Review

Bees brought to their knees: microbes affecting honey bee health

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The biology and health of the honey bee *Apis mellifera* has been of interest to human societies for centuries. Research on honey bee health is surging, in part due to new tools and the arrival of colony-collapse disorder (CCD), an unsolved decline in bees from parts of the United States, Europe, and Asia. Although a clear understanding of what causes CCD has yet to emerge, these efforts have led to new microbial discoveries and avenues to improve our understanding of bees and the challenges they face. Here we review the known honey bee microbes and highlight areas of both active and lagging research. Detailed studies of honey bee–pathogen dynamics will help efforts to keep this important pollinator healthy and will give general insights into both beneficial and harmful microbes confronting insect colonies.

Honey bee threats and impacts

Managed honey bee (*Apis mellifera*) colonies are a major component of world agriculture, providing pollination services for diverse crops along with an important 'cash crop' of their own through honey, wax, and other hive products. Honey bees and other pollinating insects also shape natural ecosystems by facilitating gene flow for the angiosperms, the most successful and diverse plant taxon. Bee colonies succumb to a variety of factors including starvation, queen loss, and an array of pathogens and parasites [1]. New tools have helped to reshape models for infection and disease in honey bees [2] and have provided a new appreciation of bee defenses against disease [3,4]. Currently, scientists and beekeepers are especially tuned to bee health, in part because of an enigmatic syndrome of colony losses termed colony-collapse disorder (CCD, Box 1). Although CCD explains only a minority of worldwide bee losses, this syndrome has had severe effects in many populations.

Next-generation sequencing techniques have identified several novel viruses and microbes in honey bees and have broadened the known ranges for others [5–7]. As such, our picture of the honey bee pathosphere (*sensu* [8], Figure 1) has recently expanded and this is likely to continue as additional cryptic species or novel introductions are identified. Here we (i) briefly describe the microbes implicated in honey bee health, (ii) present the diverse routes of infection for bees, (iii) discuss the dynamics of multi-parasite interactions, (iv) explore genetic and environmental factors important for disease risk, and (v) present future research needs to manage honey bee health.

Key pathosphere groups

Honey bees face microbes spanning several kingdoms, although the most damaging threats and hence the most researched groups are viruses, bacteria, and fungi. Here we give brief introductions to the main players and discuss in more detail the pathogens we feel are neglected or confounded in current studies. Several recent reviews have described at length some of the specific microbes of honey bees and the reader is encouraged to find detailed information from these [9–13].

Viruses

Honey bees carry nearly twenty described positive-strand RNA viruses, primarily in the families Dicistroviridae and Iflaviridae (Figure 1), with additional taxa that are not yet formally placed to family including chronic bee paralysis virus and relatives, which are putative Nodaviridae [6]. Bee viruses affect the morphology, physiology, and behavior of bees and have been widely associated with weak and dying colonies both historically and recently [12,14]. Although RNA viruses predominate in honey bees, DNA viruses have occasionally been reported [15]. A recent proteomic fingerprinting analysis purported to show a ubiquitous iridovirus in U.S. honey bees associated with

Glossary

Apiary (bee-yard): a field where beehives are placed together by beekeepers and managed, the number of which depends upon the food resources available to the bees. Short-term apiaries of thousands of colonies may be brought together for the pollination of large commercial crops whereas smaller long-term apiaries are set up in areas where a variety of crops and/or flowers are continually available.
Crop: also known as the 'honey stomach', this is a region of the foregut formed by a highly flexible sac which serves as a reservoir for nectar.
Fat body: a loose structure immersed in the hemolymph and comprised primarily of adipocytes where energy is stored in the form of glycogen and triglycerides and an important source for the biosynthesis of circulating molecules involved in growth, development, immunity, and detoxification.
Hemolymph: fluid within the circulatory system that transports cells (hemocytes), electrolytes and organic compounds among the tissues of the body.
Malpighian tubules: thread-like extensions of the gut that extend into the body to filter metabolic waste from the hemolymph.
Midgut (ventriculus): the region of the gut where most enzymatic digestion of food (i.e. pollen) takes place.
Pylorus (pyloric valve): the region of the alimentary canal that acts as a connection between the posterior midgut and the ileum (intestine), and containing a valve to separate the foregut from the hindgut.
Trophozoite: the active feeding stage of a parasite, often morphologically adapted to attach to and obtain nutrients from a host cell.

