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 in 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 are unclear. In this insight piece, we propose 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. We believe that analyzing the transmission stages separately and analyzing how they influence 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.

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 ensures the establishment of successful infections in new hosts. Transmission rate and success are then key indicators of parasite fitness [1,2] and can be defined as the number of secondary hosts infected by a host within a given period of 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 is known to affect 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 an 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 by 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 largely based 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 estimate and tackle 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].

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" (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 that contribute to the complexity of transmission rate variability [21]. These factors can include differences in host contact rate [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. 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 stages of transmission and host-parasite traits. In their study, they showed with theoretical modelling how decomposing transmission can highlight nonlinear relationships between different 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; 2) time between primary hosts and transmission potential; 3) infection of a new

primary host and transmission success (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.

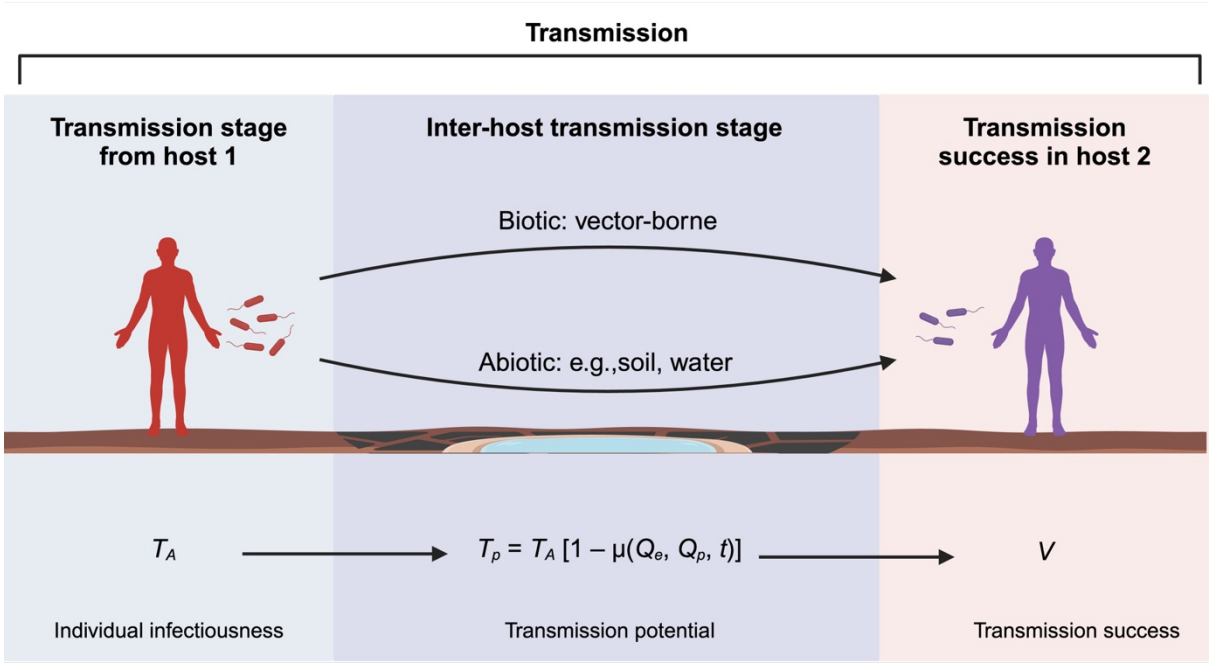

Figure 1. Stages of parasite transmission. Illustration of the different stages for a parasite to successfully transmit into a new host. The rate of production of infective cells in host 1 (T_A) [17,40] will impact its transmission potential (T_p) after a biotic or abiotic stage outside of the main host, 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.

1. Transmissibility and infectiousness

Prior to transmission to a new host/environment, a parasite must navigate its development within its primary host and address potential constraints imposed by the host. 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]. Nevertheless, a parasite still can manipulate the host behavior [56] and its physiology [57–59] to enhance their 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 [49,55,60,61]. 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. 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 a weak disease surveillance. Indeed, this variation has been observed in infections such as SARS-CoV-2 [7,62], MERS-CoV [63], Q fever [64] and tuberculosis [65], to name a few. Given the nature of tolerance, it is fair to assume this strategy might lead to more contagious infections than resistance [66], although there is no empirical evidence for it yet. Differences in how hosts allocate resources or invest into resistance or tolerance [67–69] 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 their 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), dependent on host motility which can be genetically governed [70]. For instance, transmission of the parasite *Plasmodium falciparium* is associated with its density during its infectious stage, which is regulated physiologically by the host immune system [57]. Nonetheless, the infectious stage also increases the mosquito's attractiveness to humans, increasing the chances of transmission [57] (so, its

infectiousness) behaviorally. Consequently, both types of mechanisms can differently affect parasite reproductive numbers, through variation in some of the main component's 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).

$$T_A = \beta_p \text{ x } \beta_c \text{ x } I_P$$

Each of these parameters is affected by numerous environmental and genetic factors, like 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.

