

On the evolutionary ecology of specific immune defence

Paul Schmid-Hempel¹ and Dieter Ebert²

¹ETH Zürich, Ecology and Evolution, ETH-Zentrum NW, CH-8092 Zurich, Switzerland

²Département de Biologie, Ecologie et Evolution, Université de Fribourg, Chemin du Musée 10, CH-1700 Fribourg, Switzerland

Evolutionary ecology has developed along two major conceptual avenues, starting from the observation that hosts vary in their immune defence against parasites. The first avenue, rooted in life-history theory, assumes fitness costs of immune defence and tradeoffs in the face of limited resources, rather than specific host–parasite interactions. The second avenue focuses on specific responses, especially those generated by genotype–genotype interaction between and within host and parasite species. Specificity in the interactions between hosts and parasites play a crucial role in the field but analysis is difficult. Here, we classify concepts about host–parasite interactions into these two families and discuss their reconciliation with the help of a defence component model and two-dimensional classification scheme of the individual components. This helps to clarify some of the confusing terminology and might guide further research in the field.

Immune defence is arguably one of the most complex phenomena in biology. Not surprisingly, therefore, the study of immune responses, especially from the perspective of evolutionary ecology, has led to a proliferation of research avenues that become ever more diverse as research in this area progresses. Such a pattern is an unavoidable consequence of success in a field, and is typically accompanied with an explosion of information and a proliferation of concepts and ideas, but can sometimes suffer from a lack of generality. Sections of the field can become increasingly isolated and progress in other sections might be underestimated. In the evolutionary ecology of infectious diseases, the problem is exacerbated by the potential pivotal role that evolutionary ecology concepts play in areas such as evolutionary medicine [1], vaccine development [2], agro-ecology [3], ecosystems analysis [4] behavioural studies [5] or coevolution [6], all of which have obvious and deep-rooted interests in the effects of host–parasite interactions but also have greatly differing ideas and approaches, combined with divergent terminologies.

Here, we argue that discussions about specific immune responses are particularly prone to suffering from these problems. We suggest a new framework – the defence component model – that illustrates how ‘specificity’ might result from a cascade of defence components and incor-

porates the costs of defence. This places the issue within a general framework of an adaptive defence portfolio. We neither address other functions of the immune system, such as wound healing or tumour control, nor explicitly make reference to the plant literature, which adopts yet further approaches [7] but we instead concentrate on immune action against parasites in animals. We neither intend to review the literature on this subject nor discuss the vast knowledge of molecular and cell biology; our purpose is to clarify the framework for the analysis of specific immune defences within evolutionary ecology.

In a nutshell, evolutionary ecologists are interested in the possible fitness costs of immune defence and the tradeoffs with other concurrent needs of the organism within a life-history theory framework [8,9] (Table 1). Such tradeoffs are either investigated as a plastic response of individual organisms, usually referred to as the cost of using the immune system [10], or as an evolved pattern of genetic co-variation, usually considered to be the cost of having an immune system [11]. In both cases, variation in the capacity to defend is explained by appropriate costs (Table 1). In fact, the empirical evidence available collectively indicates that such costs exist and, moreover, can be of significant magnitude [10,12,13].

By contrast, a different approach adopted by many researchers has focused on other causes of variation in the response, namely variation resulting from interactions between host and parasites. On the one hand, a considerable amount of research has focused on the obvious differences between the ability of different host species to defend themselves against a given parasite, or differences between the ability of parasite species to infect a given host. On the other hand, research, motivated especially by population and evolutionary biology, has concentrated on differences in response caused by variation within parasite or host species; that is, variation owing to different lines of the same parasite or host [14–16]. Such intraspecific variation gives rise to host–parasite interactions that can lead to negative frequency-dependent selection [17] and, consequently, to rapid coevolutionary dynamics over timescales of a few generations [18]. These ideas are formalized in the Red Queen hypothesis [19], which has been invoked to explain the evolution and maintenance of genetic variation in host populations, especially in the process of sexual reproduction [20] (Table 1).