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Box 1. Colony-collapse disorders

Few events disrupt the beekeeping world more than the sudden collapse of mature colonies across a wide area, even more so when this collapse takes place in the absence of known pathologies or environmental triggers. Historical records indicate that such losses have occurred throughout recorded beekeeping. A recent version of these declines, labeled colony-collapse disorder (CCD), began five years ago in the U.S. and in limited regions in Europe and Asia. CCD is distinct from other bee-loss events in being a relatively sudden disappearance of the majority of adult worker bees (taking place over days or weeks) from an otherwise healthy hive with a queen and brood. CCD is patchy in space and time and there is no corresponding pathology in brood or workers, nor a tight correlation with levels of parasitic mites. Queens often survive the event, albeit surrounded by an unsustainably small cluster of younger worker bees. Although explaining only a fraction of the worldwide annual losses of honey bees, CCD has been blamed for over one million lost colonies [71].

Current hypotheses for CCD focus on the adverse effects of pesticides and other anthropogenic chemicals, poor nutrition, and exposure to novel pathogenic microbes. After initial successes at identifying unusual viral profiles in some CCD colonies [5], a consensus is emerging that CCD is complex and probably cannot be ascribed to any one agent, even within the U.S. [71]. Instead, honey bee colonies appear to be resilient to most individual insults, but are vulnerable to the cumulative effects of microbes and other stress factors. Thanks to increased fees paid to beekeepers for pollination and hive products, managed U.S. honey bees have held steady at approximately 2.5 million colonies, although CCD remains an important economic drain on beekeeping – management and material costs exceed tens of millions of U.S. dollars annually.

CCD [16], but these results were soon challenged on methodological grounds [17] and diverse sequencing efforts have not yet found widespread DNA viruses in honey bees.

Bacterial associates

Two firmicute bacteria, *Paenibacillus larvae* and *Melissococcus plutonius*, are the infective agents behind American and European foulbrood disease, respectively, and the sole formalized bacterial diseases of honey bee larvae. These worldwide diseases are among the primary honey bee threats [1], leading to colony losses and expensive treatment and quarantine regimes. European foulbrood levels have surged regionally in the past few years [9] for unknown reasons. Antibiotics are used by some beekeepers (especially in the U.S. and other non-European countries) to treat both diseases, leading to concerns over antibiotic resistance [18], collateral losses of beneficial microbes, and the risks of antibiotic residues in honey and pollen destined for human consumption.

Adult honey bees are parasitized by two species of mollicute bacteria, *Spiroplasma apis* [19] and *Spiroplasma melliferum* [20]. Pathogenesis occurs when the bacteria breach the gut barrier and invade the hemolymph (Glossary), causing a systemic infection that can ultimately lead to fatal disease in the bee ('May disease' and 'spiroplasmosis'). *Spiroplasma* infections are much more difficult to recognize and diagnose than the foulbrood diseases, hindering the

