OPINION

Dissecting transmission to understand parasite evolution
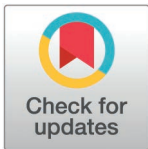
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Abstract

Parasite transmission is a complex, multi-stage process that significantly impacts host–parasite dynamics. Transmission plays a key role in epidemiology and virulence evolution, where it is expected to trade off with virulence. However, the extent to which classical models on virulence–transmission relationships apply in the real world is unclear. This insight piece proposes a novel framework that breaks transmission into three distinct stages: within-host infectiousness, an intermediate between-host stage (biotic or abiotic), and new host infection. Each stage is influenced by intrinsic and extrinsic factors to the parasite, which together will determine its transmission success. Analyzing the transmission stages separately and how they affect each other might enhance our understanding of which host-, parasite- or environmental-driven factors might shape parasite evolution and inform us about new effectors to act on when designing disease control strategies.

1. Introduction

Parasites are fundamentally driven to maximize their reproductive success, i.e., transmission rate to new hosts. This goal drives investment in machinery/traits that maximize transmission rate and ensure the establishment of successful infections in new hosts. Transmission rate and success are then key indicators of parasite fitness [1,2]. They can be defined as the number of secondary hosts infected by a host within a given time. It reflects the parasite's ability to infect a host, to survive and reproduce within it, and then to infect a new host. Several factors can influence and maintain variability in this transmission process, such as the nutritional or dietary status during the development of both host and parasite [3–7]. A poor nutritional status affects the host–parasite interaction, as host immunity might be constrained, and parasite replication slowed down due to competition for resources [8–12]. Parasite transmission is evidently a complex, multi-stage process within and among hosts (Fig 1). The extent to which a parasite invests in each transmission stage may vary depending on host conditions, parasite life history, or environment. Constraints at any one stage can significantly impact the overall transmission process and, consequently, parasite fitness.

Research on parasite transmission is vital for understanding and predicting its evolution, which has major consequences for epidemiology and virulence (i.e., detrimental effects of
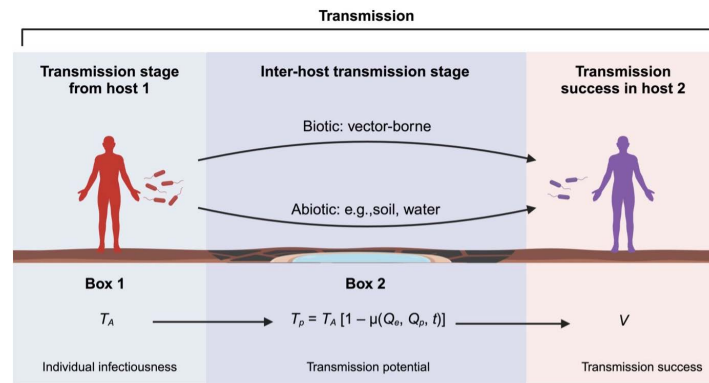
Fig 1. Stages of parasite transmission. Illustration of the different stages for a parasite to successfully transmit into a new host. The production rate of infective cells in host 1 (TA) [17,40] will impact its transmission potential (T_p) after a biotic or abiotic stage outside the main host, which is affected by several intrinsic and extrinsic parasite factors. Tp will impact the chances of infection success in a new host, reflecting the full parasite fitness or transmission (V)— figure produced in Biorender.com.

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infection on its host [13]). In recent years, epidemiological studies have integrated transmission heterogeneity into forecasts of parasite evolutionary trajectories. Superspreading, for example, is when a small number of infected individuals cause a disproportionately large number of new infections [7,14–16]. This phenomenon can undermine control measures and contribute to ongoing epidemics, leading to more frequent disease outbreaks [17,18]. Research on transmission also plays a vital role in the evolution of virulence, where the two traits are expected to be linked. Most major hypotheses, disease control strategies, and predictions regarding virulence evolution [19] are based mainly on the prevailing theory of virulence evolution [2,20,21] due to its easy and broad application. This theory postulates a trade-off between a parasite's transmission rate and its infection virulence [20], meaning a parasite that evolves to kill the host too quickly may not get the chance to be transmitted. This theory has been crucial to estimating and tackling parasite evolution that might jeopardize the survival of populations and species with low genetic diversity (e.g., cattle, endangered species) and, therefore, more susceptible to novel infections [22,23]. Since its introduction approximately 50 years ago, this trade-off theory has found empirical and theoretical support [19,21,24–27]. There are nonetheless questions about its generality across host-parasite systems, with several studies not observing the trade-off or finding that it does not apply to types of infection (e.g., tissue tropism) or transmission modes (e.g., obligate killer parasites) [27–34].

The transmission rate in standard SIR models is often represented by a single parameter: the basic reproductive number (R_0). This parameter is defined as *"the average number of secondary infections caused by a single, infected individual in a completely susceptible population"* [20,35]. R_0 is a valuable tool for predicting whether an infectious disease will become an epidemic [36,37]. It does not, however, account for the variability in transmission rate among individuals [17] or the intricate interactions of intrinsic and extrinsic parameters that influence the transmission process and its outcome [3,38]. To better understand the impact of host heterogeneity in transmission, Lloyd-Smith and colleagues (2005) introduced the concept of *"individual reproduction number"* (or V). This metric represents the expected number of secondary cases caused by each infected individual [17]. By focusing on individual contributions rather than the population average, this concept accounts for variability in transmission among individuals, which can lead to different epidemiological predictions and necessitate

more targeted disease control measures [18,39]. VanderWaal and Ezenwa (2016) expanded this transmission framework to include key aspects of infection and host–parasite interactions that are likely to impact *V*, such as infectiousness, contact rate, and the length of the infectious period [40]. While these [17,40] and other refinements [41] represent a significant advancement by addressing host heterogeneity and its effects, it still overlooks other important factors contributing to the complexity of transmission rate variability [21]. These factors include differences in host contact/behavior [39,42,43], immunocompetence [44–46], host- and parasite-specific factors like parasite load and symptom severity [38,44], and environmental factors such as population density [33,47,48]. Additionally, other factors, such as the protective role of the microbiome [49] or age [50], also play a role in influencing a host's infectiousness and parasite reproductive number.

