Maternal transfer of antibodies: raising immuno-ecology issues

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The transfer of antibodies from mother to offspring has broad potential implications in evolutionary ecology, from the adaptive value of maternal effects to the role of transgenerational plasticity in host–parasite interactions. Recent contributions have addressed key issues such as environmental and genetic factors affecting the amount of antibodies transferred and whether maternal antibodies affect offspring immunity, but little is still known about the implications of the maternal transfer of antibodies in natural populations. By its position at the crossroads between population ecology, animal science, medicine and epidemiology, current studies of the role of the maternal transfer of antibodies highlight how research in ecological immunology needs to combine functional and evolutionary approaches while also keeping in mind ecological settings.

Transfer of antibodies: an adaptive maternal effect against parasites?

Parents can have profound lasting effects on the phenotype of their offspring by mechanisms other than genetic inheritance [1]. It is now well established that mothers in particular can transfer their environmental experience and phenotype to their progeny through allocation of nongenetic resources. Such maternal effects can constitute a major source of transgenerational phenotypic plasticity that can generate a response to environmental heterogeneity by affecting offspring development and ultimately fitness [2]. One major source of environmental heterogeneity is the biotic environment, and transgenerational effects can, for instance, be expected when parents and offspring share the risk of exposure to the same deleterious parasites.

The immune system allows individuals to fight infestations by parasites. In addition to the innate, and usually nonspecific, immune response, vertebrates exposed to parasites can develop an acquired, and usually more specific, immune response [3]. A significant part of this acquired response can be transmitted to the next generation via the transfer of immunoactive compounds such as antibodies [4,5]. Such a transfer thus constitutes an induced parental effect that has the potential to have important ecological and evolutionary implications [6]. However, until very recently, the evolutionary ecology of the maternal transfer of antibodies has not received much attention [6–8]. Here, after describing key elements of the physiology of the transfer of maternal antibodies, we review evidence for the adaptive value of the maternal transfer of antibodies and recent reports on sources of variation in the transfer of antibodies. These issues are critical to evaluate the potential microevolutionary implications of this maternal effect. We then discuss the costs and benefits of the maternal transfer of antibodies for the mother and offspring. This leads us to outline some potential ecological and epidemiological implications of the maternal transfer of antibodies. The perspectives highlight the importance of combining functional and evolutionary approaches to address questions in ecological immunology.

The physiology of the transfer

Several specific aspects of the transfer of maternal antibodies have potentially interesting evolutionary and

Glossary

Antibodies (Ab): Proteins (called immunoglobulins) secreted by the immune system to identify and neutralize foreign objects (antigens) such as bacteria and viruses.
Colostrum: Form of milk produced by the mammary glands in late pregnancy and the few days after birth, containing immunoglobulins—mostly IgG—that can be absorbed by the newborns. By comparison, later milk contains a high proportion of IgA, not transferred to the newborn bloodstream but conferring local protection in the digestive tract.
Constitutive response: Response produced regardless of any external stimulating cues.
Enzyme-linked immunosorbent assay (ELISA): Immunological technique used mainly to measure the concentration of an antibody or an antigen in a sample.
Fc receptors: Family of molecular receptors with binding sites specific to the constant domains (Fc) of the different classes of immunoglobulins. Their interaction with antibodies attached to antigens leads to the activation of the immune system and they control the half-life of immunoglobulins in blood. They are also responsible for the specific transport of different classes of immunoglobulins across maternal and fœtal or newborn membranes.
Humoral immunity: Production of antibodies induced by pathogen exposure. It is an important component of the specific immune response. See also Antibodies and Induced defences.
Immunoblot (western blot): Immunological technique that enables the identification of the repertoire of antigens against which the host has produced antibodies.
Immunoglobulin classes: Immunoglobulins can be divided into different classes (five in humans: IgG, M, A, D, E) and subclasses, based on differences in the constant region (Fc) of the heavy chains of the proteins.
Immunoglobulins (Ig): see Antibodies.
Induced defences: Phenotypic changes produced in response to environmental threats (as opposed to constitutive responses produced regardless of any external cues). One example is the selective induction of immune responses by pathogen exposure.
Yolk sac: Membranous sac attached to the embryo. Nearly vestigial in placental mammals, it is, in rodents, the organ responsible for the exchanges with the mother (inverted yolk sac placenta). In birds, it serves as the nutritive source for embryonic development, and maternal IgY are transferred from the egg yolk through the yolk sac membrane into the embryonic bloodstream.

