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immunological effector cells to repair the injured site, and is thus a good thing. However, many of these receptors can also be exploited by *P. falciparum* to allow PfEMP1-mediated endothelial sequestration of infected erythrocytes, as noted in another postsurgery malaria report (Box 1) [11]. Both studies are thus likely vivid examples of stress-induced resurgence of pre-existing infections, as discussed in a fairly recent review that provides many additional examples [12].

Concluding Remarks

Case reports, speculating about the causes of sudden *P. falciparum* malaria attacks after completely unrelated events, such as traffic accidents [13], continue to crop up in the scientific literature. A few striking examples are discussed above. They all have at least two things in common. First, they involve the appearance or upregulation of vascular receptors used by *P. falciparum* to avoid splenic clearance. Second, they involve patients with past exposure to *P. falciparum* – in all likelihood individuals who carried parasitemia controlled to extremely low levels by acquired immunity before they became patients. As this immune control is delicate, it can be disrupted by any event that creates new opportunities for parasite sequestration and splenic avoidance. Such a scenario seems more parsimonious than the immunosuppression that is often invoked. If correct, clinicians should therefore be mindful of malaria as a differential diagnosis in patients with a history of long-term residence in an endemic area – even if a long time ago. As scientists, we should use these reports as an additional source of evidence regarding the pathogenic mechanisms of *P. falciparum* malaria, including evidence about the key host receptors and the parasite ligands involved.

The above notwithstanding, immunosuppression may well be involved in the pathogenesis of malaria in some cases – malaria in cancer and diabetes patients would seem likely examples [14,15] – but that is another story.

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References

1. Hviid, L. (2005) Naturally acquired immunity to *Plasmodium falciparum* malaria in Africa. *Acta Trop.* 95, 270–275
2. Covell, G. (1950) Congenital malaria. *Trop. Dis. Bull.* 47, 1147–1167
3. Hviid, L. (2011) The case for PfEMP1-based vaccines to protect pregnant women against *Plasmodium falciparum* malaria. *Expert Rev. Vaccines* 10, 1405–1414
4. Ashley, E.A. and White, N.J. (2014) The duration of *Plasmodium falciparum* infections. *Malar. J.* 13, 500
5. Giobbia, M. *et al.* (2005) Late recrudescence of *Plasmodium falciparum* malaria in a pregnant woman: a case report. *Int. J. Infect. Dis.* 9, 234–235
6. Poilane, I. *et al.* (2009) Découverte fortuite de paludisme à *Plasmodium falciparum* au cours de la grossesse: à propos de deux cas. *Gynecol. Obstet. Fertil.* 37, 824–826 (in French)
7. Tuikue Ndam, N. *et al.* (2018) Persistent *Plasmodium falciparum* infection in women with an intent to become pregnant as a risk factor for pregnancy-associated malaria. *Clin. Infect. Dis.* 67, 1890–1896
8. Eisele, T.P. *et al.* (2012) Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. *Lancet Infect. Dis.* 12, 942–949
9. Bachmann, A. *et al.* (2009) Absence of erythrocyte sequestration and lack of multicopy gene family expression in *Plasmodium falciparum* from a splenectomized malaria patient. *PLoS ONE* 4, e7459
10. Husum, H. *et al.* (2002) Postinjury malaria: a study of trauma victims in Cambodia. *J. Trauma* 52, 259–266
11. Abrard, S. *et al.* (2018) Cardiopulmonary bypass and malaria relapse. *J. Cardiothorac. Vasc. Anesth.* 32, 2282–2285
12. Shanks, G.D. (2015) Historical review: does stress provoke *Plasmodium falciparum* recrudescence? *Trans. R. Soc. Trop. Med. Hyg.* 109, 360–365
13. Lempert, M. *et al.* (2019) Fever after an open ankle fracture – a surprising diagnosis. *Praxis* 108, 1091–1095
14. Igala, M. *et al.* (2019) Malaria after chemotherapy for hematological malignancies. *Med. Sante Trop.* 29, 399–401
15. Carrillo-Larco, R.M. *et al.* (2019) Is diabetes associated with malaria and malaria severity? A systematic review of observational studies. *Wellcome Open Res.* 4, 136

Forum

Needs and Challenges in Modelling Malaria for Emergency Contexts

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While modelling is an essential component for an understanding of the epidemiology of malaria, and for designing better control measures, it rarely considers the particular contexts encountered in emergency settings. By linking these situations with the transmission parameters our aim is to correct this bias and call for a better collaboration between relief actors.