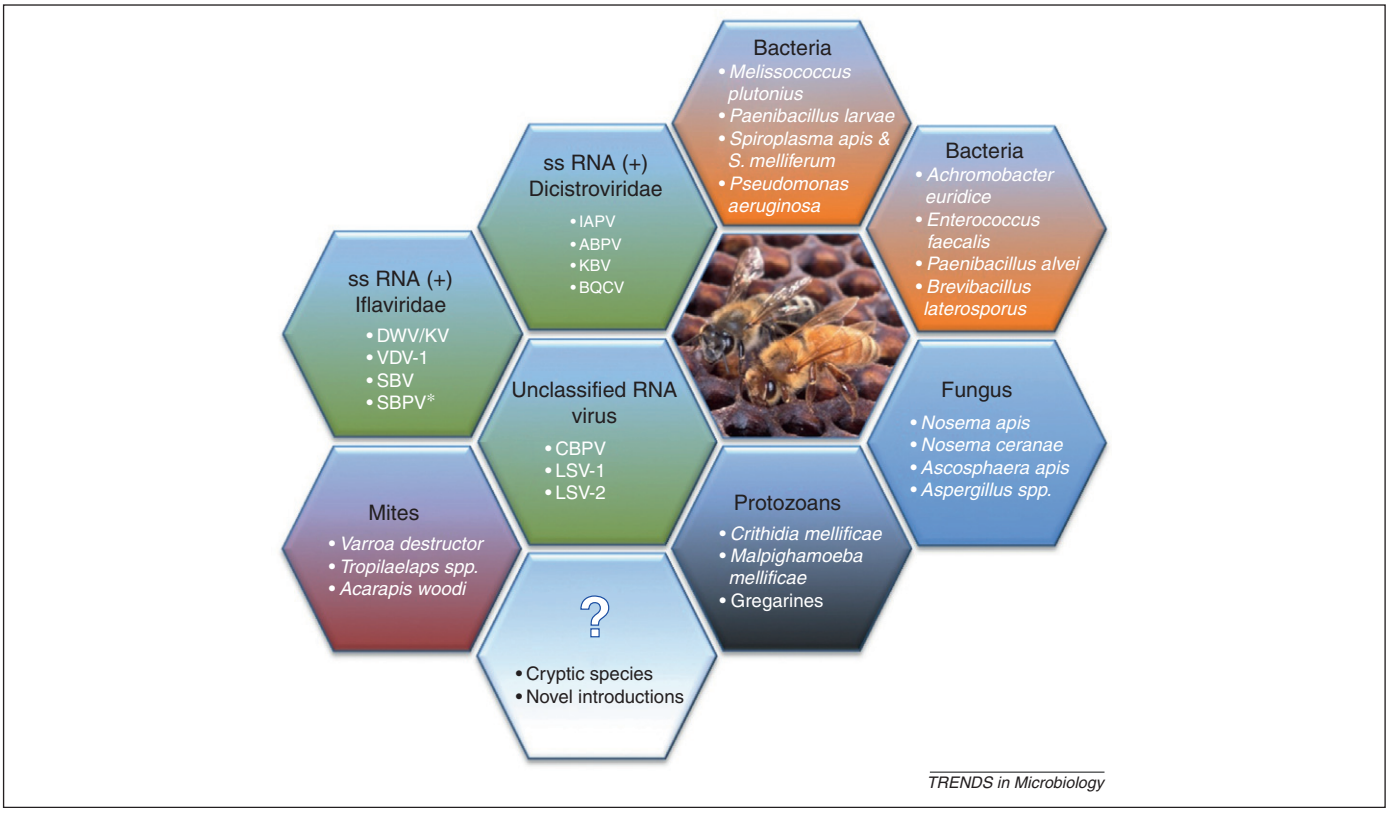

Figure 1. The 'honey bee pathosphere' diagrams the current, widely recognized community of parasites affecting the health of *Apis mellifera* globally, many of which are covered in this review. As discussed in the text, the '?' represents potential additions of cryptic parasites in the honey bee and for novel parasite introductions transmitted by the mites listed or via cross-contamination from other species at common foraging areas in the environment. Deformed wing virus (DWV) is listed with Kakugo virus (KV), a derived strain of DWV. Abbreviations: SBV, sacbrood virus; VDV, *Varroa destructor* virus; IAPV, Israeli acute paralysis virus; BQCV, black queen cell virus; KBV, Kashmir bee virus; ABPV, acute bee paralysis virus; SBPV, slow bee paralysis virus; CBPV, chronic bee paralysis virus; LSV, Lake Sinai virus; *, Classification of this virus is well supported but not yet broadly accepted [86].

ability to monitor mollicute abundance and impact on the beekeeping industry. They remain interesting targets for study, however, owing to their seasonal abundance in honey bee colonies [6], which is presumably tied to flowering cycles of specific plants that act as transmission sites [21]. Recently, spiroplasmas have been identified as the cause of several crustacean disease outbreaks in aquaculture, suggesting that the virulence of these bacteria may be related to a large number of hosts and stressful environmental conditions [22]. A similar hypothesis in honey bees would be important to test given the stressful environmental conditions they often face (below).

In addition to these pathogens, honey bees harbor a number of commensal or beneficial bacteria, and most are described as residing in the mid- and hindgut. The microbiome of adult bees includes a stable population of lactic acid bacteria that probably play roles in bee nutrition [23] and health. Moran and colleagues [24] have argued that adult honey bees harbor a consistent bacterial community comprising several proteobacteria (γ, α, and β), two firmicutes, and a bifidobacterium. Although each taxon is not present in all sampled bees worldwide, these taxa show nearly identical genetic signatures (16S sequences) across continents [25]. Healthy larvae are known to carry low levels of bacteria as well, some of which affect pathogen growth [3].

