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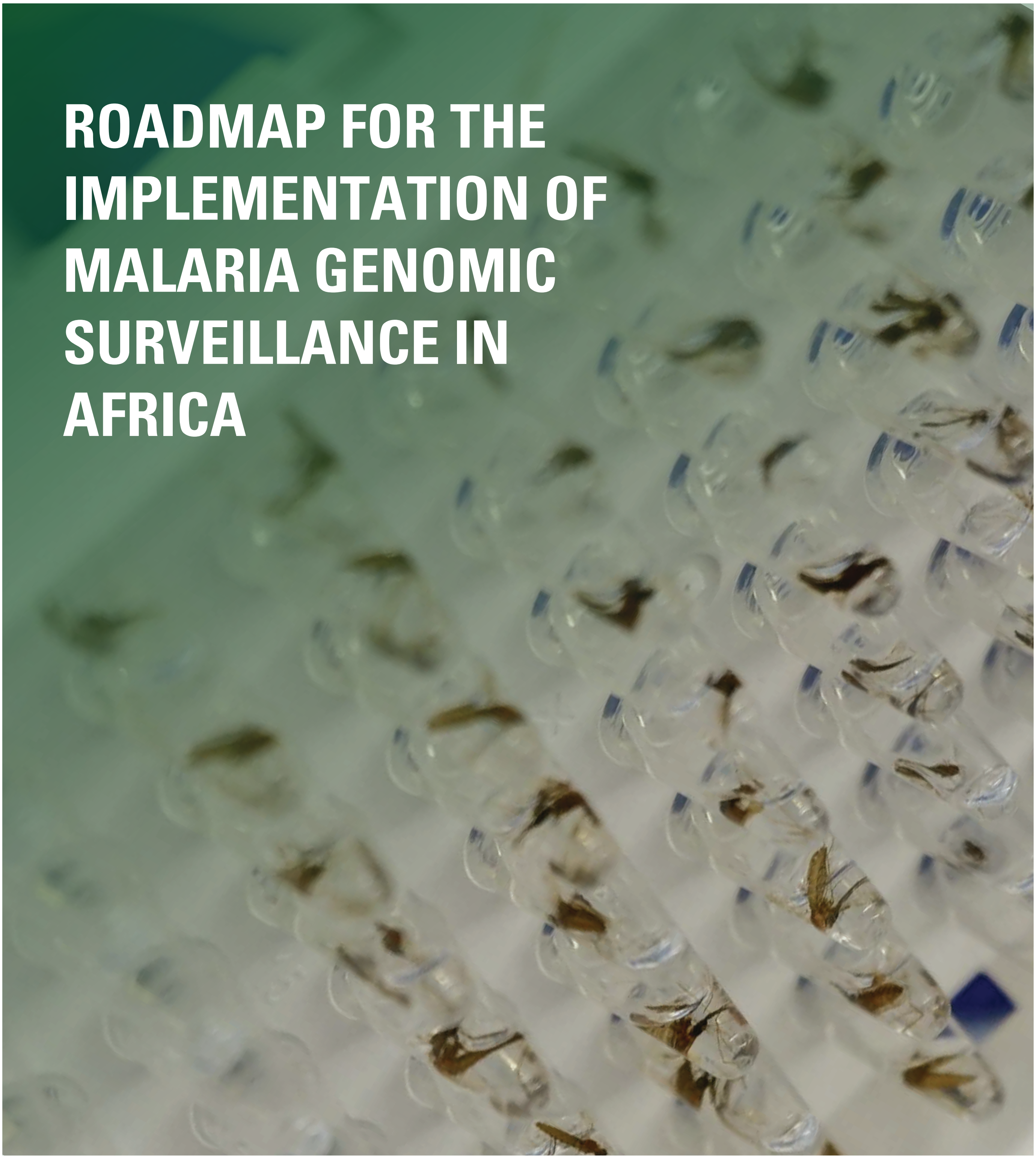
Safeguarding Africa's Health

ROADMAP FOR THE IMPLEMENTATION OF MALARIA GENOMIC SURVEILLANCE IN AFRICA



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Africa CDC is a continental autonomous health agency of the African Union established to support public health initiatives of Member States and strengthen the capacity of their public health institutions to detect, prevent, control and respond quickly and effectively to disease threats.

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FOREWORD

Malaria poses a significant public health burden in Africa, characterized by high morbidity and mortality rates, particularly among vulnerable populations such as children under five and pregnant women. The disease not only causes individual suffering but also strains healthcare systems and hampers economic development in endemic regions. Given the scale of the challenge for malaria elimination, resources are limited. Funding and healthcare infrastructure significantly impact prevention, diagnosis, and treatment efforts. Malaria parasites are becoming increasingly resistant to antimalarial drugs, and mosquitoes are similarly developing resistance to insecticides, thereby compromising their efficacy. There is insufficient data on malaria transmission, prevalence and resistance patterns, which limits the ability to deploy available resources to deliver maximum public health impact.

Despite this, the global progress towards malaria control and elimination over the last 15 years is commendable. Collaboration and innovation have substantially decreased morbidity and mortality in most endemic settings. But in recent years, progress has stalled. Drug resistance, diagnostic test resistance, insecticide resistance, and invasive mosquito species are all threatening progress.

To combat these threats to control and save more lives, we must better understand the ever-changing landscape of malaria parasites and vectors at the molecular level. We must implement malaria genomic surveillance. Strengthening surveillance systems is crucial to achieving elimination targets and integrating molecular and genomic techniques into routine surveillance could substantially enhance the quality and robustness of data to inform critical public health policy decisions. The power of genomic surveillance to accelerate disease elimination has been demonstrated on a global scale by the global response to the pandemic. Genomics has elucidated the disease transmission of tuberculosis and HIV for example. Similarly, strategic, well-connected, continent-wide genomic surveillance can accelerate the elimination of malaria and other diseases and prepare us for future pandemics.

In April 2022, the Africa Centres for Disease Control and Prevention (Africa CDC) commissioned an expert group to develop a roadmap for malaria genomic surveillance of public health use cases in Africa. This roadmap, culminating in consultation and research from an expert group, aims to empower the Africa CDC and the continental network of institutions for malaria molecular surveillance (MMS). By building on existing knowledge, partnerships and infrastructure, we can create an integrated ecosystem that accelerates malaria elimination and contributes to global health security.

H.E. Dr Jean Kaseya,
Director General, Africa CDC

EXECUTIVE SUMMARY

Africa bears the most significant malaria burden of cases and deaths globally. Despite considerable advances over the past few decades, the progress towards elimination is stalling. In recent years, while deaths have decreased compared to what was observed in the early 2000s, the reduction in malaria incidence has slowed down following an initial decline. If we continue with our current strategies, we will not meet malaria elimination targets. A crucial component of this change is the development of improved surveillance systems and tools that provide decision-makers with data and actionable knowledge. The investment in genomic platforms for enhanced surveillance of COVID-19 surveillance has facilitated a genomic revolution that can be leveraged for the surveillance of endemic diseases.

The primary goal of malaria molecular surveillance of malaria is to save lives through direct and indirect improvements in public health interventions. In 2022, a technical working group for genomic surveillance of malaria was established by the Africa Centres for Disease Control and Prevention (Africa CDC) with two goals: (1) To deliver a roadmap for implementing a continent-wide approach and (2) To integrate malaria molecular surveillance into the malaria control and elimination toolbox.

Four pillars underpin this roadmap: driven by public health needs, country leadership, a continent-wide strategy, and sustainable implementation. A strategic and sustainable implementation approach is outlined, which complements the WHO Global Genomic Surveillance Strategy guidelines. An end-to-end genomic surveillance framework is provided that outlines both the steps and cross-cutting challenges that need to be addressed.

Global use cases for genomic surveillance of malaria have been prioritised for Africa. They have been stratified into three distinct tiers. The highest priority use cases are **Tier 1,** which are:

- Antimalarial resistance.
- Malaria parasite resistance to rapid diagnostics.
- Malaria vectors are resistance to insecticides.
- Indigenous and invasive vector species.

The highest priority use cases mentioned above have established molecular and genomic surveillance approaches. They serve to guide those at the earliest stages of generating data for molecular and genomic surveillance and to focus on those generating data to accelerate the integration of that data into interoperable data resources.

Tier 2 use cases focus on those of high priority for public health but are not yet ready for continent-wide implementation across the continent. These use cases require investment from early adopters to transform them into multi-laboratory, implementation-ready products in the near term.

Tier 3 use cases are those for advanced users who are likely also leading internationally recognized research programs in malaria genomics.

A phased implementation approach for a continental network of institutions for malaria molecular surveillance, with reference laboratories, regional hubs, and national nodes, provides the necessary flexibility to meet country, regional and continent-wide needs. The roadmap concludes by addressing the need for harmonization activities across products for multi-laboratory implementation, data and data processing platform interoperability, advocacy and education, and the development of community standards.

Malaria molecular surveillance (MMS) plays a crucial role in the elimination of malaria by providing detailed insights into the biology and behaviour of the malaria parasite, Plasmodium, as well as its vector, the Anopheles mosquito. Identifying markers for antimalarial drug resistance and their monitoring. Tracking transmission dynamics and understanding transmission networks to identify hotspots. Identifying markers for vector resistance and monitoring its movement through the population. Supporting vaccine development through identifying key antigens and targets and considering genetic variability and evaluating control interventions by assessing changes in target populations and providing important feedback on their current and future effectiveness. MMS is therefore a powerful to accelerate the elimination of malaria in Africa. Member States should, therefore, integrate genomic surveillance into their national plans while remaining cognizant of continent-wide objectives; continental strategies must allow for the flexibility needed for Member States to meet national goals. Funders, regional organisations, civil society organisations, national regulatory agencies, academics, the malaria research community, and genomic surveillance implementation partners must also consider the harmonization required to implement this roadmap successfully.

This document offers guidance focusing on public health response and should be considered a living and dynamic roadmap for implementation. Any additional insights that may emerge because of scientific or operational advances will continue to be integrated into the roadmap, which aims to be a flexible guide to sustainable implementation

ACKNOWLEDGEMENTS

The Africa Centres for Disease Control and Prevention (Africa CDC) would like to thank all the contributors whose efforts helped to develop this Roadmap for the Implementation of Malaria Genomic Surveillance in Africa:

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ABBREVIATIONS AND ACRONYMS

ABBREVIATION	FULL TERM
Africa PGI	Africa Pathogen Genomics Initiative
CDC	Centres for Disease Control and Prevention
CoE	Centre of Excellence
CRF	Case Report Forms
DBS	Dried Blood Spots
ENA	European Nucleotide Archive
GMP	Global Malaria Programme
IRS	Indoor Residual Spraying
ITN	Insecticide-Treated Nets
KDR	Knock Down Resistance
MFO	Mixed-Function Oxidase
MoH	Ministry of Health
MMS	Malaria Molecular Surveillance
MPAC	Malaria Policy Advisory Committee (later became MPAG)
MPAG	Malaria Policy Advisory Group
NMPs	National Malaria Programmes
PAMCA	Pan-African Mosquito Control Association
PARMA	Antimalarial Resistance Monitoring in Africa
PCR	Polymerase Chain Reaction
PDNA	Pathogens Genomic Diversity Network Africa
PIS	Participant Information Sheet
PMI	President's Malaria Initiative
TES	Therapeutic Efficacy Studies
VGSC	Voltage-gated Sodium Channel
WHO	World Health Organization

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1.

BACKGROUND

1.1. Genomic surveillance to tackle endemic disease

Near real-time tracking of the genetic landscape of malaria parasites and vectors using genomic surveillance has long been a goal of the malaria research community. By understanding the evolution of the malaria parasite and its vectors and integrating that knowledge into public health practice, malaria control programmes can better respond with effective drugs, insecticides, and other interventions.

Over the past three decades, the science and technology required to make this goal a reality have moved iteratively from blue-sky research into the realm of public health utility. The advancement of technology and broader implementation, which had been building for years, was jump-started by a rapid increase in public awareness and genomic capacity in Africa during the COVID-19 pandemic.

At the earliest stage of the COVID-19 pandemic, the infectious disease genomics community responded to the demand for urgent action. In response to this worldwide public health threat, they reprioritised all their efforts to focus on the rapid, helpful, and open delivery of genomic geo-temporal surveillance data, which is valuable for public health decision-making on both local and global scales. All elements to deliver a quality product in a short timeline and at scale were accelerated, including sample collection and processing, supply chain and procurement, and data sharing. While it is challenging to apply the same level of response to an endemic disease as in a pandemic situation, there are lessons to be reapplied in tackling more entrenched public health threats, such as malaria.

Malaria, endemic to many African countries, has a very complex life cycle that demands a more elaborate and integrated package of control strategies. Due to this complexity, and the variability in transmission across the continent, it cannot be addressed by a 'one size fits all' response. Although the WHO guides countries and has specific national strategic plans, malaria parasites and vector species are not limited by country borders. Cross-border surveillance is crucial in addressing regional risks, such as the emergence and spread of antimalarial and insecticide resistance. To strengthen surveillance, malaria-endemic Member States need to implement harmonised systems to achieve genomic surveillance of malaria at local, national, regional and continental levels.

The progress that has been made so far has relied heavily on isolated academic and research institutions; however, the investment and infrastructure required to deliver continent-wide genomic surveillance will necessitate cross-sectoral collaboration and partnerships among public health, educational and research institutions, aligning with national, regional, and global priorities.

> The global genomic surveillance pandemic response was possible because it was built on lessons learnt from existing endemic disease surveillance.
>
> Endemic disease genomic surveillance must now learn from the pandemic response.

Considering malaria genomic surveillance in Africa, it is helpful to consider the strengths, weaknesses, opportunities and threats.

Strengths include providing early detection of malaria outbreaks, enabling decisive public health action. This strength will intensify over time alongside increased knowledge of the causes of outbreaks made possible by the integration of genomic data with additional metadata (climate, intervention deployment, etc). Understanding genetic mutations within malaria parasites and vectors will support the development and deployment of targeted interventions, facilitating advances in new interventions, such as vaccine development. The advances in technology in recent years have greatly diversified the potential for data generation and analysis in Africa. The capability for genomic surveillance has increased significantly in recent years, particularly since the COVID-19 pandemic, making it especially timely to build on these strengths. This can best be achieved through strengthening collaboration among researchers, healthcare providers, and governments, creating a robust framework for national, regional and continent-wide responses to malaria threats.

Weaknesses in the cost of malaria genomic surveillance are noteworthy. The initial investment in the necessary infrastructure is considerable, although it has decreased in recent years. Infrastructure encompasses not only the cost of equipment but also the personnel expertise required to manage, interpret, and integrate data into public health decision-making. There is considerable leadership in genomic surveillance of malaria in Africa already, but it is unevenly distributed. While the flexibility in generating data is beneficial in terms of building capability, the integration of data from multiple sources generated by different technologies requires harmonisation to store, manage, and share the data. Finally, engagement with national and regional public health leaders is essential to ensure buy-in into relevant strategies.

Opportunities are timely around public awareness of the critical importance of genomic surveillance for public health arising from the pandemic. As a result of visionary African leaders in the field, there is an evidence base for the successful implementation of genomic surveillance of malaria, which can provide a foundation for those newer to the domain. For example, they can show how the integration of genomic data into existing malaria control programs has been instrumental in enhancing the understanding of transmission dynamics and resistance patterns. Continuous innovations in sequencing technologies are making genomic surveillance not only more accessible but also significantly more cost-effective. This should further improve with greater demand from the continent.

Threats include the continued hesitancy surrounding data privacy and sharing. There is also considerable competition for resources, including funding and expertise, for other public health initiatives. Genomic surveillance is relatively novel and, therefore, could be seen as superfluous compared to more established approaches. The landscape for global health funding is also effected by political and economic instability in national, regional and international contexts.

1.2. An integrated ecosystem for malaria elimination and global health security

In 2019, a WHO global technical consultation on genomic surveillance of malaria recognised seven priority public health use cases and further identified those that had the potential to provide data to WHO in the near, medium, and long term. Progress on these use cases has been slow. In part because of the pandemic, even those that were predicted to provide data within 12 months have not yet been realized.

Several initiatives in Africa outlined in this roadmap in Africa now generate malaria molecular surveillance data and integrate that data with national public health activities. Each has been driven forward in the context of a specific country; additional work is needed to strengthen country-led approaches across Africa, to form part of a continent-wide strategy.

One of the leading continent-wide initiatives is the Africa CDC Institute of Genomics with its Africa Pathogen Genomics Initiative (Africa PGI), which was established in 2020. This initiative aims to enhance disease surveillance and public health partnerships through integrated, cross-continent laboratory networks equipped with the necessary tools, human resource capacity, and laboratory and data infrastructure to leverage advances in critical genomic sequencing technologies. These could, for example, address cross-cutting challenges for genomic surveillance across Africa, or update guidance based on new methods of data analysis and interpretation.

