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Diseases in edible insect rearing systems

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REVIEW ARTICLE

Abstract

Due to a swift and continuous growth of the insect rearing industry during the last two decades, there is a need for a better understanding of insect diseases (caused by insect pathogens). In the insect production sector, insect diseases are a bottleneck for every type and scale of rearing system with different degrees of technology investment (i.e. semi-open rearing, closed rearing, industrial production, small-scale farming). In this paper, we provide an overview of insect pathogens that are causing disease in the most common insect species reared or collected for use in food and feed. We also include a few examples of diseases of insect species, which are not (yet) reported to be used as food or feed; those examples may increase our understanding of insect diseases in general and for the development of disease prevention and control measures. We pay special attention to the effect of selected biotic and abiotic factors as potential triggers of insect diseases. We discuss the effect of such factors in combination with other production variables on disease development and insect immunocompetence. Additionally, we touch upon prevention and control measures that have been carried out and suggested up to now for insect production systems. Finally, we point towards possible future research directions with possibilities to enhance the resilience of insect production to insect disease outbreaks.

Keywords: edible insects, insect rearing systems, insect diseases, epizootics, stress factors

1. Introduction

A large body of our current knowledge on taxonomic, behavioural and pathobiological aspects of insect host-pathogens interactions is based on a limited number of studies on insect pathogens causing disease outbreaks in insects, either in wild or in captive insect populations (Boucias and Pendland, 1998; Onstad and Carruthers, 1990; Steinhaus, 1963; Weiser, 1977). Usually in the past, the discovery and description of pathogens took place because of striking epidemic disease outbreaks in insect populations or they were based on observations on a few diseased individuals (Andreadis and Weseloh, 1990; Becnel and Andreadis, 2014; Brun, 1984; Majumdar *et al.*, 2008; Valles and Chen, 2006). Historically, biological control of agricultural insect pests using microorganisms (Lacey *et al.*, 2001; Sanchis, 2011; Van Lenteren *et al.*, 2018), diseases in honey bees (Bailey, 1968) and in silkworms (Samson *et al.*, 1990) have been the focus of many studies of insect diseases. Furthermore, insect-microbe interactions have also been studied as models to understand epidemiological aspects of human diseases (Scully and Bidochka, 2006). Insect pathogens have also proven to be beneficial for humans in other ways; baculoviruses for example, are used for biotechnological applications (i.e. for vaccines, and oncological treatments) (Felberbaum, 2015; Hofmann *et al.*, 1995; Van Oers, 2006).

The presence of insect diseases in rearing facilities is definitely not new. Indeed, the most ancient insect husbandry systems developed by humans, apiculture (bee keeping) and sericulture (silk farming), have long suffered from the effects of diseases (Eilenberg and Jensen, 2018a; James and Li, 2012). Nevertheless, given the vast amount of insect and pathogen species in the world and the many different ways in which insects can be useful for humanity, there is still a lot to learn about insects and their pathogens. This is underlined by the challenge posed by

the development of infectious diseases in rearing systems of insects produced for food and feed (further referred to as edible insects). On the bright side, the widespread use of molecular techniques, has increased the discovery of (insect) pathogens, especially of viruses (De Miranda *et al.*, 2021; Junglen and Drosten, 2013; Liu *et al.*, 2015), and the understanding of the microbiome of several insect species, including that of a number of edible insects (Vandeweyer *et al.*, 2017). At the same time, new knowledge is continuously being gathered as more research is conducted on the impact of known (Lecocq *et al.*, 2021) and understudied pathogens (G. Maciel-Vergara *et al.*, unpublished data) on insect health in species commonly reared as food and/or feed.

2. Pathogens of insects collected from nature or reared as food and feed

Insects form a diverse class of arthropods harbouring a high diversity of pathogens associated with individual species. Viral, fungal, bacterial, and microsporidian pathogens are frequently found to infect insects or in association with diseased insects (Supplementary Material Table S1). Insect pathogens can be specialists, only infecting one or a few taxonomically closely related species like the fungal genus *Strongwellsea* (Eilenberg and Jensen, 2018b), or they can be generalists infecting a variety of insect species which may not be taxonomically related, which is the case for many hypocrealean fungi (Hajek, 1997). Furthermore, some insect pathogens are known to be opportunistic or facultative. Opportunistic pathogens have a broad host range and are often ubiquitous as they can survive and proliferate on a range of substrates other than the main host (Brodeur, 2012); on the other hand, obligate pathogens need their host to fulfil their life cycle (Han and Weiss, 2017). Normally, opportunistic pathogens only cause disease when insects are subjected to stressful conditions (Jurat-Fuentes and Jackson, 2012; Pagnocca *et al.*, 2012; Sikorowski and Lawrence, 1994).

Viruses infecting insects and causing concern in mass production facilities comprise RNA as well as DNA viruses belong to different virus families (reviewed by Maciel-Vergara and Ros, 2017). Among these viruses, many are host-specific. An exception is the invertebrate iridescent virus 6 (IIV-6), known to infect several hosts in the orders Orthoptera and Blattodea (Just and Essbauer, 2001; Kleespies *et al.*, 1999) including gryllids, locusts, and cockroaches. In addition, larvae of the great wax moth, *Galleria mellonella* have shown susceptibility to IIV-6 under experimental conditions (Jakob *et al.*, 2002) as well as lepidopteran and dipteran cultured cell lines (Bronkhorst *et al.*, 2014; Williams *et al.*, 2009). Most entomopathogenic viruses known up to date are taxonomically distant from vertebrate viruses (Miller and Ball, 1998).

Viruses have a high potential to cause epizootics in insect rearing systems and in some cases they pose a threat to whole production stocks. Acheta domesticus densovirus (AdDV), an important pathogen of the European house cricket *A. domesticus*, is well known to cause disease outbreaks, which in the worst case could lead to major losses and to bankruptcy of cricket rearing companies (Szelei *et al.*, 2011; Weissman *et al.*, 2012).

