Dissecting transmission to understand parasite evolution

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Keywords

transmission, virulence, parasite evolution, infection, infectivity

Abstract

Parasite transmission is a complex, multi-stage process that significantly impacts host-parasite dynamics. Transmission plays a key role in epidemiology, due to host heterogeneity in transmission, 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 opinion 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 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 to new hosts. This goal drives investment in machinery/traits that maximize transmission and ensures the establishment of successful infections in new hosts. Transmission is thus a key indicator of parasite fitness (A F Read and Schrag 1991; Anderson and May 1982). It reflects the parasite's ability to infect a host, survive and reproduce within it, and then infect a new host. Several factors can influence and maintain variability in transmission, such as the nutritional or dietary status during the development of both host and parasite (Stromberg 1997; Adamson and Caira 1994; Costa et al. 2018; P Schmid-Hempel and Koella 1994; Wong et al. 2015). 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 (Córdoba-Aguilar and Munguía-Steyer 2013; Bize et al. 2008; Zuzarte-Luís and Mota 2018; Tate and Graham 2015; Barber 2005). 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 (Andrew F Read 1994)). 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 (Teicher 2023; Wong et al. 2015; Bates, Bolton, and King 2021; Siva-Jothy and Vale 2021). This phenomenon can undermine control measures and contribute to ongoing epidemics by leading to more frequent disease outbreaks (Lloyd-Smith et al. 2005; Stein 2011). 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 (Alizon et al. 2009) are largely based on the prevailing theory of virulence evolution (Anderson and May 1991, 1982; Cressler et al. 2016) due to its easy and broad application. This

theory postulates a trade-off between a parasite's transmission rate and its infection virulence (Anderson and May 1991), 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 (Ganz and Ebert 2010; Sommer 2005). Since its introduction approximately 50 years ago, this trade-off theory has found empirical and theoretical support (Alizon et al. 2009; Leggett et al. 2017; Fenner 1983; Bérénos, Schmid-Hempel, and Mathias Wegner 2009; Acevedo et al. 2019; Cressler et al. 2016). 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) (Alizon and van Baalen 2005; Alizon and Michalakis 2015; Acevedo et al. 2019; Vallée, Faranda, and Arutkin 2023; Turner et al. 2021; Sheen et al. 2024; Godinho et al. 2023; Brown, Cornforth, and Mideo 2012).

Transmission 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 (Anderson and May 1991; Delamater et al. 2019). R_0 is a valuable tool for predicting whether an infectious disease will become an epidemic (Guerra et al. 2017; Achaiah, Subbarajasetty, and Shetty 2020). It does not however account for the variability in transmission among individuals (Lloyd-Smith et al. 2005) or the intricate interactions of intrinsic and extrinsic parameters that influence transmission (Adelman and Hawley 2017; Stromberg 1997). 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 (Lloyd-Smith et al. 2005). 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 (Rushmore et al. 2013; Stein 2011). VanderWaal and Ezenwa (2016) expanded this

96 transmission framework to include key aspects of infection and host-parasite interactions that are
97 likely to impact *V*, such as infectiousness, contact rate and the length of the infectious period
98 (VanderWaal and Ezenwa 2016). While these (VanderWaal and Ezenwa 2016; Lloyd-Smith et al.
99 2005) and other refinements (McCallum et al. 2017) represent a significant advancement by
100 addressing host heterogeneity and its effects, it still overlooks other important factors that contribute
101 to the complexity of transmission variability (Cressler et al. 2016). These factors can include
102 differences in host contact rate (Rushmore et al. 2013; Chen et al. 2014; Mousa et al. 2021),
103 immunocompetence (Burgan et al. 2019; Krist et al. 2004; Hoang, Read, and King 2024), host, and
104 parasite-specific factors like parasite load and symptom severity (Adelman and Hawley 2017; Burgan
105 et al. 2019), and environmental factors such as population density (Fenton et al. 2002; Arneberg et al.
106 1998; Godinho et al. 2023). Additionally, other factors such as the protective role of the microbiome
107 (Ford et al. 2016) or age (Izhar and Ben-Ami 2015), also play a role in influencing a host's
108 infectiousness and parasite reproductive number.
109
110 In this opinion, we address why and how existing frameworks should include the environment outside
111 of the host, and we tackle the ambiguity regarding the different transmission stages. To enhance our
112 understanding of the relationship between transmission and parasite evolution, we propose an
113 advanced framework that breaks down transmission into distinct stages. Each stage is open to its own
114 set of factors that might influence stage-specific transmission metrics or *V*. This framework is
115 designed to be simple enough for broad application across various infection types, yet flexible enough
116 to accommodate different aspects of the parasite's transmission cycle, whether intrinsic or extrinsic.
117 Moreover, we also defined the following transmission stages and respective metrics: 1) initial primary
118 host and infectiousness; 2) time between primary hosts and transmission potential; 3) infection of a
119 new primary host and transmission success (Fig. 1). We believe that by formerly decomposing
120 transmission into its stages we might acquire insights into parasite evolution, the limitations to its
121 evolvability and which factors are responsible for it.
122

