

Meeting report of the WHO Evidence Review Group on the assessment of malariogenic potential to inform elimination strategies and plans to prevent re-establishment of malaria

2–4 October 2018, Geneva, Switzerland

Summary

Malariogenic potential is the risk of transmission in a given area; it arises from a combination of receptivity (inherent potential of the vector–human ecosystem to transmit malaria), vulnerability (traditionally used within malaria to refer to the risk of importation of parasites) and infectivity (vector–parasite compatibility). Malariogenic potential is a critical factor in determining strategies to achieve elimination and prevent re-establishment of transmission. The World Health Organization (WHO) recommends that countries approaching elimination or working to prevent re-establishment of malaria stratify their geographical units by malariogenic potential, to help in targeting appropriate interventions; WHO also recommends that this assessment should determine whether vector control can be withdrawn after transmission is interrupted in an area. There is a lack of guidance on methods to measure the components of malariogenic potential and on thresholds relevant for programmatic decisions. Therefore, WHO convened an evidence review group (ERG) to review methods reported in the literature to measure receptivity and vulnerability, and to review evidence for incompatibility between vectors and parasite strains from other regions.

The report of the meeting – with a summary of the evidence presented, draft conclusions and proposed updates to definitions of terms in the WHO glossary – is submitted to the WHO Malaria Policy Advisory Committee (MPAC) for consideration.

Conclusions

- The ERG considered malariogenic potential to be an important concept, and noted the urgent need for a clear definition of the term and of its components, to be informative, consistent and useful.
- Several terms related to malariogenic potential and its components require definitions in *WHO malaria terminology* (1) to be updated to align with current use and understanding. In particular, the ERG suggested that “importation risk” was preferable to the term “vulnerability”, because the former is a clear expression of what is being measured and the latter is often used to express “susceptibility” or “risk of harm”.
- Several methods exist to assess receptivity but they have not been cross-validated or compared.
- The extent of reduced compatibility of local mosquitoes to parasite strains imported from distant areas should be further investigated, to help inform response strategies to imported cases.

- Importation risk can be measured in several different ways but these methods have not been cross-validated or compared in a systematic way.
- Development of thresholds for malariogenic potential to inform strategies to prevent re-establishment of transmission will require additional investigation and modelling.

Proposed recommendations

1. Add or update the following terms in the WHO malaria terminology document (1):
 - **[ADD] Malariogenic potential:** Likelihood of local transmission that is the product of receptivity, risk of importation of malaria parasites and infectivity of imported parasites. *Note: The concept of malariogenic potential is most relevant for elimination and prevention of re-establishment when indigenous transmission is mostly or entirely eliminated.*
 - **[UPDATE] Receptivity:** Degree to which an ecosystem in a given area at a given time allows for the transmission of *Plasmodium* spp. from a human through a vector mosquito to another human. *Note: This concept reflects vectorial capacity, susceptibility of the human population to malaria infection, and the strength of the health system, including malaria interventions. Receptivity can be influenced by ecological and climatic factors.*
 - **[MODIFY] Vulnerability:** Likelihood of malaria infection based on living conditions or behavioural risk factors, or likelihood of increased risk of severe morbidity and mortality from malaria infection.
 - **[MODIFY] Importation risk:** Risk or potential influx of parasites via infected individuals or infected *Anopheles* spp. mosquitoes. *Note: "Infected individuals" includes residents infected while visiting endemic areas as well as infected immigrants.*
 - **[ADD] Infectivity:** Ability of a given *Plasmodium* strain to establish an infection in an *Anopheles* mosquito species and undergo development until the mosquito has sporozoites in its salivary glands.
2. Update the WHO *Malaria surveillance, monitoring & evaluation: a reference manual* (2) to:
 - a. more clearly articulate the importance for entomological surveillance to identify principal versus secondary vectors, given ongoing and likely temporal and spatial changes in vector distribution and abundance; and
 - b. provide more detailed guidance on site selection, and on the frequency and timing of entomological surveillance, to inform assessment of receptivity.
3. Revise other current WHO guidance documents in line with points (1) and (2), to ensure consistency.
4. Give priority to further development of methods for assessing malariogenic potential (receptivity, importation risk and infectivity) to ensure that these are applicable and informative for programmatic use. This includes:
 - a. comparison of methods for the three potential measures of receptivity for selected countries, to ascertain comparability within countries, between countries or between neighbouring regions, to inform their use in receptivity assessments;
 - b. comparison of entomological parameters, as well as each of their associations with parasitological indicators, to identify key components that should be included in assessment of receptivity;
 - c. examination of outbreak data from certified countries, to determine the origin of the imported parasite strains and the number of resultant infections;

- d. comparison of existing data on infections identified through border or workplace screening with those identified through passive case detection at clinics, to ascertain whether information from passive case detection provides an accurate picture of importation risk; and
 - e. examination of examples where countries can generalize data on imported cases for populations in specific regions to other areas with similar population movement or influxes.
- 5. Identify relevant and feasible methods for measurement of the components of malariogenic potential, interpret these measurements and develop thresholds to guide programmatic decision-making regarding maintenance of vector control and intensified surveillance.
- 6. Further evaluate the issue of infectivity with respect to the mosquito and parasite factors that may reduce vector competence for different strains of *Plasmodium*, to determine whether there are programmatic implications for these findings. This may require additional review of evidence in future.

Contents

Summary.....	Error! Bookmark not defined.
Conclusions	1
Proposed recommendations.....	2
1 Background	6
2 Objectives of the ERG.....	6
3 Specific outputs of the ERG	7
4 Proceedings of the ERG meeting	7
4.1 Proposed methods for assessing receptivity	9
4.1.1 Review of receptivity assessments	9
4.1.2 Bayesian geospatial approaches to receptivity assessment.....	10
4.1.3 Estimation of R_0 for receptivity assessment	12
4.1.4 Experiences of using the entomological surveillance planning tool to measure receptivity	15
4.2 Proposed methods for assessing vulnerability	17
4.2.1 Approaches to assessing vulnerability to imported parasites	17
4.2.2 Vulnerability assessment through tools developed by the International Organization for Migration.....	21
4.3 National programme experience with assessing receptivity and vulnerability.....	22
4.3.1 Malaysia	22
4.3.2 Bhutan.....	26
4.3.3 Sri Lanka	29
4.4 Proposed methods for assessing infectivity	35
4.4.1 Review of mosquito susceptibility to imported exotic malaria parasites.....	35
4.5 Stratification and intervention mixes	36
4.5.1 Effectiveness of intervention mixes stratified by vulnerability and receptivity	Error!
	Bookmark not defined.
5 Conclusions.....	37
5.1 Receptivity	38
5.2 Importation risk	39
5.3 Infectivity	40
5.4 Malariogenic potential.....	40
6 Recommendations	41
References.....	43
Annexes	47

Annex 1. Agenda	47
Annex 2. List of participants.....	49
Annex 3. Declarations of interest	51
Annex 4. Overview of evidence on <i>Anopheles</i> spp. and <i>Plasmodium</i> spp. compatibility for different malaria zones	53

1. Background

Understanding the underlying potential for malaria transmission in a given geographical area provides the foundation for the design of cost-effective intervention programmes to decrease malaria burden, eliminate transmission and prevent re-establishment of malaria. This transmission hazard has been referred to as *malariogenic potential*, with various definitions presented over time. For example, during a World Health Organization (WHO) working group meeting on the topic held in 1978, malariogenic potential was defined as the product of receptivity, vulnerability and infectivity (3), and although no definition of malariogenic potential was provided in the recent *WHO malaria terminology* (1), several of the individual components as stated above were defined to some extent.

The WHO *Framework for malaria elimination* (4) recommends that transmission intensity, receptivity and vulnerability underpin subnational stratification, to inform the selection of interventions for eliminating malaria transmission. Measurement of receptivity and vulnerability is also critical to prevent the re-establishment of transmission following elimination. The *Guidelines for malaria vector control* (5) indicate that in areas where transmission has been interrupted, the scale-back of vector control should be based on a detailed analysis that includes assessment of receptivity and vulnerability, active disease surveillance, and capacity for case management and vector-control response. However, guidance on how to define, measure and classify receptivity and vulnerability has been scant, leaving countries with no clear recommendations on methods or thresholds.

Vector competence to transmit imported parasites is a component of malariogenic potential that is not frequently considered – yet there is evidence that parasite–vector specificity exists (6, 7). Parasites imported from neighbouring countries are as likely to infect local *Anopheles* spp. mosquitoes as the strains of parasites circulating within the country. However, the increased potential for local compared with distant parasite strains to avoid mosquito immune systems, reproduce sexually and infect a new human host (i.e. vector competence) should be explored.

There has been an increasing demand for WHO guidance on the assessment of malariogenic potential, especially from countries that are working to prevent re-establishment of transmission either at the subnational or national level. Additional evidence and new techniques and approaches are now available to inform the development of such guidance, along with greater accumulated experience in elimination and post-elimination settings. WHO therefore convened an evidence review group (ERG) to meet from 2 to 4 October 2018 in Geneva, Switzerland, to clarify the definition of malariogenic potential and advise on the definition, measurement and classification of its constituent components. It is anticipated that better guidance on assessing malariogenic potential will aid the development or refinement of national strategies to eliminate and prevent re-establishment of malaria, and further enable achievement of the goals and targets outlined in the *Global technical strategy for malaria 2016–2030* (8).

2. Objectives of the ERG

The main objective of the ERG meeting was to review and recommend appropriate methodologies for assessing malariogenic potential to inform elimination strategies and plans to prevent re-establishment. The specific objectives were as follows:

1. To review current definitions of receptivity, vulnerability and malariogenic potential contained in the WHO glossary and, if required, to recommend improvements to ensure that the definitions are valid and appropriate.
2. To review available methodologies for assessing receptivity, and recommend appropriate and valid methodological approaches, including data requirements, for national malaria control programmes (NMCPs) to use to measure receptivity in their respective countries.

3. To advise WHO on options for classifying receptivity according to programmatically relevant categories aimed at guiding interventions to prevent re-establishment of transmission.
4. To review the validity and practicality of available methods for assessing vulnerability, and to recommend appropriate and valid methodological approaches, including data requirements, for NMCPs to use to assess vulnerability in their respective countries.
5. To review data on the regional receptivity (“infectivity”) of endemic *Anopheles* spp. mosquitoes to exotic strains of human malaria.
6. To advise WHO on approaches to combining measures of receptivity, vulnerability and infectivity, to guide NMCPs in designing strategies to prevent re-establishment of transmission.

3. Specific outputs of the ERG

The anticipated outputs from the ERG meeting were:

- revised definitions, where needed, for updating of the WHO malaria terminology document;
- recommendations on options for classifying receptivity according to programmatically relevant categories;
- recommendations on methods and data requirements for assessment of vulnerability;
- recommendations on how measures of receptivity, vulnerability and infectivity may be combined to inform strategies to prevent re-establishment of transmission; and
- a priority list of next steps to improve guidance on assessment of malariogenic potential and the use of such assessments.

4. Proceedings of the ERG meeting

An ERG meeting was convened by the WHO Global Malaria Programme (GMP) on 2–4 October 2018. The meeting included seven ERG members, three NMCP managers, five additional subject matter experts (as presenters), one observer from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), and the WHO Secretariat. Professor Azra Ghani was appointed as chair of the meeting. The agenda is provided as Annex 1, and the list of meeting participants and their affiliations is provided as Annex 2.

The meeting included open sessions on proposed methods for assessing receptivity, vulnerability and infectivity, as well as an examination of stratification and intervention mixes. A plenary discussion was held on the final day to develop draft conclusions, which were then finalized along with recommendations in the closed session. ERG members, NMCP managers, presenters, observers and the WHO Secretariat attended the open sessions, whereas the closed sessions included ERG members and the WHO Secretariat only.

Opening and orientation to the topic (open session)

The meeting was opened and attendees were welcomed by Dr Pedro Alonso, Director of GMP. Dr Alonso reiterated the importance of the ERG in providing a basis for clearer guidance for the development of strategies for malaria elimination as well as prevention of re-establishment. A focus on high-burden countries is essential; for example, through the new WHO “high burden to high impact” initiative that focuses on the 11 countries (10 on the African continent, plus India) that account for about 70% of the global malaria burden. However, the number of countries approaching elimination continues to increase – the *World malaria report 2018* (9) indicates that there are now 46 countries

with fewer than 10 000 cases. Therefore, better guidance for these countries is deemed essential to enable achievement of the goals, milestones and targets outlined in the *Global technical strategy for malaria 2016–2030* (8), which include “prevent re-establishment of malaria in all countries that are malaria-free”. Dr Alonso thanked the ERG members, NMCP managers and presenters for their contributions to the work of WHO in support of Member States.

Declarations of interest provided by ERG members had previously been assessed by Dr Jan Kolaczinski and Dr Kim Lindblade. Based on that review, it was decided that one of the declarations constituted a conflict of interest in this context, and that one of the experts considered could participate in the meeting but be subject to partial exclusion (i.e. be recused from the final session on Day 3, in which recommendations were finalized). All of the other experts considered were able to participate fully in the meeting, subject to the public disclosure of their interests. The statement of declarations of interests was read aloud to the meeting; the declarations are provided as Annex 3.

Dr Kolaczinski then explained the background, objectives and expected outputs of the meeting (as set out above). Dr Kolaczinski stated that understanding malaria transmission risk in a given geographical area provides the foundation for the design of cost-effective intervention programmes to decrease malaria burden, eliminate transmission and prevent re-establishment of malaria. The increasing demand for WHO guidance on the assessment of receptivity and vulnerability was noted, especially from countries working to prevent re-establishment of transmission. However, there is little guidance in this area; hence, there have sometimes been substantial investments in data collection (especially entomological surveillance) without a clear link to programmatic decision-making. Vector susceptibility to imported parasites contributes to malariogenic potential, but is a factor that is often not taken into consideration. Some opportunities for the development of improved guidance were identified, including the availability of more sophisticated methods and data sources, such as model-based geostatistical frameworks, cell phone information and other remotely sensed data for population mobility. In addition, useful information to inform guidance development is increasingly becoming available, through practical experience with transitioning programmes from control activities to more targeted designs aimed at eliminating malaria or preventing its re-establishment.

The current WHO guidance related to malariogenic potential was presented. The WHO *Framework for malaria elimination* (4) recommends subnational stratification to inform the selection of interventions; measurement of receptivity and vulnerability to prevent re-establishment of transmission after elimination; and maintenance of vector-control coverage after elimination in areas with high malariogenic potential. In addition, the WHO document *Malaria surveillance, monitoring & evaluation: a reference manual* (2) identifies characterization of receptivity to guide stratification and selection of interventions as one of the main objectives of entomological surveillance. In this guidance, entomological parameters considered in risk characterization include the competency of the vector species present, and bionomic traits such as biting (e.g. time, place and host preference), dispersal and resting behaviour.

Examples of approaches used to quantify receptivity, vulnerability and infectivity were presented. An example of heterogeneity in transmission risk (based on median annual parasite incidence) was presented in brief for Sri Lanka (10), along with the current WHO terminology and understanding of components of malariogenic potential; that is, receptivity, vulnerability and infectivity (1). For each of these components, examples were drawn from the literature to reiterate the variety of approaches that have been taken for definition and measurement.

The ERG members were encouraged to consider the most practical and informative approach (or approaches) for determining malariogenic potential, considering the variation of settings and capacities across countries.

4.1 Proposed methods for assessing receptivity

4.1.1 Review of receptivity assessments

Dr Joshua Yukich presented a background paper on the definitions and practice and case studies related to receptivity, based on work completed for a literature review commissioned by WHO,¹ the purpose of which was to review the available evidence on receptivity and its assessment by NMCPs and their research partners, and to develop a draft methodology for the assessment of receptivity. This required the following approach: develop and conduct a review of peer-reviewed and grey literature; engage with countries on experiences and methods of receptivity assessment; describe methods being used and their advantages and disadvantages; provide a draft methodology and rationale for that methodology; and develop a draft paper for review at the ERG meeting and finalize it based on feedback. The literature review included 85 documents, of which 45 (53%) had qualitative definitions and 21 (25%) had quantitative definitions. Country case studies focused on Eswatini, Georgia, Malaysia and Sri Lanka.

The review found that “receptivity” to malaria is a construct developed during the era of the Global Malaria Eradication Programme (GMEP). Receptivity has been defined in varied ways in the decades since, but no consistent, quantitative definition has emerged. In the WHO malaria terminology document, the definition of receptivity – “*receptivity of an ecosystem to transmission of malaria*” – was indicated as being poorly formulated because it constitutes a circular reference and is ambiguous. The definition also includes the note that “*a receptive ecosystem should have e.g. the presence of competent vectors, a suitable climate and a susceptible population*” (1), which is not necessarily aligned with current general understanding or specific definitions used elsewhere (e.g. 11).

Despite the lack of consistency in defining this construct, the idea of receptivity has remained important in planning around malaria elimination, especially in the prevention of re-establishment period following malaria elimination. Dr Yukich presented an examination of the use of this construct through published (and unpublished) literature since the 1950s, and also used case studies to document the current use of the construct in country planning.

A definition of “receptivity” was proposed, which could be implemented in elimination and prevention of re-establishment programmes globally, along with suggested thresholds that could be used for stratification, measurement and estimation methods. These were discussed at length, with the definition later refined by the ERG, as presented below.

Based on the review of the evidence, Dr Yukich considered that the minimum approach to measuring receptivity could include one of the following:

- reproductive numbers – case counts, or case-based surveillance data classified as local or imported (relapsing);
- vectorial capacity – human landing catch or mosquito density, human blood index, extrinsic incubation period, parous rate and, possibly, vector competence; and
- historical parasite prevalence of *Plasmodium falciparum* in children aged 2–10 years (*PfPR*_{2–10}) or malaria baseline prevalence – pre-intervention parasite prevalence data, and post-intervention parasite prevalence data with additional information on intervention coverage and other confounding factors.