In this article, we address why and how existing frameworks should include the environment outside of the host, and we tackle the ambiguity regarding the metrics of different transmission stages. Note that although most parasites have an environment outside their primary host (abiotic or biotic), some do not. That is the case for several sexually transmitted infections, such as the human immunodeficiency virus (HIV), which often skips this stage and is directly transmitted from one host to the other. This framework does not apply to those. As stated by McCallum and colleagues (2017), a single transmission term hinders us from understanding the dynamics of transmission but also the relationship between different transmission stages and host-parasite traits. In their study, they showed with theoretical modeling how decomposing transmission can highlight nonlinear relationships between various components of transmission [41] Hence, to enhance our understanding of the relationship between the transmission process and parasite evolution, we enhanced McCallum's deconstruction of the transmission process and proposed an advanced framework that not only breaks down the transmission process into distinct stages but also highlights and formalizes the different factors impacting each stage for empirical testing. Each stage is open to its own set of factors that might influence stage-specific transmission rate metrics or *V*. This framework is designed to be simple enough for broad application across various infection types, yet flexible enough to accommodate different aspects of the parasite's transmission cycle, whether intrinsic or extrinsic. Moreover, we also defined the following transmission stages and respective metrics: (1) initial primary host and infectiousness, i.e., parasite numbers released to the next stage; (2) time between primary hosts and transmission potential, i.e., number of parasites that survive the time (t) outside the host; (3) infection of a new primary host and transmission success, i.e., the parasite can successfully establish an infection in the secondary host (Fig 1). We believe that by formally decomposing the transmission process into its stages, each with its respective metric, we might acquire insights into parasite evolution, the limitations to its evolvability and which factors are responsible for it.

2. Transmissibility and infectiousness

Before transmission to a new host/environment, a parasite must navigate its development within its primary host and address potential constraints the host imposes. These constraints can arise from the host immune strategy [5,51,52] to the resources available for the parasite to sequester and then utilize [53–55], which can also be affected by host microbiota [49,56]. For instance, there is contrasting evidence that microbiota can mediate protection against a parasite but also favor the evolution of virulence in certain conditions [49,57,58]. Nevertheless, a parasite can still manipulate the host's behavior [59] and physiology [60–62] to enhance its chances of transmission. Among the factors influencing this stage, two are particularly relevant: the parasite load and the duration of the infection [40].

A striking example of how within-host factors can influence parasite dynamics and evolution is through the defense strategy employed. Hosts may opt to resist or tolerate a parasite [49,55,63,64]. Resistance involves limiting the number of parasitic cells, while tolerance reduces the damage caused by the infection without directly affecting parasite growth [55]. Tolerance allows a higher parasite load to accumulate within the host. As an example of this in healthcare, a vaccine, such as the one against the common flu, would induce a higher immune response and, therefore, act through resistance instead of tolerance.

Nevertheless, tolerance vaccines have been in the making for a few years now, aiming to decrease the cost of the infection instead of killing the parasite [65–67]. Parasite load within a host is evidently linked to its infectiousness, and it is fair to expect superspreading to evolve in these circumstances. At its core, superspreading is seen when infected hosts can transmit higher parasite loads with fewer visible symptoms or costs than others [15,16]. This phenomenon might entail a population-wide heterogeneity in transmission, and the lack of symptoms in these individuals might lead to weak disease surveillance. Indeed, this variation has been observed in infections such as SARS-CoV-2 [7,68], MERS-CoV [69], Q fever [70], and tuberculosis [71], to name a few. Given the nature of tolerance, it is fair to assume this strategy might lead to more contagious infections than resistance [72], although there is no empirical evidence for it yet. Differences in how hosts allocate resources or invest into resistance or tolerance [73–75] will result in a mix of highly contagious superspreader hosts and individuals who contribute minimally to the populational transmission rate.

Transmissibility, as the ability to transmit a given infection, is determined not only by the number of parasite cells produced during a certain infection period but also by their quality and infectious potential. These factors, in turn, can be grouped into physiological or behavioral mechanisms [17,40] which may evolve independently or together. Physiological mechanisms involve factors affecting the length of the infectious period (I_p) and the infectiousness of the parasites produced (β_p). Behavioral mechanisms include host social aspects, such as population density or increased contact rates (β_c), which are dependent on host motility and can be genetically governed [76]. For instance, the transmission of the parasite *Plasmodium falciparum* is associated with its density during its infectious stage, which is regulated physiologically by the host immune system [60]. Nonetheless, the contagious stage also increases the human attractiveness to mosquitoes and behaviorally increases the chances of transmission [60] (so, its infectiousness). Consequently, both types of mechanisms can differently affect parasite reproductive numbers through variation in some of the main components of transmission: the number and quality of parasites within their host. Measured on an appropriate scale, these can be multiplied to give the ability of transmission (T_A).

$$T_A = \beta_p \times \beta_c \times I_P$$

Numerous environmental and genetic factors affect each of these parameters, such as the host's nutritional status [5,51,52] and immunocompetence [44–46] and the parasite's reproductive rate in optimal conditions. Moreover, such factors may depend on each other. For example, hosts with a high parasite load may have a lower contact rate or a shorter infectious period. It is important to note that β_c represents behavioral mechanisms contributing to parasite transmission to the next stage, such as movement in the environment *vs.* social isolation.

3. Inter-host stage and transmission potential

Most parasites are not immediately transmitted to a new host. Instead, they may be carried over and developed in vector hosts (biotic environment) or sit and wait in soil, water, or another abiotic environment before infecting a new host. The parasite must survive this

intermediate stage to continue its life cycle and be exposed to a new host. The inability to withstand this environmental intermediate stage or develop the infective stage will result in an impaired parasite transmission rate and success. The importance of survival is obvious for parasites with free-living stages and vector-borne parasites. Long-lived resting stages are slowly degraded outside the host, and vector-borne parasites must survive the insect immune response long enough to complete development and produce transmission stages. Survival in the outside environment is also critical for parasites that are directly transmitted. SARS-CoV-2 viruses, for example, are transmitted in droplets and survive for only a short amount of time [77–79].

