RESEARCH ARTICLE

One Health, One Hive: A scoping review of honey bees, climate change, pollutants, and antimicrobial resistance

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Abstract

Anthropogenic climate change and increasing antimicrobial resistance (AMR) together threaten the last 50 years of public health gains. Honey bees are a model One Health organism to investigate interactions between climate change and AMR. The objective of this scoping review was to examine the range, extent, and nature of published literature on the relationship between AMR and honey bees in the context of climate change and environmental pollutants. The review followed systematic search methods and reporting guidelines. A protocol was developed a priori in consultation with a research librarian. Resulting Boolean search strings were used to search Embase® via Ovid®, MEDLINE®, Scopus®, AGRICOLA™ and Web of Science™ databases. Two independent reviewers conducted two-stage screening on retrieved articles. To be included, the article had to examine honey bees, AMR, and either climate change or environmental pollution. The review identified key themes and gaps in the literature, including the need for future interdisciplinary research to explore the link between AMR and environmental change evidence streams in honey bees. We identified three potential linkages between pollutive and climatic factors and risk of AMR. These interconnections reaffirm the necessity of a One Health framework to tackle global threats and investigate complex issues that extend beyond honey bee research into the public health sector. It is integral that we view these “wicked” problems through an interdisciplinary lens to explore long-term strategies for change.
Introduction

The global rise of antimicrobial resistance (AMR) over the past 50 years presents troubling health projections for both public and environment sectors [1]. Antimicrobial resistance has global consequences for human health, resulting in approximately 700,000 deaths each year. By 2050, it is projected that the number of AMR-related deaths could rise to 10 million annually, with an estimated economic impact of $100 trillion USD [2]. Also at the forefront of global grand challenges lies climate change. The dire consequences of climate change have captured the focus and driven the collaboration of notable organizations such as NASA, the United Nations, and governments the world over [3–6].

Seeded into these critical contemporary issues are complex interactions that necessitate the conduct of interdisciplinary research [7,8]. Reports such as the World Health Organization (WHO) Antimicrobial Resistance Global Report, three recent Special Reports published by the Intergovernmental Panel on Climate Change (IPCC), and the Lancet Commission on Pollution and Health provide detailed insights into AMR, climate change, and environmental quality, respectively [1,9–12]. However, these reports neglect to substantially address these components through an interdisciplinary lens that links the three issues. Increasing communication between disciplines is not only helpful in understanding complex multidimensional problems, but is essential for implementing long-term solutions for mitigation [13,14].

While growing interest in areas such as One Health has helped bridge the topics of AMR, climate change, and environmental research, the majority of studies are still concerningly limited to the silo of each individual issue [1]. One Health is described as an approach to global health that focuses on linkages between the health of humans, animals, and the environment by improving intersectional communication and collaboration through research and policy [15].

Honey bees can serve as a model One Health organism to investigate the interactions between environmental change and AMR due to their inseparable symbiosis with the determinants of environmental health [16,17]. For example, environmental pollutants in water, soil, and air can negatively impact honey bee and hive health through leaching into pollen and honey foodstuffs [18,19]. Moreover, warming temperatures and other climatic factors related to climate change can increase the prevalence and spread of honey bee diseases and decrease the efficacy of antimicrobials in treating pests and pathogens [20–22]. Drug efficacy is further challenged by years of liberal antibiotic use [22,23], contributing to an increase in multidrug-resistant microorganisms. Apiaries globally are reporting greater colony losses than ever before [24,25]. It is generally believed that complex interactions between multiple environmental, pathogenic, and climatic factors are responsible for the majority of these losses, which have come to be referred to under the umbrella term of “colony collapse disorder” [26,27]. Interdisciplinary research into these interactions is therefore highly beneficial and inherently relevant to honey bee health.

How do environmental and climatic factors interact with each other to exacerbate AMR in honey bees? Given the limited evidence currently available, the objective of this scoping review was to examine the range, extent, and nature of published literature on the relationship between AMR and honey bees in the context of climate change and environmental pollutants through a One Health lens.

Materials and methods

Protocol and search strategy

The review followed systematic search methods outlined in the Joanna Briggs Institute (JBI) Reviewer’s Manual and is reported according to the PRISMA Scoping Review reporting
guidelines [28–33]. A time-stamped protocol was developed a priori in consultation with a research librarian (S1 File). The PRISMA-ScR checklist is provided in S1 Checklist.

A comprehensive search strategy was developed to identify articles that discussed AMR in honey bees in the context of environmental or climatic factors. No search restrictions were placed on language, publishing date, or geography. An example search string for Embase® via Ovid® is shown in Table 1. The complete search strings (S1 Table) were used to search Embase®, MEDLINE®, Scopus®, AGRICOLA™ and Web of Science™ databases on July 10, 2019.

After downloading all retrieved articles within Mendeley® (Elsevier, Amsterdam, Netherlands), articles were collated and de-duplicated in DistillerSR® (Evidence Partners, Ottawa, ON, Canada) and screened for eligibility via a two-stage screening process by two independent reviewers. Article titles, abstracts, and key words were screened in the first stage, followed by full-text screening in the second stage. To be included, the article had to examine honey bees, AMR, and either climate change or environmental pollution (S2 File). Antimicrobial resistance

Table 1. Search string used to search Embase® via Ovid® database for articles about honey bees, antimicrobial resistance, and environmental and/or climatic factors.

