

The Contribution of the INDEPTH Network to Malaria:

A Synthesis of Research Evidence Published from 1998 to 2009



Rockefeller Foundation

Many low and middle income countries (LMICs) in Africa, Asia and Oceania lack reliable population-based data on health, an essential evidence base for effective policy making. The International Network for the Demographic Evaluation of Populations and their Health (INDEPTH) Network, founded in 1998, is an umbrella organization for a group of independent health research centres operating health and demographic surveillance systems (HDSS) sites in LMICs [1]. The Network's mandate is to fill an important gap in global epidemiology by supporting the generation of longitudinal health and demographic evidence in LMICs [2]

The longitudinal data generated by INDEPTH HDSS sites represent an inherently strong epidemiological design, providing considerably greater analytical scope than can be achieved from other approaches e.g. cross-sectional studies. Further, the Network's platform provides the unique potential to collate data from different member HDSS sites, allowing pooled analyses and systematic comparisons to be made across sites. In the period 1998-2009, the INDEPTH Network Secretariat compiled a database of 2517 peer reviewed articles from the member centres. 201 were on various aspects of malaria.

In July 2012, INDEPTH partnered with the African Institute for Development Policy (AFIDEP) to conduct a review that would: identify and describe the work that has been done by the INDEPTH Network on malaria; highlight the main contributions of this work to the body of knowledge on malaria, and identify key knowledge gaps that can be filled

by the Network's uniquely rich longitudinal research.

The review of INDEPTH Network's contribution to malaria research for the period 1998 to 2009 uncovered a vast body of knowledge on the changing patterns in transmission; incidence of clinical disease in some sites in sub-Saharan Africa, and the significant impact of malaria control interventions such as insecticide treated bed nets (ITNs) and artemisinin combination therapies (ACTs).

The synthesis and systematic review found that socioeconomic, environmental and genetic factors were significant determinants of malaria risk in most endemic settings. In addition, knowledge gaps were identified in vector and parasite resistance, urban malaria, the impact of climate change and interventions to reduce inequities in access to malaria control interventions.

This research inbrief presents a summary of the key findings from the analysis and existing knowledge gaps that INDEPTH can contribute to.

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Study Methods

The synthesis approach was adapted from methods by Higgins and Green and the Centre for Reviews and Dissemination. Eligible peer-reviewed publications were identified from the INDEPTH Network's publication database for the period 1998-2009. Publications were reviewed if they were based on original analyses derived from data collected at INDEPTH Network centres. Publications from centre affiliated scholars that were wholly based on non-site data were excluded. This brief presents a summary of the synthesis of the INDEPTH Network's contribution to malaria research during this period (1998-2009) and the key knowledge gaps identified. Figure 1 shows the distribution of the 167 peer-reviewed studies included in the synthesis according to the countries where they took place.

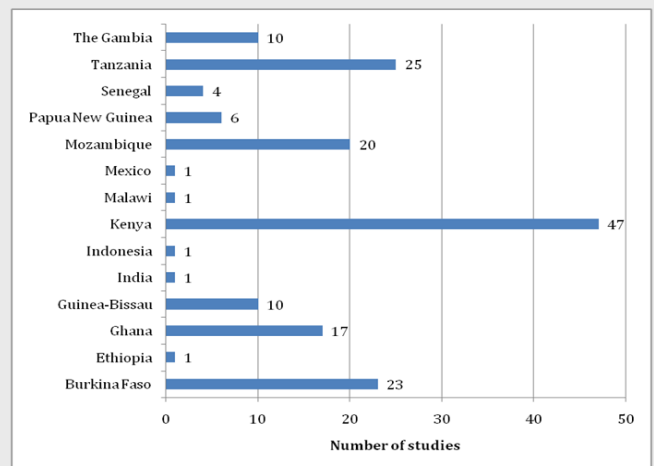


Figure 1 : Distribution of peer-reviewed articles included in the synthesis by country

INDEPTH Network's Contribution to Knowledge on Malaria

MALARIA EPIDEMIOLOGY



Children and pregnant women in sub-Saharan Africa are at the highest risk of malaria infection and subsequent death: The studies conducted by the INDEPTH Network concur with other studies that demonstrated that malaria is a major cause of morbidity and mortality, particularly in Sub Saharan Africa, with children and pregnant women being at the highest risk[3]. Whilst the risk of malaria was demonstrated to be high all year round in a few sites, the majority demonstrated a higher risk of malaria transmission in the wet rather than dry season, with infective bites occurring mostly at night.

