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Travel to mainland Tanzania as risk factor for malaria and further transmission in Zanzibar

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Abstract

Introduction: Malaria pre-elimination is reached in Zanzibar. Travel has earlier been identified as a risk factor for malaria in Zanzibar and import of malaria from Tanzania mainland has been proposed to fuel the residual transmission in Zanzibar.

Objectives: To assess travel to mainland Tanzania as a risk factor and to describe characteristics of malaria patients in Zanzibar during 2016.

Methods: This was a retrospective, descriptive and case-control study using quantitative data from a malaria surveillance system in Zanzibar. Malaria cases were clinical and confirmed by malaria rapid diagnostic test (mRDT) or microscopy. Questionnaire answers provided data for known risk factors for malaria such as recent travel history (within 30 days), not having slept under long lasting insecticide treated net (LLIN) (previous night) or not having done insecticide residual spraying (IRS) recently (within 8 months).

Results: 48% of cases at health facilities had recent travel history outside Zanzibar. Recent travel was found to be a strong risk factor for malaria, unadjusted OR's for different periods ranging 222-486 (CI 124-710, $p<0.001$). Tanzania mainland was reported as travel destination by 94% of all travel cases. LLIN was used by 64% and IRS done recently by 31% of all malaria cases, coverage varying by district.

Conclusions and implications: A high proportion of malaria cases reporting recent travel suggests a large proportion of all malaria in Zanzibar is imported. Maintained uptake of interventions such as LLIN and IRS and continued surveillance and case follow-up are factors that affects the risk for onward transmission of imported malaria. Limiting imported malaria with suitable strategies could potentially help to accelerate further reduction and eliminate malaria in Zanzibar.

Key words: Zanzibar, malaria, travel, import, Tanzania

List of abbreviations

ACT   Artemisinin Combination Therapy

DALY   Daily Adjusted Life Years

DDT   Dichlorodiphenyltrichloroethane

DMSO   District Malaria Surveillance Officer

Pf   Plasmodium falciparum

GMEP   Global Malaria Eradication Program

HF   Health facility

IRS   Indoor residual Spray

LLIN   Long Lasting Insecticide Nets

MCN   Malaria Case Notification

MDA   Mass Drug Administration

MEEDS   Malaria Early Epidemic Detection System

mRDT   Malaria Rapid Diagnostic Test

MSAT   Mass Screen and Treat

PCR   Polymerase Chain Reaction

RACD   Reactive Case Detection

RBM   Roll Back Malaria Initiative

Rc   Reproduction rate with control measures

Ro   Basic Reproduction rate with no control measures

VC   Vector control

WHO   World Health Organization

ZAMEP   Zanzibar Malaria Elimination Programme

ZMCP   Zanzibar Malaria Control Programme

Table of contents

Introduction

Global perspective on malaria

In the year of 2015 roughly half of the global population was at risk of malaria, in total 214 million malaria cases and 438´000 deaths. 70% of deaths occurring among children and 91% of all deaths in sub-Saharan Africa. (1)

Although half of the global population is at risk, malaria is above all an affliction of the poor and the children of the world. Advances in standard of living and economic growth is haltered in development countries.

Investing money in fighting malaria is next to childhood immunization considered to be the most cost-effective investment in public health, providing socioeconomic, developmental and equity benefits in addition to the more obvious health benefits. The cost of averting a malaria case is $5-8. It has been suggested that if the global malaria burden would be reduced by 50%, the estimated return of every US$1 invested would be US$36, or for sub-Saharan Africa, $60 in return of interest. If the set goals for 2030 by the World Health Organization (WHO) will be successful, the benefits are colossal in multiple aspects and perspectives and the direct economic outcome is estimated to an economic output of US$4 trillion. The cost-effectiveness of malaria control is more well-known than for malaria elimination. Efforts of malaria elimination will likely impose a greater initial investment, but will over time catch up in effectiveness when shifting toward preventing resurgence. It's estimated that the operating costs of sustaining elimination is only 65-75% that of a control programme. (2)

Malaria parasite

Malaria is a vector born infectious disease of unicellular protozoan parasites of genus Plasmodium. The parasites are transmitted from human to human by female Anopheles mosquitos. There are five different malaria parasites causing malarial sickness in humans when entering our bloodstream, *plasmodium (P.) vivax*, *P. ovale*, *P. knowlesi*, *P. malariae* and *P. falciparum.* (3) *P. falciparum* is by great length the deadliest of the malaria species, causing 99% of all deaths in malaria in 2015.(1)

Transmission intensity is determined by several factors, including the vector capability and the human recipients' susceptibility. A strong vector breeds well, prefer to bite humans, occur in large numbers, is robust to changes and live long. Transmission intensity is largely determined by the strength of the vector and its numbers. In high transmission setting people are bitten by infectious mosquitos more often than in low transmission settings, the entomological inoculation rate (EIR) varies greatly in different regions. In sub-Saharan Africa, *P. falciparum* is the dominant parasite species and in several areas there are high EIR contributing to high transmission and endemicity. "Stable transmission" is common with year-around infection due to high EIR, putting children at high risk but most adults are immunized and asymptomatic. In different regions with pronounced seasonal transmission there is so-called "unstable transmission", less frequent inoculation results in poor immunization and malaria can afflict all ages. Unstable, low transmission or seasonal transmission also results in a situation with much higher vulnerability for endemics, e.g. triggered by environmental changes, war or neglected malaria control. (4)

The malaria life cycle

Malaria parasites have stages in both human and mosquito necessary for replication. The cycle differs somewhat for different plasmodium species but have major similarities. The

knowledge of the life cycles gives insight to how to approach pharmaceutical therapies and different stages coincide with typical clinical features and symptoms of the disease.

The vector mosquito infects the human host with sporozoites from the saliva while feeding. Sporozoites invade hepatocytes and multiply, creating daughter merozoites in 5.5-8 days. The liver schizonts bursts, releasing merozoites that will infect erythrocytes in the asexual blood cycle, lasting about 48 hours. In erythrocytes, the parasite affects the cells in many ways and consumes cell contents while forming trophocytes, maturing into erythrocyte schizonts which will eventually burst and release merozoites. The asexual cycle will multiply the parasite number and after approximately 12-14 days the incubation period has passed, presenting the first clinical symptoms. This also usually marks the point when an infection could usually be detected by malaria rapid diagnostic testing (mRDT) or microscopy. *P. vivax* and *P. ovale* can form hypnozoites, causing the incubation period to range from 2 weeks to more than a year. In the blood-stage of humans there is mainly multiplication of parasite by mitosis, but some parasites will develop into the sexual form of gametocytes, that can be transferred to feeding mosquitos and peak in numbers day 7-10. Meiosis of the parasites only happens in the mosquito and together with other stages in the mosquito completes the cycle.(4)

Malaria disease

Clinical characteristics and symptoms

The initial symptoms are usually nonspecific, including malaise, headache, fever, myalgia, abdominal pain and nausea.(4)

The characteristic clinical features and symptoms of recurring fever and chills that some might develop are linked and coincide with the rupture of erythrocyte schizonts. The paroxysm of illness and symptom-free periods vary in periodicity in different species, *P. vivax*

and *P. ovale* approximately every 48 h and *P. malariae* every 72 h, *P. falciparum* might have 48 h cyclicity but is generally not showing this fever pattern but a more irregular. Remnants of parasitized erythrocytes and high levels of cytokines can in severe *P. falciparum* infections cause grave complications, causing obstruction of capillaries and post-capillary venules that will lead to hypoxia in affected organs and the release of toxic cellular products(5) In uncomplicated cases normal findings are an enlarged palpable spleen, mild anaemia, fever, jaundice (adults) and enlarged liver (children). In areas of stable high transmission chronic anaemia and splenomegaly can be found among children. Cerebral malaria is a potential symptom of *P. falciparum* in all ages, associated with general seizures and eventually followed by coma or death. Other severe outcomes vary by age but include acute kidney injury, acute pulmonary oedema, acidosis severe anaemia and hypoglycaemia. The relation between parasite density, symptoms and prognosis vary with status of immunization and availability of prompt effective treatment. (4)

Diagnosis and treatment

The WHO recommendation for handling suspected malaria is to confirm with parasitological test before treatment. In high endemic areas it's recommended to test all with history of fever or presenting with fever. In areas of very low incidence it's recommended to test only those with fever with no other obvious cause or if recent exposure to malaria (*"e.g recent travel to a malaria-endemic area without protective measures"*). (6)

Swift handling of diagnosis and treatment brings down mortality, risk of severe outcomes and reduces further transmission by reducing total length of time patients carry malaria parasites in their blood. Testing with mRDT or microscopy prior to treatment is recommended to improve management of febrile disease and to aim for use of antimalarial medicines only when necessary. Artemisinin combination treatment (ACT) is the recommended treatment for uncomplicated *P. falciparum* malaria and has been showed to reduce mortality for children

aged 1-23 months by 99%, aged 34-59 months by 97%.(1) The ACT consists of a rapid acting artemisinin derivate coupled with a longer-lasting partner drug. Some considerations affects the choice of drugs combined, doses and days of treatment.(6)

History of malaria

Malaria is one of the diseases that have had greatest impact on humans, causing serious impact on our genome, tremendous amounts of mortality and morbidity.

