Infection, Genetics and Evolution xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Life in cells, hosts, and vectors: Parasite evolution across scales

ARTICLE INFO

Article history:
Received 13 January 2012
Received in revised form
14 March 2012
Accepted 17 March 2012
Available online xx xxx xxxxy

Presented by Rob
Dedicated to Xu Zhang
Communicated to Roby

Keywords:
Disease
Virulence
Transmission
Selection
Within-host
Between-host

ABSTRACT

Parasite evolution is increasingly being recognized as one of the most important issues in applied evolutionary biology. Understanding how parasites maximize fitness whilst facing the diverse challenges of living in cells, hosts, and vectors, is central to disease control and offers a novel testing ground for evolutionary theory. The Centre for Immunity, Infection, and Evolution at the University of Edinburgh recently held a symposium to address the question "How do parasites maximise fitness across a range of biological scales?" The symposium brought together researchers whose work looks across scales and environments to understand why and how parasites 'do what they do', tying together mechanism, evolutionary explanations, and public health implications. With a broad range of speakers, our aim was to define and encourage more holistic approaches to studying parasite evolution. Here, we present a synthesis of the current state of affairs in parasite evolution, the research presented at the symposium, and insights gained through our discussions. We demonstrate that such interdisciplinary approaches are possible and identify key areas for future progress.

1. Understanding parasite traits

The study of parasites has long been in the remit of biological disciplines that seek proximate explanations of disease (e.g., parasitology and immunology), but interest in the evolutionary explanations has been increasing (e.g., Poulin, 2007; Restif, 2009; Schmid-Hempel, 2011). An evolutionary approach asks: why do parasites 'do what they do'? Why is there so much diversity in parasite traits? What has shaped these phenotypes and why do they lead to different levels of disease in hosts? Such questions are fascinating in their own right and offer novel opportunities to test the generality of evolutionary theory. But finding their answers is also important from an applied perspective. An understanding of what exactly has shaped parasite traits – and the diseases they cause – offers crucial insight into making public health interventions successful in the face of evolution.

Understanding the evolution of parasite phenotypes requires a working definition of parasite fitness and a way of quantifying how traits influence fitness. The standard metric of parasite fitness has long been the basic reproduction number, R_0, (the number of secondary infections produced from a single infected individual in a wholly susceptible population; Anderson and May, 1982; Heesterbeek, 2002). But this 'between-host transmission as fitness' paradigm overlooks the fact that transmission is a consequence of processes acting on a number of different scales and, often, across a number of vastly different environments. In other words, the simple assumption that evolution will maximize R_0 will not hold in many cases. Rather, understanding and predicting disease evolution requires an understanding of the cellular and behavioural interactions between parasites and hosts; of host demography and epidemiology; of vector ecology and immunity; and, especially, of the links between these scales and across environments. This notion formed the basis of an interdisciplinary symposium on parasite evolution hosted by the Centre for Immunity, Infection, and Evolution at the University of Edinburgh. Here, we use the main concepts presented at the symposium as a guide for, first, defining the current state of parasite evolution research and, second, providing suggestions for how the field may progress in the future.

2. Integration across scales, environments, and approaches

2.1. From within to between hosts

Evolutionary theory for parasites has historically focused on explaining 'traits' that are observed at the host population level – virulence (typically, though not exclusively, defined as disease-induced host mortality by theoretical biologists; see Alizon et al., 2009 for discussion), transmission, and recovery – using an approach that relies on the R_0 definition of fitness (e.g., Anderson and May, 1992; Frank, 1996). But these traits are at least in part a consequence of processes that are ongoing within individual hosts, so understanding their evolution may require an understanding of the precise mechanistic interactions within hosts. Likewise, processes occurring at the between-host level can have an impact on within-host processes, for example by determining who gets infected and with what. Despite occurring at different biological scales, within- and between-host processes tend to occur on the same timescales. Theory for parasite evolution has thus begun linking models of within-host dynamics to models of between-host dynamics (reviewed in Mideo et al., 2008).

