Dissecting transmission to understand parasite evolution

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Highlights

- Transmission is a complex parameter underlying parasite fitness.
- It is thus determined by a combination of features linked to the original host (e.g., parasite load and infectiousness), to the biotic and abiotic environment between hosts (e.g., longevity and quality of the parasite), and to the next host (e.g. susceptibility).
- Each of these components/steps can be correlated with each other or with other traits, such as the parasite's virulence.
- Decomposing transmission into these distinct steps should lead to a new and better understanding of parasite evolution, particularly the evolution of parasitic virulence.

Abstract

The prevailing theory of the evolution of virulence assumes that evolution maximizes its transmission and relies on a trade-off between virulence and the parasite's transmission rate. While this simple idea finds some empirical support, it is often criticized, in part because of its ambiguity about transmission, the key measure of pathogen fitness. In theoretical and empirical studies, transmission has been increasingly approximated by parasite load. Transmission, however, is a complex parameter that results from distinct steps within and among hosts, with potential correlations and trade-offs among each of the steps. We propose that decomposing explicitly transmission into these steps would enable more precise predictions and a deeper understanding of parasite transmission dynamics and virulence evolution.

Main text

Transmission is a key measure of parasite fitness [1,2], which encompasses the ability of parasites to infect a host, survive and reproduce within it, and then infect a new host. Several factors can affect and maintain variability in transmission [3–7], but regardless of the ecological and evolutionary settings, parasites will always aim to maximize their reproductive output, that is transmission. This fundamental parasite fitness trait has been the focus of study in two large research areas. The first concerns epidemiological ideas underlying the heterogeneity of transmission, which describes phenomena such as superspreading (i.e., where some infected individuals transmit the parasite disproportionately more than others) [7–10]. The latter is expected to reduce the efficiency of control measures and help to maintain an epidemic through more frequent disease outbreaks [11,12]. The second relates to one of the most debated topics in evolutionary biology, the evolution of virulence, meaning the detrimental effect of an infection on a host. Most hypotheses, strategies, and predictions employed today in fields such as medicine and conservation [13] are based on a single principle, the virulence-transmission trade-off theory [14]. This theory postulates that regardless of the parasite's agenda, a

parasite that evolves to kill the host too quickly may not be transmitted as much, or at all, and go extinct. Therefore, virulence (i.e., host mortality) should be offset by a trade-off with transmission rate. Since its introduction approximately 50 years ago, this theory has found considerable empirical support [13,15–17], justifying its rapid application in society. There are however increasing questions about its generality, with several studies failing to observe the assumed relationship between transmission rate and virulence [18–24].

In both areas of study, transmission is commonly approximated to a single parameter: the basic reproductive number (R_0), defined as the average number of secondary infections caused by a single infected individual in a susceptible population [14,25]. Although this parameter is extremely useful in many ways, e.g. by predicting whether an infectious disease will cause an epidemic or die out [26,27], it hides many important aspects of transmission, including its heterogeneity among individuals [11] or the complex and subtle interactions of parameters that determine transmission [3,28].

To better understand the impact of host heterogeneity in transmission, Lloyd-Smith and colleagues (2005) introduced the notion of individual reproduction number (V), which represents the expected number of secondary cases caused by each infected individual [11]. By focusing on the contribution of each individual rather than the average, this concept takes into account the variation in transmission among individuals, which is expected to give different epidemiological predictions and require different and targeted disease control measures [12,29]. Although the acknowledgment of host heterogeneity in transmission is a big step in the right direction, it still, however, ignores the many factors that contribute in complex ways to the complete heterogeneity of transmission. These include host factors like differences in contact rate [29–31] or immunocompetence [32–34], factors due to host-parasite interactions like parasite load or symptom severity [28,32], and environmental factors like density [24,35,36]. All of these (and other) factors, such as protective microbiome [37] or age [38], contribute in complex ways to an individual's infectiousness and reproductive number.

Hence, to reach a deeper understanding of transmission and its role in the epidemiology and evolution of parasites, we suggest decomposing transmission into components that reflect the impacts of the parasite, the host and the environment on transmission, and to study the links between these components. In particular, we focus on three distinct steps (Fig. 1): (i) the infectiousness of the first host; (ii) the transmission from one host to the next, which can be for example through direct contact with long-lived stages in the environment or vector-borne; (iii) and the transmission success once the parasite reaches the next host.

