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Abiotic and biotic factors affecting the replication and pathogenicity of bee viruses

Alexander J McMenamin[1,4], Laura M Brutscher[1,4], William Glenny[1,3] and Michelle L Flenniken[1,2,4]

Bees are important pollinators of plants in both agricultural and non-agricultural landscapes. Recent losses of both managed and wild bee species have negative impacts on crop production and ecosystem diversity. Therefore, in order to mitigate bee losses, it is important to identify the factors most responsible. Multiple factors including pathogens, agrochemical exposure, lack of quality forage, and reduced habitat affect bee health. Pathogen prevalence is one factor that has been associated with colony losses. Numerous pathogens infect bees including fungi, protists, bacteria, and viruses, the majority of which are RNA viruses including several that infect multiple bee species. RNA viruses readily infect bees, yet there is limited understanding of their impacts on bee health, particularly in the context of other stressors. Herein we review the influence environmental factors have on the replication and pathogenicity of bee viruses and identify research areas that require further investigation.

Addresses
[1] Department of Plant Sciences and Plant Pathology, Montana State University, Bozeman, MT, USA
[2] Institute on Ecosystems, Montana State University, Bozeman, MT, USA
[3] Department of Ecology, Montana State University, Bozeman, MT, USA
[4] Department of Microbiology and Immunology, Montana State University, Bozeman, MT, USA

Corresponding author: Flenniken, Michelle L (michelle.flenniken@montana.edu)

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Introduction

Honey bees (*Apis mellifera*), bumble bees (*Bombus* spp.), and other insects play a vital role in ecosystems as plant pollinators. The annual estimated value of crops directly dependent on insect pollination worldwide is $175 billion [1•] and approximately $17-18 billion in both North America and the European Union [2,3]. Wild, native, and managed bee species perform the majority of pollination services in both agricultural and non-agricultural landscapes. Bumble bees are the primary pollinators of some crops (e.g., tomatoes) and augment pollination of other crops [4]. In large-scale crop (e.g., almond, apple, cherry) production honey bees are the primary pollinators, since they forage over large distances and can be maintained in transportable hives. Honey bees were introduced to North America in the early 1600s as a managed species kept by beekeepers primarily for honey production [5]. Today, the majority of US honey bee colonies are maintained by commercial beekeeping operations. Colonies managed by small-scale beekeepers and feral (or unmanaged) colonies make up the remaining population.

High annual losses of managed honey bees and population declines of wild bumble bees are of great concern since bee pollinators are important for plant reproduction and crop production [6,7,8]. In some regions of the US, bumble bees have experienced between 23% and 86% range reduction [7,8] and annual losses of US honey bee colonies have averaged 33% since 2006 (reviewed in [9•]). Several studies have focused on assessing the relationship between colony health and the effects of multiple biotic (e.g., pathogens, bee genetics, and queen longevity) and abiotic factors (e.g., agrochemical exposure, weather, and management practices) [7,10,11,12,13,14]. These studies indicate that pathogens, agrochemical exposure, and lack of quality forage and habitat all contribute to bee losses, though investigating the relative role of these factors is an active area of research. Pathogens, including the microsporidia *Nosema ceranae*, trypanosomatids, viruses, and the ectoparasitic mite *Varroa destructor*, contribute to honey bee colony losses [15,16,17•,18•,19•,20,21,22,23,24,25] (reviewed in [11,26,27,28•,29]), and the microsporidia *Nosema bombi* is associated with declining bumble bee populations in the US [7,8].

The largest class of honey bee infecting pathogens are positive-sense single stranded RNA viruses including: Acute bee paralysis virus (ABPV), Black queen cell virus (BQCV), Israeli acute bee paralysis virus (IAPV), Kashmir bee virus (KBV), Deformed wing virus (DWV), Kakugo virus (KV), Varroa destructor virus-1 (VDV-1), Sacbrood virus (SBV), Slow bee paralysis virus (SBPV), Cloudy wing virus (CWV), Big Sioux River virus (BSRV), Aphid lethal paralysis virus (strain Brookings) (ALPV), Chronic bee paralysis virus (CBPV) (reviewed in [15,17•,28•]), the