Other issues raised by Dr Yukich for the ERG to consider when formulating conclusions and recommendations included the fact that *P. vivax* and *P. ovale* (i.e. relapsing malaria species) may necessitate separate estimates of receptivity. Measuring receptivity for these parasites will require differentiation into primary and relapsing cases, as well as consideration of Duffy negativity or other factors affecting human susceptibility to infection. The geographical scope of assessment was also

¹ The review is accessible from WHO upon request (kolaczinski@who.int).

raised because receptivity may vary dramatically over small scales, as well as parasite species and strain compatibility in relation to the competence of local vectors to transmit infections.

The ERG concluded that the current WHO definition of the term “receptivity” is poorly worded. The use of the term in the literature and practice is inconsistent, and assessment methods used are varied and poorly characterized. Measurement of the construct is likely to be difficult, but the most suitable metrics for its assessment are reproductive numbers, vectorial capacity and historical $PfPR_{2-10}$. Assessment via reproductive numbers provides the most intuitive stratification systems and methods of assessment that use only human surveillance data. All elimination programmes are already expected to collect the right surveillance data and to classify cases in the manner that would allow these data to be used for receptivity assessment (i.e. differentiation into local and imported cases). Other assessment methods are potentially useful, but many of the systems in practical use have never been tested for accuracy against any gold standard system.

4.1.2 Bayesian geospatial approaches to receptivity assessment

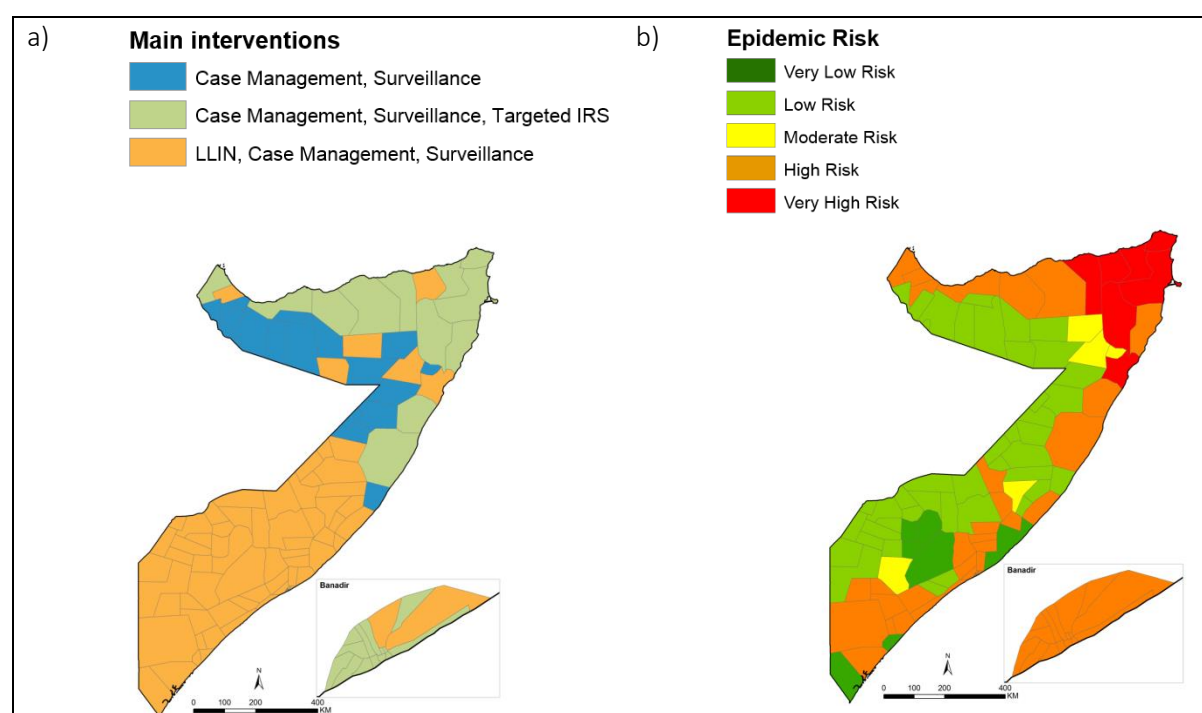
Dr Abdisalan Noor presented (remotely) on experiences in the use of model-based geostatistical analysis of historical $PfPR_{2-10}$ to estimate receptivity. His presentation drew on published examples from three countries – Somalia, Namibia and Kenya – as outlined below.

Example from Somalia

For Somalia, the purpose of the study was to explore the use of $PfPR_{2-10}$ as proxy for receptivity to guide intervention targeting (12). A total of 1558 $PfPR_{2-10}$ data points from the period 2007–2011 were used for Bayesian spatial-temporal models. Selected environmental covariates (urbanization, rainfall, temperature and distance to potential mosquito larva breeding sites) were included. Maps of $PfPR_{2-10}$ were produced at 1×1 km spatial resolution for each year from 2007 to 2010. Maximum prediction for each at a pixel level was used as a measure of receptivity. Maps of population totals at similar resolution were combined with the $PfPR_{2-10}$ maps to produce population-adjusted $PfPR_{2-10}$ ($PAPfPR_{2-10}$) by district. The “receptive” $PfPR_{2-10}$ map was then used to define packages of interventions in each district as a basis for Somalia’s grant application to the Global Fund (Fig. 1a). Case management and surveillance were recommended everywhere, with targeted indoor residual spraying (IRS) proposed in areas with $PAPfPR_{2-10}$ of less than 1% and epidemic prone (green), but not those areas where $PAPfPR_{2-10}$ was less than 1% but not epidemic prone (blue). Long-lasting insecticidal nets (LLINs) were recommended only in areas with $PAPfPR_{2-10}$ of more than 1% (orange).

Epidemic prone areas were then mapped using information on receptive $PfPR_{2-10}$; rainfall seasonality and frequency of anomalies, and their relationship with weekly malaria cases from sentinel sites; ecological zones; and village maps. A 3-month period of above normal rainfall preceded most epidemics, and the median amount of rainfall for these 3 months was about 40% above average rainfall. Villages were ranked into quintiles based on the number of such 3-month blocks from 2005 to 2015, the estimated $PfPR_{2-10}$ from the continuous prevalence maps, and the ecological zone (central south, north-east and north-west). A composite index of epidemic risk was then developed from these estimates.

Fig. 1. Example from Somalia of the use of PAPfPR_{2–10} to determine a) main intervention mixes and b) epidemic risk



IRS: indoor residual spraying; LLIN: long-lasting insecticidal net; PAPfPR_{2–10}: population-adjusted *Plasmodium falciparum* prevalence in children aged 2–10 years (Excerpt from presentation by A. Noor).

Example from Namibia

For Namibia, estimates of the spatial distribution of receptive areas and current risk using *Pf*PR_{2–10} data were generated to inform recommendations on targeting of vector control, and to provide information for future analyses of receptivity and vulnerability to inform elimination (13). Data comprised 3260 *Pf*PR_{2–10} points from 1967 to 1992 and 120 *Pf*PR_{2–10} points from 2009, with selected environmental covariates (urbanization, temperature, enhanced vegetation indices and precipitation) considered. Estimates indicated that areas of the highest historical transmission were concentrated in the Okavango and Caprivi areas. Those areas with more than 5% historical prevalence were recommended for vector-control targeting. There were no data available for the epidemic years of 1993, 1996, 2000, 2001 and 2004. It was noted that it would be worth comparing estimates with data from the recent epidemics of 2013–2015. However, this study indicated that historical maximal risks are not truly a measure of intrinsic transmission due to coincident intense control, although accuracy was higher than for estimates based on data from 2009.

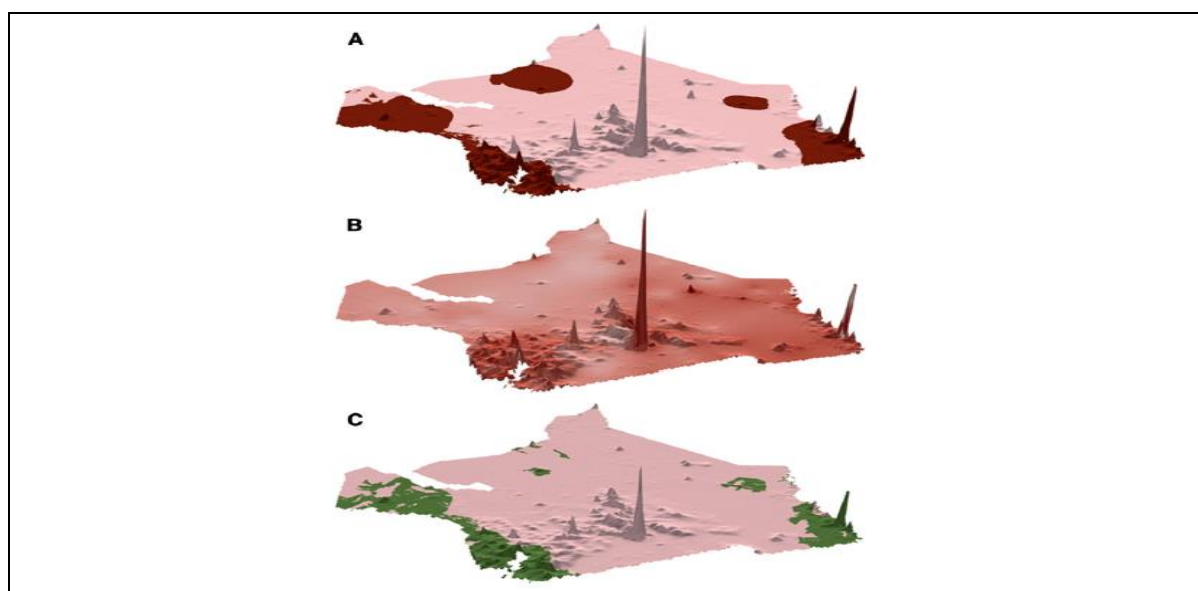
Example from Kenya

The example presented for Kenya was originally generated based on a request from the NMCP to develop an approach for better targeting of mass campaigns for insecticide-treated mosquito net (ITN) distributions where funding is limited, meaning that distributions across the whole country are not possible (14). Work was undertaken to update model-based geostatistical maps of *Pf*PR generated based on malaria indicator survey data from 2007 and other historical data (15). Three maps were developed (

Fig. 2). Under a targeted approach, the population at risk in 2010 was estimated to be 15.2 million compared with a total population of 40.5 million. The total number of LLINs needed to achieve universal coverage in the targeted area, accounting for estimated valid LLINs in the population, was 5.5 million, compared with 16.4 million across the whole country. Estimated savings in cost of commodities alone was about US\$ 55 million for the campaign that followed. This targeting approach

is still used by the Kenya NMCP. There was no evidence of increase in malaria transmission in districts where LLIN coverage was not maintained.

Fig. 2. A) A 3D population map showing areas where $PfPR_{2-10}$ was <1% (pink) and >1% (dark red); B) map showing percentage ITN use: the darker the colour the higher the predicted ITN coverage; C) population that need LLINs in areas to be targeted based on a criteria of >1% $PfPR_{2-10}$ and >1 person per km² (green) and those additional individuals who will need LLINs if the whole country were targeted (pink)



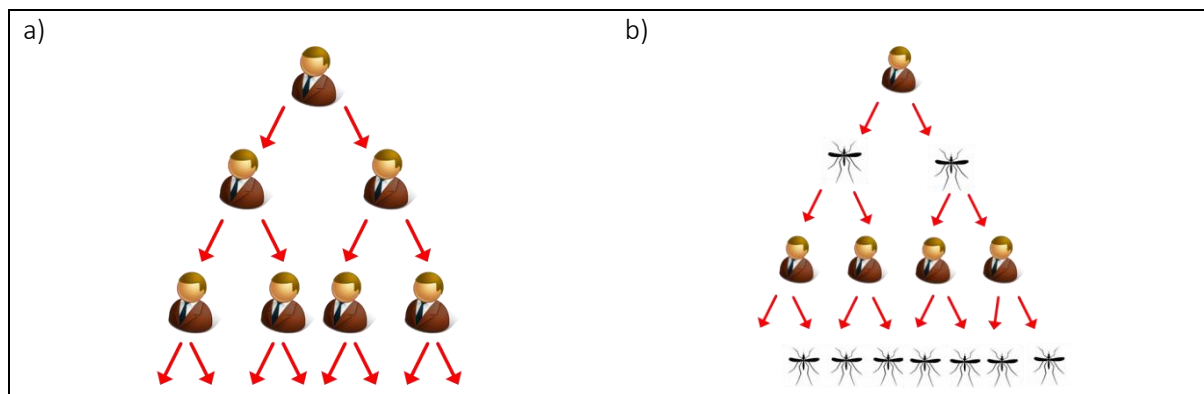
ITN: insecticide-treated mosquito net; LLIN: long-lasting insecticidal net; $PfPR_{2-10}$: population-adjusted *Plasmodium falciparum* prevalence in children aged 2–10 years (Excerpt from presentation by A. Noor).

Dr Noor concluded that use of model-based geostatistical estimates of $PfPR_{2-10}$ as surrogate measures of receptivity will depend on the context and purpose. The process of selecting maximum $PfPR_{2-10}$ prediction was not probabilistic but was instead a direct extraction of the highest mean pixel prediction; therefore, it was not possible to quantify uncertainty. The examples also showed that interventions and other secular effects and the low temporal signal in data can have a major impact on $PfPR_{2-10}$ predictions. However, it is almost impossible to find $PfPR$ data from a period of “true” absence of control. Using $PfPR$ data together with good entomological measurements is likely to be more informative.

4.1.3 Estimation of R_0 for receptivity assessment

Professor Azra Ghani presented on estimating the basic reproductive number (R_0) as a measure of malaria receptivity. The concept of R_0 was explained as a measure of how many additional people one person infects over the course of their infection, which is one of the most important quantities governing an epidemic; that is, R_0 applies to the start of an epidemic when no individuals are immune, and for an epidemic to “take off” R_0 needs to be more than 1. For vector-borne diseases, one person gets infected and that person infects mosquitoes, which then infect more people, who then go on to infect more mosquitoes. Nevertheless, the definition of R_0 remains the number of new people infected by each person (Fig. 3).

Fig. 3. Conceptual representation of the basic reproductive rate (R_0) for a) infectious diseases of humans and b) vector-borne diseases of humans



Excerpt from presentation by A. Ghani.

R_0 is closely related to vectorial capacity and is defined as “the number of secondary cases that a single infection (index case) would generate in a completely susceptible population” (1). The definition of vectorial capacity – that is, “the number of new infections that the population of a given vector would induce per case per day at a given place and time, assuming that the human population is fully susceptible to malaria” (1) – is similar but does not take into account the transmission bottlenecks (human to mosquito and mosquito to human). Also, vectorial capacity is measured on a per day basis, whereas R_0 is measured over the course of a full infection. Vectorial capacity has previously been identified as equivalent to receptivity, but it can be difficult to estimate all of the parameters for vectorial capacity in the field (16).

The basis of epidemics was explained with reference to the “growth rate”, which defines the chain reaction that gives exponential growth in an epidemic, or can lead to its rapid decline. This rate is determined by R_0 and the generation time (T_g); also sometimes referred to as the serial interval, T_g is the average time between one person getting infected and that person infecting other people. When an epidemic begins to run out of people to infect, the growth rate declines because a substantial proportion of contacts for each infected case have already been infected. Therefore, the number of secondary cases per case drops below R_0 and instead becomes defined by the effective reproductive number (R_e), which is the product of R_0 and the proportion of the population that are still susceptible (s) (i.e. $R_e = s \times R_0$). Therefore, an epidemic will go into decline once s is less than $1/R_0$ because at this point R_e will be less than 1.

The threshold of R_e greater than 1 is required for self-sustaining local transmission. However, at R_e less than 1 there will still be small outbreaks, assuming there is some importation. The probability of such outbreaks becomes less likely as R_e gets smaller. The number of locally acquired cases therefore depends on both R_e and the number of importations. This means that receptivity and importation risk are both important in determining the chances of observing locally acquired cases.

Most work to date has been to estimate malaria R_0 as a measure of the intensity of transmission in a location experiencing ongoing transmission, based on:

- a modelled relationship with other malaria metrics (often within a geospatial framework);
- the relationship between aggregate numbers of imported and locally acquired cases; or
- “reconstruction” of potential chains of transmission using detailed data on each identified case or infection.

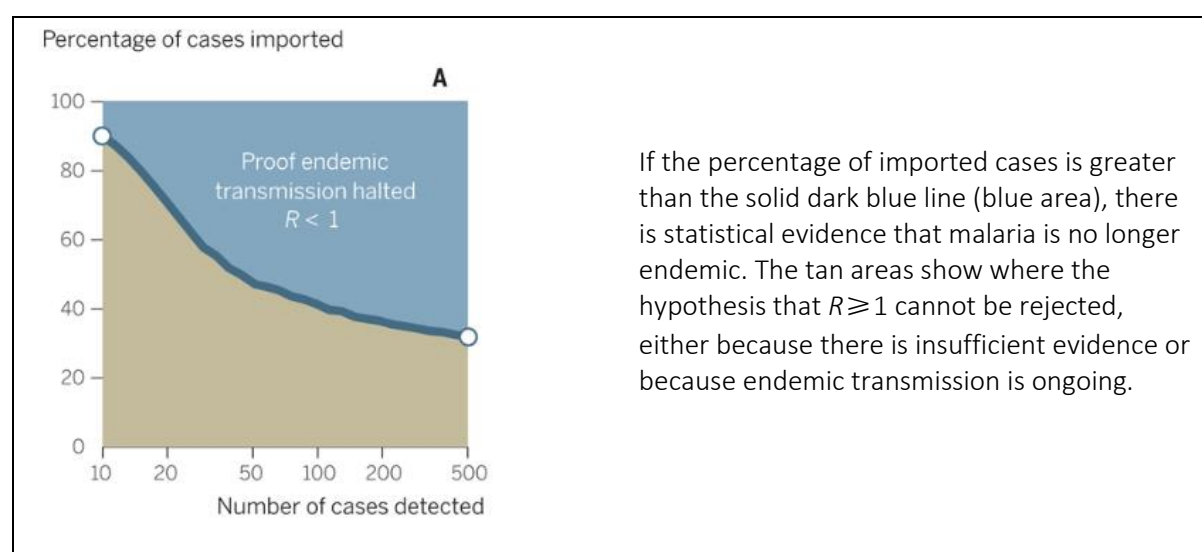
Much more work on this has been undertaken for other diseases, in particular for emerging diseases and outbreaks. Although less work has been done to date for malaria in elimination settings, the

methods used from assessing the relationship between aggregated numbers of imported and locally acquired cases remain relevant.

