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Needs and feasibility of living systematic reviews (LSRs): Experience from LSRs on COVID-19 vaccine effectiveness

Notwendigkeit und Durchführbarkeit von Living Systematic Reviews (LSRs): Erfahrungen aus LSRs zur Wirksamkeit von COVID-19 Impfstoffen

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ABSTRACT

During 2021 and 2023, a team of researchers at the Robert Koch Institute (RKI) and partnering institutions conducted two living systematic reviews (LSRs) on the effectiveness of COVID-19 vaccines in different age groups to inform recommendations of the Standing Committee on Vaccination in Germany (Ständige Impfkommission, STIKO). Based on our experience from the realization of these LSRs, we developed certain criteria to assess the needs and feasibility of conducting LSRs. Combining these with previously established criteria, we developed the following set to inform future planning of LSRs for STIKO: Needs criterion (N)1: Relevance of the research question, N2: Certainty of evidence (CoE) at baseline; N3: Expected need for Population-Intervention-Comparator-Outcome (PICO) adaptations; N4: Expected new evidence over time; N5: Expected impact of new evidence on CoE; Feasibility criterion (F)1: Availability of sufficient human resources; F2: Feasibility of timely dissemination of the results to inform decision-making. For each criterion we suggest rating options which may support the decision to conduct an LSR or other forms of evidence synthesis when following the provided flowchart.

The suggested criteria were developed on the basis of the experiences from exemplary reviews in a specific research field (i.e., COVID-19 vaccination), and did not follow a formal development or validation process. However, these criteria might also be useful to assess whether questions from other research fields can and should be answered using the LSR approach, or assist in determining whether the use of an LSR is sensible and feasible for specific questions in health policy and practice.

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ZUSAMMENFASSUNG

Zwischen 2021 und 2023 führte ein Team von Wissenschaftler*innen des Robert Koch-Instituts (RKI) und von Partnerinstitutionen zwei Living Systematic Reviews (LSRs) zur Wirksamkeit von COVID-19-Impfstoffen in verschiedenen Altersgruppen durch, welche die Evidenzbasis für die Impfempfehlungen der Ständigen Impfkommission (STIKO) in Deutschland bildeten. Auf der Grundlage unserer Erfahrungen bei der Durchführung dieser LSRs haben wir bestimmte Kriterien entwickelt, um die Notwendigkeit und die Durchführbarkeit von LSRs zu bewerten. In Kombination mit bereits etablierten

Abbreviations: LSR, living systematic review; STIKO, Ständige Impfkommission; COVID-19, Coronavirus disease 2019; PICO[S], population – intervention – comparator – outcomes – (setting).

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Kriterien haben wir den folgenden Kriterienkatalog entwickelt, um die zukünftige Planung von LSRs für die STIKO zu unterstützen: Kriterium zur Notwendigkeit (N)1: Relevanz der Forschungsfrage; N2: Vertrauenswürdigkeit der Evidenz (VdE) zu Beginn; N3: Erwartete Notwendigkeit zur Anpassung der Population-Intervention-Comparator-Outcome (PICO)-Frage; N4: Erwartetes Auftreten neuer Evidenz im Laufe der Zeit; N5: Geschätzter Einfluss der erwarteten neuen Evidenz auf VdE; Durchführbarkeit/Feasibility-Kriterium (F)1: Verfügbarkeit adäquater Ressourcen; F2: Möglichkeit der rechtzeitigen Dissemination der Ergebnisse für eine informierte Entscheidungsfindung. Für jedes Kriterium schlagen wir Bewertungsoptionen vor, die anhand eines Flussdiagramms die Entscheidung zur Durchführung eines LSR oder anderer Formen der Evidenzsynthese unterstützen können.

Die vorgeschlagenen Kriterien wurden auf der Grundlage von Erfahrungen aus beispielhaften Reviews in einem bestimmten Forschungsbereich (d. h. COVID-19-Impfung) entwickelt und folgten keinem formalen Entwicklungs- oder Validierungsprozess. Die Kriterien könnten jedoch auch in anderen Forschungsbereichen herangezogen werden, um zu beurteilen, ob eine Fragestellung mit dem LSR-Ansatz beantwortet werden kann und sollte bzw. ob der Einsatz eines LSR für bestimmte Fragen in der Gesundheitspolitik und Gesundheitspraxis machbar ist.

