

ORIGINAL RESEARCH

Informing pandemic management in Germany with trustworthy living evidence syntheses and guideline development: lessons learned from the COVID-19 evidence ecosystem

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Abstract

Objectives: We present the ‘COVID-19 evidence ecosystem’ (CEOsys) as a German network to inform pandemic management and to support clinical and public health decision-making. We discuss challenges faced when organizing the ecosystem and derive lessons learned for similar networks acting during pandemics or health-related crises.

Study Design and Setting: Bringing together 18 university hospitals and additional institutions, CEOsys key activities included research prioritization, conducting living systematic reviews (LSRs), supporting evidence-based (living) guidelines, knowledge translation (KT), detecting research gaps, and deriving recommendations, backed by technical infrastructure and capacity building.

Results: CEOsys rapidly produced 31 high-quality evidence syntheses and supported three living guidelines on COVID-19-related topics, while also developing methodological procedures. Challenges included CEOsys’ late initiation in relation to the pandemic outbreak, the delayed prioritization of research questions, the continuously evolving COVID-19-related evidence, and establishing a technical infrastructure. Methodological-clinical tandems, the cooperation with national guideline groups and international collaborations were key for efficiency.

Conclusion: CEOsys provided a proof-of-concept for a functioning evidence ecosystem at the national level. Lessons learned include that similar networks should, among others, involve methodological and clinical key stakeholders early on, aim for (inter)national collaborations, and systematically evaluate their value. We particularly call for a sustainable network. © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Evidence ecosystem; Systematic review; Guideline; COVID-19; Knowledge translation; Pandemic preparedness

Plain Language Summary

What is the context?

- The COVID-19 pandemic was one of the most extreme health, economic, and social crises worldwide.
- It challenged decision-makers like doctors and politicians who needed trustworthy information on COVID-19 shown by research.
- In Germany, we created the ‘COVID-19 evidence ecosystem’ (CEOsys), a network of researchers to help manage the pandemic and support decisions by doctors and public health officials.
- We talk about the challenges we faced in setting up the network CEOsys and what other similar networks can learn from our experience.

What is new?

- CEOsys brought together 18 university hospitals and other institutions.
- The network (1) decided which research questions are most important to answer first, (2) did ongoing reviews of the available body of information, (3) supported ongoing recommendations proven by research, (4) made sure the knowledge is understandable for different people, (5) found out where more research is needed and made suggestions for what to do next.
- We supported members of our network with technical tools and training.
- CEOsys quickly created important results by summarizing the available information on 31 research questions on a wide range of topics and by helping to develop three sets of recommendations. We also worked on setting up new methods such as a toolbox to perform COVID-19-related research, for example.
- Some difficulties we faced included starting our work later than we would have liked after the start of the pandemic, taking time to figure out which research questions to focus on, dealing with constantly changing information about COVID-19, and setting up the necessary technical systems.
- We found that working closely with both method and healthcare experts, partnering with national organizations handling recommendations and with international groups were very important to achieve good results.

What is the impact?

- Other research networks can use what we have learned from this experience to be more ready for future pandemics and other crises.
- CEOsys proved to be a working example for a national network to provide ongoing, quick, and trustworthy summaries of research and recommendations for doctors, public health officials, and the public.
- We have learned that similar networks should include important players in research and healthcare from the very beginning. They must also aim to work together with other countries and assess their success.
- Future networks need stable financing to work internationally and to keep up their work over time.

1. Introduction

The COVID-19 pandemic has been one of the most significant health, economic, and social disruptions globally experienced in recent history. Decision-makers in the health and further sectors, including clinicians, social workers, public health authorities, and politicians, sought evidence-based guidance on the prevention, treatment, and consequences of COVID-19. There was a tremendous increase in research activities worldwide and across disciplines [1].

Given the rapidly evolving evidence base, high-quality evidence syntheses that provide context-sensitive, up-to-date, trustworthy, and appropriately presented scientific data were urgently needed as a basis for evidence-informed decision-making. To fulfill this need and to initiate a collaborative COVID-19 response, scientists worldwide set up evidence networks and initiatives, including the global COVID-19 Evidence Network to support Decision-making [COVID-END; [2,3]], the World Health Organization (WHO)-initiated Evidence Collaborative on COVID-19 network [ECC-19; [4]], the COVID-Network Meta-Analysis (COVID-NMA) initiative supported by the WHO and Cochrane [5], the Canadian-based COVID-19 Evidence Synthesis Network [ESN; [6]], or the Australian National Clinical Evidence Taskforce on COVID-19 [NCET; [7,8]].

In Germany, the ‘COVID-19 evidence ecosystem’ [CEOsys; [9]] was established as a national network of methodologists and clinicians for the production of living systematic reviews (LSRs) and support of living guidelines in the context of the COVID-19 pandemic, collaborating with the Association of the Scientific Medical Societies in Germany (AWMF) Task Force COVID-19 guidelines. It was one of 13 projects within the ‘Network of University Medicine’ (NUM) to coordinate COVID-19-related research in Germany, funded from September 2020 to December 2021 by the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung [BMBF]).

CEOsys pursued four main aims: First, it aimed to identify, assess, and synthesize all available evidence on the most important questions concerning the prevention, treatment, and consequences of COVID-19, including capacity building in the field of evidence synthesis and guideline activities. Second, the network sought to support national guideline groups in developing (evidence-based) guidelines based on the results of its evidence syntheses, and third, to disseminate the results of evidence syntheses and evidence-based guideline recommendations to relevant stakeholders. Fourth, CEOsys aimed to promote better research by detecting evidence gaps, by developing and prioritizing research recommendations, and by performing meta-

What is new?**Key findings**

- COVID-19 evidence ecosystem (CEOsyst) presents a proof-of-concept for a nationwide evidence ecosystem.
- As a holistic network, it integrated (living) evidence synthesis and guideline activities, with methodologists and content experts closely interacting.
- During the COVID-19 pandemic, it was an agile ecosystem with significant output.

