Table 2. Examples of Events That Might Delay Productivity in Participating Regions

Event	Approx. length	Time period
Lunar New Year		
Cambodia/Laos/Myanmar/Thailand	1 week	Mid Apr
China/Korea/Mongolia/Tibet/Vietnam	23 days	Late Jan–early Feb
Islam		
Ramadan	1 month	Lunar calendar
Eid al Fitr/Eid al Adha	3 days/5–7 days	Lunar calendar
Juddaism		
Passover	7–8 days	Late Mar–Apr
Hanukkah	8 days	Late Nov–late Dec
Hinduism		
Diwali	5 days	Mid Oct–mid Nov
Christianity		
Easter	4 days	Mar–Apr
Christmas and New Year's Eve	1–2 weeks	Mid Dec–Jan 1
Secular		
Children school holidays	Various	Various
Maternity/paternity leave	Various	NA
Weddings and funerals	Various	NA
Major sporting events	Various	NA

Preparing for Politics

In addition to navigating the intricacies of internal team dynamics, groups engaged in international collaborations should be prepared to navigate the realities of government and institutional roadblocks. Global health has become a huge market with many agencies, firms, and academic institutions involved, all with their own internal and external agendas and interests. It is inevitable in this situation to have some level of corruption which is not only financial but also intellectual. Researchers who plan to work on collaborative research projects that cross country and disciplinary lines need to be aware of this reality and demand transparency as much as possible. Around the world, countries have varying bureaucratic structures in place to facilitate, manage, or limit researcher access to data and/or stakeholders. In some cases, potential participants might steer clear of researchers, wanting to avoid government backlash. In other cases, the time and resources required to get government or institutional research approval might be prohibitive or violate ethical guidelines (e.g., bribes). Spending time to develop good rapport with varying government entities can be instrumental in ensuring a high level of coordination and support for research projects, and in maintaining productivity. Adhering to the highest scientific standards has the best chance for affording a research team international recognition, which in turn will hopefully promote independent and free access of data. Above all, teams must work cohesively and cautiously to ensure the safety of all team members – especially those placed in politically sensitive locales.

Acknowledgments

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Resources

[i]http://journals.plos.org/plosone/s/authorship
[ii]www.who.int/neglected_diseases/news/fbti_thailand_uses_integrated_ecosystems_health_approach/en/
[iii]www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/cattle-disease-information/nws/new-world-screwworm
[iv]www.cartercenter.org/health/guinea_worm/index.html

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References
1. Davi, M. (2017) Checklist for One Health epidemiological reporting of evidence (COHERE). *One Health* 4, 14–21
2. Black, N. (2001) Evidence based policy: proceed with care. *Br. Med. J.* 323, 275–279
3. Tuckman, B. (1965) Developmental sequence in small groups. *Psychol. Bull.* 63, 384–399
4. Choi, B. and Pak, A. (2006) Multidisciplinarity, interdisciplinarity and transdisciplinarity in health research, services, education and policy: 1. Definitions, objectives, and evidence of effectiveness. *Clin. Invest. Med.* 29, 351–364
5. Proulx, J.-F. *et al.* (2002) Novel prevention program for trichinellosis in Inuit communities. *Clin. Infect. Dis.* 34, 1508–1514
6. Beard, T. (1973) The elimination of echinococcosis from Iceland. *Bull. World Health Organ.* 48, 653–660

Letter

Plasmodium: More Don'ts

Geoffrey Ian McFadden[1,*]

In a previous missive I explained why you cannot turn the genus name for malaria parasites (*Plasmodium*) into a plural noun

[1]. Here I tackle fallacious anthropocentrisms in our literature.

Malaria Is a Disease Not an Organism

Many authors use 'malaria' as a synonym for both the disease and its causative agent. Just as bubonic plague describes one medical condition caused by the prokaryote *Yersinia pestis*, malaria describes the disease caused by members of the protist genus *Plasmodium*. One can refer to the organism as the malaria-causing parasite, or even the malaria agent, but avoid phrases like 'malaria life cycle', 'malaria antigens', or 'malaria genome'.

There Are Four/Five/Six/Seven/. . . . . Species of *Plasmodium* That Naturally Infect Humans

Introduction sections of many articles (even one of mine [2]) echo the titles of recent papers [3,4] naming *Plasmodium knowlesi* as the fifth species of *Plasmodium* causing malaria in humans. However, a casual literature search revealed at least seven species of *Plasmodium* that infect humans [5–7]. One can debate whether these zoonotic infections constitute 'disease' and thus rank as genuine malarias – *P. knowlesi* certainly does [8] – but molecular tools will likely confirm more and more putative zoonoses/anthroponoses [9], so the number of infectious species will likely grow. Avoid categorical statements about the number of human-infecting/malaria-causing *Plasmodium* species unless you're willing to track that literature.