Both conceptual families – costs of defence and specific

Corresponding author: Paul Schmid-Hempel (psh@eco.umnw.ethz.ch).

Table 1. Nonexclusive concepts and their relationship to the specificity of immune response

Concept	Central idea	Refs
(a) Based on the idea that immune defence is costly^a		
Cost of resistance	Resistant host are less competitive in the absence of parasitism	[11]
Allocation problem	Available resources limit defence capacity	[8]
Immunocompetence	A quantitative measure indicating host capacity to resist infection in the absence of parasitism	[8,42]
Response in different environments	Under environmental conditions with a high likelihood to become infected, hosts should invest more in defence	[32]
Genetically engineered resistance	Transgenic organisms with overexpression of defence genes show higher resistance than wild type	[43]
Arms race with resistance costs	Host and parasite coevolve by allocating more resources to defence	[44]
Plant breeding	Breeding of hosts resistant to many parasite types	[29]
(b) Concepts based on the idea that hosts and parasites coevolve^b		
Red Queen hypothesis	Time-lagged negative frequency-dependent host fitness in relation to host and parasite genotypes	[17]
Sexual selection	Honest signals advertise health status. Frequency-dependent selection and parent-offspring correlations based on host and parasite genotypes needed	[45]
Gene-for-gene, matching alleles	Host and parasite genotypes determine outcome of interaction	[3]
Local adaptation	Because parasites track locally abundant host types, they are not adapted to hosts of other localities	[46]
Evolution of host specificity	Parasites cannot infect different host types with the same efficiency	[47,48]

^aImplicitly assuming nonspecific response, that is not dependent on parasite type.

^bEspecially with respect to specific responses dependent on both host and parasite genotypes.

responses – are based on the central idea of adaptation through evolution by natural selection and, hence, on fitness maximization principles. However, in spite of this obvious common ground, the two major research domains to date have not had much overlap [6,21], to the detriment of a comprehensive theory. For example, the concept of ‘immunocompetence’ fails if specific host–parasite interactions generate heterogeneous responses (Mucklow and Ebert, unpublished). In traditional analyses of the cost of immune defence, the presence of host–parasite specificity is thus considered to be a nuisance that is balanced, randomized by experimental design or avoided by using xenobiotics instead of parasites (e.g. nylon implants or Cephalexin beads) to stimulate an immune response [22]. *Vice versa*, specific interactions are crucial to students interested in coevolution, where the cost of defence is often not explicitly investigated [23]. This might miss potentially important ramifications. For example, the costs of defence against one parasite could manifest itself as susceptibility towards another and thus create a ‘specific’ response [24]. It is therefore important to be clear, when testing predictions, about the specific concepts being addressed.

Specific versus nonspecific responses

Immune responses have been defined and measured in very different ways. In vertebrates, for example, antibody titres [25], inflammatory response and lymphocyte ratios [26] have been used, whereas intensity of encapsulation [22], phenoloxidase activity [27], or the inducible production of antibacterial peptides [10] are typical measures in studies of insects. These measures are chosen for practicability and relevance to the research question and are often quantified with the help of artificial immune-

stimulants or implants, such as sheep red-blood cells, nylon implants or lipopolysaccharides. Evolutionary ecologists consider these measures to be tokens for the ultimate measure of interest, which is the individual fitness of hosts; that is, it is implied that the measures reflect the ability of the host to control or eliminate an infection. These implied links to fitness are highly plausible, but the empirical evidence is still largely wanting.

The most extreme case of a nonspecific defence would be one that is effective against all parasites within a range of interest and, thus, would only depend on host type or host condition (Box 1). Although such a case might never be realized, there are several phenomena close enough to this definition to illustrate the point. These include avoidance behaviour to prevent infection in the first place [28], the structure and thickness of the external surface of an organism (e.g. cuticular hairs in plants [29,30]), the phototactic responses of *Daphnia* [31], or the density-dependent increase in the activity of the phenoloxidase cascade in insects [32].