The first known note of malaria is from China 5,000 years ago, and the first of *P. falciparum* from India 3000 years ago. Malaria seems to have been known and causing epidemics in several of the great ancient civilizations, described by Egyptian texts dated over 3500 years old, Mesopotamian civilization and in ancient Greece. Alexander the Great died in 323 BC, supposedly from malaria, likely *P. falciparum* considering his young age and presumed good health otherwise.(3)

The estimates of total deaths in malaria in the 20th century is about 150-300 million, or 2-5% of all causes of deaths. In the early 20th century malaria contributed as cause of death in up to 10%. Although malaria used to be more widely spread than in modern times the magnitude of malarias toll varied greatly in different areas. In the early 20th century Europe and North America had relatively low prevalence of malaria compared to other regions and especially the regions worst affected. Large parts of Asia had a huge malaria problem from early to mid-20th century, cause of about 10% of all death. In India malaria struck perhaps hardest, and for a period causing in large parts of the country about 50% of deaths, some regions annual rates of 150 per 10´000 or locally even higher to a point when it was no longer habitable. (3)
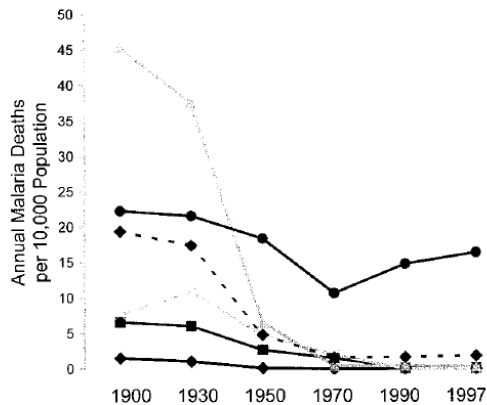
FIG. 3. Malaria mortality in the 20th century. The graph shows the number of malaria deaths per 10,000 population per year in Europe and North America (◆——◆); the Caribbean and Central and South America (■——■); sub-Saharan Africa (●——●); China and Northeast Asia (X—X); the Middle East, South Asia, and the Western Pacific (▲——▲); and worldwide (◆——◆) (see Appendix and Table 3).

(3)

Picture 1. Malaria mortality rate in the 20th century.

Spanish colonizers were introduced to the antimalarial effects of Cinchona bark, quinine in the 17th century by natives in south America. Early European colonizers and traders travelling to the tropics had often as high as 50% death rate per year, mostly contributable to malaria but dysentery and yellow fever also major causes. When Europeans in west Africa in mid-19th century learned to use Cinchona bark to treat malaria the overall mortality rates dropped to less than a quarter. (3)

Chloroquine, has contributed to malaria control and was widely used during the Global Malaria Elimination Program (GMEP) era but has since then, among other newer drugs fallen to resistance. (7) Following the abandonment of GMEP and reports of chloroquine- and DDT resistance in the 1970s the following two decades a marked increase in malaria incidence worldwide took place. (8)

The prestigious Nobel prize has been awarded in total 4 times for important discoveries regarding malaria. (9) The latest was to professor Tu Youyou for her contributions in the discoveries of using artemisinin as an antimalarial drug. Artemisinin, has been used as treatment for fever and malaria in traditional Chinese medicine with notes dating back at least

1700 years. Professor Youyou was a project leader of the Chinese project 523, at first a secret research project initiated during rule of Mao Zedong, set out to find new treatment alternatives for malaria and as a response to a request from the Vietnamese government for help with malaria. (10)

Even if GMEP failed its goal of global eradication it brought a lot good. Over the whole coarse of GMEP campaigns 15 countries and one territory successfully achieved elimination and other countries reduced malaria burden. In sub-Saharan Africa no substantial reduce was achieved and several areas had great resurges. (8) However, even in sub-Saharan Africa some long lasting benefits remains, despite the collapse of GMEP, import and spread of chloroquine resistant P. falciparum and resurgence of malaria the overall morbidity and mortality was somewhat reduced. Another valuable remnant is the infrastructure of field clinics for diagnosis and treatment, in some rural areas still the backbone of health care. (3)
The failure of GMEP has been partially blamed on importation of malaria by reintroduction of transmission and the spread of chloroquine resistance, learning from history that imported malaria infections likely needs to be addressed to obtain malaria elimination. (11)

Madagascar is an example of how quickly malaria can resurge. Madagascar managed between late 1960s to early 1980s to almost completely supress malaria transmission. The combination of an environment that naturally supports malaria transmission, almost all natural immunity against malaria lost and control efforts not sustained resulted 1986 in a reintroduction of malaria in Madagascar. For a few years an epidemic raged, affecting all age groups and likely claimed several tens of thousands of lives.(3)

Malaria remains a great disease of poverty and its toll of today is still at an unacceptable level. The wealthy countries and regions of today might not have been able to acquire the high level

of prosperity without first eliminating malaria. There are still some of the poorest regions in the world totally overwhelmed by the effects of malaria.(3)

Moderns efforts

After the collapse and discontinuation of GMEP by WHO in 1969 some regions had further achievements in reducing malaria, while it resurged in others.

The Roll Back Malaria (RBM) partnership, founded in 1998 has been central in the modern efforts of malaria control and elimination and in the aspiration to achieve the Millennium Development Goals (MDG). Since the world malaria community once again started up a massive, joint approach to fight malaria there has been an immense advancement in reducing the malaria burden and achieving malaria elimination. The RBM partnership used their Global Malaria Action Plan (GMAP) 2008-2015 and for 2016-2030 have developed the document Action and Investment to defeat Malaria 2016-2030 (AIM). WHO has defined the Global Technical Strategy for Malaria (GTSM), describing the goals and targets for 2030 that AIM describes how to achieve. (2)

Modern malaria efforts are coordinated from major players of the world malaria community such as WHO and RBM Partnership and their global policy documents. The community has endorsed a three-part strategy "for shrinking the malaria map". The strategy includes 1) Aggressive control in the malaria heartland, 2) Progressive elimination from endemic margins, 3) Continued research and development to bring forward new tools. (12)

Estimates of progress between 2000 and 2015 shows substantial reduction of malaria incidence by 41% and mortality by 62%, endemic countries and regions 91 compared to 108. (1) Also between 2000 to 2015 663 million clinical malaria cases are estimated to have been

averted by interventions, thereof ITN the largest contributor (68% of cases averted).(13)
Between 2001-2015 more than 6.8 million deaths averted, primarily in children <5 years old.
(14)

WHO definitions of phases in malaria control and elimination

WHO has defined phases of antimalarial activity and recommended agendas for malaria
programs.

1) Control – reduce and sustain disease burden to a low level.

2) Pre-elimination – <5 cases / 1000 at risk per year, 1st reorientation of malaria program.

3) Elimination – no local transmission or locally acquired cases, 2nd reorientation of malaria
program.

4) Prevention of reintroduction – if >3 years with no reported local transmission WHO can
issue a certification of successful elimination.

A control program aims to reduce disease burden by high uptake of preventive measures and
access to health care, differing from the more technical demanding approach of an elimination
program. Key-points in a malaria elimination program is to detect all malaria cases, prevent
onward transmission, manage local foci and manage importation of malaria. (7)

Continued efforts to prevent resurgence are needed until malaria incidence is reduced to zero
worldwide, i.e. malaria eradication achieved.(8)

Outlook for the future

WHO goals of GTSM defines targets for malaria globally 2030 as compared to 2015 as 1)
Reduced malaria mortality rates by at least 90%, 2) Reduced malaria case incidence by at

least 90%, 3) Eliminate malaria from 35 countries, 4) Prevent re-establishment of malaria in all countries that are malaria-free.(15)

Bold statements are once again being made regarding malaria eradication, one is that we now have the opportunity to achieve a malaria free world within a generation. Serious discussions are up about what it would take to eradicate malaria and it has been proposed to set 2040 as the goal. They highlight the need of increased funding and greater investments but stress that from a not too far off point the peak in costs will be reached, thereafter the costs is expected to decline as regions achieve malaria elimination. The outcome could result in 11 million lives saved and economic benefits of $4 trillion. (16)

The world malaria report of 2017 by WHO acknowledge substantial progress in fighting malaria globally but also identifies remaining challenges. The global malaria incidence has been reduced by 21% and mortality by 29% since 2010. The GTS goal to reduce global incidence and mortality in malaria by 40% until 2020 does not seem attainable, especially in the African region progress has been slow. The trends suggest an increased malaria burden between 2014 and 2016, circa 5 million more cases in 2016 than 2015 but number of deaths stable. Factors that might have contributed to the reversed trend were suggested to be inadequate funding, conflicts, climate patterns and inefficient implementation of interventions. Resistance to insecticides and drugs might in the future once again challenge the now still effective treatments and interventions. WHO stresses that more efforts and more resources will be needed to maintain the gains in the fight against malaria so far and to ensure further successes. (17)

Zanzibar

General information about Zanzibar

Tanzania in east-Africa consists of two semi-autonomous regions, Tanganyika which is the mainland and Zanzibar, an archipelago of islands in the Indian Ocean. Zanzibar's two larger islands are Unguja, main island and Pemba, both about 25-50 km from Tanzania mainland. The total population of Zanzibar as of latest census in 2012 is about 1.3 million with an GDP per capita of $656. Zanzibar, being just south of the equator has a hot climate year around. Hottest period is December to March. There are two rain seasons, a short period in November -December and the main period in March-May. The administrative divisions of Tanzania and Zanzibar is into districts and local wards, shehias. (18)

History of malaria control in Zanzibar

Zanzibar have had earlier attempts for control and elimination of malaria with varying outcome. In the 1960s Zanzibar benefited from an effective control program, started in 1958 and between 1961-1968 expanded to be included in the WHO GMEP. In 1968 the prevalence had decreased markedly on both islands and as malaria was no longer considered a health problem the program was abandoned. Malaria resurged rapidly and by 1980 it was the major cause of child mortality. A new major attempt to control malaria started in 1981 but faced a difficult challenge and was hindered by shortcomings. Among the difficulties there were disorganized interventions of IRS, low levels of public compliance, insecticide resistance and suboptimal recruitment of expertise. The spread of chloroquine resistance was also one of the major causes to the resurge of malaria and in 2003 there was a 60% failure rate of treatments. Malaria has been Zanzibar's number one public health problem in modern times and in 2003 accounted for 47% of all outpatient consultations at health facilities and was the disease of highest morbidity and mortality.(19)

14

Achieving effective malaria control

Zanzibar used to be a moderate- to high transmission area but has since 2003 had great success in controlling malaria. Among the most important tools were the introduction of ACT treatments in 2003/2004, followed by rapid diagnostic tests (RDTs and vector control (VC) measures of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) in 2005/2006. The implementation of modern interventions and strategies lead to a pronounced decline in malaria between 2004-2007 followed by a steady-state of low transmission. (20)

ZMCP to ZAMEP

With substantial progress in malaria control, Zanzibar Malaria Control Program (ZMCP) 2009 conducted a report, assessing the feasibility of reaching malaria elimination.