Mosquitoes Are Not the Vector

Whilst it is true that malaria is a mosquito-borne disease, and that *Plasmodium* can get from one human host to another only via a mosquito (but see [10]), the insect is not technically *the* vector. Although our disease-focused point of view makes it seem like we are the host and mosquitoes the vector, I argue here that the reverse is true.

In parasites with two or more hosts, the host in which the parasite undertakes sexual reproduction is termed the definitive or primary host [11,12]. *Plasmodium* sex (gamete fusion to produce a zygote) happens in the mosquito gut soon after she has taken her blood meal from an infected person. *Plasmodium* gametocytes – sensing that they have been extricated from the human host – begin a frenzied process of finding and fusing with a mate. The activated gametocytes produce male or female gametes. The sperm (flagellated microgamete) somehow finds an egg (female macrogamete) and fuses with it to create a diploid zygote, which is a relatively short-lived stage. When I first witnessed *Plasmodium* fertilisation, the hairs on the back of my neck stood up. I realised in that moment just how complicated and genetically sophisticated the parasite is. Little wonder that *Plasmodium* has proven harder to defeat than many virus and bacterial pathogens that cannot reshuffle their genetic deck each time they change hosts.

Plasmodium zygotes quickly metamorphose into ookinetes, a kind of escape pod whose job it is to get out of the mosquito gut and avoid being digested. Ookinetes are largish and powerful enough to barge their way through the half-digested blood meal and bust out through the gut wall, not unlike Ridley Scott's *Alien* bursting out of John Hurt [13]. In our insectary we avoid feeding too many gametocytes to mosquitoes because it kills them [14], probably through too many ookinetes perforating their gut [15].

Ookinetes do not burst completely out of the mosquito like the *Alien* though. Rather, they seek refuge in the relative safety of the mosquito's body cavity (haemocoel) where they have some remarkable things to achieve. Nourished therein by the mosquito blood (haemolymph), and able to resist the assaults of the mosquito immune system, the ookinete undergoes yet another metamorphosis to become an oocyst. The oocyst is by far and away the longest lived and slowest growing stage in the life cycle (but see an exception below). After ~2 weeks, the sporoblast mother cell (sometimes there are more than one) within the oocyst produces one to two thousand sporozoites. The sporozoites exit the protective coat of the oocyst and are wafted throughout the haemocoel with the pumping haemolymph until they somehow identify the insect's salivary glands. The sporozoites burrow into the salivary glands and line up inside the ducts to wait patiently therein for the mosquito to feed again.

The infected female mosquito typically needs another blood meal to bolster her protein resources so that she can lay another batch of eggs. As she probes the skin of her meal ticket with her proboscis, she expectorates a few nanolitres of saliva to prevent blood clotting and vasoconstriction that would prevent her feeding. The waiting sporozoites – armed with novel recombinant sets of alleles thanks to the sex and meiosis their parents had back in the mosquito gut – ride along with this saliva into the person, effectively completing the host-to-host transfer (see detailed animations of the parasite's life cycleAppendix A[i]).

Thus, from a parasite (or classical parasitology) perspective, mosquitoes are primary hosts and humans are vectors, carrying the parasite from one definitive (mosquito) host to another. I would also go as far as to label humans as amplification vectors because we enable massive multiplication of parasite numbers. At any given moment, there are perhaps as many as 5×10^{18} *Plasmodium falciparum* individuals in existence [16], which means

that humans are an extraordinarily efficient amplification vector. We are thus both an amplification *and* a geographic vector, able to support massive parasite numbers and walk them further in a day than an infected mosquito could travel in her lifetime. On the coast in Kenya I met a mother who had bundled her malarious infant into her *kikoi* and carried her 10 km to the clinic for treatment. Effectively, she had vectored parasites into the range of a new population of definitive hosts. Our technologies now make us super-vectors, able to carry parasites from continent to continent in our planes, trains, and automobiles.

Vector biologists, and those doing the crucial work of vector control, are probably groaning inwardly at my terminological pedantry, but good science needs accurate communication. As writers, editors, and presenters we must eschew lazy language. We face a terminological paradox where mosquitoes are the vector for malaria the disease, but – strictly speaking – not the vector for *Plasmodium*, the causative agent of malaria. Perhaps a way through the muddle is to say 'malaria is transmitted by mosquitoes', but avoid saying 'the mosquito is the vector', even if you are a vector biologist!