doi:http://dx.doi.org/10.1016/j.meegid.2012.03.016

Experimental work has also demonstrated that explaining parasite traits with clear consequences at one level often requires considering the less conspicuous consequences at another. For instance, biologists studying malaria parasites have long wondered why they appear to invest remarkably little in producing gametocytes, the stages required for transmitting to new hosts and, thus, responsible for fitness (Taylor and Read, 1997). A recent experimental study showed that such 'reproductive restraint' may be a consequence of multiple infections: malaria parasites reduce their investment in gametocytes when faced with competing parasite strains within a host (Pollitt et al., 2011). This corroborates theory that predicts that shifting investment more heavily into within-host survival maximizes fitness across scales when mixed-genotype infections are common (Mideo and Day, 2008). In response to competitors within a host, malaria parasites also adjust the ratio of male to female gametocytes produced as this determines their inbreeding rate once inside a mosquito vector and, ultimately, their transmission success (Reece et al., 2008). Furthermore, gametocyte-density-dependent processes inside mosquitoes also shape the consequences of investment strategies (Dawes et al., 2009; Pollitt et al., in preparation). These studies demonstrate that explaining malaria parasite strategies depends on an understanding of how those strategies influence measures of success in both the host and the vector, and reveal that parasite traits are highly sensitive to their within-host environment.

Such variation in within-host environments has been incorporated into theoretical studies of virulence evolution, where it has also been shown to alter evolutionary predictions (e.g., Alizon and van Baalen, 2008; Brown et al., 2002; Frank, 1996). However, theory has really only scratched the surface of the ecological interactions within hosts that are likely to be shaping parasite traits. For instance, studies that incorporate multiple infections tend to consider infections with two strains of the same parasite species. Despite receiving less theoretical attention, coinfections between different parasite species are common (e.g., Pedersen and Fenton, 2007; Petney and Andrews, 1998; Rigaud et al., 2010) with variable effects on host health – either exacerbating or alleviating the detrimental effects of a given parasite (Koukounari et al., 2010; Griffiths et al., 2011). Though the direct interactions between parasites occur at the within-host level, these interactions can impact host population level processes, for example if infection with one parasite alters susceptibility to, or recovery from, another (Fenton, 2008). Given the ubiquity of infections with multiple species, considering the evolution of parasite traits of one species in the context of coinfections with another is one area that is ripe for further study.

2.2. Scaling down: cellular interactions

An emerging notion from the symposium was that cell and molecular biology should be better integrated with evolutionary ecology in the study of parasites. Indeed, the vast arsenal of tools and large body of knowledge that cell and molecular parasitologists are generating about what parasites are doing has the potential to provide novel insights on why they are doing it. For instance, a combination of imaging work and proteomic profiling of the intracellular habitat of *Leishmania mexicana* parasites has shown that cholesterol sequesters around parasites in infections due to a specific lack of cholesterol chaperones, and that host cholesterol synthesis is upregulated (Osorio y Fortéa et al., 2009; Barrios-Llerena, Paape & Aebischer, unpublished data). Although an explanation for these observations has yet to be fully elucidated, it is interesting to speculate that parasites may be co-opting a natural synthetic pathway of the host for their own protection. Consider this: host defense against leishmania parasites is largely via oxidative microbicidal mechanisms (Van Assche et al., 2011) and cholesterol synthesis is an oxygen-consuming process (Galea and Brown, 2009). Upregulating cholesterol synthesis could therefore inhibit the production of compounds that attack intracellular parasites.

Integrating cell and molecular biology with evolutionary ecology at the outset of studies can lead to research that is greater than the sum of its parts. Recent work on *Salmonella enterica* combined experimental quantification of bacterial growth with mathematical models describing the spread of *S. enterica* at multiple scales, from single cells to whole host organisms. In addition to generating inferences about bacterial behaviour, demography, and distributions within the host (Brown et al., 2006; Mastroeni et al., 2009), this work inspired novel approaches for quantifying within-host bacterial infection dynamics (Grant et al., 2008). Previous methods, based on tracking the decay of various markers (e.g., fluorescent proteins, non-replicating plasmids) as bacteria divide, pose substantial technical challenges for in vivo studies and can affect the normal cycle of bacteria. Instead, using a set of wild type isogenic tagged strains of *S. enterica*, created by inserting short DNA tags in a non-coding region of the bacterial chromosome that can be identified by PCR, it is possible to estimate bacterial death rates in host organs by monitoring the presence and proportion of the tags (Grant et al., 2008).