The Pathogens Genomic Diversity Network Africa (PDNA) has a broad remit that includes engagement with national malaria programmes (NMPs) and mapping of requirements for integrating genomic surveillance into public health. PDNA conducts regional malaria genomic programmes in 16 sub-Saharan African countries.

The Pan-African Mosquito Control Association (PAMCA) is an international organization dedicated to vector control and the elimination of mosquito-borne diseases, such as malaria. It has a genomic surveillance program for malaria vectors in nine African Union Member States. PAMCA also works with the regional centre of excellence, where vector genomic analyses of insecticide resistance are conducted.

The WHO Global Malaria Programme (GMP) coordinates WHO's global efforts to control and eliminate malaria. Its work is guided by the Global Technical Strategy for Malaria 2016–2030, adopted by the World Health Assembly in May 2015 and updated in 2021. The GMP is committed to supporting Member States in achieving the global technical strategy targets.

The President's Malaria Initiative (PMI) and the PMI-supported Antimalarial Resistance Monitoring in Africa (PARMA) Network assist PMI countries in testing malaria samples from therapeutic efficacy studies (TES) for genetic markers associated with antimalarial resistance across 27 countries. PMI also performs molecular surveillance of malaria vectors.
Each of these agencies has a complementary remit to tackle African challenges.
They are each making strides towards operationalising routine genomic surveillance of malaria. Adding to these efforts are international stakeholder groups, research networks, governments and funding agencies.

A coordinated approach from all key stakeholders and implementation partners, including governments, national regulatory authorities, research partners, donors, funders, and the community, is essential to accelerate the implementation of a continent-wide genomic surveillance of malaria. Existing capacities and approaches must be harmonised and incorporated into the continent-wide strategies.

The capability and capacity for genomic surveillance for endemic disease that can be deployed and repurposed for outbreak response will further safeguard the health and economic security of the continent and the world.

The commitment of a diverse group of stakeholders to tackle malaria. Genomic surveillance will be an essential component of success.

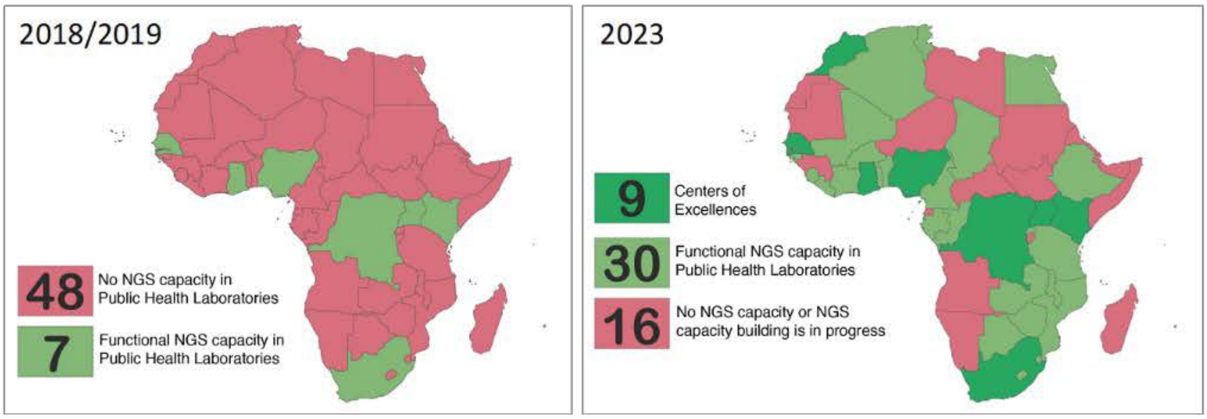
This includes policy makers, public health professionals, experts, implementing partners, non-governmental organisations, and funders both in Africa and globally.

1.3. Building on existing genomic surveillance capacity

Genomic surveillance for disease control is a recommended integral part of control and elimination strategies for diseases such as tuberculosis, HIV, foodborne pathogens, hepatitis B and C, as well as other public health issues, including antimicrobial resistance. [1] The capability and capacity for scale, geographic representation, and integration with clinical and/or epidemiological surveillance data necessary for public health impact have been insufficient; however, there are examples. Following multiple outbreaks, a genomic surveillance capability and capacity for Ebola were established in the Democratic Republic of Congo[2] for Lassa fever in Nigeria[3] and for Tuberculosis in South Africa[4].

The rapid rollout of genomic surveillance during the COVID-19 pandemic led to a significant increase in both technological capability and public awareness of the potential of genomics to inform public health decision-making. Amplicon panels, a previously used technique for selectively sequencing multiple small regions of interest from malaria parasite genomes, were rapidly developed for SARS-CoV-2, the virus that causes COVID-19. The design and implementation took a matter of months. The laser-sharp focus on decreased turnaround times resulted in impressive surveillance networks. This experience is valuable for building genomic surveillance for malaria.

Figure 1 : Capacity of pathogen genomics sequencing in Africa



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[1] Global genomic surveillance strategy for pathogens with pandemic and epidemic potential, 2022–2032, WHO, March 2022 https://www.who.int/publications/i/item/9789240046979

[2] Integration of genomic sequencing into the response to the Ebola virus outbreak in Nord Kivu, Democratic Republic of the Congo. Nat Med 27, 710–716 (2021). https://doi.org/10.1038/s41591-021-01302-z

[3] Genomic Analysis of Lassa Virus during an Increase in Cases in Nigeria in 2018. N Engl J Med 2018; 379:1745-1753 DOI: 10.1056/NEJMoa1804498

[4] Whole genome sequencing for drug-resistant tuberculosis management in South Africa: What gaps would this address and what are the challenges to implementation? J Clin Tuberc Other Mycobact Dis. 2019 doi: 10.1016/j.jctube.2019.100115.

Capitalising on the investment made available for genetic data-generating infrastructure during the pandemic, and with additional support since then, the genomics landscape has undergone significant transformation in recent years. The functional next-generation sequencing capacity in public health laboratories has accelerated. By the end of 2025, it is expected that all Member States will have local genomics data generation capabilities.

WHO encourages establishing genomic surveillance capability for pathogens of pandemic potential. To maintain and build scientific, technical, and operational infrastructure and expertise to build global health security resilience requires the application of the technology in a non-pandemic context.

Malaria is a complex disease. Plasmodium parasites and their Anopheles mosquito vectors have large, complex genomes, exhibit sexual recombination in the vector, and are epidemiologically and biologically more complicated than viral and bacterial pathogens. Through research into the genomic epidemiology of malaria parasites and vectors, resistance markers have been identified and transmission pathways elucidated. One of the foundations of the WHO's strategy for malaria elimination is to make surveillance a "core intervention." By integrating genomics into malaria surveillance, through the implementation of an end-to-end process that encompasses sample collection, data generation, and the translation of data, it is possible to deliver meaningful and actionable outputs that can accelerate elimination.

A consolidated community effort is needed to achieve this, which will require local initiative and leadership that brings together the relevant stakeholders and priorities across a large number of endemic countries. The development of a continent-wide strategy that harmonises approaches and policies and fosters an open information culture will enable the facilitation of both country-centred and continent-wide collaborations.

2.

APPROACH

2.1. Objectives and scope

The overarching objective of this roadmap is to define a pathway for the iterative strengthening of genomic surveillance of malaria infrastructure and a framework for the systematic generation and utilisation of genetic data for

This roadmap provides steps to establish effective and sustainable systems for genomic surveillance of malaria parasites and vectors in Africa. The goal of these systems is to integrate genomic surveillance into the activities of NMPs, enabling genomic data to support decision-making on malaria diagnostic and treatment guidelines, vector control interventions, and public health control measures.

To fulfil this goal, end-to-end genomic surveillance systems include several components:

- Well-defined use cases informed by public health needs, developed by subject matter experts, and iteratively improved over time with lessons learned through the process.
- The development of in-country sampling frameworks leveraging existing sampling infrastructure, where possible.
- The establishment of regional and national sequencing laboratories, coupled with capacity building.
- The generation of data through those hubs.
- The management and sharing of the resulting genetic data.
- The translation of genetic data into actionable information for public health.
- The integration of this information into public health systems.
- An efficient engagement of Governments, health policy makers, civil societies and communities for optimal impact.

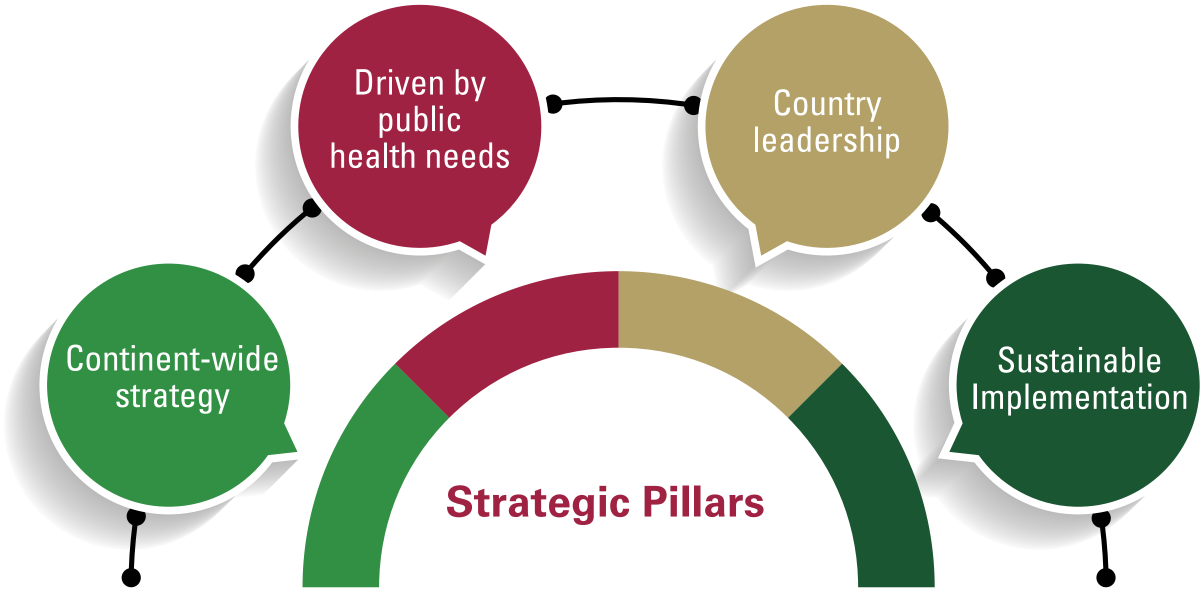
This roadmap outlines steps to be taken in the short, medium, and long term, introducing pilot activities for new interventions and collaborating to address cross-cutting challenges in genomic surveillance of malaria in Africa.

The roadmap considers all member states as part of the geographical coverage. The expectation is that the activities will vary depending on whether a country has a malaria-free, low, medium, or high transmission status. There are use cases relevant to each setting, including the importation of cases. Importantly, this roadmap considers country and continent-wide public health priorities. As a continent, malaria is a public health priority.

2.2. Strategic Pillars

Keeping in mind global WHO initiatives, we propose four strategic pillars (Figure 2) for the genomic surveillance of malaria in Africa.

Figure 2 : Four strategic pillars that underpin the roadmap



Driven by public health needs

Public health-informed decision-making is the pillar through which genomic surveillance of malaria will have a positive impact. Genomic surveillance could provide a critical evidence base for proposed recommendations, policies and implementation plans, as decisions informed by biological realities, such as drug, insecticide, or diagnostic resistance and other genomic use cases, will result in better health outcomes. To provide the most significant impact, all aspects of genomic surveillance must adapt to the needs and constraints of public health, including:

- Focusing on use cases that can maximize public health impact.
- Designing sampling frameworks that cover areas and populations of most significant public health interest, while remaining cost-effective and sustainable.
- Implementing sample handling and processing procedures that minimize turnaround time for timely results. Translating raw data into accessible formats that are easily usable and understandable by decision makers without a background in genetics; training public health staff in using the results.
- Effectively engaging Governments, health decision-makers, civil society and communities for maximum impact.

Country Leadership

The African continent demonstrated decisive leadership throughout its response to the COVID-19 pandemic, leveraging lessons learned from previous outbreaks and acting quickly to limit the impact of the SARS-CoV-2 virus. NMPs can build on these successes that call for greater collaboration between Member States. NMPs are the subject matter experts when it comes to tackling malaria in their countries. As genomic surveillance technologies and methods advance, they are best placed to integrate genomic surveillance into their malaria control or elimination strategic plans. This could include:

- Establishing national malaria genomic surveillance systems based on local priorities and relevant to interventions of malaria parasites and their vectors.
- Strengthening existing national genomic systems to support additional priority use cases.
- Scaling up capacity and capability for genomic systems to support regional surveillance through prompt data sharing and collaborative activities with neighbouring countries.
- While focusing on meeting nation needs, every effort should be made to harmonize with regional and global strategies.

Continent-wide Strategy

Regional pathogen genomic surveillance (e.g., HIV, COVID-19, TB) has been shown to provide additional benefits in informing public health decisions[5] . Mosquitoes and parasites do not respect international borders. Cross-border genomic surveillance in sub-Saharan Africa is needed to address the emergence and spread of relevant genetic variants of malaria parasites and vectors in public health. However, it requires that data is not only shared among countries; interchange of data formats is essential to merge datasets for regional analyses and public health insights.

To achieve the above, the key requirements include:

- Harmonized sampling frameworks, laboratory protocols and data resources.
- Increased geographical coverage of malaria genomic surveillance data.
- Timely data sharing among countries.
- Regional analyses for policy decisions and public health impact.

Sustainable Implementation

Continent-wide genomic surveillance necessitates a sustainable implementation approach to achieve a public health impact. Financing in a sustained manner from diverse sources, with national funding as the main driver, is critical. Multiple funding streams, such as government, development partners, the private sector, and research funding, used collectively towards a common goal, will mitigate the risk of defunding or underfunding due to competing priorities. The sustainability strategy must be costed against a robust implementation plan, including contingencies, and identify opportunities to leverage resources effectively.

Key considerations for sustainable implementation include:

- Integrated genomic surveillance with existing national malaria surveillance strategies.
- Increased local and international funding to support genomic surveillance.
- Cross-border sample referral and data sharing.
- Cross-disease optimization such that malaria genomic surveillance is not set up as a silo.

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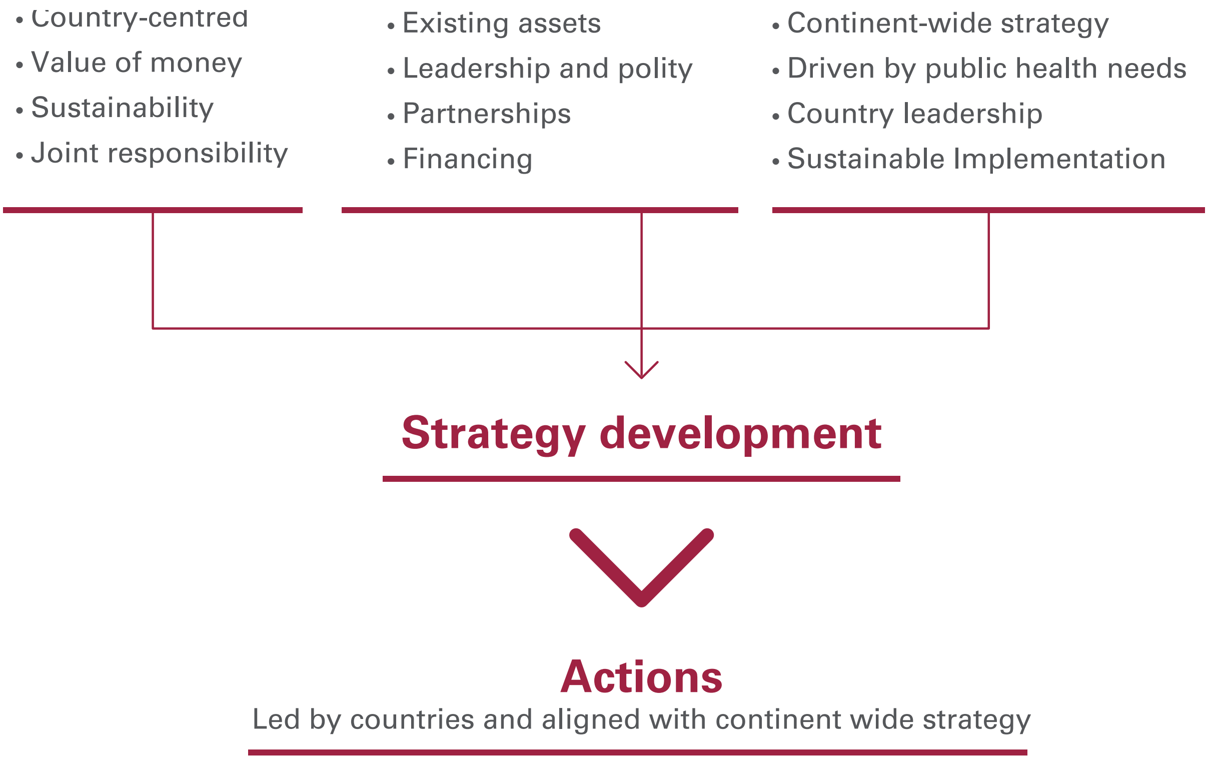
[5] Inzaule SC, Tessema SK, Kebede Y, Ogwell Ouma AE, Nkengasong JN. Genomic-informed pathogen surveillance in Africa: opportunities and challenges. Lancet Infect Dis. 2021 Sep;21(9):e281-e289. doi: 10.1016/S1473-3099(20)30939-7. Epub 2021 Feb 12. PMID: 33587898; PMCID: PMC7906676.

