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Feedbacks between nutrition and disease in honey bee health

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Declines in honey bee health have been attributed to multiple interacting environmental stressors; among the most important are forage/nutrition deficits and parasites and pathogens. Recent studies suggest poor honey bee nutrition can exacerbate the negative impacts of infectious viral and fungal diseases, and conversely, that common honey bee parasites and pathogens can adversely affect bee nutritional physiology. This sets up the potential for harmful feedbacks between poor nutrition and infectious disease that may contribute to spiraling declines in bee health. We suggest that improving bees' nutritional resilience should be a major goal in combating challenges to bee health; this approach can buffer bees from other environmental stressors such as pathogen infection.

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Introduction

Bee pollinators live in a world of increasingly disturbed habitats, where natural areas worldwide have been transformed into more and more intensive agriculture and urban landscapes [1]. At the same time, global movement of goods, including bees themselves, has increased the speed at which pests and pathogens spread [2]. While there has been substantial interest in these two sources of stress, there has been relatively little work understanding how they interact. In the real world, these stressors are co-occurring, but understanding the complex synergy between different diseases and nutritional stresses bees face is still a developing field.

The diet of bees consists of pollen and nectar collected from flowers. Together, these products provide bees with the carbohydrates, proteins, lipids, and other nutrients they need to survive [3]. In honey bees, diverse pollen diets are preferentially consumed [4] and improve lifespan [4,5]. The pollen of some flowers [5], including common mass-flowering crops [6], do not provide the necessary nutrients honey bee hives need to survive and thrive [7]. Bees' access to nutritional resources has been of increasing concern as changes in landscape use has resulted in a shift in floral resource availability and diversity, with many bees paying the dietary price [8]. The land use surrounding honey bees, for example, can have a large impact on their health and physiology [9,10]. Hives surrounded by more agricultural land show higher losses [11] and reduced fat stores entering winter [12]. However, this relationship is not always straightforward. In some landscapes more agricultural production is associated with reduced stored pollen (beebread) quality [13] (UK) and honey production [14] (Kenya); [15] (France). However, other research showed that, in parts of the Midwestern USA, honey bee hives store more honey [16] in agricultural than urban areas. Although a single coherent understanding of how landscape composition affects bee health is difficult to generalize, one thing is clear — forage availability and nutritional stress have been cited as two of the top most important challenges to bee health by researchers [3] and beekeepers [17] alike.

Another critical stressor faced by honey bees is pest and pathogen pressure. Honey bees are host to a variety of pathogens, including viruses, bacteria, fungi, as well as arthropod pests. The most detrimental of these is the Varroa mite; in addition to parasitizing developing pupae and adults, they harbor and transmit several honey bee viruses [18]. This Varroa-virus complex [19,20•,21] and the viruses alone [22,23] have been identified as major drivers in hive losses. However, other pathogens also play a role in losses. *Nosema ceranae*, a widespread microsporidian fungal gut parasite, can cause a reduction in lifespan [24,25] and hive losses [26], and European and American foulbrood are contagious bacteria that attack developing larvae and pupae [27,28].

Bee nutrition affects disease susceptibility

In many organisms, the quantity or quality of diet can affect their susceptibility to pathogens [29]. How this manifests in honey bees is still not completely understood. Pollen and nectar/honey contain variable protein, lipid, and carbohydrate content and a variety of phytochemicals and micronutrients that have the potential to affect immune response. While it is still not clear what makes the 'best' pollen, evidence suggests that a diverse diet is most likely to provide bees with the necessary inputs. Higher pollen diversity has been shown to upregulate some elements of the innate immune system [30••] and reduce mortality due to *N. ceranae* [31••] and Israeli acute paralysis virus (IAPV [32]). Protein, amino acid, and micronutrient content have all been hypothesized as contributors to these effects [31••,32,33••,34••], though no definitive driver has been identified. Likely, there is interaction between all of these components, with each playing an important role in honey bee resilience. There is still much to be learned about the mechanisms by which good diet and nutrition may provide benefits to honey bees in the form of reduced pathogenicity in the face of both viral and fungal pathogens. However, the evidence to date is compelling in suggesting that honey bees, like many other organisms, stand to benefit in their anti-pathogen responses from improved nutrition.