2.3. Scaling up: community level processes

Studies of parasites in the wild reveal that the drivers of parasite traits may be constantly changing over time. Parasites capable of infecting a number of host species may be faced with variable relative abundances of host species across space, seasons, or years (e.g., Ruiz-Gonzalez et al., in press). This means that the selection pressures and constraints parasites face – driven by different within-host environments and transmission networks – are dynamic. The traits that confer an advantage in a given season or year (or host species) might not be equally successful the following year (or in an alternative host species). Studying parasite traits at a snapshot in time may therefore give poor insight into their evolutionary causes and consequences.

A corollary of this is that parasites have an incredible capacity to deal with changes in their host communities. Despite their highly complex life cycle, schistosomes seem capable of dealing with the loss of one of their main definitive hosts – humans – via drug treatment or other disease control programs. Field data show that schistosomes are shifting the time of day at which they release infective cercarial stages in different ways across environments, reflecting the identities and activity patterns of the most abundant definitive hosts (Lu et al., 2009, 2010). Further, recent evidence suggests that hybridization between a bovine- and a human-infecting species has resulted from increased cow–human interactions (Huyse et al., 2009). What is clear from these case studies is that whilst it is important to account for the actual ecology of parasites when studying parasite evolution, the reverse can be equally informative: observing parasite evolution in action can help us understand the (emerging) ecology and natural history of parasites.

2.4. Multi-trophic interactions

Parasite traits are likely to be shaped by an incredibly complex set of interspecific interactions. A parasite that is transmitted by a vector may need to deal with host immune responses, vector immune responses, host-derived factors in vector bloodmeals, and vector responses to these factors. From an evolutionary ecology perspective, there has been a considerable amount of research on how parasites deal with host immune responses whilst in a vertebrate host (e.g., antigenic variation; see for example Barbour et al.,

2006; Lythgoe et al., 2007; Recker et al., 2011) and interest in the extent and importance of vector immunity is increasing (e.g., Tripet et al., 2008). However, the importance of the latter two sets of factors has received less attention. Host factors in a bloodmeal remain damaging to parasites and in some cases, parasites become even more susceptible once in the vector (e.g., Margos et al., 2001). These same host factors can also be damaging to the vector itself. In response, vectors have evolved mechanisms for inhibiting such host responses (e.g., Barros et al., 2009) allowing for the fascinating possibility that parasites may be able to co-opt these vector responses for their own benefit (Ooi et al., in preparation). Similarly, parasites are capable of exploiting host-derived factors to help them invade and establish in the vector (e.g., Ghosh et al., 2011).

Such complex, tri-trophic interactions are likely to be more important in parasite evolutionary ecology than is currently appreciated. Bacterial symbionts, for instance, have recently been shown to affect both the susceptibility of hosts (e.g., Koch and Schmid-Hempel, 2011) and vectors (e.g., Cirimotich et al., 2011; Dale and Welburn, 2001) to infection, raising hopes that bacteria can be exploited for the control of other disease (e.g., Enserink, 2010; Moreira et al., 2009; Turner et al., 2010). Further, in some cases, these interactions will obscure what appear to be traits of parasites. For example, it is only via a mutualistic interaction with a bacterium that entomopathogenic nematodes are parasitic at all (Kaya and Gauger, 1993), and endosymbiontic bacteria have been implicated in the pathology attributed to filarial nematodes (Saint André et al., 2002).

2.5. A parasite by any other name

A final lesson provided by the symposium was that evolutionary ecologists must keep in mind that some of the critters they study as parasites may spend much of their life in a completely different ecological role. In fact, the traits that we think are important from a host-centric perspective (e.g., virulence, drug resistance) might actually be under selection in an entirely different environment for an entirely different purpose. This is especially likely to be the case for opportunistic parasites that spend much of their time living in soil, acting as commensals in another host tissue, or living in a different species of host (Brown et al., in press).

