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1 **Instruments for investigation of epilepsy in low- and middle-income**
2 **countries: a systematic review**

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11

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14

15 **Abbreviations:**

16 GAD: Generalized Anxiety Disorder

17 IENT: Institute of Epidemiology and Tropical Neurology

18 LAEP: Liverpool Adverse Events Profile

19 LMICs: Low- and Middle-Income Countries

20 NDDI-E: Neurological Disorders Depression Inventory for Epilepsy

21 PATE: Public Attitudes Toward Epilepsy

22 QOLIE: Quality Of Life Inventory for Epilepsy

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32 **Objective:** Systematic reviews were conducted on the existence of screening tools for
33 epilepsy, quality of life or comorbidities tools, but not specifically in low- and middle-income
34 countries. This study aimed to identify the different tools developed and validated in low-
35 and middle-income countries for the investigation of epilepsy. This to facilitate research in
36 these regions and to identify needs in areas where few instruments are available.

37 **Methods:** This review was conducted according to the PRISMA (Preferred Reporting Items
38 for Systematic Reviews and Meta-Analyses) guidelines. PubMed, Embase, MedLine, Google
39 Scholar, Web of Science, SciELO, Neurology Asia, African Journal of Neurological Sciences
40 and Institute of Epidemiology and Tropical Neurology bibliographic databases were
41 investigated. Articles were included according to the following criteria: (1) to be validation
42 studies on tool for investigating epilepsy, (2) to be conducted in a low- or middle-income
43 country, (3) to be published between 1980 and 2021, and (4) to be written in English,
44 French, Spanish or Portuguese. The characteristics of the tools were collected and the
45 validation methods used. The frequency of use of the tools was estimated.

46 **Results:** Ninety-three articles were retained, corresponding to 91 tools from 44 countries.
47 The main tools targeted quality of life (n=30), comorbidities (n=19) and screening (n=13).
48 Instruments were mainly developed and validated in Asia (n= 43), then in Central and South
49 America (n= 24). The IENT (Institute of Epidemiology and Tropical Neurology) questionnaire
50 was developed in several tropical countries (Africa, South East Asia and Latin America). The
51 development and validation methods were heterogeneous from one tool to another and
52 some tools (e.g., QOLIE-31, NDDI-E, PATE, etc.) were culturally adapted.

53 **Conclusion:** This review identifies geographic specificity regarding the creation, validation
54 and use of tools for investigating epilepsy available in low- and middle-income countries. It
55 will help investigators in the choice of tools in their future epidemiological studies on
56 epilepsy in this context.

57 **Keywords:** Epilepsy, Management, Low- and middle-income countries, Tools, Development,
58 Validation

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62 **1. Introduction**

63 Epilepsy is a chronic noncommunicable disease affecting about 50 million people over
64 the world (Ngugi et al., 2010). According to the Global Burden of Diseases study, epilepsy
65 was considered the second leading neurological cause of years living with disabilities, which
66 is still an important cause of morbidity and mortality despite a decrease in the disease
67 burden from 1990 to 2016 (GBD 2016 Epilepsy Collaborators, 2019). Nearly 80% of people
68 live with epilepsy in low- and middle- income countries (LMICs), where the prevalence and
69 incidence are higher compared to high-income countries (Fiest et al., 2017). In LMICs,
70 around 75% of people with epilepsy does not have adequate treatment (Meyer et al., 2010).
71 Epilepsy and comorbidities are often associated, explaining the complexity of the disease
72 and the need to set-up a multidisciplinary management (Keezer et al., 2016). They generate
73 a huge burden not only on patients, but also on their family (Tedrus et al., 2018). The
74 management of epilepsy can be complex and include prevention wherever possible, a
75 correct diagnosis, initiation of an appropriate treatment for epilepsy and comorbidities, and
76 a careful follow-up to suppress seizures and improve quality of life (Epilepsy: A Public Health
77 Imperative. 2019).

78 Limited access to antiepileptic drugs and an absence of specialists in rural areas can
79 promote difficulties in access to health care (WHO Atlas. 2017). Expand access to primary
80 care was mentioned to improve epilepsy care. For this, primary care providers and non-
81 medically trained providers play an important role in the management of epilepsy in LMICs.
82 In this particular context, guidelines are necessary to apply a standard methodology, which
83 involves adequate instruments. The ideal tool would require to be brief, cheap, inexpensive
84 and easy to use in rural settings. Equally, validity, reliability and cultural adaptation are
85 important aspects concerning the quality of an instrument (Boateng et al., 2018; Guillemin
86 et al., 1993). Although some previous studies have already summarized tools that can be
87 used on different aspects of epilepsy as screening (Keezer et al., 2014), and anxiety or
88 depression related to epilepsy (Gill et al., 2017; Leone et al., 2005; Wang et al., 2019); this
89 study identifies all the epilepsy-related tools developed and validated in LMICs.