Microsporidia

Honey bees host two species of parasites belonging to the fungal phylum Microsporidia – *Nosema apis* and *Nosema ceranae* – both of which have received extensive attention. As obligate intracellular parasites, the microsporidia invade epithelial cells of the adult midgut and undergo repeated cell divisions to ultimately produce new infectious spores. These infections often result in heavy parasite loads, tens of millions of spores per bee [26], which may increase the nutritional requirement, morbidity, and mortality of the bee host [27].

The role of *Nosema* infection in recent bee losses is unclear [13]. It has been argued that *N. ceranae* infection is virulent and a key factor in recent colony declines in Spain [28,29]. Other studies have failed to find a direct or indirect link between either *N. ceranae* or *N. apis* and colony declines [5,14], and show that *N. ceranae* is no more virulent than its congener *N. apis* [26]. A recent five-year study in Germany showed no correlation between *N. apis* or *N. ceranae* presence and colony loss in either the Spring–Summer or Fall–Winter seasons [30]. *Nosema* infections are presumably driven by additional factors such as seasonal and climate conditions [30], nutritional status of the colony [31], the inoculum dose [26,31], coinfection with other pathogens, and host genetics.

Ascosphaera apis

The fungal pathogen *Ascosphaera apis* causes chalkbrood disease in larvae, weakening colony growth and honey production [32]. Larvae that ingest spores can mount an immune response against infection [33], although lethality is dose-dependent and exacerbated by environmental factors including temperature and humidity [34]. Larvae killed by chalkbrood disease, appropriately named mummies, become hard and desiccated by the overgrowing fungus and may produce spore-packed cysts for dissemination. Variation in strain virulence has been observed and linked in part to spore production and development [10] and enzyme production [35]. Interestingly, only larvae are susceptible to disease, possibly indicative of important differences in the commensal gut microbiome or in immune development between the larval and adult stages.

The enigmatic protozoan pathosphere

For various reasons, three protists infecting honey bees have been little studied and largely neglected for decades by researchers. Reasons for this include: (i) lack of obvious pathology, (ii) low detectability via microscopy (i.e. difficult to recognize, low abundance, or rapid degradation after bee death), (iii) difficulty in culturing, and (iv) absence of genetic markers. The tide is changing, fortunately, and the following are of increasing interest to the honey bee research community and should prove to be areas of significantly increased knowledge in the near future.

Trypanosomes

Trypanosomes have been documented from *A. mellifera* globally [36,37] with strong seasonal and/or regional variation in prevalence [6,14]. The description of the type strain isolate, *Crithidia mellificae* [38], together with that of a new isolate denominated strain SF (San Francisco) [6], provides an opportunity for a more detailed understanding of the role of this parasite in honey bee health. Trypanosomes occur primarily in the lumen of the hindgut in both a motile flagellated form and an amastigote form (non-flagellated, rounded stage) that produces encrustations on the gut epithelia surface [38,39]. The pylorus may be a unique location where trypanosomes specialize and accompany endosymbiotic bacteria [39]. Although historically associated with sick honey bees [37], their current role in honey bee health is unclear. However, a related trypanosome that infects bumble bees is pernicious, particularly during stressful conditions, affecting behavior [40] and longevity [41].

Gregarines

Gregarines are a diverse group of apicomplexan protists that parasitize many invertebrate phyla including the honey bee, which can suffer shortened life spans and colony loss [42]. Once ingested, they have complex life cycles in the midgut where they asexually replicate and differentiate into trophozoites. These attach to the epithelia and absorb nutrients from the midgut, and this could reduce nutrient processing by the bee and create tissue damage where opportunistic pathogens could attack. Sexually produced gametocysts are passed out of the host via the feces. Recent research shows that the bumble bee gregarine, *Apicystis bombi,* can crossinfect *A. mellifera* [43]. Although primarily a gut pathogen, *A. bombi* occurs in fat body tissue and thus there are unique implications on life history, pathology, and virulence from this species. Gregarines infecting other bees and social wasps inhibit foraging, reduce fecundity, and increase queen mortality [44]. Although colonies in tropical climates seem more susceptible [42], we know little about the biogeography, seasonality, virulence, and genetics of honey bee gregarines.