The modelling used by ZMCP to estimate the time frame for a potential successful elimination highlighted the importance of sustained sufficient uptake and use of vector coverage (VC) and proposed that with a 75% coverage elimination could be achieved around year 2020. One limitation mentioned of the modelling was that it simplified Zanzibar as a closed system, not considering the imported cases that could be of notable proportions. Further reasoning suggests that to confidently predict future progress in elimination, estimating and handling imported malaria cases is one of the most important factors.(21)

ZMCP conducted a programme reorientation in august 2013, becoming Zanzibar Malaria Elimination Programme (ZAMEP). (20)

Current malaria situation in Zanzibar

The public health impact of the interventions and efforts in Zanzibar has been substantial. By 2015 the *P. falciparum* prevalence with mRDT was 0.43%, down 96% since 2003. With the most pronounced reduction between 2003-2007, thereafter a steady state of low transmission. (20)

Malaria is since a few years under good control in Zanzibar for the first time since 1968. Yet with lower endemicity and exposure, natural immunity will be reduced and future generation will be more vulnerable to epidemics.(19) In 2015 there was observed an increased proportion of clinical malaria cases among patients >5 years, eventually as a result of lower immunization. The age shift could also be explained by behavioural factors affecting risk of mosquito bites, such as staying more outdoor at night or less use of LLIN and differences in travel frequency to mainland Tanzania.(20)

It has been appointed that earlier attempts at reducing malaria in Zanzibar likely failed because of inconsistencies in the efforts and that due to the nature of the disease in these settings, therefore all attempt must be followed by continuous activity to not fail. A powerful analogy is that malaria interventions should be considered a standard public health intervention, just like vaccinations, and to be continued even with low prevalence, to sustain low transmission. (22)

Once the major reduction is achieved in a region it can be a challenge to maintain the funding for malaria control. Some argue that the value of investment in sustaining low transmission should be weighted in the benefits of prevented death and morbidity, rather than the further achievements of reducing remaining cases. E.g. in Zanzibar it's estimated that in each year 660'000 malaria cases and 3300 deaths are averted, to a cost of $1183 per death prevented and $34.5 per disability-adjusted life year averted (DALY). (22)

Zanzibar today represents an example of a high endemic region in sub-Saharan Africa achieving pre-elimination and could hopefully within 10 years provide the example of proof of elimination concept in such settings. Important factors to the success so far has been the high community uptake and high level of organization, made possible by sufficient funding and dedication of the people.(20)

Malaria surveillance systems in Zanzibar

Surveillance of malaria is crucial in an elimination program. A robust and sensitive surveillance system aims to detect and report all cases of malaria to discover ongoing transmission, local foci and imported cases. The collected information is used both for interventions and future planning. Appropriate investigation and follow-up of individual cases could hopefully lead to rapid detection of imported malaria cases and outbreaks and enable targeting of counter-measures.(23)

Two central parts of the malaria surveillance system in Zanzibar are the Malaria Early Epidemics Detection system (MEEDS) and the Malaria Case Notification system (MCN). In Zanzibar's health care system, there is a surveillance and response plan including a passive and an active detection system for malaria cases.

The passive detection system reports all patients seeking a health care facility with clinical features of malaria. They are classified as negative or positive to malaria infection using mRDT or microscopy blood smear (BS) and the results are registered in the Malaria Early Epidemics Detection System (MEEDS) database. The positive tested are interviewed at the health facility (HF) using a questionnaire including relevant information such as recent travel history, ITN use, last date IRS performed, contact information, sex, age and more. All positive tested are reported to a reactive case detection (RACD) program that register information to the malaria case notification (MCN) database.

In the RACD screening an District Malaria Surveillance Officer (DMSO) will routinely start an investigation including screening of family household members and in some cases also neighbors in a defined area around the index case for malaria. In addition to testing for malaria the RACD includes all tested to answer to a questionnaire similar to that used at the HF. A difference is that in the RACD screening both negative and positive tested do the questionnaire in contrast to at the HF where only confirmed malaria positive partake, offering

limited information about risk factors for negative tested at HF level. MCN data includes results from the questionnaire protocol but also the number of screened around index case, number of positive cases and proportion tested positive. (23)

Diagnostics in Zanzibar

In Zanzibar, the standard diagnostic test at a health facility is mRDT, showing relatively low sensitivity (79%) but high specificity (99%) as of latest assessment with PCR. The detection limit of mRDT is approximately 100 parasites/µL, i.e. equal to that of estimated detection limit of blood smear (BS) microscopy in low-income countries. A shortcoming of these detection limits is that neither BS nor mRDT allow reliable detection of low density parasitemias in asymptomatic individuals that therefore continue to be potential reservoirs for malaria transmission. PCR is the most sensitive method, detection limit 0.05-10 parasites/µL and can also identify all different species of malaria. On the downside, PCR is expensive, takes longer time for result, requires advanced equipment and trained personnel. Considering above mRDT might not be optimal for malaria diagnosis in the settings of Zanzibar but PCR is not suitable for routine malaria case management in these settings. (24)

Using mRDT in screening purposes is convenient and inexpensive but considering above addressed low sensitivity and relative high detection limits affects the efficacy in use as screening, especially if low density parasitemia.

Risk factors for malaria

Risk factors of clinical malaria episode in Zanzibar were assessed in 2015. The synthesis of the results showed that for risk factor not sleeping under LLIN odds ratio (OR) 3.8 (3.2-4.5), not having done IRS recently not significant, travel outside Zanzibar OR 70 and reported by 49% of all clinical malaria cases, higher OR for females. However, for asymptomatic, PCR verified infections none of above risk factors were found significantly associated to higher risk of infection.(20)

Import of malaria

As 49% of symptomatic malaria cases in 2015 had recent travel outside of Zanzibar and OR of 70 for travel outside Zanzibar clearly points out the importance of effectively limit the number of imported malaria in the pursuit of eliminating malaria.(20)

The feasibility report of ZMCP in 2009 concludes that the efforts in achieving sustainable control and elimination of malaria will be influenced by the level of importation risk. As Zanzibar is composed of islands relatively far of the coast infected human hosts are considered to be accountable as source for the vast majority of all imported malaria, infected mosquitos almost neglectable. Further to appreciate the risk and amount of import several factors are worth considering. The number of people entering Zanzibar by all means of travel combined with the risk profile for being infected and the length of stay in Zanzibar will all affect the import of malaria to Zanzibar and further transmission. Risk of being infected vary with area of prior stay and length of stay. Residents of Zanzibar travel mainly to Tanzania mainland and which area visited will affect the risk of acquiring an infection. (21)

Receptivity and vulnerability

Two terms of interest when discussing imported malaria are vulnerability i.e. the risk of malaria importation and receptivity meaning the level of transmission. (21) The impact of import depends on the local conditions of transmission, such as climatic and vector factors. To quantify receptivity the effective reproduction number, Rc is used. Rc weigh in vector control measures and estimates the number of secondary infections from one untreated case.(25)

A study using mobile phone data to quantify the risk and significance of imported malaria to Zanzibar suggested that residents of Zanzibar travelling to malaria endemic regions contribute the most to import and that imported malaria greatly sustains and adds to the local transmission. In fact, the authors propose that with sustained levels of control measures the Rc

would be < 1 in most areas if there would be no imported malaria. This would mean that without import of malaria, elimination would be achievable for most areas of Zanzibar.(25) This has however been questioned by other research, supporting that there is a considerable import of clinical malaria, even likely increasing, but less than above modelling suggests.(20)

Sinks and Sources

Areas that are net emitters ("sources") and areas that are net receivers ("sinks") of malaria can be described. Identifying sources and sinks could possibly allow for targeted control in areas where imported infections originate or where they contribute significantly to transmission and can improve malaria control programs.(26)

Residents of Zanzibar travelling and returning contribute 1-15 times more to import of malaria than infected visitors.(25) Mainland Tanzania has been identified as the major source of malaria importation to Zanzibar. Considering the combination of travel destination risk profile (dEIR or other estimate), length of stay and other factors have concluded that a key group of few people contribute for most of the imported malaria to Zanzibar. (21)

Tanzania mainland has been found to have higher malaria risk compared to Zanzibar, due to both higher EIR and vulnerability. The malaria risk of different areas in in the mainland is very heterogenous. The variation is mostly attributable to variations in EIR, showing less tie to the level of vulnerability, which is relative high for most regions of mainland. (27)

The coverage of interventions like vector control and ACT treatment in the mainland likely have a significant effect on the numbers of imported cases to Zanzibar. Future control efforts in the mainland could possibly further greatly reduce the numbers of imported cases.(21)

Imported malaria can only contribute to further transmission if the local conditions support transmission. The receptivity is affected by factors like VC coverage, level of local transmission and vector population.