The methods used to aggregate case reports are based on how many cases each imported case is expected to generate. This draws on data on locally acquired and imported cases to specifically test whether R_e is greater than 1, and therefore whether there is self-sustaining local transmission. Simulations are used to derive the expected ratio of local to imported cases, to determine whether these are just above the threshold value of R_e equals 1. It can be scaled to any appropriate geographical level (e.g. country, province or district), depending on data availability.

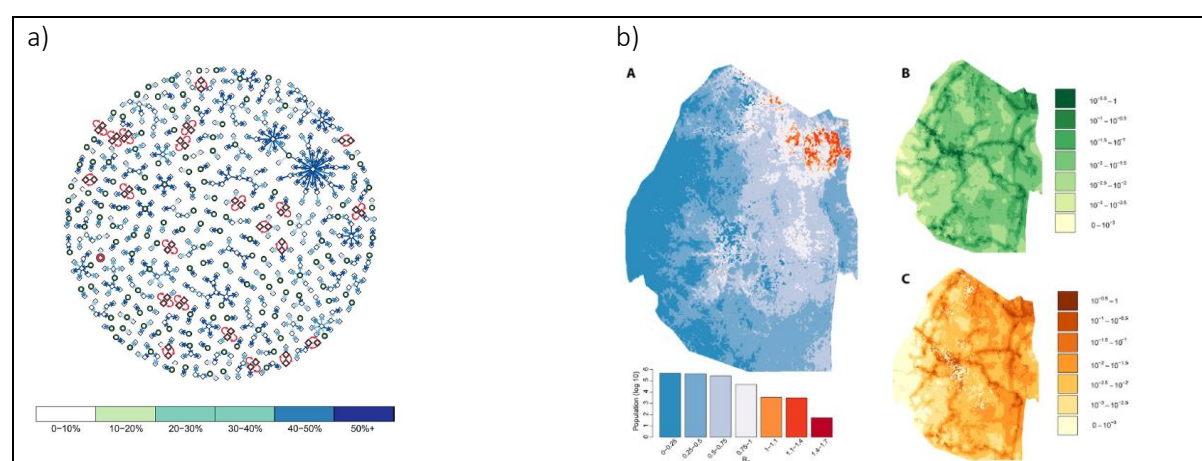
An example using this approach was presented for Eswatini (17). R_e was estimated annually and was shown to be significantly less than 1 from 2012 onwards. Estimates were used to generate a simple graph that could be used in other locations. However, for elimination, individual information on the date of the case report is required to understand the potential times in the past that an individual could plausibly have been infected (i.e. considering the Tg distribution). Such information would help to ascertain which cases could have resulted from previous cases based on examining temporal overlap, which is useful for developing a map of potential transmission networks. A detailed network map developed for Eswatini by Reiner et al. (18) was presented. This can feed into regression models, with environmental covariates used to obtain maps of R and importation probability; multiplied together, these can give malariogenic potential (Fig. 5).

Fig. 4. The percentage of imported cases required to confirm that endemic malaria transmission has been halted



Sources: Churcher et al, 2014 and Reiner et al., 2015 (18, 19).

Fig. 5. Maps for Eswatini showing a) consensus network plot of causal links and b) extrapolated R_C values to give estimates of A) vulnerability, B) receptivity and C) malariogenic potential



R_C : controlled reproductive number.

Source: Reiner et al., 2015 (18).

An example of a methodologically different approach was presented for El Salvador (20). The method relied on reconstructing transmission pathways, but also identified some “orphan” infections that do not appear to have a source. Spatial extrapolation similarly used demographic and environmental covariates, to map the probability of sustained transmission (i.e. $R_e > 1$).

Limitations

The limitations of assessing the risk of re-establishment were presented by Professor Ghani. Primarily, where there are no locally acquired cases, it is not possible to reconstruct transmission events. The branching process methods used in the estimates produced for Eswatini were therefore considered more relevant to these settings. Instead of testing the null hypothesis of R_e being greater than 1, the same method could be used to obtain an upper 95% credible interval for R_e , conditional on having observed no outbreaks (or other similar metrics). The method can easily be extended to produce geographical maps similar to those presented above for Eswatini and El Salvador (17, 18, 20).

Professor Ghani concluded that R_e/R_C (where R_C is controlled is an appropriate metric to estimate receptivity as elimination is approached. At its simplest, R_e/R_C can be estimated from counts of imported or locally acquired cases, or from case report data where such data are available. Both calendar time and geographical space can be used in assessment of risk (and potentially genetic information). Although methods development is ongoing, it has the potential to be synthesized in a form that could be accessible to NMCPs. However, it has not yet been applied or tested in areas or countries in which malaria has been eliminated.

4.1.4 Experiences of using the entomological surveillance planning tool to measure receptivity

Dr Adam Bennett presented on an entomological surveillance planning tool (ESPT) that is currently being developed, to support problem-solving and vector-control decision-making. The ESPT was developed in response to identified demand from NMCPs, owing to limited consolidated operational guidance for entomological surveillance. This was underscored by a growing need among programmes for deeper understanding of transmission dynamics and gaps in protection to inform response, with efficient and ethical entomology and vector control more important than ever.

The objectives of the ESPT are to:

- support gap-filling in operational guidance for entomological surveillance;
- align with and operationalize global normative guidance;

- develop minimum essential entomological indicators to generate data that are actionable and collectable;
- support NMCPs in making evidence-based decisions on vector control; and
- deepen the integration of entomological and epidemiological surveillance and response.

The ESPT is intended as a highly collaborative and iterative project that has been developed in alignment and in consultation with WHO. Version 1.0 was circulated in early 2018; version 2.0 is under development, based on feedback and pilots.

A number of potential use cases have been identified; for example:

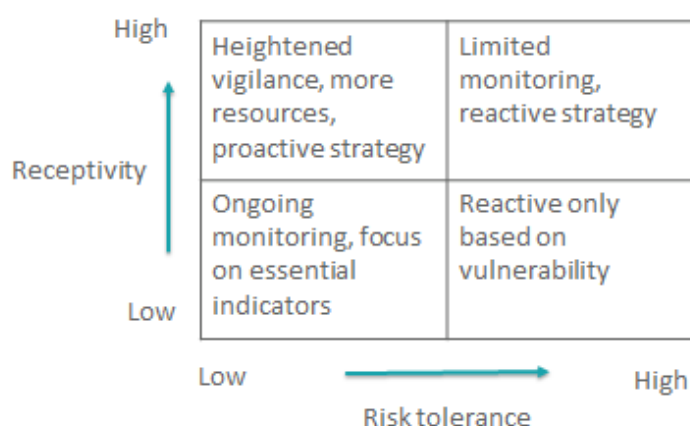
- planning annual NMCP entomological surveillance activities;
- developing a national entomological surveillance plan;
- developing and implementing training workshops;
- developing a protocol to answer a specific programmatic question;
- evaluating specific vector-control interventions in a programmatic setting;
- measuring receptivity (e.g. as part of prevention of reintroduction); and
- integrating entomological and epidemiological activities and data.

The ESPT is being piloted in five countries: Democratic Republic of the Congo, Mozambique, Myanmar, Namibia and Panama. Learnings from Mauritius thus far were presented, along with key outcomes and conclusions from work to date. In Mauritius, prevention of re-establishment strategy hinges on three activities: passenger screening (i.e. screening at ports of entry) – *vulnerability*; integrated vector management (IVM) and entomological surveillance – *receptivity*; and a strong passive surveillance system. IVM and entomological surveillance are needed to measure and maintain low receptivity. This is achieved through biweekly larval surveys and larviciding; sites include former malaria foci (routine) and high-risk areas around migrant workers' residence (proactive). Additional vector control includes enforced environmental management on personal property, and IRS and outdoor residual spraying at and around the port and airport every 6 months. Where an introduced malaria case is detected, focal larval surveys, larviciding and IRS are conducted within a 500 m radius of the case's residence, and anywhere the case stayed in the past 18–24 days. The presence of malaria vector(s) is used as a measure of receptivity, noting that climate and environment are implicit in the presence of vectors.

Numerous key questions were presented and discussed, including on minimal essential indicators, supplemental indicators, appropriate sampling methods, and frequency and location of sampling. It was emphasized that data that lead to action are vital; hence, all decision trees lead to an action in line with national strategy. Activities are also highly dependent on financial, technical and operational capacity; requirements for certification can serve as leverage to create sufficient capacity. The geographical size of areas monitoring receptivity matters; smaller pockets of malaria free areas in malaria endemic countries might implement monitoring based on vulnerability trigger, whereas larger malaria free regions or entire countries might implement routine monitoring (e.g. by historical peak or by month).

Ultimately, a ministry of health's (MoH's) prevention of re-establishment programme (and receptivity monitoring activities) will depend on the level of risk the country is willing to accept. Thus, a country that is risk averse would implement heightened vigilance and a proactive approach, whereas a country that is more risk tolerant would implement moderate vigilance and a more reactive approach (Fig. 6). The process of determining baseline risk and risk targets can be formalized – for example, through import risk analysis (as applied for zoonotic diseases and plant pests), and could be based on the quantitative or qualitative likelihood and implications of re-establishment, or the government's and public's attitude towards those potential outcomes.

Fig. 6. Representation of the influence of receptivity and risk tolerance on response actions



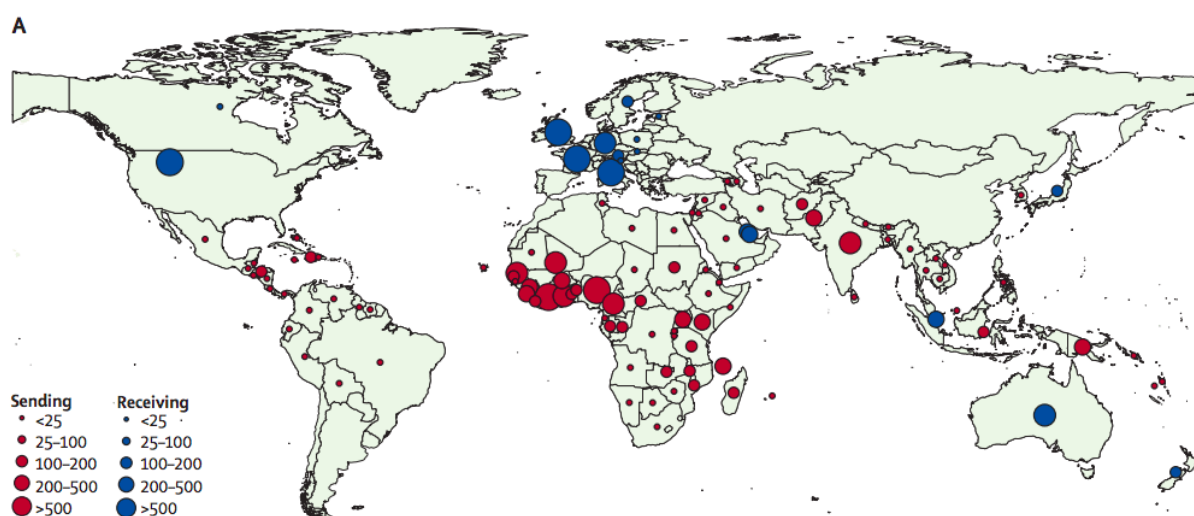
Excerpt from presentation by A. Bennett.

4.2 Proposed methods for assessing vulnerability

4.2.1 Approaches to assessing vulnerability to imported parasites

Dr Andy Tatem presented on measuring and mapping of vulnerability to malaria. Human movements contribute to the transmission of malaria on spatial scales that exceed the limits of mosquito dispersal. Identifying the sources and sinks of imported infections due to human travel, and locating high-risk sites of parasite importation, could support the targeting of limited resources. Dr Tatem presented the literature on approaches to identifying importation routes that contribute to malaria epidemiology on regional, national and subnational scales. Historical and current examples of human mobility were shown that highlight today's increasing volume of worldwide mobility; the rise has been particularly marked recently in low- and middle-income countries. Maps showing the geography of imported malaria to nonendemic countries indicated that this is a significant issue (21); the effects of such importation were presented, with clear examples of resurgence in countries across all WHO regions (22). Further country-specific examples of importation risks and origins were presented for Cabo Verde, China and Le Reunion.

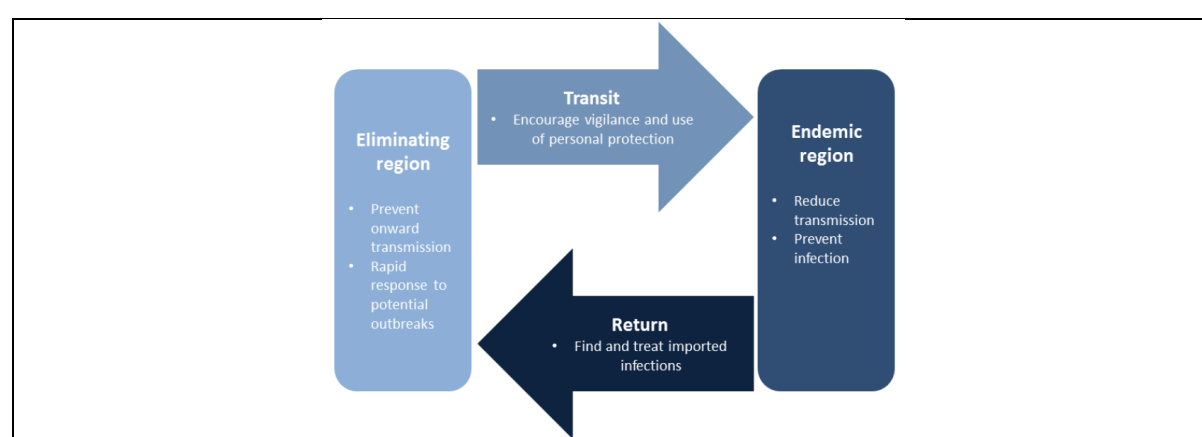
Fig. 7. Origins, destinations and flows of imported cases of malaria from endemic to nonendemic countries – average annual number of malaria cases (all species) between 2005 and 2015 exported from endemic to nonendemic countries (red) and imported cases to nonendemic from endemic countries (blue)



Excerpt from presentation by A. Tatem.

Outcomes of a qualitative assessment of malaria parasite importation into Zanzibar, United Republic of Tanzania indicate that the potential pathways by which parasites might be imported were residents infected while visiting endemic areas, infected visitors bitten by resident mosquitoes, infected migrants and infected migrant mosquitoes (23). The importance of importation of malaria parasites into receptive areas that can lead to onward transmission was discussed in the context of elimination efforts in southern Africa, where there is extensive interconnectivity between high-burden and low-burden areas. Dr Tatem noted also that importation from high-risk areas places a significant burden on the health care system, absorbing human and financial resources. Thus, even if conditions are such that local transmission eventually dies out, importation can lead to considerable numbers of local cases. Further examples were presented from El Salvador, Equatorial Guinea, Eswatini, Uganda and the Thailand–Myanmar border. For instance, in patients who had recently travelled to areas of higher transmission intensity than their home areas were nearly seven times more likely to have confirmed malaria (24). The four stages of human movement and corresponding objectives of interventions were presented (25).

Fig. 8. Human management and intervention objectives



In terms of measuring parasite movement and connectivity, the advantages and disadvantages of different approaches were presented (with examples), as summarized in Table 1.

Table 1. Summary of advantages and disadvantages of different data types for assessing vulnerability

Data type	Advantages	Disadvantages
Surveillance data: data on imported cases collected through routine or active case detection	• Provides a direct measurement of imported cases, demographics and other characteristics • Can be spatially and temporally detailed	• Can be sparse, incomplete and inaccurate • Asymptomatic carriers are typically missed • Treatment seeking rates, informal populations and private clinics may lead to missed cases • Varying amounts of information are captured • Identification of imported versus local cases is challenging • Recall biases • Definitions changing or inconsistent temporally and spatially

Data type	Advantages	Disadvantages
Parasite genetics: measures diversity and relatedness of parasite genetic samples, enabling direct measurement of parasite connectivity	• Most direct measure of parasite importation and connectivity • Overcomes issues of asymptomatic people and treatment seeking in surveillance data	• Few efforts to systematically collect and few genotype representative samples at sufficient spatial scale and density to provide useful data • Difficult to detect relevant spatial signal in parasite genetic data using traditional population genetic methods, particularly in areas such as sub-Saharan Africa that have high levels of population diversity and polyclonal infections
Travel history surveys and participatory mapping: household surveys, border surveys and expert opinion on movement patterns	• Captures movements that may be missed by surveillance system	• Recall and other biases • Expensive to undertake for large areas
Census-based migration: assembly of population and housing census data on place of residence 1–5 years ago; spatial interaction modelling for filling gaps	• Global extent and consistent measure; covers complete population • Shows strong correlations to shorter scale movements, both domestic and international • Data on imported cases are collected through routine or active case detection	• Permanent migrations only • Bias to longer spatial scales • Affected by conflicts • Coarse spatial scale
Air and sea traffic data: statistics on passengers (or flights and passenger ships) travelling between airports or ports	• Captures relevant movements where flights and ships are the primary method of introduction	• Not so useful where land travel is prevalent
Call detail records: geolocated data from mobile phone calls	• Massive sample size • Impossible to achieve with travel history surveys • National-scale data • Long time series • Relatively reliable source of destinations and lengths of stay for travel • Provides information on social networks and wealth • Cross-border measurements feasible	• Bias in representation of national population movements • Coverage gaps in the most rural areas • No demographic information • No information on activities, malaria protection etc. during travel
Internet and social media location histories: geolocated data from smartphone devices; for example, Google location history (GLH)	• Spatially precise • Long time series • Captures domestic and international data • Rapidly increasing volume of data	• Huge biases • No demographics • Variations by device • Changing sample over time

Data type	Advantages	Disadvantages
	Exploring potential for connectivity and for mobility modelling penetration	
GPS tracking: volunteers are given Global Positioning System (GPS) trackers or smartphones to monitor movement patterns	- Precise, detailed data on movements, overcomes recall bias problems - Useful for validation of other methods	- Expensive - Limited to small areas and small samples - Limitations to long-term measurement
Infrastructure: georeferenced data on transport links that form the basis of regional mobility	- Global coverage - Consistent data - Indicative of connectivity and mobility - Useful alternative measure of the connectivity and access that drive vulnerability	- No measure of actual movements - Few time series

Numerous examples of the use of movement data for mapping transmission foci were presented, including for mapping transmission foci (*e.g.* 26, 27-29). Dr Tatem concluded that a strong surveillance system, capturing imported cases and related information, is central to assessing vulnerability. Alternative sources of data and modelling approaches can complement and add value. However, no source of mobility data is perfect, and integration of multiple types of data will probably provide the most complete picture. Data on parasite movements and connectivity can be analysed in multiple ways to answer different types of questions facing programmes. Dr Tatem identified a number of other questions of interest, such as the appropriate standard metric for vulnerability, the best data sets for the different needs, and how to integrate the different data sets to draw on the strengths of each one.

