SYSTEMATIC REVIEW

Innovation ecosystems in health: countries and theoretical models used [version 1; peer review: awaiting peer review]

Mauricio Alexander Alzate Montoya\textsuperscript{1}, Gino Montenegro Martínez\textsuperscript{1}, Carolina Londoño Pelaez\textsuperscript{2}, Doris Cardona Arango\textsuperscript{1}

\textsuperscript{1}Escuela de graduados, CES University, Medellin, Antioquia, Colombia
\textsuperscript{2}Dirección de investigación e innovación, CES University, Medellin, Antioquia, Colombia

\textbf{Abstract}

This article sought to analyze the innovation ecosystems in health, countries that develop them and the theoretical models they resort to. To this end, three databases carried out a systematic review through a bibliographic search in English, Spanish and Portuguese. 40\% of health innovation ecosystems are in the USA, 13\% in South Africa, 10\% in the UK, 6.67\% in Namibia, and 30\% in various countries. Of the theoretical models used, 13\% resort to the quadruple helix, open innovation 13\%, the triple helix 10\%, and ehealth 7\%. The USA concentrated the development of innovation ecosystems. Quadruple helix and open innovation, were the theoretical models frequently used, both includes society as part of its implementation.

\textbf{Keywords}

Innovation systems, health innovation, health, health ecosystem

This article is included in the Health Services gateway.
**Introduction**

Innovation generates knowledge and comprehensively addresses solutions of all kinds, including health, environment, poverty, and security. Innovation can become a solution for health equity, this becomes tangible through medical devices, care models, health processes, and medications, where scientific and technological health knowledge is critical.

Innovation ecosystems are today considered the most prominent driver to be built and nurtured to reap innovation's benefits. It reflects a paradigm shift, where innovation is becoming a centerpiece of a socioeconomic development model for cities and regions.

Several authors have defined this structure, Walrave et al. conceive it as a network of interdependent actors that combine specialized but complementary resources or capabilities in the quest to co-create and deliver a global value proposition to end users and receive the derived gains in the process. For his part, Gobble indicates that “they are dynamic and purposeful communities with complex and intertwined relationships based on collaboration, trust, and co-creation of value and specialized in the exploitation of a shared set of complementary technologies or competencies”.

Different theoretical models have been proposed in the literature to structure or manage innovation ecosystems: quadruple helix, triple helix, open innovation, and digital systems, among others. They differ in the conformation of the actors involved and the methodology for the approach to developing innovation projects. Nevertheless, the above ends up being relevant at the moment of knowing the dynamics, not only of the components that interact within it, but also from the perspective of the actors that integrate it.

This article aims to analyze health innovation ecosystems to learn about the countries where they are developed and the theoretical models to which they resort.

**Methods**

This systematic review was conducted by searching PubMed, IEEE, and Science Direct databases for articles focused on health innovation ecosystems, published from January 2010 to December 2020, relevant to some types of health innovations articulated in an ecosystem.

**Identification**

MeSH validated search terms were used: “innovation”, “ecosystem”, “politics”, “Health”, “Process”, “System”. In addition, additional articles were identified by performing similar searches in Google Scholar and reviewing references identified in relevant publications.


**Screening**

We excluded articles related to innovation ecosystems in fields other than health. Conference presentations, congresses, or trials on innovation were excluded. The authors applied inclusion and exclusion criteria independently (abstract and full article), and consensus resolved uncertainty.

**Inclusion**

At least two authors independently extracted data using an excel template designed for this systematic review. In addition, the included results reviewed by an external reviewer.

The quality of evidence assessed using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields and the SANRA (Scale for the quality Assessment of Narrative Review Articles) guidelines. It was established that quantitative papers with a score equal to or higher than 10 would be taken into account; for qualitative papers, the score would be equal to or higher than 8, and for systematic reviews, the score would be 6.

The ROBIS tool was used to assess the risk of bias in the systematic review, using a rigorous methodology for the different research domains: study eligibility criteria, identification and selection of studies, data collection, evaluation of the study, synthesis, and findings.
The results were plotted in a structural network diagram considering the relevance, intermediation, and relevance of the different nodes (innovation ecosystem actors and innovation models), identifying the relationships between nodes according to the results to analyze the models with the best connections and the most relevant actors.

The included studies were evaluated with the screening instrument “PRISMA” and the main results met the inclusion criteria.