Overt viral infections are initially identified by the symptoms displayed by infected insect hosts. For example, a disruption in moulting, reduced oviposition, or a reduced weight gain may be symptoms. Other symptoms may be a translucent exoskeleton, swollen and/or translucent abdomen (Figure 1C), enlarged brownish or milky midgut, or hindgut, watery faeces, and paralysis (reviewed by Maciel-Vergara and Ros, 2017). The particular symptoms depend on the virus and the host. Viruses can be transmitted through horizontal transmission (between conspecifics), vertical transmission (from parent to offspring), and sexual transmission. Often, viruses are transmitted through more than one of these transmission routes. Methods for the detection of a virus, include molecular techniques, virus isolation, serological studies, histopathology, and electron microscopy (Eberle *et al.*, 2012; Harrison and Hoover, 2012). However, there is a need for guidelines for standardised methods to increase the reproducibility (including quality control) for validation of these diagnostic methods (Maciel-Vergara and Ros, 2017).

Entomopathogenic bacteria belong to various groups, which differ in biology. They can belong to spore forming (genus *Bacillus*) or non-spore forming bacterial (genera *Pseudomonas*, *Serratia* and *Rickettsiella*) groups and they can be generalists or specialists. In most cases, they infect their hosts orally (Jurat-Fuentes and Jackson, 2012). For example, a specialist bacterium, *Bacillus popilliae* is infectious to few selected species in the order Coleoptera (Rippere *et al.*, 1998). On the other hand, strains of *Bacillus thuringiensis* var. *kurstaki* have a broader host spectrum within the order Lepidoptera and can infect many species. Some generalist and opportunistic bacteria, such as non-spore forming bacteria from the genera *Pseudomonas* and *Serratia*, can cause problems in insect colonies subjected to stress. They can also multiply rapidly in hosts that are wounded and cannibalised by conspecific insects (Maciel-Vergara *et al.*, 2018). As tested by artificially induced infection, a strain of the bacterium *Aeromonas hydrophila* has been reported to be pathogenic to the yellow mealworm *Tenebrio molitor (*Noonin *et al.*, 2011).

A change in coloration, flaccidity, bad odour, and a cease of (usual) movement of infected hosts are often first signs of bacterial diseases (Figure 1F). However, bacterial pathogens like *Rickettsiella grylli* cause characteristic symptoms in their hosts such as a swollen abdomen and liquified

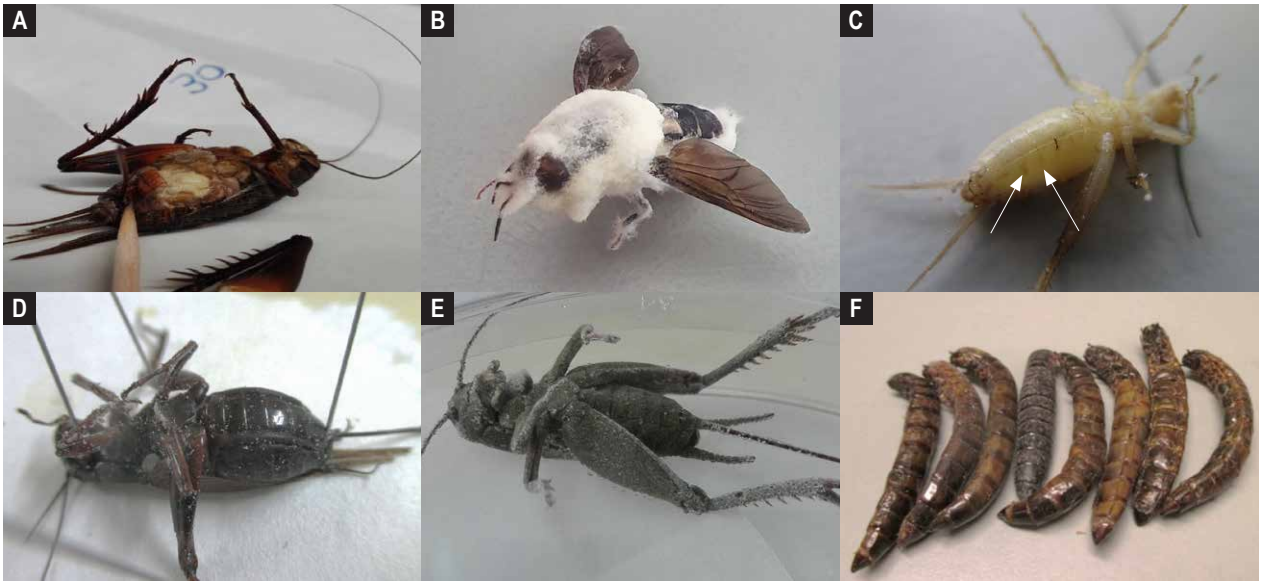

Figure 1. Clinical signs of infections in selected insects produced for food and feed. (A) Adult of the cricket, *Teleogryllus* sp. with inner organs showing a massive cell growth of *Rickettsiella grylli*. (B) Adult of black soldier fly, *Hermetia illucens* showing advanced mycosis due to an infection with *Beauveria bassiana*. (C) Nymph of the cricket, *Acheta domesticus* with swollen abdomen and liquified inner tissue (arrows) due to an infection with A. domesticus densovirus (AdDV). (D) Adult of the cricket, *Gryllus bimaculatus* with a strongly swollen abdomen due to an infection with *R. grylli*. (E) Adult of the cricket, *Modycogryllus* sp. showing advanced mycosis due to an infection with *Metarhizium* sp. (F) Larvae of the giant mealworm, *Zophobas morio* showing flaccidity and a dark coloration due to advanced septicaemia caused by an infection with *Pseudomonas aeruginosa*. Photos: A, C, D, E and F by Gabriela Maciel-Vergara, and B by Antoine Lecocq.

viscous inner organs (Figure 1A and D). Diagnosis has to be followed by microscopy and molecular methods (Fisher and Garczynski, 2012; Tedersoo *et al.*, 2019).

