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Epidemiology and risk factors of self-reported systemic allergic reactions to a Hymenoptera venom in beekeepers worldwide: a protocol for a systematic review of observational studies

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ABSTRACT

Introduction Systemic allergic reaction (SAR) to a Hymenoptera venom is a potentially life-threatening disorder. The rate of SAR between beekeepers in comparison with a healthy individual is different. The risk for an SAR is particularly high in beekeepers due to their persistent or seasonal exposure to the stinging Hymenoptera. We aim to provide a critical appraisal and a synthesis of evidence-based data from epidemiological observational studies, focusing on SARs to a Hymenoptera venom and the associated risk factors for SARs in beekeepers worldwide.

Methods and analysis Searching will include seven electronic databases for published studies without language restrictions, from inception up to 3 August 2021, and it will be rerun for all electronic databases prior publication. Only epidemiological observational studies in beekeepers will be included. The risk of bias in the included studies will be appraised by using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies and the Newcastle-Ottawa Scale, adapted for cross-sectional studies. For the certainty of evidence, the Grading of Recommendations Assessment, Development and Evaluation approach will be used. Qualitative synthesis will be presented in a tabulated format with the selected characteristics across primary studies and the main outcome of interest. A meta-analysis is planned to be performed if there will be a sufficient number of homogeneous studies with complete data. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement will guide the reporting of this systematic literature review.

Ethics and dissemination No ethics approval is needed to conduct the systematic literature review since it will be solely based on the published literature. Findings will be disseminated through the relevant conferences, peer-review and open-access journals.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To the best of our knowledge, the first systematic literature review of epidemiological observational studies in beekeepers worldwide to address the epidemiology of self-reported systemic allergic reactions (SARs) to a Hymenoptera venom and the associated risk factors for SARs.
⇒ Our systematic literature review will capture a broad and comprehensive epidemiological data (no geographical or language restrictions), providing important insights into in this field of science.
⇒ Protocol is carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.

INTRODUCTION

Stings by insects belonging to the order of Hymenoptera are very common, often occuring when they feel threatened by humans—mostly near their nests, or while fighting for food, such as at outdoor events where food is present and consumed.[1] Concerning the environmental exposure and climate conditions, stinging Hymenoptera most frequently cause a local reaction ranging from 56.6% to 94.5% of the general population during their lifetime.[2] Although being always painful with a local inflammatory response (swelling, redness and itching),[3] this type of reaction is not dangerous for healthy (non-allergic to a Hymenoptera venom) individuals but rather transient, self-limiting and completely resolving in less than 24–48 hours.[4] However, in a Hymenoptera venom sensitised individuals, the two most frequent clinical presentations of a Hymenoptera venom allergy are a large local reaction (LLR) or a systemic allergic reaction (SAR). LLR, characterised by a local swelling exceeding 10 cm in a diameter, lasting more than 24 hours and subsiding within few days, occurs with the prevalence rate of 2.4%–26.4% in general population.[5] SAR is a potentially a life-threatening condition of various grades, depending on the type of the

classification used.[4] Its self-reported prevalence rates in general adult population, assessed in a nearly 20 years long period across different European countries, range from 0.9% to 8.9%.[3]

Flying Hymenoptera is diverse and their distributional range varies in relation to the geography. From the perspective of allergy-relevant species, the most important culprits of the Apidae are honeybees (eg, the European honeybee (*Apis mellifera*), virtually occurring worldwide except the Antarctica;[6] the Africanised honeybee (African *Apis mellifera scutellata,* hybridised with local populations of the European *Apis mellifera*);[7] the Asian honeybee *Apis cerana*)[8] and wasps (*Vespula* spp) of the Vespidae, while allergic reactions (ARs) to the hornet venom (*Vespa* spp) are less common. ARs of genera Polistes (paper wasp, *Polistes* spp) or Polybia (eg, *Polybia paulista*) are of relevance, especially in the Southern Europe and Northern America, and South America, respectively, where both are more prevalent.[9]

However, detail classification is beyond the scope of this systematic literature review protocol, thus we will focus to the three most frequent elicitors of a Hymenoptera venom allergy only, that is, honeybees (hereinafter referred to as a bee) and wasps (*Vespula* spp) in particular, as well as to the hornets (*Vespa* spp) as less common ones.[9]