| Component          | Search Terms                                                                 |
|--------------------|------------------------------------------------------------------------------|
| Honey Bees         | (bee OR bees OR honey OR bee' OR honeybee' OR honey OR beekeeper' OR apiarist' OR artifice' OR apis mellifera OR apidae OR (hive AND (health OR success OR collapse OR product OR stability))) |
| AMR                | (((resistant' OR stewardship) AND (antibiotic' OR antimicrobial' OR anti-microbial' OR anti-bacterial' OR antibacterial' OR anti-viral' OR anti-viral' OR anti-fungal' OR anti-fungal' OR anti-helminthic' OR antagonelmintic' OR anti-parasitic' OR antiparasitic' OR parasiticide' OR biocide' OR antiseptic' OR disinfectant' OR sterilant' OR steriliser' OR chemosterilant' OR multidrug OR multi?drug)) OR AMR OR XDR OR TDR OR superbug' OR superbug')) |
| Climatic Factors   | ((climat' adj15 (chang' OR modeling OR predict' OR resilience OR sensitivity)) OR (environment' adj15 chang') OR climate variability OR climatic variability OR global warming OR greenhouse effect OR climate disaster OR (storm NOT (electrical OR autonomic OR thyroid'))) OR wind OR atmospheric pressure OR season' OR precipitation OR snow OR ice OR humid OR rain OR flood OR drought OR wildfire OR (heat adj15 (wave' OR extreme' OR event)) OR temperature' OR cool OR cold OR weather OR ultraviolet radiation OR UV OR El Nino-Southern Oscillation OR El Nino OR La Nina) |
| Environmental Factors | (air pollutant' OR persistent organic pollutant' OR particulate matter OR atmospheric contaminant' OR atmospheric pollutant' OR volatile organic compound' OR volatile organic pollutant OR VOC OR VOCs OR ambient air pollution OR household air pollution OR criteria air pollutant' OR biological air pollutant' OR physical pollutant' OR chemical pollutant' OR gases OR ((fossil fuel OR arivid') AND pollutant') OR ((air OR water OR soil) AND (contaminant' OR toxic' OR environment' OR health OR quality OR disease OR particulate OR metal OR metals OR lead OR lead?II OR Pb OR Pb?+ OR zinc OR Zn OR Za?+ OR silver OR Ag OR Ag?+ OR copper OR Cu OR Cu?+ OR Gallium OR Ga OR Ga?+ OR cobalt OR Co OR Co?+ OR Mercury OR Hg OR Hg?+ OR Arsenic OR As OR As?+ OR Nickel OR Ni OR Ni?+ OR vehicle' OR automobile' OR exhaust OR motorway OR roadway OR highway OR freeway OR road OR traffic OR urban OR Nor OR nitrogen oxides OR ozone OR particle')) OR dust OR dusts OR PM2.5 OR PM10 OR ultrafine particle' OR polycyclic aromatic hydrocarbons' OR PAH OR POPs OR smog OR water pollutant' OR (water' AND (potable OR healthy OR drink' OR safe OR suitable OR palatable OR edible OR tap OR fresh OR supply OR microbial contaminant')) OR waterborne OR water?borne OR aquifer OR groundwater OR pesticide' OR herbicide' OR insecticide' OR acaricide' OR fungicide' OR molluscicide' OR larvicide' OR fumigant OR anti?fungal agent' OR agricultural chemical' OR agrochemical' OR (defoliant' AND (chemical' OR agent')) OR hazardous substance' OR toxic AND action') OR chemically?induced disorder' OR furfural OR aculeximycin OR aluminum phosphate OR chromated copper arsenate OR CCA OR creosote)

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was defined as the ability of a pathogen to resist or reduce the effects of a drug or treatment meant to adversely affect its normal function [34]. Environmental change variables were defined as changes in climate due to natural or anthropogenic causes (climate change), or as an increase in organic or inorganic contaminants of soil, air, or water that alters their natural role or effect in honey bee colonies (environmental pollutants) [35]. Articles about season, weather, climate, and climate hazards in the context of climate change were also included. Honey bees were defined within the taxun Aphis mellifera due to their agricultural importance, though articles using the terms “bees” or “honey bees” were considered relevant if no taxun was mentioned. The initial protocol required articles to include honey bees, AMR, climate change, and environmental pollutants. However, after screening articles to the data extraction level, a lack of articles containing all components prompted a revision of our inclusion criteria. This second round of screening included articles that studied honey bees, AMR and at least one of either climate change or environmental pollutants. This amendment was reflected within the protocol, which was re-time-stamped on December 9, 2019. The amendment was deemed necessary to provide sufficient evidence for discussion, to allow for better identification of gaps in literature, and to provide a more meaningful project outcome as a result. Articles were excluded if they were books, book chapters, theses, dissertations, or commentaries. Conflicts between reviewers were resolved via discussion if necessary.

Data charting process and data items
Data regarding authorship, publication date, location of study, type of antimicrobial and target microbe, environmental and/or climatic factor assessed, research study design type, associated organizations, and outcomes of interest were extracted from relevant articles by two reviewers using DistillerSR®. Article information was exported to a pre-developed data extraction form within Excel® (Microsoft, Redmond, WA) for analysis (S2 Table). Articles were partitioned into thematic categories for further exploration, including: immunocompetence and multi-drug resistance (MDR) transporter downregulation, susceptibility to pests, and in-hive products.

Results
The initial search recovered 1,402 articles, with 1,146 remaining after deduplication (Fig 1). First-stage screening excluded 1,018 articles. 128 articles were eligible for second-stage, full-text screening, which reduced this number to 22. The majority of articles were excluded in this stage due to lacking mention of environmental variables or antibiotic resistance (n = 42), and failure to frame these topics in the context of honey bee health (n = 28). Despite our efforts to locate articles through both the University of Alberta and University of Guelph libraries, we were unable to locate full-text pdfs for 36 articles (S3 File). These articles were additionally requested through the University of Alberta and University of Guelph interlibrary loan systems to ensure minimal loss of articles. This process returned six additional articles that were screened, but 36 could not be obtained and were excluded.

Characteristics of sources of evidence
Twenty-two articles met the inclusion criteria and were included in our analysis. An overview of these articles is included in Table 2, while a complete listing of included articles and study characteristics is available in S2 Table. Articles were published between 1993 and 2019. Research on
AMR and effects of environmental change in honey bees steadily increased in recent years with half (n = 11/22) of included articles published in the last five years alone (2014–2019) (Fig 2).

Fig 3 shows the study location in a global context. Article publication represented research from ten countries that was distributed globally. While some articles did not specify a geographical origin (n = 4), the majority of publications occurred in high-income nations (n = 13; Czech Republic, Germany, Italy, Japan, Norway, Spain, United States) [56]. The United States constituted the largest proportion of location-specific publications (n = 6). A large proportion of articles also came from Europe, with a total of seven articles spread over six European countries (Germany, n = 2; Czech Republic, n = 1; Italy, n = 1; Norway, n = 1; Spain, n = 1; Turkey, n = 1).

Out of the 22 articles, 64% (n = 14/22) followed an experimental study design, with the rest being observational or descriptive studies (n = 16), or review articles (n = 2). There were relatively few studies with broader scope that investigated AMR and environmental change from a global or ecological perspective.