2.3. Strategic Approaches

Implementing successful genomic surveillance for malaria is a complex process. The hurdles include uncoordinated public health surveillance systems; variable laboratory capacity; unreliable access to IT infrastructure; limited technical capacity; lack of systems and capabilities; procurement challenges, poor prioritization in the roll out of use cases; difficulties translating analytical results; lack of analysis and visualization tools; competing priorities in national governments and limited resource envelope; and between national governments and other funding agencies.

To begin addressing these challenges, the WHO Global Genomic Surveillance Strategy[6] was reviewed to identify the relevant principles and enablers for an African genomic surveillance of malaria strategy (Figure 2).

Figure 3 Principles, enablers and strategic pillars inform strategy development and actions (redrawn and adapted from WHO Global Genomic Surveillance Strategy)



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[6] WHO Global Genomic Surveillance Strategy 2022 https://www.who.int/initiatives/genomic-surveillance-strategy

Guiding Principles

Core principles guide the framework, providing a solid foundation.

Country-centered

- Each country has its own unique context. This includes capacity, priorities, budget, malaria epidemiology, size, ecology, and physical environment. An understanding of these factors is crucial for enabling flexible and informed implementations.
- Vectors and pathogens travel across borders, spreading insecticide, drug resistance, and other genetic traits. Therefore, regional approaches are essential for cross-border genomic surveillance. This should include cross-border strategies and analyses alongside individual country needs to foster mutual support and benefit. Robust communication between countries is necessary for productive regional discussions on data, outcomes, and actions, as well as for promoting openness and a willingness to share data and knowledge.

Value for money

- Limited budgets and competing priorities can hinder individual countries from engaging in genomic surveillance. Countries must consider cost-effectiveness strategies and right-sizing for every component of the surveillance system.
- Sampling networks can be costly and resource-intensive. Simplifying sample collection and management procedures, while integrating them tightly into national public health processes, can lead to significant cost reductions.
- Consider whether better value could be achieved through regional hub laboratories that provide shared processing services. This may begin as a pilot stage before deciding whether to implement it nationally, or it may be considered when there are low volumes and, therefore, no economy of scale, e.g., in the near-elimination stages. It is noteworthy that the transfer of samples across borders can be expensive, increase sample-to-data turnaround time and that meeting regulatory requirements, such as those under the Nagoya Protocol, can be time-consuming.
- Informatics infrastructure, including data storage and processing capabilities, represents a significant and often underestimated part of the budget. The optimal solution for any one country will depend on its existing infrastructure, the partnerships that are in place, and whether it can set up and maintain physical or cloud-based infrastructure. The connectivity available will also determine if cloud-based infrastructure is an option at the time of decision-making.
- Due consideration needs to be given to national and continent wider needs. They can also assess the reliability, network accessibility, desirability of owning and maintaining physical equipment, and the reliability of informatics partners for support where needed.

- Consider investment in upgrading laboratory equipment and infrastructure to provide a service to other regional implementers of genomic surveillance.
- Stakeholders should be encouraged to work closely with regional CoEs to perform genomic surveillance activities for both parasites and vectors.
- Economies of scale will be essential to exploit. These are made stronger by standardised protocols and consolidated purchasing.
- Leverage existing capacity across diseases and institutions.

Sustainability

- In the long term, countries must own and run their genomic surveillance systems as part of their routine processes. This will require the development of right-sized, integrated systems, and the allocation of appropriate local resources that national malaria budgets can sustain.
- The COVID-19 pandemic generated increased public awareness of genomic surveillance, a stronger political will, and specifically earmarked NGO funding, catalysing an increase in genomic surveillance capacity across Africa. Malaria surveillance needs to capitalize on this momentum and sustain it in non-pandemic circumstances.
- Continuous assessment and refinement of genomic surveillance systems will be key to monitoring ongoing sustainability.

Joint responsibility

- All stakeholders who should bear responsibility for different aspects of strategy and implementation, including NMPs, funders, experts, community leaders and others. It will be essential to define and assign duties during the implementation phase.
- Elimination of malaria will require regional collaborations, data sharing and joint analyses. Countries will need to take collective responsibility for making regional efforts succeed.

Enablers

Each enabler is required to support the appropriate implementation of the core principles, which underpin multiple areas.

Existing assets

- Several local and regional assets, as well as ongoing projects, currently support the generation of sequence data for genomic malaria surveillance. Mapping existing assets and assessing whether they are appropriate for incorporation, strengthening, or adjustment will optimize the efficiency of the resulting systems. This includes laboratory assets and extends to all required resources, such as team capacity, analytical capabilities, surveillance strategies, data storage and computational systems, as well as community and stakeholder engagement capacity.

Leadership & policy

- Effective leadership is necessary at all levels, including community, local, national, and regional levels.

- Leadership roles should be identified in stakeholder mapping, alongside any opportunities for leadership development.
- From the WHO Global genomic surveillance strategy - "Those who drive the strategy must be empowered to advocate for capacity building and capability development to promote genomic surveillance in local to global public health practice".

Partnerships

- Surveillance systems require building partnerships between research, public health, and government. Many partnerships already exist and should be leveraged, including those with international research collaborators and funding bodies.
- When planning a strategy, it is essential to acknowledge that relationships will change and define appropriate boundaries to help navigate these changes effectively.

Financing

- Financing in a sustained manner from diverse sources is critical. Multiple funding streams will mitigate the risk of insufficient funding through competing priorities. Potential national funding streams include overarching health budgets, malaria-specific budgets, or surveillance. The strategy must be reliably costed against a robust plan, with contingencies included.
- Funding agencies should encourage participation in endorsing regional collaborations. However, ownership by countries (i.e. ministries) supported by explicit national budget lines, should be a long-term goal.

2.4. Strategy development and implementation

Each member state should develop a tailored strategy for malaria molecular surveillance that addresses its specific needs and requirements. One size does not fit all. National public health needs, as well as regional and continental strategies, must be incorporated into the development. Having considered available resources, the strategy should also plan for sustainable implementation in an appropriate timeline.

Each member state's strategy should:

- Plan for the sustainable implementation of a genomic surveillance system that meets national public health needs within its specific context. Plans should consider cross-border collaboration and continent-wide objectives in addition to national public health needs.
- Ensure plans are flexible and adaptable to changes in funding and the scientific and public health landscape. A phased approach could be considered to gradually implement and extend genomic surveillance capability as the needs for new specific use cases are met.
- Contribute to addressing cross-cutting challenges, including sampling frameworks, laboratory standard operating procedures and external quality assurance, procurement, maintenance, data integration and

analytics, and training and capacity building.

- Harmonize protocols and procedures, share knowledge within country laboratory networks, adopt standardized data formats where available, and integrate expertise and data into national repositories and public health systems.
- Advocate for national funding to support and sustain genomic surveillance.

Each member state should develop a genomic surveillance strategy for malaria.
The generation and integration of data into public health decision-making.

2.5. End-to-end genomic surveillance framework

Genomic surveillance of malaria parasites and vectors, along with curated associated metadata, provides an opportunity to study malaria and broader pathogens, as well as their transmitting vectors. These data can be integrated with information routinely collected through national public health systems, such as travel and demographic data, which can support epidemiological and transmission analyses. This would provide a strong foundation for genomic data-informed public health decision-making. The implementation of a genomic surveillance framework for malaria, which can be adapted for other pathogens and vectors, increases the opportunities for CoEs in genomic surveillance that address multiple public health challenges. (Figure 4).

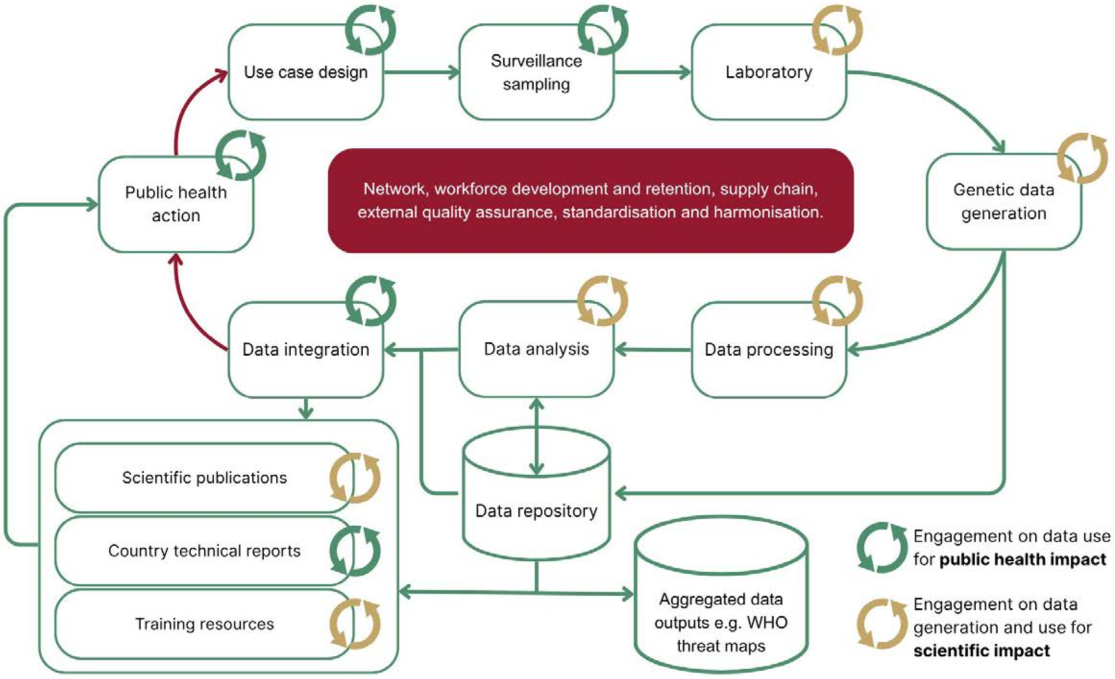


Figure 4 End-to-end malaria genomic surveillance framework.

The framework comprises several steps and outputs, all of which should be informed by public health needs and priorities. They are:

Public health action

The initial implementation will involve understanding the public health actions that can be informed by genomic surveillance data and mapping them to the next step. Once a framework is in place, it can then become what can be adapted to make the data more useful or the integration more efficient. Public health action includes informing, purchasing and rolling out of disease diagnostics and control or elimination measures.

Use case design

There are many use cases for genomic surveillance for global health. For any given context, the relevant public health bodies must inform the prioritization of use cases. In recent years, considerable efforts have been made in use case design in several disease areas. These may need to be adapted for use in a specific context.

Surveillance sampling

The sampling framework should be a part of the use case design; however, in most cases, a high-level guide is currently provided. Country transmission levels will strongly influence national sampling frameworks. Genomic surveillance sampling can leverage existing sampling frameworks (ensuring appropriate ethics requirements have been met); therefore, public health bodies will need to consider both the high-level guidance in the use case and the available sampling frameworks to leverage to make resource savings in their context. The sampling framework should be guided by statistically informed sample size guidelines, where possible.

Laboratory

Laboratory techniques focus on every step, from sample collection and compliance to receiving samples, to sample and metadata management, and minimally destructive DNA extraction and molecular methods. The capacity should be sufficient to meet the sampling strategy for national needs. Additional capacity could be provided to neighbouring countries through a partnership arrangement.

Genomic data generation

The generation of raw data is a transition step between the laboratory and data processing. The generation of genetic data will continue to evolve incrementally. Where there are CoEs with capability for multiple genomic techniques, the same sample may be used to generate genomic data using different platforms. When undertaken as standard on a subset of samples, this will provide a measure of internal quality assurance for a laboratory, or external quality assurance if the service is provided to another laboratory.

Data processing

This step encompasses everything from raw data to analysis-ready data. This step may involve contributions from wet and dry laboratory scientists and includes standard bioinformatics steps to ensure data is of appropriate quality and in a suitable condition for analysis. Ideally, this process should follow a standard procedure; if not, it should be well-documented so that standardization of similar methods can be implemented appropriately.

Data analysis

With analysis-ready genetic data in hand, data analysis involves interrogating the data to elucidate information relevant for public health use initially. This could include combining data from additional data sources, such as clinical and environmental metadata. The data analysis outputs should be produced systematically for the use case, allowing for standardised data integration with public health systems can be standardized as far as possible. Analysis steps should be well-documented and openly accessible in forums such as GitHub, which promote reproducibility and withstand scientific scrutiny.

Data integration

Data analysis outputs must be integrated with public health data resources, enabling public health decision-makers to incorporate genomic data into their decision-making confidently. This is likely to require ongoing engagement, particularly in the early stages, which should involve health policymakers and other government bodies, civil society, and the broader community.

Data repository

A non-circular step involves depositing both raw and analysis-ready data into a digital data repository archive for genetic data generation and analysis analysis. This provides security in case local data storage systems are insufficient, interrupted, or fail to function. It also provides a resource for secondary analyses that can drive forward disease intelligence. Data intended to generate action and public health impact should be shared promptly, and no later than 12 months from generation. To achieve this, national public health bodies should establish data governance mechanisms to facilitate the sharing of data. For both raw data and analysis-ready data, the terms of engagement for secondary data use should be clear and appropriate for the disease and context.

Aggregated data outputs

Available resources for malaria include aggregated data resources such as WHO threat maps. The incorporation of genomic surveillance data on malaria data into global aggregated data resources is strongly encouraged. Such resources promote data sharing and extend the knowledge produced nationally through genomic surveillance. They also provide information to national and regional authorities to inform their disease control and elimination strategies and serve as an advocacy tool for the utility of genomic surveillance.
Scientific publications – African researchers are driving forward analyses of malaria genomic data, a crucial output from these multipurpose datasets, concerning scientific discovery, workforce development, and retention.

Country technical reports

The benefit of a centralised data repository comes from being able to compare one nation's malaria profile with another, either from a neighbouring country or another area with a similar transmission profile.
Training resources – Existing publicly available data repositories can be leveraged to support capacity development for data scientists across Africa, enabling them to undertake genomic surveillance and research.

Engagement opportunities

Genomic surveillance of malaria is simply not possible without full engagement with the government, health policymakers, civil society, and communities. Given the multipurpose nature of genomic data, various actors may be involved to achieve both scientific and public health impacts.
Cross-cutting challenges
Several cross-cutting challenges in the generic framework must be considered alongside the circular steps in order to maximize benefits and minimize the challenges.

Network

To benefit from peer-to-peer engagement and the cross-pollination of knowledge, genomic surveillance practitioners, including those in public health leadership, laboratory scientists, data engineers, and researchers, must have opportunities to connect, particularly through South-South collaborations.

These include:

- Learning from experiences in similar and different transmission settings for the same disease of interest and from others implementing genomic surveillance for a disease of interest.
- Building and promoting the evidence base of impact studies for genomic surveillance to accelerate sustainable funding.
- Provide opportunity for peer-to-peer mentorship.
- Bring together subject matter expertise across multiple diseases to tackle crosscutting challenges and share experiences on what worked/didn't work to get NMPs interested and involved in genomic surveillance of malaria.

Workforce development and retention

With an increase in genomic surveillance activities comes an increased need for skilled personnel who can be retained in order to deliver a sustainable public health service. This means there must be opportunities for growth at every stage of professional development.
A standard approach to workforce development that could be adapted would be:

- Understand the current workforce and the training environment that have supported it so far, as well as the known emerging opportunities.
- Identify and analyze knowledge, skills, abilities, and talent profiles, as well as attrition rates and other factors such as views on job security, promotion opportunities, satisfaction, and opportunities outside of Africa.
- Determine future workforce needs, including the required skills and capabilities, and the likely timeframe for meeting those needs.
- Identify the gap between the present and the future and develop implementation solutions that leverage existing resources and support the development of new resources to meet continent-wide needs.