Malaria transmission rates are decreasing in some areas in sub-Saharan Africa, but are not easily predictable even across short distances: INDEPTH Network studies contributed to

current evidence demonstrating that malaria transmission is declining in most but not all sites in sub Saharan Africa[4]. In several sites, this has been accompanied by a significant decline in the incidence of clinical malaria disease. However, it is noteworthy that the reductions in the incidence of clinical disease were not immediate, highlighting the need for sustained malaria control efforts to achieve significant declines. Further, data from several INDEPTH Network studies also show that more severe disease is observed in older age groups in regions with lower transmission and lower incidence of clinical disease. The observed decline in malaria transmission and incidence of clinical disease have been associated with the effective implementation of several malaria control interventions such as insecticide treated bednets (ITNs) and artemisinin combination therapies (ACTs). This highlights the need for sustained surveillance, and public and health worker education to ensure adequate and timely malaria prevention and case management.

Interestingly, the evidence showed that malaria transmission can vary across relatively short distances, with significant differences in the risk of infection being observed even between neighbouring villages. This highlights the need to better understand malaria micro-epidemiology and consider the local context when implementing malaria control programs. To support this, there is an urgent need to put in place Health Management Information Systems (HMIS) that can provide the necessary data for a context-specific assessment. Although the creation and maintenance of robust HMIS requires increased financial and human resources, the cost of this investment in malaria control programs may be off-set by the reduced costs of malaria case management in the long term.

Climatic and environmental factors are sound predictors of malaria transmission and incidence of clinical malaria:

One study from the INDEPTH Network showed that climate factors (rainfall, humidity and temperature) were significantly associated with the risk of clinical malaria, suggesting a need for better integration between malaria control and weather surveillance programs. Further, given the increasing global significance of climate change, evaluation of malaria risk in this context should be prioritised. *Anopheles gambiae* and *Anopheles funestus* sub-species were reported as the major vectors in two African sites. Importantly, the studies highlighted the capacity of different vector subspecies to adapt to different climatic and

environmental conditions, with some flourishing in flooded or irrigated areas while others did so in savannah areas. There is a need for more studies aimed at monitoring changes in vector ecology in the dynamic context of changing malaria transmission. Importantly, such studies will greatly support the evaluation of the impact of various malaria control interventions.

Socioeconomic and environmental factors are stronger predictors of malaria transmission than genetic factors:

Various genetic factors significantly influence the risk of morbidity and mortality due to malaria. For example children with the sickle cell and alpha thalassemia genotypes (HbAS and $\alpha\alpha/\alpha\alpha$) are significantly more protected from severe malaria and resultant death than those who do not carry these genotypes. The findings of one INDEPTH study suggested that genotype testing of Human immunodeficiency Virus (HIV) positive pregnant women may predict the risk of placental malaria transmission to the unborn baby. Therefore, further research is warranted in order to generate more conclusive knowledge on the effects of various genetic factors, and how such knowledge can be translated into practice.

Despite these findings, some research evidence from INDEPTH Network studies suggested that genetic differences only account for a small variation in the outcome of malaria infection, and that various socioeconomic and environmental factors play a larger role. In support of this argument, two INDEPTH Network studies demonstrated a significant association between chronic under-nutrition in children and an increased risk of contracting severe clinical malaria, as well as a higher incidence of clinical malaria in children living near a river or swampy area. The latter finding corroborates studies that demonstrate climatic and environmental factors as predictors of malaria transmission.

Overall, the malaria epidemiology studies demonstrate the need to holistically consider genetic,

factors when designing malaria control interventions. Further, the findings environmental and socioeconomic highlight the need for a multi-sectoral approach to malaria control. Such an approach would ensure proper linkage and integration between malaria control programs and other key programs within the ministries of health (e.g. nutrition), as well as with other line ministries (e.g. Ministry of Environment) to ensure that broader development goals are achieved. Efficient coordination mechanisms are crucial to the success of such linkages and integration.

Current tools to detect malaria related deaths outside the formal health care system are unreliable:

The capacity to quantify malaria-related deaths outside the formal health care system is critical in providing accurate estimates of the malaria burden and in accurately evaluating the impact of malaria control interventions. The unreliability of the verbal autopsy method for detection of malaria-related deaths was identified as a major setback in accurately estimating malaria related deaths outside the formal health care system. This highlights the urgent need to develop a more reliable tool to support current research and practice in malaria epidemiology.

IMPACT OF MALARIA CONTROL INTERVENTIONS



Insecticide treated nets (ITNs) are highly protective against malaria infection:

Studies from the INDEPTH Network contributed to the current evidence that when used properly, bed nets and curtains treated with permethrin are highly protective against malaria in children less than 5 years in sub-Saharan Africa, with bed nets offering higher levels of protection. The optimal use of ITNs also significantly improves child growth and the chances of survival through childhood. The use of ITNs led to significant economic benefits, both at the household and health system level.