Synthesis of results
Table 3 summarizes environmental factors of interest by climatic or pollutive basis. Environmental factors of interest varied greatly, with environmental insecticides being the most common pollutive factors (n = 7) and indirect geographical differences (different climate zones as
| Reference number | Author(s) | Year | Location | Reference number | Author(s) | Year | Location | Reference number | Author(s) | Year | Location | Reference number | Author(s) | Year | Location | Reference number | Author(s) | Year | Location | Reference number | Author(s) | Year | Location |
|------------------|----------|------|----------|------------------|----------|------|----------|------------------|----------|------|----------|------------------|----------|------|----------|------------------|----------|------|----------|------------------|----------|------|----------|------------------|----------|------|----------|------------------|----------|------|----------|------------------|
| 20               | Regueira Neto et al. | 2017 | Tamandare, Brazil | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 20 | 26 |
| 21               | Ueno et al. | 2018 | 17 prefectures in Japan | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 21 | 27 |
| 22               | Ebrahimi, and Lotfalian | 2005 | Shahrekord, Central Iran | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 22 | 28 |
| 23               | James and Xu | 2011 | Not Stated/Global | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 23 | 29 |
| 24               | Travis et al. | 2014 | Not Stated/Global | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 24 | 30 |
| 25               | Bernal et al. | 2011 | Marchamalo, Spain | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 25 | 31 |
| 26               | Hawthorne et al. | 2011 | United States | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 26 | 32 |
| 27               | Guseman et al. | 2016 | United States | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 27 | 33 |
| 28               | Brandt et al. | 2007 | Germany | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 28 | 34 |
| 29               | O’Neal et al. | 2019 | United States | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 29 | 35 |
| 30               | Prodelalova et al. | 2017 | Czech Republic | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 30 | 36 |
| 31               | Ozkirim, Aktas, and Keskin | 2007 | Turkey | Antimicrobial Target microbe | Climate variable of interest | Environmental quality factor of interest | Hive/honey bee health aspects of concern | 31 | 37 |
| Reference number | Author(s) | Year | Location | Hive/honey bee health aspects of concern | Antimicrobial | Target microbe | Climate variable of interest | Environmental quality factor of interest |
|------------------|-----------|------|----------|--------------------------------------|--------------|---------------|-----------------------------|------------------------------------------|
| [48]             | Alippi et al; 2005 | Not Stated/ Global | American foulbrood | Tylosin | Paenibacillus larvae, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus | Geography/general variations in climate | -- |
| [49]             | Erler and Moritz 2015 | Not Stated/ Global | American foulbrood, European foulbrood, varroa mite, deformed wing virus immunocompetence, chalkbrood, self-medication. | Beeswax, bee food jelly including royal jelly, bee venom, resin, propolis | Enterococcus faecalis, Paenibacillus larvae, acute bee paralysis virus, black queen cell virus, deformed wing virus, sacbrood virus, Paenibacillus alvei, Galleria mellonella, Apis flavae, Aspergillus fumigatus, Aspergillus niger, Nosema apis, Nosema ceranae, Aethina tumida, Oecophylla smaragdina, insects, dead mammals | Temperature, precipitation, climate type | -- |
| [50]             | Chaimanee et al. 2013 | Thailand | Nosema | Immune competence, Antimicrobial peptides | Nosema ceranae from Canada and Thailand | Geography/general variations in climate | -- |
| [51]             | Bastos et al. 2007 | Brazil | American foulbrood | Propolis, Vancomycin, Tetracycline, Tylosin | Paenibacillus larvae | Indirect, general climate affecting hive product antimicrobial strength | -- |
| [52]             | Krongdang et al. 2017 | United States | American foulbrood | Oxytetracycline, tetracycline, tylosin, lincomycin | Paenibacillus larvae | Geography/general variations in climate | -- |
| [53]             | Gregorc et al. 2012 | United States | Varroa mite, immunocompetence | Antimicrobial peptides (abaecin, hymenoptaecin, defensin1) | Deformed Wing Virus | Environmental pesticides (chloropyrifos, imidacloprid, amitraz, fluvalinate, coumaphos, myclobutanil, chlorothalonil, glyphosate, simazine) | -- |
| [54]             | Tian et al. 2012 | United States | American foulbrood, European foulbrood, gut dysbiosis | Oxytetracycline | Melissococcus pluton, Paenibacillus larvae | Geography/general variations in climate | Environmental broad-spectrum antimicrobial exposure |
| [55]             | Loglio 1993 | Italy | Varroa mite | Fluvalinate | Varroa mite | Temperature, seasonal variability, sunlight, altitude, climate type | -- |
| [56]             | Dickel et al. 2018 | Norway | Immunocompetence | Thiacloprid | Enterococcus faecalis | Environmental neonicotinoid thiacloprid | -- |
a result of different geographical locations) accounting for the majority of climatic factors (n = 6). Although most articles revealed potential indirect links to AMR in honey bees, few articles directly linked specific pollutive variables to AMR, the most common of which was the effect of neonicotinoids (n = 6).

The 22 articles can be broadly divided into three thematic categories based on the focus of the study and linkage of AMR to environmental factors: 1) immunocompetence and MDR transporter downregulation; 2) interactions with pest susceptibility; and 3) influences on in-hive antimicrobial properties (categorization shown in Table 4).

**Immunocompetence and MDR transporter downregulation.** Of these 22 articles, nine focused on immunocompetence [20,38,43–45,49,50,53] and two investigated the downregulation of MDR transporters [41,42]. Combined, these eleven articles studied the synergistic effects of pesticides and climatic factors on honey bee innate immunity inhibition. Most
articles found correlations between exposure to antibiotics or pathogens and decreasing honey bee immune function. One article found an increase in immune function when exposed to contaminants and infection, and one final article noted that dual exposure of pathogens and pesticides may increase transmission of disease [38,55]. Most articles focused on alterations in honey bee immunocompetence resulting from the inhibition of immune-essential endogenous microbiota within the gastrointestinal tract [20,38,43–45,49,50,53]. These articles described defensive reactions on the part of the biota (e.g. drug efflux, gene expression) to pollutants and environmental contaminants, as well as inhibition of these defensive mechanisms. Several articles explored alteration of MDR transporters, which are natural efflux pumps present in the

Table 3. Summary of environmental factors of change in the included articles.