A suite of impressive bacterial generalists and part-time parasites (*Pseudomonas aeruginosa*, *Escherichia coli*, *Serratia marcensens*) provide a number of examples of the complex selective pressures shaping clinically important traits. Resistance to antibiotics in bacteria appears to be subject to a delicate interplay between key molecular parasites of the bacteria: plasmids, which carry resistance genes, and phages, which exploit the plasmids as a means of entry into bacteria (Jalasvuori et al., 2011). The expression of traits underpinning virulence has also been shown to be sensitive to the presence of protist predators and viral parasites of bacteria (Friman et al., 2009, 2011). Whilst host–parasite interactions form the basis of theory for virulence (and other trait) evolution, these studies make clear that entirely distinct interactions can modulate the evolution of such important traits.

3. Conclusions

Parasite traits have causes and consequences at a number of different scales and across environments. Taking a narrow view of parasite evolution therefore risks missing important environmental constraints and selection pressures, and could lead to misascribing the adaptive function of those traits. The potential for more holistic research on parasite evolution to fundamentally change what we know about why parasites 'do what they do' is exciting. We hope this report will encourage further studies that look across scales and environments and integrate between disciplines to understand the biology of these fascinating and important organisms.

Acknowledgements

The symposium was organized by Nicole Mideo and Sam Brown, and funded by the Centre for Immunity, Infection, and Evolution (CIIE), an initiative with the remit to connect evolutionary biology to infection research in order to gain an interdisciplinary perspective on challenges to global health. The CIIE is supported by a Strategic Award from the Wellcome Trust (Grant 095831). We wish to thank the symposium participants for inspiring discussions.

References

Alizon, S., van Baalen, M., 2008. Multiple infections, immune dynamics, and the evolution of virulence. Am. Nat. 172, E150–E168. http://dx.doi.org/10.1086/590958.

Alizon, S., Hurford, A., Mideo, N., van Baalen, M., 2009. Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. J. Evol. Biol. 22, 245–259.

Anderson, R.M., May, R.M. (Eds.), 1982. Population Biology of Infectious Diseases. Springer-Verlag, Berlin.

Anderson, R.M., May, R.M., 1992. Infectious Diseases of Humans. Oxford University Press, Oxford.

Barbour, A.G., Dai, Q., Restrepo, B.I., Stoenner, H.G., Frank, S.A., 2006. Pathogen escape from host immunity by a genome program for antigenic variation. Proc. Natl. Acad. Sci. U S A 103, 18290–18295.

Barros, V.C., Assumpção, J.G., Cadete, A.M., Santos, V.C., Cavalcante, R.R., Araújo, R.N., Pereira, M.H., Gontijo, N.F., 2009. The role of salivary and intestinal complement system inhibitors in the midgut protection of triatomines and mosquitoes. PLoS ONE 4 (6), e6047.

Brown, S.P., Hochberg, M.E., Grenfell, B.T., 2002. Does multiple infection select for raised virulence? Trends Microbiol. 10, 401–405.

Brown, S.P., Cornell, S.J., Sheppard, M., Grant, A.J., Maskell, D.J., Grenfell, B.T., Mastroeni, P., 2006. Intracellular demography and the dynamics of *Salmonella enterica* infections. PLoS Biol. 4, e349. http://dx.doi.org/10.1038/nrmicro2034.

Brown, S.P., Cornforth, D., Mideo, N. Evolution of virulence in opportunistic pathogens: generalism, plasticity, and control. Trends Microbiol., in press.

Cirimotich, M., Ramirez, J.L., Dimopoulos, G., 2011. Native microbiota shape insect vector competence for human pathogens. Cell Host Microbe 10, 307–310.

Dale, C., Welburn, S.C., 2001. The endosymbionts of tsetse flies: manipulating host–parasite interactions. Int. J. Parasitol. 31, 628–631.