Amoeba

The amoeba *Malpighamoeba mellificae* [45] is known to infect adult bees in temperate to tropical regions, with a prevalence apparently greater in the latter [46]. Ingested cysts develop into trophozoites and invade the Malpighian tubules. Within this unique niche the trophozoites feed upon the epithelia lining the tubule lumen, degrading the tissue in the process [45]. Damaged Malpighian tubules will inhibit metabolic waste excretion and solute exchange with the hemolymph, and 'amoebiasis disease' ultimately can weaken and kill bees. As the amoebae replicate they pack the lumen of the tubules, forming up to 500 000 cysts per bee that are shed through the feces [47]. Associated with spring dwindling of bee colonies, *M. mellificae* is also linked with dysentery symptoms in adult bees and the tendency of infected bees to 'disappear inexplicably' from the hive [45]. Genetic markers are currently lacking for *M. mellificae*, and this limits more sensitive identification using modern molecular techniques.

Modes of microbial transmission

As holometabolous insects, bees proceed through embryonic, larval, pupal, and adult development stages that each comprises a distinct ecological niche for microbes. How and if microbes transition successfully through these stages is largely unknown, although most microbes have adapted to infect a single life-stage of the honey bee. Here, we focus on transmission routes and infection strategies for microbes, where the social structure of honey bees adds unique opportunities and challenges.

Vertical transmission

Honey bee queens transmit viruses to their offspring at low titers, leading to asymptomatic infections in these offspring [48,49]. Viral genomes have also been found in association with semen; it seems probable that drones transmit viruses either vertically to offspring or horizontally to their queen mates [50]. Other than viruses, honey bee embryos harbor few microbes – it is unclear whether those present are derived from true vertical transmission versus surface exposure. Nevertheless, given that individual queens produce tens of thousands of offspring over their lifetimes, vertical transmission of microbes presents a considerable management risk for honey bees, and is a phenomenon that justifies regulation of queen movement in managed beekeeping.

Horizontal transmission

As social organisms living at high density, honey bees can receive microbial inoculations horizontally via nestmates, the hive environment, or hive parasites. Transferring contents of the crop from one individual to another, termed trophallaxis, establishes a web of interaction among all members of the colony and is a key characteristic of honey bees [51]. This food-sharing among hivemates provides an efficient means of dispersal for orally communicable pathogens, as shown for *N. apis* [52] and for several viruses that occur in honey and pollen stores [48,53].

Worker bees typically remove larvae that have succumbed to diseases such as chalkbrood and foulbrood by discarding them outside of the hive or cannibalizing them, a hygienic behavior that reduces pathogen load in the hive. At the same time, however, workers can become contaminated with microbial spores from these corpses and subsequently spread them to other surfaces within the hive or to nestmates [54]. As one way of minimizing this risk, it was recently discovered that some colonies produce 'hygienic workers' that recognize larvae infected with chalkbrood fungus earlier in the disease process than workers from typical colonies, and remove them before spore maturation [55].

The parasitic mite *Varroa destructor* serves as an active horizontal vector of several viruses. Among these, deformed wing virus (DWV) seems to be especially tied to mite parasitizm, and essentially all visible pathologies due to this virus arise in the company of mites and are dependent on the context of transmission and virus dose [53]. This connection seems to result from high virus replication within the mite, leading to a greater DWV inoculation titer to the bee [49,56] than occurs when DWV is transmitted in the absence of the mite (Box 2). Although currently contained in Southeast Asia, *Tropilaelaps* spp. mites similarly feed on bee hemolymph and pose an additional microbial vector threat because they have been found to carry DWV [57].

Intercolony encounters are common, presenting a risk of acquiring parasites from conspecifics. Drifting events, whereby individual foragers enter and become integrated

Box 2. The diseased superorganism

By assuming that individual colony members are bound together in the name of their colony, the superorganism concept has been a useful tool for describing emergent behaviors in social insect colonies [81]. Simplistically, insect colonies can be viewed as a single organism, with a germ line (often one queen and reproductive males) and a vegetative soma comprised of largely sterile workers (always females in ants, wasps, and bees, often both sexes in other taxa). This concept ignores genetic diversity in colonies as well as various conflicts over which colony members reproduce. Nevertheless, it helps to explain the heightened risk of colonies to disease (e.g. by greater apparency to parasites and high rates of horizontal transfers) and the contrast between colony-level (systemic) responses, such as hygienic behaviors and other means for changing the hive environment, and individual (localized) responses including innate immunity [82].