What this adds to what is known?

- Our lessons learned can support similar networks and help be better prepared for pandemics.

What is the implication and what should change now?

- Sustainable, international networks are needed which require permanent basic funding.

research. Overall, CEOsyst served as a proof-of-concept for an evidence ecosystem in a thematically defined area. It represented a holistic approach, characterized by the idea that our evidence ecosystem and its properties should be considered as a whole and not just as a composition of its parts. As a holistic network, CEOsyst linked different (methodological) levels of evidence synthesis and guideline activities, represented by the four main aims mentioned above, and combined methodological and content expertise.

2. Objectives and outline

In this article, members of the CEOsyst consortium report on the activities, methodology, results, and experiences of the network. We shortly describe the design of the CEOsyst infrastructure and key activities in the network, followed by presenting the output and impact of CEOsyst. Details on the methodology and results are provided in the Supplement. We then mainly focus on the challenges faced when organizing and maintaining the network infrastructure and its activities. Based on our experiences, we provide lessons learned for initiating similar networks during pandemics or other health-related crises.

3. CEOsyst infrastructure, technical realization, and capacity building

CEOsyst brought together 18 university hospitals in Germany, 2 national and 2 international collaborators

(see [Supplementary File 1](#)), which enabled the ecosystem to dovetail with national structures and the international research landscape. The network comprised more than 100 clinical and nonclinical scientists including research methodologists. Ten work packages (WPs) structured the CEOsyst workflow, and six topic areas (TAs) included clinical and nonclinical scientists working in key areas of emerging COVID-19 research (see [Fig 1](#)). The focus on both the workflow-based WPs and TAs ensured that the work conducted in CEOsyst was grounded in both state-of-the-art methodology and topical expertise in clinical care and public health.

In terms of content, the clinical management (eg, treatment) of COVID-19 and public health issues were the two overarching topics addressed by the network, to which the 6 more specific TAs were assigned to and for which research questions were prioritized. Methodologists of WP3 ‘Critical appraisal’, WP4 ‘Living evidence syntheses’, and WP5 ‘Living recommendations’ participated in the capacity building within the network (see [Supplementary File 1](#)). In addition to WP2 ‘Identification/classification of studies’, WP3 and WP4 also collaborated to coordinate the evidence synthesis activities (see 4.2). The support of living guidelines in CEOsyst (see 4.2) was coordinated by WP5 ‘Living recommendations’ in close cooperation with the information specialists from WP2, the review teams of clinicians/public health experts and methodologists from WP3 and WP4, the collaborating AWMF guideline methodologists and coordinators of the national guideline groups. Members of WP6 ‘Knowledge translation (KT)’ included, eg, researchers, clinicians, and science journalists.

For technical realization, Atlassian Confluence was used to organize communication, data management, and exchange across all WPs and TAs. Based on agreements with Cochrane International and the AWMF, all CEOsyst contributors received access to software tools (eg, Covidence, RevMan Web, MAGICapp), standardized templates (eg, data extraction), and continually updated reference collections (see 4.2).

Capacity building was part of establishing the CEOsyst infrastructure but also presented an ongoing activity accompanying the network’s evidence synthesis/guideline tasks (see 4). Based on heterogeneous skills within the network, tandems of methodologists and clinicians or public health experts were established, allowing methodological and clinical or public health experts to benefit from each other’s knowledge (see [Supplementary File 1](#)).

4. CEOsyst key activities and ways of working across the ecosystem

4.1. Prioritization of research questions (activity 1)

In the face of limited time and resources to conduct LSRs and support guideline activities during a pandemic, WP1

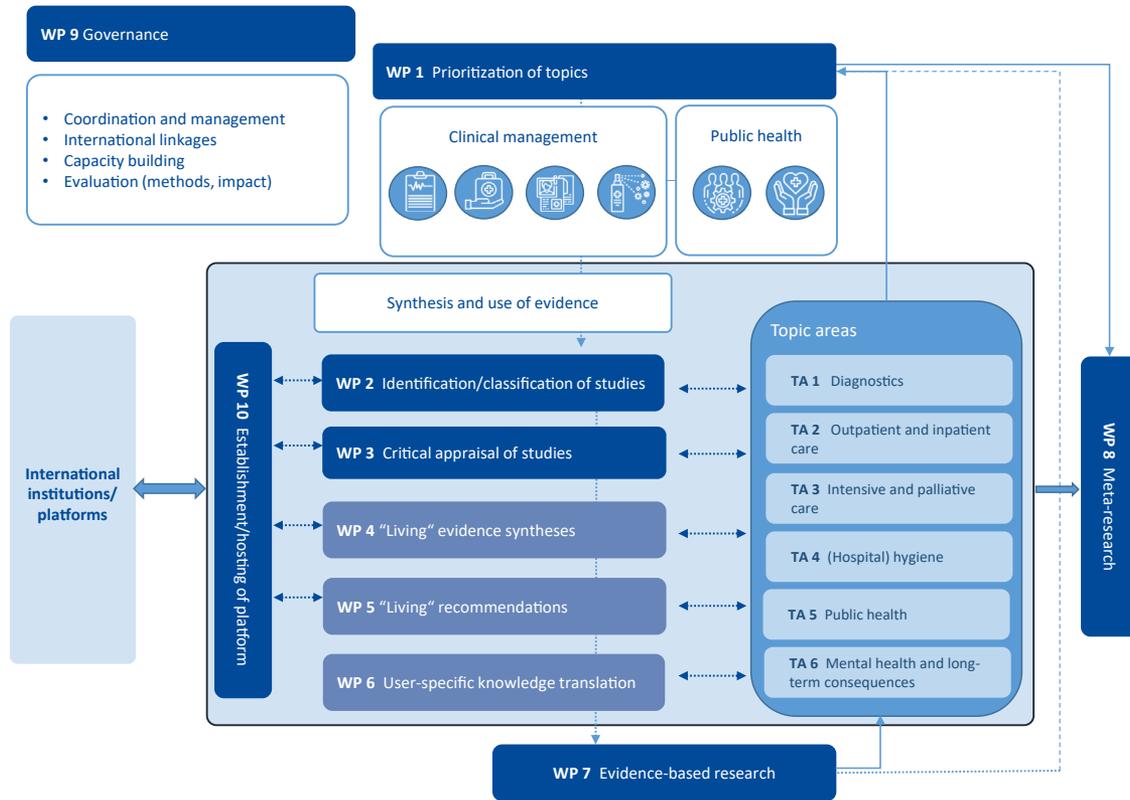


Figure 1. Structure of the CEOsys network (in color). TA, topic area; WP, work package. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