The intermediate transmission stage outside the primary host can significantly impact the parasite life [80] cycle and transmission potential (T_p). We defined T_P as the number of infective cells that will have the opportunity to infect a new host, if it gets in contact with it. It, therefore, represents the subset of T_A that is able to survive the between-host environment. An important aspect of this framework is that the quality of the parasites at this stage (Q_p) is heavily influenced by the environment in which they were produced and their adaptability to specific conditions. Q_p is affected by parasite taxa and the trade-offs associated with the parasite's development in its initial host. For instance, lines of the parasite *Vavraia culicis* can have a negative correlation between parasite growth within the host and survival outside of the host [81]. Mortality at this stage is also influenced by the favorability of the environment (Q_e). This environment can be anything outside the primary host: (i) a vector host, (ii) a water stream, or (iii) a surface. Nevertheless, using the same model as an example, *V. culicis*, which has a relatively long intermediate stage, is highly sensitive to abiotic factors such as temperature and UV light [82], which can significantly reduce its T_p [81]. Similarly, in vector-borne diseases, the mosquito's nutrition can impact the development of malaria parasites within the vector [5]. Both factors can have aggravated costs/benefits with increased time in the environment (t) and, therefore, prolonged exposure to the factors. These factors can also be applied to vector-borne diseases if we think of them as generic descriptions of complex processes of vector-borne transmission. Thus, Q_e can refer to processes like the immune response of a vector or its mortality rate. Q_p is linked to the growth rate of the parasite in its vector, and t is the developmental time of the parasite in its vector. The two latter factors (Q_p and t) may also be linked to the first transmission stage within the host.

According to life-history theory [83,84], investment in one stage of a parasite's life cycle often involves trade-offs that might affect subsequent stages. So, it is expected that a high parasite load within a primary host is linked to a reduced ability of the parasite to endure different environments. For instance, *Plasmodium* parasites produce more gametocytes, increasing their infectiousness to other mosquitoes [85], but this increase comes at the expense of reduced survival and longevity inside a vector [86]. A similar result is observed in a schistosome parasite whereby higher parasite growth in the final mammal host is associated with lower growth in the intermediate snail host [87].

The importance of such trade-offs is crystallized in the Curse of the Pharaoh hypothesis. The latter posits that infective cells that are able to live for a long time in the environment can exhibit high levels of virulence [88–90]. This hypothesis implies then that in some cases, the usual trade-off between virulence and transmission rate might be less pronounced, or they might be decoupled, challenging the traditional virulence trade-off theory. Furthermore, this hypothesis reinforces the influence of the intermediate between-host environment on the parasite's transmission strategy. Although the Curse of the Pharaoh hypothesis remains relatively unexplored, a meta-analysis has identified examples of the nature of such phenomena [90]. This study also concluded that the relationship between virulence and environmental persistence is often taxa-specific [90] and likely driven by the unique evolutionary histories of

each parasite. Nonetheless, this hypothesis suggests that we may be missing important aspects of the transmission process by not closely examining its stages and how they interact with parasitic traits [40,41]. Theoretical work indicates that additional factors, such as epidemiological dynamics and within-host competition among parasites, are vital for understanding virulence evolution [56,88,89]. Whether long-lived parasites evolve to be more or less virulent depends on the trade-off between virulence and longevity during their free-living stage [91,92] and the environment [93]. Distinguishing between classical transmission metrics and transmission potential can enhance our understanding of disease spread and virulence evolution. Here, we explicitly describe this intermediate stage of transmission among hosts and propose a simplified framework adaptable to most parasites:

$$T_p = T_A\left[1 - \mu\left(Q_e, Q_p, t\right)\right]$$

where μ is the parasite's mortality during the inter-host stage, Q_e and Q_p indicate the quality of the environment and the parasite, respectively, and t is the time spent in this environment. The framework proposed here considers the impact of different ecological and evolutionary effectors on transmission potential.

Here, we provide an example of the applicability of this framework, as conducted by Silva and Koella (2024) (Fig 2). In brief, the parasite *V. culicis* was selected for early- or late-transmission within the host *Anopheles gambiae*, or not (i.e., stock treatment) [94]. The differently selected parasite lines resulted in different levels of virulence within the host [94], with late-selected followed by early-selected and then stock. Hence, we applied this framework to measure their survival and which intrinsic (Q_p) and extrinsic (Q_e) factors impact their survival in the environment outside of the host throughout 90 days and at one of two temperatures, i.e., 4 °C and 20 °C. The effect of Q_p and Q_e on both infectivity (i.e., the proportion of secondarily infected hosts) and infection severity (i.e., parasite burden for those infected) were calculated as demonstrated in Fig 2a and 2b. Regarding infectivity, while Q_p was estimated by subtracting the number of successful transmissions on day 90 by the respective value for 0 days, Q_e was calculated as the difference in successful transmissions on day 90 between 20 °C and 4 °C. The same was performed for infection severity, but instead of the number of successful transmission events, the parasite burden of infected hosts was used. Through the use of this framework, we were able to explain parasite differences in survival outside of the host and, more importantly, that the differences are intrinsic to the parasite, meaning in spore quality and not due to environmental conditions [81].

4. Susceptibility of new host and transmission success

The last transmission stage covers parasites that survived the intermediate stage between hosts and therefore might be exposed to a new primary host, and potentially successfully infect it. If we call the probability of infecting the next host $\beta_p{}'$, overall transmission (thus, V) becomes:

$$V = T_p \times \beta_p{}'$$

or

$$V = T_A\left[1 - \mu\left(Q_e, Q_p, t\right)\right] \times \beta_p{}'$$

and ergo:

$$V = \beta_p \times \beta_c \times I_P\left[1 - \mu\left(Q_e, Q_p, t\right)\right] \times \beta_p{}'$$
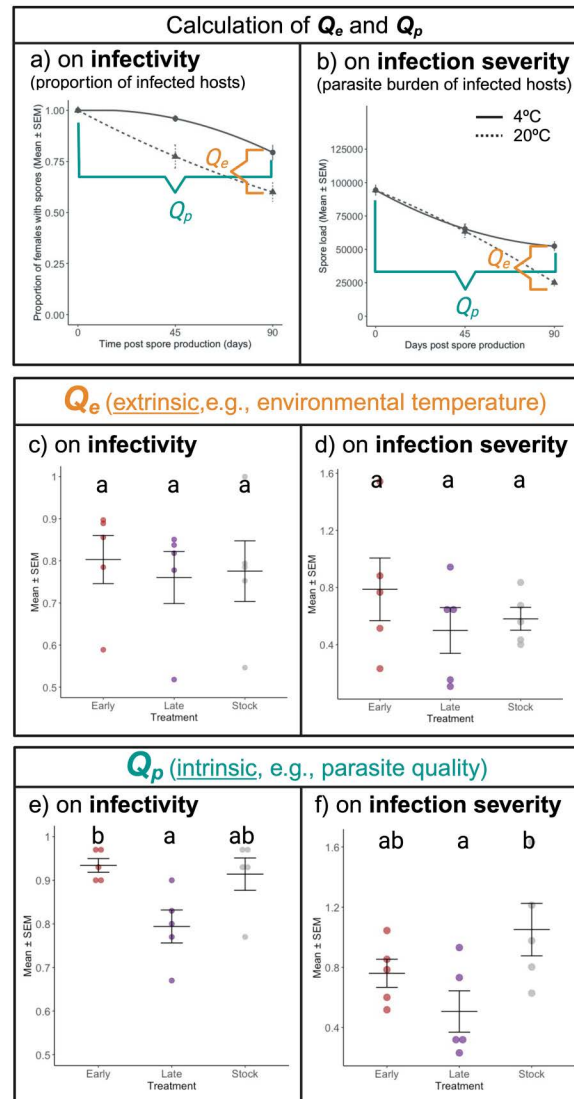
Fig 2. An empirical example of this framework. Silva and Koella (2024) selected the parasite *Vavraia culicis* for early or late transmission within the natural host *Anopheles gambiae*. Differently selected lines presented different levels of virulence within the host [94], which contrasted with different survival outside of the host [81]. To quantify the impact of the parasite quality (Q_p) and environment (Q_e), we used the framework presented in this article. The effects of Q_p and Q_e on (**a**) infectivity (proportion of infected individuals) and (**b**) infection severity (parasite burden of infected individuals) were calculated as demonstrated in the figures (**a**, **c**). Q_p was measured as the mean difference in the proportion of females with spores/spore load between infection with 90-days and 0-days old spores at 4 °C. Q_e, as the effect of environment temperature in this model, was calculated by subtracting the mean proportion of females with spores/spore load after exposure to spores kept at 20 °C for 90 days from the mean proportion of females with spores/spore load at 4 °C for 90 days. The resulting means of each replicate from each treatment were then used in (**c**–**e**). The effects of parasite selection on the parasite spore quality (Q_p) and environmental temperature (Q_e) for (**c**, **e**) infectivity and (**d**, **f**) infection severity (i.e., spore load). Each data point represents the mean value of one of the five replicated selection lines. Letters denote significant differences between treatments according to the multiple comparisons test. Further information can be found in [81].

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Note that β_p' depends on the susceptibility of the new host [15], which can be on factors such as life history [95,96], the immune strategy employed [53,54], the host's genotype [15,97,98], and overall parasite fitness. β_p' can also depend on the quality of the parasites (Q_p), which depends on the previous two stages and is affected by, for example, the first host's

nutrition, genotype and immune response [5,94,99,100] and the between-host environment [101,102]. Finally, β_p' can depend (non-linearly) on the number of parasites in the intermediate stage.

5. Concluding remarks and future directions

Transmission is a critical process of infection. Transmission rate influences parasite and host fitness in the short- and long-term, as well as at an individual and populational level. All these factors can determine the spread of disease and the rate and direction of evolution. Recent work on decomposing [40,103] and extensively studying the components of infection [46,104] and their relationships [94,105,106] is crucial. We propose that incorporating the parasite's life history across different stages of the transmission process, rather than relying solely on classical transmission rate metrics, could improve predictions of infection outcomes in new hosts. The framework developed here is simple and broadly applicable to various parasites and transmission types. While several factors, such as parasite dispersal [107,108], host social aggregation [109,110], and multiple biotic environments (e.g., various vector hosts), are often case-specific, they can be integrated into this framework during the intermediate between-host stage.

The insights and solutions discussed here have significant implications for epidemiology, zoonotic disease emergence, outbreak management, and for understanding virulence evolution. For instance, many "so-called" emerging diseases already have been circulating within human populations but remain below transmission levels high enough to be classified as emergent. While genetic tools alert us of the chances of a zoonotic jump, we do not have much information on which host and parasite factors contribute to an alarming increase in transmission rates. Without the latter, we are unable to fully avoid zoonotic jumps or transmission evolution in a susceptible population.

Although infection biology is entering a new era, a significant gap remains in understanding how host and parasite biology interact to drive heterogeneity in transmission. Our framework directly addresses this gap by allowing transmission to be dissected step-wise and then integrated as a whole. This approach has important implications for disease treatment (medicine), prevention, and prediction (epidemiology). As we move toward increasingly threatened by multi-resistant microbes, it is crucial to exercise greater caution as a species and consider investing in novel disease control strategies, such has been the case of host disease tolerance. However, while much has been hypothesized about the evolutionary implications of host tolerance, relatively little attention has been given to its impact on parasite evolution—particularly in scenarios where evolution favors higher transmission rates, such as superspreading or supershedding.

We cannot overstate the importance of virulence evolution theory and its far-reaching impact on fields essential to human society and nature survival. The ongoing debate over the optimal theory of virulence and transmission evolution is unlikely to be settled soon, given the vast diversity of parasite infection strategies and life cycles—many of which remain poorly understood or entirely unknown. Through the dissection of different components of the transmission process, particularly transmission potential, we may uncover further evidence supporting the trade-off proposed by Anderson and May [2]—or we may not. Ultimately, the dynamics and constraints of infection play a crucial role in shaping transmission. Equally important is identifying which trade-offs could help pinpoint the most effective stages of transmission to target when designing control strategies (and which factors increase or reduce it).

Nonetheless, we can strive for a framework that enables the comparison of diverse parasite taxa under a unified model, which allows transmission to be analyzed as a whole or by individual transmission stages. The framework proposed in this article aims to achieve this while

also establishing a standardized cross-disciplinary terminology applicable across various infections and parasite life cycles. Beyond advancing our understanding of infection and parasite evolution, this approach hopes to invite researchers from different fields to critically assess the limitations of current study models and explore new directions for future research in the field.