Dawes, E.J., Churcher, T.S., Zhuang, S., Sinden, R.E., Basáñez, M.-G., 2009. Anopheles mortality is both age- and *Plasmodium*-density dependent: implications for malaria transmission. Malaria J. 8, 228. http://dx.doi.org/10.1186/1475-2875-8-228.

Enserink, M., 2010. Infectious diseases: Australia to test "mosquito vaccine" against human disease. Science 330, 1460–1461.

Fenton, A., 2008. Worms and germs: the population dynamic consequences of microparasite-macroparasite co-infection. Parasitol. 135, 1545–1560.

Frank, S.A., 1996. Models of parasite virulence. Quart. Rev. Biol. 71, 37–78.

Friman, V.-P., Lindstedt, C., Hiltunen, T., Laakso, J., Mappes, J., 2009. Predation on multiple trophic levels shapes the evolution of pathogen virulence. PLoS ONE 4, e6761.

Friman, V.-P., Hiltunen, T., Jalasvuori, M., Lindstedt, C., Laanto, E., Örmälä, A.-M., Laakso, J., Mappes, J., Bamford, J., 2011. High temperature and bacteriophages can indirectly select for bacterial pathogenicity in environmental reservoirs. PLoS ONE 6, e17651.

Galea, A.M., Brown, A.J., 2009. Special relationship between sterols and oxygen: were sterols an adaptation to aerobic life? Free Radical. Biol. Med. 47, 880–889. http://dx.doi.org/10.1016/j.freeradbiomed.2009.06.027.

Ghosh, A.K., Coppens, I., Gardsvoll, H., Ploug, M., Jacobs-Lorena, M., 2011. *Plasmodium* ookinetes coopt mammalian plasminogen to invade the mosquito midgut. Proc. Natl. Acad. Sci. U S A 108, 17153–17158.

Grant, A.J., Restif, O., McKinley, T.J., Sheppard, M., Maskell, D.J., Mastroeni, P., 2008. Modelling within-host spatiotemporal dynamics of invasive bacterial disease. PLoS Biol. 6, e74.

Griffiths, E.C., Pedersen, A.B., Fenton, A., Petchey, O.L., 2011. The nature and consequences of coinfection in humans. J. Infect. 63, 200–206. http://dx.doi.org/10.1016/j.jinf.2011.06.005.

Heesterbeek, J.A.P., 2002. A brief history of R_0 and a recipe for its calculation. Acta. Biotheor. 50, 198–204.

Huyse, T., Webster, B.L., Geldof, S., Stothard, J.R., Diaw, O.T., Polman, K., Rollinson, D., 2009. Bidirectional introgressive hybridization between a cattle and a human schistosome species. PLoS Pathog. 5, e1000571. http://dx.doi.org/10.1371/journal.ppat.1000571.

Jalasvuori, M., Friman, V.-P., Nieminen, A., Bamford, J.K.H., Buckling, A., 2011. Bacteriophage selection against a plasmid-encoded sex apparatus leads to the loss of antibiotic-resistance plasmids. Biol. Lett.. http://dx.doi.org/10.1098/rsbl.2011.0384.

Kaya, H.K., Gauger, R., 1993. Entomopathogenic nematodes. Annu. Rev. Entomol. 38, 181–206.

Koch, H., Schmid-Hempel, P., 2011. Socially transmitted gut microbiota protect bumble bees against an intestinal parasite. Proc. Natl. Acad. Sci. U S A. http://dx.doi.org/10.1073/pnas.1110474108.

Koukounari, A., Donnelly, C.A., Sacko, M., Keita, A., Landoure, A., Dembele, R., Bosque-Oliva, E.C., Gabrielli, A., Gouvras, A., Traore, M., Fenwick, A., Webster, J.P., 2010. The impact of single versus mixed schistosome species infections on liver, spleen and bladder morbidity within Malian children pre- and post-praziquantel treatment. BMC Infect. Dis. 10, 227.