‘Prioritization’ developed a process to prioritize research questions in the course of the CEOsys project. For the initial round of defining research questions for evidence syntheses in CEOsys, prioritization was performed through expert discussions and following pre-existing guideline activities. The later developed systematic process of prioritization followed six steps and was iteratively refined (see [Supplementary File 2](#)).

4.2. Evidence synthesis and guideline activities (activity 2 and 3)

Conducting evidence syntheses and supporting living guidelines (see [Supplementary File 2](#)) were both major objectives of CEOsys. The activity of conducting LSRs aimed at synthesizing all available evidence on the detection of SARS-CoV-2, diagnosis, prevention, treatment, and consequences of COVID-19, as well as measures to contain the pandemic. Given the large number of identical working steps, we aimed to create and utilize synergies between evidence syntheses and living guidelines, with many CEOsys evidence syntheses being transferred into guidelines and review teams working on LSRs also participating in guideline activities. The search process to identify primary studies for LSRs was

streamlined by information specialists through a weekly monitoring of all published randomized controlled trials (RCTs) on COVID-19 by using the Cochrane COVID-19 Study Register [10], supplemented by more extensive searches when needed (see [Supplementary File 2](#)).

4.3. KT (activity 4)

From the very beginning, public outreach and KT were an integral part of CEOsys (see [Supplementary File 2](#)). KT activities aimed to disseminate the results arising from the network activities, primarily LSRs and guideline recommendations concerning COVID-19 therapy. This was carried out after the information needs and preferred information seeking behavior of different target groups like healthcare workers and the general public were surveyed eg, [11–14], with the KT strategy being continuously adapted. Primary target recipients comprised 6 user groups (see [Supplementary File 2](#)).

4.4. CEOsys activities to promote better research (activity 5)

WP7 ‘Evidence-based research’ systematically identified evidence gaps based on evidence syntheses produced

within and outside our network, prioritized these gaps and derived evidence-based research recommendations. WP8 ‘Meta-research’ addressed questions of meta-research and quality control in the field of evidence generation and dissemination for COVID-19-related research questions (see [Supplementary File 2](#)).

5. Outputs and impact of CEOsys

The first major output of CEOsys concerned the establishment of the evidence network with the successful definition of governance structures, financial and legal settings, meeting structures, and technical implementation. Indeed, under pandemic conditions, it was possible to create and maintain a temporary, functional evidence ecosystem with many different actors that were well connected to each other and to additional partners.

Building on this infrastructure and through the network activities outlined above, CEOsys provided very rapid, up-to-date evidence products in an integrated manner across multiple sites and on a very broad range of issues during the pandemic. The network’s impact (see [Fig 2](#), [Supplementary File 3](#)) is reflected by:

- its extensive and multifaceted scientific output, ie, published Cochrane reviews, other systematic

reviews, and publications on new methods and processes in particular,

- the support of guidelines by providing the evidence base to transform 2 pre-existing and consensus-based clinical guidelines into evidence-based guidelines,
- the support of guidelines by initiating and providing the evidence base for a new public health guideline,
- dissemination and implementation formats for stakeholder-specific KT, and
- systematically identified evidence gaps and a catalog of evidence-based research recommendations.

[Figure 3](#) displays the timeline of establishing and maintaining the CEOsys infrastructure and its key activities, with a focus on (living) evidence synthesis and guideline activities.

6. Challenges and lessons learned in CEOsys

During the project, our evidence ecosystem faced several challenges, both with respect to establishing the network infrastructure and the key activities, which required flexibility during the highly dynamic pandemic situation. [Tables 1](#) and [2](#) highlight the challenges encountered, many of them arising from the fact that establishing the network structures and conducting the actual activities had to happen largely simultaneously.