Insect pathogenic fungi can be specialists or generalists. Entomophthorales, an ancient order of fungi, is mostly comprised of specialists (Boomsma *et al.*, 2014; Vega *et al.*, 2012). The species *Entomophthora muscae* infects the house fly *Musca domestica*. The fungus discharges conidia from dead hosts, which increases the likelihood of the conidia to be spread effectively to new hosts (Bellini *et al.*, 1992). Hypocreales (Ascomycota) is another order of fungi that includes genera like *Metarhizium* and *Beauveria*; species in these genera are mostly generalists and can cause diseases in a wide range of insect species. Fungal species belonging to the two genera can infect mealworms (*T. molitor*, a coleopteran species), silkworms *Bombyx mori*, (a lepidopteran species), *M. domestica* (a dipteran species), and *Locusta migratoria* (an orthopteran species) (see references in Supplementary Material Table S1). A recent study found *Beauveria bassiana* to be pathogenic to adults of the black soldier fly (*Hermetia illucens*) in laboratory infection trials (Lecocq *et al.*, 2021) (Figure 1B). Most fungi infect via penetration of the insect cuticle followed by growth in the haemolymph, and they sporulate externally upon host death. The first diagnosis of a fungal infection can be done by observing conidia or other external features on dead insects (Figure 1B and E) and by subsequent analysis using a microscope to identify the fungal genus. Molecular methods such as DNA sequencing help to identify the fungal species in most of the cases (Castrillo and Humber, 2009; Hajek *et al.*, 2012; Humber, 2012; Inglis *et al.*, 2012).

Microsporidia are unicellular parasitic organisms closely related to fungi. In order to infect their hosts the spores must be orally ingested (Solter *et al.*, 2012a). Most known microsporidian species are specialists, although some species have been reported to 'jump' to another host. Microsporidian infections are classified as chronic and rarely as acute (Becnel and Andreadis, 2014). Their presence is not necessarily immediately lethal to an insect population, although they can cause harm upon reaching a critical mass. The most studied microsporidian species have been found in honey bees and locusts.

Another group of unicellular insect pathogens are gregarines (Lange and Lord, 2012), which occur in the insect gut. Gregarines are only known to be parasitic to insects and mostly non-lethal, but can anyway lower the insects' fitness. They can be present in insect populations without being immediately noticed. The reported effects of gregarines in adult fall field crickets (*Gryllus pennsylvanicus*) are decreased longevity and weight loss under nutritional stress (Zuk, 1987). In addition, a *Gregarina* sp. isolated from the German cockroach *Blattella germanica* was reported as being highly pathogenic, and furthermore as being

able to increase the susceptibility of its host to microbial and chemical challenges (Lopes and Alves, 2005). High prevalence of gregarines was found in a survey of protozoan parasites in edible insect species including *Gromphadorhina portentosa* (Madagascar hissing cockroach), *T. molitor*, *A. domesticus*, and *L. migratoria* (Gałęcki and Sokół, 2019). Gregarines have also been reported to occur in tenebrionids *Zophobas morio* (Jahnke, 2005) and *Alphitobius diaperinus* (Bala *et al.*, 1990) (Devetak *et al.*, 2013; Steinkraus *et al.*, 1992). To our knowledge, there is very limited information on the effect of gregarines to edible insects in rearing systems. Conducting more comprehensive research might give insight into the role of gregarines in insect production. Insects that are heavily infected with gregarines can exhibit symptoms such as a swollen abdomens and lethargy (Lopes and Alves, 2005). As for microsporidia, gregarines can be detected by examination of gut samples under the microscope, and quantification can be achieved by staining gut fluid (Solter *et al.*, 2012b).

3. Triggering factors for disease development

In insect rearing systems, the development of insect diseases caused by pathogens is determined by several factors (biotic and abiotic) related to the host and to the pathogen. Such factors are interconnected and largely determined by the production conditions inherent to insect mass rearing. Often, disease outbreaks occur when stressful conditions for an insect population which may converge with favourable conditions for a pathogen. Potential triggers that generate stressful conditions in insect colonies include changes in temperature and/or relative humidity, dietary changes and nutrient deficiency, overcrowding, infection with multiple natural enemies (i.e. pathogens and/or parasitoids), and toxic compounds (Figure 2).

Temperature and relative humidity

Insects are poikilothermic animals; their body temperature vary in line with the environmental temperature. Temperature and relative humidity have a substantial influence on the growth, development and survival of insects and microbes alike (Brindley, 1930; Holmes *et al.*, 2012; Ment *et al.*, 2017; Ratte, 1985). Insects and their pathogens have each an optimal temperature range that overlap to a certain extent. The optimal temperature range for pathogens can be similar among species within a taxon at genus or species level (i.e. bacteria, fungi, protozoa), although in some cases, the optimal temperature range for a pathogen in a certain host-pathogen interaction is pathogen-specific. Nevertheless, temperature has a direct effect on insect mortality and on the speed at which infected insects become symptomatic (Blanford and Thomas, 1999; Hurpin, 1968; Inglis *et al.*, 1997).

Four isolates of *Metarhizium flavoviridae*, a pathogenic fungus of the desert locust *Schistocerca gregaria*, caused nearly 100% mortality in 8 days regardless of the incubation temperature (25 and 30 °C), but the higher temperature (30 °C) increased the pathogen's growth and significantly reduced the time to death (Fargues *et al.*, 1997). Likewise two strains of the pathogenic bacteria *Serratia* sp. showed a dose and temperature dependent effect on the mortality and LT_{50} values when infecting the tobacco hornworm (*Manduca sexta*) (Petersen and Tisa, 2012).

At normal hive temperatures, 33 °C for the European honey bee (*Apis mellifera*), the two common microsporidian pathogens *Nosema apis* and *Nosema ceranae* were equally virulent, however *N. apis* was less infectious than *N. ceranae* at extreme temperatures (below 25 and above 37 °C) (Martín-Hernández *et al.*, 2009). Temperature can also influence transmission capacity, illustrated by the duration and yield of the conidial discharge from insect cadavers for the fungus *E. muscae* after infecting its natural host, the common house fly (*M. domestica*), with higher conidial yield at lower temperatures (10 and 20 °C, compared to 30 and 38 °C) (Watson and Petersen, 1993).