Possible actions of control programs to counter imported malaria might be to educate about risk of travel, how behaviour affects the risk and to routinely target surveillance strategies to high-risk areas. (26) Other possible measures of action could be to hand out chemoprophylaxis or screening of travellers. (25)

Challenges and future strategies in Zanzibar

Some of the major challenges for further progress towards malaria elimination in Zanzibar are a substantial asymptomatic parasite reservoir, changes in vector species and biting behaviour, insecticidal resistance and imported malaria cases. Also continued sufficient funding, high uptake of interventions, preserved efficacy of treatment and persistence in fighting resurgence is likely needed for longstanding successful outcome.

A significant number of asymptomatic malaria cases has been observed in cross-sectional studies in two districts of Zanzibar, showing that earlier estimates of incidence could be underestimates. Estimates based on epidemiological data suggest that rather than the approximately 3000 clinical malaria cases the actual incidence is over 10´000 cases yearly, when including asymptomatic cases.(20)

Screen and treat in Zanzibar in current settings hasn't proved effective, partly due to low sensitivity of mRDT in low density parasitemia. New highly sensitive diagnostics for mass screen and treat (MSAT) or mass drug administration (MDA) has been suggested as alternative strategies to get hold of the asymptomatic infected individuals. An asymptomatic individual poses a risk for further transmission and could fuel the ongoing transmission.(28)

To address the challenges new tools are suggested to intensify the control and efforts in eliminating malaria in Zanzibar. This could include new highly sensitive screening methods or different targeting of treatment. Supplemental treatment strategies could be mass drug administration (MDA) and / or seasonal chemoprevention. Case detection might need

improvements and new approaches to prevent secondary transmission, especially considering imported cases. (20)

A MDA pilot project has been conducted in Zanzibar showing promising outcome. The pilot project has been followed up by a study of MDA treatment in 3 districts of Zanzibar, results are still being analysed. (Morris et al, unpublished)

Extended collaboration between different neighbouring regions could also reduce risk of imported malaria and reinforce the local achievements. Zanzibar would likely especially benefit from reductions of local transmission of malaria in Kenya and mainland Tanzania. (21)

Aim of the study

To describe characteristics of clinical malaria patients in Zanzibar during 2016, and especially to assess travel to mainland Tanzania as a risk factor.

Specific aims

Primary aims

- To assess reports of travel outside Zanzibar one month before malaria diagnosis as a risk factor for imported malaria
    - To assess the spatial distribution of locally infected vs. travel malaria cases
    - To assess the temporal trends of malaria transmission among locally infected vs travel malaria cases
    - To address if there is any sign of clusters of cases following initial imported cases
        - to assess frequency of testing positive for malaria among patients screened in MCN RACD
    - To assess age and sex distribution of travel vs non-travel cases

Secondary aims

- To compare the proportion of LLIN/IRS coverage among locally infected patients vs. patients with history of travel to/from Zanzibar during the past 30 days (travel patients)
- To present descriptive frequencies of travel destination areas outside Zanzibar

Material and Methods

Study design

This was a retrospective, descriptive and case-control study using quantitative data from a malaria surveillance database. Supplementary data has to some extent been obtained from other data sources to create a context of presented information, make comparisons and to aid in reasoning of conclusions and implications.

Study population

The study population consisted of all passively and actively detected malaria cases[1] in MCN database, i.e. from health facilities and from case follow-up, re-active case detection (RACD) screening. The limited data available for negative tested for those in RACD screening was also included. Period for inclusion was whole year of 2016. All areas of Zanzibar were included, both Unguja and Pemba.

Inclusion criteria's

- Symptomatic malaria case testing positive at health facility or screened individuals in RACD follow-up
    - Confirmed *P. falciparum* or other species of malaria by mRDT or microscopy
- Available data registered in MCN or MEEDS database

Exclusion criteria

- If missing information in questionnaire at health facility or RACD screening for a specific variable that case was excluded from the analysis

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[1] Symptomatic malaria cases confirmed by mRDT or microscopy

Data collection

Surveillance data from MCN and MEEDS systems were provided by ZAMEP (29) and converted to *Microsoft Excel* files.

MCN data

The data from MCN database includes information about malaria positive at health facilities and positive and negative RACD screened.

In the registered information of the databases malaria positivity was confirmed by mRDT or microscopy and all other information was obtained from questionnaires.

Of total 3816 malaria cases detected at health facilities in 2016, data for 2534 (66%) were reported into the MCN system for follow up. Cases were included in an analyse if they had the sought information registered from the questionnaire, see table 1 for availability by variable. If the questionnaire was not fully entered into the database a case could sometimes be used in one situation but not in another. Due to the varying availability of information this sometimes led to different numbers of cases included in different data sets and comparisons. This approach ensured highest possible number of cases included in each analysis. This study was not set out to evaluate the surveillance systems of Zanzibar and therefore assumes that the difference in sampling will be random and not greatly affect the results. Cleaning of the data was done to match inclusion and exclusion criteria.

Table 1. Showing coverage of data available in MCN database for malaria positive at health facilities 2016. Not considering eventual inclusion / exclusion criteria's.

Variable	available data[1] %/nr
Recent travel history	97% / 2462
LLIN last night	85% / 2149
Date of IRS	74%/ 1874
Age	97% / 2463
Sex	97%/ 2462
District	100% / 2522
MCN cases	2534
All malaria cases[2]	3816

[1] Of MCN cases followed-up with available questionnaire results in database
[2] Symptomatic cases at HF, confirmed positive

Definitions and details of variables

"Malaria positive" refers to symptomatic malaria cases confirmed positive by mRDT testing or microscopy for P. falciparum infection or other malaria species. The malaria cases were from MCN data, including both detected at health facilities or in follow-up screening RACD.

"Recent travel history" was defined as having travelled outside of Zanzibar in the recent 30 days.

"Travel destination" was reported in the HF questionnaire by those with recent travel history. If multiple recent travel destinations only the most recent destination was considered.

"IRS done recently" is defined as within 8 months (240 days), in accordance to recent research about resistance to insecticides in Zanzibar (30) and WHO recommendations of adequate residual efficacy of >80% mosquito mortality within 24 hours(31). If IRS was done more recent than within 2 recent weeks these cases were excluded. These cases were excluded to be able to more accurately distinguish if a case had effective IRS coverage or not, taking into account a normal incubation period of malaria of about 14 days.

LLIN usage was assessed as having slept under LLIN or not the night prior to being screened or visiting HF.

Supplemental data

Rainfall data was obtained from "*Zanzibar Malaria Elimination Programme"(29)*, Malaria prevalence data of mainland district from "*Tanzania Demographic and Health Survey and Malaria Indicator Survey", 2015-2016(32).*

Background information on malaria and Zanzibar from various sources, see references in text.

Statistical analysis

Data from MCN database was cleaned using *Microsoft Excel 2016*. Descriptive statistics was used to summarize and present outcome variables using *Microsoft Excel 2016*. Statistical analyses were performed for CI 95% and statistical significance p<0.05 using MedCalc for Windows, version 15.9.7 (MedCalc Software, Ostend, Belgium). Calculations were done for unadjusted OR's, RR, test for one proportions and comparison of proportions (*"N-1" Chi-squared test*).

Calculation of OR for travel

Data on malaria positive[2] cases from HF were obtained from the MCN database. Data on malaria negative[3] controls were from a MDA study survey (Morris et al, unpublished), for two different periods during 2016. MDA survey data were used for controls as there were no data available for malaria negative at HF.

Matching for geographic areas and time periods were done for the surveys and the MCN data. MDA data included some shehias and MCN data included all shehias for the same districts. MCN data included all shehias to ensure enough cases for a case-control. To assess if the MDA shehias could be considered representable for the whole districts in a case-control

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[2] Confirmed positive by mRDT or microscopy

[3] Confirmed negative by PCR

analysis a comparison of the MDA and non-MDA shehias was done. MCN data was used to assess if there was a significant difference in proportions reporting recent travel in malaria positive in MDA shehias vs non-MDA shehias during 2016, using "N-1" Chi-squared test.

Ethical consideration

For a patient to be included in MEEDS and MCN databases informed consent is not a requirement. By seeking health care, patients accept registration in medical health system and to be asked relevant questions. Choosing to not seek health care for the sake of not wanting to be included in MEEDS database was considered unlikely and was not taken into consideration. No person was put at risk during the study and all data used was already registered. No identification of individual persons from database is possible in results after data is cleaned and analyzed. Findings of the study could potentially benefit ZAMEP and therefore the spent time of personnel assisting was considered a reasonable investment of resources.

Results

Testing rate and findings

As seen in Table 2, a total of 4181 confirmed symptomatic malaria cases were detected in Zanzibar in 2016, this figure includes all cases at HF and during RACD screening. At HF 3816 cases were detected, testing rate 0.26. In RACD case follow-up screening another 365 cases were detected. Testing rate of the whole population of Zanzibar when summarizing HF tests and RACD screening tests was 0.22, same person tested more than once possible.

Risk factors at HF

The results show that among those tested positive for malaria at HF 48% had recent travel history outside Zanzibar within 30 days, 31% lived in a house which interior walls had been treated with IRS within effective interval and 64% had slept under LLIN the prior night.

Table 2. Presenting numbers of Zanzibar's population, malaria in Zanzibar and findings of the active and passive detection of malaria in Zanzibar's health system.