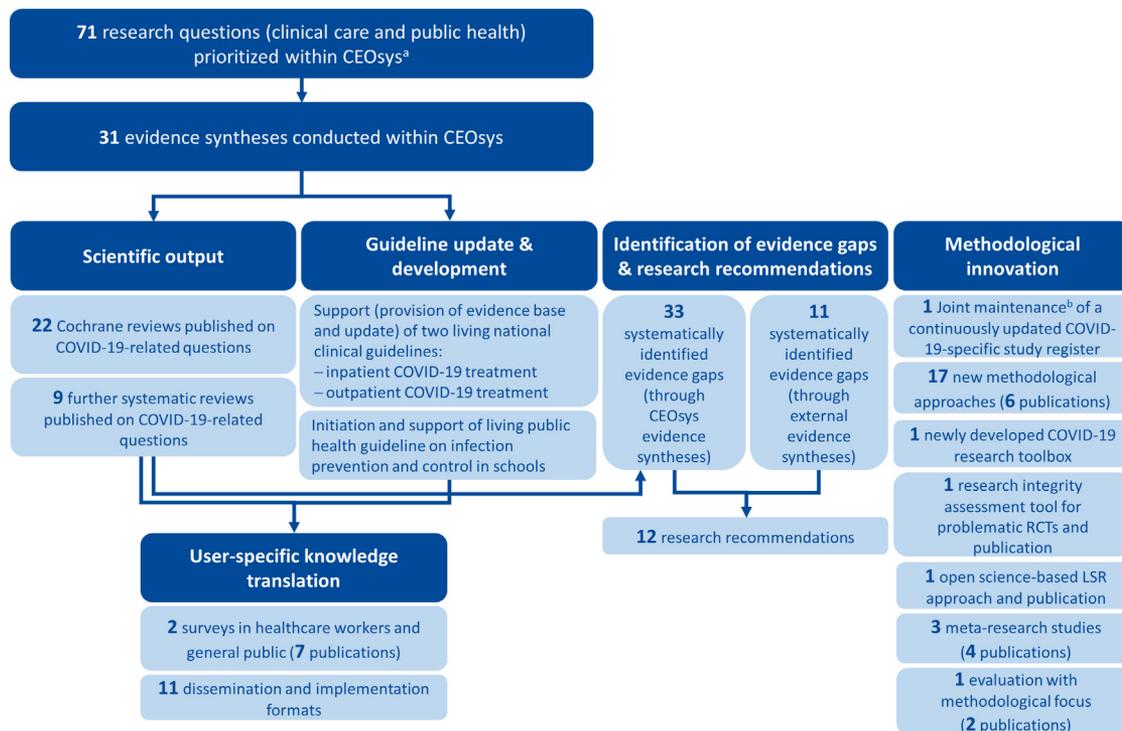


Figure 2. Summary of CEOsys impact (in color). ^aPrioritization performed by prioritization panel (see 4.1) and topic areas in CEOsys. ^bJoint maintenance: The COVID-19-specific study register was mainly developed by Cochrane; however, CEOsys substantially participated in updating the study register. CEOsys, COVID-19 evidence ecosystem; RCT, randomized controlled trial. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

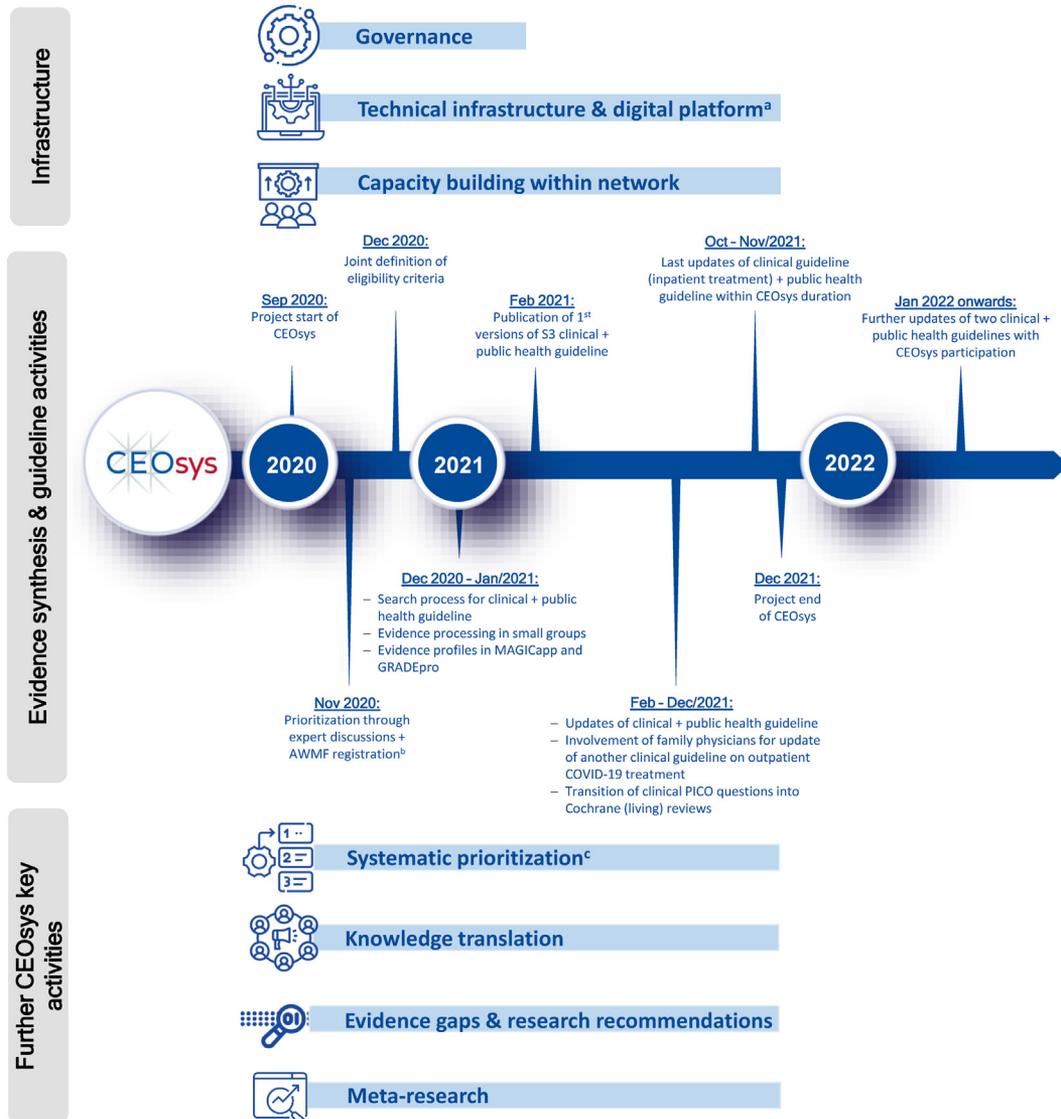


Figure 3. Timeline of the CEOsys project (in color). While establishing the governance structures was performed in parallel to starting the key activities in CEOsys, this part of the project was mostly completed until spring 2021. ^a After choosing Confluence as data management and exchange tool for CEOsys, WP10 continuously provided user guidance. ^b AWMF registration of the clinical guideline on inpatient COVID-19 treatment and of the public health guideline on infection prevention and control in schools. ^c Initial reviews in CEOsys were prioritized through expert discussions (see 4.1), however, from the very beginning of the project, WP1 worked on the development of a systematic process of prioritization which was applied over the further course of the CEOsys. AWMF, Association of the Scientific Medical Societies in Germany; CEOsys, COVID-19 evidence ecosystem; WP, work package. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Supplementing previous discussions [for example, [15–17]], Tables 1 and 2 also present our main lessons learned which might support initiating and maintaining similar but more sustainable networks for (living) evidence syntheses and guidelines (see Supplementary File 4).