By contrast, specific defence is directed against a restricted set of parasite species or parasite types (Box 1). In many recent models of host–parasite coevolution, particularly those of the ‘matching alleles’ type [33], specific responses are generated by the interaction of host and parasite genotype. Nongenetic factors, such as host condition, are considered to be less important and are usually experimentally excluded or ignored. Extreme cases, such as the matching allele type, might not exist, but several examples come close. These include the interactions of *Daphnia* with its bacterial parasite *Pasteuria ramosa* [23], of the bumblebee *Bombus terrestris* with its trypanosome parasite *Crithidia bombi* [34], and plants interacting with their fungal pathogens [3].

Box 1. Specific immune response

In Fig. 1, different parasites (horizontal bars) are arranged hypothetically along the *x*-axis. Types 1–3 might represent three different parasite species, or, alternatively, three different strains of the same parasite. Here, the outcome of an ecological interaction between host and parasite is shown by the strength of an immune response as measured in the host (*y*-axis; an analogous graph could be drawn from the point of view of the parasite). The lines (A–F) show different outcomes that can be interpreted in the light of the ‘specificity’ of an immune response.

Within the tested range of parasites (i.e. types 1–3; parasites outside of this range have not been tested) and in statistical language, specificity might result from the main effect caused by host and parasite as well as from their interaction effect. Host main effects are found when the immune response of the host is the same for all tested parasites but varies among hosts (e.g. lines A and B), and vice versa for parasite main effects. The patterns are illustrated by the interaction between the bacterial parasite *Pasteuria ramosa* and its host, the crustacean *Daphnia magna* within the same population. Table I shows the percentages of hosts (nine different clones of *Daphnia* were tested) that can be successfully infected by different isolates of *Pasteuria* (nine isolates

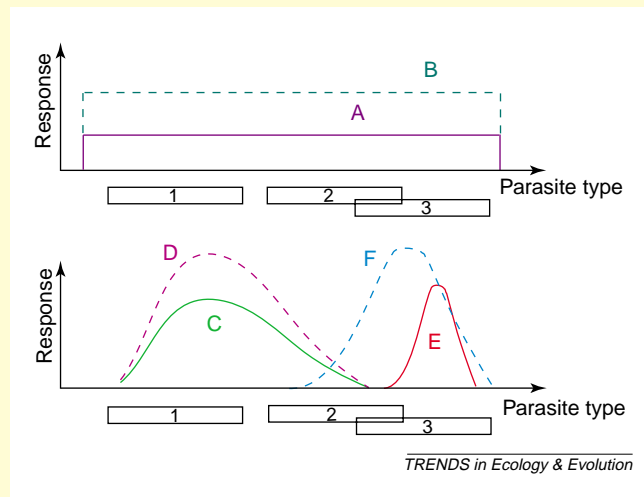


Fig. 1. Immune response profiles of hosts (A–F) infected by different parasites (types 1–3).

Table I. Variation in interactions between host and parasite

Pasteuria isolates	Daphnia clones ^a									Average
	1	3	4	5	7	8	13	14	15	
1	78	89	94	11	0	11	17	0	83	42
3	83	89	89	61	11	56	50	16	89	60
4	0	78	61	94	55	0	0	50	33	41
5	0	89	67	94	50	0	0	61	28	43
7	0	78	55	83	39	0	0	39	28	36
8	0	78	0	0	0	56	33	0	0	19
13	33	78	44	11	0	67	44	0	44	36
14	0	67	39	83	22	0	0	16	22	28
15	89	89	100	0	0	0	0	0	100	41
Average	31	81	61	49	20	21	16	20	48	

Modified from Ref. [b].

^aEntries are the percentages of hosts (average across two dose levels) that can be successfully infected by parasites.

were used). The main effect of host clones is shown in the variation among columns in Table I, the main effect of parasite isolates in the variation among rows. Interaction effects are shown by variation along the diagonals. In this example, all effects are statistically highly significant (i.e. $P < 0.05$). Note, however, that differences in responses (e.g. between hosts A and B in Fig. 1) and susceptibility to parasitism might also result from differences in host condition rather than from any difference in the immune system.