Zanzibar population		Health facility attendees		RACD screen	
Total population	1467477	Total health facility attendees	1239180	Total intended to screen	8746
Total tests for malaria[1]	325514	Total tested	317013	Tested	8501
Total testing rate per resident[2]	0.22	Testing rate	0.26	Testing rate	0.97
Total malaria positive[3]	4181	Total positive	3816	Positive	365
Cumulative incidence, per resident per year	0.28%	Positivity rate	0.012	Positivity rate	0.043
		Positive - with travel history recent month	48%	Positive with recent travel history[4]	71%
		Positive - IRS done recently (<8 months)	31%	Total index cases	2534
		Positive - LLIN usage (slept under last night)	64%		
		MCN reported	2534		

[1] Including at HF and RACD
[2] Including at HF and RACD
[3] Microscopy or mRDT confirmed, including cases detected at HF and in RACD
[4] Only available and included for period January 1 – February 8, 2016

Travel as risk factor

Unadjusted ORs for recent travel as risk factor

Reported recent travel within 30 days outside Zanzibar as risk factor for testing positive for malaria is displayed in Table 3. The proportion reporting recent travel history among malaria positive at HF where found to be 51% during MDA baseline, 55% during MDA follow-up and 61% for the whole year of 2016. The proportion reporting recent travel among malaria negative were found as 0.3% at MDA baseline and 0.4% at MDA follow-up.

Recent travel was found to be a highly associated risk factor for malaria with statistical significance for all periods included.

Table 3. Presentation of unadjusted ORs for recent travel outside Zanzibar as risk factor for malaria. Travel in symptomatic cases of malaria (collected in the MCN database, confirmed positive by mRDT at HF) was compared against travel in malaria negative individuals (collected during cross-sectional surveys, confirmed negative by PCR) (Morris et al, unpublished). Data are matched by district and date (survey period), but not for age.

Malaria positive cases MCN data Period	Malaria negative controls Survey data -Period	Cases travel % (n/N)	Controls travel % (n/N)	OR	CI	Significance level
Same as MDA baseline	MDA baseline[1]	51% (34/67)	0.4% (33/7789)	222	124-397	P < 0.001
Whole 2016		61% (511/841)	0.4% (33/7789)	334	234-476	P < 0.001
Same as MDA follow-up	MDA follow-up[2]	55% (11/20)	0.3% (31/9762)	384	149-991	P < 0.001
Whole 2016		61% (511/841)	0.3% (31/9762)	486	333-710	P < 0.001

[1] MDA baseline – 30/4-15/5 2016, West, Central and South district.
[2] MDA follow-up – 27/8-9/9 2016, West, Central and South district.
See appendix for calculations and assessment of comparability between the different sources of data for cases and controls.

The different sources of data for malaria positive and negative were assessed for fitness of use in comparison above. In the travel data from malaria positive cases there was no significant difference between the data collected in Shehias included in the malaria negative data, and the Shehias that were not included (P =0.1), indicating that the malaria negative data is representative of the whole shehias. See table 2.1 in appendix for comparison of shehias.

Interannual trend in travel

As seen in Table 4, in 2016 the distribution of all tested positive for malaria at health facilities reporting recent travel outside Zanzibar within 30 days was 48%. The interannually trends for 2013-2016 displayed in Table 4 shows that from 2013 to 2015 the distribution of cases reporting recent travel history increased from 31% to 53%, then in 2016 back to 48%. Reported travel only within Zanzibar was differing from 0.2% in 2013 to 5% in 2014, for 2016 3.6%.

Table 4. Showing recent travel history for malaria positive in MCN data 2013-2016. Absolute numbers and % presented.

	No travel		Travel outside of Zanzibar		Travel within Zanzibar		Total Nr	Total %
Year	Nr	%	Nr	%	Nr	%		
2013	1392	69.0%	623	30.9%	4	0.2%	2019	100.00%
2014	1884	59.7%	1116	35.4%	157	5.0%	3157	100.00%
2015	1655	43.1%	2045	53.2 %	142	3.7%	3842	100.00%
2016	1191	48.4%	1183	48.1 %	88	3.6%	2462	100.00%
Grand Total	6122	53.3 %	4967	43.3%	391	3.4%	11480	100.00%

Temporal trends

As can be seen in Figure 1 in 2016 there were two peaks of malaria incidence in Q1 and Q2, the one in Q2 coinciding with the normal yearly peak of transmission in Zanzibar. The proportion of malaria cases reporting recent travel outside Zanzibar varied by month, from lowest 37% in May to highest 71% in October.

During peak malaria transmission season both total number of malaria cases increased and the absolute number of malaria cases with recent travel. During the normal peak malaria transmission season in Q2 the total number of malaria cases increased more than the cases reporting recent travel, resulting in a lower proportion with recent travel history for that period. On the contrary, in relative low season for malaria transmission in Q3-Q4 the proportion of malaria cases reporting recent travel history peaked in proportion.
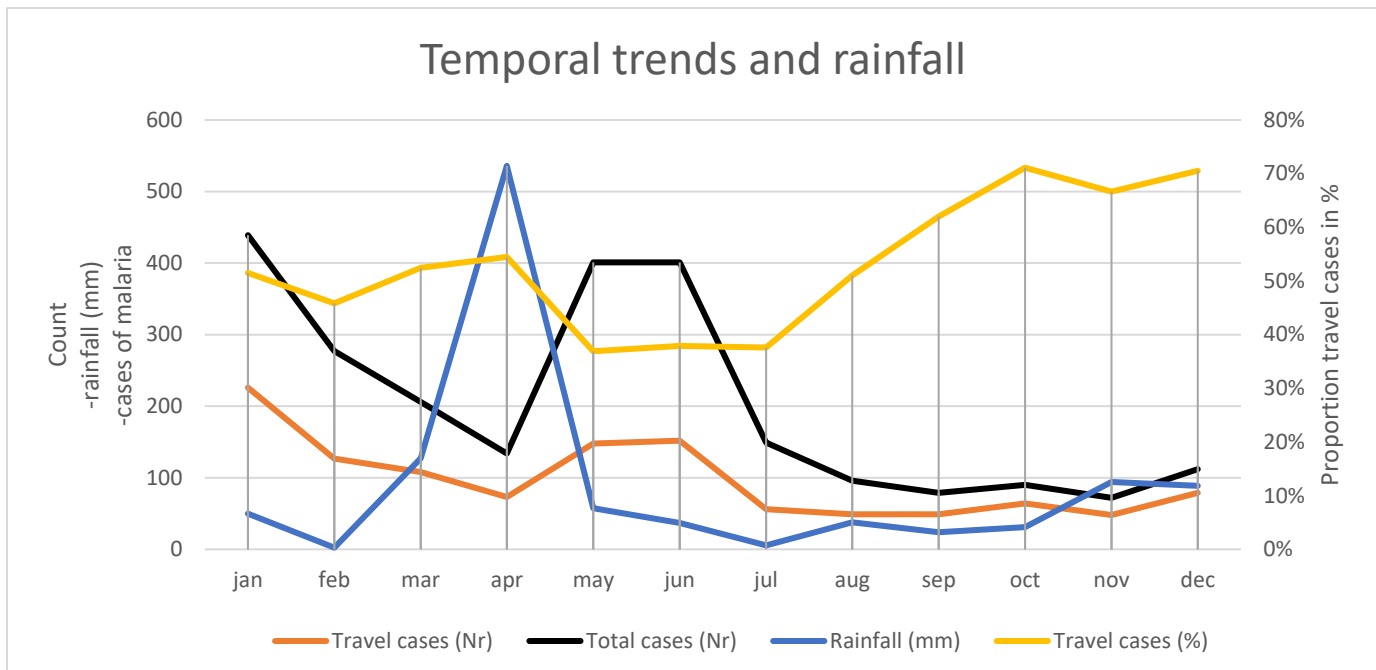
Figure1. Presentation of temporal trends in travel in relation to rainfall and time of year. Malaria positive in MCN data for health facilities.

Demographics

A seen in Figure 2, a large proportion of all malaria cases were in ages 10-29 years and fewer cases in the youngest (0-9 years) and above 30 years age. The proportion reporting recent travel in different age groups varied. The highest proportion reporting recent travel were in ages 20-50 in both sexes.