In addition, parasites and pathogens that exploit members of a superorganism face entirely different evolutionary pressures than do those infecting individual insects. As one example, a bacterial strain that is highly virulent upon chance infections of solitary individuals may prove vulnerable to unique defenses of superorganisms – such as hygienic removal of diseased individuals from the system or the use of the antimicrobial resin propolis to help prevent surfaces within the hive from acting as microbial reservoirs [83]. However, colony life allows pathogens to exploit more sophisticated transmission routes, and several bee viruses are adept at using honey bee parasitic mites as active vectors for switching bee hosts within and between colonies (as described above under 'Horizontal transmission'). Serial exploitation of colony members might also allow highly mutable pathogens to 'explore' protein sequence space as a means of evading defenses and improving their chances of moving on to new hosts. Intriguingly, several honey bee viruses appear to be capable of recombination [84], and Moore and colleagues suggest that this recombination is one route for acquiring virulence traits [85]. Sequence-level point mutations might also be effective in increasing virus infection and growth rates, or disrupting the insect antiviral response. Either way, a reservoir of microbes in a long-lived colony, perhaps maintained by the ever-present parasitic mites, has considerable evolutionary time for 'within-host' evolution.

into a new colony, may carry disease to new colonies. Strong honey bee colonies often rob weaker neighbors for resources, acquiring bacteria and other microbes harbored by these weak colonies [58]. Honey bee colonies are able to reproduce by division, wherein a large portion of the worker force departs with the old queen as a swarm to colonize new nest sites, leaving the remaining colony members and resources to a new queen. These swarms can carry disease with them and further its distribution, or may become contaminated by infectious spores from prior inhabitants of the nesting site. In a similar manner, apiarists can spread disease across colonies using contaminated tools or hive components. Because bees in the U.S.A. and other countries are routinely moved long distances to fulfill pollination contracts, and because some countries permit the introduction of intercontinental bee materials, human-induced exposure to pathogens can occur on a large scale.

Gut pathogens of bees are often adapted to a fecal–oral mode of transmission and may cause dysentery as a virulence factor, enhancing their transmission (e.g. *N. apis*). Resilient spores, such as those of *P. larvae* and *Nosema* spp. provide a vehicle enabling survival outside of hosts for extended periods. Several viruses are also transmitted in the feces [48,59]. Bees generally defecate outside the hive itself, lowering colony spore-loads but contaminating flowers, nectar, pollen, and water sources.

Many different pollinators (solitary bees, bumble bees, wasps, flies, beetles, moths and butterflies) use common foraging areas. For foraging honey bees, such aggregation enhances encounters with a dynamic pathogen complex and potentiates interspecific pathogen transmission. The bumble bee gregarine *A. bombi* has been detected in honey bees and may indicate a transmission route for gregarines indiscriminately among pollinators at common foraging sites [43]. Such cross-infection may not be particularly rare because prevalence levels of 7% and 13% were documented from honey bee colonies. Pathogen spillover also occurs with several viruses [48,59] that may move between different insect host species at common foraging sites [7], as shown for the orally communicable DWV [53]. Several *Spiroplasma* bacterial species do not appear to have evolved specific insect–host associations [60] and thus may also commonly cross-infect pollinators. For example, *S. apis* has been isolated from tabanid flies (Diptera:Tabanidae) as well as from honey bees [22].

Microbial interactions

Given the plentiful and shared transmission routes for many bee parasites, multi-parasite infections within individuals and colonies are frequent, leading to direct or indirect interactions with mutualistic, neutral, or antagonistic outcomes. Owing to their similar niche and transmission mode, gut parasites may be mutually beneficial to one another. For example, infections by *N. apis* and *M. mellificae* appear to be positively correlated [45,47,61], arguably because both cause dysentery to mutually enhance their distribution from the bee, and because of their non-overlapping niches within the bee gut. Similarly, a positive correlation between *C. mellificae* and *N. ceranae* was recently documented in the U.S. [6], although the nature of this association is unknown. By contrast, direct competition among microbes for host resources may limit the replication success of a competitor. Mixed microsporidia infections in other insects involve antagonistic interactions [62]; such interactions are plausible between *N. apis* and *N. ceranae*.