Beekeepers are at especially high risk for developing an AR to a Hymenoptera venom due to their persistent or seasonal exposure to the stinging *Hymenoptera*.[10–12] According to the previous literature and systematic literature review, prevalence rates of the (self-reported) SARs to a Hymenoptera venom range from 14% to 30% (studies performed in beekeepers only)[10] and from 4% to 26%,[11] respectively, according to some authors even up to 43%.[12]

To the best of our knowledge, no systematic literature review in the epidemiology of the self-reported SARs to a Hymenoptera venom in beekeepers, carried out in accordance to the International Prospective Register of Systematic Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020 statement) (http://www.prisma-statement.org) has been performed. Given this gap in literature, we aim to provide a critically appraise and a synthesis of evidence-based data from epidemiological observational studies in beekeepers, with the objectives as follows:

1. To assess a self-reported prevalence of SARs to a Hymenoptera venom in beekeepers worldwide.
2. To explore whether climate and environmental differences in different geographical regions affect the self-reported prevalence rates of SARs to a Hymenoptera venom in beekeepers.
3. To update the principal risk factors (age, annual stings, time from the start of beekeeping to the first SAR to a bee venom, symptoms of upper respiratory allergy during work in the beehive, an atopic constitution) for SARs to a Hymenoptera venom in beekeepers.

From the perspective of public health and clinical medicine, it is of paramount importance to collect and evaluate these epidemiological data in order to identify changes in the trends of the epidemiology of the self-reported SARs to a Hymenoptera venom in beekeepers worldwide and the associated risk factors. This will enable to prepare evidence-based measures in public health and will provide important information for the clinicians that may prevent life-threatening conditions in this high-allergic risk group of population.

METHODS

The systematic literature review protocol will be reported in accordance with the PRISMA-Protocols 2015 statement.[13] Any modifications in the protocol during the systematic literature review will be reported and documented in the final manuscript.

Inclusion criteria

The following inclusion criteria concerning the study participants will be applied:

- Beekeepers of any age engaged in beekeeping activity.
- A prevalence of the self-reported SARs to the culprit Hymenoptera or a Hymenoptera venom, whenever possible, assessed by a questionnaire.

The following inclusion criteria concerning the study will be applied:

- Epidemiological observational studies (cohort; cross-sectional).
- Culprit Hymenoptera species (bee, vespid, hornet).
- All geographical regions of the world.
- No language restrictions.

Exclusion criteria

The following exclusion criteria will be applied:

- Other self-reported reactions to Hymenoptera stings (eg, LLR, systemic toxic reaction (ie, toxic reaction occurring only after stings of many insects (more than 100))).[14]
- Other causes for SARs.
- Meta-analysis, systematic reviews and reviews.
- Clinical studies.
- Qualitative studies.
- Case reports and case series.
- Experimental ex vivo and in vivo studies.
- Articles reporting editorials, comments, opinions and other types of papers that did not report original research data.
- Conference abstracts.
- Articles not related to the systematic literature.
- Studies not available in a full form.

Information sources and search strategy

We will search the following seven electronic databases:

- MEDLINE via PubMed.
- Web of Science Core Collection.
- Scopus.
- Academic Search Complete (EBSCO host).
- ScienceDirect.
- CINAHL (EBSCO host).

- Zoological records (Web of Science).

The list of proposed search terms and the search strategies, applied to MEDLINE via PubMed and then adapted to the other databases (table 1), will be reviewed by an experienced librarian at the University of Ljubljana, Faculty of Medicine, Central Medical Library. We will search for all epidemiological observational studies without language and geographical restrictions from inception up to 3 August 2021. Where necessary, translations will be ensured. In order to maximise the currency of a review, a rerun for all electronic databases is expected to be performed. To identify additional articles, references cited by the original studies will be searched manually.

Study records

Data management

Searching results will be automatically or manually uploaded into a Zotero reference manager to undergo initial screening for duplication removal, and management of the retrieved records. Review process will include screening the title and/or abstract, and full-text, data extraction, assessing risk of bias (RoB) and the strength of body evidence.

Selection process

Titles and/or abstracts will be independently screened by the two reviewers (TC and AK) according to the inclusion and exclusion criteria, and tagged in the Zotero reference manager as »included«, »excluded«, or »unsure«. Initially, a calibration between the both reviewers is expected to be taken after the first 50 screens to check for any disagreements. Abstracts, categorised as »unsure« will be reviewed, and subsequently re-categorised into one of the two categories (»included«, »excluded«). A third reviewer (IL or MK) will be arbitrated in case of any disagreements between the both reviewers to reach a consensus. The process of identification, screening and inclusion of studies will be shown by using the PRISMA 2020 flow diagram (http://www.prisma-statement.org/) of article retrieval.