Search
For this, a peer review is applied, blindly and independently, who must review the list of studies thrown by title or abstract for a first sieve, following a checklist (inclusion criteria) to make the decision if the study is included/excluded. In the first stage, controversies (contrary decisions between the two evaluators) were resolved by consensus; in case of not achieving it, a third evaluator made the decision. Items included in the first sieve were equally divided for full-text reading for the purpose of evaluating the usefulness of the article and extracting the information of interest defined in the domain of analysis.

Rayyan was implemented as a tool to manage evaluation and inclusion of the studies organized by labels according to the inclusion and exclusion criteria. Once the title had been read, and the abstract was classified into labels according to the criteria, if the article was excluded, the reason was related according to already established labels.

The protocol rests on the research and innovation committee at the Faculty of Medicine and the Graduate School of Universidad CES.

Results
The variables taken into account in the results are: year, city, theory or model used in the innovation ecosystem, health area involved, type of health professionals who participated.

The initial search yielded 285 articles; after eliminating duplicates, 278 articles remained; after reading the titles, 94 articles were selected; after reading the abstracts, 56 articles were selected, and 20 papers focusing on information technologies were not taken into account. Finally, the articles were read applying the defined inclusion criteria, and 32 articles were selected.

According to the SANRA guide (scale for the quality assessment of narrative review articles), 30 articles were analyzed for review of quality criteria; two articles were excluded since the qualification according to the defined guide was lower than indicated (Figure 1). The data is available in the dataset called Ecosystem in health located in the DOI https://doi.org/10.7910/DVN/NKFCKF

The possible causes of the heterogeneity between the results of the study are that the studies were classified in terms of: Emerging technologies, Innovation and research, and Information technology, these were included; Conferences, Smart cities, Other health issues, Education, and Ecology, were excluded due to the focus of what is intended in the objective of the study.

Regarding the health innovation ecosystems reviewed, 40% are located in the USA, 13.3% in South Africa, 10% in the UK, 6.67% in Namibia, and the remaining ecosystems represent 30% (Figure 2).

Concerning the models used in the analyzed health innovation ecosystems, we observed that the quadruple helix is equivalent to 13%, open innovation represents 13%, the triple helix corresponds to 10%, and ehealth (use of information and communication technologies for health) corresponds to 7%. In addition, the review shows other models which were the basis for this design.

The innovation ecosystems found in the literature were specialized in the health area. Thus, six models were widely applied to health areas; eight were about digital health and other specialized ecosystems (Table 1).

Actors involved in these ecosystems, which also promote healthcare, have primarily supported the concept that new, emerging innovations and technologies can transform healthcare into an increasingly patient-centered and transparent model, thus improving outcomes and reducing costs.

One of the analyzed categories was the functioning of the ecosystem in terms of its processes in certain relevant aspects such as ethical, political, and legal components. As well as management of ideas, involvement of users in usability
Figure 1. Article selection algorithm.