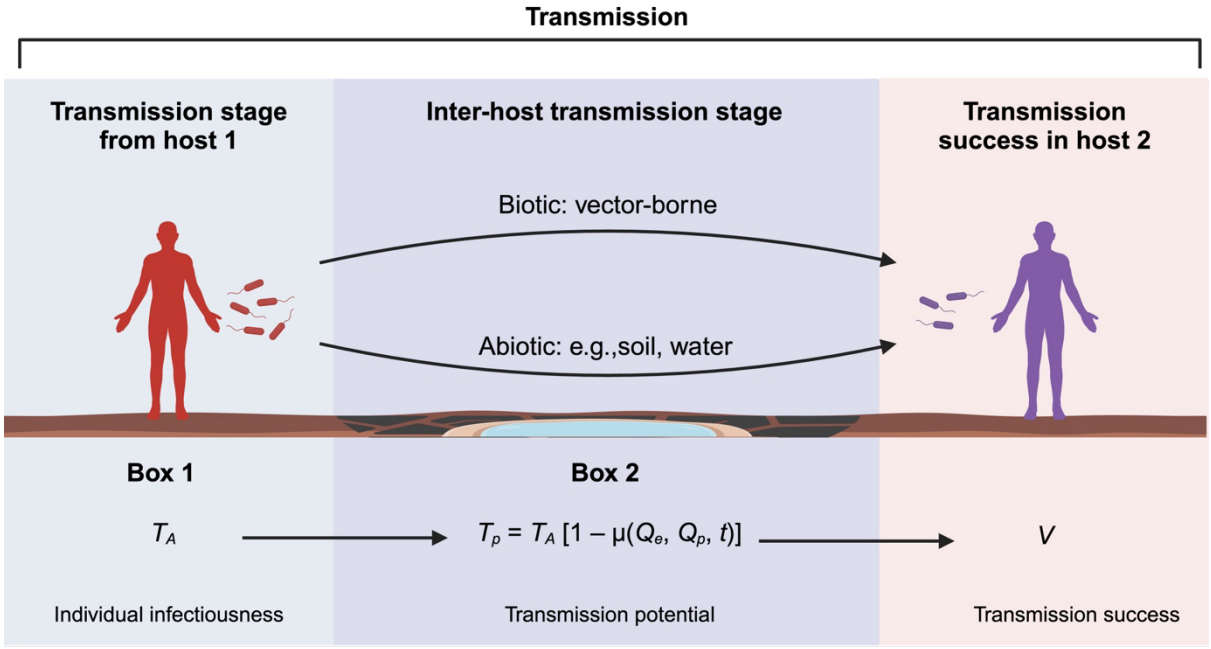

Figure 1. Stages of parasite transmission. Illustration of the different stages for a parasite to successfully transmit into a new host. The rate of production of infective cells in host 1 (T_A) (Lloyd-Smith et al. 2005; VanderWaal and Ezenwa 2016) will impact its transmission potential (T_p) after a 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, 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 (Costa et al. 2018; Hall et al. 2007; De Roode et al. 2008) to the resources available for the parasite to sequester and then utilize (Macedo da Silva 2021; Andrew F Read, Graham, and Råberg 2008; Megan A M Kutzer and Armitage 2016). Nevertheless, a parasite still can manipulate the host behavior (Koella, Rieu, and Paul 2002) and its physiology (Lacroix et al. 2005; Robinson et al. 2018; Luong, Grear, and Hudson 2014) 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 (VanderWaal and Ezenwa 2016).