90 This study identifies instruments developed and validated in LMICs for investigating
91 epilepsy.

92

93 **2. Methods**

94 A systematic review in two steps was performed using the Preferred Reporting Items for
95 Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

96 **2.1. STEP I: Validation studies of tools**

97 **2.1.1. Identification of studies**

98 Studies were identified through indexed (PubMed, Embase, MedLine, Google Scholar and
99 Web Of Science), and non-indexed databases (African Journal of Neurological Sciences,
100 Scielo, Neurology Asia and Institute of Epidemiology and Tropical Neurology database's)
101 (Bramer et al., 2017). Bibliographic search was conducted in June 2021. Search strategies
102 included keywords or MeSH terms related to: epilepsy, low- or middle-income countries,
103 epidemiology, tools and validity (*Appendix A*). Manual search was also performed on the
104 basis of the reference lists of all studies included in this review.

105 **2.1.2. Selection of studies**

106 Articles were included according to the following criteria: (1) validation studies of a tool for
107 investigating epilepsy, (2) validation in a low- or middle-income country, (3) studies
108 published between 1980 and 2021, and (4) studies in English, French, Spanish or Portuguese.
109 In contrast, we excluded: (1) reviews, editorials, abstracts, case reports, (2) validation studies
110 of tools not on epilepsy (ex: neurological diseases or neurodevelopmental disorders), and (3)
111 unpublished studies. Two reviewers independently assessed titles, abstracts and full texts
112 (EA and MV). Disagreements on the eligibility of studies were resolved by consensus (FB).
113 The selection process was done using Rayyan[®] software (Qatar Computing Research
114 University) (Ouzzani et al., 2016).

115 **2.1.3. Data extraction**

116 Data were collected using a pre-established standardized form (MV) and peer-reviewed
117 (PMP). For each study, following information were extracted: publish year, country, study
118 site, population target, topic of the tool, language and details on the steps of the validation
119 process (translation, back-translation, pre-testing, validity type, reliability type, gold

120 standard, etc.) based on the best practice model proposed by Boateng et al., (Boateng et al.,
121 2018). This model aims to advice on the different steps to follow to develop and validate
122 scales in health, social and behavior research. This model is composed of nine steps:
123 “Identification of domain and item generation”, “Content validity”, “Pre-testing”, “Sampling
124 and survey administration”, “Item reduction”, “Extraction of factors”, “Tests of
125 dimensionality”, “Tests of reliability” and “Tests of validity”. Data were collected and
126 preserved in Access® and references were managed using Zotero®.

127 **2.2. STEP II: Frequency of use of developed and validated tools**

128 **2.2.1. Identification and selection of studies**

129 The frequency of use of the tools was investigated through a citation search in Web Of
130 Science and Google scholar. Articles were selected according to the following steps: reading
131 of title, abstract and full-text. Articles mentioning the use of a tool were retained. Articles
132 reported on the same population, the same period and the same study location were
133 considered one study.

134 **2.2.2. Data extraction, synthesis and analysis**

135 For each study, the publication year and number of uses were collected. Additionally, sites of
136 use were collected concerning the screening tools. The usage ratio was calculated as the
137 number of uses over the number of years since the publication of the tool.

138 **2.3. Statistical analysis**

139 In cases where more than one article refers to the same tool (e.g. different validation steps
140 or sub-scales), all publications were included and grouped in a single tool validation’s study.
141 Low-, lower middle- and upper middle-income countries were categorized according to the
142 World Bank 2019 fiscal year classification. For descriptive statistics, qualitative variables
143 were expressed as numbers and percentages. Analysis was performed using STATA® version
144 11 (StataCorp, College Station, Texas) and the cartography with QGIS® software version
145 2.6.1.

146

147 **3. Results**

148 **3.1. Instruments developed and validated in LMICs to investigate epilepsy**

149 The study selection process is detailed in *Figure 1*. After gathering papers from
150 indexed, non-indexed and manual research, 1722 articles were obtained. After screening the
151 titles and abstracts, 103 were included. However, after attention to details in the full-texts,
152 10 of them were excluded. Finally, we included 93 articles corresponding to 91 tools
153 validation studies (*Appendix B*).

154 **3.1.1. Geographical areas and development periods**

155 Instruments were mainly developed and validated in Asia (n= 43), then in Central and
156 South America (n= 24) (*Figure 2*). Only three tools were created in low-income countries
157 (Tanzania, Rwanda and Uganda), 19 in lower middle-income countries and 69 in upper
158 middle-income countries, including in China (n= 19) and in Brazil (n= 14), with a high number
159 and diversity. The IENT questionnaire has been developed by experts from different
160 countries over the world, including African where few instruments have been developed and
161 validated.