Temperature also has a significant effect on the ability of insects to overcome or slow down the infection by pathogens in various ways. A well-known example is the thermoregulatory behaviour displayed in most species of grasshoppers, locusts, and crickets (Order: Orthoptera) when infected with fungi (Blanford and Thomas, 1999; Carruthers *et al.*, 1992; Inglis *et al.*, 1996), bacteria (Louis *et al.*, 1986), and microsporidia (Boorstein and Ewald, 1987). The migratory locust *L. migratoria* raises its body temperature (behavioural fever) in order to suppress or slow down the infection time of fungal diseases caused by *B. bassiana* and *Metarhizium anisopliae* (Ouedraogo *et al.*, 2003; Sangbaramou *et al.*, 2018). Moreover, Mediterranean crickets (*Gryllus bimaculatus*) reared in a temperature gradient, were able to clear the pathogenic form of *R. grylli* off their bodies by rising their body temperature (due to actively moving to a higher temperature zone). However, the effectiveness of behavioural fever is dose- and species-specific, and therefore in some cases, it does not prevent pathogens killing their host (Adamo, 1999; Clancy *et al.*, 2018; Stahlschmidt and Adamo, 2013). Very importantly, thermal behaviour is heavily influenced by the intricate effects of relative humidity and temperature combined, all together determining the dynamics of host-pathogen interactions in insect species that are able to thermo-regulate.

Overall, relative humidity and moisture have an effect on the development of disease outbreaks in insect colonies (Benz, 1987; Chakrabarti and Manna, 2008; Fuxa *et al.*, 1999; Mostafa *et al.*, 2005). Relative humidity has been

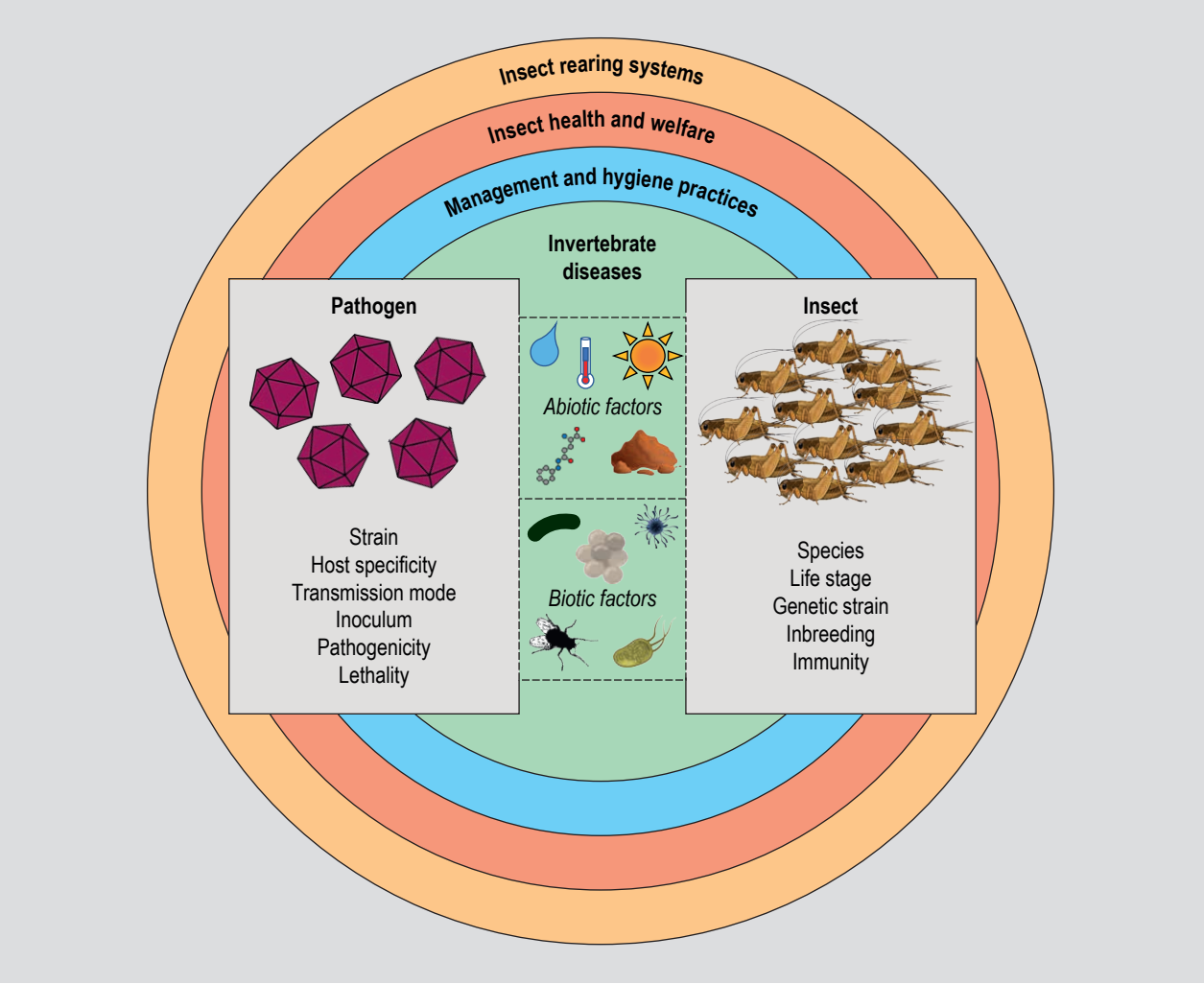

Figure 2. Schematic view of the interrelation of aspects inherent to pathogens and insect hosts with factors (i.e. biotic and abiotic) that trigger disease outbreaks and that concern insect health and welfare in insect rearing systems.

studied more extensively as a key factor for infections caused by fungal pathogens than for pathogens from other taxa (Hajek, 1997; Hall and Papierok, 1982). The effects of relative humidity on the virulence, conidial germination and other aspects related to the infectivity of fungi such as *B. bassiana* and *M. anisopliae* on grasshoppers and locusts are well documented (Arthurs and Thomas, 2001) (Fargues *et al.*, 1997). In another host-pathogen system, mortality of *Tribolium confusum* larvae caused by *M. anisopliae* was negatively correlated with the tested levels of relative humidity (55% and 75%) (Michalaki *et al.*, 2006). For *E. muscae*, relative humidity values did not have any effect on the infection rate of house flies at a constant temperature of 25 °C. However, the effect of the relative humidity on the germination rate was isolate-specific (Watson and Petersen, 1993). Relative humidity did not have a significant effect on the efficacy (measured as the median lethal time, LT_{50}) of two *M. anisopliae* strains to infect the red palm weevil, *Rhynchophorus ferrugineus* (Cheong and Azmi, 2020).