Innovative targeting and delivery strategies can optimise the public health benefits of ITNs:

The proportion of households with ITNs (coverage), the proportion of individuals properly using ITNs each night (adherence), and the proportion of nets properly treated with insecticide (treatment) are the three key determinants of effectiveness of large-scale ITN programs, and thus should serve as the basis for program objectives and monitoring and evaluation efforts.

Although children and pregnant women (who are most at risk of malaria infection) should be the primary target groups for this intervention, the INDEPTH Network surveillance evidence suggests that universal coverage with ITNs may result in substantial declines in infection rates in the community at large. As household socioeconomic status strongly influences the access to and optimal use of ITNs, innovative delivery mechanisms that appropriately target different segments of the population according to socioeconomic status can optimise the

public health benefit of this intervention. For example, INDEPTH studies showed that social marketing of ITNs led to higher overall levels of coverage in the lowest socioeconomic groups and in those living on the periphery of villages.

Widespread ITN use may lead to vector resistance:

It is feared that ITN use may be compromised by the selection of mosquito genotypes that are resistant at the biochemical or behavioral level. Therefore, as ITNs are deployed, there is a need to properly monitor the behavior of the mosquito vector and the efficacy of the insecticides to detect any signs of vector resistance.

Prompt, accurate diagnosis and treatment with ACTs are important cornerstones of malaria control:

Prompt access to primary health care facilities is essential in promoting early treatment and reducing gravity of malaria episodes, and has been shown to reduce the malaria burden. Studies from the INDEPTH Network contributed to the current evidence that combination therapies with artemisinin derivatives (ACTs) are more effective in clearing malaria parasites than older monotherapies (such as chloroquine and sulphadoxine-pyrimethamine), and advocated for the continued use of the integrated Management of Childhood Illness (IMCI) approach in paediatric malaria case management.

However, development of drug resistance to ACTs was cited as a major concern, highlighting the need to promote adherence to treatment, monitor the emergence and spread of resistance and conduct research to discover alternative treatments. INDEPTH studies also showed that fever had a low predictive diagnostic value of

less than 40%, with this limitation being more evident in older age-groups. These and other studies have contributed to the current efforts to deviate from symptom-based treatment and to promote the use of microscopy and perhaps to a greater extent, rapid malaria diagnostic tests (RDTs), to ensure accurate diagnosis and rational use of ACTs.

Public health facilities and the retail sector play complementary roles in providing access to treatment:

Although biomedical care was the preferred choice for an overwhelming majority of suspected malaria cases in the INDEPTH Network sites, treatment-seeking at health facilities was not prompt. Therefore, there is a need to identify and address the barriers that prevent care givers from accessing prompt care in health facilities. Two identified barriers in INDEPTH sites were distance to health facility (incidence of hospitalized malaria more than doubled as travel time to the nearest primary care facility increased) and affordability of treatment, which impeded the efficacy and equity of the newly introduced ACTs. Socioeconomic status was identified as an important determinant of access to effective antimalarial treatment with people in a higher socioeconomic status more likely to obtain antimalarials than those in the middle or poor stratum in a number of sites. These findings highlight the urgent need to address physical and economic barriers to access in order to curb malaria.

The highly accessible retail market, in particular drug shops, was found to be complementary to public health facilities in improving the coverage of effective antimalarial treatment. However, concerns were raised that this market could promote irresponsible access and thereby diminish quality of care if not adequately regulated. Providing subsidized ACTs to the most vulnerable groups through the retail sector has been explored as one approach to galvanize current efforts to promote prompt and effective malaria case management.

In summary, these findings emphasize the importance of ensuring of equitable access and adherence to prompt and effective treatment in order to achieve adequate malaria control.

Public education strategies such as Information Education & Communication (IEC) and Behavior Change Communication (BCC) are key to achieving adequate malaria control:

Local understanding of the cause, prevention and treatment of malaria affects the uptake of malaria intervention by community members. The INDEPTH Network found that although most community members may recognize the term 'malaria' they often have limited biomedical knowledge of the disease, including its aetiology, the role of the vector, and preventive measures.

For example, in a Kenyan study, mothers identified protection from bugs and debris falling from the roof as some of the advantages of using ITNs, but failed to recognize their protective effect against malaria infection. Public education programs and mass communication campaigns increased awareness and led to better use of malaria prevention measures such as ITNs. This highlights the need to incorporate IEC and BCC strategies when deploying malaria control interventions.