Figure 2. Countries where health innovation ecosystems are developed.
<table>
<thead>
<tr>
<th>Author</th>
<th>Ecosystem name</th>
<th>Country</th>
<th>Health area</th>
<th>Quality of the paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peltier J. et al. 2020</td>
<td>Digital health innovation ecosystems</td>
<td>United States</td>
<td>SDI focuses on how value creation occurs</td>
<td>23</td>
</tr>
<tr>
<td>Herselman M. et al. 2016</td>
<td>Digital Health Innovation Ecosystem for South Africa</td>
<td>South Africa</td>
<td>Quadruple-helix components</td>
<td>20</td>
</tr>
<tr>
<td>Minoi J. et al. 2014</td>
<td>Ecosystem of mHealth Malaysia</td>
<td>Malaysia</td>
<td>Very Small Aperture Terminal</td>
<td>20</td>
</tr>
<tr>
<td>Iyawa G. E. et al. 2017</td>
<td>Digital health innovation ecosystem</td>
<td>South Africa</td>
<td>Triple Helix systems</td>
<td>20</td>
</tr>
<tr>
<td>Banda G. et al. 2018</td>
<td>Innovation ecosystem of regenerative medicine</td>
<td>England</td>
<td>STRATIS (Strategic planning of advanced technological innovation systems)</td>
<td>20</td>
</tr>
<tr>
<td>Klucken J. et al. 2018</td>
<td>Ecosystem of medical care for patients with Parkinson’s disease</td>
<td>Germany</td>
<td>Personal health record (PRR) - Parkinson</td>
<td>20</td>
</tr>
<tr>
<td>Bockhaven et al. 2018</td>
<td>Personalized medicine innovation ecosystem</td>
<td>Belgium</td>
<td>Triple Helix systems</td>
<td>20</td>
</tr>
<tr>
<td>Ngongoni M. et al. 2018</td>
<td>Healthcare innovation ecosystems</td>
<td>South Africa</td>
<td>Quadruple-helix components</td>
<td>20</td>
</tr>
<tr>
<td>Reynolds et al. 2018</td>
<td>Advanced manufacturing innovation ecosystems</td>
<td>United States</td>
<td>Regional Innovation Systems (RIS)</td>
<td>20</td>
</tr>
<tr>
<td>Shi X. et al. 2018</td>
<td>Entrepreneurial ecosystem health</td>
<td>England</td>
<td>Definition and dimensions of ecosystem health</td>
<td>19</td>
</tr>
<tr>
<td>Author</td>
<td>Ecosystem name</td>
<td>Country</td>
<td>Health area</td>
<td>Quality of the paper</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------</td>
<td>--------------</td>
<td>--------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Hudes M. K. 2017</td>
<td>The Health Care Ecosystem</td>
<td>United States</td>
<td>Prediction and verification model</td>
<td>17</td>
</tr>
<tr>
<td>Tripoli et al. 2019</td>
<td>Hearten KMS</td>
<td>United States</td>
<td>New York Heart Association (NYHA) estimate</td>
<td>18</td>
</tr>
<tr>
<td>Chong N. K. et al. 2020</td>
<td>Tuberculosis innovation ecosystem</td>
<td>South Africa</td>
<td>Tuberculosis</td>
<td>19</td>
</tr>
<tr>
<td>Dakka et al. 2016</td>
<td>Digital Child Health Ecosystem</td>
<td>England</td>
<td>Learning health care system</td>
<td>18</td>
</tr>
<tr>
<td>Catarinella F. S. et al. 2016</td>
<td>Digital health assessment in rheumatology</td>
<td>The Netherlands</td>
<td>Digital health assessment in rheumatology</td>
<td>16</td>
</tr>
<tr>
<td>Hesse B. W. et al. 2011</td>
<td>Oncology Health Information Ecosystem</td>
<td>United States</td>
<td>Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009</td>
<td>16</td>
</tr>
<tr>
<td>Mitra S. et al. 2020</td>
<td>Surgical innovation ecosystem</td>
<td>India</td>
<td>Conceptual model to health hackathons in low-resource settings</td>
<td>16</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Ecosystem name</td>
<td>Country</td>
<td>Health area</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------</td>
<td>-----------------------------------------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pombo-Juárez et al.</td>
<td>2017</td>
<td>Multi-layer innovation ecosystem</td>
<td>Austria</td>
<td>Government, companies, universities</td>
</tr>
<tr>
<td>Rucinski A. et al.</td>
<td>2013</td>
<td>Disruptive Innovative e-Health Ecosystem for Regenerative Medicine</td>
<td>Poland</td>
<td>Smart Specialization and Cohesion Policy</td>
</tr>
<tr>
<td>Chen S. C. et al.</td>
<td>2020</td>
<td>Connected health ecosystem</td>
<td>China</td>
<td>Digital health ecosystems</td>
</tr>
<tr>
<td>Iyawa G. E. et al.</td>
<td>2019</td>
<td>Namibian Digital Health Innovation Ecosystem framework</td>
<td>Namibia</td>
<td>Digital health ecosystems</td>
</tr>
<tr>
<td>Ejehien G. et al.</td>
<td>2016</td>
<td>Digital health ecosystems</td>
<td>United States</td>
<td>Digital ecosystems</td>
</tr>
<tr>
<td>Park A. et al.</td>
<td>2019</td>
<td>Personalised medicine ecosystem</td>
<td>Canada</td>
<td>Open innovation and Model the Moore</td>
</tr>
<tr>
<td>Silva P. J. et al.</td>
<td>2018</td>
<td>Omics innovation ecosystem</td>
<td>United States</td>
<td>Open Innovation</td>
</tr>
<tr>
<td>Tseng et al.</td>
<td>2018</td>
<td>Brigham and Women's Hospital Digital Health Innovation Group (DHIG)</td>
<td>United States</td>
<td>Quadruple-helix components</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Ecosystem name</th>
<th>Country</th>
<th>Health area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pombo-Juárez et al.</td>
<td>2017</td>
<td>Multi-layer innovation ecosystem</td>
<td>Austria</td>
<td>Government, companies, universities</td>
</tr>
<tr>
<td>Rucinski A. et al.</td>
<td>2013</td>
<td>Disruptive Innovative e-Health Ecosystem for Regenerative Medicine</td>
<td>Poland</td>
<td>Smart Specialization and Cohesion Policy</td>
</tr>
<tr>
<td>Chen S. C. et al.</td>
<td>2020</td>
<td>Connected health ecosystem</td>
<td>China</td>
<td>Digital health ecosystems</td>
</tr>
<tr>
<td>Iyawa G. E. et al.</td>
<td>2019</td>
<td>Namibian Digital Health Innovation Ecosystem framework</td>
<td>Namibia</td>
<td>Digital health ecosystems</td>
</tr>
<tr>
<td>Ejehien G. et al.</td>
<td>2016</td>
<td>Digital health ecosystems</td>
<td>United States</td>
<td>Digital ecosystems</td>
</tr>
<tr>
<td>Park A. et al.</td>
<td>2019</td>
<td>Personalised medicine ecosystem</td>
<td>Canada</td>
<td>Open innovation and Model the Moore</td>
</tr>
<tr>
<td>Silva P. J. et al.</td>
<td>2018</td>
<td>Omics innovation ecosystem</td>
<td>United States</td>
<td>Open Innovation</td>
</tr>
<tr>
<td>Tseng et al.</td>
<td>2018</td>
<td>Brigham and Women's Hospital Digital Health Innovation Group (DHIG)</td>
<td>United States</td>
<td>Quadruple-helix components</td>
</tr>
</tbody>
</table>
processes, all centered on protocols, guidelines or care models, confidentiality or privacy in the handled information, staff training and education, culture management, and in some cases, investors are included in the ecosystem. All always have healthcare at the center or as a relevant topic.