| Article Environmental Factor of Change | # of relevant articles | Article reference |
|---------------------------------------|------------------------|-------------------|
| **Climatic Factors**                  |                        |                   |
| Season                                | 3                      | [20,37,54]        |
| Geography                             | 6                      | [23,36,47,48,50,52] |
| Temperature                           | 5                      | [37,40,46,49,54]  |
| Sunlight                              | 2                      | [40,54]           |
| Precipitation                         | 2                      | [20,49,49]        |
| General/Climate type                  | 3                      | [49,51,54]        |
| **Pollutive Factors**                 |                        |                   |
| Pesticides                            | 4                      | [38,39,42,53]     |
| Insecticides                          | 7                      | [38,39,41–44,55]  |
| Fungicides                            | 1                      | [45]              |
| Other/General                         | 2                      | [23,39]           |

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Table 4. Summary of article characteristics by thematic category.

| Article General Topic of Interest     | # of relevant articles | Article reference |
|---------------------------------------|------------------------|-------------------|
| Immunocompetence and multidrug resistance (MDR) transporter downregulation |                        |                   |
| Immunocompetence                      | 9                      | [20,38,43–45,49,50,53,55] |
| MDR transporter downregulation        | 2                      | [41,42]           |
| Increased morbidity                   | 10                     | [20,38,41–45,49,50,53] |
| Increased Transmission                | 1                      | [38]              |
| Susceptibility to pests               |                        |                   |
| Parasites                             | 4                      | [41,49,53,54]     |
| Fungi                                 | 2                      | [42,50]           |
| Chalkbrood (Ascosphaera apis)         | 1                      | [49]              |
| General                               | 1                      | [38]              |
| Bacteria                              | 9                      | [23,36,40,41,47–49,51,52] |
| American foulbrood (Paenibacillus larvae) | 9                      | [23,36,40,41,47–49,51,52] |
| European foulbrood (Melissococcus plutonius) | 2                      | [23,49] |
| Other                                 | 1                      | [55]              |
| Viruses                               | 3                      | [38,45,53]        |
| Hive Products                         |                        |                   |
| Brazilian Red Propolis                | 3                      | [20,49,51]        |
| Other/General                         | 1                      | [49]              |

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cells of almost all animal species [41,42]. They pump many different classes of harmful compounds out of the cell, such as heavy metals, pesticides, and in some cases, antimicrobials [57]. Exposure to one of these compounds can trigger an upregulation of MDR efflux pump expression, thereby increasing resistance to multiple other types of compounds without direct exposure. In this way, MDR transporters can have substantial impact of the efficacy of drug dosages [42]. No article extrapolated this effect to the development of AMR.

**Susceptibility to pests.** Most studies investigated bacterial infections, with almost half of all articles focusing on *Paenibacillus larvae*, the causative agent of American foulbrood (n = 9/22) [23,36,40,47–49,51,52]. *Melissococcus plutonius*, the causative agent of European foulbrood, and *Enterococcus faecalis* was also studied [23,49,55]. The parasitic mite *Varroa destructor* (n = 4/22) [41,49,53,54] and the fungal genus *Nosema* (n = 2/22) [42,50] received some marginal exploration. These articles linked increased pollutants to reduced honey bee health in the form of antimicrobial peptide (AMP) expression modulation. Antimicrobial peptides are critical to insect immune defence, and by altering their transcription or expression, environmental pollutants may lead to increased infection and transmission of pests and pathogens [38]. Articles largely neglected to evaluate how this increase in disease may necessitate the need for increased drug treatment in the hive and to the development of AMR. Articles that predominantly focused on *V. destructor* infection investigated also investigated morbidity as a result of deformed wing virus infection due to the strong association between these two pathogens [58]. Morbidity as a result of Varroa mite infection often occurs due to secondary infection via deformed wing virus, *Escherichia coli*, or other bacterial or viral infections [58]. Therefore, most papers included in this review investigating pest susceptibility explored more than one pathogen at a time. The strong association between pest exposure and immune response, combined with the two-punch approach of most honey bee parasites (destruction of the cuticle followed by secondary viral or bacterial infection), and the broad-spectrum nature of honey bee immune factors resulted in significant overlap between articles binned under pest susceptibility and immunocompetence.

**In-hive products.** The third thematic category explored by this study was the self-administration of in-hive antimicrobial products on AMR. Three articles were included on this topic, all of which discussed the effect of the hive product propolis, an antibiotic and sealant made by the honey bees from resinous plant products, beeswax, and salivary enzymes [20,49,51]. Two of these three articles focused exclusively on the use of propolis [20,51], while one also investigated all-natural, pharmaceutically active compounds made and used by honey bees in the hive [49]. In regards to climatic variables, one article investigated seasonality and another investigated geographical origin as factors that impact the efficacy of propolis [20,51]. Together, these found that propolis was more inhibitory to bacteria, particularly *P. larvae*, when it was sourced from Brazil during the dry season. The remaining article looked how environmental factors influence self medicative behaviour among honey bees [49].

**Discussion**

This study synthesized current interdisciplinary research on AMR, climate change, and environmental pollution in honey bees through a One Health lens in order to characterize past studies and identify potential avenues for future research. The scoping review identified 22 articles published between 1993 and 2019 that examined how interactions between climatic, pollutive, and microbial factors influenced honey bee health through AMR risk and development. Most of these studies were experimental, indicating that research in this area is largely empirical and topically isolated. In general, articles described linkages between environmental factors such as temperature or insecticide pollution and the ability of honey bees to resist or
treat hive infection, either at the colony or individual bee level, or at the biological or behavioural level. However, broad research on the linkage between AMR, climate change, and environmental pollutants on honey bee health was generally lacking, indicating a future need for interdisciplinary research in this field.

Honey bee immunity is complex and dependent on both behavioural and biological factors outside of, and within, the honey bee. Our study identified an opportunity for further investigation of immunocompetence and MDR transporter regulation as a consequence of environmental determinants. The relationship between immune function and MDR transporter regulation is pertinent to the field of AMR for a number of potential reasons. Firstly, any resistance acquired by honey bee cells via MDR transport upregulation could possibly increase the risk of AMR in symbiotic microbes [59,60]. Bacterial pathogens can acquire resistance genes through horizontal genetic transfer (HGT) [60]. There is evidence that insects transfer genetic material bidirectionally through HGT with intracellular primary endosymbiont bacteria within polyplloid bacteriocyte cells [61]. Evidence of exchange of bacterial genes with fungal pathogens by HGT further strengthens this possibility [62], but specific evidence of the transfer of AMR genes through these mechanisms remains largely unstudied. As this theme did not emerge from the papers included in our scoping review, evaluation of its possibility for honey bees is outside the scope of this paper, but presents an intriguing area of interest for future One Health research.