Author contributions

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References

1. Read AF, Schrag SJ. The evolution of virulence: experimental evidence. 1991.
2. Anderson RM, May RM. Coevolution of hosts and parasites. Parasitology. 1982;85 (Pt 2):411–26. https://doi.org/10.1017/s0031182000055360 PMID: 6755367
3. Stromberg B. Environmental factors influencing transmission. Vet Parasitol. 1997;72:247–64.
4. Adamson ML, Caira JN. Evolutionary factors influencing the nature of parasite specificity. Parasitology. 1994;109 Suppl:S85–95. https://doi.org/10.1017/s0031182000085103 PMID: 7854854
5. Costa G, Gildenhard M, Eldering M, Lindquist RL, Hauser AE, Sauerwein R, et al. Non-competitive resource exploitation within mosquito shapes within-host malaria infectivity and virulence. Nat Commun. 2018;9(1):3474. https://doi.org/10.1038/s41467-018-05893-z PMID: 30150763
6. Schmid-Hempel P, Koella JC. Variability and its implications for host-parasite interactions. Parasitol Today. 1994;10(3):98–102. https://doi.org/10.1016/0169-4758(94)90007-8 PMID: 15275489
7. Wong G, Liu W, Liu Y, Zhou B, Bi Y, Gao GF. MERS, SARS, and Ebola: the role of super-spreaders in infectious disease. Cell Host Microbe. 2015;18(4):398–401. https://doi.org/10.1016/j.chom.2015.09.013 PMID: 26468744
8. Córdoba-Aguilar A, Munguía-Steyer R. The sicker sex: understanding male biases in parasitic infection, resource allocation and fitness. PLoS One. 2013;8(10):e76246. https://doi.org/10.1371/journal.pone.0076246 PMID: 24194830
9. Bize P, Jeanneret C, Klopfenstein A, Roulin A. What makes a host profitable? Parasites balance host nutritive resources against immunity. Am Nat. 2008;171(1):107–18. https://doi.org/10.1086/523943 PMID: 18171155
10. Zuzarte-Luís V, Mota MM. Parasite sensing of host nutrients and environmental cues. Cell Host Microbe. 2018;23(6):749–58. https://doi.org/10.1016/j.chom.2018.05.018 PMID: 29902440
11. Tate AT, Graham AL. Dynamic patterns of parasitism and immunity across host development influence optimal strategies of resource allocation. Am Nat. 2015;186(4):495–512. https://doi.org/10.1086/682705 PMID: 26655573
12. Barber I. Parasites grow larger in faster growing fish hosts. Int J Parasitol. 2005;35(2):137–43. https://doi.org/10.1016/j.ijpara.2004.11.010 PMID: 15710434
13. Read AF. The evolution of virulence. Trends Microbiol. 1994;2(3):73–6. https://doi.org/10.1016/0966-842x(94)90537-1 PMID: 8156274
14. Teicher A. Super-spreaders: a historical review. Lancet Infect Dis. 2023;23(10):e409–17. https://doi.org/10.1016/S1473-3099(23)00183-4 PMID: 37352877
15. Bates KA, Bolton JS, King KC. A globally ubiquitous symbiont can drive experimental host evolution. Mol Ecol. 2021;30(15):3882–92. https://doi.org/10.1111/mec.15998 PMID: 34037279
16. Siva-Jothy JA, Vale PF. Dissecting genetic and sex-specific sources of host heterogeneity in pathogen shedding and spread. PLoS Pathog. 2021;17(1):e1009196. https://doi.org/10.1371/journal.ppat.1009196 PMID: 33465160
17. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. Nature. 2005;438(7066):355–9. https://doi.org/10.1038/nature04153 PMID: 16292310
18. Stein RA. Super-spreaders in infectious diseases. Int J Infect Dis. 2011;15(8):e510-3. https://doi.org/10.1016/j.ijid.2010.06.020 PMID: 21737332

19. Alizon S, Hurford A, Mideo N, Van Baalen M. Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. J Evol Biol. 2009;22(2):245–59. https://doi.org/10.1111/j.1420-9101.2008.01658.x PMID: 19196383

20. Anderson R, May R. Infectious diseases of humans: dynamics and control. 1991.

21. Cressler CE, McLEOD DV, Rozins C, VAN DEN Hoogen J, Day T. The adaptive evolution of virulence: a review of theoretical predictions and empirical tests. Parasitology. 2016;143(7):915–30. https://doi.org/10.1017/S003118201500092X PMID: 26302775

22. Ganz HH, Ebert D. Benefits of host genetic diversity for resistance to infection depend on parasite diversity. Ecology. 2010;91(5):1263–8. https://doi.org/10.1890/09-1243.1 PMID: 20503859

23. Sommer S. The importance of immune gene variability (MHC) in evolutionary ecology and conservation. Frontiers in Zoology. 2005;2(1):1–18.

24. Leggett HC, Cornwallis CK, Buckling A, West SA. Growth rate, transmission mode and virulence in human pathogens. Philos Trans R Soc B Biol Sci. 2017;372: 20160094.

25. Fenner F. The Florey lecture, 1983. Biological control, as exemplified by smallpox eradication and myxomatosis. Proc R Soc Lond B Biol Sci. 1983;218(1212):259–85. https://doi.org/10.1098/rspb.1983.0039 PMID: 6136042

26. Bérénos C, Schmid-Hempel P, Wegner KM. Evolution of host resistance and trade-offs between virulence and transmission potential in an obligately killing parasite. J Evol Biol. 2009;22(10):2049–56. https://doi.org/10.1111/j.1420-9101.2009.01821.x PMID: 19732263

27. Acevedo MA, Dillemuth FP, Flick AJ, Faldyn MJ, Elderd BD. Virulence-driven trade-offs in disease transmission: a meta-analysis. Evolution. 2019;73(4):636–47. https://doi.org/10.1111/evo.13692 PMID: 30734920

28. Alizon S, van Baalen M. Emergence of a convex trade-off between transmission and virulence. Am Nat. 2005;165(6):E155-67. https://doi.org/10.1086/430053 PMID: 15937740

29. Alizon S, Michalakis Y. Adaptive virulence evolution: the good old fitness-based approach. Trends Ecol Evol. 2015;30(5):248–54. https://doi.org/10.1016/j.tree.2015.02.009 PMID: 25837917

30. Vallée A, Faranda D, Arutkin M. COVID-19 epidemic peaks distribution in the United States of America, from epidemiological modeling to public health policies. Scientific Reports. 2023;134996.