Within the tested range, the responses of hosts D–F differ according to parasite type and are thus generated, in statistical language, by interaction effects. The responses by hosts E and F are narrower and thus more ‘specific’ than those by C and D. In addition, hosts C and D only differ in the strength of a response and, hence, might also differ by a main effect component. By contrast, hosts E and F differ in both the overall strength and the range of a response and, thus, by main and interaction effects. Note that by adding additional parasites, beyond types 1–3, to the tested range, even hosts A and B might show specificity because of interaction effects. In a trivial sense, therefore, every host is specific by virtue of interaction effects, given that enough different parasite types are tested. Hence, it is the biological question of interest that defines the range of host and parasite types for which ‘specificity’ is to be analyzed (e.g. types 1–3).

Nevertheless, the detection of specificity based on interactions between host and parasite (as in cases C–F) is typically more difficult, because the statistical power to detect interaction terms is much less than that for main effects (i.e. larger sample sizes are needed [a]). Similarly, experimental studies of immune defences often include only one or a restricted range of different parasite types (as for hosts A and B in Fig. 1). Such studies therefore often fail to detect specificity or take variation caused by host condition as a sign of host specificity. Combined, these problems are bound to bias the literature against finding specific immune responses, especially with respect to variation within host or parasite species.

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- b Carius, H.J. et al. (2001) Genetic variation in a host–parasite association: potential for coevolution and frequency-dependent selection. *Evolution* 55, 1136–1145

In addition to problems raised by particular kinds of experimental design and analysis (Box 1), confusion about ‘specificity’ might arise from using immunological terminology. For example, for vertebrate immunologists, ‘specificity’ typically means discussing the specific binding capacity of antibodies [produced by the humoral arm of the immune system (B cells)] to different antigens (e.g.

different oligopeptide motifs) and, thus, focusing on a recognition mechanism. By contrast, for evolutionary ecologists, the overall response towards different parasite types matters regardless of the mechanism. In fact, specificity, in the functional sense, of a response to a limited set of parasites (Box 1) is not bound to the presence of antibodies. Invertebrates produce no antibodies, yet

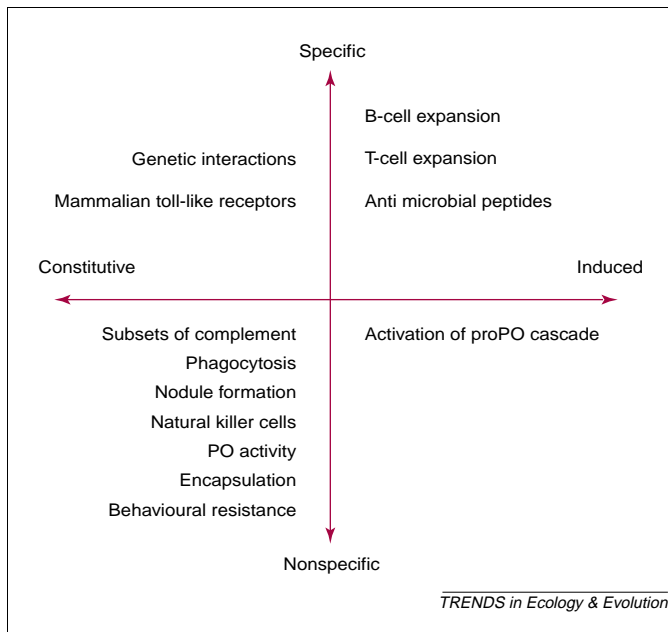


Fig. 1. The defence chart. From an evolutionary ecology point of view, immune responses of a host to a parasite can be located in a chart according to the tactics of use (constitutive versus induced) and degree of specificity. For example, the formation of the B-cell populations of the antibody complement in the vertebrate immune system is constitutive, because it is formed early and then maintained. Yet, most of these cells assume their function as an induced response, which involves cytotoxic killing and antibody production by specific activation. In addition, a fraction of the circulating cells (natural killer cells) has no known activating target antigen and are therefore thought to form the nonspecific, constitutive part of the response (see text for further details). Abbreviation: PO, phenoloxidase.

their response can be quite specific, as in the examples of *Daphnia* or *Bombus* [23,34].