Data collection process

Data of those full-text reports, fulfilling the inclusion criteria, will be independently extracted by the same two reviewers (TC and AK) using the data extraction form, predesigned in the Microsoft Excel software. A third reviewer (IL or MK) will be consulted for consensus in case of disagreements.

Data items

The following data items concerning the study and methodology will be extracted: authorship; year of publication; study design; location (country/geographic region/city); aim; observed population (beekeepers—number of participants, gender, age); methodology, including the observed health outcome (self-reported SARs to a Hymenoptera venom with the classification and grading system), exposure as an independent variable, confounding factors and data source (questionnaire); statistical analysis (descriptive statistics, association analysis); results.

Outcome

The main outcome of the systematic literature review will be the self-reported prevalence of SARs to a Hymenoptera venom in beekeepers.

RoB in individual studies

RoB in individual studies will be assessed at the study level and the observed health outcome, and conducted independently by the two reviewers (TC and AK) by using two quality assessment tools, that is,

1. The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies (https://jbi.global/critical-appraisal-tools).
2. The Newcastle-Ottawa Scale (NOS), adapted for cross-sectional studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). In the JBI critical appraisal checklist, graded criteria will be adapted to the systematic review of Stanhope *et al*,[11] and classified as »high« (0–3 scores), »moderate« (4–6 scores) and »low« (7–10 scores) RoB. In NOS, adapted for cross-sectional studies, each of the three domains (selection, comparability, outcome) will be rated as »very good« (9–10 stars), »good« (7–8 stars), »satisfactory« (5–6 stars) and »unsatisfactory« (0–4 stars)«.[15] In case the articles will be classified differently by using the both two checklists, only the result of JBI critical appraisal checklist will be used. Any discrepancies between the reviewers will resolved by a consensus, with a third reviewer (IL or MK) brought in to arbitrate if needed.

Data synthesis

Qualitative synthesis of the selected data items will be presented by the summary of tabulated data across primary studies. A meta-analysis is planned to be performed if there is a sufficient number of homogeneous studies with complete data.

Certainty assessment

For the certainty assessment, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool based on the study design, RoB, imprecision, inconsistency, indirect evidence and publication bias will be applied. Each domain will be categorised as »high«, »moderate«, »low« or »very low«. The summary of evidence tables will be developed by using the GRADEpro GDT (Guideline Development Tool) (https://gradepro.org). Two reviewers (TC and AK) will independently appraise the certainty of evidence, and any discrepancies will be resolved by a consensus and, if necessary, a third reviewer (IL or MK) will be consulted.

Patient and public involvement

Not applicable.