31. Turner WC, Kamath PL, van Heerden H, Huang Y-H, Barandongo ZR, Bruce SA, et al. The roles of environmental variation and parasite survival in virulence-transmission relationships. R Soc Open Sci. 2021;8(6):210088. https://doi.org/10.1098/rsos.210088 PMID: 34109041

32. Sheen JK, Rasambainarivo F, Saad-Roy CM, Grenfell BT, Metcalf CJE. Markets as drivers of selection for highly virulent poultry pathogens. Nat Commun. 2024;15(1):605. https://doi.org/10.1038/s41467-024-44777-3 PMID: 38242897

33. Godinho DP, Rodrigues LR, Lefèvre S, Delteil L, Mira AF, Fragata IR, et al. Limited host availability disrupts the genetic correlation between virulence and transmission. Evol Lett. 2023;7(1):58–66. https://doi.org/10.1093/evlett/qrac008 PMID: 37065437

34. Brown SP, Cornforth DM, Mideo N. Evolution of virulence in opportunistic pathogens: generalism, plasticity, and control. Trends Microbiol. 2012;20:336–342.

35. Delamater PL, Street EJ, Leslie TF, Yang YT, Jacobsen KH. Complexity of the basic reproduction number (R0). Emerg Infect Dis. 2019;25(1):1–4. https://doi.org/10.3201/eid2501.171901 PMID: 30560777

36. Guerra FM, Bolotin S, Lim G, Heffernan J, Deeks SL, Li Y, et al. The basic reproduction number (R0) of measles: a systematic review. Lancet Infect Dis. 2017;17(12):e420–8. https://doi.org/10.1016/S1473-3099(17)30307-9 PMID: 28757186

37. Achaiah NC, Subbarajasetty SB, Shetty RM. R0 and Re of COVID-19: Can we predict when the pandemic outbreak will be contained?. Indian J Crit Care Med. 2020;24(11):1125–7. https://doi.org/10.5005/jp-journals-10071-23649 PMID: 33384521

38. Adelman JS, Hawley DM. Tolerance of infection: a role for animal behavior, potential immune mechanisms, and consequences for parasite transmission. Horm Behav. 2017;8879–86. https://doi.org/10.1016/j.yhbeh.2016.10.013 PMID: 27984034

39. Rushmore J, Caillaud D, Matamba L, Stumpf RM, Borgatti SP, Altizer S. Social network analysis of wild chimpanzees provides insights for predicting infectious disease risk. J Anim Ecol. 2013;82(5):976–86. https://doi.org/10.1111/1365-2656.12088 PMID: 23734782

40. VanderWaal KL, Ezenwa VO. Heterogeneity in pathogen transmission. Funct Ecol. n.d.;30(6):1606–22.

41. McCallum H, Fenton A, Hudson PJ, Lee B, Levick B, Norman R, et al. Breaking beta: deconstructing the parasite transmission function. Philos Trans R Soc Lond B Biol Sci. 2017;372(1719):20160084. https://doi.org/10.1098/rstb.2016.0084 PMID: 28289252

42. Chen S, White BJ, Sanderson MW, Amrine DE, Ilany A, Lanzas C. Highly dynamic animal contact network and implications on disease transmission. Sci Rep. 2014;4:4472. https://doi.org/10.1038/srep04472 PMID: 24667241

43. Mousa A, Winskill P, Watson OJ, Ratmann O, Monod M, Ajelli M, et al. Social contact patterns and implications for infectious disease transmission—a systematic review and meta-analysis of contact surveys. Elife. 2021;10:e70294. https://doi.org/10.7554/eLife.70294 PMID: 34821551

44. Burgan SC, Gervasi SS, Johnson LR, Martin LB. How individual variation in host tolerance affects competence to transmit parasites. Physiol Biochem Zool. 2019;92(1):49–57. https://doi.org/10.1086/701169 PMID: 30481116

45. Krist AC, Jokela J, Wiehn J, Lively CM. Effects of host condition on susceptibility to infection, parasite developmental rate, and parasite transmission in a snail–trematode interaction. J Evol Biol. 2004;17:33–40.

46. Hoang KL, Read TD, King KC. Incomplete immunity in a natural animal-microbiota interaction selects for higher pathogen virulence. Curr Biol. 2024.

47. Fenton A, Fairbairn J, Norman R, Hudson P. Parasite transmission: reconciling theory and reality. J Anim Ecol. 2002;71:893–905.

48. Arneberg P, Skorping A, Grenfell B, Read AF. Host densities as determinants of abundance in parasite communities. Proc R Soc Lond B. 1998;265(1403):1283–9. https://doi.org/10.1098/rspb.1998.0431

49. Ford S, Kao D, Williams D, King K. Microbe-mediated host defence drives the evolution of reduced pathogen virulence. Nat Commun. 2016;7:13430.

50. Izhar R, Ben-Ami F. Host age modulates parasite infectivity, virulence and reproduction. J Anim Ecol. 2015;84(4):1018–28. https://doi.org/10.1111/1365-2656.12352 PMID: 25661269

51. Hall S, Sivars-Becker L, Becker C, Duffy M, Tessier A, Cáceres C. Eating yourself sick: transmission of disease as a function of foraging ecology. Ecol Lett. 2007;10:207–18. https://doi.org/10.1111/j.1461-0248.2007.01019.x

52. De Roode JC, Pedersen AB, Hunter MD, Altizer S. Host plant species affects virulence in monarch butterfly parasites. J Anim Ecol. 2008; 120–126.

53. Macedo da Silva LM. Pathogen infection dynamics and the evolution of host resistance and tolerance. 2021.

54. Read AF, Graham AL, Råberg L. Animal defenses against infectious agents: is damage control more important than pathogen control. PLoS Biol. 2008;6(12):e4. https://doi.org/10.1371/journal.pbio.1000004 PMID: 19222305

55. Kutzer MAM, Armitage SAO. Maximising fitness in the face of parasites: a review of host tolerance. Zoology (Jena). 2016;119(4):281–9. https://doi.org/10.1016/j.zool.2016.05.011 PMID: 27373338

56. Armitage SA, Genersch E, McMahon DP, Rafaluk-Mohr C, Rolff J. Tripartite interactions: how immunity, microbiota and pathogens interact and affect pathogen virulence evolution. Curr Opin Insect Sci. 2022;50100871. https://doi.org/10.1016/j.cois.2021.12.011 PMID: 34999035

57. Bian G, Joshi D, Dong Y, Lu P, Zhou G, Pan X, et al. Wolbachia invades *Anopheles stephensi* populations and induces refractoriness to Plasmodium infection. Science. 2013;340(6133):748–51. https://doi.org/10.1126/science.1236192 PMID: 23661760

58. Teixeira L, Ferreira A, Ashburner M. The bacterial symbiont Wolbachia induces resistance to RNA viral infections in *Drosophila melanogaster*. PLoS Biol. 2008;6(12):e2. https://doi.org/10.1371/journal.pbio.1000002 PMID: 19222304

59. Koella JC, Rieu L, Paul REL. Stage-specific manipulation of a mosquito's host-seeking behavior by the malaria parasite *Plasmodium gallinaceum*. Behav Ecol. 2002;13(5):816–20.