7. Discussion

In the face of the COVID-19 pandemic as a major global disruption, CEOsys provided a proof-of-concept for a functioning, agile evidence ecosystem at the national level. In

the following, we discuss positive aspects and barriers of our network, and compare our experience with those of other COVID-19-related evidence networks.

7.1. Strengths of CEOsys

Resembling the metaphor of ‘building a plane while flying it’, involved sites in CEOsys contributed time and expertise, while at the same time being engrossed by emergency and healthcare for COVID-19 patients. It was key to involve institutions and individuals who had worked on joint research projects in the past and favored setting up

Table 1. CEOsys infrastructure—challenges and main lessons learned for future evidence ecosystems

Challenges encountered	Main lessons learned
1. Infrastructure components including governance	
a. Close collaboration between methodologists and content experts	<ul style="list-style-type: none"> • Use methodological underpinning, including methodological capacity building for content experts (eg, clinicians), for evidence synthesis/guideline activities
b. Flexibility regarding topic areas represented in the network	<ul style="list-style-type: none"> • Ensure a certain thematic flexibility of the network, especially during pandemics with individual, pathogen-dependent aspects, with additional topic areas becoming relevant over the course of a pandemic or another health crisis
c. Sustainable network funding	<ul style="list-style-type: none"> • Aim for permanent funding to set up a sustainable network with established infrastructure, ensuring a sufficient (fixed) number of available network partners and preventing double functions
d. National collaborations	<ul style="list-style-type: none"> • Closely collaborate with nationally operating bodies and institutions (eg, governmental public health institutions) • Use established communication channels to organizations that develop recommendations for clinical care/public health • Cooperate with organizations coordinating the guideline-developing activities • Ensure information flow to national partners about which (methodological) capacities within network can be tapped
e. Commitment of network partners	<ul style="list-style-type: none"> • Include new partners using formal accreditation process and commitment agreements
f. Systematic evaluation of network impact and visibility	<ul style="list-style-type: none"> • Systematically evaluate the network's impact on decision-makers (eg, clinicians, politicians) and the general population • Use feedback to improve network activities, ensure its practical relevance and the implementation of results
2. Technical realization (eg, collaboration platform, website, systematic review and guideline platforms)	
a. Underestimation of monetary, human and legal resources required to build a digital platform	<ul style="list-style-type: none"> • Aim for sufficient funds (eg, software licenses), expert personnel and requirement analysis to solve challenges • Use existing platforms for publishing guidelines (ie, MAGICapp, GRADEpro) • Include early training of network members and agree on digital workflows • Clarify who is responsible for website contents and bring in external parties with creative/communication expertise, which also needs resources • Adapt tools for data transfer/use for interoperability and automate processes for data transfer/use as much as possible • Maintain highest standards of data protection and privacy
3. Capacity building	
a. Time-constricted capacity building	<ul style="list-style-type: none"> • Use hands-on capacity building ('learning by doing') due to similar methodological structures/procedures in projects • Establish small groups of methodologists and content experts to facilitate each other's learning process

CEOsys, COVID-19 evidence ecosystem.

the CEOsys infrastructure in parallel to already undertaking relevant evidence synthesis and guideline activities.

Within the network, interconnecting methodologists and content experts from public health, clinical infectious diseases, outpatient, inpatient and intensive care, and virology, who worked collaboratively on conducting LSRs and supporting evidence-based guidelines, represented one of the main strengths of CEOsys and a major advantage for ensuring high-quality standards. Mediated by the AWMF, CEOsys benefited from closely collaborating with national guideline groups, who appreciated the network's methodological and content expertise, allowing the evidence ecosystem to successfully support updates or the development of (living) guidelines at high frequency and even beyond project duration. In Germany, no central organization is responsible for guideline development. Guideline groups, which are initiated

by national scientific medical societies according to AWMF regulations, organize the guideline development process. CEOsys succeeded in coordinating prioritized research questions with the respective guideline groups as similar concerns were in the foreground, respectively.

The collaboration between CEOsys, Cochrane, and various Cochrane Review Groups ensured sophisticated methodological standards and enabled the use of existing infrastructure (eg, collaboratively established study register). Given that several methodological steps are identical (eg, searching, study selection etc.), the synergies between the activities of conducting LSRs and supporting living guidelines proved to be very efficient for the network. While CEOsys activities in supporting evidence-based guidelines focused on national-level action, the conduct and publication of LSRs in accordance with guideline work (ie, Cochrane and non-Cochrane

Table 2. CEOsys activities—challenges and main lessons learned for future evidence ecosystems