The innovation ecosystems' functioning, processes, and tools vary according to the model used and the actors involved, as shown in Table 1. The cooperation of the actors is essential for articulating and generating the expected results for the developed ecosystem. Synergy is presented to achieve joint actions of the ecosystem elements and to give better results. Cooperation among several actors allows for more significant overall effects than the sum of the benefits each would achieve individually. This is why an innovation ecosystem determines the evolving set of actors, activities, artifacts, and institutions, including complementary and substitutive relationships, which are essential for the innovative performance of an actor or a population of actors. It is where these structures' different actors' connections must be recognized.

A network diagram was used to identify which innovation models were most relevant in this systematic review and which actors were most connected (Figure 3).

When analyzing the trends or critical nodes in the health innovation ecosystems and the actors that are part of them (Figure 2), the first most relevant trend or node is that of hospitals/clinics, which are considered as the “enterprise” and cover different levels of care, and for the present review, are of a medium or high level of complexity. This trend or node is related to 13 theories presented in this work and the different actors (state, academia, and community).

In second place is the tendency or node of patients who are part of the community and are people who have different pathologies or are related to their country's health system in different ways. This node has 11 connections with the theories, and the theory of the triple helix systems presents the most significant relationship.

Regarding the nodes with the highest relevance according to the quadruple helix theory, in the community helix, the patients’ node has a relevance of 0.917/1; in the state helix, the government node has a relevance of 0.739/1; in the company helix, the pharmaceuticals node has a relevance of 0.661/1, and in the academy helix the researchers' node has a relevance of 0.470/1.

The node of the actors had the highest intermediation with hospitals/clinics with a value of 367.17, indicating that this is a cut-off vertex for many geodesics between actors. Likewise, the node of models with the highest intermediation was the

Figure 3. Graph of relationship nodes of the actors in the framework of innovation ecosystems.
triple helix system with a value of 279.14, showing that this node had the highest frequency among the geodesics or the shortest paths of other actors.

Nodes with the highest relevance or importance were hospitals/clinics, with a value of 1/1, patients with a value of 0.917/1, and the triple helix system with a value of 0.851/1. In fourth place was the government node with 0.739/1, and in fifth was the digital health community network with a value of 0.729/1. These nodes were the most involved in many ties, being the most popular.