Supply chain

Current supply chains and servicing arrangements for genome sequencing equipment and consumables in sub-Saharan Africa are inadequate to meet the planned scale-up of activities in this area. This should be addressed through multiple approaches, including:

- Demand aggregation for specific equipment, reagents, and consumables for MMS. This will pave the way for realistic estimates to optimize supply, through pooled procurement for the implementation of specific genomic surveillance products when implemented at an appropriate scale.
- Partnerships with other actors who can support the procurement of complicated items in specific contexts.

- Industrial partnerships for co-development of assays, training and technical advice, feedback and troubleshooting.
- Advocacy to suppliers, governmental and non-governmental actors to accelerate addressing the issue.

Quality Management Systems

Implementing a genomic surveillance framework with the capability and capacity to meet national and regional public health objectives must include appropriate quality management. However, as many existing systems have arisen from academic research collaborations, quality assurance for MMS has not been adequately addressed.

Therefore, a phased approach is needed until a robust assurance process is in place. Incrementally, this could include:

- Establishing initial conditions for genomic surveillance implementation systems in place, with mapping and documentation of the end-to-end process.
- Self-assessment review of end-to-end process, potentially including repeating samples using complementary techniques where available, and validation of data outputs undertaken internally.
- An external review of the end-to-end process is undertaken, potentially including the repetition of samples using control samples and/or complementary techniques where available, as well as the validation of data outputs. Ideally, this will be conducted in partnership with an independent external agency; however, reciprocal arrangements could be made until this is available and validated.
- Genomics labs are recommended to implement quality management systems and work towards accreditation of their processes.

Standardization and harmonization

Without compromising national leadership, standardization of sample frameworks, laboratory techniques, and data is essential to achieve genomic surveillance of any disease at the continental level. With the standardization of wet laboratory processes comes the benefits of scale, which can drive down the financial cost. With the standardization of dry laboratory processes comes the considerable benefit of data interoperability across different geographical regions and diseases. This will include, but is not limited to:

- Early adopters for a given MMS use case should harmonize existing approaches and identify steps that can be taken to improve public health impact through standardisation, which could include cohesion on a standard set of markers that must be monitored to aid interoperability.
- Genomic surveillance products should include complete infrastructure requirements and standard operating procedures for all steps, from sample collection to data generation, at a minimum and these should be publicly accessible.
- The development of a central core of activity, implemented in a small number of countries with training and support capacity will encourage new adopters to align with these activities and drive forward the harmonization necessary for continent-wide delivery.

3

GENOMIC SURVEILLANCE SYSTEMSTO ADDRESS COUNTRY AND CONTINENTAL PRIORITIES IN AFRICA

Member States' considerations for malaria genomic surveillance implementation include:

- Develop a national strategy and capacity and capabilities to generate better quality and standardized genomic surveillance data.
- Increase coverage of MMS and monitoring systems of interventions on treatment efficacy and resistance.
- Increase the collection of additional, more detailed and harmonized data at select sites.
- Improve data dissemination systems to facilitate a reactive and coordinated response to genomic surveillance data outputs.

3.1. National Strategy to support the malaria genomic surveillance system

For genomic surveillance of malaria to be a tool in the elimination armoury for Africa, national public health needs must be met in the context of continent-wide goals. Each member state is best placed to determine how genomic surveillance needs should be met. Beyond malaria, some Member States may also consider other pathogens that could be included in their genomic surveillance programmes for broader public health goals. National strategies should be developed in partnership with relevant national stakeholders and include appropriate community engagement. The strategy should consider sustainability in terms of funding and workforce development. They must be costed against a robust implementation plan, with contingencies included, and leverage opportunities to leverage must be identified to optimize limited resources.

Recommendations include:

- All Member States to develop national strategies for malaria genomic surveillance
- Where appropriate, malaria genomic surveillance should be considered within the framework of a multi-pathogen national genomics strategy, as integration will assist with resource optimisation
- Countries can consider collaborating with other countries in a collaborative way to develop their malaria molecular surveillance strategies

The national context, diseases of public health interest, and existing infrastructure and resources will determine the balance between a malaria-focused strategy and a multi-pathogen strategy.

3.2. Continental network of institutions for malaria genomic surveillance

Genomic surveillance of malaria is a reality in some African nations. Expanding these efforts to a continental network of institutions for malaria genomic surveillance will require considerable time, effort and funding. Each member state is responsible for developing a plan for a genomic surveillance system tailored to the needs of its public health system and the available financial resources available for these activities.

Continent-wide objectives should inform the strategy and include a pathway to the platform's sustainability. Engagement with organisations with a mandate to strengthen the capacity and capability of Africa's public health institutions is encouraged.

The continental network will comprise institutions with different levels of capacity and capability.

Level 1: Africa CDC Reference Laboratories

Africa CDC will:

- Coordinate Member States, CoEs, partnerships and resource mobilization
- Facilitate the development? of MTA and DTA between Member States
- Coordinate the continental sample referral scheme, including biobanking
- Facilitate regional data sharing, archiving, analysis and reporting
- Support the harmonization and standardization of protocols and data analytics
- Support quality management systems
- Support public health-focused method development
- Coordinate the supply chain and pooled procurement
- Coordinate workforce development

Level 2: Regional hubs and Centres of Excellence for malaria genomic surveillance

Regional hubs and CoEs should have a proven capacity to support national and regional surveillance, workforce development, high-throughput sequencing capacity, maintenance, data analytics, storage and reporting capacities within a reasonable timeframe. They should undertake research and development activities with national or international partners. The regional hubs and CoEs can be public health, academic and/or research institutions based in Africa.

Regional hubs and CoEs for malaria genomic surveillance should:

- Develop their own capacity and capabilities to generate high-quality, standardized data on all priority use cases.
- Support Member States with no or limited genomic surveillance systems, including sample and metadata management, sample and data transfer compliance, training, research, and data analyses, storage and reporting.
- Expand capacity and capability for training and timely support for regional surveillance.
- Expand their ability to mentor other laboratories to develop capacity and capability for national and regional genomic surveillance.
- Support Member States in developing quality management systems and ensuring assurance for malaria genomic surveillance.
- Address regulatory requirements for cross-border sample and data sharing

Level 3: National Nodes for Malaria Genomics Surveillance

Level 3.1 National Reference Labs

Member States with local genomic surveillance capabilities should work to generate high-quality, standardised data on one or more MMS priority use cases. This should consider available resources and provide appropriate support for implementation. While there are products have been developed for multi-laboratory implementation, they still require tailoring to specific contexts, including laboratory processes, data generation, and integration with public health systems. They could also expand the scale of their capability to support routine MMS nationally. The national nodes should leverage the regional hubs and CoEs to support the local capacity development, use-case design, quality assurance, data management, analysis, and interpretation.

Level 3.2 Subnational sequencing labs

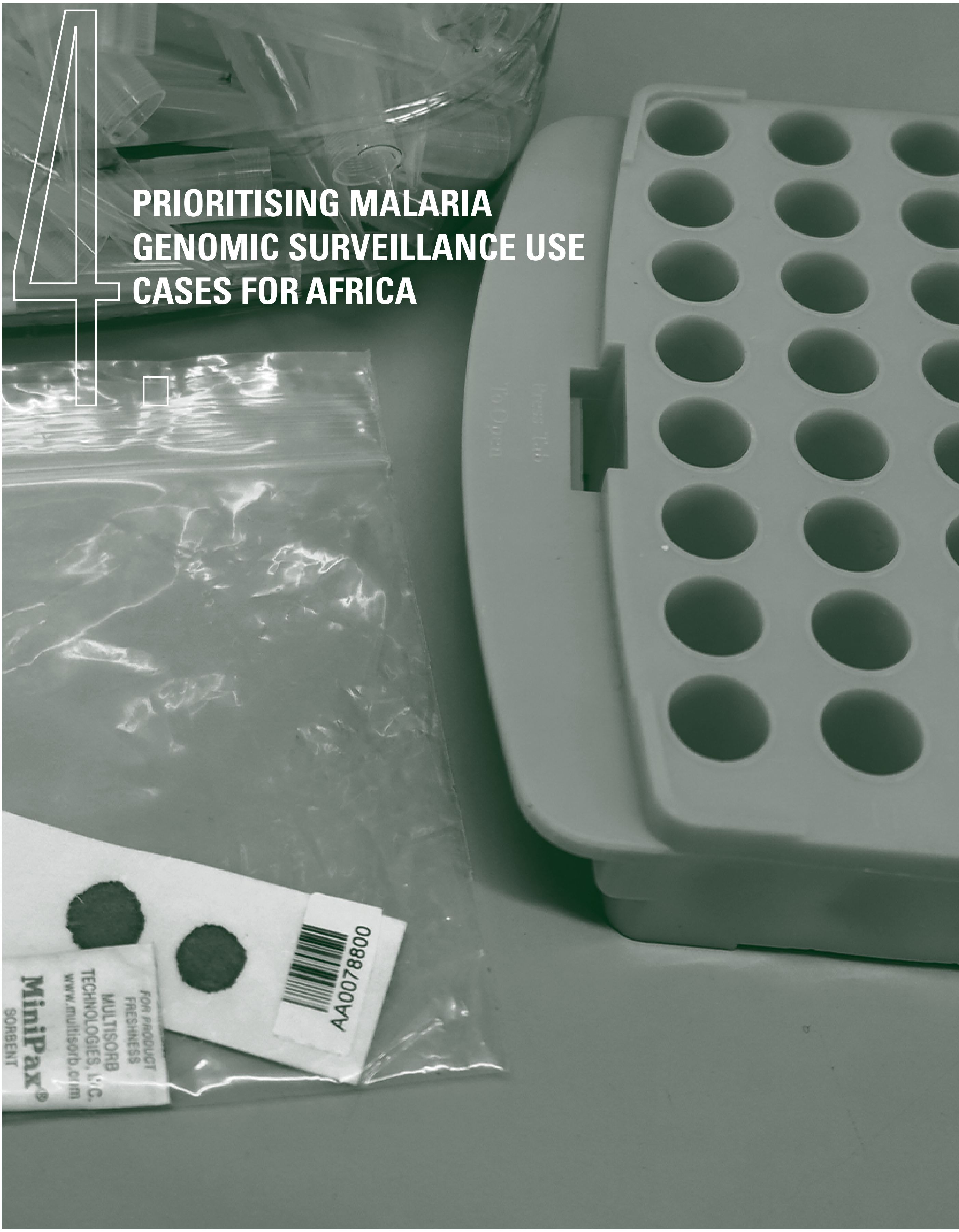
- Should conduct local genomic surveillance
- Ensure the timely collection of samples with relevant metadata
- Should be linked with the national reference lab and refer samples when needed

Member states with no local malaria genomic surveillance capability should leverage regional sequencing hubs and CoEs, preferably in the same geopolitical region, to generate high-quality, standardised data, prioritize use cases, and to develop the appropriate capacity and capabilities, for the data generated to be integrated with public health systems, data analytics and interpretation capacity must be leveraged both regionally and also developed locally.

A high-level review of the phased approach considering enablers for genomic surveillance of malaria is shown in Figure 4.

Figure 5 Phased implementation model for malaria genomic surveillance Considering Enablers for Genomic Surveillance of Malaria in a Phased Implementation Model. The scale, ranging from ●○○○○ (limited) to ●●●●● (well-developed), indicates what is in place for each enabler across four different implementation approaches.

ENABLERS FOR GENOMIC SURVEILLANCE OF MALARIA	LEVEL 3.2 →	LEVEL 3.1 →	LEVEL 2 →	LEVEL 1 →
EXISTING ASSETS Map and assess existing assets, including laboratory infrastructure, data processing infrastructure, data analysis infrastructure, sampling frameworks, data storage, and computational systems.	●○○○○	●●●○○	●●●●●	●●●●●
LEADERSHIP AND POLICY Appropriate leadership must be in place at all levels, from health centre managers to ministries, academic institutions, and policymakers. Opportunities for leadership development should also be considered.	●●○○○	●●●●○	●●●●●	●●●●●
PARTNERSHIPS Existing research, public health initiatives, and government partnerships should be leveraged to ensure the successful implementation of this initiative. International research and implementation support, as well as collaborations with funding bodies, are also important considerations.	●●○○○	●●●○○	●●●●●	●●●●●
FINANCING Diverse funding sources mitigate the risk of defunding through competing priorities. Activities must be reliably costed against a robust plan, with contingencies included. Ownership by countries (i.e., ministries) supported by explicit national budget lines, should be a long-term goal.	●●○○○	●●●○○	●●●●○	●●●●●



4. PRIORITISING MALARIA GENOMIC SURVEILLANCE USE CASES FOR AFRICA

A 2019 WHO technical consultation meeting identified seven priority use cases broken down into specific applications, including operational, sampling, laboratory, ethics and data sharing, added value and challenges for implementation. The speed at which evidence could be provided to the WHO was also determined. Since the report, there has been further progress, with more examples of success, and WHO has produced various strategies, protocols and guidance that have moved the field forward. These include a plan to respond to antimalarial drug resistance in Africa[8] , a manual for monitoring insecticide resistance in mosquito vectors and selecting appropriate interventions[9] and a malaria surveillance assessment toolkit[10] .

While each use case was declared a ‘priority use case’, a further level of prioritization is needed to identify which are the most urgent to tackle. This is a multifaceted challenge. Not every use case is at the same stage of research, technology implementation and methods development. Even where the necessary items are in place, successful implementations are often limited to low transmission settings or near elimination of the disease. For example, use cases such as determining the origins of drug resistance or identifying the causes of an outbreak have been successfully demonstrated on a surveillance platform in Southeast Asia. [11,12], But less so in Africa. To drive forward the most pressing use cases for Africa, this roadmap recommends three tiers of use cases:

Tier 1:

Use cases to respond to malaria threats

Tier 2:

Use cases for monitoring and evaluation of malaria control/elimination interventions.

Tier 3:

Use cases for research and development of malaria genomic tools

The highest priority use cases are Tier 1 and Tier 2. These will yield an impact that can be leveraged for broader continental goals, including sustainable implementation. A summary of each tier is provided in Figure 6.

TIER 1	TIER 2*	TIER 3*
Prevalence and spread of drug resistance ◊ Prevalence and spread of diagnostic resistance ◊ Insecticide resistance ◊ Vector species	Drug efficacy ◊ Insecticide efficacy ◊ Vaccine efficacy ◊ Parasite species ◊ Ongoing transmission	Origins of drug resistance ◊ Origins of diagnostic resistance ◊ Vaccine escape and outbreak analysis ◊ Causes and spatio-temporal evolution of insecticide resistance ◊ Parasite population structure ◊ Vector population structure

*These use-cases can be customised depending on national-level priorities

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[8] Strategy to respond to antimalarial drug resistance in Africa. WHO. 2022. https://www.who.int/publications/i/item/9789240060265

[9] Manual for monitoring insecticide resistance in mosquito vectors and selecting appropriate interventions. WHO 2022. https://www.who.int/publications/i/item/9789240051089

[10] Malaria surveillance assessment toolkit. WHO. 2022. https://www.who.int/publications/i/item/9789240055278

[11] Emergence of artemisinin-resistant Plasmodium falciparum with kelch13 C580Y mutations on the island of New Guinea. PLOS Pathogens 2020. https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1009133#sec021

[12] Malaria outbreak in Laos driven by a selective sweep for Plasmodium falciparum kelch13 R539T mutants: a genetic epidemiology analysis. The Lancet Infectious Diseases. 2023. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00697-1/fulltext

In the following sections, we will provide some general ideas and considerations for sampling frameworks, laboratory implementation, data analysis methods, data interoperability and external quality assurance. Additional support may be required to adapt the use cases to specific contexts, ensuring that sampling frameworks provide sufficient statistical power considering transmission intensity, study design, and clustering. As the number of successful implementations of genomic surveillance for specific use cases increases, further guidance based on lessons learned will be incorporated into this material.

4.1. Tier 1 use cases

Different use cases address various operational needs for public health decision-making in controlling and eliminating malaria. Member States are advised to collaborate on implementing high priority use cases for continent-wide efforts.

Table 1 Tier 1 Use Cases

TIER 1 USE CASES – HIGH PRIORITY AND READY FOR IMPLEMENTATION

Prevalence and spread of drug resistance - Monitoring of known genetic markers of resistance to antimalarials

Prevalence and spread of diagnostic resistance - Identifying and monitoring HRP2/3 deletions

Insecticide resistance - Monitoring known genetic resistance markers to insecticides

Vector species - Monitoring indigenous and invasive species

Tier 1 use cases involve responding to malaria threats by utilising known markers or methods for species identification.

Several successful implementations of genomic surveillance for malaria have been achieved in these use cases. However, in some cases, their approaches are considerably diverse. It is essential that early adopters share lessons learned about how data analysis, data integration and public health actions are currently undertaken to ensure the interoperability of data outputs and optimize the impact of public health initiatives.