Conclusions

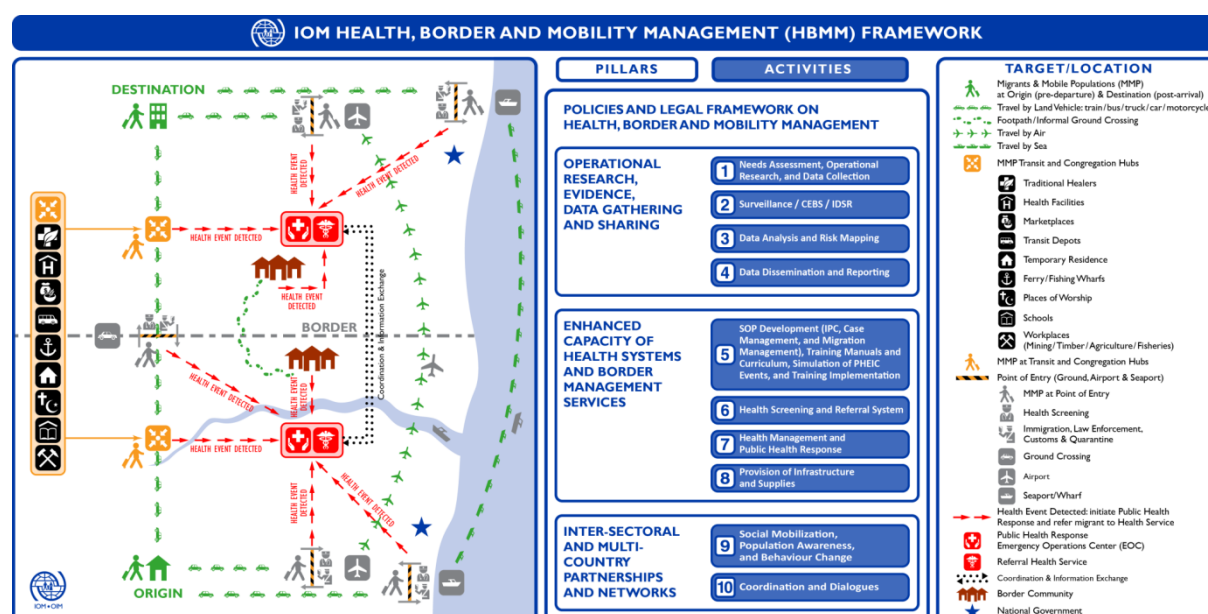
After considering the information presented, the ERG identified the core priority on vulnerability as it pertains to malariogenic potential to be identification of the points of entry and the numbers of people coming from areas of malaria endemicity to areas where transmission had been interrupted. Discussions centred on whether surveillance data are sufficient to determine this, or whether there can be full reliance on mobile data or other data sources for some or all areas. A number of limitations of mobile data were indicated, such as not being able to detect movement between countries owing to differences in mobile providers and the need for service roaming functions, and the fact that multiple service providers may complicate access to a complete data set. Although data collected through routine or active case detection provide a direct measurement of imported cases and hence should be the central component of surveillance, these show the number but not the risk of importations because of limited knowledge on the denominator. Therefore, mobile data could be of supplementary use to show the actual volume and patterns of human movement, to determine how these relate to importation risk.

The ERG concluded that there is utility in comparison of multiple types of data, to give confidence that other types of data can be used in settings where the surveillance system is not yet sufficiently strong and the surveillance data are not yet of an acceptable standard to support elimination and prevention of reintroduction.

4.2.2 Vulnerability assessment through tools developed by the International Organization for Migration

Dr Carlos van der Laet and Mr Nawar Sattar Tashbid presented on the International Organization for Migration (IOM) Health, Border and Mobility Management (HBMM) framework and population mobility mapping (30). Originally developed for Ebola virus outbreaks, the HBMM framework empowers governments and communities to prevent, detect and respond to the spread of infectious diseases and other potential health threats along the mobility continuum (i.e. at origin, transit, destination and return points), with particular focus on border areas. At the core of HBMM is the understanding that the mobility continuum extends beyond the physical or regulated border areas, such as the official points of entry (PoEs) as articulated within the International Health Regulations (IHR) 2005, to include pathways and spaces of vulnerability. Grounded on this understanding, the scope of HBMM ranges from the collection and analysis of information on mobility patterns, to disease surveillance and health threat response mechanisms at spaces of vulnerability along mobility pathways. Thus, HBMM ultimately contributes to health system strengthening that is sensitive to mobility dynamics, notably at the primary health care level.

Fig. 9. Overview of the IOM HBMM framework



Excerpt from presentation by C. van der Laet.

The IOM has identified vulnerability to malaria based on the key areas of service access, knowledge, health care seeking behaviours, exposure and other risk factors. As with mobility, the definition of vulnerability considers it to be a known social determinant of health, a direct contributor to the spread of diseases, and a continuum wherein to better understand vulnerability is to enable better prevention, detection and response to public health threats. According to the IOM definition, spaces of vulnerability are human mobility bridges in areas of high-risk exposure to diseases, where human mobility connects communities and defines common spaces of vulnerability (e.g. those that can have increased risk of exposure to malaria). It was clear that the IOM concept of vulnerability differs from the malaria-specific definition provided in *WHO malaria terminology* (1). The former considers “spaces of vulnerability” as being related to the places within the migration cycle where migrants are at greater risk for disease; it focuses on the space, the community or the site where migrants gather, such as the market or the church. This reiterates the ambiguity in the use of the term “vulnerability” to refer to what could more accurately be referred to as “importation risk”.

IOM undertake three phases to ensure that better mobility information has a positive impact on public health:

1. Identify geographical areas of interest with human mobility dynamics and patterns, and other vulnerabilities that may increase the impact of public health risk of international, national and community concern.
2. Collect data – assess the characteristics, vulnerabilities and extent of human mobility into, from and between identified areas of interest, including their congregation points. This includes carrying out vulnerability and capacity assessments for disease surveillance and response at spaces of vulnerability (e.g. health facilities, PoEs and “at-risk” communities).
3. Analyse mobility patterns in the context of the public health event, to guide resource and response needs.

Examples were presented on identification of migration routes and risks in Ghana through data collected via participatory mapping with stakeholders at the national and subnational levels. Mapping of results was through the software ArcGIS and Illustrator, to define mobility corridors, connectivity and mobility trends. The Ghana case study was of particular interest to the ERG members, with further inquiries on methodology. Dr van der Laet and Mr Tashbid clarified that the initial step of national mapping required about US\$ 30 000 for convening, printing of basemaps and payment of experts in facilitation, note taking and ArcGIS. The stakeholder consultation included 25–30 people from different backgrounds (i.e. different actors in public health) working for about 2–3 days, with the total exercise taking less than 1 week. From this, key priority districts were identified for further participatory mapping, with local mappings to identify key community areas of vulnerability. Direct observations could then be made, and public health interventions could be developed and implemented.

A similar approach is being undertaken with support of the IOM in several other countries in Africa; preliminary results were presented for Côte d'Ivoire, Democratic Republic of the Congo, Liberia and Sierra Leone. Sites are defined based on clear administrative and geographical boundaries for consistency and replicability, as well as the feasibility of covering those sites. Their selection is based on existing information on health risks and epidemiology, population mobility dynamics indicated by locally available information, and the accessibility and availability of resources. Examples of similar undertakings were presented for the response to the international emergency of public health concern declared for Ebola and Zika, as well as for cholera outbreaks.

The main areas identified as requiring work were the need to:

- improve tools, methodologies and practice for assessing and understanding local mobility dynamics;
- link prevention, treatment and surveillance data, and initiatives across migration routes and borders;
- strengthen multisectoral engagement; and
- promote migrant inclusion in national, state and provincial health service planning, and all malaria services.

4.3 NMCP experience with assessing receptivity and vulnerability

4.3.1 Malaysia

Dr Jenarun Jelip presented on Malaysia's experience with assessing receptivity. Vulnerability assessments were presented later in the meeting, but are summarized here for continuity, along with the overall use of this information for stratification and intervention. Vulnerability in the Malaysian

context referred to importation risk, but also included the likelihood of malaria infection given the characteristics of the population.

Malaysia has 14 states with 147 districts and more than 55 000 localities, covering an area of 329 847 km². In 2017, the population was estimated at 32 million, and is multiracial, with a multitude of ethnic groups. In 2003, Malaysia achieved an annual parasite index (API) of less than 1 per 1000 population. The latest national stratification was undertaken in 2015, and was based on disease burden (i.e. by API); it indicated that 97.3% of the localities in Malaysia were free of malaria. The MoH therefore decided to use receptivity and vulnerability as measures for risk of malaria reintroduction. Methods were developed to measure these parameters, and these methods formed the main component of the national *Guideline for prevention of malaria re-introduction*, which was published in 2016. The definitions of receptivity and vulnerability that were applied, as well as the definition of malaria focus, were guided by the WHO *Framework for malaria elimination* (4).

Measurement of receptivity

Parameters included in the receptivity index are indicated in Table 2; each is assigned a weighting factor, and an overall receptivity score is then generated. A standardized form is used for the preliminary ecological assessment for *Anopheles* reproduction – which in Bahasa Malaysia is “*Penilaian Awal Kesesuaian Ekologi Pembiakan Anopheles*” (PAKEPA). The PAKEPA form has four parts:

- case information (if available);
- basic data on locality;
- receptivity variables and possible vector species; and
- vulnerability level and conclusion from an entomological risk assessment (ERA) or entomological investigation (EI).

Table 2. Receptivity assessment used in Malaysia

No.	Parameters	Weighting factor	NOTE
1	PAKEPA (preliminary ecological assessment)	Suitable	Select one
		Not suitable	
2	Discovery of <i>Anopheles</i> spp. larvae	• In permanent pool	
		• In non-permanent pool	
3	Distance from positive breeding to household	• <2 km	
		• >2 km	
4	Discovery of <i>Anopheles</i> spp. resting outdoor	• Density >2 pmh	Select one
		• Density <2 pmh	
5	Discovery of <i>Anopheles</i> spp. resting indoor	• Density >2 pmh	Select one
		• Density <2 pmh	
6	Discovery of <i>Anopheles</i> spp. biting outdoor	• HBR >1 pmh	Select one
		• HBR >1 pmh	
7	Discovery of <i>Anopheles</i> spp. biting indoor	• HBR >1 pmh	Select one
		• HBR >1 pmh	
8	Discovery of parous <i>Anopheles</i> spp.	• Parity rate ≥80%	Select one
		• Parity rate 30–80%	
		• Parity rate ≤30%	
9	Discovery of <i>Anopheles</i> spp. with sporozoite and/or oocyst	10	

pmh: per man hour (Excerpt from presentation by J. Jelip).

Since it is almost impossible to measure receptivity for each of the 55 000 localities in Malaysia, those with similar ecology are grouped together and considered “one ecosystem”. One locality within the ecosystem is then selected as the reference, and the PAKEPA is conducted there. The PAKEPA classification for the reference locality is then generalized to all localities within the ecosystem. Ecosystems are dynamic; hence, constituent localities can alter over time as a result of ecological changes.

Entomologists used PAKEPA classification of a locality to determine the need for a complete ERA/EI; these assessments are conducted by the health staff in charge of the respective area, with validation by the entomologist. In Malaysia, there are currently 114 entomologists working at headquarters (4), state (43) and district (62) level, or in the Institute for Public Health (3) or Public Health Laboratory (2); the presence of this professional staff underpins the system.

A preliminary study was conducted in 129 localities in Sabah State to pretest this receptivity assessment tool. Based on data from this preliminary study, thresholds were identified to stratify the localities. The thresholds were decided in such a way that a manageable number of localities were classified as having a low, medium or high receptivity index, with low being less than 6, medium being 6–17 and high being greater than 17.

Appropriate vector-control strategies were identified based on the receptivity index, such as larval source management to be applied where PAKEPA is equal to 2, and where there are *Anopheles* in permanent and non-permanent pools that are found within 2 km of a household. IRS is applied where *Anopheles* spp. are found resting or biting indoors (irrespective of density), or where *Anopheles* spp. are discovered harbouring sporozoites or oocysts. ITNs or IRS are likewise recommended under these conditions, as well as where the parity rate is equal to or greater than 80%. Personal protection measures and insecticide-treated curtains are recommended in the case of outdoors resting or biting *Anopheles* spp., and where sporozoites or oocysts have been found. Space spraying is also used where higher densities of vectors and sporozoites or oocysts are found, irrespective of whether this is for mosquitoes found resting or biting indoors or outdoors.

Measurement of vulnerability

Parameters included in the vulnerability index are indicated in Table 3; each is assigned a weighting factor, and an overall receptivity score is then generated. A preliminary study was conducted in 957 localities in Sabah State to pretest this vulnerability tool. Based on the observed data from this preliminary study, thresholds were identified to stratify the localities; thresholds were decided in such a way that a manageable number of localities are classified as having a high vulnerability index, with low being less than 21, medium being 21–26 and high being greater than 26.

Table 3. Vulnerability assessment used in Malaysia

No.	Parameters	Weighting factor	Possible scenario
1	Malaria case with gametocyte in the previous 6 months	10	
2	Imported human malaria in the previous 6 months	9	
3	Locality with high risk of malaria	8	• Plantation, logging • Aboriginal settlement (Peninsular Malaysia) • Penan settlement • Refugee camp or detention camp • Illegal entry routes
4	Presence of illegal immigrant population (PATI) from malaria endemic countries	7	
5	Presence of legal immigrant population (PADI) from malaria endemic countries	6	
6	Presence of local high-risk population	5	• Aboriginal community • Penan community • People living in houses with incomplete walls • People with no access to health services • People without public transportation facilities
7	People involved in high-risk activities	4	• Hunting • Fishing • Jungle recreation activities • Security force • Wildlife protection • Forestry • Land surveyor
8	Local people working in high-risk sector in malaria endemic countries	3	• Logging • Road construction • Dam construction • Mining
9	Localities at immediate border with malaria endemic area	2	
10	Construction projects of more than 2 months duration	1	

Excerpt from presentation by J. Jelip.

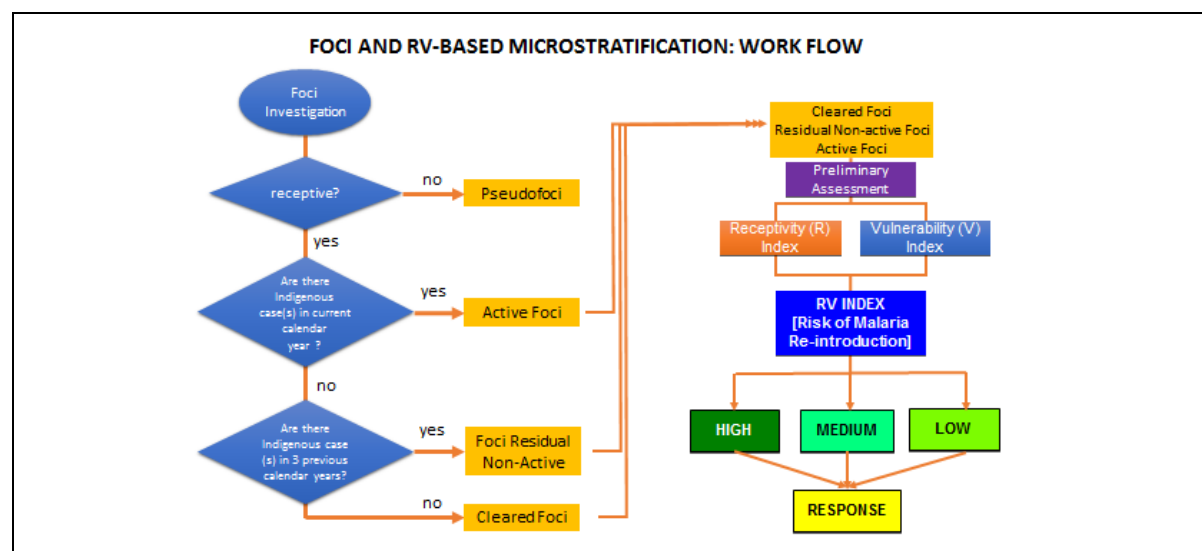
Stratification of reintroduction risk

The receptivity and vulnerability indices are multiplied together to produce a stratification of reintroduction index. This is then used to classify the malaria reintroduction risk as low (≤ 2), medium (3–5) or high (≥ 6).

An overview of the work flow for stratification based on the receptivity and vulnerability assessments is presented below (Fig. 10). The foci type and reintroduction risk index are then used to determine the appropriate interventions (Table 4).

Information to determine receptivity and vulnerability is entered online using MyFoci v2.0 software,¹ which automatically calculates some indices (e.g. receptivity, vulnerability and reintroduction matrix) and hence appropriate interventions.

Fig. 10. Work flow of foci and receptivity/vulnerability-based microstratification



Excerpt from presentation by J. Jelip.