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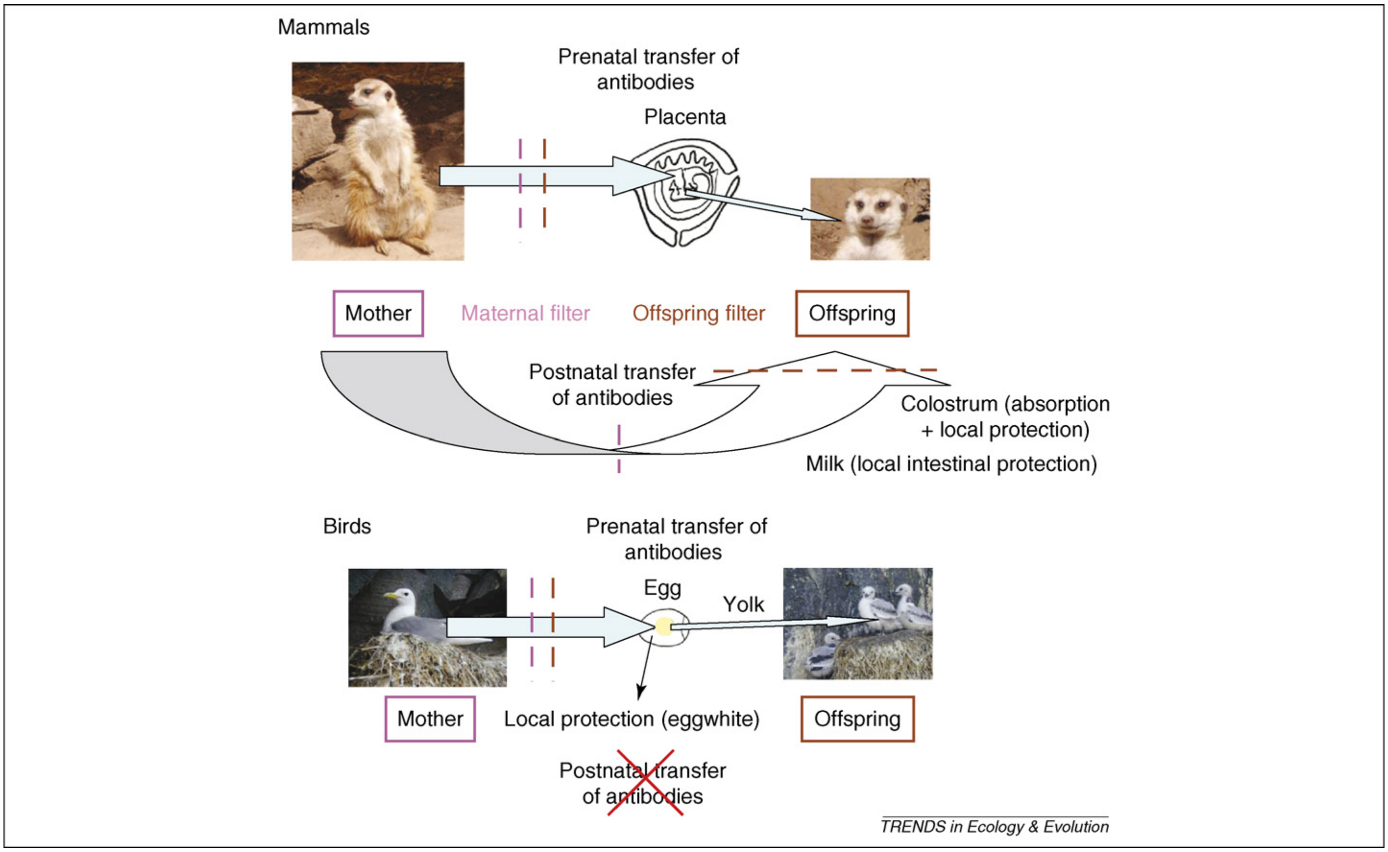