Secondly, honey bee cell membrane transporters may reduce microbial exposure to administered antimicrobials. Natural honey bee cell membrane transporters remove intracellular compounds from the cytoplasm [57]. When pesticides are introduced to the hive, these transporters are activated to prevent the compounds from accumulating. Both pesticides and antimicrobials (including vital acaricides such as coumaphos) are substrates of these transporters [41,42]. As a result, pesticide-induced upregulation of these transporters may concurrently accelerate the removal of antimicrobials from the cell and decrease the intracellular concentration. With less antimicrobials circulating within the honey bee cells, intracellular pathogens such as Nosema spp. and pathogens that live within the body cavity such as Ascosphaera apis may be exposed to lower dosages during this upregulation of membrane transporters [61,62]. By “shading” potential pathogens from antimicrobial treatment, there presents an increased risk for AMR development by the microbes. A similar effect has been studied in the public health sector through the use of small colony variants of Staphylococcus aureus, whereby the microbe is theorized to shelter from antimicrobial treatment within host cells to increase resistance against treatment and allow recurring infections [63,64]. One article in our study highlighted the synergistic effect of simultaneous exposure to contaminants and pathogens [55]. Although this article demonstrates linked immune responses between two distinct etiological agents, the specific pathway was not explored and represents an opportunity for future study [55].

Lastly, with a decrease in honey bee immunity, pathogens are able to more quickly spread and develop inside the hive. Articles within our study primarily focused on immunity as a factor of honey bee endogenous microbiota, highlighting correlations between environmental pollutants and changes in microbiota function. These microbiota have been found to be exceptionally important both in honey bee pathogenic defence, as well as in recovery [65]. Small changes in the immune function of the honey bee linked to changes in these microbes can have drastic effects on the ability of honey bees to fight off disease. However, the articles in this study failed to evaluate how an adjustment in immunity may correspond to an increased risk of AMR. Notably, human studies have shown that a compromised immune system increases the risk of AMR emergence [66,67]. This can be due to inhibition of synergistic actions between the immune system and the antimicrobial in reaching an effective minimum
inhibitory concentration at the site of infection, an overall increase in disease prevalence, or a
higher rate of mutation resulting from unhindered population growth. However, these con-
nections are absent in the articles in this study, and therefore there remains the opportunity to
address these connections in the future.

Our scoping review exposed correlations between environmental factors and an increased sus-
ceptibility of honey bees to disease. The predominant cause of vulnerability in the hive was due to
modulation of AMPs by environmental pollutants. These peptides serve a critical role in innate
defences against pathogens in all insects, including honey bees [68]. The effect of AMP on bacteria
and viruses was a key focus of included articles due to the high incidence of American foulbrood
(a bacterial infection) and Varroa Mite, which normally increase morbidity in the hive through
secondary bacterial and viral infections [53]. Therefore, because most articles investigated mor-
bidity as a result of bacteria and viruses either directly or indirectly, it follows that AMPs, the pri-
mary defence against these organisms, would also be investigated. As shown in human and
livestock animal studies, an increase in disease susceptibility inevitably corresponds to an increase
in antimicrobial drug treatment, with a subsequent increased risk of AMR [69–71]. Although
increased antimicrobial usage is commonly inferred to correlate with an increased risk of AMR,
one of the studies in this review investigated this connection. Therefore, there remains an oppor-
tunity to holistically connect evidence streams between disease susceptibility, treatment require-
ment, and risk of AMR to determine their interdependencies.

Although external antimicrobial treatment by beekeepers was the primary focus of research
included in this review, our study revealed an increased interest in zoopharmacognostic (self-
medicating) behaviours within the hive itself. While normal drug treatment in apiaries occurs
once or twice per year in the spring and fall, self-medication processes by honey bees themselves
within the hive are continuously implemented [72]. Additionally, honey bee self-medication uti-
lizes products within the hive that are prone to variable strength and efficacy, partly due to outside
factors. Our study exposed some contributors to this antimicrobial variance, namely temperature
and seasonality. However, domestication has led to some additional challenges and consider-
ations, such as the mixing of honey bees and antimicrobial products (e.g., honey and propolis)
from multiple geographic sources. Given the sensitivity of hive products to climatic conditions,
the relocation of honey bees to new climates and environments may alter the antimicrobial prop-
erties and efficacy of hive products. There is an opportunity to investigate how the alteration of
these products may influence the ability of colonies to appropriately self-medicate. Despite this
growing concern, we did not identify any studies that directly correlated honey bee hive product
self-medication with an increased threat of AMR. Given that inconsistent antimicrobial strength

can lead to AMR, and environmental conditions have been shown to contribute to antimicrobial
inconsistency both in bees as well as the general population [20,73], connecting these two areas
remains an opportunity for future interdisciplinary research.

Strengths and limitations

While all literature reviews face the possibility of failing to capture all eligible articles, we
aimed to minimize this risk by following a rigorous, systematic approach [74]. We adopted a
search strategy without language limitations in order to reflect the global breadth of the issues
at hand. However, this global undertaking resulted in the necessary exclusion of 36 articles
that were deemed eligible through abstract screening but were not available to us for full-text
review (S3 File). We recognize that 8/22 included articles were observational/descriptive stud-
ies or review articles, and less useful than the 14 experimental studies for identifying causal
relationships. We also recognize one article with a questionable link between AMR and climate
change or environmental pollution. The Prodelalová et al. (2017) paper used a surrogate virus
to assess the effectiveness of disinfectants against the viruses of interest (picornaviruses) at different temperatures. The experimental model itself was tenuous and did not factor largely into our findings. However, the novel insights derived from this study allowed for the identification of multiple literature gaps and future areas of interdisciplinary research and still illustrate the usefulness of honey bees as an organism to determine the One Health impacts of AMR, climate change, and environmental pollution.