Table 4. Response based on foci type and reintroduction risk index

TYPE OF FOCI	RV INDEX	INTERVENTIONS
Pseudofoci	—	- Case management (imported or relapse) - Passive case detection
Active foci	HIGH	
	MEDIUM	
	LOW	
Residual non-active foci	HIGH	- Epidemiological surveillance - Consider active case detection - Vector control (continuation) - Entomological risk assessment after six cycles of vector control
	MEDIUM	
	LOW	
Cleared foci	HIGH	- Epidemiological surveillance - Integrated vector management - Epidemic risk assessment every two cycles of vector control
	MEDIUM	
	LOW	- Case management (imported or relapse) - Passive case detection

4.3.2 Bhutan

Mr Rinzin Namgay presented on receptivity and vulnerability assessments for Bhutan, which has experienced a significant decline in malaria since a peak of 39 852 cases in 1994. In 2017, only 62 cases were reported. Most of the cases from 2013 to 2016 were non-Bhutanese; however, of the 62 cases in 2017, 38 were Bhutanese and 24 were non-Bhutanese. There has been no local transmission of *P. falciparum* in Bhutan since 2016. Contributing to the marked reduction in the number of malaria

¹ See <http://myfoci.jknsabah.gov.my>

cases were the massive deployment of rapid diagnostic tests (RDTs) and artemisinin-based combination therapies (ACTs) down to community level, and large-scale LLIN campaigns with two rounds of focal IRS, along with enhanced malaria surveillance. By 2010, the country had moved into the elimination phase. Bhutan is progressing well towards the stated goal of the National Malaria Strategic Plan 2015–2020, which is to interrupt indigenous transmission by 2018. However, there is an example from Samtse wherein after 5 years with no transmission, local transmission recommenced; this indicates how malaria can resurge.

Measurement of receptivity

The parameters considered in the receptivity assessment in Bhutan are shown in Table 5. The programme has three entomologists and five insect collectors, with malaria technicians in health centres being responsible for basic entomological services. The border populations live in close proximity and intermingle; therefore, a division by administrative boundaries makes little biological sense. The limits of malaria transmission are probably due to the interaction of extrinsic incubation period (EIP) and the longevity of the vectors.

Table 5. Malaria receptivity and its relevance and mitigation in Bhutan

Receptivity index	Relevance	Mitigation measures
Topography: low altitude, plain, forested foothills	Yes for proliferation and vectorial roles	High LLIN and IRS coverage in risk areas
Climate: more rain, humid, favourable temperature	Yes for vector proliferation and survival; people do not use nets during the hot season	High LLIN and IRS coverage in risk areas with IEC campaigns
Environment alteration: development, forestation or deforestation	Yes for vector proliferation and transmission	Control coverage and IEC
Border malaria: sporadic cases appear in border villages only	Yes – no reservoirs detected by RACD nor any imported cases to link	In addition to LLIN and IRS, fogging is done
Housing type: especially among people with a low income, migrant workers, cattle herders and crop guards	Yes for more human–vector contact	LLIN coverage; IRS is often not applicable in temporary structures

IEC: information, education and communication; IRS: indoor residual spraying; LLIN: long-lasting insecticidal net; RACD: reactive case detection (Excerpt from presentation by R. Namgay).

Receptivity assessments indicate that seven districts fall in the high receptivity category, nine have pockets of receptivity and four have no receptivity for malaria. In terms of vulnerability, a number of vulnerable population types have been identified, along with their relevance to malaria transmission and mitigation measures for their protection from malaria (Table 6).

Table 6. Malaria vulnerability and its relevance and mitigation in Bhutan

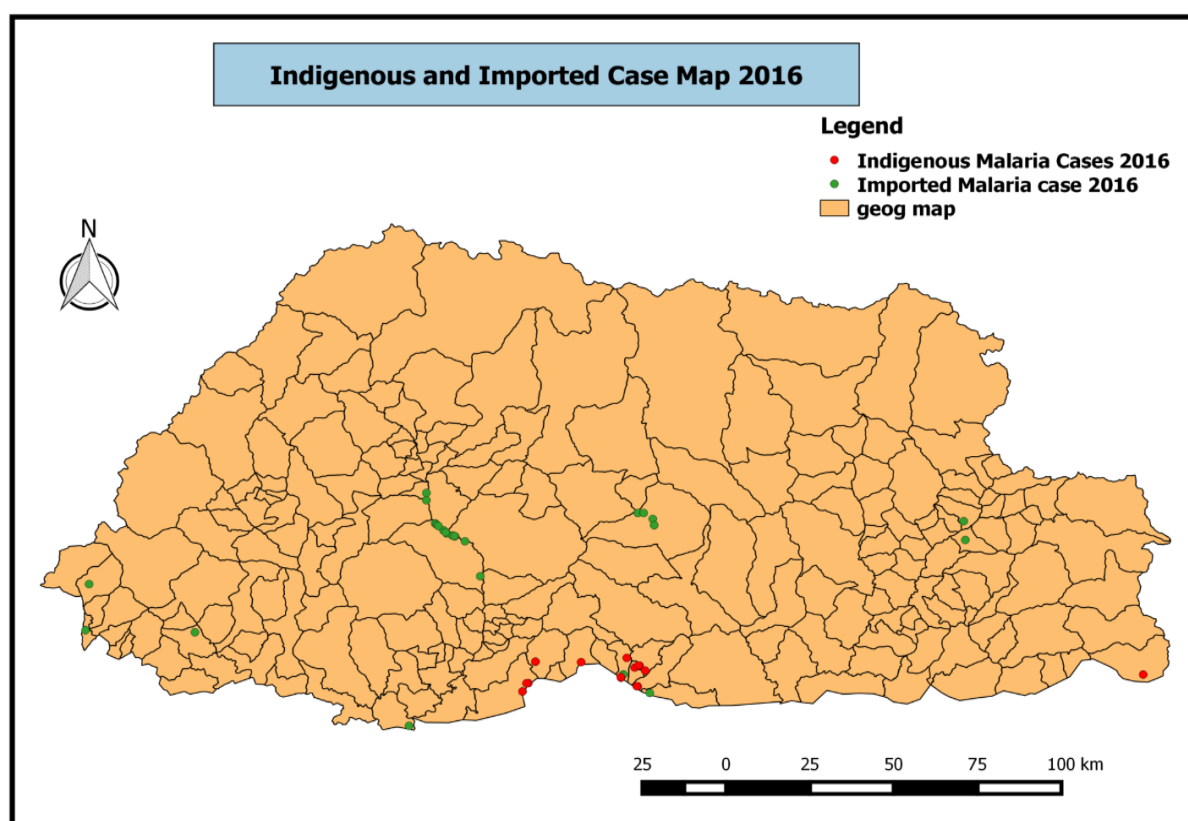
Vulnerable population type	Relevance	Mitigation measures
Migrant workers: hydroelectricity projects, public and private constructions (contractors bring workers in batches and are responsible for them getting screened)	65 000–70 000 per year (as per MoL)	• Mandatory screening at entry points by eight private clinics and report to VDCP • Rescreening at work site by health centres and VDCP • LLIN provision
Tourists: mostly to northern Bhutan	Unknown	No screening till now
Outgoing populations: UN peace keepers, students, business people, workers, pilgrims to India and Nepal	Programme trying to obtain information from relevant sources	Screening during return and rescreening after 1–2 weeks will be established
Uniform patrolling personnel: army, police, forest guards and community peace keepers		Odorous repellents supplied by programme
Visits: family visits across the border	Unknown	No screening unless reported to health centres

LLIN: long-lasting insecticidal net; MoL: Ministry of Labor; UN: United Nations; VDCP: Vector-borne Disease Control Programme (Excerpt from presentation by R. Namgay).

Anyone can access free malaria diagnosis, treatment and 3 days admission in health centres in Bhutan. Day workers and other population along border areas are registered as N3 in the malaria register, since they have not spent nights in Bhutan. However, these populations often do not consent to admission for 3 days, and cannot be traced for the requisite follow-up required to day 42. Therefore, completion of the course of treatment is often compromised.

The number of workers screened at the entry point by private clinics was outlined; the total was 2057 and 2537 in consecutive years, with wide variation in the number originating from neighbouring regions of India and elsewhere. Private clinics do not treat malaria; hence, all positive cases were referred to public health facilities. Geomaps of the number of indigenous and imported cases were presented for 2016; they indicated that imported cases were predominantly from migrant workers from hydroelectricity projects in Punatsangchu I, Punatsangchu II, Mangdachu and Kholongchu (Fig. 11).

Fig. 11. Geomap of indigenous versus imported cases of malaria in Bhutan, 2016



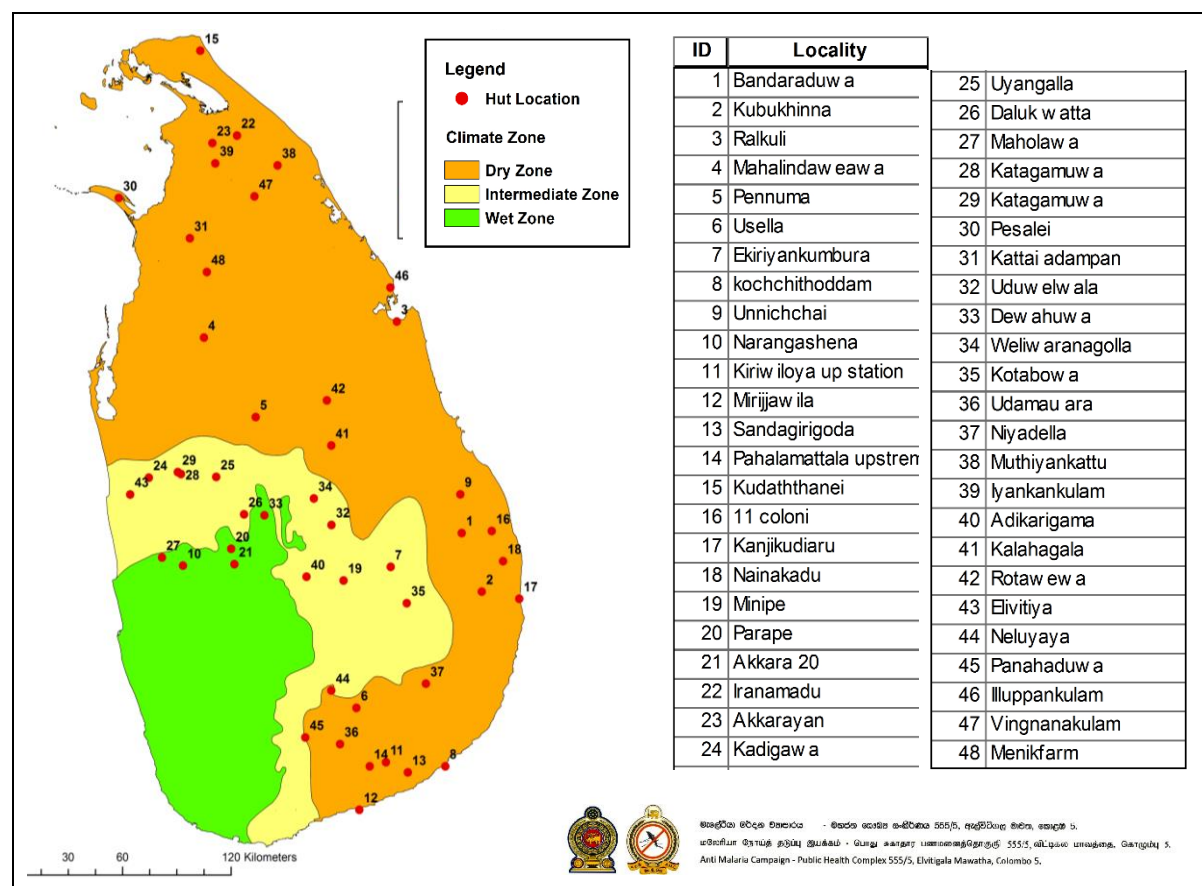
Excerpt from presentation by R. Namgay.

4.3.3 Sri Lanka

Ms Mihirini Hewavitharane presented on the experience from Sri Lanka on the assessment of receptivity and vulnerability for prevention of reintroduction of malaria. There has been no local transmission of malaria in Sri Lanka since October 2012, with the country certified as malaria free in 2016. Historical malaria transmission patterns in the country are considered a reflection of receptivity. Malaria was typically endemic in the dry and intermediate rainfall zones of the country with the wet zone becoming prone to malaria during exceptional dry conditions caused by a failure of the monsoons. The climatic pattern is determined by the monsoonal wind patterns in the surrounding oceans; 55% of the rainfall is monsoonal and the mean annual rainfall is 900–6000 mm. Based on the rainfall patterns and amount, the country is divided into three main climatic zones: dry, intermediate and wet zones. The climate of Sri Lanka is conducive to vector mosquito breeding and malaria transmission.

Malaria vectors in Sri Lanka have diverse breeding habitats, resting and biting behaviours, and seasonal patterns of abundance. They therefore vary in their potential for transmission of malaria. The principal malaria vector species present in the country has been *An. culicifacies*, with *An. subpictus* the secondary vector and *An. annularis* and *An. varuna* potential vectors. *An. stephensi* was recently found to be present in six districts of Sri Lanka. Extensive entomological information is collected on a routine basis in the country, through sentinel surveys, spot surveys and case-based reactive surveys. Sentinel sites are distributed throughout the three zones of the country, with sites in the wet zone positioned along the margins with the intermediate zone (Fig. 12).

Fig. 12. Distribution of entomological sentinel sites in 2017



Excerpt from presentation by M. Hewavitharane.

Measurement of receptivity

Entomological tools and indicators monitored in Sri Lanka to determine receptivity for prevention of reintroduction are:

- *Anopheles* spp. composition and densities (including seasonal fluctuations) measured monthly by larval surveys, cattle-baited trap collections, cattle-baited hut collections, indoor hand collections and pyrethrum spray catches;
- larval density by aquatic habitats measured via larval surveys;
- vector species behaviour in terms of indoor/outdoor resting measured via hand collections indoors and outdoors and pyrethroid spray catches;
- vector species human biting behaviour in terms of endophagy/exophagy and human biting rate measured monthly via human landing catches indoors and outdoors;
- mosquito age as indicated by parity rates for mosquitoes collected by human landing catches and ovary dissections;
- vector incrimination as indicated by sporozoite detection via salivary gland dissection and molecular techniques;
- insecticide resistance from knock-down and corrected mortality rate in susceptibility tests at sentinel sites; and
- bio-efficacy levels of insecticides used in vector-control interventions via bioassays on sprayed walls or nets.

The mean larval densities and adult densities of *An. culicifacies* in different districts have been used as an indication of receptivity, to identify receptive and non-receptive districts following elimination. Even after elimination of malaria some districts remain highly receptive, while some have moderate to low levels of receptivity. This information has been used for risk management and resource assignment for the districts.

However, it was well acknowledged that programmes require a quantitative measurement for receptivity for application in the prevention of reintroduction phase. This should support reorientation towards sustaining malaria eliminated status through a suitable entomological surveillance system which supports the decision-making. The large quantity of entomological data collections required reorganization in a way that would help in the assessment of malariogenic potential, and to reorient entomological surveillance and response. This requires identification of the geographical distribution and relative density of vector species and, particularly, identification of newly introduced vector species. It is also important to determine whether potential vectors have regained high vectorial efficiency in receptive areas, and to track the reaction of vectors to vector control to recommend measures to prevent reintroduction.

A workshop was therefore convened to provide guidance on the broad principles of entomological surveillance during the prevention of reintroduction of malaria phase and to supply information needed to produce risk assessments on malaria in receptive and vulnerable areas (Table 7). It also aimed to provide recommendations in the development of implementation strategy for routine entomological surveillance, and to initiate risk mapping. The outcome was a two-staged approach: it involved assessment of the history of malaria transmission (including outbreaks) and relative abundance of vectors and potential vectors (larvae and adults) and other entomological data collected in the last 3 years in order to generate a preliminary stratification of the areas according to receptivity risks (of high, medium and low); and the update of the map based on entomological data collected during spot checks (reactive), during spot checks (proactive) conducted in high, moderate and low vulnerable areas with no entomological data, and from spot checks at sites where vulnerability risk has increased.

Table 7. Receptivity measuring guide for Sri Lanka

No.	Factor	Possible scenario	Weighting
1	Presence of potential breeding places – primary, secondary or potential vectors	Permanent Semi-permanent Temporary Unavailable	3 2 1 0 (max. 6)
2	Discovery of the primary vector – <i>An. culicifacies</i> (larva) during the period of previous year	Yes No	3 0
3	Discovery of the secondary vector – <i>An. subpictus</i> (larva) during the period of previous year	Yes No	2 0
4	Discovery of the potential vector – <i>An. varuna</i> , <i>An. annularis</i> , (larva) during the period of previous year	Yes No	1 0
5	Discovery of the primary vector – <i>An. culicifacies</i> (adult) during the period of previous year	Yes No	3 0
6	Discovery of the secondary vector – <i>An. subpictus</i> (adults) during the period of previous year	Yes No	2 0
7	Discovery of the potential vector – <i>An. varuna</i> , <i>An. annularis</i> , (adults) during the period of previous year	Yes No	2 0
8	Human biting behaviour of primary vector – <i>An. culicifacies</i>	Positive Negative	4 0

No.	Factor	Possible scenario	Weighting
9	Human biting behaviour of secondary vector – <i>An. subpictus</i>	Positive Negative	3 0
10	Human biting behaviour of potential vector – <i>An. varuna</i> , <i>An. annularis</i>	Positive Negative	2 0
11	Resting behaviour of primary vector – <i>An. culicifacies</i>	Endophilic Exophilic	3 2
12	Discovery of parous vectors	Yes No	2 0
13	Conducive environment conditions or presence of developmental projects creating more breeding sites	Yes No	2 0

Excerpt from presentation by M. Hewavitharane.

Information from receptivity measurements as in Table 7 was used to generate a vulnerability level of high, moderate and low risk (Fig. 13a), where low is less than 4, medium is 4–8 and high is greater than 12.