Prevalence and spread of drug resistance: Monitoring genetic resistance markers to antimalarials

Monitoring changes in frequencies of molecular markers of drug resistance over time and space is a key priority use case. This is essential for detecting populations at risk of treatment failure, informing decisions on first-line drugs, and ensuring effective patient treatment. The WHO has developed a strategy to address antimalarial drug resistance in Africa. [13] That is particularly relevant to this use case.

PROGRAMME USE CASES:
Monitor treatment efficacy and resistance to inform the selection of antimalarial drug policies.

GENETIC EPIDEMIOLOGY USE CASES:
Monitor known genetic markers, detect treatment failures, describe gene flow, identify changes in parasite population structure, and detect circulating strains.

OPERATIONAL USE CASES:
Targeted TES; first-line drug policy decisions and identifying populations at risk of treatment failure.

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[13] WHO Strategy to respond to antimalarial drug resistance in Africa, 2022. https://www.who.int/publications/i/item/9789240060265

Considerations for the sampling framework
Routine genomic surveillance, conducted annually, biannually, or continuously, using dried blood spots, will rapidly detect changes in the frequencies of drug resistance genetic markers. Particularly in high-transmission settings, while it is most informative to conduct continual routine sampling, this must be weighed against budget constraints. This could be addressed through the use of appropriate sentinel surveillance strategies.

The level of routine sampling should be at the appropriate administrative level that could inform the implementation of a change in national drug policy. While routine sampling incurs more cost in the initial stages of implementation, this approach is less expensive and easier to roll out and maintain than a TES over time; provides an early warning of clinical failure risk; has a simple DBS sample collection procedure; and allows dense sampling in time and space and at epidemiological scales.

At a top level, the sampling framework considerations are:

- Passive case detection, after RDT or microscopy confirmation.
- At regular intervals (e.g. 3, 6, 12 months), depending on epidemiological conditions.
- Dried blood spot samples.
- The spatial sampling strategy should be relevant to NMP's strategic needs, which could include targeted sampling of key populations.

Genomic surveillance laboratory implementation
Genetic markers should be included but are not limited to those for artemisinin (K13, C469Y, R561H, R622I, A675V) and the partner drugs amodiaquine, chloroquine, halofantrine, lumefantrine, mefloquine, piperaquine, proguanil, pyrimethamine pyronaridine, quinine and sulfadoxine (such as pfmdr1; pfcrt; pfdhfr; pfdhps; pfcytb, pfpm2, pfpm3). National plans should prioritize monitoring partner drug resistance relevant to their context. With several examples of national implementation for this use case, it is possible to learn from these examples to establish the capability in new laboratory settings and/or to leverage existing capacity and capability in regional genomic centres, subject to available resources.

While some African countries have high levels of non-falciparum malaria parasites, there are not yet validated molecular markers of resistance to the key drugs used for treating those species. When available, this should be incorporated into genomic surveillance practices in relevant settings.

The implementation guidelines are:

- Capability for analysis of pfk13, pfcrt, pfdhfr, pfdhps, pfmdr1 at a minimum through targeted sequencing, PCR, molecular inversion probes, etc.
- Capacity sufficient to meet the sampling strategy for national needs. Additional capacity could be provided to neighbouring countries through regional networks.
- Whole-genome sequencing on a subset of samples to identify new resistance markers. While national capability may be available for monitoring known markers, external capability providers may be required for this laboratory approach.

Genomic surveillance data and metadata
Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should also be shared as openly as

possible, through national data-sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic and anonymised minimum metadata. The minimum required metadata for aggregated datasets includes the date of collection, location, and genotyping technology used.

Quality Assurance

Sequencing laboratories must strive to generate high-quality genomic data to inform public health decision-making. Resources such as The Next Generation Sequencing Quality Initiative. [14] It can be used to implement quality management systems. With a phased approach to national genomic surveillance systems, while a formal malaria-specific external quality assurance system is being established, inter-lab comparisons can be used to ensure the appropriate data quality.

Prevalence and spread of diagnostic resistance. Identifying and monitoring HRP2/3 deletions

Identifying and monitoring changes in Pfhrp2/3 gene deletions is a high priority use case for parasite genomic surveillance. In addition to informing RDT selection, it can also identify issues arising with the storage and shipment of RDTs that may compromise their integrity. As confidence in RDTs remains fragile in many places, surveillance across all settings where HRP2 RDTs are used enables early detection of Pfhrp2/3 deletions that cause false negatives. The WHO has produced template protocols to support surveillance and research for pfhrp2/pfhrp3 gene deletions. [15]That is particularly relevant to this use case.

PROGRAMME USE CASES:
Monitor the efficacy of diagnosis.

GENETIC EPIDEMIOLOGY USE CASES:
Monitor genetic markers.
OPERATIONAL USE CASES:
Directly informs RDT selection for national programmes.

Considerations for the sampling framework
This use case is critical to countries with reports of Pfhrp2/3 deletions. If >5% Pf cases are missed due to Pfhrp2/3 deletions, replace RDTs in the country; if <5%, repeat survey in 1–2 years. It may also be possible to integrate this into a routine genomic surveillance monitoring product, providing the benefit of routine surveillance without the cost of increased sampling.

At a top level, the sampling framework considerations are:

- Sampling frameworks should encompass various epidemiological and geographic settings within the country, selected by NMP for their relevance to the study. Ideally, surveys could leverage existing surveillance activities, such as those alongside TES.
- Prospective surveys of symptomatic patients presenting to health facilities.
- Comparative testing using HRP2 rdts vs pf-LDH rdts or microscopy, and collection of dried blood spot samples.
- Prioritize HRP2 negative + pf-LDH or microscopy positive cases for Pfhrp2/3 genotyping.
- After the initial baseline, surveys should not be conducted more than once every 1-2 years.

Genomic surveillance laboratory implementation

Multiple protocols have been published for the detection of Pfhrp2/3 deletions. The

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[14] https://www.cdc.gov/labquality/ngs-quality-initiative.html

[15] template protocols to support surveillance and research for pfhrp2/pfhrp3 gene deletions. WHO. 2021. https://www.who.int/publications/i/item/9789240002036

approach recommended is:

- Use a standardised, published protocol and work according to the WHO guidelines.
- Obtain baseline data and then increase periodicity if the prevalence is greater than 5%, as per WHO guidelines.
- Capability: PCR to confirm Pf infection; Pfhrp2 and Pfhrp3 and at least two other single-copy genes; Flanking genes, serology, whole genome sequencing, and next generation sequencing are optional.
- Capacity: Sufficient to meet sampling strategy for national needs. Additional capacity could be provided to neighbouring countries through a partnership arrangement.

Data Sharing
Genomic data must be shared with malaria control programmes to inform public health decision-making. Data outputs should report the prevalence of HRP2/3 deletions with confidence intervals for each geographical site. These data should be shared as openly as possible, through national data-sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic and anonymised minimum metadata. The minimum required accompanying metadata for aggregation includes date of collection, location, and the genotyping/sequencing technology used.

External quality assurance
To support high-quality and rapid molecular analysis, the WHO established a network of reference laboratories experienced in Pfhrp2/3 genotyping and a proficiency-testing scheme that includes Pfhrp2/3-deleted parasites.
It is noteworthy that reference laboratories are not yet established in Africa, and it remains challenging to ship samples internationally. Centres of excellence for malaria genomics across Africa, when established, will be able to support this external quality assurance function and remove barriers to sample shipment.

Insecticide resistance: Monitoring known genetic resistance markers to insecticides

Monitoring insecticide resistance markers is the highest priority use case for vector routine genomic surveillance. It allows for the selection of specific interventions (e.g., pyrethroid-PBO nets) based on the prevalent resistance mechanisms (e.g. mixed-function oxidase (MFO) resistance mechanisms) over time. Such monitoring also enables programmes to assess the value of different insecticide resistance management strategies (e.g. indoor residual spraying (IRS) rotation, new types of insecticide-treated nets (ITNs), attractive toxic sugar baits).

Given the complexity of the anopheles' genome and the introduction of novel insecticides in recent years, implementing this use case will require adaptation over time as new markers are identified and additional reference genomes are assembled. Genomic surveillance is simpler to implement than phenotypic assays, which require larvae rearing, and shifts in allele frequencies may be easier to detect than shifts in phenotype over short periods.

A Tier 3 use case on the causes and spatio-temporal evolution of insecticide resistance is a connected use case. The identification of new markers across all Anopheles species that transmit malaria in Africa is an essential research activity whose outputs will be incorporated into this use case over time.

PROGRAMME USE CASES:
Monitor the efficacy of mosquito control measures and assess cross-resistance between different classes of insecticides.

GENETIC EPIDEMIOLOGY USE CASES:
Monitor the prevalence and spread of genetic markers, as well as changes in population structure.

OPERATIONAL USE CASES:
Map the distribution of resistance alleles; Inform choice of specific interventions based on prevalent resistance mechanisms (e.g., pyrethroid PBO-based nets if P450-based resistance mechanism is predominant); Assessment of fitness cost to better design resistance management strategies (e.g., IRS rotation, and new types of ITNs such as dual active ingredient nets).

Considerations for the sampling framework

WHO provided a manual[16] for monitoring insecticide resistance in mosquito vectors and selecting appropriate interventions. Aimed at field entomologists and biologists from ministries of health or other partner institutions, the document guides on assessing insecticide resistance in mosquito vectors. The recommendations within the manual do not extend to all current technology approaches. It focuses on the WHO tube test, the WHO bottle bioassay and the CDC bottle bioassay. The principles around the sampling framework can also be utilised for genomic surveillance tools. The manual provides clear guidance on sampling recommendations that are relevant and representative.

At a top level, the sampling framework considerations are:

- Routine annual sampling at the appropriate administrative or health district level could inform the implementation of a change in national vector control strategies, including a sub-tailoring approach.
- A subset of routine samples should be applied to discovery genomic surveillance, looking at the whole genome to identify new markers of resistance; this sampling should also support RNAseq-based transcriptomic detection of significant resistance genes
- Longitudinal sampling that is suitable for studying malaria transmission and its environmental context.
- Spatial density is dependent on differential sources of resistance selection (e.g, hotspots of agriculture practices, collection from areas with different insecticide-based interventions).
- Larval sampling, adult sampling (inside and outside buildings to detect behavioural change or shifts in species composition).

Genomic surveillance laboratory implementation

Genetic markers to be included should cover central resistance mechanisms, notably target-site resistance (knockdown resistance through L1014F/S markers, G119S acetylcholinesterase Ace-1), metabolic resistance [(P450S such as CYP6P4/CYP6P3 in An. gambiae or CYP6P9a/b in An. funestus), glutathione S-transferase (GST) such as GSTe2]. Lessons could be learned from research centres with expertise in the field to establish the capability in new laboratory settings and/or to leverage existing capacity in regional laboratories (subject to available resources).

Several protocols that have been published for detecting these markers. The approach recommended is:

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[16] Manual for monitoring insecticide resistance in mosquito vectors and selecting appropriate interventions. WHO. 2022. https://www.who.int/publications/i/item/9789240051089.

- Capability for minimally destructive mosquito DNA extraction technique and generate sequence data of Voltage Gated Sodium Channel (VGSC, kdr), acetylcholinesterase (Ace-1), major P450s (CYP6P3, CYP6P4 in An. Gambiae, CYP6P9a/b and CYP9K1 in An. Funestus and GST (gste2)) at a minimum through genotyping of key mutations, amplicon sequencing (miseq, nanopore etc), molecular inversion probes etc;
- Capacity sufficient to meet the sampling strategy for national needs. Additional capacity could be provided to neighbouring countries through a partnership arrangement.
- Whole-genome sequencing on a subset of samples to identify new markers of resistance. This could also be considered a pooled whole-genome sequencing (poolseq) approach for early and rapid screening of significant resistance loci. While national capability may be available for monitoring known markers, it is likely that, given the complexity of the genomes and of resistance mechanisms, external capability providers will be required for this laboratory approach, potentially through regional research hubs.

Genomic surveillance data and metadata

Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should also be shared as openly as possible, through national data-sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic, and anonymised minimum metadata. The minimum required accompanying metadata for aggregation includes date of collection, location and genotyping technology used.

Quality Assurance

The subset of sample samples that are provided for whole-genome analysis serves as an external quality assurance method for the broader sample set.

Vector species: Monitoring indigenous and invasive species

Africa has more than 50 potential malaria vector species, some of which belong to sibling species that are not distinguishable morphologically. Furthermore, their vectorial capacity and behaviour (indoor vs outdoor) vary significantly, requiring a good understanding of vector composition or shifts to ensure the continued efficacy of control interventions. Even within a single species, it is essential to assess the extent of gene flow to predict the risks of spreading alleles of interest, such as insecticide resistance.

The case of regular monitoring of vector species distribution has been highlighted with the spread of Anopheles stephensi in Africa[17] . This mosquito species is capable of transmitting both Plasmodium falciparum and P. vivax malaria parasites. With detections reported in Djibouti (2012), Ethiopia and Sudan (2016), Somalia (2019), Nigeria (2020), Ghana and Kenya (2023), the invasion is continuing at a pace. In the case of Djibouti in 2012, many of the malaria cases were reported in the capital city, rather than in the disease's more typical rural setting. An. Stephens has most likely already spread to other African countries but has not been detected due to limited large-scale surveillance efforts of this invasive

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[17] WHO initiative to stop the spread of Anopheles stephensi in Africa, https://www.who.int/publications/i/item/WHO-UCN-GMP-2022.06

species. The challenge of malaria control and elimination will only become more difficult if this invasion, with its considerable impact on malaria epidemiology, is not understood and addressed.

PROGRAMME USE CASES:
Monitor the efficacy of mosquito control measures, shifts in behavior or composition, and invasive species.

GENETIC EPIDEMIOLOGY USE CASES:
Monitor genetic markers and population structure, as well as spatio-temporal changes.

OPERATIONAL USE CASES
Guide the choice of vector control interventions, help predict the efficient implementation of interventions such as IRS, and assess the value of different insecticide resistance management strategies (e.g. IRS rotation, new types of ITNs) in the context of varied resistance mechanisms in other species.

Considerations for the sampling framework

Sampling should be both relevant and representative and could leverage off existing sampling collection frameworks. At a top level, the sampling framework considerations are:

- Longitudinal routine sampling at an appropriate administrative level that could inform the implementation of a change in national mosquito control policy that is tailored to the local malaria transmission and environmental context.
- A subset of routine samples should be used for discovery genomic surveillance, examining the whole genome to identify new markers of resistance and assess the scale of resistance selection by detecting a signature of selective sweep.
- Spatial density is dependent on differential sources of resistance selection (e.g., hotspots of agriculture practices, collection from areas with different insecticide-based interventions).
- Larval sampling, adult sampling (inside and outside buildings to detect behavioural change).

Genomic surveillance laboratory implementation

At a top level, the laboratory implementation guidelines are:

- Capability for minimally destructive mosquito DNA extraction technique and molecular taxonomic identification and genotyping (PCR of ITS2, microsatellite and mitochondrial markers) at a minimum through amplicon sequencing (SANGER, MiSeq, nanopore, etc), molecular inversion probes, etc.
- Capacity sufficient to meet the sampling strategy for national needs. Additional capacity could be provided to neighbouring countries through a partnership arrangement.
- Whole-genome sequencing on a subset of samples to identify new markers of resistance. This could also be considered a pooled whole-genome sequencing (PoolSeq) approach for early and rapid screening of significant resistance loci. While national capability may be available for monitoring known markers, it is likely that, given the complexity of the genomes of species genomes and their diverse resistance mechanisms, external capability providers will be

required for this laboratory approach, potentially through regional research hubs. (see Tier 2 accelerator use case on new markers of resistance).

Genomic surveillance data and metadata
Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should also be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic and anonymised minimum metadata—the minimum required accompanying metadata for aggregation: date of collection, location, and genotyping technology used.

Quality Assurance
Morphological assessments complemented by whole genome sequencing on a subset of samples.