“ Given the growing need for evidence-based health policies and programmes, the INDEPTH Network examines the extent to which its published and other research outputs have influenced policies and programs at national, regional as well as global levels. Documenting and sharing lessons on how malaria research influenced policies and programs is vital for enhancing the contribution of research in improving people’s lives across countries covered by the INDEPTH Centres and beyond. ”

MALARIA CONTROL INTERVENTIONS THAT REQUIRE FURTHER EVALUATION



regulatory file submission), which has been underway since May 2009 in 11 sites in seven African countries (Gabon, Mozambique, Tanzania, Ghana, Kenya, Malawi, and Burkina Faso)[5].

Other candidate vaccines such as the FP9 ME-TRAP primer and MVA ME-TRAP booster vaccination and the multistage synthetic peptide vaccine (SPf66) were shown to confer significant levels of protection making them potential candidates for future vaccine development.

It was noted that a vaccine strategy targeting specific forms of the parasite (e.g. the combination B candidate vaccine comprising of the candidate antigens MSP1, MSP 2 and RESA) risks being only partially protective, as it may not confer protection against common parasite forms not included in the formulation. Clearly, such a vaccine would not be cost-effective. This highlights the need to ensure that all important parasite forms are included in future vaccine formulations to ensure complete protection.

Progress in rational vaccine development has been partially hampered by a lack of understanding of the immunological mechanisms underlying protection, and inadequate knowledge on reliable surrogate markers that correlate with protective immunity. In agreement with similar findings in this field, a study from the INDEPTH Network cited IFN- γ as a potentially useful marker of protective immunity against severe malaria anemia in young children.

In summary, further studies are warranted to improve our understanding of the parasite's biology and the host's immune response in order to hasten the development of a safe and effective malaria vaccine for use in malaria endemic areas.

More research is needed to determine the role and applicability of malaria chemoprophylaxis in endemic areas:

Malaria chemoprophylaxis has been cited as a potentially useful strategy for malaria control. However, there is relatively little evidence to adequately determine its effectiveness and applicability in various populations living in endemic areas. Further, it is feared that the widespread use of chemoprophylaxis could lead to the rapid development of drug resistance.

Although Intermittent Preventive Treatment during pregnancy (IPTp) and Intermittent Preventive Treatment of infants (IPTi) have been shown to confer protection against malaria-related morbidity and mortality in controlled trials, relatively few studies from the INDEPTH Network investigated various aspects of this intervention including effectiveness of coverage, perceptions, and practice. The uptake of IPTp in most areas was low, and was attributed to low ante-natal care (ANC) attendance rates after the first visit. In general, pregnant women were more likely to take their first IPTp dose than subsequent doses. Further, first time mothers were more likely to take IPTp. The beneficial effect of IPTi was found to be higher during the high transmission than low transmission season. There is therefore an urgent need to determine the best way to optimize the use of IPTp and IPTi.

Two INDEPTH Network studies examined malaria chemoprophylaxis in adults. The first study demonstrated a dose-response protective effect of tafenoquine against *P. falciparum* infection in semi-immune adults whilst the second demonstrated that radical cure of asymptomatic *P. falciparum* led to an increased risk of clinical malaria in adults living in an endemic area in Africa. Further research is needed for more conclusive evidence on the role of chemoprophylaxis in malaria control.

A safe and effective malaria vaccine is feasible:

Although there is no licensed malaria vaccine currently in clinical use, there are three main types of malaria vaccines under development:

- 1) Vaccines targeted at the pre-erythrocytic stages (sporozoites and liver stages);
- 2) Asexual blood-stage vaccines; and
- 3) Transmission-blocking vaccines.

The availability of a safe and effective malaria vaccine has the potential to greatly reduce the malaria burden. Most of the research carried out in INDEPTH Network sites focused on the first and second categories of vaccines.

The RTS,S pre-erythrocytic subunit candidate vaccine was found to be promising, with studies demonstrating that it confers protection against malaria infection and a range of clinical illnesses caused by *P. falciparum* in young African children. RTS,S (also known as RTS,S/AS) is the first malaria vaccine candidate to ever reach large-scale Phase III clinical testing (the last stage of development before

Summary of Knowledge Gaps

- 1. National level impact evaluation of malaria interventions:**

In most malaria endemic countries, measuring the impact of malaria control interventions is greatly hampered by inadequate health management information systems (HMIS), and inadequate tools (such as the verbal autopsy method) to estimate malaria deaths outside the formal health care system. The INDEPTH Network can contribute to this by improving on current tools, collecting requisite data using their robust longitudinal platform, and working more closely with the national divisions of malaria control to collate such data with other national level data.
- 2. Urban malaria:**