If infected *Anopheles* spp. are detected then receptivity categorization should be “high”, regardless of other factors. Similarly, if life stages (larva or adult) of *An. stephensi* are detected, receptivity categorization should be “high”, regardless of other factors. If more than one possible scenario is present, then all are considered for the weighting.

The approach presented is an initial attempt to quantify receptivity, but further technical guidance and refinement may be needed. It took into account only the presence of vectors, vector bionomics and environmental factors conducive to vector breeding and abundance. Thresholds were identified based on weighted measures and varied from 0 to 36; however, the resulting stratification and assessment approach have not been validated. The stratification is currently conducted by Sri Lanka’s MoH, although it would be preferable for this to be devolved to the locality. At present, there are also no comprehensive entomological surveillance data available from the previously nonendemic yet currently highly vulnerable areas, such as Western Province.

Measurement of vulnerability

In Sri Lanka, the principal evidence in favour of a case being imported is considered to be one of the following:

- travel history overseas to a malaria endemic country in the recent past;
- a past history of malaria when the person was overseas, in which case a relapse would also be considered if the malaria was *P. vivax* or *P. ovale*;
- absence of a malaria infection or evidence of malaria transmission in the location of the patient’s residence in Sri Lanka after the patient’s return, particularly based on the case investigation and entomological surveillance conducted in response to a case; or
- a malaria infection in a co-traveller.

Risk management requires an assessment of vulnerability for a given area in a certain period of time. Therefore, steps were taken to assess vulnerability, taking into account the importation of malaria cases, as well as high-risk groups in the country after malaria elimination. An effort to quantify vulnerability in the country in a more standard manner was attempted in late 2017 (Table 8).

Table 8. Vulnerability measuring guide for Sri Lanka

No.	Factor	Weightage	Possible scenario (and weightage)
1	Number of imported malaria cases in the previous 3 years	0.5 per case	In the absence of specific guidelines for countries in elimination or prevention of reintroduction on effective ways of vulnerability mapping, the geographical distribution of imported malaria cases over the recent years has been considered as a proxy measure
2	Locality with high risk of importing malaria	4 (maximum)	• Ports of entries (2) • Illegal entry routes (2) • Tourist areas (1) • Asylum camps (1) • Detention camps (1) • Resettlement areas (1) • Camps for security forces (1)
3	Presence of immigrant population from malaria endemic countries	5	• Illegal (3) – fishers, agricultural workers from India, etc. • Legal (2) – foreign workers
4	Local people working in high-risk sector in malaria endemic countries	4 (maximum)	• Gem traders and miners (2) • Businesspeople (1) • UN peace-keeping missions (1) • Professionals (1)
5	Local people returning from malaria endemic countries within 1 year	2	• Pilgrims (1) • Returnees from safari (1)
6	Localities at close proximity to India – risk of importing infected mosquitoes	2	Coastal borders with anchorage facilities

Excerpt from presentation by M. Hewavitharane.

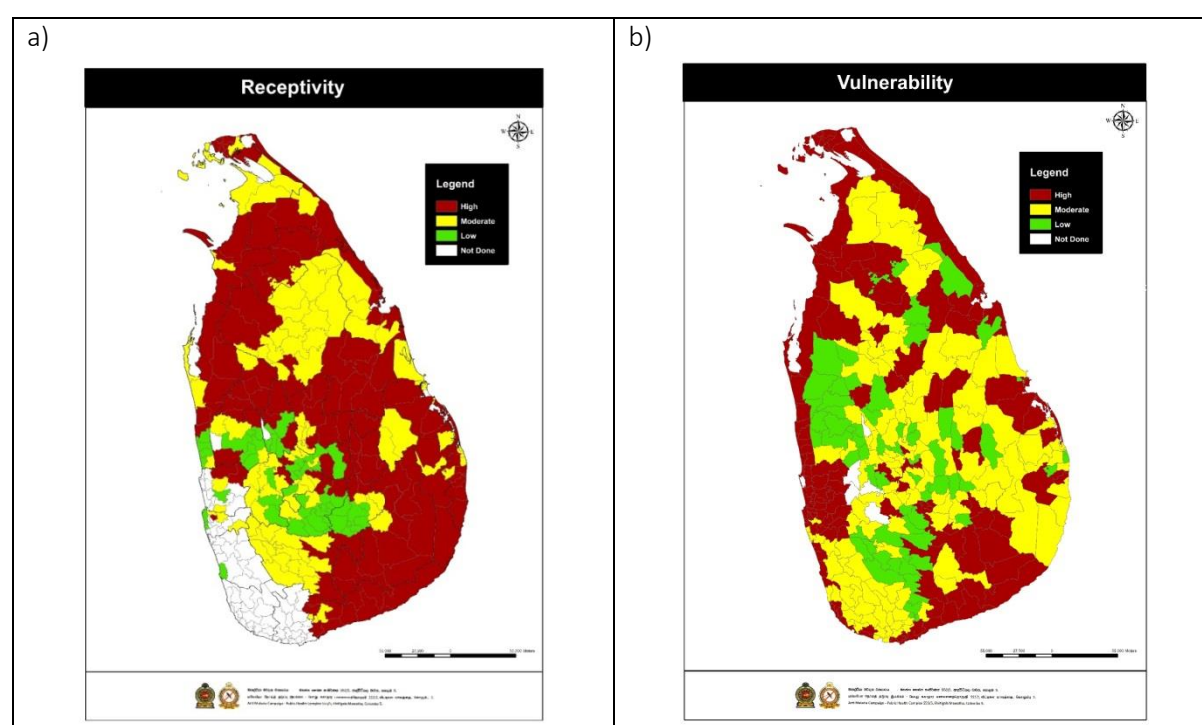
Most of the imported malaria cases were identified as Sri Lankans returning from travel to malaria endemic countries, with foreign nationals coming to Sri Lanka constituting 28–38% of imported malaria cases during the past 5 years. Most cases of imported malaria were contracted in South-East Asia, with India as the single largest source. Travel is quite extensive between India and Sri Lanka, owing to Sri Lankan business travellers, pilgrimage and Indian migratory labour. Pakistan contributed to imported malaria, with almost all cases being asylum seekers. The African continent accounted for most of the cases during the past 2 years, with Sri Lankans travelling there for business, tourism and peace-keeping missions; there were also cases imported by foreigners. Within Sri Lanka, most of the imported cases were reported from the Western Province, which is a previous nonendemic area. This is in contrast to the districts reporting indigenous malaria in 2011 and 2012. Thus, it can be concluded that highly vulnerable districts and receptive districts are quite distinct, with little overlap between them.

The identified high-risk groups for Sri Lanka were foreigners, especially those from India (workers), Pakistan (asylum seekers) and China (workers); Sri Lankans with a travel history to a malaria endemic country; travellers returning from Africa for occupation (gem business) and leisure tours; travellers returning from Asia (e.g. pilgrims, businesspeople or those travelling for study or leisure); armed forces personnel returning from peace-keeping missions and training; and Sri Lankan refugee returnees from India.

Information from vulnerability measurements as in Table 8 was used to generate a vulnerability level of high, moderate and low risk (Fig. 13b), where low is less than 2, moderate is equal to 2 or greater but lower than 4, and high is equal to 4 or greater.

A number of challenges and gaps were identified for vulnerability assessments. Imported malaria has been considered as a reasonable proxy for measuring vulnerability, but it requires a higher degree of vigilance. It requires sustained efforts for an active surveillance strategy to detect imported cases, strong awareness of the system among health staff and communities, involvement of international partnerships, intersectoral collaboration between local institutions, field vigilance and sustained financial commitment. However, there are difficulties with locating high-risk groups such as pilgrims.

Fig. 13. Map of a) receptivity and b) vulnerability for Sri Lanka



Excerpt from presentation by M. Hewavitharane.

Composite index

A composite index was developed that combined the receptivity and vulnerability index (Table 9).

Table 9. Classification of Sri Lanka MoH areas according to receptivity and vulnerability

	Receptivity		
Vulnerability	Low	Moderate	High
Low	(Low risk)	(Low risk)	(Moderate risk)
Moderate	(Low risk)	(Moderate risk)	(Moderate risk)
High	(Moderate risk)	(Moderate risk)	(High risk)

Excerpt from presentation by M. Hewavitharane.

Periodic updates of receptivity and vulnerability assessments are required because of changes in the ecosystem. There is a need to develop and validate thresholds that inform appropriate stratification, and it would be best if such efforts were guided locally rather than centrally. Further technical guidance and refinement are required.

4.4 Proposed methods for assessing infectivity

Elimination of malaria vectors is generally unattainable; hence, the strategic objective of vector control is conventionally to reduce vectorial capacity below the threshold for sustained malaria transmission. Despite the interruption of transmission of malaria in many countries, and from extensive areas within other countries, *Anopheles* malaria vectors remain entrenched throughout most of their natural ranges. Endemic anthropophilic *Anopheles* spp. mosquitoes are mostly susceptible to exotic strains of human malarias, although some *Anopheles* show refractory parasite–vector interactions, depending on the imported *Plasmodium* species and strain.

Such parasite–vector specificities influence the receptivity of an area to local malaria transmission in the event of an imported infection. The phenomenon of “anophelism without malaria” was recognized by early malariologists, whereby *Anopheles* mosquitoes existed in regions that were not malarious, although they could have been, given the climatic and ecological conditions. Information on these specificities may therefore be of use in guiding programmatic responses, such as to de-prioritize vector control where an imported case is caused by a parasite strain to which local vectors are known to be refractory.

4.4.1 Review of mosquito susceptibility to imported exotic malaria parasites

Professor Graham White presented results from a systematic review of literature on the susceptibility of endemic *Anopheles* spp. mosquitoes to imported exotic strains of human malaria parasites. This susceptibility, or potential to become infective, is termed “vector competence”, and is defined as the “*ability of the mosquito to support completion of malaria parasite development after zygote formation and oocyst formation, development and release of sporozoites that migrate to salivary glands, allowing transmission of viable sporozoites when the infective female mosquito feeds again*” (1). The review catalogues species reports from various countries classified as malaria endemic, approaching elimination or malaria free, and includes a summary table of examples of the range of *Anopheles* competence to human malaria parasites. A concise overview of *Anopheles* competence or incompetence to *P. falciparum* and *P. vivax* originating from different malaria zones was also presented (Annex 4).

Professor White stressed the importance of understanding the bionomics and behaviour of all the vector species responsible for *Plasmodium* transmission to humans, rather than reliance on information generalized to species complex or group level. For vector control and surveillance, it is essential to distinguish between similar species having differential vectorial capacity or contrasted vector competence.

The ERG discussed the alarming recent expansion of *An. stephensi* as an urban malaria vector from the Indian subcontinent to Sri Lanka and the African continent, first in Djibouti and then in Ethiopia, and indicated that this issue requires further consideration and potential intervention by WHO.

Because the 12 main malariological regions are defined by their competent species of malaria vectors, the ERG concluded that there are no broadly applicable demonstrated regional incompatibilities between human malaria parasites and their vector species. Hence, the working assumption should be that none of the proven malaria vectors are refractory to specific *Plasmodium* parasite strains. Further investigations of interactions between strains of *Plasmodium* and *Anopheles* spp. are warranted; if clear cases of incompetence or low competence are identified, this may be informative for decision-making on the level of response required to decrease vectorial capacity.

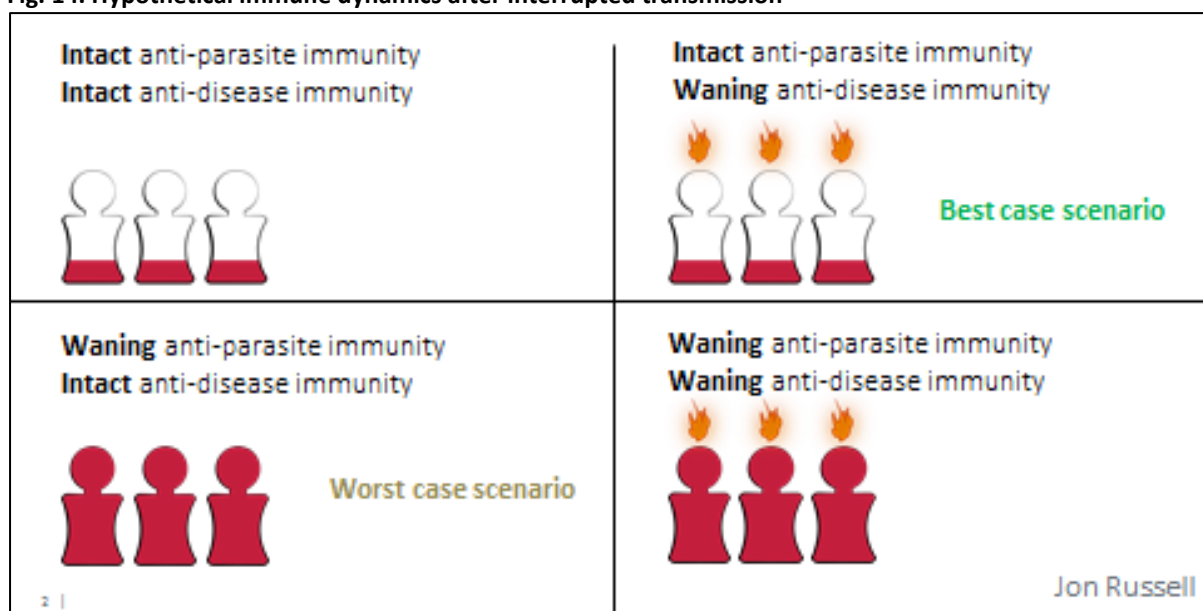
The ERG was informed of the approach taken in China, whereby the response to imported cases caused by *Plasmodium* spp. originating from countries of South-East Asia is given higher priority than the response to those imported from Africa, putatively based on differential competence of the main vector *An. sinensis*. The scientific evidence used to inform this approach was not reviewed by the ERG. Therefore, it was recommended that a case study be conducted to examine and document the evidence for refractoriness of *An. sinensis* to Afrotropical malarias, such as the well-established incompetence of European *Anopheles* spp. to transmit African strains of *P. falciparum* (31, 32).

4.5 Stratification and intervention mixes

Dr Jaline Gerardin presented on the effectiveness of intervention mixes, as stratified by vulnerability and receptivity. This included a consideration of hypothetical immune dynamics after the interruption of transmission, based on two predominant components of malaria immunity: anti-parasite immunity (or immunity to high parasite density) and anti-disease immunity (or immunity to developing symptoms, even though infected) (

Fig. 14). These types of immunity are considered separately here to isolate their impact on human infectiousness (anti-parasite immunity) and the ability of the surveillance system to detect new infections (anti-disease or anti-symptom immunity). If both components of immunity remain intact through elimination, then it would be expected that an outbreak would result in multiple lower density infections for which individuals are largely asymptomatic. Conversely, if both components of malaria immunity wane through elimination, then it would be expected that higher density infections would result in symptomatic cases. Noting that immunity is complex, in fact the result could also be low-density infections leading to visible symptoms, or high-density infections leading to numerous asymptomatic individuals.

Fig. 14. Hypothetical immune dynamics after interrupted transmission



Excerpt from presentation by J. Gerardin.

Analyses based on earlier data from Garki, Nigeria, indicated that asexual parasite densities for new infections tend to increase with an increase in the malaria free interval (comparing <80 days with >365 days) for individuals aged more than 5 years, 5–11 years and more than 11 years (33). In this analysis, individuals are considered to experience a “malaria free interval” when they are slide negative during a routine cross-sectional prevalence survey. However, it is possible these individuals

may not be malaria free but rather free from patent infection, or that they may be experiencing short infections during the 1 month between surveys. Analyses using recent field data from Tororo, Uganda, did not identify a clear trend in the detection of new infections with fevers following a malaria free interval of between 0 and 600 days, for those aged more than 5 years, 5–11 years or more than 18 years (34). Although data were relatively sparse (especially for adults) and further investigations are underway, this finding indicates that new infections may not be significantly more likely to be symptomatic after a malaria free interval of less than 2 years. Therefore, should importations happen in an area with previously high levels of population immunity, transmission may be fairly easily re-established owing to individuals who are largely asymptomatic but have higher density infections and are more infectious (i.e. the bottom left quadrant of

Fig. 14). Such immune dynamics in the short term (i.e. 2–3 years) could present operational challenges to maintaining elimination, but much more evidence is needed.

Results from a modular agent-based model using Epidemiological MODelling software (EMOD) were presented (35). Used for simulation modelling of other diseases (e.g. HIV and tuberculosis), the malaria model was developed to support data-driven malaria control and elimination efforts. It combines detailed vector population dynamics and interactions with human populations, and includes microsimulations for human immunity and within-host parasite dynamics. The model builds on the work of Ross and MacDonald, leverages the Garki model, and incorporates current modelling efforts to model multiple vector species simultaneously interacting with a human population. Simulation modelling presented drew on data from the Lake Kariba region, which borders Zambia and Zimbabwe, because this represents a setting with diverse transmission dynamics for which a relatively rich data set is available (36, 37).

Outcomes of the simulation modelling from the Lake Kariba region indicated that in an area with historically limited vectorial capacity, good case management (i.e. 50–75% of symptomatic cases treated) alone was sufficient to prevent resurgence, and fair case management (i.e. 50% treatment rate) could be compensated by good reactive case detection (i.e. 50% of treated cases receive follow-up). However, in an area with a historically high transmission before recent elimination, vector control must be maintained along with continuing excellent case management rates and reactive case detection. Modelling also indicated that reactive IRS may be as effective as, or more effective than, routine IRS, even when it results in 10-fold fewer houses being sprayed. Treatment rates, vector-control coverage and appropriate radius of reactive activities necessary to maintain elimination in these areas depend on the degree of household clustering, in that denser areas require more intense interventions.

It was also indicated that the current use of “asymptomatic individuals” is not useful from a programmatic perspective, because it is difficult to define given differences in factors such as what would be considered “symptoms” (e.g. is this limited to fevers only or does it consider other effects such as anaemia), the time of day of testing and health care seeking behaviour.