Action plan for Tier 1 use cases

Table 2 Accelerating Tier 1 use cases

OVERALL GOAL	12-MONTH GOAL	24-MONTH GOAL	36-MONTH GOAL
Implement continent-wide malaria genomic surveillance. • Drug resistance and efficacy - Monitoring known genetic resistance markers to antimalarials • Diagnostic resistance - Identifying and monitoring HRP2/3 deletions • Insecticide resistance - Monitoring known genetic resistance markers to insecticides • Vector species - Monitoring indigenous and invasive species	A detailed map of malaria genomics surveillance capacity and capability produced by the Africa CDC **Activities:** • Resource mobilization for the roadmap implementation • Survey of key stakeholders addressing each use case with genomic technologies to map where each is being implemented and the suitability of how it is being implemented for multi-laboratory implementation • Review of how data analysis, data integration and public health action are currently undertaken for decision making in Africa • Survey of African laboratories with existing sequencing infrastructure to understand prior malaria experience, the institution's connection to the NMP	Pilot implementation of tier-1 use cases. **Activities:** • Collate existing nationwide data where available • Develop sampling strategies for nationwide surveillance • Identification of regional hubs • Identification of target countries for prospective nationwide genomic surveillance of use cases	Scale-up regional and continent-wide implementation of tier-1 use cases

4.2. Tier 2 use cases

Whereas Tier 1 use cases focus on high-priority public health use cases that are (near) implementation-ready, Tier 2 focuses on the preservation of control measures and monitoring the genetic impact of control measures. These use cases can be layered on top of existing surveillance activities. Monitoring the genetic effect of these control measures, along with accompanying information on clinical outcomes, will significantly accelerate the identification of changes in the genome. This can inform the future development of monitoring genetic marker products for parasites and vectors, as well as guide the development of vaccines.

TIER 2 ACCELERATOR USE CASES

Drug efficacy - new markers of drug resistance

Insecticide efficacy - new markers of insecticide resistance

Vaccine efficacy - Genetic impact of malaria vaccines

Parasite species - Monitoring indigenous and emerging species
Ongoing transmission

In addition to the genomic surveillance use cases described in Tier 1, which focus on what is known, Tier 2 use cases employ a more discovery-focused approach.
For accelerator use cases that identify new forms of resistance, whole-genome surveillance and transcriptomics can be used as complementary technologies for early detection and characterization of new resistance variants, to raise the alarm, focus attention and effort, and assess impact. New markers identified should be rapidly validated and then integrated into surveillance of known marker use cases (Tier 1).

For accelerator use cases that involve monitoring genetic impact in known regions, whole amplicon sequencing can be used, as the genome region is smaller.

In all cases, a partnership across multiple stakeholder groups should work together with research and public health initiatives that implement trials or the rollout of new interventions to preserve their efficacy for as long as possible. This would include generating preliminary data, developing the use case and sampling strategy, and developing the project plan to scale up this high-priority activity.

Drug efficacy: New markers of drug resistance

The operational use of this activity is to guide the targeting of interventions for the containment of resistance and inform regional drug policies. This use case can leverage samples from Tier 1 use cases; however, additional information about the clinical outcome is highly desirable. Challenges to overcome include access to whole-genome sequencing, which may require outsourcing. An extensive database of parasites from multiple geographic regions is needed for comparison, and further research is necessary to identify molecular markers in different geographical settings.

PROGRAMME USE CASES:
Monitor the efficacy of drug control measures.

GENETIC EPIDEMIOLOGY USE CASES:
Identify new genetic markers of resistance and monitor changes in the population over time.

OPERATIONAL USE CASES
First-line drug policy decisions.

Sampling framework:

- Passive case detection.
- Active sampling is desirable.
- Desired frequency: annual or semi-annual.
- Dried blood spots.
- Clinical outcome knowledge is highly desirable and
- Could be a subset of continent-wide drug resistance monitoring samples.

Laboratory implementation:

- Whole genome sequencing or genome-wide genotyping.

Data:
Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic, and anonymised minimum metadata. The minimum required accompanying metadata for aggregation includes date of collection, location, and genotyping technology used.

Insecticide resistance and efficacy: New markers of insecticide resistance, particularly for new interventions

The operational use of this activity is for the early detection of resistance alleles to new insecticides before they become highly selected and likely difficult to remove or mitigate through resistance management strategies, as well as for improved surveillance of insecticide resistance and the impact of interventions. When the outputs of this use case are implemented, it will improve timeliness and resource allocation for insecticide monitoring and potentially inform the development and deployment of gene drives. Challenges to overcome include the entomological capacity in the country and the need for a spatial sampling strategy (i.e., geospatial expertise and entomological expertise). Access to whole-genome sequencing is also required, which can be achieved through outsourcing when necessary.

PROGRAMME USE CASE:
Early detection of resistance alleles and monitoring the continued efficacy of new mosquito control measures.

GENETIC EPIDEMIOLOGY USE CASES:
Identify new genetic markers of resistance and monitor changes in the population over time.

OPERATIONAL USE CASE:
First-line vector control policy decisions; assess selection pressure from novel interventions.

Sampling Framework:

- Larval sampling and adult sampling (traps, human landing catches).
- Laboratory selection of insecticide-resistant strains to anticipate development in the field.
- Generate baseline genetic diversity related to novel insecticide-based interventions (LLINs or IRS) through whole genome sequencing and RNAseq-based transcriptomics.
- This could be a subset of the insecticide resistance surveillance Tier 1 priority use case.

Laboratory Implementation:

- Whole genome sequencing or targeted amplicon sequencing.
- Transcriptomics.

Data:
Genomic data must be shared with the malaria control programme to inform public health decision-making. These

data should also be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic, and anonymised minimum metadata. The minimum required accompanying metadata for aggregation includes date of collection, location and genotyping technology used.

Vaccine efficacy: Genetic impact of malaria vaccines

The WHO guidelines for malaria, updated in March 2022, recommend using the RTS, S/AS01 malaria vaccine to prevent P. falciparum malaria in children residing in regions with moderate to high transmission, as defined by the WHO. The vaccine targets two areas of the gene csp, a central repeat region and the C-terminal of the gene. Potential mutations in either of these regions could render the vaccine less effective and hence could be under positive selection in areas where the vaccine is being used. In October 2023, the R21/Matrix-M vaccine was included in WHO recommendations. The R21 vaccine also targets the same regions of this gene, so a similar approach is suitable for both vaccines. While changes in vaccine efficacy cannot be deduced from genetic studies (this will require vaccine efficacy studies), monitoring the evolution of csp alongside vaccine efficacy may be possible to derive markers for vaccine failure.

PROGRAMME USE CASE:
Monitor the efficacy of malaria vaccines.

GENETIC EPIDEMIOLOGY USE CASES:
Identify the genetic impact of malaria vaccines and monitor changes in the population's genetic makeup.

OPERATIONAL USE CASE
First-line vaccine implementation decisions.

Sampling framework:

- Sampling framework alongside where the vaccine is being rolled out.
- A local and global repository of genetic sequences that can be queried and ideally integrated with existing databases within the malaria community to inform parasite origins.
- Dried blood spots.
- An AA sampling framework is required to support this use case.

Laboratory implementation:

- Whole genome sequencing or genome-wide genotyping to generate baseline genetic diversity related to new vaccines.
- Amplicon sequencing.

Data:

- Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should be shared as openly as possible, through national data-sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic, and anonymised minimum metadata—the minimum required accompanying metadata for aggregation: date of collection, location, and genotyping technology used.

Parasite species – Monitoring indigenous and emerging species

Plasmodium falciparum is the deadliest and most prevalent malaria parasite on the African continent. However, other malaria species that can infect humans are also present, including P. vivax, P. malariae, P. ovale wallikeri and P. ovale curtisi. Additionally, just as Anopheles stephensi is a significant concern for vector control, there are emerging species of malaria parasites. In recent years, Plasmodium cynomolgi, a simian malaria parasite first described in 1907, has made the zoonotic jump and begun to infect humans naturally.[18] As we drive elimination programmes, the distribution of parasite species will likely change, which could inform NMP activities.

PROGRAMME USE CASE:
Monitor the efficacy of drug control measures and track the distribution of parasite species.

GENETIC EPIDEMIOLOGY USE CASES.
Monitor genetic markers, Monitor population changes.

OPERATIONAL USE CASE
First-line drug policy decisions.

Sampling framework

Routine genomic surveillance through active sampling annually or biannually using dried blood spots. The level of routine sampling should be at the appropriate administrative level. It could be aligned with drug-related use case sampling, with the caveat that drug resistance monitoring using RDT to screen patients will impact the ability to detect non-falciparum species.

The sampling framework guidelines are:

- Passive case detection, after RDT or microscopy confirmation , at regular intervals (e.g., 3, 6, 12 months) depending on epidemiological conditions.
- Dried blood spot samples; and
- The spatial sampling strategy should be aligned with NMP's strategic needs.

Genomic surveillance laboratory implementation

At a top level, the laboratory implementation guidelines are:

- Capability for parasite species analysis through RT-PCR, amplicon sequencing (Illumina, nanopore, etc), molecular inversion probes, etc.
- Capacity sufficient to meet the sampling strategy for national needs. Additional capacity could be provided to neighbouring countries through a partnership arrangement.
- Whole genome sequencing on a subset of samples, possibly to develop reference genomes. While national capability may be available for monitoring known species, it is likely that, given the complexity of the genome, external capability providers will be required for this laboratory approach. (see Tier 2 accelerator use case on new markers of resistance).

Genomic surveillance data and metadata

Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic and anonymised minimum metadata—the minimum required accompanying metadata for aggregation: date of collection, location, and genotyping technology used.

Ongoing transmission – local or imported cases

This use case is crucial for certification and the prevention of malaria reintroduction, as well as for understanding the flow and movement of drug resistance and diagnostic

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[18] Bykersma A. The New Zoonotic Malaria: Plasmodium cynomolgi. Trop Med Infect Dis. 2021 Apr 5;6(2):46. doi: 10.3390/tropicalmed6020046. PMID: 33916448; PMCID: PMC8167800. https://www.mdpi.com/2414-6366/6/2/46

resistance within a country and across countries. It also involves identifying critical human sub-populations that may be key targets for reducing malaria transmission.

PROGRAMME USE CASE:
Monitor ongoing local transmission, particularly in near-elimination settings, to establish malaria-free status.

GENETIC EPIDEMIOLOGY USE CASES
Identify imported cases.

OPERATIONAL USE CASE
Improve the classification of cases as indigenous or imported across country borders (combined with travel history); identify transmission foci/sources and provide additional information about the parasite origin for imported cases.

Sampling Framework
Targeted genomic surveillance using dried blood spots. The level of routine sampling should be at the appropriate administrative level and could be aligned with drug-related use case sampling.

The sampling framework guidelines are:

- A local and global repository of genetic sequences that can be queried and ideally integrated with existing databases within the malaria community to inform parasite origins.
- Travel history data.
- Routine malaria surveillance data for elimination settings, including case investigation data.
- Dried blood spots.

Genomic surveillance laboratory implementation
At a top level, the laboratory implementation guidelines are:

- Whole genome sequencing or genome-wide genotyping.
- Amplicon sequencing (requires a consensus set of markers for data interoperability).

Genomic surveillance data and metadata
Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic and anonymised minimum metadata. The minimum required accompanying metadata for aggregation includes date of collection, location, and genotyping technology used.

Action Plan: Tier 2 use cases

Table 3 Tier 2 Use Cases

OVERALL GOAL	24-MONTH GOAL	36-MONTH GOAL
Integrate genomic approaches into the monitoring and evaluation of malaria control and elimination interventions. **Drug efficacy** New markers of drug resistance **Insecticide efficacy** New markers of insecticide resistance and their impact on control tools **Vaccine efficacy** Genetic impact of malaria vaccines **Parasite species** Indigenous and emerging species **Ongoing transmission** (local or imported cases)	Pilot integration of genomics into the monitoring and evaluation toolbox • Engagement with stakeholders to support regional hubs for the implementation of genomic tools for the monitoring and evaluation of malaria interventions • Capacitate selected regional hubs to integrate genomics tools for the monitoring and evaluation of malaria interventions	Scale up the integration of genomics into the monitoring and evaluation toolbox in all regional hubs and selected national nodes.

4.3. Tier 3 use cases

Potentially impactful for public health. They may already be in operation in Africa in settings with more advanced genomic surveillance infrastructure. Typically, they require further development before being implementation-ready at a scale suitable for public health use.

For several of these use cases, there is a need for high-resolution data, which can be beyond what is possible with amplicon sequencing. There is also a need to compare national data to global databases. Advances in these critical use cases will significantly benefit from the contribution of genomic surveillance data on malaria into global, well-curated databases that facilitate data interrogation and analysis.

TIER 3 – ADVANCED USER USE CASES

Origins of drug resistance (independent emergence vs spread)

Origins of diagnostic resistance

Vaccine escape and outbreak analysis

Causes and spatio-temporal evolution of insecticide resistance

Parasite population structure

Vector population structure

Research and development activities in malaria genomics across Africa cannot be fully captured by Tier 1 and 2 use cases. However, advances made in the coming years will inform those included herein and lead to further use cases, for example, around the implementation of gene drive technologies.

Tier 3 use cases are typically implemented in reference laboratories, regional hubs, or national CoEs. They usually have firm research profiles that align with public health programs. Their expertise will have been established over many years of investment. They play a crucial role in advancing the state of the art.

For these use cases to be applied in more contexts, challenges that need to be overcome include:

- Access to whole-genome sequencing, which may be achieved through local or regional capability building and/or outsourcing, may be necessary.
- Standardization across data, genotyping and analysis types for comparison.
- Quality assurance/quality control.
- An extensive database of parasites and vectors from multiple geographic regions is necessary for comparison, and further research is required to identify molecular markers in different geographical settings.
- Translation of genetic data into information that can easily be used for control and elimination programmes.

Origins of drug resistance (independent emergence vs spread)

This use case is relatively straightforward to implement from a sampling perspective. Shared haplotypes associated with drug resistance mutations provide evidence of origins that may be difficult to infer using standard epidemiological approaches.

This use case requires high-resolution data and comparison of current surveillance data to global reference data resources. For global reference data resources to be representative, national data should be incorporated where possible.

PROGRAMME USE CASES:
Monitor treatment efficacy and resistance to inform the selection of antimalarial drug policies.

GENETIC EPIDEMIOLOGY USE CASES:
Monitor genetic markers, detect treatment failures, describe gene flow, identify changes in parasite population structure, and detect circulating strains.

OPERATIONAL USE CASE:
Guide targeting of interventions for containment of resistance and inform regional drug policies.

Sampling framework:

- Passive case detection (in eliminating settings, this will likely be replaced by active case detection).
- Continuous sampling is possible; active sampling is desirable.
- Desired frequency: annual or semi-annual.
- Dried blood spots.

Laboratory Implementation:

- Amplicon sequencing or other genotyping methods.
- Followed by whole genome sequencing.

Data:

- Only simple methods, such as fundamental clustering analysis, can be applied to amplicon sequencing data for this use case. This use case relies on high-resolution data, such as that available from whole-genome sequencing, for more sophisticated reconstruction of ancestry, including

identity-by-descent analysis. Analyses can be further enhanced by comparison with global data resources.
- Country information can be sufficient for identifying local transmission, but it requires shared data to identify sources of imported infections from other regions within the country or other countries. May require data sharing between administrative boundaries within the country. Respect governance that protects patient confidentiality.
- Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should be shared as openly as possible, through national data-sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic, and anonymised minimum metadata. The minimum required accompanying metadata for aggregation includes date of collection, location, and genotyping technology used.

Origins of diagnostic resistance

This use case is in addition to the "Diagnostic resistance- Identifying and monitoring HRP2/3 deletions" Tier 1 high-priority use case. Whereas the Tier 1 use case aims to identify and monitor HRP2/3 deletions, the Tier 3 use case aims to understand the origins of diagnostic resistance. This could inform the implementation of control measures and/or further development of RDTs.

This use case requires high-resolution data and comparing current surveillance data to global reference data resources. For global reference data resources to be representative, national data should be incorporated where possible.

PROGRAMME USE CASES:
Monitor diagnostic treatment failure and select diagnostic tests to minimise false negatives.

GENETIC EPIDEMIOLOGY USE CASES:
Detect diagnosis treatment failures; detect changes in parasite population structure.

OPERATIONAL USE CASE:
Guide the transition from RDTs based on HRP2 to non-HRP2 RDTs in specific regions.

Sampling framework:

- Prospective surveys of symptomatic patients presenting to health facilities.
- Comparative testing using HRP2 RDTs vs pf-LDH RDTs or microscopy, and collection of dried blood spot samples.
- Prioritize HRP2 negative + pf-LDH or microscopy positive cases for Pfhrp2/3 genotyping.
- Dried blood spots.

Laboratory implementation:

- PCR to confirm Pf infection; Pfhrp2 and Pfhrp3, and at least two other single copy genes.
- Serology.
- Whole genome sequencing.

Data:

- Analyses of the origins of diagnostic resistance require comparison of generated data with global reference data resources.
- Country information can be sufficient for identifying local transmission, but it requires shared data to identify sources of imported infections from

other regions within the country or other countries. May require data sharing between administrative boundaries within the country. Respect governance that protects patient confidentiality.
- Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic and anonymised minimum metadata. The minimum required accompanying metadata for aggregation includes date of collection, location, and genotyping technology used.