Figure 1. Pre- and postnatal transfer of antibodies in birds and mammals. Maternal transfer of antibodies has been reported in a wide range of vertebrate species, from cows to sharks [4,65]. Maternal secretion and absorption by the young occur only prenatally in birds (with the exception of pigeon crop milk), but both pre- and postnatally in mammals (with variations among species; see Figure S1 online for detailed routes and types of antibodies transferred). The processes of transfer involve maternal and offspring structures, such as receptors, and have different levels of 'selectivity.' For example, IgG1, and no other IgG, are selectively transferred in cow milk by being secreted in the colostrum; conversely, there is a nonselective uptake of antibodies along with other proteins in the gut of the calf. Antibodies can be transferred from blood to blood but can also confer local protection (e.g. IgA in human milk) or be a source of food (e.g. antibodies digested in ruminants after the colostrum absorption period). Photographs reproduced with permission (copyright David Gremillet and Thierry Boulinier).

ecological implications. In particular, the pattern of variability among species and individuals in the ways antibodies are transferred could be critical.

Antibodies can be transferred to offspring blood via (i) direct exchange with the yolk sac or the blood of their mother or (ii) via ingestion before or after birth (Figure 1). However, not all types of antibodies are transferred, because transfer routes can be specific (Figure 1; see also Ref. [9]). In vertebrates, IgG are the only class of immunoglobulins that crosses the placenta [10]. In birds, IgY (the avian equivalent of IgG) are the principal class of immunoglobulins transferred into eggs, mostly in the egg yolk. Other classes of immunoglobulins are transmitted to the egg yolk but in smaller quantities [9,11]. Antibodies transferred to the egg white will not reach the blood of the offspring, but can be ingested. The fact that different classes or subclasses of immunoglobulins are transferred via different routes is important because different antibodies are known to be involved in different immunological mechanisms of response toward various antigens [12]. Because maternally transferred IgG (or IgY) reach the offspring blood where they constitute the most abundant class, they are expected to play an important role in the case of systemic infections. Alternatively, studies on IgA, IgE and IgM transmitted through the egg white [13], colostrum or breast milk [14] have highlighted the critical role of these antibody types in the local intestinal protection of newborns.

Well-designed classical studies have thus provided key information about the route of transfer of maternal antibodies using model species [4,15], but comparable information is not available for natural populations. In particular, information on subclassification of antibodies is still not available for most species [16], which leaves room for speculations about how transfer routes have evolved in different species [17]. Within a subclass, there is no clear indication that antibodies against different antigens are differentially transferred [9].

Two other key physiological issues concern the amount of antibodies transferred and the timing of the transfer relative to antibody production. In general, there is clear evidence that the amount of antibodies transferred is correlated to the concentration of antibodies in the blood of the female around the time the egg is laid or birth occurs, or at the time the offspring is receiving antibodies via the milk of the mother [4]. Despite such strong correlations, various factors are suspected to affect the amount of antibodies transferred, such as female condition and offspring characteristics, and those factors might differ depending on the route of transfer. The fact that the female antibody level at the time of breeding also directly affects the amount of antibody transferred to the offspring underlines the potential importance of factors affecting the dynamics of female humoral immunity along the breeding cycle [18,19].

Overall, although a better knowledge of the molecular mechanisms involved in the transfer of maternal antibodies would be valuable [20], sufficient knowledge is already available to make the study of its ecological and evolutionary significance promising. Key issues are thus whether maternal antibody transfer increases the fitness of the offspring and the mother, and what factors affect maternal antibody transmission.