5. Conclusions

The ERG considered malariogenic potential to be an important concept and noted the urgent requirement for a clear definition of the term and of its components. In particular, it was noted that the definition of “receptivity” as appears in the WHO malaria terminology document is ambiguous and circular. The ERG also felt that use of the term “vulnerability” is at odds with its use in common parlance in the fields of health and development. The ERG discussed the appropriate scope and wording of definitions, and reached consensus on the proposed definitions. These definitions are included below, and in the recommendations section.

5.1 Receptivity

In terms of assessing receptivity, the ERG identified three methods based on the evidence presented:

- historical data
- entomological composite methods
- R_0/R methods.

Discussion points and conclusions related to each of these methods, as well as their utility in determining malariogenic potential, are outlined below.

Historical data

Many programmes use data from recent years to assess receptivity of areas as elimination is approached, and to prioritize surveillance to prevent re-establishment following malaria elimination. Data from more than 3 years ago are not used for receptivity estimates in Bhutan, Malaysia and Sri Lanka because it was indicated by the presenters that older data may not accurately reflect the current situation owing to ongoing changes in the ecosystems (including health systems). The ERG agreed that the appropriate duration (i.e. number of years) of data to be used will depend on the context and changes in the ecosystem, and should be decided upon by the individual programme. However, the ERG felt that older data can provide a useful baseline for assessment of receptivity. Data should be examined in the context of the interventions in place at the time and how these have changed since, and should consider changes in the ecosystem. Examples of such data types include entomological data, API, parasite prevalence and case counts; such data would need to have been collected before the implementation of current control measures to be informative about what might happen in the absence of such interventions. Data from serological surveys may be useful, although this approach has not yet been standardized and validated – a review of the evidence from such surveys was deemed to be beyond the scope of the meeting.

Entomological composite methods

The examples presented by Malaysia and Sri Lanka were developed by countries with significant entomological capacity. Data collected included adult vector occurrence and density; immature vector aquatic habitat availability and occupancy, and larval density; adult vector biting and resting behaviour; insecticide resistance frequency and status; and sporozoite rates. However, the ERG noted that this level of entomological surveillance may not be realistic in all countries undertaking prevention of re-establishment of malaria activities. On the basis of the evidence considered, the ERG concluded that a smaller number of key entomological indicators should be monitored as a minimum, in the context of prevention of re-establishment. These indicators are described in *Malaria surveillance, monitoring & evaluation: a reference manual (2)*; they are vector adult occurrence (high priority), resistance (moderate priority) and aquatic habitat surveys (but only if larval source management is considered or ongoing). It was also noted that investigating the identity of principal and secondary vectors should be a priority in settings where vector incrimination has not been comprehensively conducted or where such studies date back to the control phase of the programme. Programmes should also consider reducing insecticide resistance monitoring frequency to once every 2 years in prevention of re-establishment settings. Overall, it was thought that further investigation into key components of vectorial capacity following earlier work by Dye (16) would be valuable, to further focus entomological surveillance efforts.

Once transmission has been interrupted, adjustment of entomological surveillance strategies will be required to guide appropriate response, such as selection of vector-control intervention (e.g. selection of insecticides for IRS depending on resistance status). This is especially important if a programme is considering scaling back vector-control interventions based on enhanced capacity for focal response and a review of the malariogenic potential of the area.

The ERG felt that baseline entomological data can also be informative for identifying high-risk areas but that the selection of sites for ongoing surveillance should be further informed by changes in the ecosystem and context. The appropriate sampling frame (i.e. number and location of sites) for a representative sample will depend on the context and available resources. The ERG indicated that clearer WHO guidance on sentinel site selection and frequency or timing of surveillance would be of use in ensuring that the appropriate approach and extent of monitoring is undertaken. Specific situations or concerns may warrant intensified surveillance to guide response, such as if invasive species are suspected or identified, as for *An. stephensi*.

R₀/R_e methods

The methods of estimating risk from the basic reproductive number and the effective reproductive number capture both vector and human aspects. Counts of imported versus locally acquired cases (and their ratio) were noted as being useful where the quality of surveillance data is high. Probabilistic methods can be used to link local cases to imported cases based on plausible distance in time and space, to determine the risk of re-establishment. However, a more standardized definition to classify imported cases is required for these methods to provide estimates of risk that can be compared between countries.

Selection of receptivity measures

The ERG noted that there has been no validation or comparison of the three potential measures of receptivity, nor an examination of their complementarity. An aggregate approach considering historical transmission data, entomological data and calculation of effective reproductive numbers from the ratio of imported to indigenous cases importation risk may be required, even within a single country. Guidance on the minimum quality of data required would be useful. The ERG indicated that further development of these methods is required to make them applicable and informative for programmatic use.

5.2 Importation risk

Because “vulnerability” also refers to the potential for being harmed and is used in public health to refer to disadvantaged or at-risk populations, the ERG recommended that the term should not be used to refer to importation risk, especially when a clear and unambiguous term is available.

The ERG acknowledged that there are multiple methods and measures for importation risk, the relevance of which will be heavily dependent on the local context. However, it is important that the unit of interest for importation risk – including cross-border and subnational movement – be the same as or able to be correlated to the unit at which receptivity is assessed. The primary measure should be case-based surveillance that determines travel history as related to malaria risk. The surveillance system may not encounter all imported cases, and attempts should be made to capture all cases if possible, including population movement to and from areas (e.g. residents returning from endemic countries).

Participatory focus group discussions and key informant interviews exemplified in the presentation from the IOM can be used to identify major human movement patterns and factors related to malaria importation risk. Human movement patterns can be similar across areas; thus, programmes may be able to generalize imported cases from one area to other areas that have similar population influxes. Importation of infected mosquitoes is likely to be an issue, mainly at land boundaries geographically adjacent to those with ongoing malaria, or along major human or goods transportation routes.

Efforts to describe malaria importation risk should ensure that data are captured from other sectors of the health system (e.g. other ministries and local government authorities), including data on movement of visitors, the military, peace-keeping forces and migrants. Where possible, stratification by occupational risk, age, gender, season and economic status should be considered. Census population surveys can give an indication of general levels of influx and connectivity to endemic

countries, and hence can provide a proxy for risk of importation. Mobile phone data may be of use for determining population movement, although this will require close engagement with service providers and utility will depend on mobile phone ownership and use within and between countries.

The utility of border screening to measure importation risk is unclear. A review of the data – for example, comparison of infections identified through border or workplace screening compared with passive case detection at clinics – is needed to ascertain whether border screening is informative.

5.3 Infectivity

The ERG noted that the proposed updates to the definitions would mean that mosquito vector competence (or infectivity) is included as a component of vectorial capacity and would therefore be a component of receptivity. The variations in receptivity of *Anopheles* mosquito species (and populations) to exotic *Plasmodium* species (and strains) revealed by the literature review may mean that this compatibility is a driver of receptivity – or lack of receptivity – of the local ecosystem to transmission of particular parasite strains, such as a strain from another continent. This parasite–vector infectivity specificity should be adequately acknowledged in related WHO documents, including the vector competence entry in the WHO malaria terminology document.

Further information on infectivity may be gleaned from an examination of outbreak data from countries that eliminated malaria, after determining the origin of the imported parasite strains and the number of resultant infections transmitted by local mosquitoes. For this, the surveillance system must capture the origin of cases, and programmes would need to review their data periodically to ascertain which imported cases led to onward transmission (or otherwise). In particular, the generation and use of vector competence data in China to guide action (e.g. de-prioritization of responses to Africa *P. falciparum* imported cases) may present a good example that may be applied elsewhere.

5.4 Malariogenic potential

The ERG noted that the components of malariogenic potential – receptivity and importation risk – have some overlap in the way they are measured. A pragmatic approach should be taken during the assessment of malariogenic potential; the approach should use surveillance data to validate assumptions of receptivity and importation risk, and use these to refine estimates. For instance, adjustment of receptivity estimates should be informed by examining transmission in relation to importation risk; for example, when the importation risk is high but onward transmission is low, then receptivity may be relatively low. The priority should be measurement of receptivity in areas with high importation risk, and vice versa.

Further work will be needed to define relevant thresholds for receptivity and risk of importation to inform programmatic decisions. Modelling may be helpful to inform relevant thresholds. Ongoing modification of thresholds and classifications will be required due to local specificities; this should be informed by local information rather than predetermined on a national basis.

6. Recommendations

On the basis of the evidence reviewed and discussed, the ERG recommended the following to MPAC:

1. Update the *WHO malaria terminology* document (1) be updated as follows:
 - a. Add or update terms as shown in the table below.

Action	Term	Definition and comments
Add	Malariogenic potential	Likelihood of local transmission that is the product of receptivity, risk of importation of malaria parasites and infectivity of imported parasites. <i>Note: The concept of malariogenic potential is most relevant for elimination and prevention of re-establishment when indigenous transmission is mostly or entirely eliminated.</i>
Update	Receptivity	Degree to which an ecosystem in a given area at a given time allows for the transmission of <i>Plasmodium</i> spp. from a human through a vector mosquito to another human. <i>Note: This concept reflects vectorial capacity, susceptibility of the human population to malaria infection, and the strength of the health system, including malaria interventions. Receptivity can be influenced by ecological and climatic factors.</i>
Update	Vulnerability	Likelihood of malaria infection based on living conditions or behavioural risk factors, or likelihood of increased risk of severe morbidity and mortality from malaria infection.
Update	Importation risk	Risk or potential influx of parasites via infected individuals or infected <i>Anopheles</i> spp. mosquitoes. <i>Note: "Infected individuals" includes residents infected while visiting endemic areas as well as infected immigrants.</i>
Add	Infectivity	Ability of a given <i>Plasmodium</i> strain to establish an infection in an <i>Anopheles</i> mosquito species and undergo development until the mosquito has sporozoites in its salivary glands.

- b. Align all cross-references to these terms throughout the *WHO malaria terminology* document, with the final agreed upon definitions for the terms listed above.
2. Update the *WHO Malaria surveillance, monitoring & evaluation: a reference manual* (2) to:
 - a. more clearly articulate the importance for entomological surveillance to identify principal versus secondary vectors, given ongoing and likely temporal and spatial changes in vector distribution and abundance; and
 - b. provide more detailed guidance on site selection, and on the frequency and timing of entomological surveillance, to inform assessment of receptivity.
3. Revise other current WHO guidance documents in line with points (1) and (2), to ensure consistency.
4. Give priority to further development of methods for assessing malariogenic potential (receptivity, importation risk and infectivity) to ensure that these are applicable and informative for programmatic use. This includes:

- a. comparison of methods for the three potential measures of receptivity for selected countries, to ascertain comparability within countries, between countries or between neighbouring regions, to inform their use in receptivity assessments;
 - b. comparison of entomological parameters, as well as each of their associations with parasitological indicators, to identify key components that should be included in assessment of receptivity;
 - c. examination of outbreak data from certified countries, to determine the origin of the imported parasite strains and the number of resultant infections;
 - d. comparison of existing data on infections identified through border or workplace screening with those identified through passive case detection at clinics, to ascertain whether information from passive case detection provides an accurate picture of importation risk; and
 - e. examination of examples where countries can generalize data on imported cases for populations in specific regions to other areas with similar population movement or influxes.
5. After relevant and feasible methods for measurement of the components of malariogenic potential have been identified, interpret these measurements and develop thresholds to guide programmatic decision-making regarding maintenance of vector control and intensified surveillance.
 6. Further evaluate the issue of infectivity with respect to the mosquito and parasite factors that may reduce vector competence for different strains of *Plasmodium*, to determine whether there are programmatic implications for these findings. This may require additional review of evidence in future.

The ERG members also suggested that WHO consider developing a more standardized approach to classifying imported cases that is appropriate across different settings, as there is currently ambiguity on this issue. This topic was, however, considered beyond the scope of the current ERG.

References

- 1 World Health Organization. WHO malaria terminology. Geneva: World Health Organization; 2016 (<https://www.who.int/malaria/publications/atoz/malaria-terminology>, accessed 17 October 2018).
- 2 World Health Organization. Malaria surveillance, monitoring and evaluation: a reference manual. Geneva: World Health Organization; 2018 (<https://www.who.int/malaria/publications/atoz/9789241565578/>, accessed 16 October 2018).
- 3 World Health Organization Regional Office for Europe. Receptivity to malaria and other parasitic diseases: report on a WHO working group. Copenhagen: World Health Organization; 1979 (<http://apps.who.int/iris/handle/10665/204466>, accessed 17 October 2018).
- 4 World Health Organization. A framework for malaria elimination. Geneva: World Health Organization; 2017 (<http://www.who.int/malaria/publications/atoz/9789241511988>, accessed 17 October 2018).
- 5 World Health Organization. Guidelines for malaria vector control. Geneva: World Health Organization; 2018 (in press).
- 6 Molina-Cruz A, Canepa GE, Kamath N, Pavlovic NV, Mu J, Ramphul UN et al. Plasmodium evasion of mosquito immunity and global malaria transmission: the lock-and-key theory. PNAS. 2015;112(49):15178–83.
- 7 Molina-Cruz A, Garver LS, Alabaster A, Bangiolo L, Haile A, Winikor J et al. The human malaria parasite Pfs47 gene mediates evasion of the mosquito immune system. Science. 2013;340(6135):10.
- 8 World Health Organization. Global technical strategy for malaria 2016–2030. Geneva: World Health Organization; 2016 (http://www.who.int/malaria/areas/global_technical_strategy/, accessed 17 October 2018).
- 9 World Health Organization. World malaria report 2018. Geneva: World Health Organization; 2018 (<https://www.who.int/malaria/publications/world-malaria-report-2018/en/>, accessed 17 October 2018).
- 10 Wickremasinghe AR, Gunawardena DM, Mahawithanage STC. Use of routinely collected past surveillance data in identifying and mapping high-risk areas in a malaria endemic area of Sri Lanka. Southeast Asian J Trop Med Public Health. 2002;33(4):678–84.
- 11 World Health Organization. From malaria control to malaria elimination: a manual for elimination scenario planning. Geneva: World Health Organization; 2014 (<https://www.who.int/malaria/publications/atoz/9789241507028/en/>, accessed 11 March 2019).
- 12 Noor AM, Alegana VA, Patil AP, Moloney G, Borle M, Yusuf F et al. Mapping the receptivity of malaria risk to plan the future control in Somalia. BML Open. 2012;2:e001160.
- 13 Noor AM, Uusiku P, Kamwi RN, Katokele S, Ntomwa B, Alegana VA et al. The receptive versus current risks of *Plasmodium falciparum* transmission in Northern Namibia: implications for elimination. BMC Infectious Diseases. 2010;13:184.
- 14 Noor AM, Alegana VA, Pail P, Snow RW. Predicting the unmet need for biologically targeted coverage of insecticide-treated nets in Kenya. Am J Trop Med Hyg. 2010;83(4):854–60.

- 15 Noor AM, Gething PW, Alegana VA, Pail AP, Hay SI, Muchiri E et al. The risks of malaria infection in Kenya in 2009. *BMC Infectious Diseases*. 2009;9:180.
- 16 Dye C. Vectorial capacity: must we measure all its components? *Parasitol Today*. 1986;2(8):203–9.
- 17 Churcher TS, Cohen JM, Novotny J, Ntshalintshali N, Kunene S, Cauchemez S. Measuring the path toward malaria elimination. *Science*. 2013;344(6189):1230–2.
- 18 Reiner RC, Menach AL, Kunene S, Ntshalintshali N, Hsiang MS, Perkins TA et al. Mapping residual transmission for malaria elimination. *eLife*. 2015;4:e09520.
- 19 Churcher TS, Cohen JM, Novotny J, Ntshalintshali N, Kunene S, Cauchemez S. Measuring the path toward malaria elimination. *Science*. 2014;344:1230–2.
- 20 Routledge I, Romero Chevéz JE, Cucunubá ZM, Rodríguez MG, Guinovart C, Gustafson KB et al. Estimating spatiotemporally varying malaria reproduction numbers in a near elimination setting. *Nature Communications*. 2018;9:2476.
- 21 Tatem AJ, Jia P, Ordanovich D, Falkner M, Huang Z, Howes R et al. The geography of imported malaria to non-endemic countries: a meta-analysis of nationally reported statistics. *Lancet Infect Dis*. 2017;17(1):98–107.
- 22 Cohen JM, Smith DL, Cotter C, Ward A, Yamey G, Sabot OJ et al. Malaria resurgence: a systematic review and assessment of its causes. *Malaria Journal*. 2012;11:122.
- 23 Le Menach A, Tatem AJ, Cohen JM, Hay SI, Randell H, Patil AP et al. Travel risk, malaria importation and malaria transmission in Zanzibar. *Scientific Reports*. 2011;1:93.
- 24 Lynch CA, Bruce J, Bhasin A, Roper C, Cox J, Abeku TA. Association between recent internal travel and malaria in Ugandan highland and highland fringe areas. *Trop Med Int Health*. 2015;6:773–80.
- 25 Sturrock HJW, Roberts KW, Wegbreit J, Ohrt C, Gosling RD. Tackling imported malaria: an elimination endgame. *Am J Trop Med Hyg*. 2015;93(1):139–44.
- 26 Erbach-Schoenberg EZ, Alegana VA, Sorichetta A, Linard C, Lourenço C, Ruktanonchai NW et al. Dynamic denominators: the impact of seasonally varying population numbers on disease incidence estimates. *Population Health Metrics*. 2016;14:35.
- 27 Ruktanonchai NW, DeLeenheer P, Tatem AJ, Alegana VA, Caughlin TT, zu Erbach-Schoenberg E et al. Identifying malaria transmission foci for elimination using human mobility data. *PLoS Comput Biol*. 2016;12(4):e1004846.
- 28 Tatem AJ, Qiu Y, Smith DL, Sabot O, Ali AS, Moonen B. The use of mobile phone data for the estimation of the travel patterns and imported *Plasmodium falciparum* rates among Zanzibar residents. *Malaria Journal*. 2009;9:287.
- 29 Wesolowski A, Erbach-Schoenberg EZ, Tatem AJ, Lourenço C, Viboud C, Charu V et al. Multinational patterns of seasonal asymmetry in human movement influence infectious disease dynamics. *Nature Communications*. 2017;8:2069.
- 30 International Organization for Migration. Health, border and mobility management. Geneva: 2016
(https://www.iom.int/sites/default/files/our_work/DMM/IBM/updated/Health_and_Humanitarian_Border_Management.pdf, accessed 19 December 2018).