Background

Concept of living systematic reviews and their increasing relevance

Systematic reviews are the current state-of-the-art methodology to synthesize evidence. Conducting systematic reviews requires both time and human resources, as well as methodological expertise. A scoping search in PROSPERO, an international database of systematic reviews, using the search terms "systematic review" OR "systematic" AND "review" and the filtering option "systematic review" as method type revealed that > 150,000 systematic reviews have been registered since 2014, exponentially increasing throughout the years (2014: 241; 2018: 10,145; 2023: 36,568). Conducting the same search in PubMed filtering by "systematic review" as article type, showed that in the same time period > 230,000 systematic reviews have been newly indexed, with the same pattern of increase (2014: 9721; 2018: 18,607; 2023: 37,982). In 2020 the number of registered systematic reviews in PROSPERO showed a jumping increase (2019: 10,161; 2020: 28,231), whereas in PubMed this increase was most prominent in 2021 (2020: 28,216; 2021: 36,197).

In contrast, updating existing systematic reviews seems not a priority for many authors: in the same time period (2014–2023) approximately 440 review updates have been indexed in PROSPERO and 780 published in PubMed, with a steady increase in numbers in both registers (scoping search using the search terms ("review"[Title] AND "update"[Title]) OR "review update"[Title] and filtering options "systematic review" for method/article type). Despite the non-systematic approach of the illustrated scoping searches, the low number of review updates compared to the high number of systematic reviews was surprising, as a systematic review that is not updated with evidence that evolved since its publication is at risk to become outdated in its conclusions and inappropriate for decision-making. According to Shojania et al., the median survival time of systematic reviews relevant for clinical practice was 5.5 years whereas 7% of the reviews were outdated already at the time of publication. For 23% of the included systematic reviews in the analysis new evidence became available already within 2 years [1]. As this analysis included studies published between 1995 and 2005, the life expectancy reported there reflects a situation about 20 years ago. Nowadays, survival time of a systematic review might be even shorter due to an increase in publication speed in many fields of science.

To address the challenge of the "aging" of systematic reviews, Elliot et al. introduced the concept of "living systematic reviews" (LSR) [2]. According to this concept LSRs provide the opportunity to develop "up-to-date online summaries [...], that are updated as new research becomes available" while maintaining high quality standards. With this LSRs follow the same standard systematic review methods but update the results continuously or at least in a pre-defined frequency (e.g., few months or shorter), and with this integrate relevant new evidence as it becomes available [3,4].

The shorter interval between literature searches for an LSR does not necessarily imply a lower workload per update cycle, or fewer studies to be included, as LSRs are often performed in the context of rapidly evolving evidence [5]. Having a constant LSR author team may ease the work process.

Since the introduction of the LSR-methodology the number of LSRs indexed in PROSPERO has increased from 3 in 2014 to 358 in 2023. In PubMed 41 LSR were indexed in 2014, 346 in 2023 (highest number in 2022, with 368 indexed LSRs; search terms ("living"[Title] AND "review"[Title]) OR "living review"[Title] in respective data platforms, filter: "systematic review" for method/article type; all searches were conducted on 22 December 2023). The COVID-19 pandemic, with its rapidly evolving evidence base, its uncertainty in particular in the early phase of the pandemic, and the likely changes to policy and practice decisions due to new evidence becoming available provided the ideal context to conduct LSRs.

Our global vivid research community, and the increasing public interest may lead to the assumption that LSRs should become state of the art for synthesizing evidence. But there are differences in the relevance, pace and amount of research development across various health and health care fields.

Approach to derive criteria on the needs and feasibility of future LSRs for STIKO

In 2021, with the first COVID-19 vaccines coming to market the evidence on their efficacy and effectiveness became increasingly relevant for decision-makers. As the initial evidence was uncertain but a large number of emerging studies were expected to be published soon, we decided in 2021 to initiate two LSRs on the efficacy and effectiveness of COVID-19 vaccination in different age groups to inform the vaccination recommendations of the Standing Committee on Vaccination in Germany (Ständige Impfkommission, STIKO) [6,7]. Findings of every updating cycle were integrated into the living STIKO-recommendations on COVID-19 vaccination [8] (latest version available here https://www.rki.de/DE/Content/Infekt/Impfen/ImpfungenAZ/COVID-19/Impfempfehlung-Zusfassung.html) and published in international journal articles [9–12]. All review versions considered the evolving body of evidence on the topic and the changing PICO(S) (Population, Intervention, Outcomes, [Setting])-elements of the underlying research question.

Based on our experience from conducting those LSRs and how their findings informed STIKO recommendations, we reviewed

the previously outlined criteria on when to do an LSR. Reassessing the needs and feasibility of conducting the LSRs, we identified further aspects that should be considered before initiating an LSR project to inform future STIKO recommendations. We therefore pragmatically defined additional criteria that should be taken into account when deciding upon the needs and feasibility of future LSRs for STIKO in a first step and adapted these in an iterative group discussion followed by finally decided upon these in an informal consensus process.