The most relevant model was the triple helix system with 0.851 out of 1, with 11 relationships and intermediation of 279.14. On the other hand, the least relevant model was the so-called learning healthcare system with 0.163/1 with three relationships and intermediation of 27.49.

Discussion
The analyzed health innovation ecosystems recognized the complexity and importance of the interactions of the different actors in the innovation process. They had very accentuated factors in health, facilitated the understanding of the dynamics of health in the city where they were installed, some supported the formulation of public policies, and facilitated the identification of regulatory failures. Also, they recognize the role of users/patients/citizens, companies, organizations, and government as essential factors for creating social value.

The models had components consisting of university, industry, and government spheres. Each with a range of actors, such as individual and institutional; innovators in R&D and between institutions hybrids. Relationships between components technology, transfer, collaboration, conflict moderation, collaborative leadership, substitution, and networking. Performance systems generate diffusion and utilization of knowledge and innovation in business, social, cultural, and political environments seeking consensus.

Starting from the notion of Walrave et al. on an innovation ecosystem and throughout this review, it can be understood that the actors identified in said ecosystems are diverse but have a common goal, to enhance an aspect of health in which the region or country wishes to advance due to its impact. Health areas with this development range from pediatrics, urology, and surgery, among others. Ultimately, these ecosystems integrate actors, processes, tools, and resources, generating an impact on patients. All ecosystems aim to improve citizens’ quality of life and medical care.

The most used model in these ecosystems is the quadruple helix, based on the approach of Etzkowitz and Leydesdorff. These authors conceptualize innovation ecosystems as “inclusive because the university leads the generation and transfer of knowledge to society through reciprocal and continuous relationships with industry”. This model increases the probability of innovation regardless of the type (product, process, services, or a combination of these). Furthermore, the greater the number of agents that cooperate in the model, the greater the chances of business innovation, confirming a synergistic effect between agents.

In particular, the quadruple helix model was identified in the review as one of the most frequent in the included publications. This model focuses on taking advantage of the learning processes and dynamics that allow the hierarchical policies of the university, industry, government, and society's priorities to interact with each other. In this way, and taking into account the current dynamics of societies and, in line with including inclusive models, their increased frequency can be explained.

The growing potential to benefit from innovations highlights a significant problem faced by health systems: how to take advantage of the knowledge developed in these solutions that generally face many resource challenges in reaching patients. Access to health services through hub-and-spoke service delivery models that as drivers of diffusion have complementarity with the existing medical infrastructure of institutions and reduce barriers to solution-mediated access with solutions such as the implementation of telehealth and other approaches.

The impact of innovation processes has been widely explored in the public health literature, and there is a consensus among the innovation ecosystem actors and public health policymakers that adopting innovation in its different types promotes an increase in the population's health status.

However, the frameworks, models, and tools used by the different innovation ecosystems in the world and identified in this review correspond only to those that have been the subject of academic analysis and are published in scientific journals. Thus, gray literature may have left out other ecosystems presented to the community in general. Therefore, the results of this review should be considered in this sense.
Future studies suggest evaluating ecosystems in terms of integrity, efficiency, effectiveness and robustness, fragility, and evaluation of medium and long-term impacts and from other perspectives.

Conclusions
Innovation ecosystems are today considered the most prominent driver to be built and nurtured to reap innovation’s benefits. This reflects a paradigm shift, whereby innovation is becoming a centerpiece of a socioeconomic development model for cities and regions.

This paper provided the results of a systematic literature review to identify the variety of health innovation ecosystems in developed and developing countries. Also, the present work identified models, methodologies, and tools in these structures. Different themes emerged from the selected literature on health innovation, clinical application areas, and institutions involved.

Quaduple helix and open innovation, the theoretical models most frequently used, both include society as part of their implementation.

Data availability
Underlying data
Havard Dataverse: Underlying data for “Innovation ecosystems in health: countries and theoretical models used”, https://doi.org/10.7910/DVN/NKFCKF.39

Reporting guidelines
OSF: PRISMA reporting guidelines for “Innovation ecosystems in health: countries and theoretical models used”, https://doi.org/10.17605/OSF.IO/M8H2Z.

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Acknowledgements
This article was supported by CES University through the Graduate School. This research is considered risk-free, according to the ethical parameters established by Resolution 008430 of 1993 of the Colombian Ministry of Health and the Declaration of Helsinki.

References


The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com