Table 1 Search strategies

Electronic database	Timespan	Additional criteria	SQ 1	SQ 2	SQ 1 and SQ 2
MEDLINE via PubMed	Up to 3 August 2021	Advanced; MeSH; Title/Abstract	(((Hypersensitivity/epidemiology[MeSH Terms]) OR (Hypersensitivit*[Title/Abstract])) OR (Allerg*[Title/Abstract])) OR ("Allergic Reaction*"[Title/Abstract])	((((((Beekeeping[MeSH Terms]) OR (Beekeep*[Title/Abstract])) OR ("Bee Keep*"[Title/Abstract])) OR (Keep* Bees[Title/Abstract])) OR (Honey Farm*[Title/Abstract])) OR (Apiarist*[Title/Abstract])) OR (Apicultur*[Title/Abstract])	((((Hypersensitivity/epidemiology[MeSH Terms]) OR (Hypersensitivit*[Title/Abstract])) OR (Allerg*[Title/Abstract])) OR ("Allergic Reaction*"[Title/Abstract])) AND (((((((Beekeeping[MeSH Terms]) OR (Beekeep*[Title/Abstract])) OR ("Bee Keep*"[Title/Abstract])) OR (Keep* Bees[Title/Abstract])) OR (Honey Farm*[Title/Abstract])) OR (Apiarist*[Title/Abstract])) OR (Apicultur*[Title/Abstract]))
Web Of Science Core Collection	Up to 3 August 2021	Advanced; Abstract	AB=(hypersensitivit* OR allerg* OR "allergic reaction*")	AB=(beekeep* OR "bee keep*" OR "keep* bees" OR "honey farm*" OR apiarist* OR apicultur*)	(AB=(hypersensitivit* OR allerg* OR "allergic reaction*")) AND AB=(beekeep* OR "bee keep*" OR "keep* bees" OR "honey farm*" OR apiarist* OR apicultur*)
Scopus	Up to 3 August 2021	Advanced; Textual content: Doc Title, Abstract, Keyword (TITLE-ABS-KEY)	TITLE-ABS-KEY(hypersensitivity) OR TITLE-ABS-KEY(allergy) OR TITLE-ABS-KEY(allergic reaction)	TITLE-ABS-KEY(beekeeping) OR TITLE-ABS-KEY(bee keeper) OR TITLE-ABS-KEY(keeping bees) OR TITLE-ABS-KEY(honey farmer) OR TITLE-ABS-KEY(apiarist) OR TITLE-ABS-KEY(apiculturist)	(TITLE-ABS-KEY (hypersensitivity) OR TITLE-ABS-KEY (allergy) OR TITLE-ABS-KEY (allergic AND reaction)) AND (TITLE-ABS-KEY (beekeeping) OR TITLE-ABS-KEY (bee AND keeper) OR TITLE-ABS-KEY (keeping AND bees) OR TITLE-ABS-KEY (honey AND farmer) OR TITLE-ABS-KEY (apiarist) OR TITLE-ABS-KEY (apiculturist))
Academic Search Complete (EBSCO host)	Up to 3 August 2021	Advanced; Abstract	AB hypersensitivit* OR allerg* OR "allergic reaction*"	AB beekeep* OR "bee keep*" OR "keep* bees OR "honey farm*" OR apiarist* OR apicultur*	AB (hypersensitivit* OR allerg* OR "allergic reaction*") AND AB (beekeep* OR "bee keep*" OR "keep* bees" OR "honey farm*" OR apiarist* OR apicultur*)
Science Direct	Up to 3 August 2021	Advanced; Title, abstract or author-specified keywords	hypersensitivity OR allergy OR "allergic reaction"	beekeeping OR "bee keeping" OR "keeping bees" OR beekeeper OR "bee keeper" OR "honey farmer" OR apiarist OR apiculturist	(hypersensitivity OR allergy OR "allergic reaction") AND (beekeeping OR "bee keeping" OR beekeeper OR "bee keeper" OR "honey farmer" OR apiarist)
CINAHL (EBSCO host)	Up to 3 August 2021	Advanced; Abstract	AB hypersensitivit* OR allerg* OR "allergic reaction*"	AB beekeep* OR "bee keep*" OR "keep* bees" OR "honey farm*" OR apiarist* OR apicultur*	AB (hypersensitivit* OR allerg* OR "allergic reaction*") AND AB (beekeep* OR "bee keep*" OR "honey farm*" OR apiarist* OR apicultur*)
Zoological record	Up to 3 August 2021	Advanced; Abstract	AB=(hypersensitivit* OR allerg* OR "allergic reaction*")	AB=(beekeep* OR "bee keep*" OR "keep* bees" OR "honey farm*" OR apiarist* OR apicultur*)	(AB=(hypersensitivit* OR allerg* OR "allergic reaction*")) AND AB=(beekeep* OR "bee keep*" OR "keep* bees" OR "honey farm*" OR apiarist* OR apicultur*)

SQ 1, search query 1; SQ 2, search query 2.

ETHICS AND DISSEMINATION

As the data retrieved will base solely on the published literature, no ethics approval is required. However, all the collected and analysed data will be kept in a database with a limited access to the authors only. Also, since we will conduct a systematic literature review, there will be no direct patient and public involvement.

We will use a broad dissemination strategy with the findings submitted for publication in high-impact peer review and open-access journals, and presenting our results at the relevant national and international scientific conferences, and at the meetings organised by the Slovenian Beekeepers' Association (https://en.czs.si/). Given the importance of SARs to a Hymenoptera venom as a potentially life-threatening condition, not only in beekeepers but at the community level, we are planning to organise meetings with general practitioners and other healthcare providers, public health specialists and the presidents of the local beekeeping societies to discuss our findings and their potential implications. In addition, this review will be undertaken as a first step prior planning a cross-sectional study in the Slovenian population of beekeepers and it is anticipated to be completed by the end of 2022.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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