60. Lacroix R, Mukabana WR, Gouagna LC, Koella JC. Malaria infection increases attractiveness of humans to mosquitoes. PLoS Biol. 2005;3(9):e298. https://doi.org/10.1371/journal.pbio.0030298 PMID: 16076240

61. Robinson A, Busula AO, Voets MA, Beshir KB, Caulfield JC, Powers SJ, et al. Plasmodium-associated changes in human odor attract mosquitoes. Proc Natl Acad Sci U S A. 2018;115(18):E4209–18. https://doi.org/10.1073/pnas.1721610115 PMID: 29666273

62. Luong L, Grear D, Hudson P. Manipulation of host-resource dynamics impacts transmission of trophic parasites. Int J Parasitol. 2014;44:737–42.

63. Råberg L, Graham AL, Read AF. Decomposing health: tolerance and resistance to parasites in animals. Philos Trans R Soc Lond B Biol Sci. 2009;364(1513):37–49. https://doi.org/10.1098/rstb.2008.0184 PMID: 18926971

64. Medzhitov R, Schneider DS, Soares MP. Disease tolerance as a defense strategy. Science. 2012;335(6071):936–41. https://doi.org/10.1126/science.1214935 PMID: 22363001

65. Ichino M, Mor G, Conover J, Weiss WR, Takeno M, Ishii KJ, et al. Factors associated with the development of neonatal tolerance after the administration of a plasmid DNA vaccine. J Immunol. 1999;162(7):3814–8. https://doi.org/10.4049/jimmunol.162.7.3814 PMID: 10201898

66. Hozé N, Bonhoeffer S, Regoes R. Assessing the public health impact of tolerance-based therapies with mathematical models. PLoS Comput Biol. 2018;14(5):e1006119. https://doi.org/10.1371/journal.pcbi.1006119 PMID: 29727455

67. Schofield L, Hewitt MC, Evans K, Siomos M-A, Seeberger PH. Synthetic GPI as a candidate anti-toxic vaccine in a model of malaria. Nature. 2002;418(6899):785–9. https://doi.org/10.1038/nature00937 PMID: 12181569

68. Kirkegaard JB, Sneppen K. Superspreading quantified from bursty epidemic trajectories. Sci Rep. 2021;11(1):24124. https://doi.org/10.1038/s41598-021-03126-w PMID: 34916534

69. Hui DS. Super-spreading events of MERS-CoV infection. Lancet. 2016;388(10048):942–3. https://doi.org/10.1016/S0140-6736(16)30828-5 PMID: 27402382

70. Porten K, Rissland J, Tigges A, Broll S, Hopp W, Lunemann M, et al. A super-spreading ewe infects hundreds with Q fever at a farmers' market in Germany. BMC Infect Dis. 2006;6147. https://doi.org/10.1186/1471-2334-6-147 PMID: 17026751

71. Lee RS, Proulx J-F, McIntosh F, Behr MA, Hanage WP. Previously undetected super-spreading of *Mycobacterium tuberculosis* revealed by deep sequencing. Elife. 2020;9:e53245. https://doi.org/10.7554/eLife.53245 PMID: 32014110

72. Gopinath S, Lichtman JS, Bouley DM, Elias JE, Monack DM. Role of disease-associated tolerance in infectious superspreaders. Proc Natl Acad Sci U S A. 2014;111(44):15780–5. https://doi.org/10.1073/pnas.1409968111 PMID: 25331868

73. Lefèvre T, Williams A, de Roode J. Genetic variation in resistance, but not tolerance, to a protozoan parasite in the monarch butterfly. Proc R Soc B Biol Sci. 2010;277(1685):. https://doi.org/10.1098/rspb.2010.1479

74. Mazé-Guilmo E, Loot G, Páez DJ, Lefèvre T, Blanchet S. Heritable variation in host tolerance and resistance inferred from a wild host-parasite system. Proc Biol Sci. 2014;281(1779):20132567. https://doi.org/10.1098/rspb.2013.2567 PMID: 24478295

75. Zeller M, Koella JC. Effects of food variability on growth and reproduction of *Aedes aegypti*. Ecol Evol. 2016;6(2):552–9. https://doi.org/10.1002/ece3.1888 PMID: 26843938

76. Krajacic P, Shen X, Purohit PK, Arratia P, Lamitina T. Biomechanical profiling of *Caenorhabditis elegans* motility. Genetics. 2012;191(3):1015–21. https://doi.org/10.1534/genetics.112.141176 PMID: 22554893

77. Bhardwaj R, Agrawal A. Likelihood of survival of coronavirus in a respiratory droplet deposited on a solid surface. Phys Fluids (1994). 2020;32(6):061704. https://doi.org/10.1063/5.0012009 PMID: 32574230

78. Chatterjee S, Murallidharan JS, Agrawal A, Bhardwaj R. Why coronavirus survives longer on impermeable than porous surfaces. Phys Fluids (1994). 2021;33(2):021701. https://doi.org/10.1063/5.0037924 PMID: 33746485

79. Chatterjee S, Murallidharan JS, Agrawal A, Bhardwaj R. How coronavirus survives for hours in aerosols. Phys Fluids (1994). 2021;33(8):081708. https://doi.org/10.1063/5.0059908 PMID: 34471334

80. Mideo N, Alizon S, Day T. Linking within- and between-host dynamics in the evolutionary epidemiology of infectious diseases. Trends Ecol Evol. 2008;23(9):511–7. https://doi.org/10.1016/j.tree.2008.05.009 PMID: 18657880

81. Silva L, Koella J. Virulence evolution: thinking outside of the host. bioRxiv. 2024;2005–24.

82. Becnel JJ, Weiss LM. Microsporidia: pathogens of opportunity. John Wiley & Sons Incorporated; 2014.

83. Flatt T, Heyland A. Mechanisms of life history evolution: the genetics and physiology of life history traits and trade-offs. OUP Oxford; 2011.