Lake Sinai viruses (LSV) [21], and Bee macula-like virus (BeeMLV) [30]. In addition, one double-stranded DNA virus, Apis mellifera filamentous virus (AmFv) has been isolated from honey bees [31]. The majority of bee-infecting viruses were originally discovered and characterized in honey bees, likely since they are the most investigated species. Detection of these viruses in other arthropods indicates that origin of discovery does not necessarily reflect host-range, host–pathogen evolution, or directionality of inter-species transmission (i.e., ABPV, IAPV, DWV, BQCV, SBV, SBPV, LSV and VdMLV) [32••,33••,34,35•,36,37••]. Bee viruses are transmitted both vertically and horizontally [38], including between and among co-foraging wild and managed bee populations [32••,39,40••]. Viruses are also transmitted by *Varroa destructor* mites, which also support replication of a subset of these viruses [41,42,43,44]. Honey bee virus infections may cause deformities, paralysis, death, or remain asymptomatic [15]. The severity of virus infection is influenced by numerous factors that impact bee health, including genetic composition of both host and virus, immune response, synergistic and/or antagonistic pathogenic infections, microbial composition, nutritional status, and agrochemical exposure [15,27,28•,45•,46•,47]. The focus of this review is to highlight recent studies on the abiotic and biotic factors that affect bee virus replication and pathogenicity.

Bee health, nutrition, habitat, and colony management

Bees obtain nutrients from nectar and pollen, and adequate nutrition is important for proper immune system function (reviewed in [48]). Though there have been few quantitative assessments of the relationship between nutritional status and pathogen burden ([49••] and reviewed in [47]), several studies suggest that insufficient protein and low-diversity diets negatively impact bees' ability to defend against pathogens [49••,50,51]. In laboratory-based studies, naturally DWV-infected honey bees that were fed a protein-free sucrose-syrup diet had significantly higher DWV levels compared to bees fed either pollen or a protein-supplement [50]. Intriguingly, the pollen-fed group had reduced DWV virus load by day four of the trial, whereas the protein supplement fed group exhibited reduced virus load several days later [50]. While an adequate amount of protein is important, a diverse pollen diet, as opposed to monofloral pollen or additional protein, enhanced adult bee immunocompetence (i.e., haemocyte concentration, fat body mass, and phenoloxidase and glucose oxidase activities) [49••]. Together these studies suggest that while protein is important, the source of this protein is also critical to proper immune function. Similarly, bees fed honey, which consists of 30–45% fructose, 24–40% glucose, 0.1–4.8% disaccharides including sucrose, and minute amounts of micronutrients and amino acids, exhibited increased expression in more genes involved in detoxification, immunity, aromatic amino acid metabolism, and oxidation and reduction, as compared to bees fed either sucrose or high fructose corn syrup [51,52]. Together, these studies indicate that proper nutrition (i.e., adequate protein and carbohydrates) and natural and diverse food sources (i.e., nectar and pollen) enhance bee immune function. However, the mechanisms and gene regulatory pathways involved in nutrition-dependent immunocompetence require further characterization. Future studies should employ both cage-studies, which provide a well-controlled environment to investigate individual bee responses and facilitate standardization of multiple variables (e.g., pathogen dose), and colony level studies. A more thorough understanding of the role of diet on bee health is important, as it is common for beekeepers to provide supplemental feed when natural sources are scarce. Overall, these studies indicate that managing landscapes to enhance floral, and therefore nutritional diversity will benefit the health of both managed and wild bee populations.

While floral resources are essential to bee health, flowers also serve as a hub for pathogen transmission and agrochemical exposure [32••,33••,40••]. The most well documented intra- and inter-species transmissible bee pathogens are RNA viruses [32••,33••,39,53••,54,55••]. Transmission of these viruses is thought to be associated with bee foraging activities, as BQCV, SBV, and DWV have been detected in honey bee collected pollen [32••,40••]. In addition, inter-species transmission was demonstrated experimentally in greenhouse studies in which IAPV was transmitted from honey bees to bumble bees and vice versa [32••]. Phylogenetic analyses of virus genome sequences (i.e., BQCV, DWV, and IAPV) obtained from foraging honey bees, pollen pellets, and non-*Apis* hymenopteran, including solitary bees, wasps, and bumble bees, did not cluster by host, providing further evidence of inter-species transmission [32••]. In addition, IAPV was detected in non-*Apis* hymenopteran species collected from sites near IAPV-infected honey bee colonies, whereas wild hymenopterans obtained from areas proximal to honey bees that were not infected with IAPV were also IAPV-negative [32••]. Likewise, recent evaluation of the viruses associated with sympatric honey bee and bumble bee populations in Great Britain and the Isle of Man indicated they were infected with similar strains of DWV and VDV [39], and BQCV, DWV, ABPV, SBPV, and SBV were detected in both honey bees and bumble bees in the same geographic area, though viral prevalence and abundance varied by species [33••]. Based on modeling data, it was suggested that the directionality of DWV transmission was from honey bees to bumble bees, since DWV was more prevalent and abundant in honey bees than in bumble bees where ranges overlapped [39]. This relationship was reversed for ABPV and SBV, which were more prevalent in bumble bees than in honey bees where ranges overlapped [33••]. Although viruses