Lu, D.-B., Wang, T.-P., Rudge, J.W., Donnelly, C.A., Fang, G.-R., Webster, J.P., 2009. Evolution in a multi-host parasite: chronobiological circadian rhythm and population genetics of *Schistosoma japonicum* cercariae indicates contrasting definitive host reservoirs by habitat. Int. J. Parasitol. 39, 1581–1588.

Lu, D.-B., Wang, T.-P., Rudge, J.W., Donnelly, C.A., Fang, G.-R., Webster, J.P., 2010. Contrasting reservoirs for *Schistosoma japonicum* between marshland and hilly regions in Anhui, China – a two-year longitudinal parasitological survey. Parasitol. 137, 99–110.

Lythgoe, K.A., Morrison, L.J., Read, A.F., Barry, J.D., 2007. Parasite-intrinsic factors can explain the ordered progression of trypanosome antigenic variation. Proc. Natl. Acad. Sci. U S A 104, 8095–8100.

Margos, G., Navarette, S., Butcher, G., Davies, A., Willers, C., Sinden, R.E., Lachmann, P.J., 2001. Interaction between-host complement and mosquito-migut-stage *Plasmodium berghei*. Infect. Immun. 69, 5064–5071.

Mastroeni, P., Grant, A.J., Restif, O., Maskell, D.J., 2009. A dynamic view of the spread and intracellular distribution of *Salmonella enterica*. Nat. Rev. Microbiol. 7, 73–80.

Mideo, N., Day, T., 2008. On the evolution of reproductive restraint in malaria. Proc. R. Soc. B 275, 1217–1224.

Mideo, N., Alizon, S., Day, T., 2008. Linking within- and between-host dynamics in the evolutionary epidemiology of infectious diseases. Trends Ecol. Evol. 23, 511–517.

Moreira, L.A., Iturbe-Ormaetxe, I., Jeffery, J.A., Lu, G.J., Pyke, A.T., Hedges, L.M., Rocha, B.C., Hall-Mendelin, S., Day, A., Riegler, M., Hugo, L.E., Johnson, K.N., Kay, B.H., McGraw, E., van den Hurk, A.F., Ryan, P.A., O'Neill, S.L., 2009. A Wolbachia symbiont in *Aedes aegypti* limits infection with dengue, chikungunya, and *Plasmodium*. Cell 139, 1268–1278.

Ooi, C.P., Haines, L.R., Lehane, M.J., Acosta-Serrano, A. African trypanosomes use tsetse serine protease inhibitors (serpins) to evade being killed by complement in the fly. in preparation.

Osorio y Fortéa, J., de La Llave, E., Regnault, B., Coppée, J.-Y., Milon, G., Lang, T., Prina, E., 2009. Transcriptional signatures of BALB/c mouse macrophages housing multiplying *Leishmania amazonensis* amastigotes. BMC Genomics 10, 119. http://dx.doi.org/10.1186/1471-2164-10-119.

Pedersen, A.B., Fenton, A., 2007. Emphasizing the ecology in parasite community ecology. Trends Ecol. Evol. 22, 133–139.

Petney, T.N., Andrews, R.H., 1998. Multiparasite communities in animals and humans: frequency, structure and pathogenic significance. Int. J. Parasitol. 28, 377–393.

Pollitt, L.C., Mideo, N., Drew, D.R., Scheider, P., Colegrave, N., Reece, S.E., 2011. Competition and the evolution of reproductive restraint in malaria parasites. Am. Nat. 177, 358–367.

Pollitt, L.C., Churcher, T., Khan, S., Shahid, M., Dawes, E. Basenez, M.G., Colegrave, N., Reece, S.E. Costs of crowding for the transmission of malaria parasites. in preparation.

Poulin, R., 2007. Evolutionary Ecology of Parasites. Princeton University Press, Princeton, New Jersey.

Recker, M., Buckee, C.O., Serazin, A., Kyes, S., Pinches, R., Christodoulou, Z., Springer, A.L., Gupta, S., Newbold, C.I., 2011. Antigenic variation in *Plasmodium falciparum* malaria involves a highly structured switching pattern. PLoS Pathog. 7, e1001306.