Plasmodium Is Not an Obligate Intracellular Parasite

Whilst it is true that *Plasmodium* is predominantly intracellular in humans, this is the shorter part of its life cycle and involves only a minority of the myriad morphological forms the parasite can adopt. Most of the life cycle, and most of the remarkable parasite forms, are extracellular. For instance, the above-mentioned male and female gametes, the zygote, the ookinete, the oocyst, the sporoblast mother cell, the midgut sporozoites, and the salivary gland sporozoites (i.e., all the mosquito stages) are extracellular parasites. Even some of the human phases (bloodstream sporozoites and merozoites) are essentially extracellular, albeit ever so briefly. The only intracellular stages in the life cycle are the exoerythrocytic forms within human hepatocytes (namely trophozoites, schizonts, and merozoites – which are sometimes referred to as metacryptozoites but are yet to be shown to be fundamentally different to blood stage merozoites) and the human erythrocytic forms (namely, rings, trophozoites, schizonts, and gametocytes). Extracellular forms thus outnumber intracellular forms by about ten to seven (depending on your definitions of a form). Moreover, the extracellular mosquito sector of the parasite's life cycle (~3 weeks) is 50% longer than the intracellular human sector (~2 weeks). A notable exception is *Plasmodium vivax* hypnozoites, an intracellular liver form that can persist for months or years.

Plasmodium is therefore a facultative intracellular parasite, with a protracted extracellular phase in the definitive (mosquito) host, and a typically shorter intracellular phase in the secondary (human) host, which is also the true vector. Avoid describing *Plasmodium* (or indeed the entire Phylum Apicomplexa) as obligate intracellular parasites, and – these admonitions aside – keep up the good work.

Resources

[i] www.wehi.edu.au/wehi-tv/animation

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References

1. McFadden, G.I. (2012) *Plasmodia* – don't. *Trends Parasitol.* 28, 306
2. Rathnapala, U.L. *et al.* (2017) A novel genetic technique in *Plasmodium berghei* allows liver stage analysis of genes required for mosquito stage development and demonstrates that *de novo* heme synthesis is essential for liver stage development in the malaria parasite. *PLoS Pathog.* 13, e1006396
3. Kantele, A. and Jokiranta, S. (2010) *Plasmodium knowlesi* – the fifth species causing human malaria. *Duodecim* 126, 427–434
4. Kantele, A. and Jokiranta, T.S. (2011) Review of cases with the emerging fifth human malaria parasite, *Plasmodium knowlesi*. *Clin. Infect. Dis.* 52, 1356–1362
5. Ta, T.H. *et al.* (2014) First case of a naturally acquired human infection with *Plasmodium cynomolgi*. *Malar. J.* 13, 68
6. Lalremruata, A. *et al.* (2015) Natural infection of *Plasmodium brasilianum* in humans: man and monkey share quartan malaria parasites in the Venezuelan Amazon. *EBioMedicine* 2, 1186–1192
7. Jongwutiwes, S. *et al.* (2004) Naturally acquired *Plasmodium knowlesi* malaria in human, Thailand. *Emerg. Infect. Dis.* 10, 2211–2213
8. Cox-Singh, J. *et al.* (2008) *Plasmodium knowlesi* malaria in humans is widely distributed and potentially life threatening. *Clin. Infect. Dis.* 46, 165–171
9. Coatney, G.R. (1971) The simian malarias: zoonoses, anthroponoses, or both? *Am. J. Trop. Med. Hyg.* 20, 795–803
10. Dodd, R. (1998) Transmission of parasites by blood transfusion. *Vox Sang.* 74, 161–163
11. Cox, F. (1993) *Modern Parasitology: A Textbook of Parasitology.* (2nd edn), Blackwell Scientific Publications
12. Boyd, M. (1949) *Malariology,* Saunders
13. Scott, R. (1979) *Alien,* 20th Century Fox
14. Dawes, E.J. *et al.* (2009) *Anopheles* mortality is both age- and *Plasmodium*-density dependent: implications for malaria transmission. *Malar. J.* 8, 228
15. Ramasamy, M.S. *et al.* (1997) Interactions of human malaria parasites *Plasmodium vivax* and *P. falciparum*, with the midgut of *Anopheles* mosquitoes. *Med. Vet. Entomol.* 11, 290–296
16. White, N.J. and Pongtavornpinyo, W. (2003) The *de novo* selection of drug-resistant malaria parasites. *Proc. Biol. Sci.* 270, 545–554

Spotlight

A Major Step towards Defining the Elusive Stumpy Inducing Factor in *Trypanosoma brucei*

Lauriane Sollelis[1] and Matthias Marti[1,2,*]

Trypanosoma brucei **stumpy forms are the only stage that can transmit from human to tsetse fly. Stumpy formation is regulated by a quorum sensing mechanism that depends on parasite density and an unknown stumpy induction factor (SIF). Recently, an elegant**