There were more malaria cases testing positive among males than among females (1408/1042). Number of cases with reported recent travel history were almost equal among sexes, male 47% and female 49% (difference 2%, CI -2 to 6, p=0.33).
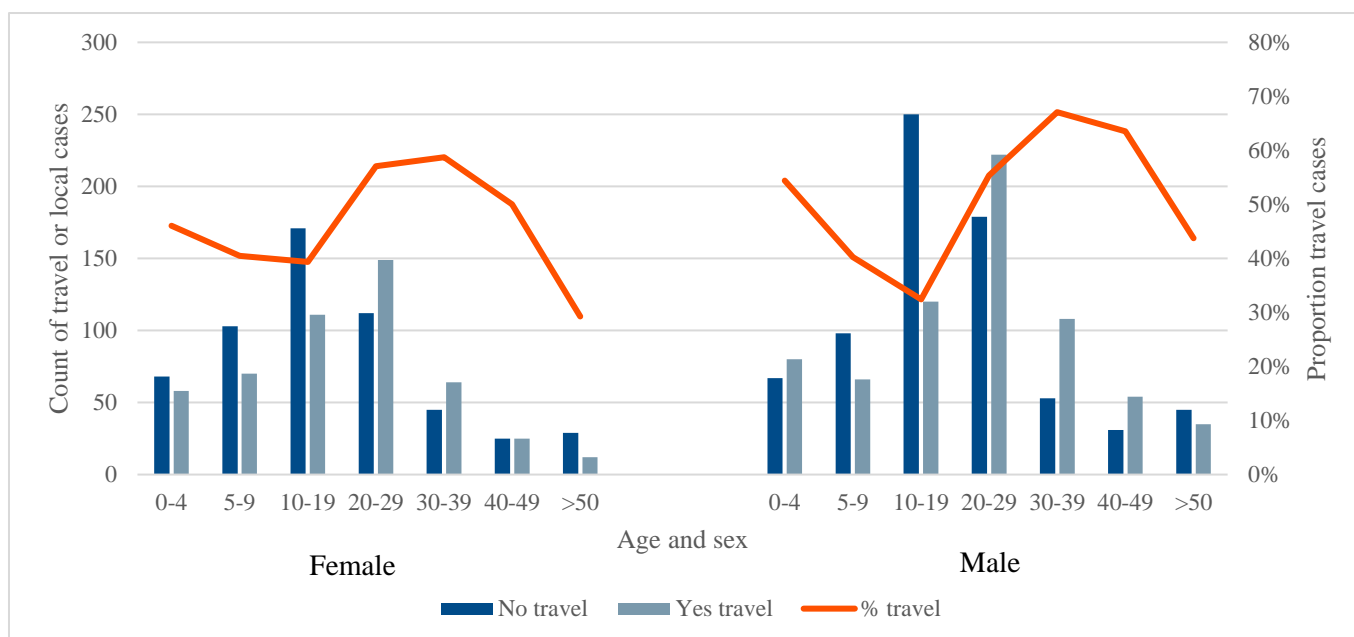
Figure 2. Showing recent travel history for malaria positive by sex and age grouping. Absolute numbers presented as bars and proportions as lines. Malaria positive in MCN data for health facilities.

Vector coverage

As seen in Table 5, vector coverage among malaria positive at HF was overall less for IRS than for LLIN. Vector coverage varied whether they had recent travel history or not, LLIN higher coverage if recent travel history than if not, 68% vs 61% (difference 7%, CI 1.9-12, p=0.007) and IRS less coverage if recent travel history 29% vs 33% (difference 4%, CI -4,4-12.1, p=0.35).

Table 5. Coverage of IRS and LLIN by recent travel history, all ages and sexes. Displayed as % of row and (nr). Malaria positive at HF in MCN data.

Travel history	Slept under LLIN last night			IRS recently	
	No	Yes		No	Yes
No travel	39% (459)	61% (711)		67% (600)	33% (292)
Yes travel	32% (308)	68% (657)		71% (493)	29% (203)
Total	36% (767)	64% (1368)		69% (1093)	31% (495)

Vector coverage by district

Table 6 shows variation by district in usage of LLIN the night before testing positive. Micheweni district had the lowest proportion of malaria positive reporting use of LLIN last night, and highest proportion in Magharibi district.

Table 6. Districts sorted by lowest coverage of LLIN. Malaria positive in MCN data for health facilities.

Districts	Used LLIN last night before testing positive for malaria			
	No		Yes	
	%	Nr	%	Nr
MICHEWENI	56%	240	44%	189
KUSINI	40%	35	60%	52
KATI	36%	105	64%	188
CHAKE CHAKE	35%	20	65%	37
MKOANI	33%	27	67%	54
KASKAZINI B	31%	95	69%	209
MJINI	29%	64	71%	156
WETE	29%	45	71%	111
KASKAZINI A	28%	45	72%	118
MAGHARIBI	25%	85	75%	253
Grand Total	**36%**	**761**	**64%**	**1367**

The IRS coverage by district presented in Table 7 shows that overall there was a low coverage of IRS, just 31% of all malaria positive at HF had done it within effective interval of <8 months. Coverage varied greatly between districts, in Chake Chake 100% had not done IRS <8 months compared to Kusini, 57% had done it.

Table 7. Districts sorted by lowest coverage of IRS. Malaria positive in MCN data for health facilities.

	IRS within 8 months				
	No			Yes	
Districts	**%**		**Nr**	**%**	**Nr**
CHAKE CHAKE	100%		57	0%	0
MKOANI	100%		1	0%	0
MJINI	96%		85	4%	4
WETE	90%		54	10%	6
MAGHARIBI	74%		189	26%	67
MICHEWENI	71%		294	29%	123
KASKAZINI A	64%		101	36%	57
KATI	63%		128	37%	76
KASKAZINI B	55%		145	45%	117
KUSINI	43%		33	57%	43
All districts	**69%**		**1087**	**31%**	**493**

Sources and sinks

Sources

51 different travel destinations were in total reported by malaria positive with recent travel history outside Zanzibar. Tanzania mainland was reported as travel destination by 94% of all travel cases. Top ten reported destinations were all districts of the mainland, reported by 81% of total.

As displayed in Figure 3, Dar es Salaam district was the top reported destination, reported by 30% of the travel cases. As comparison district Morogoro was reported by 10%, districts Lindi and Kigoma each reported as travel destinations by 2% of all.
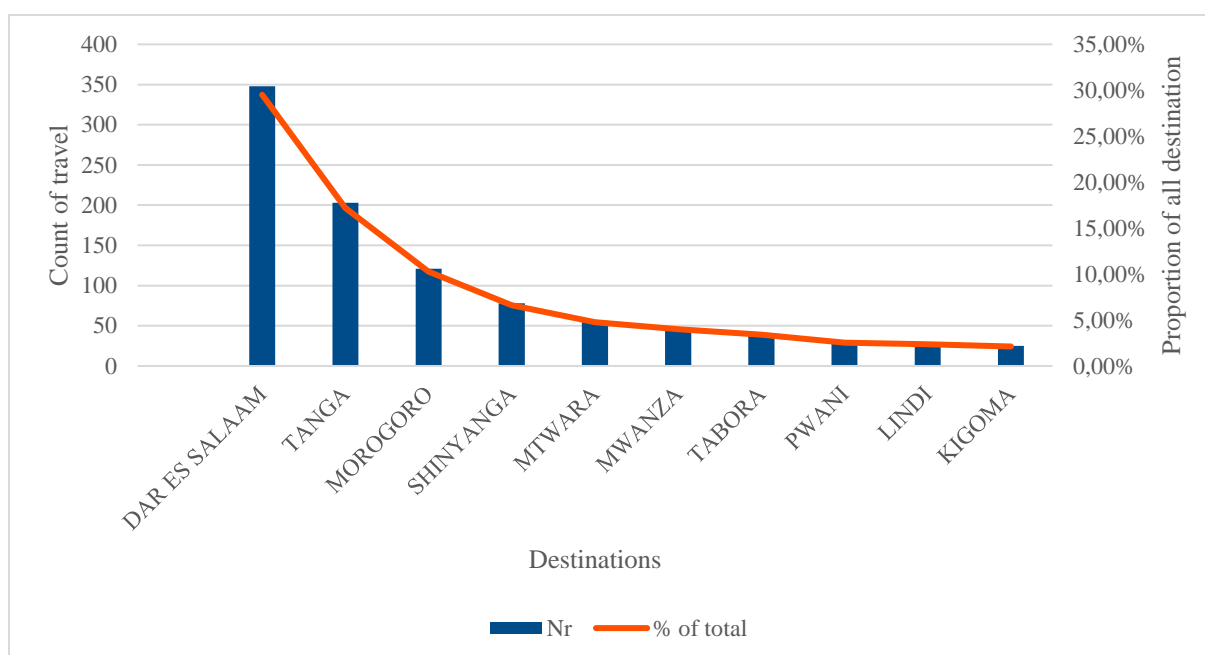
Figure 3. Top ten travel destinations of total 51 different destinations reported. Showing count and proportion of destinations. Line showing % of total malaria cases with recent travel history. Malaria positive in MCN data for health facilities.

Sinks

As seen in Table 8, the proportion of malaria positive reporting recent travel history outside of Zanzibar or not varied greatly by district. Mjini district, the city area of Stone Town, had the largest proportion reporting recent travel in comparison to Micheweni district with the lowest, 80% vs 6%.

Table 8. Showing distribution of recent travel history in malaria positive, by district. Sorted by largest to smallest proportion with recent travel. Malaria positive in MCN data for health facilities.

	Travel history					
	No travel		Yes travel		Total Nr	Total %
District	Nr	%	Nr	%		
MJINI	64	20,00%	256	80,00%	320	100,00%
MAGHARIBI	126	30,51%	287	69,49%	413	100,00%
KASKAZINI A	54	30,68%	122	69,32%	176	100,00%
CHAKE CHAKE	25	36,76%	43	63,24%	68	100,00%
KATI	149	45,29%	180	54,71%	329	100,00%
KUSINI	55	55,56%	44	44,44%	99	100,00%
KASKAZINI B	196	56,48%	151	43,52%	347	100,00%
WETE	118	72,84%	44	27,16%	162	100,00%
MKOANI	75	79,79%	19	20,21%	94	100,00%
MICHEWENI	412	94,28%	25	5,72%	437	100,00%
All districts	1274	52,11%	1171	47,89%	2445	100,00%

RACD

RACD risk factors

As shown in Table 2, 365 malaria cases were detected by the active follow-up of index cases detected at health facilities. As seen in Table 9, 71% of those found positive reported recent travel. The reported LLIN usage the night before testing positive was 56%. IRS data not available.

Table 9. Figures for presence of risk factors in RACD screen for those who tested positive for malaria.