Potential adaptive value of the maternal transfer of antibodies

The protective effects of maternal antibodies against several disease agents are clear in a veterinary and human medicine context [9], and wide-scale vaccination programmes of mothers are implemented to protect newborns [21]. This does not mean that the transfer is adaptive in a natural context. Despite a growing number of ecological studies on the maternal transfer of antibodies, little is known about whether the transfer of maternal antibodies in natural populations is beneficial in terms of individual fitness.

Effects on offspring growth and survival

In the case of early exposure to deleterious parasites, a protective effect of antibodies against those parasites is expected to improve the growth and survival of offspring. The early experimental study by Heeb and colleagues [7] (1998) showed a positive effect on nestling growth rate and recruitment from previous exposure of female great tits *Parus major* to an ectoparasite (fleas), which suggested that maternally transferred antibodies against the ectoparasite might have benefited offspring. However, few studies have suggested a positive effect of antibodies since then [22–24]. Studies are constrained by methodological limitations (Boxes 1 and 2) and lack of knowledge about natural host–parasite systems where protective antibodies are known to play a role.

Box 1. Quantifying maternal antibodies: methodological issues in ecological studies

Studies of maternal antibody transfer conducted with domestic or model species use a series of routine immunological methods which can raise particular methodological issues when used in an ecological context.

Extracting antibodies from egg yolk or milk

Simple methods of extraction of antibodies, such as chloroform extraction, can be used with egg yolk [66] or milk [67] to avoid technical problems due to high lipid content. These methods have been developed for the routine control of milk quality, and to enable a more ethical production of large amounts of immunoglobulins [54].

Quantification of antibody levels

The quantification of antibodies from a wild animal species is often problematic because several methods of antibody quantification (e.g. noncompetitive ELISA) specifically target antibodies of the species of interest [9]. Nevertheless, antibodies from related species can be used, and commercially available anti-chicken antibodies have been successfully used with a series of bird species [8,43,68]. Kits originally developed to quantify specific antibodies in mammals can thus be adapted to other species [8,19]. Qualitative tests such as western blots can be used to confirm the validity of such tests [19,68].

Timing of sampling

Studies aimed at relating maternal antibody level in the egg or newborn to antibody levels in maternal plasma can face problems related to the timing of sampling. The timing of the collection of the samples needs to be set so that the concentration of antibodies can be compared among mother–offspring pairs [63,69]. Knowledge about the dynamics of the immune response of the mother, and notably the time elapsed between the exposure to an antigen and the quantification of the antibodies potentially transferred, can be critical (see Antigen exposure of the mother).

Antigen exposure of the mother

The amount of antibodies transferred by a female reflects her capacity to produce antibodies and transmit them but also her past exposure to the antigen against which antibodies have been produced. When studying antibody transfer, it is thus critical to control maternal exposure. In particular, patterns of variation of maternal antibodies among eggs within clutches are difficult to attribute to differential investment of the females with egg rank if no information is available on maternal exposure. The injection of mothers with known antigens such as vaccines is an efficient way to control the timing of exposure of individuals [70].

Type of antibody

Many studies quantify the concentration of total IgG (IgY in birds) rather than the concentration of antibodies against specific antigens, which can be problematic because it pools the response to antigens with different patterns of exposure and effects. One important point is that not all antibodies are effective [12], and more is not necessarily better [71]. Thus, the study of the dynamics of the transfer of any antibody, even developed against a known pathogenic organism, will not necessarily inform us about its implications for the fitness of the offspring.

Box 2. Disentangling pre- and postnatal maternal effects: design issues

When investigating the effects of maternal antibodies on offspring phenotype and fitness components, other maternal effects could confound potential relationships. In particular, postnatal effects, such as differential feeding by the parents or level of parasite exposure, can lead to differences among offspring that might not be a result of a prenatal effect such as the transfer of maternal antibodies via the egg yolk or placenta. This type of problem has been classically addressed in evolutionary ecology by the use of cross-fostering designs [72].