Parasites and pathogens affect bee nutrition

Pathogen infection and susceptibility is affected by the nutrition of the host, but also can contribute to the malnourishment itself. This phenomenon can take two forms in honey bees — infection affecting physiological nutrition via digestion and effects on behavior that impact hive level nutrition. *Nosema apis* and *N. ceranae* infect the gut, robbing bees of nutrients and causing digestive problems that can reduce lifespan [35]. *N. ceranae* also has the ability to cause immunosuppression in their honey bee hosts [36,37]. Because mortality associated with *Nosema* is exacerbated by lower quality pollen diet [31••], high *Nosema* loads, with accompanying malnutrition and immunosuppression could result in a feedback loop resulting in a higher incidence of pathogen-induced mortality. This malnourishment also has the potential to affect susceptibility to other pathogens; with reduced nutrition and immunity, honey bees may become more prone to normally-tolerable levels of virus infection. Co-infection with multiple pathogens has been frequently observed in weak or sick hives (e.g. in studies of 'colony collapse disorder' [22], and malnutrition could be part of this phenomenon.

Pathogen infection may also affect the nutritional health of individuals and colonies through behavioral perturbation that changes colony-level nutrition. Both *Nosema* and sacbrood virus (SBV) infection have been linked to reduced pollen collection [38], and *Nosema* can lead to reduced levels of the storage protein vitellogenin, and increased juvenile hormone levels, resulting in early onset of foraging behavior [25].

Varroa mites are considered the main pest threat to honey bees today. Their parasitization of developing pupae results in smaller bees with lower hemolymph volumes [18], and also results in the transmission of multiple viruses [39]. Further, Varroa infestation has been linked to a reduction in colony-level lipid stores [12], and high pollen stores have been linked to reduced Varroa infestation [40], again showing how a pest/pathogen complex can reduce group nutrition, though it is unclear the mechanism by which this reduction occurs. However, because Varroa is so tightly linked to the viruses it vectors, it is not yet clear whether nutritional deficits are caused by the mites themselves, or whether viral infection per se may also influence honey bee nutrition. Like *Nosema*, some viruses penetrate their hosts at the gut interface [41], raising the possibility that the viruses themselves could disrupt gut physiology, digestion, and/or nutrient acquisition.

In summary, there have been relatively few studies that have addressed the physiological consequences of pathogen infection in honey bees, but the emerging picture from studies to date suggest that many of the several major honey bee pathogens and pests can have negative impacts on bee nutrition.

Synthesis: feedbacks between nutrition and disease

In the wake of serious concerns about declining honey bee health over the past several decades, both nutritional and pathogen stress have intensified simultaneously. In many areas of the world, recent years have seen increasing transformation of landscapes into intensively managed crops that provide little forage for bees. This has had some of the largest impact in areas where forage was once plentiful [42•]. Thus, some managed honey bees have experienced massive shifts in food availability and diversity just in the last few decades. At the same time, there has been increased stress from pathogens due to globalization and Varroa pressure, with pathogenic virus strains spreading quickly [2,43] and the introduction of a new form of *Nosema* [44].

The feedback between nutrition and pathogens has the potential to create a cycle of stress that could have major impacts on bee health (Figure 1). As reviewed above, poor nutrition can leave bees more susceptible to infections, resulting in disease losses that could be recoverable under better dietary conditions. Some pathogen infections interfere with nutrition, burning up reserves or interfering with digestion. As co-infections of multiple pathogens likely occur, there is even the capacity for even interactions between these — creating a network of pathogen and dietary stresses that can affect bees at the individual and colony levels. Both nutritional stress [45,46] and pathogen infection [25,26] have been associated with a premature onset of foraging behavior and associated physiological changes; it is possible that, together, these effects synergize and are amplified. For example, recent

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