	Yes		No		Total
Risk factors	Nr	%	Nr	%	
LLIN used last night	206	56%	159	44%	365
RACD screened, recent travel history[1]	73	71%	30	29%	103

[1] Only available and included for period January 1 – February 8, 2016

As seen in Table 10, not having used LLIN showed to be a significant risk factor for those screened in RACD, unadjusted OR 1.6 (P<0.001, CI 1.3-1.9). Travel outside Zanzibar in the recent 30 days was also found to be a significant risk factor for those positive in RACD, unadjusted OR 21.8 (CI 13.8-34.6, P<0.001). Information regarding IRS was not available.

Table 10. Showing risk factors for malaria in RACD screened quantified by unadjusted ORs.

Variable	OR	CI	Significance	Nr (total)
LLIN not slept under last night	1.6	1.3-1.9	P<0,001	159 (365)
Travel outside Zanzibar in recent 30 days[1]	21.8	13.8-34.6	P<0,001	73 (103)

[1] Only available and included for period January 1 – February 8, 2016

RACD positivity rate by index case recent travel history

As seen in Table 11, there was a higher positivity rate in the RACD screened who had index cases with recent travel history, 6.8% vs 2.6%. RR 2.7 (CI 95% 2.2-3.3, p<0.001) for RACD screened with index case with recent travel history vs no recent travel history.

Table 11. RACD screening positivity rate by index case recent travel history.

Recent travel history for index case of RACD screened	Screened	Positive	Positivty rate
No travel outside Zanzibar	4805	123	2.6%
Yes, travel outside Zanzibar	3436	235	6.8%

Discussion and conclusions

Imported malaria has been suggested to contribute to sustained local malaria transmission in settings of low transmission like in present Zanzibar.(20, 21, 25, 33) Not using LLIN or not having done IRS recently has earlier been found to be associated with increased risk of being infected with malaria in Zanzibar.(20)

The findings of this study explore characteristics and risk factors such as recent travel history, use of vector control, age, sex, temporal trends and seasonal variations for confirmed malaria cases in 2016 in Zanzibar.

Demographics

A relative shift in malaria towards older age groups has earlier been reported in Zanzibar. In year 2002 47% of all malaria in two studied districts was among <5 years of age, for 2015 17%. (20) The results of this study support that there has been an age shift, showing that malaria was found in relatively high proportions in adults. The observed age shift might be explained by a presumed lower malaria immunity in the general population as a consequence of the lowered malaria transmission.(34) Malaria cases in age 20-50 years had a relatively high proportion reporting recent travel history, which might have contributed to the relatively many malaria cases in adults.

The higher proportion of malaria cases among men, 57% vs 43% for women might be partially explained by behavioural factors. Men had a slightly higher proportion of malaria cases reporting recent travel history 49% vs women 47%. The proportion of men reporting recent travel was slightly higher but more information regarding travel statistics for the

population, outdoor activities, differences in vector coverage etc would likely be needed to explain the difference.

Travel as risk factor

That a proportion of 48% of all malaria positive at HF reported recent travel imply that a large portion of all symptomatic malaria cases were imported.

As expected recent travel proved to be a significant risk factor for malaria at HF. The unadjusted ORs for different periods, ranging 222-486 were quite high compared to earlier findings of adjusted OR of 70 for clinical malaria cases in Zanzibar 2015. (20) There were however several differences in the data used for calculations, for example the use of adjusted OR and different areas and time periods used.

The OR for MDA follow-up period Q3 was higher compared to OR for MDA baseline Q2. As seen in Figure 1 this corresponds to the relative higher proportion reporting recent travel history in Q3-4 compared to Q1-2. The variation in proportion of travel cases and non-travel cases could likely partly be explained by the known seasonal variation in local transmission, mainly related to rainfall and vector capacity. To further assess other factors affecting the seasonal variation in proportion travel cases, information regarding seasonality of malaria transmission in Tanzania mainland and travel statistics for malaria negative or general population would be relevant. There might be seasonal variation in both travel behaviour and risk associated with travel as earlier theorized.(21)

Interannual trends

In 2010 the proportion with recent travel history was 7%, OR 9. (35) For 2013 to 2015, as seen in Table 4 there seems to have been a continued trend of an increased malaria positive reporting recent travel history. This might indicate an actual increase in proportion of

imported malaria cases vs locally infected in Zanzibar. If this assumption is correct it would imply that for further achievements in controlling and eliminating malaria in Zanzibar the control of imported malaria is growing increasingly important as it has been suggested it would do.(21) In 2016 there was a slightly lower proportion of travel cases but when considering the whole period 2013-2016 the trend has been towards an increased proportion with travel history. The period observed is quite short and to compensate for yearly variations due to natural variation and errors of database it would be useful to expand the time period by including earlier years and to continue follow the trend in coming years.
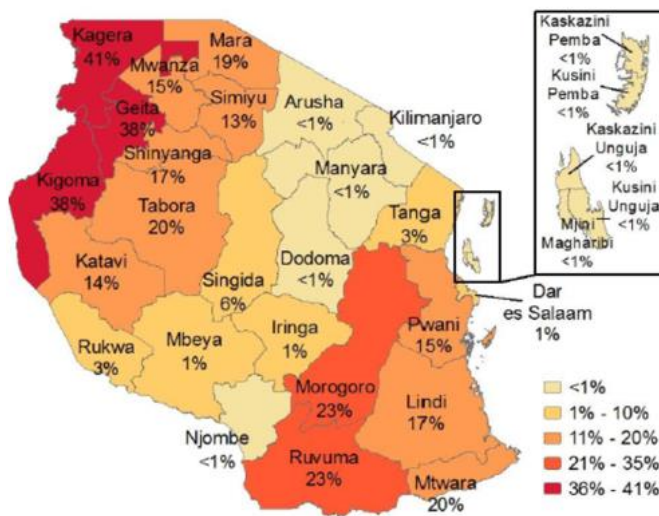
Sources and sinks

Sources

As concluded in the results a clear majority, 94% of all travel outside Zanzibar reported by malaria cases was to Tanzania mainland. That the top ten travel destinations reported cover 81% of all patients with recent travel history suggests that there are a few destinations in the mainland attributable for the vast majority of imported malaria to Zanzibar. Focusing on key regions might give insight were and how interventions might be best introduced.

Different districts of mainland Tanzania has different epidemiology of malaria and therefore likely pose different risk while visiting to get infected by malaria.

Percentage of children age 6-59 months who tested positive for malaria by microscopy

Kaskazini Pemba <1%
Kusini Pemba <1%
Kaskazini Unguja <1%
Kusini Unguja <1%
Mjini Magharibi <1%

Kagera 41%
Mara 19%
Mwanza 15%
Geita 38%
Simiyu 13%
Arusha <1%
Kilimanjaro <1%
Shinyanga 17%
Manyara <1%
Kigoma 38%
Tabora 20%
Tanga 3%
Katavi 14%
Singida 6%
Dodoma <1%
Rukwa 3%
Mbeya 1%
Iringa 1%
Pwani 15%
Dar es Salaam 1%
Morogoro 23%
Lindi 17%
Njombe <1%
Ruvuma 23%
Mtwara 20%

<1%
1% - 10%
11% - 20%
21% - 35%
36% - 41%

Picture 2.(32) Showing malaria prevalence by districts of mainland Tanzania, in children age 6-59 months, confirmed cases.

Two factors that affect the number of imported malaria from different districts of mainland Tanzania are epidemiology and volume of travellers visiting. (25),(33), (21) Some districts might be possible to consider as key districts for risk of imported malaria. These districts would be more suitable for interventions by having a relative high risk profile but also quite many travellers visiting. It would probably be more effective to target travellers going to high risk areas rather than low risk areas to make an impact on imported malaria from mainland Tanzania to Zanzibar.

Dar es Salaam had the highest number of malaria positive reporting it as recent travel destination but a low prevalence of malaria, 30% respectively 1%. Kigoma had relative to Dar es Salaam few malaria cases reporting it as travel destination but a high prevalence of malaria in the district, 2% and 38%. Morogoro had a combination of reported as travel destination by many and a high malaria prevalence, 17% and 23%. Targeting travellers who visited / who are going to visit e.g. Morogoro might be easier and more effective than for Dar es Salaam.

Targeting key traveller groups to limit malaria importation has been proposed by earlier studies, e.g. by distribution of chemoprophylaxis, education about risks and protective

measurements such as mosquito repellent, covering clothing, not staying out late at night, use of LLIN, screening at ports / on ferries or presumptive treatment. (21, 25, 33)

Sinks

There was a high variation by district in proportion of malaria cases reporting recent travel history. Mjini was the district reporting highest proportion with travel history among malaria positive compared to Micheweni the lowest proportion, 80% vs 6%. This difference likely presents a corresponding difference in actual proportion of imported malaria. Mjini could likely be considered an area of net import of malaria, a sink.

To further assess sinks of malaria import with higher accuracy could possibly aid in finding key traveller groups or give directions how to best prioritize interventions. Targeted recurring screenings, education or distributing chemoprophylaxis could be possible interventions.

Vector coverage

As seen in Table 5, the IRS coverage of 31% vs 64% for LLIN for malaria positive at HF might suggest that there is an overall low effective coverage of IRS in the population compared to the uptake of LLIN. After a change of policy in 2012 IRS spraying was no longer universal but targeted to focal hotspots. (24) The change of policy led to a decreased coverage of IRS, 2008-2011 91% in Micheweni and 85% in Kaskazini A reported having done IRS within last year but for 2013-2015 corresponding 79% and 54%.(20) This study concluded that among malaria positive in 2016 29% in Micheweni and 36% in Kaskazini A reported having done IRS within 8 months, as seen in Table 7. Comparing different years, different time periods for IRS coverage and general uptake vs uptake in malaria positive it's still fair to conclude that the effective IRS coverage has continued to remain quite low.