Challenges encountered	Main lessons learned
1. Prioritization of research questions	
a. Development of systematic prioritization over project course	<ul style="list-style-type: none"> • Establish systematic process for prioritization of research questions as early as possible for a functioning ecosystem
b. Prioritization panel of high-ranking experts	<ul style="list-style-type: none"> • Focus on few, but high-ranking and nationally active committees during emergencies like a pandemic • Perform risk analysis of competing commitments and use risk distribution across several sites • Define the role and tasks of potential panel members (eg, letter of intent or commitment agreement) and ascertain multidisciplinary • Aim for panel leadership by more than two members and a double occupancy for each discipline
c. Involvement of external stakeholders	<ul style="list-style-type: none"> • Include external key stakeholders like clinicians, public health experts, interdisciplinary and interprofessional guideline groups with patient involvement in all network activities, especially with regard to coordinating prioritization and supporting evidence syntheses and very early in the process • Strive for balance between having research questions prioritized by key stakeholders vs accelerated process during active phases to adapt to rapidly evolving priorities
d. Dealing with changing priorities in the face of the pandemic	<ul style="list-style-type: none"> • Aim for continuous prioritization with the possibility to involve additional key stakeholders • Regularly discuss the processing state and resource allocation for single review questions • Aim for close collaboration between groups working on evidence syntheses/guidelines and those responsible for prioritization within the ecosystem • Strive for fast and flexible consensus on individual justified deviations from prioritization
2. Living systematic reviews (LSRs)	
a. Decisions about eligibility criteria for evidence syntheses	<ul style="list-style-type: none"> • Implement regular and ongoing interaction between methodologists and content experts (eg, clinicians) from within and outside the network (eg, from guideline groups)
b. Search strategy and search process	<ul style="list-style-type: none"> • Organize streamlined search process by information specialists, making use of specific information sources • Search for previous evidence syntheses: <ul style="list-style-type: none"> - Schedule necessary short-term adjustments if relevant information sources produced outside the network to identify relevant evidence syntheses are not available (eg, 'COVID-19 Reviews' updated continuously by the U.S. Veterans' Affairs Evidence Synthesis Program in CEOsys) - Consider producing LSRs within the network if high-quality evidence syntheses are not available from outside the network (eg, also to provide a formal evidence base for guidelines)^a • Search for primary studies: Consider to use/maintain a specific and pre-established study register (eg, like Cochrane COVID-19 Study Register) allowing an efficient search process, with maintenance activity being made even more efficient over time by including machine-learning approaches based on previous human input
c. Maintenance of LSRs	<ul style="list-style-type: none"> • Define procedures for performing updates of evidence syntheses (eg, criteria on when/how to perform updates) and ensure necessary resources (eg, personnel)
3. Living guidelines in collaboration with the AWMF and guideline groups	
a. Time pressure in supporting living guidelines	<ul style="list-style-type: none"> • Ensure extremely motivated actors on each site (ie, review teams, stakeholders and guideline groups, guideline secretariat) as much as possible
b. Evidence to Decision (EtD) framework	<ul style="list-style-type: none"> • Use EtD framework to structure the background texts of guidelines
c. International overlap and redundancies in evidence synthesis and guideline projects	<ul style="list-style-type: none"> • Establish close collaborations between network and important international partners (eg, Cochrane, World Health Organization [WHO], National Institute for Health and Care Excellence [NICE], U.S. Department of Veterans Affairs) to avoid redundancies and establish better standards for evidence synthesis/guideline activities within a network • Strive for use of collaboratively created and freely available database or register of studies to gather information and perform efficient information/literature monitoring instead of multiple initiatives worldwide

(Continued)

Table 2. Continued

Challenges encountered	Main lessons learned
	<ul style="list-style-type: none"> • Aim for stronger integration of international efforts, eg, by establishing a cross-country evidence ecosystem
4. Knowledge translation	
a. Complexity of evidence vs effective knowledge translation (KT)	<ul style="list-style-type: none"> • Invest time in stakeholder mapping and prioritization (where relevant across multiple sectors) • Develop stakeholder group-specific KT strategies to improve clarity (eg, use of absolute risk reduction in clinical guidelines)
b. Provision of information about results of CEOsys in living documents	<ul style="list-style-type: none"> • Aim for balance between traditional publishing of the network's findings in journal publications providing further quality assurance (peer review), scientific credibility and important academic milestones for young researchers vs living (online) documents to ensure immediate access to evidence
5. CEOsys activities to promote better research (eg, identifying evidence gaps, deriving research recommendations, meta-research)	
a. Dealing with cross-registration of trials	<ul style="list-style-type: none"> • Develop automated/manual activities for identifying cross-registrations and checking for consistency
b. Time delays by deriving research recommendations from evidence gaps within the project	<ul style="list-style-type: none"> • Use external methodological/quality evidence analyses (eg, analysis of international guidelines, existing registers) as secondary sources
c. Responding quickly on identified evidence gaps with research projects	<ul style="list-style-type: none"> • Prepare research infrastructure, establish networks and funding during crises to uptake prioritized evidence gaps and transform them into fast-response clinical trials, especially large-scale co-ordinated platform trials

AWMF, Association of the Scientific Medical Societies in Germany; CEOsys, COVID-19 evidence ecosystem.

^a High-quality evidence syntheses not readily available and had to be produced in CEOsys to provide a formal evidence base.

reviews) also helped to increase the network's international visibility. From project start to the present date, the CEOsys consortium published 22 Cochrane reviews on both clinical and public health topics, producing some of the most cited Cochrane reviews in the years 2020–2022 [eg [18], on ivermectin for preventing/treating COVID-19 within top 1% in the field of clinical medicine].

We also consider the technical realization of CEOsys a success, with unforeseen challenges being solved pragmatically and swiftly. The possibility to use evidence synthesis software based on agreements with Cochrane was a major facilitator. Furthermore, the use of a collaborative tool like Atlassian Confluence, which met the legal requirements of individual partners, was very helpful in coordinating the organization of CEOsys.

Overall, the extraordinarily high level of motivation and institutional commitment of all network partners in the evidence ecosystem should be emphasized, which was also a special feature of the pandemic situation and may not be maintained with the same intensity in phases between pandemics or crises (see 8).

7.2. Weaknesses of CEOsys

Starting 5 months after the WHO declared COVID-19 a pandemic, CEOsys was initiated very late. Early in the project, many resources were invested in setting up the

infrastructure, defining common methods of working and coordinating the various partners, resulting in a 4-month constitutional phase. The late timing for setting up the evidence ecosystem led to the problem of already existing parallel structures at the (inter)national level that had been active in the field of COVID-19-related evidence syntheses and guidelines before CEOsys. In particular, the search for a technical solution took up a considerable amount of time. In terms of pandemic or health crisis preparedness, these experiences underline the need for a permanently available, sustainable network with a pre-existing infrastructure (eg, information technology), which is operational at a baseline level (see 8).