2. Inter-host stage and transmission potential

Most parasites are not immediately transmitted to a new host. Instead, they may be carried over and develop 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 which are directly transmitted. SARS-CoV-2 viruses, for example, are transmitted in droplets, and survive for only a short amount of time [71–73].

The intermediate transmission stage outside the primary host can significantly impact the parasite life 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. It therefore represents the subset of T_A 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 [74]. Mortality at this stage is also influenced by the favorability of the environment (Q_e). 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 [75], which can significantly reduce its T_p [74]. 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 [76,77], 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 [78] but this increase comes at the expense of reduced survival and longevity inside a vector [79]. 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 [80].

The importance of such trade-offs is crystallized in the Curse of the Pharaoh hypothesis. The latter posits that infective cells able to live for a long time in the environment can exhibit high levels of virulence [81–83]. 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 in nature of such phenomena [83]. This study also concluded that the relationship between virulence and environmental persistence is often taxa-specific [83], 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 [81,82]. 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 [84,85] and the environment [86]. 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:

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

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.

3. 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 β_p', overall transmission (thus, V) becomes:

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

or:

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

and ergo:

$$V = \beta_p \text{ x } \beta_c \text{ x } I_P\,[1 - \mu(Q_e, Q_p, t)] \text{ x } \beta_p'$$

Note that β_p' depends on the susceptibility of the new host [15], which can be on factors such as life history [87,88], the immune strategy employed [53,54], the host's genotype [15,89,90], 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 [5,91–93] and the between-host environment [94,95]. Finally, β_p' can depend (non-linearly) on the number of parasites in the intermediate stage.

4. Concluding remarks and future directions

Transmission is a critical process of infection. Transmission rate influences parasite fitness, host fitness, and the overall infection process. All of which can determine disease spread and the rate and direction of evolution. 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 factors such as parasite dispersal [96,97], host social aggregation [98,99], 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 and disease outbreak management, with implications for how we study virulence evolution. The ongoing debate about virulence and transmission is in part a consequence of the oversimplification of these components. Recent work on decomposing [40,100] and extensively studying the components of infection [46,101], and their relationships [92,102,103], is crucial. A new era in infection biology has begun. Addressing the different components of the transmission process – in particular, transmission potential – we might find more evidence of the trade-offs raised by Anderson and May [2]. After all, the different dynamics and limitations of parasite life history play a major role in shaping transmissibility. Equally important, such trade-offs might reveal which aspects or stages of the transmission process will be more efficient to act on when designing disease control strategies.

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: 411–426.
3. Stromberg BE. Environmental factors influencing transmission. Vet Parasitol. 1997;72: 247–264.
4. Adamson ML, Caira JN. Evolutionary factors influencing the nature of parasite specificity. Parasitology. 1994;109: S85–S95.
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: 3474.
6. Schmid-Hempel P, Koella JC. Variability and its implications for host-parasite interactions. Parasitol Today. 1994;10: 98–102.
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: 398–401.
8. Córdoba-Aguilar A, Munguía-Steyer R. The sicker sex: understanding male biases in parasitic infection, resource allocation and fitness. PLoS One. 2013;8: e76246.
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: 107–118.
10. Zuzarte-Luís V, Mota MM. Parasite sensing of host nutrients and environmental cues. Cell Host Microbe. 2018;23: 749–758.
11. Tate AT, Graham AL. Dynamic patterns of parasitism and immunity across host development influence optimal strategies of resource allocation. Am Nat. 2015;186: 495–512.
12. Barber I. Parasites grow larger in faster growing fish hosts. Int J Parasitol. 2005;35: 137–143.
13. Read AF. The evolution of virulence. Trends Microbiol. 1994;2: 73–76.
14. Teicher A. Super-spreaders: a historical review. Lancet Infect Dis. 2023.
15. Bates KA, Bolton JS, King KC. A globally ubiquitous symbiont can drive experimental host evolution. Mol Ecol. 2021;30: 3882–3892.