Several bacteria coinfect honey bee larvae with the etiologic agent of European foulbrood, *M. plutonius*, including *Achromobacter euridice*, *Brevibacillus laterosporus, Enterococcus faecalis*, and *Paenibacillus alvei* [9] (Figure 1). Although a poorly understood dynamic, some of these associated bacteria increase the pathogenicity of foulbrood disease (*A. euridice* and *E. faecalis*) whereas others appear to be saprophytic (*B. laterosporus* and *P. alvei*). Commensal bacteria are a special case of microbial association with varied benefits to honey bees [63]. Commensal lactic acid bacteria within the crop of adult bees, notably *Lactobacillus* spp. and *Bifidobacterium* spp. [23], have been found to inhibit the growth of the larval pathogen *P. larvae* [64]. Several firmicute bacteria also inhibit both *P. larvae* [3,65] and the fungal pathogen *A. apis* [66]. Although the mechanism by which commensals control pathogenic species in honey bees is largely unknown, the secretion of cytotoxic metabolites (e.g. surfactin by *Bacillus* spp.) and acidification (short-chain fatty acids by lactic acid bacteria) appear to play roles [66,67]. In addition, indirect effects among pathogens might arise from stimulation of the host immune system, as shown for fruit flies in which infection by *Wolbachia* bacteria triggers a response that inhibits viral infection [68]. Thus, the impact of parasites on the health of a bee colony is dependent upon the palette of microbes present, but may also be influenced by other environmental and genetic factors.

Environmental and genetic factors in disease

By storing nectar and pollen when food is available, honey bee colonies are able to buffer themselves against nutritional stress. Even so, protein levels and physiological health can decrease within individual bees from colonies with low protein availability, arguably leading to decreased immunocompetence [69] and greater susceptibility to viruses [70]. One of the most stressful times for honey bee colonies in temperate climates is the overwintering period, when foraging opportunities are absent. Although beekeepers mitigate this stress by providing pollen supplements and monitoring for treatable diseases, most colony losses occur during or soon after winter [71]. Exposure to anthropogenic pesticides and fungicides used on crops and for treating bee parasites can have non-target consequences on bees. Bees collect a diverse set of such chemicals [72] and, whereas acute poisoning events are relatively rare, long-term effects on immune function and combined effects with microbial infections [73] seem likely.

To minimize chemical management of bee pests, bee breeders are working toward resistant bee lines (predominately *Varroa*-resistant) by allowing their apiaries to go untreated during disease or parasite outbreaks [74]. Colonies that survive such population bottlenecks are selectively adapted for resistance to the parasite and would reduce dependence on chemical therapeutics. Although the genetics behind such resistance in honey bees are poorly

Box 3. Outstanding questions

- Will continued gene-based sampling efforts reveal high β-diversity for bee microbes, or are efforts indicating an asymptote?
- Do strain variants of viruses and *Nosema* spp. lead to disparate impacts on bee hosts, or are observed inconsistencies best explained by external factors such as nutrition, host genetics, or spore dose?
- What are the effects of concurrent multi-parasite infections, and how do they impact the host bee?
- What is the abundance, distribution, and genetic diversity of the 'enigmatic protozoan pathosphere', and what biological impacts do they have on their host?
- What are the long-term effects of pesticide accumulation on the microbial diversity (both parasitic and beneficial) within honey bees?
- What management strategies will be effective to limit parasite resistance to chemical controls?

understood, behavior-based components are probably involved, as mentioned previously for hygienic bees and chalkbrood. Another scenario involves Africanized honey bees (hybrids between European subspecies and *A.m. scutellata*) that are known for their resilience against varroa mites, arguably reflecting both host traits and differential exposure to virulent parasites and pathogens [75].

Concluding remarks

Honey bees face a diverse pathosphere and their ability to resist these threats depends upon commensals, nutritional status, the accumulation of toxic compounds, and genetically based resistance and tolerance mechanisms. Although honey bee pathology has been a field of study since ancient Greece (Aristotle referred to contagious brood disease as a 'wildness' in colonies), many questions remain regarding the impacts of microbes upon bee health (Box 3). Genome sequences are now available for the primary honey bee pathogens (http://hymenopteragenome.org/beebase/?q=bee_pathogens) and sophisticated new tools for genotyping and quantifying these threats are changing the models used to explore honey bee host–pathogen relationships. New tools, including stable cell cultures [76], heterologous infection systems [77], improved microscopy, and reverse genetics of bee pathogens [78–80], enable more precise experiments involving honey bee disease, and mitigate the drawbacks of working with an organism for which genetic lineages are difficult to generate and maintain. Honey bees contribute both honey and key pollination services to much of the world, justifying efforts to understand and better manage their interactions with microbes, chemicals, and other threats.

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