Activities in CEOsys had to be initiated and conducted under enormous time pressure, leading to numerous activities being performed simultaneously or in a rapid stepwise manner. For example, clinicians, who had just been trained using the capacity-training concept (see 3), supported the evidence synthesis and guideline activities. This training concept was also developed and adapted for the purposes of CEOsys in parallel to ongoing evidence synthesis/guideline activities. Besides, given the time-consuming development of this activity and the challenges encountered (see Table 2, Supplementary File 4), the prioritization of research questions was delayed and may have been too rigid considering the need for fast decision-making during a pandemic.

The secondary definition and activation of stakeholders outside the primary (and funded) network (eg, to involve them in prioritization) proved to be particularly difficult. Therefore, CEOsys faced some problems in winning over primarily noninvolved stakeholders for its evidence synthesis and guideline projects.

Regarding the 6 TAs, the aims of CEOsys seemed partly inadequate in relation to the project's duration. For example, while TA6 aimed to investigate pandemic-related psychosocial and mental health effects, including long-term consequences, the evidence base during CEOsys was relatively poor, with a paucity of longitudinal studies. Consequently, living evidence syntheses could not be applied for all prioritized questions in all TAs. Besides, the definition of distinct TAs in CEOsys could only address some obvious COVID-19-related topics after the first 6 months of the pandemic, with other unexpected subject areas emerging as the pandemic progressed (eg, children's contribution to the incidence of infection, school testing, and closures). Given that every pandemic is likely to have individual, pathogen-dependent aspects, that are not foreseeable and have to be taken up in the course, the need for thematic flexibility is an important lesson learned from CEOsys.

We did not consistently succeed in our approach of establishing a holistic ecosystem that aimed to integrate different (methodological) levels of evidence synthesis and guideline activities ranging from the prioritization of questions for evidence syntheses to deriving evidence-based research recommendations. For three of 6 TAs (ie, diagnostics, [hospital] hygiene, mental health), which were also some of the busiest disciplines during the pandemic and therefore partly lacked sufficient resources, the results of evidence syntheses were not transferred into evidence-based guidelines during CEOsys. In addition, links to take up relevant results from CEOsys could not be fully established. A catalog of evidence-based research recommendations based on the detected evidence gaps was a key output of WP7. However, a further weakness of CEOsys and NUM concerned the lack of definition of addressees for these recommendations. For example, it would have been possible to transfer parts of the COVID-19-based research gaps and recommendations identified by CEOsys to real research activities. Nevertheless, the evidence-gap-informed recommendations of CEOsys on urgent research needs were not taken up by a fast-response research network.

CEOsys established numerous collaborations with international partners like the Center of Research in Epidemiology and StatisticS and cooperated with other networks (eg, COVID-END) and organizations (eg, NICE, WHO/WHO Europe in the field of public health) on an informal, nonfinanced level. In practice, however, concrete collaboration also proved to be difficult, as manifested by international overlaps in major evidence synthesis and guideline projects on COVID-19-related topics (see [Table 2](#) and [Supplementary File 4](#)).

To date, the impact of CEOsys regarding the implementation of its findings into clinical practice, the influence on decision-makers or the general population has not been examined. Meta-research activities in CEOsys did not specifically address the methods developed within our network, such as KT strategies. An internal, accompanying evaluation of CEOsys was performed by the Section of Health Care Research and Rehabilitation Research (SEVERA), Medical Center of the University of Freiburg. Members of WPs and TAs were interviewed from December 1, 2020 to February 5, 2021 (wave 1: $n = 14$) and from September 27, 2021 to November 20, 2021 (wave 2: $n = 14$). Topics included their perception of the overall project, the progress of the project and its success, the cooperation, CEOsys' impact on the pandemic and future research, perceived barriers, and lessons learned. Results were presented within CEOsys meetings and summarized in an internal report, although not published elsewhere. Based on this evaluation, the project was considered very meaningful and important (see [Supplementary File 4](#)). However, CEOsys was not systematically assessed by an external institution, limiting conclusions to objectively determine our network's value. We did not formally assess the integrity of network partners in using methodological standards, eg, by using quantitative and qualitative methods [eg, [19–21]]. Besides, we did not perform any outcome evaluation to investigate the impact of our network's results and its visibility to various user groups (eg, public) which would have been possible by, eg, assessing the efficacy of KT strategies (eg, [22]).

Due to the time-limited funding, the evidence ecosystem set up could not be maintained beyond December 2021. Learning from the COVID-19 pandemic, the experiences of CEOsys informed the follow-up project PREPARED ('Preparedness and PAndemic REsponse in Germany') which partly uses the infrastructure and activities established to design a blueprint for a more sustainable future ecosystem. However, because of the 1-year time gap between the end of CEOsys and the launch of PREPARED, many capacities—especially at the 'nonmanagement' level (eg, trained scientists/assistants/doctoral students etc.)—were partially lost again, also emphasizing the need for permanent funding to ensure the long-term maintenance of these resources.

7.3. Comparison between CEOsys and similar initiatives

To the best of our knowledge, publications presenting the experiences of other evidence ecosystems are only available for few networks.

7.3.1. Initiation

Contrary to CEOsys, other networks were initiated earlier in the pandemic, such as the NCET or COVID-END established in March [8] and April 2020 [3]. Besides, in contrast to CEOsys, whose infrastructure and ways of

working were mostly set up while already being active, COVID-NMA might have benefitted from implementing a previously proposed model for evidence ecosystems [17,23].

7.3.2. Commitment

Like CEOsys, other initiatives were characterized by high commitment of network members working under high pressure on COVID-19-related evidence in view of an extraordinary global situation. eg, the Australian NCET involved 20 staff and more than 250 experts across all domains of health care [8].