Informal consensus criteria for the needs and feasibility assessment of LSRs

Existing criteria for the NEEDS assessment of LSRs

Existing criteria for the needs assessment of LSRs are (1) the relevance of the research question, (2) the assessment of the current and (3) the expected evolving evidence [3,4]. Accordingly, we consider LSRs particularly useful to inform guideline panels in highly dynamic research areas; ideally aiming to inform anticipated guideline or policy discussions. Therefore, we first evaluate the relevance of the research question from a clinical or public health perspective, including political, public, or research interests (criterion N1). When assessing the current and expected evidence, we evaluate the uncertainties of the existing evidence (criterion N2), the pace and quantity of arising evidence (criterion N4), and its expected impact on the certainty of evidence (criterion N5).

> *Experience from conducted LSRs:*
> *Considering the global burden of COVID-19, and the interest in COVID-19 vaccination as soon as the first vaccines got available, the research question of our LSRs became top priority for STIKO and their stakeholders. The primary data obtained from pivotal trials of different COVID-19 vaccines answered some but not all relevant aspects for informed recommendation making. Uncertainty remained for example regarding rare adverse events, the duration of protection provided by COVID-19 vaccines especially in the light of new arising virus variants, and the transferability of clinical trial results to the local context. With implementation of vaccination campaigns, scientists around the world published data on real-world effectiveness (and safety) of vaccines. Continuous monitoring of the emerging evidence allowed more target-oriented vaccination recommendations (e.g., for people with immunodeficiencies or pregnant individuals). Given the fast pace of the research environment, high numbers of studies were published, especially as preprint publications that had not yet undergone peer-review. Considering the global interest and the massive increase of data (through increasing vaccination rates), we anticipated a continuous emergence of new evidence over time.*

Additional criteria for the NEEDS assessment of LSRs

In dynamic research fields, relevant changes might occur that impact the elements of the PICO question. Therefore, in addition to considering the impact of new evidence to the initially defined PICO, we also assessed any likely developments within the prioritized research field (e.g., in disease epidemiology through surveillance activities at RKI, approval of new vaccines through contact with experts in the field and information exchanges with regulatory authorities) (criterion N3).

> *Experience from conducted LSRs:*
> *With the ongoing of the pandemic we noticed a constant change and fast development in our research field: The epidemiological landscape changed by time (e.g., shift from the Delta- to the Omicron-variant), baseline immunity in the population increased (through vaccination and natural infection) and new vaccines were introduced to the market. Therefore, we did not experience a saturation of knowledge for our broader PICO, but rather constant uncertainties about evolvements in the field and its impact on existing and arising evidence. Even though, those changes could also have been addressed through several systematic or rapid reviews, we identified the framework and infrastructure of an LSR extremely helpful to timely address any changes in subgroups/ -elements.*

Existing criteria for the FEASIBILITY assessment of LSRs

Required resources to produce and maintain LSRs are a well-known challenge in the successful delivery of LSRs [13]. Therefore, the assessment of human resources, including their skills, availabilities, and commitment to initiate and maintain an LSR is of utmost importance (criterion F1). The impact of possible changes within the author team on the LSRs conduct should be considered, as well as the workload for any contributor in order to deliver the targets on time (i.e., when needed by a decision-making body). Strategies to tackle any unexpected resource barriers should be considered ahead of time.

> *Experience from conducted LSRs:*
> *The required resources to maintain our LSR were constantly high. Not only was the literature exponentially increasing, but also did our author team change over time due to other responsibilities. This required replacement of team members with relevant skills and constant training of new review team members. Furthermore, the evolvement of the research question was rather ad-hoc instead of long planned requiring prompt STIKO recommendations. Therefore, the main challenge for the maintenance of the LSR was the constraint availability of human resources and the competition against time.*

Additional criteria for the FEASIBILITY assessment of LSRs

Ideally, LSRs should incorporate new findings as evidence becomes available. This includes a prompt re-publication of the review with any new findings. However, traditional publication routes usually take several months from study completion to publication (i.e., peer-reviewed publications of full review-manuscripts) (14). Therefore, other possibilities must be considered when conducting LSRs, to facilitate timely information of relevant stakeholders about the (updated) findings through ongoing (or live) publication (criterion F2).

Experience from conducted LSRs:
When conducting LSRs on COVID-19 vaccine effectiveness, evidence sometimes changed on a weekly basis. Close collaboration with STIKO allowed us to share any new findings, as they became available. Additionally, good cooperation with publishers (in our case: in-house publishing within the Epidemiological Bulletin), and the use of pre-print servers increased the reach of our updated findings to a broader national and global audience. To adhere to international standards for research integrity, peer-reviewed publications completed our publishing plans.