Vaccine escape and outbreak analysis

This use case is critical for directing public health resources appropriately and preventing unnecessary investigations or interventions.

PROGRAMME USE CASES:
Respond to outbreaks.

GENETIC EPIDEMIOLOGY USE CASES:
Monitor genetic markers, detect treatment failures, describe gene flow, identify changes in parasite population structure, and detect circulating strains.

OPERATIONAL USE CASE:
Validate epidemiological linkages (or lack thereof) and determine the source of the outbreak (local vs. imported).

Sampling framework:
- A local and global repository of genetic sequences that can be queried and ideally integrated with existing databases within the malaria community to inform parasite origins.
- Travel history, occupation and behavioural data.
- Routine malaria surveillance data for elimination settings, including case investigation data.
- Dried blood spots.

Laboratory Implementation:
- Whole genome sequencing or genome-wide genotyping.
- Amplicon sequencing.

Data and Metadata:
- Country information can be sufficient for identifying local transmission, but it requires shared data to identify sources of imported infections from other regions within the country or other countries. May require data sharing between administrative boundaries within the country. Respect governance that protects patient confidentiality.
- Genomic data must be shared with the malaria control programme and other countries to inform national and regional public health decision-making. These data should be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic and anonymised minimum metadata.

Causes and spatio-temporal evolution of insecticide resistance

Identifying new markers across all Anopheles species that transmit malaria in Africa is an essential research activity whose outputs will be incorporated into relevant use cases over time.

Shared haplotypes associated with insecticide resistance mutations provide evidence of origins that may be difficult to infer using standard epidemiological and entomological approaches.

PROGRAMME USE CASES:
Early detection of resistance alleles; Monitor continued efficacy of mosquito control measures and resistance; Select vector control intervention strategy.

GENETIC EPIDEMIOLOGY USE CASES:
Monitor genetic markers; Identify new genetic markers of resistance; detect changes in vector population structure.

OPERATIONAL USE CASE:
First-line vector control policy decisions; assess selection pressure from novel interventions.

Sampling framework:

- Larval sampling and adult sampling (using traps and human landing catches).
- Laboratory selection of insecticide-resistant strains to anticipate development in the field.
- Generate baseline genetic diversity related to novel insecticide-based interventions (LLINs or IRS) through whole genome sequencing and RNAseq-based transcriptomics.

Laboratory Implementation:

- Whole genome sequencing.
- Transcriptomics.

Data:

- Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic and anonymised minimum metadata. The minimum standard required for accompanying metadata for aggregation is the date of collection, location, and genotyping technology used.

Parasite population structure - genetic impact of control intervention

Control interventions have been shown to have a genetic effect on their target population. It is essential to understand this impact to mitigate adverse effects and optimize the utility of the control measure.

PROGRAMME USE CASE:
Monitor changes in the parasite population to inform potential interventions and future decisions.

GENETIC EPIDEMIOLOGY USE CASES:
Monitor population changes.

OPERATIONAL USE CASE:
Intervention decisions, such as first-line drug policy decisions.

Sampling framework:

- Sampling framework alongside control intervention rollout.
- A local and global repository of genetic sequences that can be queried and ideally integrated with existing databases within the malaria community to inform parasite origins.
- Dried blood spots.
- An AA sampling framework is required to support this use case.

Laboratory Implementation:

- Whole genome sequencing or genome-wide genotyping to generate baseline genetic diversity related to the control intervention.
- Amplicon sequencing.

Data:

- Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic, and anonymised minimum metadata—the minimum required accompanying metadata for aggregation: date of collection, location, and genotyping technology used.

Vector population structure: Control intervention genetic impact

All control interventions have a genetic effect on their target population. It is essential to understand this impact to mitigate adverse effects and optimise the utility of the control measure.

PROGRAMME USE CASE:
Monitor changes in vector population structure that could inform mosquito control measures.

GENETIC EPIDEMIOLOGY USE CASES:
Monitor population changes.

OPERATIONAL USE CASE:
First-line vector control policy decisions.

Sampling framework:

- Sampling framework alongside control intervention and rollout of change.
- A local and global repository of genetic sequences that can be queried and ideally integrated with existing databases within the malaria community to inform vector origins.
- Larval sampling and adult sampling (traps, human landing catches).
- Generate baseline genetic diversity related to novel insecticide-treated bed nets through whole genome sequencing.
- This could be a subset of the insecticide resistance surveillance Tier 1 priority use case.

Laboratory Implementation:

- Whole genome sequencing or genome-wide genotyping to generate baseline genetic diversity related to the control intervention.
- Transcriptomics.

Data:

- Genomic data must be shared with the malaria control programme to inform public health decision-making. These data should be shared as openly as possible, through national data sharing policies. Genomic surveillance data should be accompanied by epidemiological, demographic, and anonymised minimum metadata—the minimum required accompanying metadata for aggregation: date of collection, location, and genotyping technology used.

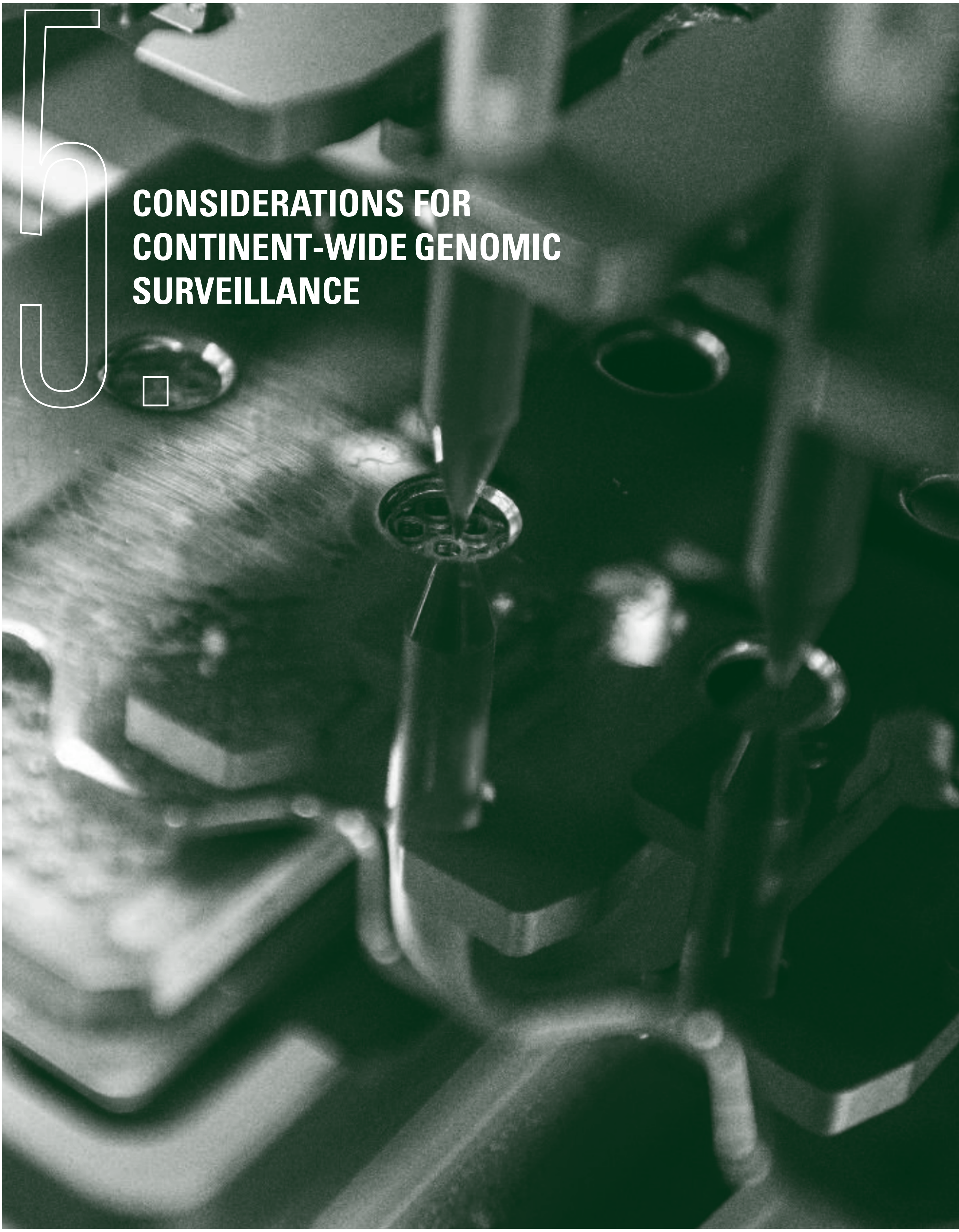
Action Plan: Tier 2 use cases

Table 3 Tier 2 Use Cases

OVERALL GOAL	24-MONTH GOAL	48-MONTH GOAL
Enhance research and development for malaria genomic tools for public health impact: Origins of drug resistance (independent emergence vs spread) Origins of diagnostic resistance Vaccine escape and outbreak analysis Causes and Spatio-temporal evolution of insecticide resistance Parasite population structure control intervention genetic impact Vector population structure control intervention genetic impact	Refine genomic tools for Tier 1 and Tier 2 use cases.	Research and development for putative novel genomic tools for malaria control and elimination

5.

CONSIDERATIONS FOR CONTINENT-WIDE GENOMIC SURVEILLANCE



Across the continent, various research laboratories have developed genomic surveillance approaches tailored to their specific use cases, leveraging their unique contexts and resources, including partnerships. This means that there is a diversity of successful implementations for each use case. To maximize the benefits of genomic surveillance for malaria, we need to harmonize sampling frameworks, genomic surveillance products, data, metadata and quality assurance. This is essential for scaling up capability and capacity to support a continent-wide approach. Public health, academic and research institutions must come together to harmonize their approaches, particularly concerning laboratory strategies that lead to greater data interoperability.

Cross-cutting challenges across Africa must be addressed to scale up malaria genomic surveillance.

Specific challenges include, but are not limited to:

- Sampling framework and strategies.
- Laboratory standard operating procedures and quality assurance.
- Procurement.
- Data integration and analytics.
- Training, capacity building and mentoring.

6. HARMONISING FOR SUSTAINABLE IMPLEMENTATION

A central core of activities implemented in multiple countries will drive forward the harmonization necessary for continent-wide delivery and provide considerable benefits for new adopters to align with these activities. These include:

- A common validation platform that could lead to product endorsement, including assays and techniques.
- Simplify supply chain challenges – centralization of some procurement for the implementation of specific genomic surveillance products, when implemented at an appropriate scale.
- Reducing data interoperability challenges that could lead to a shared data repository and highly beneficial cross-border analyses.
- Shared training resources for sample collection, laboratory implementation and data interpretation.
- The central core of activity features two distinct but complementary areas: from sample to data generation and the interoperability and use of that data.
- All outputs should be accessible to the broader community and, ideally, held in a central repository. This should not impede the rights to publish or host material on other public-facing repositories or websites.

6.1. Genomic surveillance products for multi-laboratory implementation and support

There are African laboratories that are actively working to support national or regional genomic surveillance programmes. Among these, a small number of institutions can be considered as CoEs. They have developed a strong sampling framework in partnership with their relevant NCMPs. They provide a broad spectrum of malaria surveillance activities, potentially including multiple genomic surveillance technologies. Over many years, these high-resolution programmes have emerged due to consistent and long-term investment in malaria and genomics, including people and infrastructure. While high-resolution programmes build the evidence base for the impact of genomic surveillance for endemic diseases, their infrastructure is not readily transferable from research to a public health setting. A modular approach is required to facilitate continent-wide engagement.

Genomic surveillance products are the foundation of genomic surveillance. They are the instrument for delivering data that meets the needs of genetic epidemiology use cases. These, in turn, perform genetic epidemiology functionality to provide evidence for program use cases, leading to informed public health decision-making.

Many surveillance products currently in operation are implemented in a single laboratory, and adaptation may be necessary to operate at the scale required for public health impact. To deliver a continental approach to genomic surveillance, a key principle for the development of genomic surveillance products must be multi-laboratory implementation. In addition to economies of scale, with more parties using the same approach, it may be possible to drive down the cost; it also facilitates the sharing of resources and catalyses a community around those resources.

Genomic surveillance product for multi-laboratory implementation requirements include:

- Standard operating procedures suitable for implementation in multiple laboratories.
- An equipment list, including a review of viable alternative equipment and its

impact on the data outputs.

- Support and exchanges to troubleshoot protocol implementation.
- Considerations for high-throughput versus low-throughput systems.
- Reagent list including suppliers and product codes (where applicable).
- Data processing and/or bioinformatics pipelines to turn raw data into a data product that (with manual intervention in the first instance) can meet a public health use case.
- Analytical methods to translate processed data into reliable data products.
- Accessible computing infrastructure (e.g. cloud cloud-based) to enable interrogation of data.
- Quality control protocols.
- Guidance on validation steps at each stage.

This information should be readily available, if not publicly available, and accompanied by an implementation plan that supports the generation and validation of raw data, data processing, production of the appropriate surveillance data product and training materials on how to use and interpret the data.

Once a genomic surveillance product is operational, a further process should be implemented to validate the product's outputs. Ideally, this will be achieved by a laboratory similarly implementing the product. The rationalization of genomic surveillance products will facilitate external quality assurance processes until a more formalised process is in place.

Genomic surveillance products that meet public health use cases and are suitable for multi-laboratory implementation are crucial for achieving continent-wide objectives.

6.2. Interoperability of data and data processing platforms

During the pandemic, there was considerable interest in global health. However, the political, technical, and bureaucratic challenges of data sharing are more complex when applied to endemic diseases in large research communities. As the primary pillar of this roadmap is to be driven by the needs of public health, their needs must be given priority.

Regional data analyses can provide significant value to individual countries by providing greater context to country results. Interoperability and open sharing of data are crucial requirements for cross-border analyses.

Since the problem of standard data formats and information interchange is too complex and onerous for any single country or implementer, strategies for data interoperability, interchange, and sharing should be developed collaboratively. For example, technical working groups are made up of early adopters and key stakeholders. Promoting and achieving consensus on best practices for interoperable and open data sharing and access principles for Africa is a significant undertaking. Among things to consider are:

- Openness of data deposited in primary data repositories with non-identifiable metadata.
- Linking data to data generators to facilitate appropriate authorship and acknowledgement.
- Integrate curated data from multiple sources and technologies to produce high value aggregated regional analyses made available to NMPs.

- Data Sharing and Authorship Guidelines as Part of a Code of Practice.
- Development of collective training, including around shared resources.
- Standardization of data metadata, including data dictionaries, metadata, and summary tools for WHO threat maps, etc.
- Mechanisms of shared data storage, security, analytical support, essential visualization tools and other practical aspects of data aggregation and sharing.

Uniting data from multiple genomic surveillance products, from member states across Member States in Africa provides a greater context for individual countries.

Developing guidelines for data interoperability of data is a significant undertaking.

Bringing together the heterogeneous results, guaranteeing attribution and setting standards will be a very substantial body of work, which goes beyond the scope of the present document. Indeed, it extends beyond the scope of genomic surveillance of malaria in Africa to encompass all pathogens and vectors. A task force of African genomic surveillance leaders and other subject matter experts must come together to deliver a consensus option for a continent-wide approach to data sharing and interoperability.

Mechanisms for countries to undertake initial implementations of data integration and demonstrate what is possible with a unified approach will provide a crucial foundation stone for full-scale data sharing and integration. The Genre-Mekong experience has shown that convincing early results can be vital for securing public health buy-in.

Just as with standardization for genomic surveillance laboratory products, bringing together early adopters to harmonize where possible is an essential step in scaling up from current surveillance to continent-wide activities. Providing mechanisms for people to integrate their data as much as possible and demonstrating what is possible with a unified approach will further enhance the evidence base of public health impact.

6.3. Advocacy and education programme

The power of genomic surveillance demonstrated during the COVID-19 pandemic has set high expectations for what is achievable and within what timeline. The WHO has published numerous studies supporting the role of genomic surveillance, both in general and specifically for malaria. We must capitalize on the opportunity.

The implementation of genomic surveillance across Africa requires engaging with a complex landscape of stakeholders, with a plurality of opinions and diverse drivers. Genomic surveillance is multifaceted, and considerable effort must be invested to make the information accessible. This includes standard information, such as use cases, and context-specific information, including case studies that demonstrate public health impact. It is essential to capture crucial information about exemplars of success efficiently, effectively, and in an accessible manner. The measure of impact should not be limited to scientific publications and peer review. Lessons learned and decisions made in the public health context are equally valuable in building the evidence base for informed decision-making.

With the most significant burden of malaria, Africa must prioritize research and development to meet emerging public health needs. Recent control measures include the introduction of new bed nets and vaccines. In both cases, their potential impact in the fight against malaria is huge. If compromised, the risk is catastrophic. Those most affected should lead the development of working with key stakeholders, use cases around these new interventions, and how they are implemented.