84. Stearns SC. The evolution of life histories. Oxford University Press, Oxford; 1992.

85. Bradley J, Stone W, Da DF, Morlais I, Dicko A, Cohuet A, et al. Predicting the likelihood and intensity of mosquito infection from sex specific *Plasmodium falciparum* gametocyte density. Elife. 2018;7:e34463. https://doi.org/10.7554/eLife.34463 PMID: 29848446

86. Dawes E, Churcher T, Zhuang S, Sinden R, Basáñez M-G. Anopheles mortality is both age-and Plasmodium-density dependent: implications for malaria transmission. Malar J. 2009;8:1–16. https://doi.org/10.1186/1475-2875-8-1

87. Davies CM, Webster JP, Woolhous ME. Trade-offs in the evolution of virulence in an indirectly transmitted macroparasite. Proc Biol Sci. 2001;268(1464):251–7. https://doi.org/10.1098/rspb.2000.1367 PMID: 11217894

88. Gandon S. The curse of the pharaoh hypothesis. Proc Biol Sci. 1998;265(1405):1545–52. https://doi.org/10.1098/rspb.1998.0470 PMID: 9744106

89. Bonhoeffer S, Lenski RE, Ebert D. The curse of the pharaoh: the evolution of virulence in pathogens with long living propagules. Proc Biol Sci. 1996;263(1371):715–21. https://doi.org/10.1098/rspb.1996.0107 PMID: 8763793

90. Rafaluk-Mohr C. The relationship between parasite virulence and environmental persistence: a meta-analysis. Parasitology. 2019;146(7):897–902. https://doi.org/10.1017/S0031182019000015 PMID: 30777585

91. Barrett LG, Bell T, Dwyer G, Bergelson J. Cheating, trade-offs and the evolution of aggressiveness in a natural pathogen population. Ecol Lett. 2011;14(11):1149–57. https://doi.org/10.1111/j.1461-0248.2011.01687.x PMID: 21951910

92. Messenger SL, Molineux IJ, Bull JJ. Virulence evolution in a virus obeys a trade-off. Proc Biol Sci. 1999;266(1417):397–404. https://doi.org/10.1098/rspb.1999.0651 PMID: 10097397

93. Mikonranta L, Friman V-P, Laakso J. Life history trade-offs and relaxed selection can decrease bacterial virulence in environmental reservoirs. 2012;

94. Silva LM, Koella JC. Complex interactions in the life cycle of a simple parasite shape the evolution of virulence. 2024. https://doi.org/10.1101/2024.01.28.577571

95. Kurtz J. Specific memory within innate immune systems. Trends Immunol. 2005;26(4):186–92. https://doi.org/10.1016/j.it.2005.02.001 PMID: 15797508

96. Lorenz LM, Koella JC. Maternal environment shapes the life history and susceptibility to malaria of *Anopheles gambiae* mosquitoes. Malar J. 2011;10:382. https://doi.org/10.1186/1475-2875-10-382 PMID: 22188602

97. Howick VM, Lazzaro BP. Genotype and diet shape resistance and tolerance across distinct phases of bacterial infection. BMC Evol Biol. 2014;14(1):56. https://doi.org/10.1186/1471-2148-14-56 PMID: 24655914

98. Kutzer MAM, Kurtz J, Armitage SAO. Genotype and diet affect resistance, survival, and fecundity but not fecundity tolerance. J Evol Biol. 2018;31(1):159–71. https://doi.org/10.1111/jeb.13211 PMID: 29150962

99. Futo M, Armitage SAO, Kurtz J. Microbiota plays a role in oral immune priming in *Tribolium castaneum*. Front Microbiol. 2015;6.

100. Betts A, Rafaluk C, King KC. Host and parasite evolution in a tangled bank. Trends Parasitol. 2016;32(11):863–73. https://doi.org/10.1016/j.pt.2016.08.003 PMID: 27599631

101. Penczykowski RM, Laine A-L, Koskella B. Understanding the ecology and evolution of host-parasite interactions across scales. Evol Appl. 2015;9(1):37–52. https://doi.org/10.1111/eva.12294 PMID: 27087838

102. Didelot X, Walker AS, Peto TE, Crook DW, Wilson DJ. Within-host evolution of bacterial pathogens. Nat Rev Microbiol. 2016;14(3):150–62. https://doi.org/10.1038/nrmicro.2015.13 PMID: 26806595

103. Hidalgo BA, Silva LM, Franz M, Regoes RR, Armitage SAO. Decomposing virulence to understand bacterial clearance in persistent infections. Nat Commun. 2022;13(1):5023. https://doi.org/10.1038/s41467-022-32118-1 PMID: 36028497

104. Hanson MA, Dostálová A, Ceroni C, Poidevin M, Kondo S, Lemaitre B. Synergy and remarkable specificity of antimicrobial peptides in vivo using a systematic knockout approach. Elife. 2019;8:e44341. https://doi.org/10.7554/eLife.44341 PMID: 30803481

105. Hanson MA, Lemaitre B, Unckless RL. Dynamic evolution of antimicrobial peptides underscores trade-offs between immunity and ecological fitness. Front Immunol. 2019;10:2620. https://doi.org/10.3389/fimmu.2019.02620 PMID: 31781114

106. Hasik AZ, King KC, Hawlena H. Interspecific host competition and parasite virulence evolution. Biol Lett. 2023;19(5):20220553. https://doi.org/10.1098/rsbl.2022.0553 PMID: 37130550

107. Nørgaard LS, Zilio G, Saade C, Gougat-Barbera C, Hall MD, Fronhofer EA. An evolutionary trade-off between parasite virulence and dispersal at experimental invasion fronts. Ecology Letters. 2021;24739–50.

108. Wild G, Gardner A, West SA. Adaptation and the evolution of parasite virulence in a connected world. Nature. 2009;459(7249):983–6. https://doi.org/10.1038/nature08071 PMID: 19474791

109. Schmid-Hempel P. Sociality and parasite transmission. Behav Ecol Sociobiol. 2021;75(11):156. https://doi.org/10.1007/s00265-021-03092-3 PMID: 34720348

110. Kappeler PM, Cremer S, Nunn CL. Sociality and health: impacts of sociality on disease susceptibility and transmission in animal and human societies. Philos Trans R Soc Lond B Biol Sci. 2015;370(1669):20140116. https://doi.org/10.1098/rstb.2014.0116 PMID: 25870402