LLIN/ITN coverage was quite high between 2005 and 2015 in Micheweni and Kaskazini A, means of 68% and 74% for all. Children <5 years higher use than individuals >5 years, 81%

slept under LLIN/ITN compared to 69%. (20) This report showed that for malaria positive in 2016 44% in Micheweni and 72% in Kaskazini A had slept under LLIN the night prior to testing positive. The uptake of LLIN seemed to be lower among malaria positive in 2016 than for the general population 2005-2015 for these two districts. The reported lower use of LLIN among malaria positive compared to the general population might give some support that not using LLIN is a risk factor for clinical malaria. The earlier reported lower use of LLIN for individuals >5 years old compared to <5 years old in 2005-2015 might have affected the observed relative high proportion malaria in >5 years old.

The uptake of vector coverage among malaria positive varied by district, LLIN coverage ranged from 75% to 44% and IRS coverage ranged 0% to 57%. A high proportion not covered by VC implies that some of the malaria cases might be preventable. Further quantifying differences of certain areas in uptake of control measures and the attributable proportion of malaria theoretically preventable might aid in prioritizing resources and target areas. For example, the low uptake of LLIN in a certain district might prompt education and handing out of LLIN to the residents.

The results showed higher LLIN use (not significant) and lower IRS coverage (significant) among travel cases than non-travel cases. The VC coverage for those reporting recent travel was not assessed for the travel and therefore the information about their actual VC coverage is limited. However, vector control affects the receptivity of malaria and high uptake could limit the secondary transmission of imported malaria. (21)

Future research could assess the use of LLIN during travel, type of accommodation, length of travel, use of mosquito repellents and other factors affecting the risk of acquiring malaria while travelling.

RACD screening of households

A high proportion of reported recent travel in malaria positive in RACD screening and by HF cases could be interpreted as support for that travel is a risk factor for malaria and that family members likely have travelled together to some extent. There was observed a clustering of secondary transmission around travel cases, in RACD screening positivity rate 6.8% for travel cases respectively 2.6% non-travel cases, RR of 2.7. To explain the clustering around travel cases more information would be need, such as if the families travelled together, what other factors affecting receptivity were present.

Reported recent travel and not having used LLIN were both significant risk factors for malaria in RACD screened. The relative lower reported use of LLIN in RACD positive compared to positive cases at HF, 56% vs 64% might also support that not using LLIN is a risk factor for malaria. As both malaria positive in RACD screen and at HF reported high proportions with recent travel history there was a risk of bias when calculating OR for recent travel as risk factor for malaria. Risk of being infected by malaria for household members to a malaria case seems to be highly related to recent travel history outside Zanzibar, either by own travel, travel of family member or both. A limitation in the assessment of recent travel as risk factor for RACD screened was that the data was only available for a short period, 1/1-8/2 2016.

Methodological considerations

Symptomatic and asymptomatic malaria

The confirmed 4181 symptomatic cases of malaria in 2016 should be known to likely be an understatement of the actual malaria burden in Zanzibar. It has recently been shown by using PCR analysis that there is a large proportion of asymptomatic malaria in Zanzibar.(20) The asymptomatic malaria cases might not present similar characteristics as the findings in the

symptomatic cases, making the findings in this study only applicable for a portion of all malaria in Zanzibar.

Malaria testing is mainly done by mRDT in Zanzibar. mRDT has earlier been reported to have high specificity but low sensitivity compared to PCR.(24) The low sensitivity might suggest that some clinical malaria patients were missed.

MCN database

As a result of both incomplete follow-up of malaria cases detected at HF's by DMSO's and errors of the MCN database only 66% of HF cases were reported to MCN, the falling-off was likely random.

As much of the data from the MCN database is based on questionnaires the results could be affected by recall bias.

The missing data in MCN database varied by variable as shown in results Table 1. The results might be affected by the incomplete questionnaires and chosen methodology for handling this. Although this study was not set out to evaluate the accuracy of the malaria surveillance systems and databases of Zanzibar it´s a limitation that that the chosen methodology and data available not necessarily ensures highest possible reliability of the results.

Travel

Recent travel history reported by a malaria case implies that the patient could have acquired malaria during travel. The patient could however also have acquired malaria in Zanzibar and therefore this information couldn't replace what e.g. a PCR analysis of malaria strains could tell about the origin of the infection. Actual confirmed imported malaria cases would be more accurate to estimate the volume of imported malaria.

45

Limitations of the OR calculations presented in Table 3, are that different sources of data were used for malaria negative and positive (sources including different shehias) and that the data were not matched by age. As there was found no significant difference in the shehias included for malaria negative in surveys and malaria positive in MCN data (see appendix) the different sources of information seemed fit to use in absence of alternative options.

Conclusions and implications

With high ORs for recent travel as risk factor for malaria and a high proportion of all malaria cases reporting recent travel it's reasonable to assume that imported malaria contributes considerably to the malaria burden of Zanzibar. As the clear majority of all malaria cases reporting recent travel had travelled to mainland Tanzania it's reasonable to believe that the success in limiting imported malaria cases to Zanzibar could benefit greatly by advances in malaria control in the mainland and that it's in Zanzibar's interest to promote further collaboration.

Uptake of VC measurements as IRS and LLIN will likely continue to be of importance to limit malaria transmission. The observed shift of vector species, the proposed increased outdoor biting rate and resistance to insecticides will likely pose challenges.(20)

This study provides support to earlier study's findings, proposing that imported malaria plays an important role in sustaining malaria in the pre-elimination setting of Zanzibar. An effective approach and strategy to fight imported malaria in Zanzibar would likely aid in reaching the goal of achieving elimination. Identifying and targeting key travel groups with interventions to limit imported malaria could be a resource-effective strategy. If other data would be available, such as general travel data and statistics for each district this could be used in a case control analysis and the results likely present more useful quantified risk profiles of each districts and attributable numbers. There are also other known variables

determining the risk of acquiring malaria while travelling apart from endemicity, such as length of stay, type of accommodation, type of traveller typically visiting the area, VC availability and usage etc.(21) These data would also be of interest to assess in future research.

Populärvetenskaplig sammanfattning

"Resa till Tanzanias fastland som riskfaktor för malaria och vidare spridning i Zanzibar 2016"

Bakgrund: Malariabördan i Zanzibar har historisk varit hög men är nu låg, fortsatt minskning och elimination har dock uteblivit. Resa utanför Zanzibar har tidigare identifierats som en riskfaktor för malaria i Zanzibar och import av malaria från Tanzanias fastland har föreslagits underhålla den kvarvarande malariabördan på Zanzibar.

Syfte med studien: Att undersöka resa till Tanzanias fastland som riskfaktor för malaria och att beskriva karaktäristika för malariapatienter i Zanzibar under 2016.

Metod: Detta var en retrospektiv, deskriptiv och fall-kontrollstudie som använde data från ett övervakningssystem för malaria i Zanzibar. Malariafallen var kliniska och bekräftades med snabbtest för malaria eller med mikroskopi. Övervakningssystemets databas innehöll information om kända riskfaktorer såsom att nyligen ha rest utanför Zanzibar, ej sovit under myggnät och ej gjort sprayning med insektsmedel av hemmet.

Resultat: 48% av malariafallen på vårdcentraler uppgav att de rest utanför Zanzibar nyligen innan de blev sjuka. 94% av alla resor gjordes till Tanzanias fastland. Att nyligen ha rest utanför Zanzibar visade sig vara en stark riskfaktor för malaria med statistisk signifikans. 64% av alla malariafall hade använt myggnät och 31% hade gjort sprayning med insektsmedel av sin bostad.

Slutsatser: Att en hög andel av alla kliniska malariafall i Zanzibar nyligen hade rest utanför Zanzibar antyder att en stor andel av all malaria i Zanzibar är importerad. Användning av myggnät, sprayning med insektsmedel av bostad och smittspårning av malaria är faktorer som sannolikt påverkar spridningen av importerad malaria. Att begränsa den importerade malarian till Zanzibar kan vara viktigt för att åstadkomma ytterligare minskning av malaria och på sikt eliminera malaria i Zanzibar.

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Appendix

Assessment of different sources of data

The use of different sources of data for negative controls and malaria positive in OR

calculations for travel as risk factor for malaria at HF was assessed for fitness of use.

As seen in Table 2.1, 16 out of 128 shehias were included in MDA surveys. The travel % of

non-MDA shehias was 62% and MDA shehias 55%. Comparison of proportions reporting

recent travel in MDA shehias vs non-MDA shehias showed no significant difference, 7.8%

(CI -2-18, P=0.1).

Table 2.1. Comparison of differences in included material from MCN data for malaria positive and survey data for malaria negative for period of MDA baseline survey, 30/4-15/5 in 2016 (Morris et al, unpublished). Fewer included shehias/municipal regions in survey data.
South, West and Central district included.
MCN data for all of 2016 was used in the asssessment to get enough cases.

Source	Periods of comparison	Shehias included	Range in number of cases per district	Travel n/N (%; CI 95%)	Range travel by district
Malaria positive (MCN)	Whole of 2016	Non-MDA shehias (N=112)	61-387	455/730 (62% 58.7-65.9)	46-71%
		MDA shehias (N=16)	26-57	66/121 (55%, 45.2-63.6)	42-63%
		All shehias (N=128)	99-413	521/851 (61%, 57.9-64.5)	44-69%
Malaria negative (MDA)	MDA baseline		645-4353	36/7792 (0.99%, 0.32-0.64)	0.4-0.5%