In 2018, approximately 70 million people were considered to be forcibly displaced, whether internally displaced, returnees, or people living in humanitarian emergencies [1]. A quarter of these were located in sub-Saharan Africa. At the same time, 90% of worldwide malaria-associated deaths currently occur in sub-Saharan Africa, about a third of which take place within complex humanitarian emergency settings[i–iii] [1–3].

Unlike normative contexts, in which malaria control is routine and even elimination strategies are being implemented, in unstable conditions the incidence of malaria is poorly understood and is subject to composite short-term changes. Controlling malaria in such settings requires tools with particular target profiles, amongst which rapid deployment, adaptability, practicality, and ease of implementation are paramount. While modelling is often considered essential in determining if, and how, a

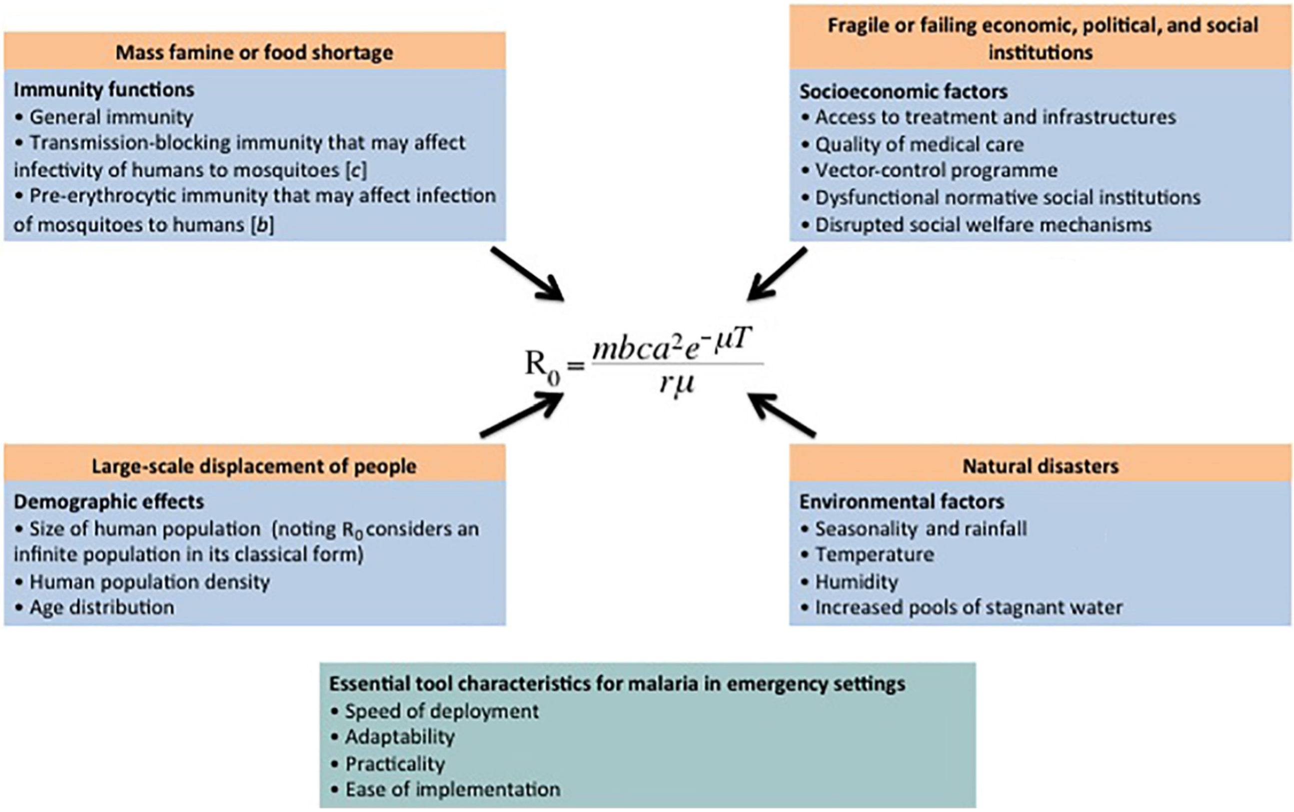

Figure 1. Parameters Related to the Definition of Emergency Settings and Their Potential Impact on the Transmission of Malaria. Abbreviations: R_0, basic reproductive ratio; *m*, number of mosquitoes per human host; *a*, biting rate of the mosquitoes on their human host; *b*, infectivity of mosquitoes to humans; *c*, infectivity of humans to mosquitoes; *μ*, mortality of adult mosquitoes; *T*, incubation period of parasites within the mosquito vector; *r*, rate of recovery of infected humans.

strategy or a combination of strategies can impact the malaria burden [4,5], the case of emergency settings is rarely considered. Our aim here is to highlight, through defining an emergency setting, how modelling approaches could help to design more efficient and effective malaria-control programmes while fostering collaboration between the actors involved in humanitarian aid.

What Defines an Emergency Situation?

According to the World Health Organization, complex emergencies are situations of disrupted livelihoods and threats to life produced by warfare, civil disturbance, and large-scale movements of people, in which any emergency response has to be conducted in a difficult political and security environment. Complex emergencies combine internal conflict with large-scale displacements of people, mass famine or food shortage, and fragile or failing economic, political, and social institutions. Often, complex emergencies are also exacerbated by natural disasters [6].

Adapting Malaria Modelling to Emergency Settings: What Can Be Done?

It is unlikely that a ´one size fits all´ modelling approach will work in emergency settings, and a variety of scenarios would need to be considered. Even more than in less complex contexts, the adaptation to heterogeneous and unstable situations and the ability to provide long-term sustainable solutions are major hurdles to consider when conducting an efficient programme aimed at decreasing malaria mortality and morbidity.