Just as different countries have different priorities, so will there be differences in how these priorities are met. Remaining flexible to this diversity is crucial, although standardising approaches to genomic surveillance products will provide easier access for new adopters. This is further improved if information is available through user-friendly portals.

Several highly successful standalone genomic surveillance initiatives are currently underway across Africa. They are well-integrated with public health systems and deeply connected to communities that have been engaged over many years. They result from many person-years of effort to understand a specific context and tailor the initiative to the context. These initiatives are examples that should be drawn upon to understand the underpinning elements that made them successful. Among the many reasons these initiatives are successful is that they understood the stakeholder landscape; the roles and responsibilities of those involved in the partnership were clear at the outset, and the effort on all sides was focused on a shared vision to use genomics to address a specific public health need.

Capturing information on these successes builds the evidence base and prepares it for integration into future global summaries and strategies.

Examples should be collated across Africa and globally to capture the diversity of contexts that genomic surveillance can support. Specific examples of high-resolution national surveillance include those in Tanzania and Uganda. Network and regional examples include the genomic surveillance of the malaria network in West Africa and Southeast Asia, as well as the GenRe project. In addition to information about the projects themselves, decisions made based on genomic surveillance data should be highlighted. For example, in Uganda, following the WHO's determination of partial artemisinin drug resistance, as determined from genomic data, TES were initiated in the region.

6.4. Action Plan: Harmonisation

Table 5 Harmonization Action Plan

OVERALL GOAL	24-MONTH GOAL	48-MONTH GOAL	48-MONTH GOAL
Accelerate the development of genomic surveillance sample processing products for multi-laboratory implementation.	Identify key stakeholders for certification of genomic surveillance platforms.	Process for reviewing, approving, and endorsing genomic surveillance products as suitable for rollout in specific use cases.	A suite of standardised information for genetic product platforms that is accessible, e.g. on the Africa CDC website.

OVERALL GOAL	24-MONTH GOAL	48-MONTH GOAL	48-MONTH GOAL
	Survey existing implementations of genomic surveillance to identify transferable platforms and best practices. Standard template developed in partnership with early adopters and implementation laboratory specialists.	Adapting transferable products to a template involves identifying and filling gaps in the transferable products necessary for Multi-laboratory Implementation.	
Guidelines for interoperability of data from multiple genomic surveillance products.	Identify key stakeholders for the interoperability of data for genomic surveillance products. Survey existing implementations of genomic surveillance to identify high-resolution national surveillance programmes and hub laboratories across priority use cases.	A draft plan for implementing interoperability has been circulated to key stakeholders, including members of the Data Analysis and Integration Technical Working Group.	Ratified plan addressing key data interoperability challenges that is accessible, e.g. on the Africa CDC website.

7

RECOMMENDATIONS FOR KEY STAKEHOLDER GROUPS

7.1. Member States

- Develop a national genomic surveillance system that meets national needs. The optimum implementation of these systems may include national capabilities and/or partnerships with international laboratories. Member States are strongly advised to leverage and build on existing capacities to support Malaria genomics surveillance and engage Africa CDC expertise to develop their system plan.

- Collect and report data on Tier 1, 2 and 3 priority use cases of interest that can be implemented.
- Consider incremental improvement to the capability and capacity of national genomic systems and strengthening partnerships with regional laboratories and CoEs.

7.2. Africa CDC and other regional public health bodies

- Develop and implement a continental programme for genomic surveillance of malaria, including surveillance and reporting standards and tools, data definitions, and external quality assessment schemes. This programme will also establish a network of genomic surveillance laboratories to support genomic surveillance of malaria and external quality assurance in each African region.
- Develop standards for reporting, sharing, and publication of data on genomic surveillance of malaria in Africa, in consultation with Member States and other multi-sectoral stakeholders.
- Collaborate with partners to establish a continental repository for information on genomic surveillance of malaria and the evidence base for its impact in research, development, and public health.

7.3. Stakeholders and partners

- The international research community should support studies to improve the products to meet use cases
- Implementation partners should standardize and simplify products as far as possible, with a few to a continent-wide rollout.
- Encourage and support Member States in forging in-country as well as regional and global coalitions and alliances

8. SUSTAINABILITY

At every stage of implementing the genomic surveillance framework, opportunities to accelerate sustainability should be identified and pursued from both national and continent-wide perspectives. We will all benefit and accelerate our sustainable implementation goals by keeping a dual focus on establishing critical mass in Africa and nationally.

Four key considerations include:

National strategy

Developed in partnership with relevant national and regional stakeholders, national strategies should consider sustainability as a core development pillar. Initially, focusing on how genomic surveillance needs can be best met in the national context and which of the Continent's network of institution types is most appropriate for their needs; further, considerations should be made for cross-disease optimization in order not to have malaria as a silo. The strategy must be costed against a robust plan, including contingencies, and identify leverage opportunities to optimize limited resources.

Diversified funding streams

Utilising multiple funding streams collectively towards a common goal will mitigate the risk of de- or under-funding due to competing priorities. Funding streams include, but are not limited to, government, development partners, the private sector, and research funding. We must aim to secure the increased local and national funding necessary to bridge the funding gap for the elimination of malaria, including for genomic surveillance.

Domestic funding

National strategies should aim to include local funding for genomics surveillance of malaria wherever possible. Incorporating even a modest budget in the first instance is a foundation for growth. Local funding is essential to securing buy-in from senior national and regional stakeholders and ensuring the diversified funding streams necessary for sustainable implementation.

People

In addition to the challenges of equipment and infrastructure, there is a need to retain trained personnel to deliver genomic surveillance ambitions for sustainable public health impact. At a national and continental level, the current and future needs of the workforce must be identified, and suitable training environments and opportunities must be made available. Through sustained investment across Africa, we will create opportunities spanning data generation, analysis, and interpretation, as well as a professional development environment for genomic surveillance in Africa.

9. CONCLUDING REMARKS

To achieve comprehensive genomic surveillance of malaria across Africa, it is crucial to strengthen the evidence base for the surveillance of malaria parasites and vectors. National plans for genomic surveillance of malaria should align with global action plans, for example, WHO recommendations for monitoring hrp2/3 deletions.

A more standardised approach to genomic surveillance of malaria, including the use cases and the products that generate data to support these use cases, is required. This is a key step towards validation, external quality assurance, and measuring the impact of public health.

With best practices agreed upon and a policy in place, dissemination of this change to the broader community of laboratory medicine professionals and healthcare professionals on the continent is required. Ideally, representatives of these groups will be included in the stakeholder group for consultation to aid in the receptiveness of proposed changes through co-ownership of initial idea generation.

Maintaining communication between Ministries of Health, implementation partners, and the public will be essential to facilitate continued support and integration of genomic surveillance services.
Africa CDC will be the driving force in creating and maintaining political will through its close working relationship with the African Union. This is essential for policy development and securing sustainable funding routes for genomic surveillance.

ADDITIONAL INFORMATION

Stakeholder database: As part of the development of this roadmap, key stakeholders and funders in Malaria Genomic Surveillance (including government, private, public, philanthropic, and other sectors involved in malaria genomic surveillance) were invited to comment on the document prepared by the contributors. The database of those stakeholders consulted is available here.

Annexe 1:

Implementation checklist for parasite use cases

Annexe 2:

Implementation checklist for vector use cases

ANNEXURES

Annexe 1: Genomic Surveillance Systems Implementation Checklist – Parasite Use Cases

This is a list of components that need to be considered for implementing genetic surveillance to address a specific use case for genomic surveillance of malaria, particularly for parasite-related use cases.

The list is derived from experience in implementing genomic surveillance projects; not all items may apply to every new country implementation, and in some cases, implementors may be able to leverage existing processes or infrastructure.

Study Management (in-country, or regional)

- A study protocol, detailing the purpose, procedures, and coverage, is needed if the surveillance project is classified as research.
- Consent and assent forms, as well as a Participant Information Sheet (PIS), may be required if the surveillance project is classified as research, unless a national ethical committee grants dispensation due to the public utility of the study (usually requested by NMP or MoH).
- Study-specific Case Report Forms (CRFs) must be designed if additional information about the malaria case (e.g., travel history) is to be captured (optional).
- Ethical approval from a local Ethics Board must be obtained.

Sample Collections (in-country)

- A sampling framework must be agreed upon with the NMP, detailing the frequency of sampling, sampling locations, and projected sample size. The projected sample size at each area depends on the case incidence and should be sufficient to draw confident conclusions from the data produced.
- A catalogue of sampling sites should be agreed upon. Location information should include:
  - Site code (unique identifier to be used in collection records).
  - Site name.
  - Country.
  - Administrative Divisions 1 and 2 (e.g. Province and District), as defined by the State.
  - Administrative Divisions 1 and 2 identifiers from a public database (e.g. GADM) (desirable).
  - GPS coordinates (desirable).
  - Administrative Division 3 (e.g. Subdistrict/Commune) and its identifier are also desirable in countries where they are defined.
- A barcoding system must be in place to track samples anonymously. Typically, four barcode stickers are required per sample: one for the DBS filter paper, one for the Sample Collection Record, one for the CRF (if applicable), and one for the patient records at the location, allowing public health to associate sample data with the patient.

- A Sample Collection Record must be designed, with one line for each sample, showing: the barcode sticker, the date of collection, the code of the collection location, and the species detected.
- One or more Sample Coordinators should be appointed, whose role is to receive samples from sites, aggregate them, verify metadata, distribute collection materials, and train and support the field staff.
- Training sessions must be conducted to train public health staff at the collection facilities on the DBS collection and metadata entry process.
- Sample collection kits should be assembled and distributed to the collection sites in packs (e.g., 20 kits per pack). Each kit may contain the following items: a strip of filter paper of the desired type, an alcohol swab, a disposable lancet, a miniature pipette for collecting the correct amount of blood, a plastic pouch with silica gel for DBS storage, and a larger, lightproof plastic pouch for storage.
- The sample collection SOP must be defined and illustrated.
- A system must be put in place for periodically routing collected samples to the coordinator for aggregation, e.g., the coordinator travels to collection sites or a courier system is in place.
- There must be a procedure for creating manifests of aggregated samples, including location codes and dates, ready for shipment to the laboratory.

Sample Processing (in-country or regional laboratory)

- The lab will be equipped to receive the samples, unpack them, check them, and enter the data into a Sample Management System.
- The lab will possess a DBS paper punch with an anti-contamination mechanism.
- The lab will genotype a set of markers as defined by the use case. This may be executed with different technologies, e.g. PCR, qPCR, Amplicon Sequencing, WGS, Sanger sequencing. Both short-read (e.g. Illumina) and long-read technologies (e.g. Nanopore) are suitable. A mix of technology may be required. The following targets are currently necessary or desirable:

o Essential targets- resistance to artemisinin (used in ACT frontline) and resistance to SP (used in preventative interventions):

- kelch13 (any mutation found in BTB/POZ and propeller domains): artemisinin resistance.
- dhfr mutations 51, 59, 108, 164: resistance to pyrimethamine.
- dhps mutations 436, 437, 540, 581, 613: resistance to sulfadoxine.

o Historical targets (optional)- these may be interesting because of historical drug use:

- CRT mutations 76.
- Optional targets-These may be interesting for epidemiological studies or because they are widely studied, but do not necessarily generate actionable predictions.
- mdr1 mutations 86, 184, 1246.

o Potential targets (optional)- these

are predictors of drug resistance in other regions of the world, but their phenotype in Africa has not been demonstrated:

- Plasmepsin 2/3 amplification: resistance to piperaquine in SE Asia (not shown to be relevant in Africa but may be of interest in African countries using DHA-PPQ).
- Mdr1 amplification: resistance to mefloquine in SE Asia.
- The lab will deliver sample genotype data in a tabular format, with consistent column names and value encodings. These encodings should be documented clearly in a data dictionary.

Genotype Analysis (in-country or scientific partners)

- The analyst group will receive the genotype and, optionally, aggregated it with previous batches of genotypes.
- Predictions on drug resistance will be made from the genotype data. These will be delivered in tabular form, with consistent column names and value encodings. These encodings should be documented clearly in a data dictionary. The predictions will be made using rules that are applied consistently and reported transparently.
- Genotype and prediction data will be aggregated geographically, e.g., by site, district, or province, and the prevalence of mutations or resistance to each drug will be estimated. These will be delivered in tabular form, with consistent column names and value encodings. The process for estimating prevalence and handling missing data and heterozygous genotypes must be documented.
- Maps can be generated that show the prevalence of mutations and/or resistance across the territory. This may be automated (e.g. with a tool such as the grcMalaria R library) or created with GIS systems, etc.
- The raw and derived data, along with maps, are delivered to the NMP, preferably accompanied by a report that explains the interpretation of the data.
- Discussion sessions usually follow the delivery of the data to support NMPs and make the data more useful for their decision-making.

Annexe 2 - Genomic Surveillance Systems Implementation Checklist – Mosquito Use Cases

This is a list of components that need to be considered for implementing genetic surveillance to address a specific use case for genomic surveillance of malaria, particularly in mosquito-related contexts.

The list is derived from experience in implementing genomic surveillance projects; not all items may apply to every new country implementation and in some cases, implementors may be able to leverage existing processes or infrastructure.

Study Management (in-country, or regional):

- A study protocol, detailing purpose, procedures, coverage, etc., is needed if the surveillance project is classified as research
- Ethical approval from a local Ethics Board must be obtained.

Sample Collections (in-country):

- A sampling framework must be agreed upon with the NMP, detailing the frequency of sampling, sampling locations, and projected sample size. The projected sample size at each area depends on the case incidence and should be sufficient to draw confident conclusions from the data produced.
- An AA catalogue of sampling sites should be agreed upon. Location information should include:
  - o Site code (unique identifier to be used in collection records).
  - o Site name.
  - o Country.
  - o Administrative Divisions 1 and 2 (e.g. Province and District), as defined by the State.
  - o Administrative Divisions 1 and 2 identifiers from a public database (e.g. GADM) (desirable).
  - o GPS coordinates (desirable).
  - o Administrative Division 3 (e.g. Subdistrict/Commune) and its identifier are also desirable in countries where they are defined.
- AA barcoding system for tracking samples must be in place. Barcode. Typically, two barcode stickers are required per sample: one for the collection tube and one for the sample collection records at the location.
- A Specimen Collection Record must be designed, with one line for each sample, showing: the barcode sticker, the date of collection, the code of the collection location, and the species detected.
- One or more Sample Coordinators should be appointed, whose role is to receive samples from sites, aggregate them, verify metadata, distribute collection materials, and train and support the field staff.
- Training sessions must be conducted to train public health staff at the collection facilities on the mosquito collection and metadata entry process.
- Sample collection kits should be assembled and distributed to the collection sites in packs (e.g., 20 kits per pack).
- A sample collection SOP must be defined and illustrated.
- A system must be implemented to periodically route collected samples

to the coordinator for aggregation, such as when the coordinator visits collection sites or a courier service is in place.

- There must be a procedure for creating manifests of aggregated samples, including location codes and dates, ready for shipment to the laboratory.

Sample Processing (in-country or regional laboratory):

- The lab will be equipped to receive the samples, unpack them, check them, and enter the data into a Sample Management System.
- The lab will possess the necessary equipment and reagents for a minimally destructive extraction of mosquito DNA.
- The lab will process mosquito DNA according to the genomic surveillance product.
- The lab will deliver sample genotype data in a tabular format, with consistent column names and value encodings. These encodings should be documented clearly in a data dictionary.

Genotype Analysis (in-country or scientific partners)

- The analyst group will receive the genotype and optionally aggregate it with previous batches of genotypes.
- Predictions on drug resistance will be made from the genotype data. These will be delivered in tabular form, with consistent column names and value encodings. These encodings should be documented clearly in a data dictionary. The predictions will be made using rules that are applied consistently and reported transparently.
- Genotype and prediction data will be aggregated geographically, e.g., by site, district, or province, and the prevalence of mutations or resistance to each drug will be estimated. These will be delivered in tabular form, with consistent column names and value encodings. The process for estimating prevalence and handling missing data and heterozygous genotypes must be documented.
- Maps can be generated that show the prevalence of mutations and/or resistance across the territory. This may be automated (e.g., with a tool such as the grcMalaria R library) or created with GIS systems, etc.
- The raw and derived data, along with maps, are delivered to the NMP, preferably accompanied by a report that explains the interpretation of the data.
- Discussion sessions usually follow the delivery of the data to support NMPs and make the data more useful for their decision-making.

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Africa CDC is a continental autonomous health agency of the African Union established to support public health initiatives of Member States and strengthen the capacity of their public health institutions to detect, prevent, control and respond quickly and effectively to disease threats.

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