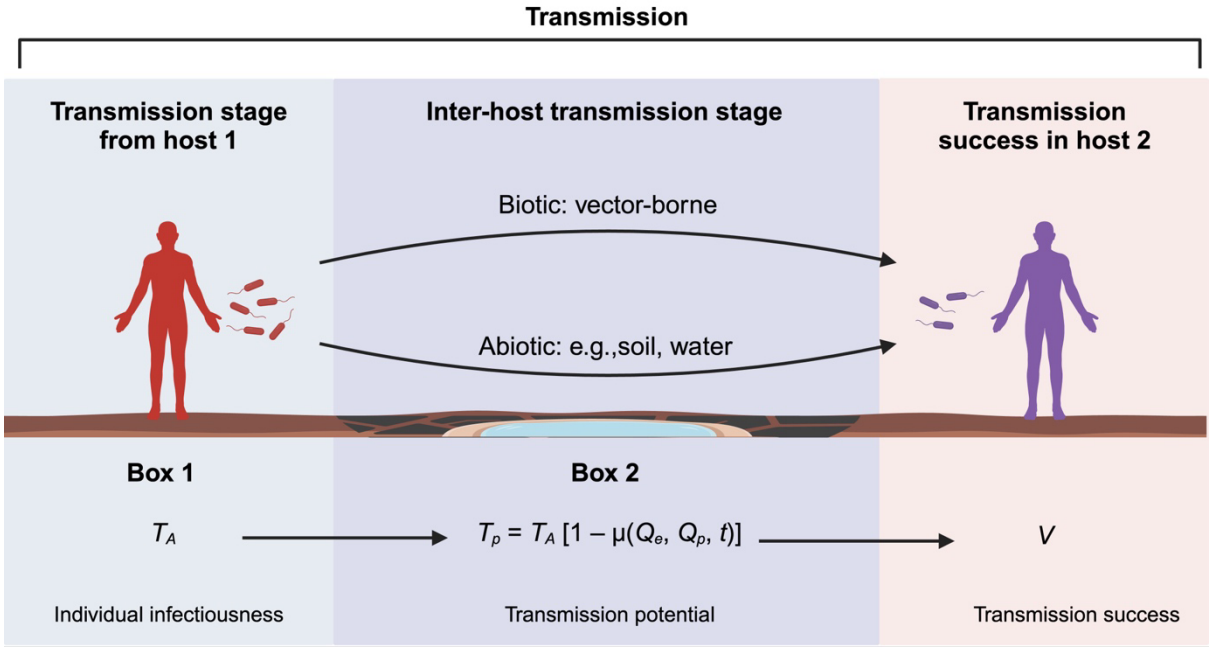

Figure 1. Stages of parasite transmission. Illustration of the different steps a parasite needs to surpass to achieve a successful transmission into a new host. The rate of production of infective cells in host 1 (T_A; described in Box 1) [11,39] will impact its transmission potential (T_p) after a biotic or abiotic step outside of the main host (described in Box 2), 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.

1.1 Individual infectiousness

Prior to transmission, a parasite needs to deal with the development within its host and its intrinsic properties, that being the immune strategy a host opts to employ [40–42] or the number of resources available [5,43,44] for the parasite to sequestrate. Nevertheless, a parasite is also capable of manipulating the host behavior [45] and its physiology [46–48] to facilitate the probability of transmission or increase its rate. From the listed properties, two factors are especially important and reflective of the complexity of this step: the parasite load and the duration of the infection [39]. A striking example of how these can easily be a product of the different factors is through the defense strategy employed by the host. For instance, a host might opt to resist or tolerate a parasite [42,49,50]. However, these defense strategies can be mediated by the host directly or via parasite-microbiota interactions within the host [37]. Resistance acts by limiting the number of parasitic cells, whereas tolerance reduces the damage caused by the parasite without directly interfering with the parasite's growth. Tolerance can enable a high number of parasites to accumulate in the host. As a result, the distinction between resistance and tolerance is important to understand in the context of superspreading, where infected hosts also show fewer symptoms of infection upon transmitting higher numbers than their counterparts [9,10]. Such variation has been observed, for example, in humans infected by SARS-CoV-2 [7,51], MERS-CoV [52], Q fever [53]

and tuberculosis [54], to name a few. Since tolerant hosts are expected to have high parasite loads and to be more contagious than resistant ones [55], variation in the allocation strategies to resistance and tolerance [56–58] will lead to a mixture of highly contagious superspreaders and individuals that contribute only slightly to transmission.