Conclusions

This study mapped current literature investigating the relationship between AMR and honey bees in the context of climate change and environmental pollutants through a One Health lens. We identified considerable potential for further interdisciplinary research to holistically correlate environmental influences on honey bee immunity, disease susceptibility, and self medicative behaviours on AMR risk. Despite the immense agricultural and economic significance of honey bees globally, we identified a lack of literature on honey bee health in the context of AMR. Our findings provide the basis for future research to understand the complex linkages of AMR, climate change, environmental pollution and honey bee health in the context of One Health. This study will contribute to the growing body of One Health and interdisciplinary research to find novel solutions for global “wicked” problems beyond the beehive.

Supporting information

S1 Checklist. Completed checklist.
(PDF)

S1 Table. Screening questions that define the inclusion and exclusion criteria used in the two-level screening process by two independent reviewers.
(PDF)

S2 Table. Data extraction table of complete study characteristics of included articles.
(XLSX)

S1 File. Protocol outlining the systematic scoping review created using JBI guidelines and following the PRISMA-ScR checklist–time-stamped on December 19, 2019.
(PDF)

S2 File. Complete search strings for all databases searched in this scoping review.
(PDF)

S3 File. List of papers excluded due to the inability to obtain full-text documents.
(PDF)

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**References**

1. World Health Organization, editor. Antimicrobial resistance: global report on surveillance. Geneva, Switzerland: World Health Organization; 2014. 232 p.

2. O’Neill J. Tackling drug-resistant infections globally: Final report and recommendations [Internet]. 2016 [cited 2020 Sep 13]. Available from: https://amr-review.org/Publications.html.

3. Government of Canada. Climate change: Canada’s action, climate future, partnerships, adaptation, health, science, emissions reporting [Internet]. 2017 [cited 2020 Sep 13]. Available from: https://www.canada.ca/en/services/environment/weather/climatechange.html.

4. IPCC (Intergovernmental Panel on Climate Change). Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. [Internet]. Stocker TF, Qin D, Plattner GK, Tignor M, Allen SK, Boschung J, et al., editors. Cambridge, United Kingdom and New York, NY, USA: Cambridge University Press; 2013 [cited 2020 Sep 13]. 1535 p. Available from: https://www.ipcc.ch/report/ar5/wg1/.

5. NASA (National Aeronautics and Space Administration). Climate Change: Vital Signs of the Planet [Internet]. Climate Change: Vital Signs of the Planet. 2019 [cited 2020 Sep 13]. Available from: https://climatel.nasa.gov/.

6. United Nations. Climate Change [Internet]. 2016 [cited 2019 Sep 13]. Available from: https://www.un.org/en/issues/depth/climate-change/.

7. Holm P, Goodsie ME, Cloetingh S, Agnolletti M, Moldan B, Lang DJ, et al. Collaboration between the natural, social and human sciences in Global Change Research. Environ Sci Policy. 2013 Apr 1; 28:25–35. https://doi.org/10.1016/j.envsci.2012.11.010

8. Van Noorden R. Interdisciplinary research by the numbers. Nature. 2015 Sep 17; 525(7569):306–7. https://doi.org/10.1038/525306a PMID: 26381967

9. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu N (Nil), et al. The Lancet Commission on pollution and health. The Lancet. 2017 Oct 19; 391(10119):462–512. https://doi.org/10.1016/S0140-6736(17)32345-0 PMID: 29056410

10. Masson-Delmotte V, Zhai P, Pörtner H-O, Roberts D, Skea J, Shukla PR, et al., editors. Global Warming of 1.5°C. An IPCC Special Report on the impacts of global warming of 1.5°C above pre-industrial levels and related global greenhouse gas emission pathways, in the context of strengthening the global response to the threat of climate change, sustainable development, and efforts to eradicate poverty. 2018 [cited 2020 Sep 13]; Available from: https://www.ipcc.ch/sr15/.

11. Pörtner H-O, Roberts DC, Masson-Delmotte V, Zhai P, Tignor M, Poloczanska E, et al., editors. IPCC Special Report on the Ocean and Cryosphere in a Changing Climate. 2019 [cited 2020 Sep 13]; Available from: https://www.ipcc.ch/srocc/.

12. Shukla PR, Skea J, Buendia EC, Masson-Delmotte V, Pörtner H-O, Roberts DC, et al., editors. Climate Change and Land: an IPCC special report on climate change, desertification, land degradation,
sustainable land management, food security, and greenhouse gas fluxes in terrestrial ecosystems. 2019 [cited 2020 Sep 13]; Available from: https://www.ipcc.ch/srccl/.

13. Lyall C, Fletcher I. Experiments in interdisciplinary capacity-building: The successes and challenges of large-scale interdisciplinary investments. Sci Public Policy. 2013 Feb; 40(1):1–7. https://doi.org/10.1093/scipol/scs113

14. Olesen DS, Borlau SB, Klikou A, Lyall C, Yearley S. A Better understanding of Interdisciplinary research in Climate Change. Clim Change. 2013;28.

15. World Health Organization. One Health [Internet]. WHO. 2017 [cited 2020 Sep 13]. Available from: http://www.who.int/features/qa/one-health/en/.

16. Conti ME, Botrè F. Honeybees and Their Products as Potential Bioindicators of Heavy Metals Contamination. Environ Monit Assess. 2001 Jul 1; 69(3):267–82. https://doi.org/10.1023/a:1010719107006 PMID: 11497382

17. Porrini C, Sabatini A, Girotti S, Ghini S, Medrzycki P, Grillenzoni F, et al. Honey bees and bee products as monitors of the environmental contamination. APIACTA. 2003 Jan 1; 38:63–70.

18. Mullin CA, Frazier M, Frazier JL, Ashcraft S, Simonds R, vanEngelsdorp D, et al. High Levels of Miticides and Agrochemicals in North American Apiaries: Implications for Honey Bee Health. PLoS ONE. 2010 Mar 19; 5(3):e9754. https://doi.org/10.1371/journal.pone.0009754 PMID: 20332988

19. Smart M, Pettis J, Rice N, Browning Z, Spivak M. Linking Measures of Colony and Individual Honey Bee Health to Survival among Apiaries Exposed to Varroa Japonica. PLoS ONE. 2016 Mar 30; 11(3):e0152685. https://doi.org/10.1371/journal.pone.0152685 PMID: 27027871

20. Regueira MS, Tintino SR, da Silva ARP, Costa M do S, Boligon AA, Matias EFF, et al. Seasonal variation of Brazilian red propolis: Antibi activity, synergistic effect and phytochemical screening. Food Chem Toxicol. 2017 Sep; 107(Pt B):572–80. https://doi.org/10.1016/j.fct.2017.03.052 PMID: 28359875