Proposed models would involve a number of parameters, including relevant information on epidemiological and medical aspects of the population and a consideration of the type and quality of tools and their potential combinations. Some examples of this include population composition and movement, human ecology, pre-existing local activities of malaria control, diagnosis and access to healthcare. This should ultimately allow a determination on which specific tools would be more adapted to the situation [e.g., insecticide-treated covers and blankets, repellents, and indoor residual spraying (IRS) campaigns] The approaches should also acknowledge that there might be some context-specific challenges in emergency settings in using some of these approaches, whether classical or innovative.

Translation into Parameters

In the definition of an emergency setting, a number of aspects can be translated into parameters to feed epidemiological models of malaria (Figure 1). The most straightforward manner is to consider the classical basic reproductive number, R_0, describing the number of secondary cases of malaria arising from a single case in an otherwise uninfected population [7] – and its more recent neoclassical assumptions taking into account a variety of parameters affecting malaria transmission [8,9].

The Impact of Large-Scale Displacement of People

One of the major aspects associated with emergency settings is large-scale population displacement, which, in terms of malaria epidemiology, can affect transmission in a variety of ways. Such changes may not only be in absolute numbers but in other major determinants of malaria epidemiology [9], such as age distribution (with often more children, young adults, and women of childbearing age), as well as migration [10], and the malaria immune status [11] affecting the spread of the disease. Using spatially-explicit models can be particularly useful in scenarios where the heterogeneity of the environment (e.g., disturbed landscapes), interactions between human populations (e.g., differences in immunity in long-term nearby residents vs newly displaced people), and vector or parasite factors (e.g., vectorial capacity varying over short distances and potentially different parasite species) are important.

Mass Famine or Food Shortage

When herd immunity can be impaired – due to an influx of malaria-susceptible populations arriving from an area with no or little malaria transmission – the compounding effect of mass famine and food shortage, leading to acute or chronic malnutrition, may have an important impact on disease incidence and evolution [12,13]. This will typically lead to a diminished immunity (affecting the recovery rate, the factor r in R_0) and an increased malaria-related mortality.

Fragile or Failing Economic, Political, and Social Institutions

Often an emergency setting is intricately linked to a fragile social and socioeconomic system as well as to an inadequate infrastructure with limited access to rapid diagnosis where the risk of misdiagnosis is high [14]. This highlights a number of aspects that should be considered in models whose aim is to include access to treatment and infrastructure, quality of medical care, and the presence or absence of vector-control activities that will influence several mosquito-related parameters (m, a, and μ).