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 (Råberg, Graham, and Read 2009; Megan A M Kutzer and Armitage 2016; Medzhitov, Schneider, and Soares 2012; Ford et al. 2016). Resistance involves limiting the number of parasitic cells, while tolerance reduces the damage caused by the infection without directly affecting parasite growth (Megan A M Kutzer and Armitage 2016). 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 symptoms than others (Bates, Bolton, and King 2021; Siva-Jothy and Vale 2021). 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 (Kirkegaard and Sneppen 2021; Wong et al. 2015), MERS-CoV (Hui 2016), Q fever (Porten et al. 2006) and tuberculosis (Lee et al. 2020), to name a few. Given the nature of tolerance, it's fair to assume this strategy might lead to more contagious infections than resistance (Gopinath et al. 2014), although there is no empirical evidence for it yet. Differences in how hosts allocate resources or invest into resistance or tolerance (Lefèvre, Williams, and de Roode 2010; Mazé-Guilmo et al. 2014; Zeller and Koella 2016) will result in a mix of highly contagious superspreader hosts and individuals who contribute minimally to transmission.

Transmissibility 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 (Lloyd-Smith et al. 2005; VanderWaal and Ezenwa 2016) 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). 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 (Lacroix et al. 2005). Nonetheless, the infectious stage also increases the mosquito's attractiveness to humans, increasing the chances of transmission (Lacroix et al. 2005) (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 (Costa et al. 2018; Hall et al. 2007; De Roode et al. 2008) and immunocompetence (Burgan et al. 2019; Krist et al. 2004; Hoang, Read, and King 2024), 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. 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 (Bhardwaj and Agrawal 2020; Chatterjee et al. 2021b, 2021a).

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 (Silva and Koella 2024a). 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 (Becnel and Weiss 2014), which can significantly reduce its T_p (Silva and Koella 2024a). Similarly, in vector-borne diseases, the mosquito's nutrition can impact the development of malaria parasites within the vector (Costa et al. 2018). 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 (Flatt and Heyland 2011; Stearns 1992), 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 (Bradley et al. 2018) but this increase comes at the expense of reduced survival and longevity inside a vector (Dawes et al. 2009). 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 (Davies, Webster, and Woolhouse 2001).

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 (Gandon 1998; Bonhoeffer, Lenski, and Ebert 1996; Rafaluk-Mohr 2019). This hypothesis implies then that in some cases the usual trade-off between virulence and transmission 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 (Rafaluk-Mohr 2019). This study also concluded that the relationship between virulence and environmental persistence is often taxa-specific (Rafaluk-Mohr 2019), and likely driven by the unique evolutionary histories of each parasite. Nonetheless, this hypothesis suggests that we may be missing important aspects of transmission by not closely examining its stages and how they interact with parasitic traits (McCallum et al. 2017; VanderWaal and Ezenwa 2016). Theoretical work indicates that additional factors, such as epidemiological dynamics and within-host competition among parasites, are vital for understanding virulence evolution (Bonhoeffer, Lenski, and Ebert 1996; Gandon 1998). 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 (Barrett et al. 2011; Messenger, Molineux, and Bull 1999) and the environment (Mikonranta, Friman, and Laakso 2012). 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 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:

$$V = T_p \text{ x } \beta_p'$$

or:

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

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 (Bates, Bolton, and King 2021), which can be on factors such as life history (Kurtz 2005; Lorenz and Koella 2011), the immune strategy employed (Macedo da Silva 2021; Andrew F Read, Graham, and Råberg 2008), the host's genotype (Howick and Lazzaro 2014; M A M Kutzer, Kurtz, and Armitage 2018; Bates, Bolton, and King 2021), 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 (Costa et al. 2018; Futo, Armitage, and Kurtz 2015; Silva and Koella 2024b; Betts, Rafaluk, and King 2016) and the between-host environment (Penczykowski, Laine, and Koskella 2016; Didelot et al. 2016). 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 parameter of infection. Transmission 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 transmission, rather than relying solely on classical transmission 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 (Nørgaard et al. 2021; Wild, Gardner, and West 2009), host social aggregation (Paul Schmid-Hempel 2021; Kappeler, Cremer, and Nunn 2015), 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 (Acuña-Hidalgo et al. 2022; VanderWaal and Ezenwa 2016) and extensively studying the components of infection (Mark Austin Hanson et al. 2019; Hoang, Read, and King 2024), and their relationships (Mark A Hanson, Lemaitre, and Unckless 2019; Hasik, King, and Hawlena 2023; Silva and Koella 2024b), is crucial. A new era in infection biology has begun. Addressing the different components of transmission – or in particular, transmission potential – we might find more evidence of the trade-offs raised by Anderson and May (Anderson and May 1982). 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 transmission will be more efficient to act on when designing disease control strategies.

Author contributions

LMS conceptualized the idea. JCK and LMS formalized it. JCK, KCK and LMS discussed and wrote the manuscript.

Acknowledgments

LMS is supported by SNF grant 310030_192786. KCK is supported by an NSERC Canada Excellence Research Chair.

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