Although cross-fostering can only be conducted with some model species of mammals [15], in many bird species, eggs can readily be transferred between nests, and this approach has been used for investigating the potential role of maternally transferred antibodies in natural populations [7,27]. Birds provide especially interesting natural systems, as nestlings are also often exposed to ectoparasites in the nest, and maternal antibodies might play a role in the defence against these [7,8].

Although convenient, egg swapping does not correct for covariations between genetic and nongenetic prenatal effects and the maternal effect of interest (prenatal effects other than the transfer of maternal antibodies, such as the transfer of other compounds through the egg, cannot be controlled for by egg swapping). A possible solution, which has been successfully used in the study of the effects of hormones deposited in the yolk [73] but has not yet been implemented in the case of maternal antibodies, could be to directly manipulate the concentration of maternal antibodies in the egg yolk by injecting antibodies and track fitness components of offspring reared in various environments.

Effects on offspring immunity

Maternally transferred antibodies might not only confer passive protection to young but could also affect the development of the juvenile's immune response. Vaccination studies on domesticated animals and humans have reported that maternal antibodies can interfere with the juvenile immune response via a mechanism described as a 'blocking effect' [25]. When juveniles are exposed to an antigen at an early age and over a short window of time (as in the case of vaccinations), the presence of passively acquired maternal antibodies might block the immune response and, thus, reduce the efficiency of a vaccine. This blocking effect has been shown in the context of controlled exposure of offspring to pathogens [26] and in natural populations [27]. In addition to a protective role, such blocking of the immune response could be adaptive by limiting the need for investing in immunity at a critical period for offspring development. By contrast, studies on mice have reported that these maternal antibodies might also enhance juvenile immune response [28,29]. Some recent studies in wild bird populations suggest similar results [30–32]. The potential mechanisms involved in these priming or educational effects are still under debate. What is clear is that maternal antibodies, despite their effect on the early development of the immune system, have potential for far-reaching fitness consequences [33].

Sources of variation in the transfer of antibodies

To infer how the traits associated with the transfer of maternal antibodies can evolve at an ecological time scale, it is necessary to identify the relative contributions of environmental and genetic factors affecting this maternal effect [34].

Genetic effects

As stressed by Grindstaff and colleagues [6], there is a large body of evidence about the genetic variability in the humoral response of females exposed to various antigens [35], notably in the poultry literature [36]. Hens of chicken lines selected for antibody production transmit higher amounts of antibodies to their chicks than hens from lines not selected for antibody production [36]. It is, nevertheless, not clear whether this is only due to higher levels of circulating antibodies in the females, or also to higher transmission rate. Females with comparable levels of circulating plasma antibodies could indeed differ genetically in their tendency to transfer antibodies [37]. Although a few recent poultry science papers have touched on this question by comparing the rate of transfer among selected lines of chickens [11,37], there is no clear answer yet. Apparent differences in the ability to transfer antibodies could reflect genetic differences in the ability of females to deposit antibodies, or of offspring to absorb them. Absorption differences could be due to differences in receptor density on epithelial cells, receptor binding affinity or metabolic rates [37]. To our knowledge, no information is available from natural populations on this question. Further investigations on these aspects should thus be very valuable, notably to fully discard the possibility that the maternal transfer of antibodies is only a passive, possibly nonadaptive, mechanism, simply reflecting the fact that antibodies, like other molecules, pass through the placenta or yolk sac barrier. If there is genetic variability in the ability of females to transfer antibodies, it would be important to know whether it is correlated with their ability to mount an immune response, as both processes would affect the amount of antibodies received by the offspring.