The evolutionary ecology chart to immune defence

The evolution of specific defences is an important part of the larger puzzle that evolutionary ecologists seek to understand: the adaptive nature of the organization and use of the immune system. Obviously, immune defences are somehow beneficial, but in which precise way? For example, one seeks to understand, and for this purpose, predict how scarce resources should be allocated to immune defence; that is, to identify some kind of 'optimal' defence, or an optimal 'portfolio' of defences, and to test whether this optimum is found in natural systems.

Specific responses therefore need to be placed in the broader context of the defence portfolio, for which we propose, as a conceptual guideline, a two-dimensional chart (Fig. 1) that classifies several often-discussed defence components along two dimensions. The first dimension refers to the tactics of use of the immune response. The two extreme cases are: (1) a constitutive response that is always present and capable of defence without previous contact; and (2) an induced response that is only deployed after an invader has been recognized. This distinction focuses the attention on the temporal dynamics. For example, a constitutive defence reacts immediately and should be selected for if the major challenge is by parasites that have a high potential of multiplication within the host combined with a substantial damage potential and that therefore require a swift response [35]. Induced responses, however, could have

evolved to avoid a costly permanent defence capability [36] at the price of a delayed response and the potential risk that the parasite escapes host control.

The second dimension of the chart refers to the degree of specificity of the response; that is, by which parasites the response can be triggered and/or is effective against (Box 1). The two extremes are the 'nonspecific' and 'specific' response. Characterization of the defence response along this axis naturally lends itself to asking about the design of the immune system with respect to its degree of specialization, as indicated by the location of different kinds of immune response in the chart (Fig. 1). Among the specific immune responses, some are constitutive; for example, those associated with mammalian toll-like receptors. However, most specific responses appear induced. It thus seems that specificity is associated with the evolution of induced responses.

The defence component model

'Specificity' describes a certain form of host-parasite interaction, such as the outcome of a particular interaction, that cannot be predicted without knowledge about both the host and the parasite. In other words, hosts differ in their susceptibility to different parasite types and parasite types differ in their ability to infect and/or grow in different host types. The host defence system comprises several components that act specifically or nonspecifically to varying degrees. How these different components act together affects the overall 'specificity' of a given host-parasite system. This can be visualized as a series of defence barriers that an invading parasite is confronted with, and which together determine the overall response [37-39] (Fig. 2). For example, as a first line of defence, avoidance behaviour can reduce the probability of an infection. Avoidance behaviour is probably often specific with regard to different parasite species (contact with which is therefore avoided) but nonspecific with regard to within-parasite species variation. For example, wintering great tits *Parus major* roost in tree holes and avoid holes that are infested by hen fleas, even if such holes were the only ones available in their territories [40]. However, the same behaviour would not prevent contact with mosquito-borne infections, such as bird malaria, for example.

Subsequent steps in the defence barriers involve impediments to penetrate the external skin of the host, or to establish, multiply, or reproduce within an organ. Importantly, because of the chain-like nature of this process, if only one of the components is specific, the overall response is also likely to be specific (Fig. 2). Similar to the decomposition of total lifetime reproductive success into a complex function of fitness components, overall defence can also be decomposed into constituent defence components. In immunological experiments, some steps of the defence cascade are typically eliminated for matters of practicability and to accommodate a given research interest. This can lead to the apparent inflation of the effect of a certain step that might, under natural conditions, not be relevant. For example, when studying the interaction of *Drosophila* and its parasitoids in the laboratory [41], behavioural defences are largely eliminated. Similarly, bioassays involving subcutaneous application of parasites