Dietary changes and nutrient deficiencies

Diet composition and nutritional stress play an important role in the insects' immune response to pathogens and their ability to cope with diseases (Alaux *et al.*, 2010b; Ayres and Schneider, 2009; Ponton *et al.*, 2013; Srygley *et al.*, 2009). The protein and carbohydrate contents are especially important for the immune response and survival of insects (Cotter *et al.*, 2011; Ponton *et al.*, 2020). Larvae of the Egyptian cotton ball armyworm *Spodoptera littoralis* (potential feed for quail chicks, (Sayed *et al.*, 2019) challenged with a baculovirus, showed higher immune response and survival when fed on a diet with a high protein content relative to carbohydrate content (P:C ratio) (Lee *et al.*, 2006). In the same study, a group of larvae were allowed to select among diets with varying P:C ratio after being challenged with the virus; those larvae who survived the infection showed a preference for the diet with higher P:C ratio, in comparison to control and dying larvae, suggesting a purposeful change in their feeding

behaviour to compensate for the protein costs of building up immunity (Lee *et al.*, 2008).

Similar research on other insect species underlines the dynamics of host feeding behaviour in relation to immunity and survival (prophylactic and therapeutic effects), and adds to the notion that the balance between protein and carbohydrates in the diet varies among insect-host systems and is key for mounting immunity and overcoming infection (Brunner *et al.*, 2014; Povey *et al.*, 2014; Wilson *et al.*, 2019), unless another challenge comes along (see section 'Infection with multiple natural enemies').

Nutritional stress related to food availability or nutrient content has also been connected to cannibalism, which is known as an important route of transmission for pathogens including viruses and bacteria, when healthy individuals feed upon heavily infected (or dead) conspecific insects that are too weak to avoid being preyed on. Baculoviruses have been reported to be transmitted by cannibalism in larvae of the corn earworm *Helicoverpa armigera* (Dhandapani *et al.*, 1993), the beet armyworm *S. exigua* (Elvira *et al.*, 2010), and the fall armyworm *Spodoptera frugiperda* (Chapman *et al.*, 1999). Viruses that are also transmitted due to cannibalism are densoviruses in crickets (Weissmann *et al.*, 2012), entomopoxviruses in grasshoppers (Streett and McGuire, 1990), and iridoviruses in a wide range of hosts (Williams and Hernández, 2006).

Population density

When the population density reaches levels beyond a certain threshold which may be different for each species (overcrowding), an insect colony is in theory at high risk for diseases to develop, due to an increased transmission rate, physiological stress, nutritional stress, and reduced immune response (Anderson and May, 1979; May and Anderson, 1979). Crowding is a stress factor that may be influenced or have an influence on other stressors like temperature, relative humidity, and CO_2 levels. Additionally, in crowded insect populations, increased chances for horizontal pathogen transmission occur as large numbers of seemingly healthy individuals feed on a big supply of food contaminated by the faeces and saliva (i.e. in dipteran production systems) of diseased individuals.

Cannibalism is usually observed in crowded populations as well, increasing the risks for the entry and spread of pathogens through the open wounds that the insects inflict on conspecifics (Steinhaus, 1958). Cannibalism and scavenging were more prevalent in groups of the giant mealworm (*Z. morio*) larvae, when exposed to the opportunistic bacterium *P. aeruginosa* compared to non-exposed larvae. Individual larvae that were artificially injured prior to exposure to *P. aeruginosa*, suffered from higher mortality rates in comparison to non-exposed larvae (Maciel-Vergara *et al.*, 2018). Another opportunistic bacterial pathogen, *Serratia marcescens*, has a higher chance to develop in insect colonies (i.e. silkworms) and mite colonies, when the hosts were subjected to crowding stress (Doane, 1960; Lighthart *et al.*, 1988; Vasantharajan and Munirathnamma, 2013). Solitude can on the other hand lead to a decrease in the melanisation which is part of the immune response as shown in *S. exempta* larvae infected with the virus Spodoptera exigua nucleopolyhedrovirus, SpexNPV or in *T. molitor* infected with the fungus *M. anisopliae* (Reeson *et al.*, 1998; Barnes and Siva-Jothy, 2000).

Nevertheless, the effects of crowding on insect health are not always negative as such effects also depend on behavioural and physiological aspects of specific insects.

Infection with multiple natural enemies

In insects, immune response and disease resistance vary when challenged by multiple pathogens/parasites/parasitoids (simultaneously or sequentially) compared to a challenge by only one pathogen (Malakar *et al.*, 1999; Martin *et al.*, 2012). In nature, mixed infections are fairly common (Virto *et al.*, 2014) and in insect rearing systems, such kind of infections may be more common than we may think (Maciel-Vergara *et al.*, in preparation). Mixed infections can become a stress factor by boosting the pathogenicity of one or more other types of pathogens prevalent in the same host (Hughes *et al.*, 1993). The dynamics between such pathogens in the whole disease process can be synergistic, additive, antagonistic, or independent (Carballo *et al.*, 2017). For instance, research on the effects of a mixed infection by entomopathogenic fungi, showed an additive effect of a low virulent *B. bassiana* strain on the effectiveness of a highly virulent strain of *Metarhizium acridum* when infecting *S. gregaria* (Thomas *et al.*, 2003). Other studies on competition among (viral, microsporidian, bacterial, and fungal) pathogens to thrive in the same host have been conducted using and observing different insect species, although most of the knowledge has been generated for bees and locusts (Evans and Armstrong, 2006; Tounou *et al.*, 2008).

Usually, the shift of a pathogen from being almost innocuous to becoming a threat for its host is related to the suppression of the immune system by competition among various organisms. Similarly, covert viruses can turn overt if their host becomes infected with another viral pathogen or gets challenged by a parasitoid or a parasite. Often, the virus becomes infectious, hosts develop disease symptoms, and mortality increases. Examples of a covert virus becoming overt due to a secondary infection with a non-homologous virus or pathogen are described (Hughes *et al.*, 1993), but maybe the most remarkable is the activation of a number of naturally present viruses in

honey bees due to the prevalence of the *Varroa* mite in bee colonies (Alaux *et al.*, 2011; DeGrandi-Hoffman and Chen, 2015; Tritschler *et al.*, 2017).