Environmental effects

The potential effect of several environmental factors, such as host density, offspring rank and parasite exposure, on the transfer of maternal antibodies has been considered in recent ecological studies (Table S1 online). Methodological aspects have nevertheless to be considered carefully when interpreting the results (Box 1). Intrinsic factors associated with the physiological status of individuals relative to reproduction might be important, as well as extrinsic factors such as the timing of exposure or re-exposure of females to parasites relative to the timing of antibody transfer [19]. This needs to be considered when designing studies to infer a potential adaptive role of these antibodies (Box 2). Breeding density and local level of infestation by ticks have been associated with higher levels of antibodies in eggs of two colonial bird species [8,38]. Such factors are expected to affect the transfer of antibodies because they are likely to be associated with higher maternal exposure to parasites. The results of studies of the effects of the diet of the mother or her body condition are less clear. Because the vertebrate immune system relies upon significant supplies of proteins and amino acids [39], mothers in better condition are expected to transmit more antibodies to their offspring if the transfer of antibodies is beneficial for the offspring [40]. Contrasted results have nevertheless been obtained [40,41]. The interpretation of the results is complicated by the fact that the level of immunoglobulin might relate to the immunocompetence of the mother and offspring or, alternatively, might reflect greater response to infection resulting from a poorer condition [41].

Other factors that have been considered to affect maternal antibody transfer are male mate characteristics [42,43], other egg compounds such as androgens and antioxidants [44,45], egg rank in the clutch [44] and egg colour [46] (Table S1 online). The results are nevertheless not consistent among studies, making it difficult to detect clear patterns. Various adaptive or nonadaptive interpretations can be proposed, but overall these results suggest that we still know relatively little about the factors affecting changes in maternal antibody levels within and among broods.

Environmental variability, costs of transfer and potential tradeoffs

An induced transgenerational effect

Induced responses are expected to evolve when constitutive responses are too costly to develop [47]. The humoral immune response of vertebrates is a clear example of this, as it represents a cost-effective way for individuals to defend themselves against parasites without having to constantly maintain specific defences against all the parasites they could potentially encounter [48]. Environmental variability, in terms of likelihood of exposure and re-exposure to specific deleterious parasites, will thus affect the potential benefits of this induced response. Exposure to parasites is well known to vary spatially [49] but also seasonally [50], and hence the costs and benefits of the transfer of maternal antibodies should vary dramatically according to the ecological context in which individuals live. In the case of species reusing the same breeding sites year after year, offspring are likely to be exposed to the same parasites as their mothers. Offspring would thus benefit directly from the transfer of passive immunity against those parasites. This is likely the case for bird species exposed to ectoparasites at the nest [7,19]. The potential benefit will nevertheless depend on the parasite species. For instance, pathogens showing rapid antigenic variation might escape the immunity that has been transferred from mother to offspring. Moreover, even if an offspring benefits from the experience of its mother by receiving maternal antibodies, it will nevertheless lack antibodies against parasites against which its mother has not yet mounted a humoral immune response. This might be the case when a new pathogen spreads within a host population. It should be noted that in some mammalian species, allosuckling could provide the opportunity for newborns to secure maternal antibodies against a wider repertoire of parasites than if they only obtained milk from their mother [51]. The occurrence of such behaviours should depend on the relative costs and benefits to the mother and the young.

Costs of the transfer for the mother

The evolutionary interests of the mother and of the young do not always coincide because the investment in the current reproductive event potentially lowers the capacity to invest in future breeding events, notably by lowering the condition of the mother [52]. Indeed, the transmission of antibodies to eggs might represent a significant immunological and resource drain for ovulating females because up to 45 mg day^{-1} of IgY can be accumulated in the egg yolk during the few days before laying. Once mature, hen oocytes contain 100–200 mg of maternal IgY, or 10–20% of the hen's steady-state level [53] (this is even used as an alternative way of producing antibodies industrially [54]). Females might thus face tradeoffs relative to their potential investment in the transfer of maternal antibodies.

Mothers, not fathers, transmit antibodies

The fact that in most cases it is females, and not males, that transmit antibodies can lead to interesting predictions associated with the transfer of passive immunity. For instance, when considering the role of parasites in sexual selection, one hypothesis would be that females have evolved ways to signal their ability to transfer antibodies to obtain mates, or that females might be able to vary their investment in terms of antibody transferred as a function of the potential quality of their mate [42,43]. However, these hypotheses rest on the assumption that the transfer is itself adaptive. In particular, the relative importance of the capacity to transfer antibodies to the young, compared to other presumably important traits (genetic background, nutritional status, age, etc.), would need to be assessed. Paradoxically, one could also envisage a reason why females should not signal the transfer of large amounts of antibodies to the young: this is because this transfer reflects current and past exposure to parasites, and males might want to avoid females showing signs of a history of parasite exposure.