However, transmissibility is determined not only by the number of parasites produced throughout a certain infection period but also by their quality and their infectiousness potential. These in turn can be grouped into physiological or behavioral mechanisms [39] that can evolve independently or together (See Box 1 for further details). Physiological mechanisms entail some of the factors described above that affect the length of the infectious period and/or the infectiousness of the produced parasites, while behavioral include host social aspects like density or other forms of increased contact rate. Transmission of the malaria parasite *Plasmodium falciparum*, for example, is linked to the density of its infectious stage, which is regulated physiologically by the immune system. Nonetheless, the infectious stage also increases the mosquito's attractiveness to humans [46], thus increasing the chances of transmission (so, its infectiousness) behaviorally.

Box 1. Transmissibility from a host

The ability of a parasite to be transmitted out of its host is determined by the interactions of physiological and behavioral mechanisms [11,39]. As above mentioned, 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 (which may be summarized as infectiousness (β_p), the contact rate (β_c) and the duration of the infectious period (I_P)). 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 [5,43,44] and immunocompetence [32–34], and the parasite's reproductive rate in optimal conditions. Furthermore, they may depend on each other. For example, hosts with a high parasite load may have a lower contact rate or a shorter infectious period. Such trade-offs come as no surprise to evolutionary biologists, for they are at the center of the trade-off theory of virulence evolution [14].

1.2 Inter-host stage and transmission potential

Once transmitted, the parasite may come into contact with the subsequent host or encounter a new biotic (e.g., its vector) or abiotic (e.g., water bodies or soil) environment. Only if the (infectious) parasite survives this stage and is exposed to the next host, will it continue its life cycle. The importance of survival is obvious for parasites with free-living stages and vector-borne parasites: long-lived resting stages are slowly degraded throughout the time they spend outside of a host, and a

vector-borne parasite must survive its vector's immune response long enough to complete its development and produce the stages that are transmissible to the next host. But survival is also critical for parasites that are directly transmitted. SARS-CoV-2 viruses, for example, are transmitted in droplets in which they survive for only a short amount of time [59–61].

Therefore, although this transmission stage is often overlooked, it can significantly influence what we refer to as transmission potential (T_P). This parameter is defined as the number of infectious parasites that survive this between-hosts stage and are exposed to the next host. This survival and transmission potential depend on the aspects of the environment (Q_e), on the parasite's quality (Q_p) and on the time it spends in this environment (t) (see Box 2). These factors have straightforward meanings for parasites with free-living stages. However, they 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.

However, the two latter factors (Q_p and t) may well also be linked to the important factors mentioned during the first step, within the host. Indeed, according to standard ideas of life-history theory [62,63], we can expect that investing in the first stage – by having a high parasite load – trade-off with the success in the next stage – by decreasing the ability of the parasite to withstand its environment. For example, *Plasmodium* parasites produce more infective stages (i.e., gametocytes) which lead to greater infectiousness to mosquitoes [64] but come at a cost to their longevity and survival inside the vector [65]. A similar result is observed in a schistosome parasite which has an indirect life cycle that includes a mouse and a snail host [66]. In the latter, higher parasite production in the (main) mammal host is correlated to lower production in the intermediary mollusk host.

The importance of such trade-offs is crystallized in the Curse of the Pharoah hypothesis. The latter posits that infective cells able to live for a long time in the environment can exhibit high levels of virulence [67–69]. The latter hints that, at least for this case, the cost of virulence in transmission might be eroded or the two might be decoupled from each other, and incompatible with the trade-off theory of virulence evolution. Although both the virulence trade-off theory and the Curse of the Pharaoh hypothesis are found in the wild, a meta-analysis has shown the relationship between virulence and persistence in the environment is often taxa-specific [69] and a result of taxa-specific adaptations. However, it is likely we are not observing the full picture without dissecting the components of transmission. These two distinct theories are just one of the examples of why considering the stages of transmission is increasingly important to the full understanding of infection evolution. Indeed, theoretical work suggests that additional components of transmission– in particular the epidemiological dynamics and competition of parasites within hosts – are critical to understanding evolution [67,68].

Nevertheless, literature has shown that whether long-lived parasites evolve to become more or less virulent mostly depends on the trade-off between the parasite's virulence and its longevity during its

free-living stage [70,71] and on the properties of the environment [72]. Thus, separating classical transmission metrics and transmission potential might contribute to the understanding of both disease spread and virulence evolution. The framework proposed here considers the impact of different ecological and evolutionary effectors on transmission potential (Box 2 for further details).