Other stressors and factors related to disease development

Although vast knowledge on the effects of CO_2 on insect development has been collected (reviewed by Guerenstein and Hildebrand, 2008; Nicolas and Sillans, 1989; Sage, 2002), there is limited evidence of CO_2 as stressor to account for the development of insect diseases. The effects of high levels of CO_2 (either as high – and pure – to induce anaesthesia, or high in proportion to other gases in a mixture) on the insect's physiology and behaviour are described for the house cricket *A. domesticus* (Edwards and Patton, 1965), the German cockroach *B. germanica* (Tanaka, 1982) and other insect species (Bartholomew *et al.*, 2015; Brooks, 1957; Gunasekaran and Rajendran, 2005; Krishnamurthy *et al.*, 1986). Nonetheless, the effects of CO_2 seem to vary greatly in solitary insects compared to social insects, not only in relation to physiological and behavioural aspects but to their immune response as well. A positive correlation between CO_2 anaesthesia and enhanced immunocompetence was found for the common eastern bumble bee, *Bombus impatiens* (Amsalem and Grozinger, 2017) and leaf-cutting ants (Römer *et al.*, 2018).

In the context of host-pathogen interactions, a unique scenario of hyper reactivity to CO_2 and associated high mortality at high concentrations of CO_2 has been registered for *Drosophila melanogaster* infected with the rhabdovirus Drosophila melanogaster sigma virus (reviewed by (L'Héritier, 1948). Moreover, other rhabdoviruses cause hyper reactivity to CO_2 in other dipteran species (Rosen, 1980). Additionally, in a multifactorial set-up where various stressors were tested, reduced virulence of entomopathogenic fungi on S. *gregaria* and *A. domesticus* at increasing CO_2 concentration was observed (2015). An interesting fact relevant for large scale insect rearing systems, is that the effects of CO_2 may vary greatly depending on the insect's developmental stage. In this regard and for future studies, an analogy to the results found by Callier *et al.* (2015) could apply in the sense that while dipteran larvae can thrive in highly hypoxic conditions, these same conditions can severely affect individuals in the adult stage.

Other stressors to take into consideration are heavy metals, toxins and pesticides; chemicals that are known for their diverse effects on insect behaviour (Burden *et al.*, 2019; Chicas-Mosier *et al.*, 2017; Guo *et al.*, 2014; Hladun *et al.*, 2015) and host-pathogen interactions (Jiang *et al.* 2021; Odemer *et al.*, 2018), especially with regards to the immunocompetence of insect hosts (Mir *et al.*, 2020; Shaurub, 2003; Van Ooik *et al.*, 2008). Some studies have evaluated the positive effects of specific chemicals (i.e. silver nanoparticles, silica nanoparticles) on the survival of insects challenged by pathogens (*B. mori* infected with B. mori nucleopolyhedrovirus, BmNPV), however more research is needed to evaluate the effectiveness of using these and other chemicals to manage disease outbreaks in the insect rearing industry (Das *et al.*, 2013; Govindaraju *et al.*, 2011). On the contrary, there is ample evidence of the detrimental effects that chemical exposure has on insect health (particularly pesticide-related chemicals and heavy metals). An example of such negative effects is the increased prevalence and mortality caused by the microsporidian pathogen *N. ceranae* in honey bees and stingless bees exposed to neonicotinoid pesticides (Alaux *et al.*, 2010a; Macías-Macías *et al.*, 2020; Tesovnik *et al.*, 2020). Honey bees exposed to neonicotinoid pesticides, have also been reported to have reduced immunocompetence and increased replication of the deformed wing virus (Di Prisco *et al.*, 2013).

A couple of factors that are not stressors *per se* but that have a crucial effect on the development of insect diseases are the insect developmental stage (Blaser and Schmid-Hempel, 2005; Briggs and Godfray, 1995), and the prevalence of endosymbionts. The effect of endosymbionts (Chrostek *et al.*, 2020; Martinez *et al.*, 2014; Rottschaefer and Lazzaro, 2012; Zug and Hammerstein, 2015) on the insects' health has been explored in the last two decades, although limited knowledge is available for most insect species reared as food or feed (Dillon *et al.*, 2005; Muhammad *et al.*, 2019).

The insects' life stage is one more factor that plays a key role on the disease dynamics in insect colonies. Usually, one or few of the life stages of an insect host are (highly) susceptible to specific pathogens while the other life stages are less susceptible or not susceptible at all (Engelhard and Volkman, 1995; Goulson *et al.*, 1995).

4. Measures to control diseases and pests on rearing systems

Disease outbreaks in farmed insects are inevitable and unfortunately, most diseases are discovered when there is already a significant damage to the insect colony. Depending on the severity of each case, the best solution in many cases has been to perform a thorough inspection, cleaning and eventual disinfection of the production facilities and to start the production over again. A routine inspection for pathogens should be implemented in every insect rearing system. Diagnostics, as suggested by Eilenberg *et al.* (2018), are to be done in collaboration with experts on invertebrate diseases. Diagnostic protocols are available for a handful of insect pathogens, but the most challenging scenarios are posed by the presence of covert infections (i.e. viruses) and other chronic diseases (i.e. protozoa and obligate bacterial pathogens).

Covert viral infections can be detected before a disease outbreak occurs but their detection does not necessarily means that their presence will cause a severe disease outbreak in a rearing system, since such epizootics depend on many trigger factors (Section 3). Some preventive and corrective measures have been used in laboratories, insectaries and in insect rearing systems (i.e. sericulture, apiculture, sterile insect technique facilities), and have helped on the mitigation of insect pathogens (Bindroo and Verma, 2014; Formato and Smulders, 2011; Kariithi, 2013). Such measures are related to the implementation of hygiene at different levels of the production facilities, to the modification of specific steps in the rearing process and to the application of immune-intervention strategies. The application and effectiveness of these measures vary depending on the type of production system (e.g. open, semi-open, closed), on the biology of the insect species, and on the pathogens present in each production system, as well as, on the legislation in place in each region/country.