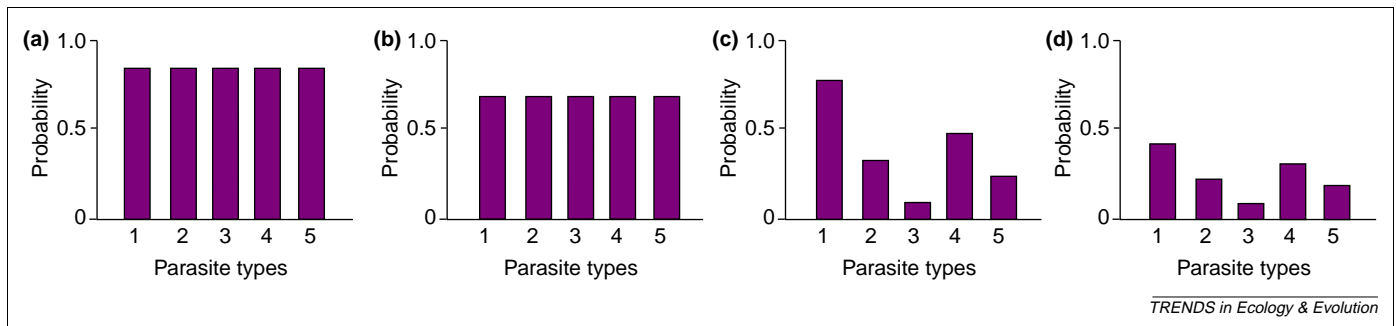


Fig. 2. The defence component model in a hypothetical host–parasite interaction with three levels of defence (a–c). The numbers on the horizontal axis indicate five different parasite types (i.e. genotypes, isolates, strains, or species). The vertical axis is the probability that a given parasite will break through this defence barrier. In this example (a) is the probability to infect in spite of the hosts avoidance behaviour, (b) indicates the probability of the parasites to penetrate the host skin and establish inside the host; and (c) is the probability of the parasite to escape recognition by the hosts immune system. For simplicity, we assume that probabilities multiply to produce the overall probability for each parasite type to successfully infect the host (d). Hence, the specific components of the defence system determine the specificity observed for the entire system. In reality, these probabilities might combine in different ways, but we believe that the overall specificity of the system is unlikely to be much lower than that predicted by a simple multiplicative model. Real systems might be much more complex, with alternative defence components working in parallel or in a network. The simplest form chosen here is for illustrative purposes.

or artificial implants [22] sidestep all previous elements of the defence cascade. Nevertheless, such experimental studies can provide an opportunity to study particular elements of the defence cascade. By contrast, specificity might get lost with nonspecific effectors; for example, when antigen-specific responses lead to an inflamed gut that expels all its contents.

Although for the evolution of host resistance, the overall resistance is probably more important than individual defence components, the costs and benefits associated with each component are important for its evolution. The total cost of defence must be balanced by the effectiveness of a defence barrier, weighted by the likelihood that a parasite will challenge this step, the fitness loss through infection, and by the interplay of these barriers with other defence components. It is unclear, however, whether every component has costs and whether all costs can be measured in the same currency. For example, some components might have energetic costs, whilst others might carry the cost of ‘lost opportunity’ (when one defence option excludes another). Given this complex situation, a more detailed knowledge of these single steps might be crucial for interpreting experimental results, for example understanding why some systems show strong costs of defence, whereas no costs have been found in other systems. Moreover, because defence occurs at several levels, graded rather than strictly nonspecific or specific responses are to be expected.

Conclusions

Different research traditions, varying terminologies as well as an inherent underestimation of the role of specific responses, are prone to impede research of the evolutionary ecology of immune defences. Integrating insights from currently rapidly diverging fields, especially from the analysis of the cost of immune defence and from the analysis of specific host–parasite interactions, therefore seems timely. Research to date has generated solid evidence for both. The challenge now is to understand the role of specific responses within an entire defence cascade and to analyze how costs constrain the evolution of different defence components. More generally, the evolutionary

ecology analyses of immune responses need to be charted by their functions within the entire defence portfolio, which will eventually lead to a more comprehensive view of the evolution and extant adaptations of the immune system.

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