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Monitoring parasite diversity for malaria elimination in sub-Saharan Africa

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Abstract

The African continent continues to bear the greatest burden of malaria and the greatest diversity of parasites, mosquito vectors and human victims. The evolutionary plasticity of malaria parasites

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and their vectors is a major obstacle to elimination of the disease. Of current concern is the recently reported emergence of resistance to the front-line drug, artemisinin, in South-East Asia in *Plasmodium falciparum*, which calls for pre-emptive surveillance of the African parasite population for genetic markers of emerging drug resistance. Here we describe the *Plasmodium* Diversity Network Africa (PDNA) which has been established across eleven countries in sub-Saharan Africa to ensure that African scientists are enabled to work together and to play a key role in the global effort for tracking and responding to this public health threat.

Africa is home to the most successful malaria vector (*Anopheles gambiae* complex) and of the deadliest malaria parasite (*Plasmodium falciparum*). Despite efforts to eradicate malaria in the 1950s and early 1960s, 207 million cases and 627,000 malaria deaths were estimated to have occurred in 2012, mostly in sub-Saharan Africa and in children under 5 years of age (1). The inability to eradicate malaria reflects the complex co-evolution of the three eukaryotic genomes involved and represents the major biological challenge to vaccine and drug development. Since publication of the full genome of a reference clone, many other model and population isolates have been sequenced (2), providing some insight into genetic variation responsible for phenotypes like drug resistance and virulence. However, the global genome-wide pattern of genetic diversity across most endemic regions is poorly understood as few natural *Plasmodium falciparum* populations have been analyzed.

Malaria elimination efforts in Africa are heavily reliant on artemisinin combination therapies (ACT) yet no coordinated effort for monitoring emergence or prevention of spread of artemisinin resistance is in place in Africa. In addition, introduction of new malaria vaccines or mass therapeutic approaches to control and elimination will increase selection for resistance in parasite populations that could damage the effectiveness of these and future tools.

Rationale and Mission for an African Plasmodium Diversity Network

The emergence of antimalarial resistance to artemisinin in Southeast Asia (3,4) calls for global monitoring of the parasite population (5). The MalariaGEN community has already built a successful framework for data-sharing (6); hence, we have adopted this model to form the *Plasmodium* Diversity Network Africa (PDNA). The concept of PDNA was seeded by several African scientists during the Genomic Epidemiology of Malaria conference at Hinxton in 2012. In May 2013, the network was formally launched in Accra, Ghana, when scientists and clinical researchers met from 13 research groups from across Africa (Fig. 1).

The mission of PDNA is to explore the malaria parasite's genetic and phenotypic diversity to advance the malaria elimination and eradication agenda in sub-Saharan Africa. We have initiated or will initiate projects to investigate *Plasmodium* population structure and evolution, survey the frequencies of current and novel molecular markers of antimalarial drug resistance, and specifically monitor for the emergence and spread of artemisinin resistance in sub-Saharan Africa.

How will PDNA contribute to malaria elimination?

To succeed, malaria elimination requires knowledge of parasite genome variation in different geographical locations, recent evolutionary selection and a better understanding of the factors that determine gene flow between locations, such as rates of inbreeding and population structure. The PDNA membership represents the range of malaria diversity in Africa. The Network is in its infancy and is bound to evolve with time. Each PDNA member brings specific scientific expertise (supplemental Table 1) and capacity to collect local biological material, as well as clinical data. *Plasmodium* DNA will be either analyzed on-site or dispatched to various laboratories, such as the Wellcome Trust Sanger Institute, UK, for sequencing, genotyping, and various wet laboratory investigations to survey for evidence of evolution in response to recent or on-going elimination measures. PDNA studies will translate genomics data on *Plasmodium* diversity into evidence to be shared with the sub-Saharan Ministries of Health, National Malaria Control Programs, Regional and International Health Authorities, such as the Africa Bureau of World Health Organization (WHO), WHO Global Malaria Program and other Stakeholders (Fig. 2).

Pooled analysis of data will provide larger sample size and comparable information across the African continent as well as the detection of rarer genetic events, site-specific issues, and opportunities for modelling. Hence PDNA will have an Africa-wide dynamic view of malaria diversity and recent evolution. Through real-time knowledge sharing and dissemination, lessons learned will be openly available to the various stakeholders.

Current projects

Each study site will adopt common protocols, common standard operating procedures and whenever possible the same reagents and supplies. For example, using seed funding from the UK Medical Research Council we have initiated a baseline investigation of *P. falciparum* diversity in sub-Saharan Africa. Each site collected 100 leucocyte-depleted *P. falciparum* infected blood samples. DNA was extracted and shipped to the Wellcome Trust Sanger Institute for whole genome sequencing and data analysis is underway with support from the MalariaGEN resource centre. As the new K13 propeller polymorphisms have been described as a molecular marker for artemisinin resistance (7), we have also been investigating their presence and prevalence in each of our African sites. Within weeks, each PDNA site collected, processed and shipped genomic DNA or dried blood spots for sequencing. Together, these projects show how a coordinated network of African scientists can mount a rapid surveillance response.

The institutions involved in PDNA are at different levels of scientific expertise and hence a priority will be to engage in training and capacity development at each participating institution for know-how as well as ethics. Although the primary focus of the PDNA project is *Plasmodium*, the process of obtaining parasite DNA involves the collection of blood samples from human volunteers. Thus, in accordance with international ethical guidelines, voluntary informed consent of research participants will be sought in each of the projects, and all PDNA research proposals will be submitted to relevant ethics committees for review and approval.

Conclusion

The PDNA represents an African initiative for assessment of endemic-country malaria parasite diversity at the genotype and phenotype levels to address scientific questions most relevant to the successful elimination of malaria in sub-Saharan Africa. PDNA will use its range of scientific, geographic, epidemiologic, political and ethno-linguistic diversity to engage local and international stakeholders, including health policy decision makers, to ensure that we contribute directly to the global agenda for malaria elimination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References and Notes

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Figure 1.
Countries represented by the Plasmodium Diversity Network Africa members (Map by Free Vector Maps, <http://freevectormaps.com>)

PDNA

Figure 2.
Flow diagram of how PDNA will contribute to malaria elimination policy decisions