Summary of criteria and rating options

Table 1 provides a summary of the formulated criteria, including rating options to decide upon the needs and feasibility for any future LSRs to inform STIKO.

Using the above criteria, we developed a pragmatic decision path to determine different scenarios (A-C), allowing to decide, whether an LSR for STIKO is needed and feasible to conduct (see Figure 1). The flowchart is not meant to provide methodological guidance. However, if according to the needs assessment no LSR is needed, other formats of evidence synthesis (e.g., standard systematic review) should be considered, irrespective of the feasibility assessment (A). If a need is identified and an LSR is considered feasible, it should be initiated (B). If an LSR is needed but not considered feasible (C), it should be realistically assessed if the feasibility issues can be resolved. If successfully addressed, the LSR should be initiated (C1). If feasibility issues cannot be resolved, other formats of evidence synthesis need to be considered (C2).

Given the likely changes in infectious disease epidemiology and vaccine research, the needs and feasibility assessment should be regularly reconsidered.

Table 1
Criteria and rating options to decide upon the needs and feasibility of a living systematic review.

Criteria		Rating options[a]
Needs assessment (N)		
N1	Is the research question of relevance[b]?	Yes, no
N2	What is the certainty of evidence (CoE)[c] at baseline?	High/moderate certainty, low/very-low certainty
N3	Are PICO-adaptations likely to be required due to changes in the research landscape?	Yes, no
N4	How fast is relevant new evidence likely to emerge?	Fast, slow[d]
N5	What is the estimated impact of the expected new evidence on the CoE?	High/moderate impact on CoE, low/very-low impact on CoE
Feasibility assessment (F)		
F1	Are sufficient human resources available to conduct a sustainable LSR?	Yes, no
F2	Can the results be timely disseminated to inform decision-making bodies?	Yes, no

[a] Rating options are displayed in a binary form for simplicity, acknowledging that ratings may have a broader range.
[b] Clinical, political or public interest in research question.
[c] e.g., based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach or generalizability/transferability of the evidence.
[d] This fluent term should allow a self-assessment of the amount of literature published in a certain time for which an LSR would or would not be conducted. The applied definitions likely go in line with the individually defined rhythm of literature searches (e.g. weekly, monthly, ...).

Experience from conducted LSRs:
When the Omicron variant of SARS-CoV-2 rapidly spread across the globe, we were confronted with a scenario that prompted the needs to overcome contextual barriers to maintain our LSR, even though we were facing resource issues. Initial studies suggested a substantial difference in vaccine effectiveness against the Omicron variant than observed against previous virus variants. We thus recruited further human resources to maintain the LSR, confirming a waning of vaccine effectiveness (11). This highlighted a potential need for additional boosters, especially in high risk groups, which were subsequently recommended by STIKO (15).

However, we also noticed, that for many research questions the conduct of an LSR was too resource and time intense to allow timely information of STIKO. In these cases, other formats of rapid evidence synthesis were conducted to inform the STIKO recommendations.

Discussion and conclusions

Our experience with conducting LSRs on COVID-19 vaccinations to inform STIKO recommendations showed that the approach was valid and appropriate in the pandemic setting. The research question was highly relevant and the PICO evolved over time due to new variants arising and a growing population having hybrid immunity. The research landscape showed a high turnover with new evidence impacting policy decisions. Nevertheless, keeping up to date was highly resource intensive, and additional formats of evidence synthesis were needed to complement the evidence base of STIKO recommendations.

Previously established criteria to decide whether to undertake an LSR were reviewed based on experience from exemplary reviews in a concise research field and in an informal process. Overall, we agree that previously defined criteria for the needs and feasibility of LSRs (3,4) are also suitable in the context of vaccination. However, we also identified additional criteria, we would deem relevant to decide upon undertaking any future LSRs to inform STIKO. Our discussions align with experiences from research teams involved in living guidelines of other disciplines. For example, Cheyne et al. suggest in their guidance on selecting and prioritizing questions for living guidelines, that apart from the general relevance of the research question, the CoE in the existing evidence base and the landscape of arising evidence should be assessed [16]. Other guidances suggest, that the impact of out-of-date recommendations on safety should be considered as a key factor to decide upon the need for updating [17]. Further, our experience from LSRs on COVID-19 vaccinations contributed to the systematic development of criteria for the prospective assessment of the needs for updating guideline recommendations, the AGIL-criteria (Assessment of Guidelines for Updating Recommendations) [18].