7.3.3. Collaborations

CEOsys, COVID-NMA, and COVID-END relied on a close collaboration between clinicians and methodologists [3,5]. However, while CEOsys was a primarily national network that also interacted with international partners, COVID-END and COVID-NMA seemed to pursue a more global approach by connecting globally leading evidence synthesis, guidance, and support organizations as primary network members from the very beginning. Thus, they represented examples for cross-country evidence ecosystems, which we consider as substantial based on our lessons learned. COVID-NMA involved national public health institutes [eg, Center of Research in Epidemiology and Statistics; France; 5]. COVID-END emphasized the aspect of equity by including evidence synthesis/guideline organizations representing both high and low-to-middle income countries [3]. These characteristics might present advantages in translating the networks' results for end users.

7.3.4. Capacity building

Capacity building on conducting LSRs and living guidelines was a strong component in CEOsys, whereas little information on its role in other initiatives is available based on project websites or publications.

7.3.5. Content focus

Like CEOsys, other initiatives (eg, COVID-NMA) did not focus on a specific COVID-19 treatment but provided comprehensive living syntheses of all available evidence evaluating the effect of interventions for the prevention or treatment of COVID-19 [5]. CEOsys also included public health questions (eg, mental health consequences). On the other hand, COVID-NMA, eg, also conducted LSRs on vaccines for COVID-19 while this topic was excluded in CEOsys (see 3). COVID-END, similar to CEOsys, convened working groups [3], although resources were primarily bundled for evidence synthesis and guideline development in contrast to more specific working groups in CEOsys, that also included activities like prioritization, KT or meta-research.

7.3.6. Searches

The use of regularly updated reference collections to identify relevant RCTs partly differed (eg, Cochrane COVID-19 Study Registry in CEOsys vs WHO International Clinical Trials Registry Platform in COVID-NMA). However, the high-frequency screening of these registries were identical [eg, [5]].

7.3.7. Quality of primary studies

Similar to CEOsys, other networks (eg, COVID-NMA, NCET) also had to deal with limited quality of primary studies on COVID-19 treatment or the lack of data while producing LSRs [5] and living clinical guidelines, partly restricting the ability to make strong, evidence-based recommendations in view of the infodemic [7].

7.3.8. KT & methods development

While initiatives like COVID-NMA succeeded in providing a living mapping of available evidence to visualize their findings, CEOsys seemed to lag somewhat behind in this field, once again illustrating the importance of sufficient funding for a network's technical infrastructure. Comparable to CEOsys, other initiatives published evidence briefs or briefing notes (eg, ESN), although stakeholder-specific KT does not seem to have been a focus of these networks. The same applies to methods development, while both CEOsys and COVID-END have been working on a prioritization process for research questions of LSRs [2].

7.3.9. Evaluation

To the best of our knowledge, to date, there is no published evaluation systematically assessing the value of other COVID-19 evidence networks. However, the Canadian-based ESN, eg, integrated a survey for users on their website to assess the experience of using their evidence synthesis services and the ESN briefing notes.

7.3.10. Sustainability

The need for sustainable network structures, supported by secure funding, has also been highlighted by other initiatives [eg, [2,5]]. For example, investing resources into maintaining digital platforms would allow established ecosystems also considering the increasing volume of new evidence in the aftermath of acute or between crises—a more cost-effective approach than funding new networks with every upcoming crisis.

8. Conclusions

CEOsys is a successful proof-of-concept for the first evidence ecosystem in Germany in the field of COVID-19 research. Using a holistic approach, it integrated various methodological levels in the field of evidence synthesis and guideline activities. Furthermore, the network involved highly efficient tandems of methodologists and content

experts that collaborated on numerous COVID-19-related research questions in a unique way. CEOsys produced substantial output representing a best-practice example of a highly collaborative, multidisciplinary evidence ecosystem that helped to overcome both the methodology-clinical gap and the evidence-practice gap under pandemic-related time pressure. Our lessons learned might support similar networks to be better prepared for pandemics and other health-related crises. Future evidence ecosystems should aim to involve both methodologists and content experts, strengthening multidisciplinary and ensuring thematic flexibility. Permanent (at least basic) funding is critical for building a sustainable network infrastructure, with an ecosystem working with fewer resources during intercrisis phases (ie, resting mode), while, in terms of pandemic or health crisis preparedness, it should be able to (re)act quickly and purposefully in the face of acute public health emergencies. To avoid the loss of built-up capacities in a resting mode, it might also be worth considering that an evidence ecosystem is permanently integrated into existing systems of (evidence-based) decision-making at the national level by collaborating with established structures (eg, AWMF or Robert Koch Institute in Germany). Ideally, an evidence ecosystem would pursue a holistic approach by ensuring a continuous flow of processing research questions from prioritization to conducting evidence syntheses, transferring the results into guidelines or recommendations for policy and practice, disseminating this knowledge, and deriving recommendations for future research. Importantly, by establishing cross-country evidence ecosystems, redundancies in producing evidence syntheses and guidelines could be avoided, while also harmonizing research prioritization and methodological standards. Finally, for future initiatives, we suggest ensuring an objective process and outcome evaluation of evidence ecosystems.

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Data availability

No data was used for the research described in the article.

Declaration of competing interest

F.B. reports a relationship with Pfizer that includes: speaking and lecture fees; reports a relationship with Hans-Bockler-Foundation that includes: funding grants; reports a relationship with German Research Foundation that includes: funding grants; reports a relationship with German Federal Ministry of Health that includes: funding grants; reports a relationship with Federal German Ministry of Education and Research that includes: funding grants; reports a relationship with Charité Foundation that includes: funding grants; reports a relationship with Joint Federal Committee that includes: funding grants; reports a relationship with General Electric that includes: speaking and lecture fees; reports a relationship with Medtronic that includes: board membership.

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Supplementary data

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