Discussions on the risks posed by various insect pathogens to different rearing systems have been published, as well as general recommendations on how to try keeping insects healthy (Eilenberg and Jensen, 2018b; Eilenberg *et al.*, 2015, 2018). A guide on good hygiene practices has been made available by the International Platform of Insects for Food and Feed (IPIFF), covering aspects of the insect production and the processing of insect-derived products. The advice in this guide is related to the general hygiene mainly to avoid food-borne pathogens (yet most procedures would also be effective for several insect pathogens) (https://ipiff.org/wp-content/uploads/2019/12/ipiff-guide-on-good-hygiene-practices.pdf). Lately, advances in methods and equipment have been made for the design of a more hygienic, and easy-to-handle insect production; these advances focus on closed high-tech insect production (i.e. crickets and black soldier fly – BSF – production) (Joosten *et al.*, 2020; Mellberg and Wirtanen, 2018;). In addition, a manual for semi-open production of crickets has been recently released. It provides an overview of the good practices advised for the entire rearing process and a guide on how to inspect the cricket rearing process and facilities (Hanboonsong and Durst, 2020).

Hygiene and good practices

Hygiene is without doubt an essential component of any husbandry system and the production of edible insects for feed or food is not an exception. It is important to keep in mind that an integral approach of the hygiene measures and the good production practices should be part of the entire rearing process, concerning: the physical structure (i.e. building, pens, containers, equipment), the feed, the personnel, the insects (i.e. eggs, parent stock), the frass, etc. Hygiene and good production practices are basic aspects for the prevention of food-borne diseases and insect diseases, and are key for starting to engage in the dialogue on insect welfare within the edible insect industry. In our view, and in agreement with the logic of the Brambell's five freedoms (Van Huis, 2019), insect welfare relates to (among other aspects) the ability of captive insect populations to thrive, and to experience less the effects of disease outbreaks by being reared in *ad hoc* conditions. In summary, advices that reinforce the available general recommendations on hygiene and good practices include:

- Cleaning and disinfection agents should be used but they should be approved disinfectants by the corresponding agencies in charge of the regulation of such substances (i.e. EPA, ECHA) and especially, in the production of insects for food, disinfectants should be approved for use in the food industry.
- All the equipment and every surface that is in contact with the insects should be thoroughly washed, disinfected and rinsed every time a new batch of insects is reared.
- If available, steam may be used to disinfect rearing rooms, equipment, oviposition substrate, etc.
- Feed should be inspected (visually) and treated prior to use if needed (i.e. heat). It should be stored in proper conditions, depending on the nature of the feed.
- Fresh feed should be provided regularly to insects (depending on each species need), avoiding the formation and accumulation of moulds.
- Water stagnation and formation of moulds in drinking systems (i.e. for crickets) should be avoided by providing fresh water regularly and by using/designing devices that can be cleaned easily and preferably with materials where microorganisms are not able to thrive.
- Insect frass should be treated prior to disposal, irrespectively if the insect colony was healthy or not, by heating up or fermenting (i.e. compost/silage).
- If applicable to the rearing system, air filtration equipment should be put in place and maintained in appropriate functioning conditions.

Differentiated breeding (parent stock and 'the rest of the population')

Parent stocks may be reared separately from the rearing of all other instars (i.e. other isolated room in closed containers), as a measure to prevent diseases. Also, more selective and nutritious diet and care may be provided to parent stocks to ensure the quality of egg production. Keeping the parent stock separated from the main production (physically and in terms of nutrition, and care) also ensures a higher biological quality for the parents and a backup solution if the entire production needs to be eventually re-started.

Mechanical control of pests

Ants, flies, parasitic wasps and mites are the most common insect pests for insect production. Different methods in specific rearing systems are used to keep pests at bay. For

example, placing cages or crates for the production of dipteran species (i.e. house fly and BSF) and crickets on elevated platforms with stands submerged in oil or molasses, have been effective to deter ants from entering cages in Ghana, Kenya and Uganda. In closed production systems, double doors prevent the entrance of pests and the escape of insects in rearing systems. Sticky traps and UV-lamp traps are also useful to prevent insect pests to remain inside production facilities. Mites are a major problem, especially in insect rearing systems where substrates have high moisture contents and /or high relative humidity prevails. The most efficient way to control mites is by cleaning the facilities on a regular basis, lowering the relative humidity, keeping the trays/pens free of debris, and preventing the feed from getting too wet and mouldy. A possibly effective but expensive method that might be used to combat mites is the use of the predatory mites e.g. *Stratiolaelaps scimitus*, *Cheyletus eruditus*, and *Cheyletus malaccensis* (Cabrera *et al.*, 2005; Cebolla *et al.*, 2009; Pulpan and Verner, 1965; Rangel and Ward, 2018), however more research should be done to prove their efficacy.

5. Prospects on the control of insect diseases in rearing systems

In the future, novel control strategies can be inspired by methods from other life stock production systems or developed from a deeper understanding of the biology and physiology of host-microbe interactions within the context of insect mass-rearing. Practical constraints for the control of insect diseases in insect rearing systems are especially related to: the insect species, the pathogen species, the size and structure of the facility, the technological investment, the availability of reliable prevention methods, diagnostic tools and direct control methods, and the risk of toxic residues if chemical treatment is pursued (i.e. antibiotics or antivirals).

Breeding of disease-resistant/ tolerant strains

Selective breeding to improve desirable traits in animals and plants has been used by humans for many years and breeding for disease resistance is a classical discipline found within all production systems e.g. crop production (Nelson *et al.*, 2018), aquaculture (Gjedrem, 2015), poultry, pigs, (Proudfoot *et al.*, 2019) and honey bees (Guichard *et al.*, 2019). One of the challenges in resistance breeding is the trade-off with other important traits, which includes responses to abiotic factors, nutritional uptake, growth, and other fitness traits. In addition, resistance to one pathogen might induce susceptibility to another.

In the late 20th century, genomic selection was added to the livestock breeding toolbox; by reading specific locations in the genome and assigning them to measurable production traits, faster improvement in livestock production efficiency has been achieved and the novel CRISPR/Cas technology even allows for genome editing. The CRISPR/Cas gene-editing technique has shown promising results as an antiviral therapy in silkworms (Wei *et al.*, 2017).