Our set of criteria might therefore also be used to assess whether policy questions from other research fields (e.g., oncology, climate health) can and should be answered using the LSR approach, or assist in determining whether the use of an LSR is feasible for specific questions in health policy and practice (e.g., living guideline development).

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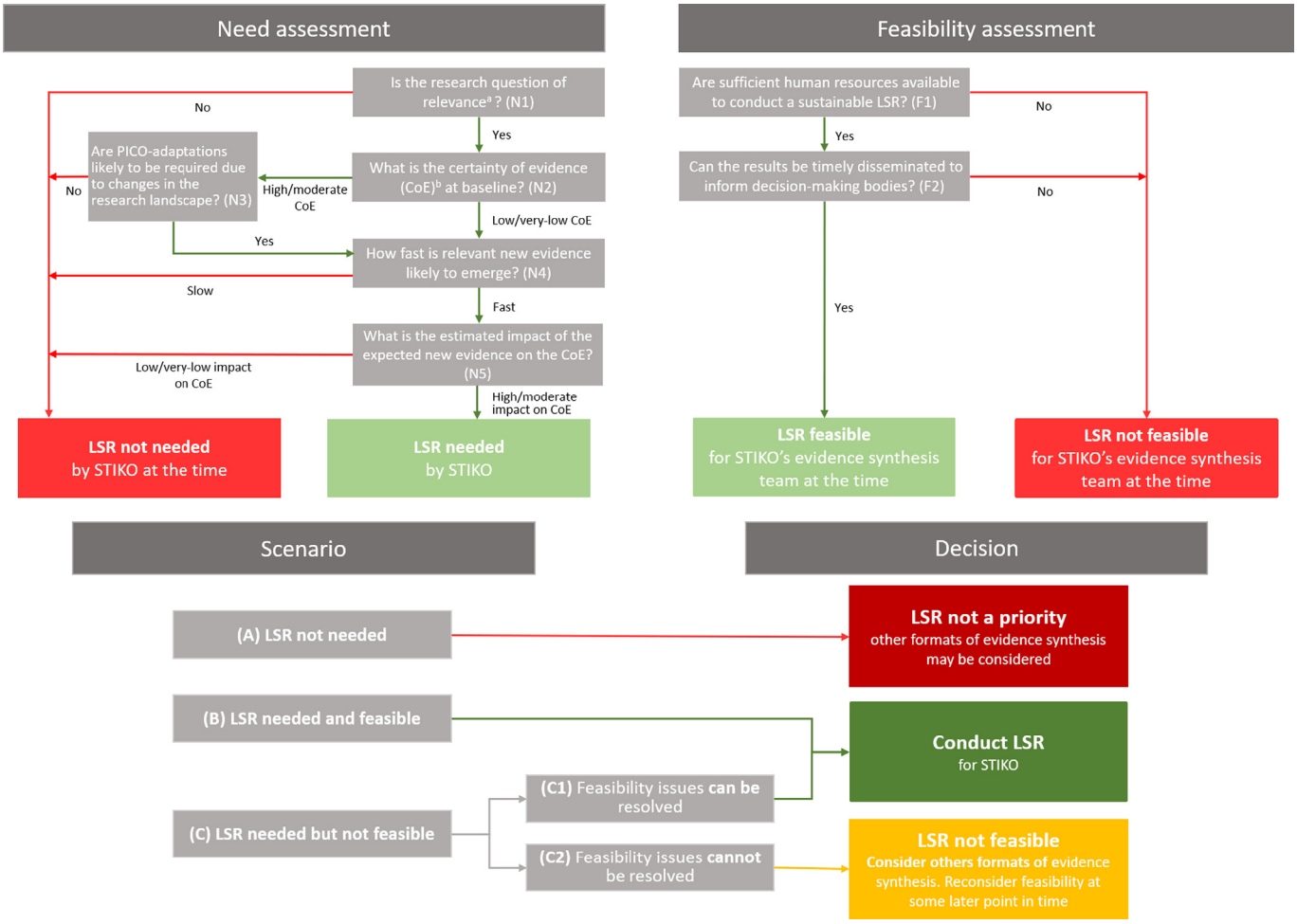

Figure 1. Flowchart to assess the needs and feasibility of a living systematic review for a specific research question.
Other formats of evidence synthesis could be, e.g., standard systematic reviews, rapid reviews, or prospective meta-analysis. [a] clinical, political or public interest in research question; [b] e.g., based on the GRADE approach or generalizability/transferability of the evidence.

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Conflict of interest

All authors declare that there is no conflict of interest.

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