16. Siva-Jothy JA, Vale PF. Dissecting genetic and sex-specific sources of host heterogeneity in pathogen shedding and spread. PLoS Pathog. 2021;17: e1009196.
17. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. Nature. 2005;438: 355–359.
18. Stein RA. Super-spreaders in infectious diseases. Int J Infect Dis. 2011;15: e510–e513.
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: 245–259.
20. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford university press; 1991.
21. Cressler CE, McLeod D V, Rozins C, Van Den Hoogen J, Day T. The adaptive evolution of virulence: a review of theoretical predictions and empirical tests. Parasitology. 2016;143: 915–930.
22. Ganz HH, Ebert D. Benefits of host genetic diversity for resistance to infection depend on parasite diversity. Ecology. 2010;91: 1263–1268.
23. Sommer S. The importance of immune gene variability (MHC) in evolutionary ecology and conservation. Front Zool. 2005;2: 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 FJ. The Florey Lecture, 1983-Biological control, as exemplified by smallpox eradication and myxomatosis. Proc R Soc London Ser B Biol Sci. 1983;218: 259–285.
26. Bérénos C, Schmid-Hempel P, Mathias Wegner K. Evolution of host resistance and trade-offs between virulence and transmission potential in an obligately killing parasite. J Evol Biol. 2009;22: 2049–2056.
27. Acevedo MA, Dillemuth FP, Flick AJ, Faldyn MJ, Elderd BD. Virulence-driven trade-offs in disease transmission: A meta-analysis. Evolution (N Y). 2019;73: 636–647.
28. Alizon S, van Baalen M. Emergence of a convex trade-off between transmission and virulence. Am Nat. 2005;165: E155–E167.
29. Alizon S, Michalakis Y. Adaptive virulence evolution: the good old fitness-based approach.

Trends Ecol Evol. 2015;30: 248–254.

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. Sci Rep. 2023;13: 4996.

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: 210088.

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: 605.

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: 58–66.

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.

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: e420–e428.

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 peer-reviewed, Off Publ Indian Soc Crit Care Med. 2020;24: 1125.

38. Adelman JS, Hawley DM. Tolerance of infection: a role for animal behavior, potential immune mechanisms, and consequences for parasite transmission. Horm Behav. 2017;88: 79–86.

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: 976–986.

40. VanderWaal KL, Ezenwa VO. Heterogeneity in pathogen transmission. Funct Ecol. 2016;30: 1606–1622.

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 B Biol Sci. 2017;372: 20160084.
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.
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.
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: 49–57.
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 JP, Norman R, Hudson PJ. 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 London Ser B Biol Sci. 1998;265: 1283–1289.
49. Ford SA, Kao D, Williams D, King KC. 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: 1018–1028.
51. Hall SR, Sivars-Becker L, Becker C, Duffy MA, Tessier AJ, Cáceres CE. Eating yourself sick: transmission of disease as a function of foraging ecology. Ecol Lett. 2007;10: 207–218.
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: e1000004.

55. Kutzer MAM, Armitage SAO. Maximising fitness in the face of parasites: a review of host tolerance. Zoology. 2016;119: 281–289.

56. 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: 816–820.

57. Lacroix R, Mukabana WR, Gouagna LC, Koella JC. Malaria infection increases attractiveness of humans to mosquitoes. PLoS Biol. 2005;3: e298.

58. 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. 2018;115: E4209–E4218.

59. Luong LT, Grear DA, Hudson PJ. Manipulation of host-resource dynamics impacts transmission of trophic parasites. Int J Parasitol. 2014;44: 737–742.

60. Råberg L, Graham AL, Read AF. Decomposing health: tolerance and resistance to parasites in animals. Philos Trans R Soc B Biol Sci. 2009;364: 37–49.

61. Medzhitov R, Schneider DS, Soares MP. Disease tolerance as a defense strategy. Science (80-). 2012;335: 936–941.

62. Kirkegaard JB, Sneppen K. Superspreading quantified from bursty epidemic trajectories. Sci Rep. 2021;11: 24124.

63. Hui DS. Super-spreading events of MERS-CoV infection. Lancet (London, England). 2016;388: 942.

64. 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;6: 1–13.

65. 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.

66. Gopinath S, Lichtman JS, Bouley DM, Elias JE, Monack DM. Role of disease-associated

tolerance in infectious superspreaders. Proc Natl Acad Sci. 2014;111: 15780–15785.

67. Lefèvre T, Williams AJ, de Roode JC. Genetic variation in resistance, but not tolerance, to a protozoan parasite in the monarch butterfly. Proc R Soc London B Biol Sci. 2010; rspb20101479.

68. Mazé-Guilmo E, Loot G, Páez DJ, Lefèvre T, Blanchet S. Heritable variation in host tolerance and resistance inferred. Proc R Soc B, Biol Sci. 2014;281: 2013–2567.

69. Zeller M, Koella JC. Effects of food variability on growth and reproduction of A edes aegypti. Ecol Evol. 2016;6: 552–559.

