urge greater investment into HBV clinical research in Africa.