Box 2. Inter-host stage and transmission potential

Many parasites are not immediately transmitted to a new host, but they are carried over by (and develop in) vector hosts (biotic environment) or they either develop to an infectious stage or sit-and-wait in soil, water or any other abiotic environment before infecting a new host. In both cases, transmission might be affected by several factors, which combine with what we define as transmission potential (T_p). Hence, we here explicitly describe this stage of transmission, with the aim to generate a simplified framework that can be easily adapted and applied 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.

In this framework, T_p is the number of infective cells that will have the opportunity to infect a new host and therefore represents the subset of T_A that can survive the inter-host environment and time between hosts. An important aspect of this framework is that the quality of the parasites in this stage (Q_p) is strongly affected by the environment in which they were produced and their adaptive potential to certain conditions. Thus, it is affected strongly by parasite taxa and by the trade-offs of the parasite's development within its first host. But mortality can also be strongly influenced by the favorability of the environment (Q_e). For instance, the microsporidian *Vavraia culicis*, which has a relatively long inter-host stage, is very sensitive to abiotic factors like dryness or UV light [73], which can severely reduce their transmission potential the longer they are exposed. An example for a vector-borne disease is the impact of a mosquito's nutrition on the development of malaria parasites within their vector [5].

1.3 Susceptibility of new host and transmission success

What is still missing is that the parasites surviving the inter-host stage must infect the next host. 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 [9], which can be on factors such as life history [74,75], the immune strategy employed [40,41], the host's genotype [9,76,77], and its overall fitness. It can also depend on the quality of the parasites, which depends on the previous two stages and is thus affected by, for example, the first host's nutrition, genotype and immune response [5,78–80] and the inter-host environment [81,82]. Finally, it can depend (non-linearly) on the number of parasites in the inter-host stage.

1.4 Concluding remarks and consequences for virulence-transmission trade-off theory

As demonstrated and discussed in this article, transmission is a crucial parameter of infection. It affects not only parasite fitness, but also that of the host and shapes the infection process, which in turn determines disease spread and evolution. Here, we propose that considering the parasite's life history in different stages of the transmission process, rather than classical transmission metrics, could enhance our predictions of infection outcomes in new hosts. The framework developed in this paper is purposefully simple so that it can be applied to as many parasites and transmission types as possible. Factors like parasite dispersal [83,84] , host social aggregation [85,86] , or multiple biotic environments (e.g. multiple vector hosts) are often case-specific and therefore not applicable to all parasite life cycles and strategies. Nevertheless, these factors can be implemented in this conceptualization by considering them in the inter-host phase of transmission and extending the framework as necessary.

We believe the points and solutions discussed here have evident consequences for epidemiology and how we contain disease outbreaks, but perhaps even more lasting and valuable implications for how we study infection and virulence evolution. The ongoing controversy between virulence and transmission is an expected result of the simplification of the components of infection. Recent work on decomposing [39,87] and extensively studying the components of infection [34,88], and their relationship to each other [79,89,90], is crucial and is marking a new era in infection biology. We believe the points mentioned and the framework designed here, will considerably push the field forward and help to better understand infection, namely the evolution of virulence. As above mentioned, many of the recent studies on virulence do not observe a trade-off between virulence and transmission [19]. However, by addressing the relationship between virulence and the different components of transmission, or for instance transmission potential, we might detect such 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 transmission will be more efficient to act on when designing disease control strategies, regardless of the parasite or infection type. Ultimately, we hope this article contributes to the understanding of how parasite evolves, how hosts adapt, and what can be done to prevent disease spread by also inspiring future studies to expand beyond current transmission metrics to help generate better predictive models of disease spread and control.

Box 3. Outstanding questions

In light of the framework and questions brought to light in this article, we set forth some of the intriguing questions this article might raise.

- To what extent do classical metrics of transmission relate to the different components of transmission raised in this study? We demonstrated why classical metrics do not always reflect the full fitness of a parasite, and hence, we await to see if this helps consolidate and bring to the future the trade-off theory of virulence evolution currently in use.
- What is the limitation of the plasticity of this framework? As we discussed, this framework was kept fairly simple to maximize its applicability to different model organisms. With this question, we wonder what parasite-specific aspects of their life cycle might be implemented, how they fit within the current framework, and if there are constraints that do not allow it.
- How do the different components relate to each other? One of the biggest fascinations for evolutionary biologists is, as we know, the existence of trade-offs. Therefore, we look forward to which trade-offs might arise from the application of this framework and how they contribute to society's needs.

Author contributions

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

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