21. Prodelálová J, Malenovská H, Mouteliková R, Titěra D. Viruscides in apiculture: persistence of surrogate enterovirus under simulated field conditions. Pest Manag Sci. 2017 Dec; 73(12):2544–9. https://doi.org/10.1002/ps.4653 PMID: 28643881

22. Runckel C, Flenniken ML, Engel JC, Ruby JG, Ganem D, Andino R, et al. Temporal Analysis of the Honey Bee Microbiome Reveals Four Novel Viruses and Seasonal Prevalence of Known Viruses, Nosema, and Crithidia. PLoS ONE. 2011 Jun 7; 6(6):e20656. https://doi.org/10.1371/journal.pone.0020656 PMID: 21687739

23. Cox-Foster D, vanEngelsdorp D. Solving the Mystery of the Vanishing Bees. Scientific American. 2009 Apr; 300(4):40–7. https://doi.org/10.1038/scientificamerican0409-40 PMID: 19363919

24. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005 Feb 1; 8(1):19–32. https://doi.org/10.1080/1364557032000119616

25. COLOSS. Honey Bee Research Association: Colony losses monitoring [Internet]. COLOSS. 2019 [cited 2020 Sep 13]. Available from: https://coloss.org/core-projects/colony-losses-monitoring/.

26. Peters M, Godfrey C, McInerney P, Baldini Soares C, Khalil H, Parker D. Chapter 11: Scoping Reviews [Internet], 2017 [cited 2020 Sep 13]. Available from: https://wiki.joannabriggs.org/display/MANUAL/Chapter+11%3A+Scoping+reviews.
33. Tricco AC, Lilie E, Zarin W, O’Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018 Oct 2; 169(7):467–73. https://doi.org/10.7326/M18-0850 PMID: 30178033

34. World Health Organization. Antimicrobial resistance [Internet]. WHO. 2019 [cited 2020 Sep 13]. Available from: http://www.who.int/antimicrobial-resistance/en/.

35. United Nations Framework Convention on Climate Change. Fact sheet: Climate change science—the status of climate change science today. 2011 Feb;7.

36. Ueno Y, Yoshida E, Misumi W, Watando E, Suzuki K, Hirai Y, et al. Population structure and antimicrobial susceptibility of *Paenibacillus* larvae isolates from American foulbrood cases in *Apis mellifera* in Japan. Environ Microbiol Rep. 2018; 10(2):210–216. https://doi.org/10.1111/1758-2229.12623 PMID: 29393586

37. Ebrahimi A, Lotfalian S. Isolation and antibiotic resistance patterns of *Escherichia coli* and coagulase positive *Staphylococcus aureus* from the digestive tract of honey bees. Iran J Vet Res. 2005; 6(2(Ser. 12)):51–97.

38. James RR, Xu J. Mechanisms by which pesticides affect insect immunity. J invertebr pathol. 2011; 109(2):175–182. https://doi.org/10.1016/j.jip.2011.12.005 PMID: 22206912

39. Guseman AJ, Miller K, Kunkle G, Dively GP, Pettis JS, Evans JD, et al. Multi-drug resistance transporters and a mechanism-based strategy for assessing risks of pesticide combinations to honey bees. PLoS ONE. 2016; 11(2):e0148242. https://doi.org/10.1371/journal.pone.0148242 PMID: 26840460

40. Brandt A, Gorenflo A, Meixner M, Buchler R, Siede R, Meixner MD, et al. The neonicotinoids thiacloprid, imidacloprid, and clothianidin affect the immunocompetence of honey bees (*Apis mellifera L*.). J insect physiol. 2016; 86:40–47. https://doi.org/10.1016/j.jinsphys.2016.01.001 PMID: 26776096

41. Hawthorne DJ, Dively GP, H.D.J., Dively GP, Hawthorne DJ, Dively GP. Killing them with kindness? in-vitro study of the antimicrobial activity of Brazilian propolis against *Paenibacillus larvae* Subsp Larvae Strains Isolated from the Different Regions of Turkey. Mellifera. 2007; 7(13–14):2–8.

42. Alippi AM, Albo GN, Reynaldi FJ, De Giusti MR. In vitro and in vivo susceptibility of the honeybee bacterial pathogen *Paenibacillus larvae* subsp *larvae* to the antibiotic tetracyclin. Vet microbiol. 2005; 109(1–2):47–55. https://doi.org/10.1016/j.vetmic.2005.03.008 PMID: 15951140

43. Prodelalova J, Malenovska H, Moutelıkova R, Titera D. Virucides in apiculture: persistence of surrogate enterovirus under simulated field conditions. Pest Manag Sci. 2017; 73(12):2544–2549. https://doi.org/10.1002/ps.4653 PMID: 28643881

44. Ozkirim A, Aktas S, Keskin N. Screening Alternative Antibiotics Against *Paenibacillus larvae* Subsp Larvae Strains Isolated from the Different Regions of Turkey. Mellifera. 2007; 7(13–14):2–8.

45. O’Neal ST, Reeves AM, Fell RD, Brewster CC, Anderson TD, O.S.T., et al. Chlorothalonil Exposure Alters Virus Susceptibility and Markers of Immunity, Nutrition, and Development in Honey Bees. J insect sci. 2019; 19(3). https://doi.org/10.1093/jisesa/iez051 PMID: 31120492

46. Chaimanee V, Pettis JS, Chen YP, Evans JD, Khongphintubunjong K, Chantawannakul P. Susceptibility of *Paenibacillus melaninogen* to the antibio tic tylosin. Vet microbiol. 2005; 109(1–2):47–55. https://doi.org/10.1016/j.vetmic.2005.03.008 PMID: 15951140

47. Erler S, Moritz RFA. Pharmacophagy and pharmacophory: mechanisms of self-medication and disease prevention in the honeybee colony (*Apis mellifera*). Apidologie. 2015; 47(3):389–411. https://doi.org/10.1016/j.apido.2015.03.008 PMID: 16959281

48. Chainmanee V, Pettis JS, Chen YP, Evans JD, Khongphintubunjong K, Chantawannakul P. Susceptibility of four different honey bee species to *Nosema ceranae*. Vet parasitol. 2013; 193(1-3):260–265. https://doi.org/10.1016/j.vetpar.2012.12.004 PMID: 23290277