70. Krajacic P, Shen X, Purohit PK, Arratia P, Lamitina T. Biomechanical profiling of Caenorhabditis elegans motility. Genetics. 2012;191: 1015–1021.

71. Bhardwaj R, Agrawal A. Likelihood of survival of coronavirus in a respiratory droplet deposited on a solid surface. Phys Fluids. 2020;32.

72. Chatterjee S, Murallidharan JS, Agrawal A, Bhardwaj R. Why coronavirus survives longer on impermeable than porous surfaces. Phys Fluids. 2021;33.

73. Chatterjee S, Murallidharan JS, Agrawal A, Bhardwaj R. How coronavirus survives for hours in aerosols. Phys fluids. 2021;33.

74. Silva LM, Koella JC. Virulence evolution: thinking outside of the host. bioRxiv. 2024; 2005–2024.

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

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

77. Stearns SC. The evolution of life histories. Oxford university press Oxford; 1992.

78. 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.

79. Dawes EJ, Churcher TS, Zhuang S, Sinden RE, Basáñez M-G. Anopheles mortality is both age-and Plasmodium-density dependent: implications for malaria transmission. Malar J.

2009;8: 1–16.

80. Davies CM, Webster JP, Woolhouse MEJ. Trade–offs in the evolution of virulence in an indirectly transmitted macroparasite. Proc R Soc London Ser B Biol Sci. 2001;268: 251–257.

81. Gandon S. The curse of the pharoah hypothesis. Proc R Soc London Ser B Biol Sci. 1998;265: 1545–1552.

82. Bonhoeffer S, Lenski RE, Ebert D. The curse of the pharaoh: the evolution of virulence in pathogens with long living propagules. Proc R Soc London Ser B Biol Sci. 1996;263: 715–721.

83. Rafaluk-Mohr C. The relationship between parasite virulence and environmental persistence: a meta-analysis. Parasitology. 2019;146: 897–902.

84. 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: 1149–1157.

85. Messenger SL, Molineux IJ, Bull JJ. Virulence evolution in a virus obeys a trade off. Proc R Soc London Ser B Biol Sci. 1999;266: 397–404.

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

87. Kurtz J. Specific memory within innate immune systems. Trends Immunol. 2005;26: 186–192.

88. Lorenz LM, Koella JC. Maternal environment shapes the life history and susceptibility to malaria of Anopheles gambiae mosquitoes. Malar J. 2011;10: 1–8.

89. Howick VM, Lazzaro BP. Genotype and diet shape resistance and tolerance across distinct phases of bacterial infection. BMC Evol Biol. 2014;14: 56.

90. Kutzer MAM, Kurtz J, Armitage SAO. Genotype and diet affect resistance, survival, and fecundity but not fecundity tolerance. J Evol Biol. 2018;31: 159–171.

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

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

93. Betts A, Rafaluk C, King KC. Host and parasite evolution in a tangled bank. Trends Parasitol.

2016;32: 863–873.

94. Penczykowski RM, Laine A, Koskella B. Understanding the ecology and evolution of host–parasite interactions across scales. Evol Appl. 2016;9: 37–52.

95. Didelot X, Walker AS, Peto TE, Crook DW, Wilson DJ. Within-host evolution of bacterial pathogens. Nat Rev Microbiol. 2016;14: 150–162.

96. Nørgaard LS, Zilio G, Saade C, Gougat-Barbera C, Hall MD, Fronhofer EA, et al. An evolutionary trade-off between parasite virulence and dispersal at experimental invasion fronts. Ecol Lett. 2021;24: 739–750.

97. Wild G, Gardner A, West SA. Adaptation and the evolution of parasite virulence in a connected world. Nature. 2009;459: 983–986.

98. Schmid-Hempel P. Sociality and parasite transmission. Behav Ecol Sociobiol. 2021;75: 156.

99. Kappeler PM, Cremer S, Nunn CL. Sociality and health: impacts of sociality on disease susceptibility and transmission in animal and human societies. Philosophical Transactions of the Royal Society B: Biological Sciences. The Royal Society; 2015. p. 20140116.

100. Acuña-Hidalgo B, Silva LM, Franz M, Regoes RR, Armitage SAO. Decomposing virulence to understand bacterial clearance in persistent infections. Nat Commun. 2022;13: 1–14. doi:10.1038/s41467-022-32118-1

101. 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.

102. Hanson MA, Lemaitre B, Unckless RL. Dynamic evolution of antimicrobial peptides underscores trade-offs between immunity and ecological fitness. Front Immunol. 2019;10: 2620.

103. Hasik AZ, King KC, Hawlena H. Interspecific host competition and parasite virulence evolution. Biol Lett. 2023;19: 20220553.