Reece, S.E., Drew, D.R., Gardner, A., 2008. Sex ratio adjustment and kin discrimination in malaria parasites. Nature 453, 609–614.

Restif, O., 2009. Evolutionary epidemiology 20 years on: challenges and prospects. Infec. Genet. Evol. 9, 108–123.

Rigaud, T., Perrot-Minnot, M.-J., Brown, M.J.F., 2010. Parasite and host assemblages: embracing the reality will improve our knowledge of parasite transmission and virulence. Proc. R. Soc. B 277, 3693–3702. http://dx.doi.org/10.1098/rspb.2010.1163.

Ruiz-Gonzalez, M.X., Bryden, J., Moret, Y., Reber-Funk, C., Schmid-Hempel, P., Brown, M.J.F. Dynamic transmission, host quality and population structure in a multi-host parasite of bumble bees. Evolution, in press.

Saint André, A., Blackwell, N.M., Hall, L.R., Hoerauf, A., Brattig, N.W., Volkmann, L., Taylor, M.J., Ford, L., Hise, A.G., Lass, J.H., Diaconu, E., Pearlman, E., 2002. The role of endosymbiotic Wolbachia bacteria in the pathogenesis of river blindess. Science 295, 1892–1895. http://dx.doi.org/10.1126/science.1068732.

Schmid-Hempel, P., 2011. Evolutionary Parasitology: The Integrated Study of Infections, Immunology, Ecology, and Genetics. Oxford University Press, Oxford.

Taylor, L.H., Read, A.F., 1997. Why so few transmission stages? Reproductive restraint by malaria parasites. Parasitol. Today 13, 135–140.

Tripet, F., Aboagye-Antwi, F., Hurd, H., 2008. Ecological immunology of mosquito–malaria interactions. Trends Parasitol. 24, 219–227.

Turner, J.D., Tendongfor, N., Esum, M., Johnston, K.L., Langley, R.S., Ford, L., Faragher, B., Specht, S., Mand, S., Hoerauf, A., Enyong, P., Wanji, S., Taylor, M.J., 2010. Macrofilaricidal activity after doxycycline only treatment of *Onchocerca volvulus* in an area of Loa loa co-endemicity: a randomized controlled trial. PLoS Negl. Trop. Dis. 4, e660. http://dx.doi.org/10.1371/journal.pntd.0000660.

Van Assche, T., Deschact, M., Inocêncio da Luz, R.A., Maes, L., Cos, P., 2011. Leishmania–macrophage interactions: insights into the redox biology. Free. Rad. Biol. Med. 51, 337–351. http://dx.doi.org/10.1016/j.freeradbiomed.2011.05.011.

Nicole Mideo
Centre for Immunity, Infection & Evolution, School of Biological Sciences, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom
Center for Infectious Disease Dynamics, Department of Biology, Pennsylvania State University, University Park, PA 16802, USA
E-mail address: nlm12@psu.edu

Alvaro Acosta-Serrano
Molecular and Biochemical Parasitology Group, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, United Kingdom

Toni Aebischer
Parasitology Laboratory, Robert Koch Institute, Berlin, Germany

Mark J.F. Brown
School of Biological Sciences, Royal Holloway, University of London, Egham, Surrey TW20 0EX, United Kingdom

Andy Fenton
Institute of Integrative Biology, University of Liverpool, Crown Street, Liverpool L69 7ZB, United Kingdom

Ville-Petri Friman
Biosciences, University of Exeter, Penryn, Cornwall TR10 9EZ, United Kingdom

Olivier Restif
Department of Veterinary Medicine, University of Cambridge, Cambridge CB3 0ES, United Kingdom

Sarah E. Reece
Centre for Immunity, Infection & Evolution, School of Biological Sciences, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom
Institutes of Evolution, Immunology and Infection Research, School of Biological Sciences, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom

Joanne P. Webster
Department of Infectious Disease Epidemiology, Imperial College, St. Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom

Sam P. Brown
Centre for Immunity, Infection & Evolution, School of Biological Sciences, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom
Institutes of Evolution, Immunology and Infection Research, School of Biological Sciences, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom

Available online xxxx