- 31 Ejov M, Davidyants V, Zvantsov A. Regional framework for prevention of malaria reintroduction and certification of malaria elimination 2014–2020. Copenhagen: World Health Organization Office for the European Region; 2014.
- 32 Ejov M, Sergiev V, Baranova A, Kurdova-Mintcheva R, Emiroglu N, Gasimov E. Malaria in the WHO European Region. On the road to elimination 2000–2015. Copenhagen: World Health Organization Office for the European Region; 2018.
- 33 Molineaux L, Gramiccia G. The Garki project: research on the epidemiology and control of malaria in the Sudan savanna of West Africa. Geneva: World Health Organization; 1980.
- 34 Rodriguez-Barraquer I, Arinaitwe E, Jagannathan P, Kamya MR, Rosenthal PJ, Rek J et al. Quantification of anti-parasite and anti-disease immunity to malaria as a function of age and exposure. *eLife*. 2018;7:e35832.
- 35 Bershteyn A, Gerardin J, Bridenbecker D, Lorton CW, Bloedow J, Baker RS et al. Implementation and applications of EMOD, an individual-based multi-disease modeling platform. *Pathogens and Disease*. 2018;76(5):fty059.
- 36 Eisele TP, Bennett A, Silumbe K, Finn TP, Chalwe V, Kamuliwo M et al. Short-term impact of mass drug administration with dihydroartemisinin plus piperaquine on malaria in Southern Province Zambia: a cluster-randomized controlled trial. *Journal of Infectious Diseases*. 214(12):1831–9.
- 37 Gerardin J, Bever CA, Bridenbecker D, Hamainza B, Silumbe K, Miller JM et al. Effectiveness of reactive case detection for malaria elimination in three archetypical transmission settings: a modelling study. *Malaria Journal*. 2017;16(1):248.

Abbreviations

AIDS	acquired immunodeficiency syndrome
API	annual parasite index
DOI	declaration of interest
EI	entomological investigation
ERA	entomological risk assessment
ERG	evidence review group
ESPT	entomological surveillance planning tool
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Global Malaria Programme
HBMM	Health, Border and Mobility Management
HIV	human immunodeficiency virus
IOM	International Organization for Migration
IRS	indoor residual spraying
ITN	insecticide-treated mosquito net
IVM	integrated vector management
LLIN	long-lasting insecticidal net
MoH	ministry of health
MPAC	Malaria Policy Advisory Committee
NMCP	national malaria control programme
PAKEPA	<i>Penilaian Awal Kesesuaian Ekologi Pembiakan Anopheles</i>
PAPfPR _{2–10}	population-adjusted <i>Plasmodium falciparum</i> prevalence in children aged 2–10 years
PfPR	<i>Plasmodium falciparum</i> prevalence
PfPR _{2–10}	<i>Plasmodium falciparum</i> prevalence in children aged 2–10 years
PoE	point of entry
R_0	basic reproductive number
R_e	effective reproductive number
R_c	controlled reproductive number
Tg	generation time
WHO	World Health Organization

Annexes

Annex 1. Agenda

Tuesday, 2 October 2018		
09.00 – 09.10	Opening remarks and welcome	Pedro Alonso
09.10 – 09.20	Declaration of interests	Jan Kolaczinski
09.20 – 09.40	Background, objectives and expected outcomes WHO guidance on prevention of re-establishment	Jan Kolaczinski and Kim Lindblade
Part I: Proposed methods for assessing receptivity		
9.40 – 10.30	Systematic review of assessment of receptivity	Josh Yukich
10.30 – 10.45	Discussion	Chair
11.15 – 11.45	Bayesian geospatial approaches to assessment of receptivity	Abdisalan Noor
11.45 – 12.00	Discussion	Chair
12.00 – 12.30	Estimation of R0 to assess receptivity	Azra Ghani
12.30 – 12.45	Discussion	Chair
13.45-14.15	Experiences with the entomological surveillance planning tool to measure receptivity	Adam Bennett
14:15-14:30	Discussion	Chair
14.30 - 15.30	National programme experiences with assessing receptivity • Malaysia • Bhutan • Sri Lanka	Jenarun Bin Jelip Rinzin Namgay Mihirini Hewavitharane
15.45 – 16.00	Discussion	Chair
16.00 – 16.30	Initial conclusions on assessing measures of receptivity	Chair
Wednesday, 3 October 2018		
Part II: Proposed methods for assessing vulnerability		
09.00 – 09.45	Approaches to assessing vulnerability to imported parasites	Andy Tatem
09.45 – 10.00	Discussion	Chair
10.00 – 10.30	Assessment of vulnerability through tools developed by the International Organization for Migration	Carlos Van Der Laat
10.30 – 10.45	Discussion	Chair
11.15 – 12.15	National programme experiences with assessing vulnerability • Malaysia	Jenarun Bin Jelip Rinzin Namgay Mihirini Hewavitharane

	• Bhutan • Sri Lanka	
12.15 – 12.30	Discussion	Chair
12.30 – 13.00	Initial conclusions on assessment of vulnerability	Chair
Part III: Proposed methods for assessing infectivity		
14.00 – 14.45	Systematic review of the susceptibility of mosquitoes to imported exotic malaria parasites	Graham White
14.45 – 15.30	Discussion and initial conclusions on infectivity	Chair
Part IV: Stratification and intervention mixes		
16.00 – 16.30	Effectiveness of intervention mixes stratified by vulnerability and receptivity	Jaline Gerardin
16.30 – 16.45	Discussion	Chair
16.45 – 17.00	Programme of work for the following day	Jan Kolaczinski
Thursday, 4 October 2018		
Part V: Group discussion		
09.00 – 10.30	Conclusions on: • assessment of receptivity and approaches to identifying meaningful thresholds • assessment of vulnerability and approaches to identifying meaningful thresholds • review of infectivity • priority research questions	Chair
11.00 – 13.00	Continue discussion, as above	Chair
Part VI: Closed session (ERG members and WHO Secretariat only)		
14.00 – 15.00	Finalization of recommendations	Chair
15.00 – 15.30	Meeting closure	Jan Kolaczinski and Kim Lindblade

Annex 2. List of participants

ERG Members

Prof Azra GHANI (**Chair**)
School of Public Health
Imperial College London
London
UNITED KINGDOM

Dr Justin COHEN
Clinton Health Access Initiative
Boston, MA
USA

Dr Jackie COOK
London School of Hygiene and Tropical
Medicine
London
UNITED KINGDOM

Dr Jaline GERARDIN
Institute for Disease Modeling
Intellectual Ventures
Bellevue
USA

Dr William HAWLEY
Centers for Disease Control & Prevention
Atlanta
USA

Dr Fredros OKUMU
Ifakara Health Institute
Ifakara
UNITED REPUBLIC OF TANZANIA

Dr Kevin PALMER
Vectorborne Diseases Associates LLC
Hawaiian Islands
USA

NMCP Managers

Ms. Mihirini HEWAVITHARANE
Entomologist
Ministry of Health
Colombo
SRI LANKA

Dr Jenarun JELIP
Senior Assistant Director
Disease Control Division
Ministry of Health
MALAYSIA

Mr Rinzin NAMGAY
VDCP
Department of Public Health
Ministry of Health
Thimphu
BHUTAN

Presenters

Dr Adam BENNETT
Malaria Elimination Initiative
University of California
San Francisco
USA

Mr Nawar Sattar TASHBID
International Organization for Migration
Geneva
SWITZERLAND

Prof Andy TATEM
WorldPop and Flowminder
University of Southampton
Southampton
UNITED KINGDOM

Dr Carlos VAN DER LAAT
Migrants Health Assistance Programme
Coordinator
International Organization for Migration
Geneva
SWITZERLAND

Prof Graham WHITE
Entomology & Nematology
University of Florida IFAS
Gainesville
USA

Dr Joshua YUKICH
Department of Tropical Medicine Tulane
University School of Public Health and
Tropical Medicine
New Orleans
USA

Observers

Dr Roopal PATEL
Technical Advisor, Malaria
The Global Fund
Geneva
SWITZERLAND

WHO Secretariat

Dr Pedro ALONSO
Director
Global Malaria Programme
WHO Headquarters, Geneva

Dr John APONTE
Technical Officer
Surveillance
Global Malaria Programme
WHO Headquarters, Geneva

Dr Maru AREGAWI WELDEDAWIT
Scientist
Surveillance
Global Malaria Programme
WHO Headquarters, Geneva

Ms Lucia FERNANDEZ MONTOYA
Consultant
Entomology and Vector Control
Global Malaria Programme
WHO Headquarters, Geneva

Dr Tessa KNOX
Technical Officer
Entomology and Vector Control
Global Malaria Programme
WHO Headquarters, Geneva

Dr Jan KOLACZINSKI
Coordinator
Entomology and Vector Control
Global Malaria Programme
WHO Headquarters, Geneva

Dr Oscar MESONES LAPOUBLE
Specialist
Malaria and Vector-borne Diseases
Pan American Health Organization,
Suriname

Dr Xiao Hong LI
Technical Officer
Elimination
Global Malaria Programme
WHO Headquarters, Geneva

Dr Kim LINDBLADE
Team Leader
Elimination
Global Malaria Programme
WHO Headquarters, Geneva

Dr Abdisalan NOOR
Team Leader
Surveillance
Global Malaria Programme
WHO Headquarters, Geneva

Annex 3. Declarations of interest

All ERG members and technical experts participating in the meeting submitted declaration of interest (DOI) and confidentiality undertaking forms. DOI forms were assessed by the WHO Secretariat. The following participants declared interests that required further consideration and discussion with the WHO Office of Compliance, Risk Management and Ethics.

Professor Azra Ghani is employed by the School of Public Health, Imperial College London in the United Kingdom of Great Britain and Northern Ireland. She reported the following potential conflicts of interest related to the topic of the meeting:

- a. Received travel support (airfare) for meetings with GlaxoSmithKline in Belgium between 2011 and 2015.
- b. Conducted mid-term independent evaluation of United Kingdom Department for International Development malaria programme for Oxford Policy Management, with over US\$ 5000 received in 2013.
- c. Conducted consultancy projects with Global Fund for which she received over US\$ 5000 between 2016–2017.
- d. Received academic grant funding from multiple organizations (Bill & Melinda Gates Foundation, Innovative Vector Control Consortium, Malaria Vaccine Initiative, Medical Research Council (Gambia), Medicines for Malaria Venture, National Institutes of Health, Wellcome Trust) of over US\$ 5000 over 3 years.
- e. Serves as a Charity Trustee for Malaria No More United Kingdom without funding provided.

In an email exchange on 27 September 2018, Professor Ghani clarified that none of the research funding she receives relates directly to the subject of the meeting, except for the Wellcome Trust, but that funding is provided for a PhD student and the funders have no direct relationship with her. All the declarations (a–e) were considered insignificant potential conflicts of interest because they are unlikely to affect the expert's judgement.

Dr Justin Cohen works for Clinton Health Access Initiative, Boston, United States of America (USA) and reported two potential conflicts of interest related to the topic of the meeting:

- a. Employed as Senior Director for Global Malaria in which capacity he and his team are paid to assist governments with issues related to the topic of the meeting.
- b. Received several grants from the Bill & Melinda Gates Foundation, United Kingdom Department for International Development and Malaria No More United Kingdom to assist governments with work related to the topic of interest.

In an email exchange on 28 September 2018, Dr Cohen clarified that there is a grant of over US\$ 5000 from the Bill & Melinda Gates Foundation and over US\$ 5000 from the US Centers for Disease Control and Prevention (CDC) Foundation with, among others, specific outputs related to mapping malaria risk and mapping parasite movement. This interest was considered significant and relevant. Dr Cohen was therefore subject to partial exclusion from the decision-making process and excluded from the closed session during which recommendations were finalized on the afternoon of Wednesday 4 October 2018.

Dr Adam Bennett works for the Global Health Group Malaria Elimination Initiative (MEI) at the University of California, San Francisco, USA. Dr Bennett reported one potential conflict of interest:

- a. As Program Lead at MEI and an Assistant Professor of Epidemiology and Biostatistics, his research focuses primarily on modelling spatial and climatic variability in the context of surveillance, monitoring and evaluation for vector-borne disease control interventions. He leads the MEI's surveillance efforts to develop and recommend new and efficient strategies for identifying, tracking and targeting malaria cases in elimination settings.

Dr Bennett's potential conflicts of interest were considered personal and nonspecific but financially significant. As he is not an ERG member, he was already to be excluded from the closed session during which recommendations were finalized on the afternoon of Wednesday 4 October 2018. Therefore, no further action was required.

Further "due diligence" internet research was conducted on profiles of all ERG members and technical experts. Nothing significant was found that was not already disclosed through DOIs.

Note: According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single malaria-related company exceeds US\$ 10 000 in a calendar year. Likewise, a shareholding in any one malaria-related company in excess of US\$ 1000 would also constitute a "significant shareholding".

Last update: 10 March 2016

Annex 4. Overview of evidence on Anopheles spp. and Plasmodium spp. compatibility for different malaria zones

Summary of *Anopheles* spp. competence or incompetence for *P. falciparum* in the 12 malaria zones. Excerpt from presentation by G. White.

<i>P. falciparum</i> origin	vector competence (+) or incompetence											
Malaria Zones	1: North American	2: Central American	3: South American	4: North Eurasian	5: Mediterranean	6: Desert	7: Afro-tropical	8: Indo-Iranian	9: Indo-Chinese	10: Malaysian	11: Chinese	12: Australasian
1: North American	all+?	–	–	–	–	–	–	–	–	–	–	–
2: central American	<i>freeborni</i>	all? except <i>pseudopunctipennis</i>		+	+	+	+	+	+	<i>dirus maculatus</i>	+	+
3: South American	+	+	all+?	+	+	+	+	+	+	+	+	+
4: North Eurasian	+	+	+	all+?	+	+	+	+	+	+	+	+
5: Mediterranean	+	+	+	+	all+?		+	+	+	+	+	+
6: Afro-Arabian Desert	+	+	+	<i>atroparvus</i>	+	all+?	+	+	+	+	+	+
7: Afrotropical	+	+	+	<i>atroparvus</i> <i>claviger</i> <i>labranchiae</i> <i>messae</i> <i>plumbeus</i> <i>sacharovi</i> <i>subalpinus</i>	<i>claviger</i> <i>plumbeus</i> <i>sacharovi</i>	+	all+?	+	+	+	+	+
8: Indo-Iranian	+	+	+	<i>atroparvus</i> <i>messeae</i>	+	+	+	all+ except <i>culicifacies</i> B	<i>maculatus</i>	+	+	+
9: Indo-Chinese	+	+	+	<i>atroparvus</i>	+	+	<i>coluzzii</i> <i>gambiae</i>	<i>stephensi</i>	<i>barbirostris</i> <i>campestris</i> <i>cracens</i>	+	+	+
10: Malaysian	+	+	+	+	+	+	+	+	<i>maculatus</i>	all+?	+	+
11: Chinese	<i>freeborni</i>	+	+	+	+	+	<i>gambiae</i>	<i>culicifacies</i> <i>stephensi</i>	<i>dirus</i>	+	all+?	+
12: Australasian	+	+	+	+	+	+	+	+	+	+	+	all+?

Summary of *Anopheles* spp. competence or incompetence for *P. vivax* in the 12 malaria zones. Excerpt from presentation by G. White.

<i>P. vivax</i> origin	<i>Anopheles</i> competence (+) or incompetence or [very low susceptibility]											
Malaria Zones	1: North American	2: central American	3: South American	4: North Eurasian	5: Medi-terranean	6: Desert	7: Afro-tropical	8: Indo-Iranian	9: Indo-Chinese	10: Malaysian	11: Chinese	12: Aus-tralasian
1: North American	all+?	–	–	–	–	–	–	–	–	–	–	–
2: central American	<i>freeborni</i> <i>quadrimaculatus</i>	<i>pseudo-punctipennis</i>	<i>albitarsis</i>	<i>atroparvus</i>	+	+	<i>gambiae</i>	<i>culicifacies</i> <i>stephensi</i>	<i>dirus</i> <i>maculatus</i>	+	+	<i>farauti</i>
3: South American	<i>freeborni</i> <i>quadrimaculatus</i>	<i>pseudo-punctipennis</i>	all+?	<i>atroparvus</i>	+	+	<i>gambiae</i>	<i>culicifacies</i> <i>stephensi</i>	<i>dirus</i> <i>maculatus</i>	+	+	+
4: North Eurasian	+	+	+	all+?	+	+	+	+	+	+	+	+
5: Mediterranean	+	+	+		all+?	+	+	+	+	+	+	+
6: Afro-Arabian Desert	+	+	+	<i>atroparvus</i>	+	all+?	+	+	+	+	+	+
7: Afrotropical	+	+	+	+	+	+	all+?	+	+	+	+	+
8: Indo-Iranian	<i>freeborni</i>	[<i>albimanus</i>]	+	<i>atroparvus</i>	+	+	<i>gambiae</i>	all+ except <i>culicifacies</i> B	<i>dirus</i> <i>maculatus</i>	<i>balabacensis</i>	+	+
9: Indo-Chinese	<i>freeborni</i>	+	+	<i>atroparvus</i> <i>messeae</i> <i>sacharovi</i>	+	+	<i>gambiae</i>	<i>culicifacies</i> <i>stephensi</i>	<i>barbirostris</i> <i>campstris</i> <i>cracens</i>	+	+	+
10: Malaysian	+	+	+	+	+	+	+	+	+	all+?	+	+
11: Chinese	<i>freeborni</i>	+	+	+	+	+	<i>gambiae</i>	<i>culicifacies</i> <i>stephensi</i>	<i>dirus</i> <i>maculatus</i>	+	all+?	+
12: Australasian	<i>freeborni</i> <i>quadrimaculatus</i>	[<i>albimanus</i>]	+	<i>atroparvus</i>	+	+	<i>gambiae</i>	<i>culicifacies</i> <i>stephensi</i>	<i>dirus</i> <i>maculatus</i>	<i>balabacensis</i> <i>maculatus</i>	+	all+?