Taking the ethical considerations around genome editing into account (i.e. by CRISPR/Cas) (Charo and Greely, 2015; Gjerris *et al.*, 2018), and it will be interesting to see if and how this technology will be used for disease resistance or other functional traits within insects used for mass rearing.

Heat shock/thermal therapy

Temperature plays a key role on the different immune responses of insects against pathogens (5.3.1). The severity of a heat shock (thermal stress) may impact the duration of the immune responses, which varies among insect-pathogen systems. For instance, subjecting *G. mellonella* to a short heat shock (38 °C, 30 min) prior to infection with *B. bassiana* blastospores reduced the infection rate of the fungus, prolonging the host lifetime (Wojda *et al.*, 2009). Conversely, a prolonged thermal stress (30 and 37 °C, 24 h), provided *G. mellonella* only temporary resistance against *Aspergillus fumigatus* (Browne *et al.*, 2014). Thermal therapy of honey bees at 42 °C for 4 h and back to the normal 32 °C have shown to reduce the viral load of green fluorescent tagged SINV-GFP Sindbis virus in honey bees (McMenamin *et al.*, 2020)

Gut microbiota/probiotics

Gut microbiota modulate insect immune response, enhancing the resiliency of insects against pathogens (Muhammad *et al.*, 2019) or assisting the pathogens to overcome the immune system of their host (Jakubowska *et al.*, 2013). A comprehensive work on this regard has focused on honey bee immunity and its response to bacterial, fungal, and viral pathogens (Evans and Armstrong, 2006; Moran, 2015; Reynaldi *et al.*, 2004).

On the other hand, composition of microbial gut communities in insects (and other animals as well) (Krams *et al.*, 2017; Martínez-Solís *et al.*, 2020; Ponton *et al.*, 2013, 2015) can vary depending on the insect diet. From the perspective of insect rearing, modifying the diet would also modify the microbial composition of insect guts, a feature that could promote higher disease resistance of insects reared under mass-production schemes. As an example, an indigenous gut bacterial strain *Pediococcus pentosaceus* showed increased growth and survival of *T. molitor* larvae (Lecocq *et al.*, in press), and an isolate of the bacterium *Enterococcus mundtii* offered the model insect *Tribolium castaneum* protection towards the bacterial pathogen *B. thuringiensis* (Grau *et al.*, 2017).

Biological control

To our knowledge, very limited information exists on the utilisation of microorganisms to control insect pathogens in insect rearing systems. As mentioned earlier in this paper, virus discovery has increased over the last decade and generally speaking, new viruses that are found by New Generation Sequencing (NGS) technology (Datta *et al.*, 2015) in otherwise healthy hosts, are referred to as insect-specific viruses (ISV's). ISV's are not able to replicate in vertebrate hosts and it is suggested that they persist in insect populations through vertical (transovarial) transmission. Although, we do not exclude the possibility that some newly discovered (covert) viruses may end up being pathogenic to insects reared under stressful conditions in insect rearing systems, the antagonistic interaction between (engineered and wild-type) insect-specific viruses (ISV's) and arboviruses vectored by insects (Adelman *et al.*, 2001; Airs and Bartholomay, 2017; Bolling *et al.*, 2015; Powers *et al.*, 1996), is a starting point to evaluate the trade-offs if ISV's were to be used to increase pathogen resistance in edible insect species. Nouri *et al.* (2018) reviewed the potential applications that ISV's may have for different purposes. An additional alternative to investigate is the use of bacteriophages for the control of bacterial diseases in insects. Bacteriophages have the ability to alter the bacterial genomic material, and might thus disrupt the infection process (Li *et al.*, 2016b; Zimmer *et al.*, 2013).

RNA interference

RNA interference (RNAi) is a technology used for the inhibition of virus replication based on gene-expression regulation, by the neutralisation of targeted mRNA molecules (Aguiar *et al.*, 2016). This biological process is known to protect vertebrate, invertebrate, and plant hosts from virus attacks (Burand and Hunter, 2013; La Fauce and Owens, 2013; Li *et al.*, 2016a; Sidahmed and Wilkie, 2010). RNAi has been used to control (to a low extent), the prevalence of *Glossina pallidipes* salivary gland hypertrophy virus in tsetse fly rearing systems (Abd-Alla *et al.*, 2011a,b). More promising results were seen in reducing the prevalence of the Israeli acute paralysis virus and deformed wing virus in honey bees using RNAi (Brutscher and Flenniken, 2015; Burand and Hunter, 2013; Desai *et al.*, 2012; Hunter *et al.*, 2010).

6. Concluding remarks

Although pathogens and beneficial insects have coexisted in insect rearing systems since ancient times, the recent fast growth of the insect rearing industry (for protein production) has exposed the need for a better understanding of insect diseases that develop in production facilities. Notably, there is more research to be done on the biology of insect pathogens and the interactions they have with their insect hosts (for the subject of this paper focusing on insects produced as food and feed). At the same time, more knowledge is needed on the correlation and/or interaction between production variables and host-pathogen dynamics. Such multifactorial relations are rather complex, with stress factors being critical for the development of disease outbreaks, with often more than one pathogen involved, and several trade-offs that challenge the management of insect diseases in insect production processes.

Additionally, and since many aspects of insect production have an implication on disease development (from insect physiology to in-house hygienic measures), old and novel techniques and possibilities should be extensively explored as preventative and corrective measures. Needless to say, no single solution can address all problems when it comes to the management of diseases. Rearing practices should be continuously revised and changed accordingly. Doing so will allow to find a better balance between enhancing productivity (by optimizing the production) and avoiding insect disease outbreaks while at the same time, taking into account the insects' health.

Ultimately, a holistic approach in understanding the various aspects related to insect diseases in connection with the production process should be taken. Such approach is relevant for the ongoing development of protocols for the management, prevention, and control of diseases.

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Figure 2 was designed including the use of selected free available graphic resources at www.freepik.com.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material can be found online at https://doi.org/10.3920/JIFF2021.0024.

Table S1. Literature review of pathogens of insects produced or collected in nature as food and feed.

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