Many malaria endemic countries, particularly in sub-Saharan Africa are experiencing rapid urbanization, which is largely characterized by the growth of an urban poor population who can neither afford protection from malaria nor access quality health care. Further, the continuous changes in urban ecology highlight the need to investigate changes in the risk of malaria transmission in order to adequately tailor malaria control strategies in these settings. The INDEPTH Network centres operating in urban settings provide a suitable platform to generate this knowledge.
- 3. The impact of climate change on malaria:**

Although there is increasing awareness on the impact of climate change globally, there is still very little knowledge on the impact of climate change on malaria. This calls for the establishment of prospective systems to monitor and forecast future malaria transmission risk in the context of climate change. Such knowledge will be required to ensure that current gains in malaria control are sustained, and that future control strategies at the community and health system levels are well adapted. The INDEPTH Network together with the Global Working Group on Climate Change and Health (GWG o CCH) can play a central role in steering this work.
- 4. Malaria eradication and elimination:**

Although current efforts in sub-Saharan Africa must be focused on achieving adequate malaria control, the INDEPTH Network is uniquely placed to steer the knowledge discourse and future strategies towards sustainable strategies for effective eradication and elimination, in line with the agenda of the Malaria Eradication Research Agenda (malERA) initiative.
- 5. The effectiveness and applicability of malaria Chemoprophylaxis in malaria control:**

Reliable knowledge on the effectiveness and applicability of malaria chemoprophylaxis strategies (including IPTp and IPTi) in various populations living in endemic areas is lacking. Therefore further research is warranted to determine the role of malaria chemoprophylaxis and the best ways to optimize this strategy in various populations.
- 6. Effectiveness of interventions aimed at reducing inequities in access to malaria prevention and treatment:**

As the burden of malaria is greatest among the poorest in the population, it is necessary to achieve proper coverage of all key interventions in this group in order to ensure optimal and sustainable malaria control. There is therefore a need to determine the best strategies to reduce inequities in access to effective prevention and treatment.
- 7. Translation of genetic knowledge on malaria into practice:**

There is a need for more research to determine the best ways of translating genetic knowledge in malaria into practice.
- 8. Vector and parasite resistance:**

Understanding the dynamics of behavioral and genetic vector resistance was cited as a major priority, particularly in the context of changing malaria transmission. Malaria drug resistance is also a major concern, with resistance to ACTs already reported in South East Asia. There is therefore an urgent need to develop the right methods and tools to track the emergence and spread of drug resistance, particularly in sub-Saharan Africa where ACTs have been most recently deployed. The INDEPTH Network is uniquely placed to work with other stakeholders such as the World Wide Antimalarial Resistance Network (WWARN) to this end.
- 9. Understanding parasite biology and host immune response:**

Studies in malaria vaccine development highlighted the need for more fundamental knowledge in host and parasite biology in order to accelerate current efforts to develop a safe and effective malaria vaccine. To this end, there is an urgent need to identify the best surrogate markers of protective immunity to support the clinical evaluation of vaccines.

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The citations of the 167 publications included in the review can be found in the detailed report. Please visit www.afidep.org OR www.indepth-network.org to access the detailed report.

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About AFIDEP

AFIDEP is a regional non-profit policy think tank whose purpose is to facilitate the translation and utilization of research evidence in strengthening political leadership, and increasing investment and program effectiveness in Africa. AFIDEP was established in 2009 to help close the gaps between research, policy, and practice by translating research evidence and promoting its use by policy makers and development practitioners at national, regional, and international levels. The Institute also builds local capacity in knowledge generation, translation, and utilization.

The Institute's work covers the African continent, with a particular focus on sub-Saharan Africa, where it is currently carrying out in-depth knowledge synthesis and evidence-based advocacy in selected focal countries. The Institute's work currently focuses on the following inter-related issues: population change, environment, and development; maternal and child health; sexual and reproductive health; and family planning.

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About INDEPTH Network

INDEPTH's mission is to harness the collective potential of the world's community-based longitudinal demographic surveillance initiatives in resource constrained countries to provide a better, empirical understanding of health and social issues, and to apply this understanding to alleviate major health and social problems. We will continue to pursue this mission through interlocking programs in research, policy engagement and research capacity strengthening.

The Network's key objectives include: supporting and strengthening the ability of INDEPTH sites to conduct longitudinal health and demographic studies in defined populations; facilitating the translation of INDEPTH findings to maximize impact on policy and practice; facilitating and supporting research capability strengthening relevant to INDEPTH activities and stimulating and co-coordinating multi-site applications to research funding bodies for specific research activities.

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