Ecological and epidemiological implications

The maternal transfer of antibodies has the potential to play a significant role in the dynamics of host–parasite interactions, and thus the epidemiology of wildlife diseases. This is because the maternal transfer of antibodies can alter the proportion of naïve individuals that will be exposed to a disease agent. This was illustrated in a theoretical study of the potential effect of the maternal transfer of antibodies in a rabbit population infected by the myxomatosis virus [55]. Further modelling work considered how the transfer of maternal antibodies could explain the fact that an intense circulation of a parasite in a host population can help reduce its severity and how this could be related to the rate of transmission of the parasite among groups of hosts [56]. This can occur when maternal antibodies reduce the severity of a disease and thus lead to an increase in disease severity with age. If the parasite is prevalent, which is the case when there is a high rate of parasite transmission among hosts, most individuals are not showing a severe form of the disease because either they still have maternal antibodies (for young individuals) or they had maternal antibodies when they first encountered the parasite. Passive immunity acquired via the maternal transfer of antibodies could also be important to consider when studying the evolution of acquired immunity. It would, for instance, be interesting to incorporate maternally acquired immunity in theoretical models addressing the effects of acquired immunity on the evolution of disease resistance [57] and parasite virulence [58].

Even if the role of maternal antibodies is still seldomly incorporated in epidemiological or ecological modelling, it is interesting to note that several recent studies published on the transfer of maternal antibodies deal with systems involving emerging disease agents, such as West Nile, chikungunya and avian influenza viruses, or the Lyme disease bacterium *Borrelia burgdorferi* [8,59–62]. In addition to potentially playing a role in the dynamics of the host–parasite interactions considered, the presence of antibodies in egg yolks or young offspring can be used to infer the proportion of individuals of the host population which carry antibodies, without the need to capture breeding adults. Field studies considering maternal antibodies, combined with experimental approaches testing specific aspects of the host–parasite systems, could thus provide important baseline information for building predictive models and addressing eco-epidemiological issues.

Challenges for future research

In 2003, Grindstaff and colleagues [6] published a review highlighting the potential evolutionary implications of the maternal transfer of antibodies. Since then, several studies have addressed questions of ecological and evolutionary interest with regard to maternal antibodies, although the bulk of the empirical work has dealt with environmental factors affecting the transfer of maternal antibodies, rather than its genetic basis or fitness implications. Several significant questions still lack clear answers, and research on this topic should combine various approaches from theory to empirical research in the field.

In general, there is a need for more studies relying on natural host–parasite systems where detailed knowledge of the dynamics of antibody response and the benefit to offspring can be investigated. Experimental approaches investigating the effect of age on the susceptibility of individuals to various naturally occurring parasites and on the efficiency of antibodies to clear parasitemia [63] should provide much needed information for evaluating the eco-epidemiological implications of the maternal transfer of antibodies. Such studies could also provide information for comparative approaches to test whether the involvement of maternal antibodies is constrained by tradeoffs [64] and related to the patterns of exposure of individuals of different age classes to more or less deleterious parasites.

Studies should also combine detailed knowledge about the exposure of individuals to parasites with information on their fitness and genetic relatedness. It is, for instance, surprising that almost no studies yet exist on the genetics of the maternal transmission of antibodies, despite a growing interest in quantitative genetic studies in wild animals [34]. Such studies should benefit from being developed within long-term research programmes where the role of parasites and host genetics has already been considered [35]. Field studies could, moreover, directly benefit from more mechanistic studies conducted with model species [20]. By its position at the crossroads between population ecology, animal science, medicine and epidemiology, current studies of the role of maternal antibodies thus highlight how research in ecological immunology needs to combine functional and evolutionary approaches, and to do so while keeping ecological settings in mind.

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Supplementary data

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