49. Bastos EMAF, Simone M, Macedo Jorge D, Egea Soares AE, Spivak M. In vitro study of the antimicrobial activity of Brazilian propolis against *Paenibacillus larvae*. J invertebr pathol. 2007; 97(3):273–281. https://doi.org/10.1016/j.jip.2007.10.007 PMID: 18054037

50. Krongdang S, Evans JD, Pettis JS, Chantawannakul P. Multilocus sequence typing, biochemical and antibiotic resistance characterizations reveal diversity of North American strains of the honey bee pathogen *Paenibacillus larvae*. PLoS ONE. 2017; 12(5):e0176831–e0176831. https://doi.org/10.1371/journal.pone.0176831 PMID: 28467471
53. Gregorc A, Evans JD, Scharf M, Ellis JD. Gene expression in honey bee (Apis mellifera) larvae exposed to pesticides and Varroa mites (Varroa destructor). J insect physiol. 2012; 58(8):1042–1049. https://doi.org/10.1016/j.jinsphys.2012.03.015 PMID: 22497859

54. Loglio G. Varroa jacobsoni Oud.: Is it becoming resistant to fluvalinate? Apicolture Moderno. 1993; 84(1):7–10.

55. Dickel F, Münch D, Amdam GV, Mappes J, Freitak D. Increased survival of honeybees in the laboratory after simultaneous exposure to low doses of pesticides and bacteria. PLoS One. 2018; 13(1): e0191256. https://doi.org/10.1371/journal.pone.0191256 PMID: 29385177

56. United Nations. World Economic Situation and Prospects 2014 [Internet]. 2014 [cited 2020 Sep 13]. Available from: https://www.un.org/en/development/desa/policy/wesp/wesp_current/2014wesp_country_classification.pdf.

57. Wales AD, Davies RH. Co-Selection of Resistance to Antibiotics, Biocides and Heavy Metals, and Its Relevance to Foodborne Pathogens. Antibiotics. 2015 Dec; 4(4):567–604. https://doi.org/10.3390/antibiotics4040567 PMID: 29385177

58. Martin SJ, Highfield AC, Brettell L, Villalobos EM, Budge GE, Powell M, et al. Global Honey Bee Viral Landscape Altered by a Parasitic Mite. Science. 2012 Jun 8; 336(6086):1304–6. https://doi.org/10.1126/science.1220941 PMID: 22679096

59. Baron SA, Diene SM, Rolain J-M. Human microbiomes and antibiotic resistance. Hum Microbiome J. 2018 Dec 1; 10:43–52. https://doi.org/10.1016/j.humic.2018.08.005

60. von Wintersdorff CJH, Penders J, Villalobos EM, Budge GE, Powell M, et al. Global Honey Bee Viral Landscape Altered by a Parasitic Mite. Science. 2012 Jun 8; 336(6086):1304–6. https://doi.org/10.1126/science.1220941 PMID: 22679096

61. Burnham AJ. Scientific Advances in Controlling Nosema ceranae (Microsporida) Infections in Honey Bees (Apis mellifera). Front Vet Sci. 2019 Mar 15; 6. https://doi.org/10.3389/fvets.2019.00079 PMID: 30931319

62. Jensen AB, Aronstein K, Flores JM, Vojvodic S, Palacio MA, Spivak M. Standard methods for fungal brood disease research. J Apic Res. 2013 Jan 22; 52(1). https://doi.org/10.3896/IBRA.1.52.1.13 PMID: 24198438

63. Moldovan A, Fraunholz MJ. In or out: Phagosomal escape of Staphylococcus aureus. Cell Microbiol. 2019; 21(3):e12997. https://doi.org/10.1111/cmi.12997 PMID: 30576050

64. Tuchscher L, Medina E, Hussain M, Völker W, Niemann S, et al. Staphylococcus aureus phenotype switching: an effective bacterial strategy to escape host immune response and establish a chronic infection. EMBO Mol Med. 2011; 3(3):129–41. https://doi.org/10.1002/emmm.201000115 PMID: 21268281

65. Raymann K, Shaffer Z, Moran NA. Antibiotic exposure perturbs the gut microbiota and elevates mortality in honeybees. PLoS Biology. 2017 Mar 14; 15(3):1–22. https://doi.org/10.1371/journal.pbio.2001861 PMID: 28291793

66. Handel A, Margolis E, Levin BR. Exploring the role of the immune response in preventing antibiotic resistance. J Theor Biol. 2009 Feb 21; 256(4):655–62. https://doi.org/10.1016/j.jtbi.2008.10.025 PMID: 19056402

67. Margolis E, Rosch JW. Fitness Landscape of the Immune Compromised Favors the Emergence of Antibiotic Resistance. ACS Infect Dis. 2018 Sep 14; 4(9):1275–7. https://doi.org/10.1021/acsinfecdis.8b00158 PMID: 3001470

68. Wu Q, Patocka J, Kucza K. Insect Antimicrobial Peptides, a Mini Review. Toxins (Basel). 2018 Nov 8; 10(11). https://doi.org/10.3390/toxins10110461 PMID: 30413046

69. CCA (Council of Canadian Academies). When Antibiotics Fail: The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada [Internet]. 2019 [cited 2020 Sep 13]. Available from: https://cca-reports.ca/reports/the-potential-socio-economic-impacts-of-antimicrobial-resistance-in-canada/.

70. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications. Molecules. 2018 Mar 30; 23(4). https://doi.org/10.3390/molecules23040795 PMID: 29601469

71. Public Health Agency of Canada. Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action [Internet]. 2017 [cited 2020 Sep 13]. Available from: https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/tackling-antimicrobial-resistance-use-pan-canadian-framework-action.html.

72. Simone-Finstrom M, Spivak M. Propolis and bee health: the natural history and significance of resin use by honey bees. Apidologie. 2010 May 1; 41(3):295–311. https://doi.org/10.1051/apido/2010016
73. Kaba HEJ, Kuhlmann E, Scheithauer S. Thinking outside the box: Association of antimicrobial resistance with climate warming in Europe–A 30 country observational study. Int J Hyg Environ Health. 2020 Jan 1; 223(1):151–8. https://doi.org/10.1016/j.ijheh.2019.09.008 PMID: 31648934

74. Pham MT, Rajić A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. Res Synth Methods. 2014 Dec; 5(4):371–85. https://doi.org/10.1002/jrsm.1123 PMID: 26052958