Natural Disasters

Natural disasters typically exacerbate and amplify pre-existing challenges encountered in complex humanitarian settings. This can imply changes in ecological conditions (e.g., flooding) and may result in the initial destruction of breeding sites but also in the creation of new ones that can result in an 'off-season' malaria peak. In addition, natural disasters are likely to deepen logistic constraints affecting the delivery of control tools.

Data Collection

One of the major challenges in emergency humanitarian contexts, particularly in the acute phase, is the difficulty in getting accurate data, which would be important in the calibration of models [15]. Typically, most emergency assessments are ´quick and dirty´, and, as such, the number, type, and characteristics of data parameters and points to be collected need to be carefully considered and prioritised, including those of the resident/host populations.

Implementation

Time-efficiency of implementation is also an essential aspect of tackling malaria in an emergency setting. The speed and the quality of the tool, and the subsequent control strategy deployment, are critical to prevent avoidable malaria-associated deaths. Choosing between a less effective strategy, that can be quickly implemented, and more efficacious options that require more time to develop, resulting in significant implementation delay, is where such a tool will have the greatest value. Models could be a real asset to guide such decisions, particularly if they are operationalizable through easily accessed and user-friendly interfaces with minimum prior training.

Concluding Remarks

Overall, there is a need for modelling approaches that would not only consider the biological and epidemiological parameters for malaria control in emergency settings but also the various factors, often difficult to estimate, that are unique to such situations. Such models should build upon existing tools and available solutions (low-hanging fruits) to analyse and suggest improved designs that consider the whole range of tools available for malaria control (e.g., case management, drugs, vector control). This could also lead to improved planning, budgeting, and collaboration between the actors providing emergency relief and assistance. The use of models and a better collaboration and service delivery between the various actors involved in relief in emergency settings should develop beyond malaria in multiple other conditions in a more holistic and multisectorial manner.

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Resources

[i] https://malariaatlas.org/
[ii] www.severemalaria.org/
[iii] http://popstats.unhcr.org/en/overview

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References

1. UNHCR (2019) *Global Trends – Forced Displacement in 2018*, UNHCR
2. WHO (2019) *World Malaria Report 2019*, WHO
3. International Rescue Committee (2020) *Emergency Watchlist, 2020*, IRC
4. Chitnis, N. *et al.* (2010) Comparing the effectiveness of malaria vector-control interventions through a mathematical model. *Am. J. Trop. Med. Hyg.* 83, 230–240
5. Killeen, G.F. and Smith, T.A. (2007) Exploring the contributions of bed nets, cattle, insecticides and excitorepellency to malaria control: a deterministic model of mosquito host-seeking behaviour and mortality. *Trans. R. Soc. Trop. Med. Hyg.* 101, 867–880
6. Wisner, B., Adams, J., eds (2002) *Environmental Health in Emergencies and Disasters: a Practical Guide*, World Health Organization
7. Macdonald, G. (1957) *The Epidemiology and Control of Malaria*, Oxford University Press
8. Smith, D.L. *et al.* (2007) Revisiting the basic reproductive number for malaria and its implications for malaria control. *PLoS Biol.* 5, e42
9. Mandal, S. *et al.* (2011) Mathematical models of malaria – a review. *Malar. J.* 10, 202
10. Ngwa, G.A. and Shu, W.S. (2000) A mathematical model for endemic malaria with variable human and mosquito populations. *Mathe. Comput. Model.* 32, 747–763
11. Koella, J.C. (1991) On the use of mathematical models of malaria transmission. *Acta Trop.* 49, 1–25
12. Young, H. and Jaspars, S. (1995) Nutrition, disease and death in times of famine. *Disasters* 19, 94–109
13. Ajakaye, O.G. and Ibukunoluwa, M.R. (2020) Prevalence and risk of malaria, anemia and malnutrition among children in IDPs camp in Edo State, Nigeria. *Parasite Epidemiol. Control* 8, e00127
14. Amexo, M. *et al.* (2004) Malaria misdiagnosis: effects on the poor and vulnerable. *Lancet* 364, 1896–1898
15. Anderson, J. *et al.* (2011) The burden of malaria in post-emergency refugee sites: A retrospective study. *Confl. Health* 5, 17