162 The period of development and validation of tools in LMICs for investigating epilepsy
163 started around 2005 (*Figure 3*). It began with a trend toward the creation of Quality of Life
164 tools for about ten years following by the development of psychiatric comorbidities
165 tools. More recently, some diagnostic and self-management instruments were developed
166 and validated. Some tools were developed more than 20 years ago, such as the first
167 Ecuadorian screening tool and the standardized IENT questionnaire.

168 **3.1.2. Themes of the tools**

169 The tools have been developed to investigate different aspects related to epilepsy
170 (*Figure 3, Appendix A*). Thirteen screening tools were developed and validated, regarding
171 comorbidities' (n= 19) and quality of life's scales (n= 30). Some tools have been found in
172 several versions due to different cultural adaptations (e.g. QOLIE-10: Turkish and Chinese
173 versions; NDDI-E: Brazilian, Chinese, Serbian, Argentinian versions). Few instruments based
174 on diagnosis, self-management or seizure severity have been created. Among all these
175 instruments, the IENT questionnaire was the only data collection tool developed to promote
176 a standardized data collection during the investigation of epilepsy in tropical countries.

177 **3.1.3. Tool development and validation process**

178 The validation processes have been heterogeneous (*Appendix C*). They differed for an
179 instrument from one version to another. Only 58.2% (53/91) of tools were pre-tested during
180 their development. Reliability was the psychometric properties the most evaluated (72.5%:
181 66/91), more especially internal consistency (92.4%: 61/66), following test-retest (40.9%:
182 27/66). Regarding the development of scales (n=76), 42.1% of studies have used factorial
183 analysis. Construct validity alone was used in 47.3% of studies, criterion validity alone in
184 1.3% and 6.6% of studies have mixed construct and criterion validities. Diagnostic type
185 validation (sensitivity, specificity and predictive values) was mainly employed for
186 comorbidities (89.5%: 17/19) and screening tools (100%: 15/15).

187 Among the 91 tools, only 10 were developed and validated in rural areas. Three
188 instruments were validated in both rural and urban areas. Only 11% of the tools were
189 developed and validated in population-based. These were Knowledge, Attitudes and
190 Practices (n=6), medication (n=1) and screening (n=3) instruments. Most screening tools
191 were developed in hospital-based or using an affected-case versus unaffected-control design
192 (11/15).

193 **3.2. Frequency of use of these instruments developed and validated in LMICs to**
194 **investigate epilepsy**

195 Among the 91 tools identified in the first step, 50 have been used since their creation
196 (*Appendix D*). A greater number of quality of life scales were used (n=13). However, the
197 usage ratio (number of use / years of existence) remains low with a maximum of 0.2 for the
198 Brazilian QOLIE-31. Among the 7 comorbidity tools, the most used were the Chinese versions
199 of the GAD-7 and NDDI-E, with a usage ratio of 0.7 and 0.8 respectively. Concerning the
200 stigma, the Stigma Scale Epilepsy was the most used (Brazilian, Kenyan or Turkish versions).
201 The Public Attitudes Toward Epilepsy scale (n=4) was the main tool applied to assess
202 knowledge and attitudes in the general population. The data collection support has been
203 used regularly since its creation in 2000, including a usage ratio of 1.3 (27/21).

204 Among the 13 epilepsy screening tools identified in the first step, 8 of them have been used
205 (*Figure 4, Appendix D and E*). The Ecuadorian screening tool developed by Placencia, had the
206 highest usage ratio at 1.4 (41/29), and has been used on all three sub-continent of the

207 tropical area. The screening tool validated by Diagana et al. shows consistent use with a
208 usage-ratio of 1 (15/15) and it was used mainly in sub-Saharan African countries. The third
209 screening tool used in Africa was the one developed by Ngugi et al. for epilepsy associated
210 with convulsive seizures. Four screening tools have been developed and validated in India,
211 but are less used with usage ratios between 0.1 and 0.3.

212

213 **4. Discussion**

214 This systematic review has shown that many tools have been developed and
215 validated in LMICs for investigating epilepsy. These tools are intended to assess or measure
216 different concepts related to epilepsy, such as quality of life, the presence of comorbidities,
217 knowledge, attitudes and practices, etc. The development and validation processes have
218 been heterogeneous and few tools have been developed on the African continent. In fact, 14
219 tools have been developed in Africa. This can be explained by the regular use of sufficient
220 tools already developed. The IENT questionnaire developed in various African countries, has
221 been regularly used since its creation (usage-ratio=1.3). Also, the screening part validated in
222 Mauritania by Diagana et al. is used mainly on the African continent. The use of the same
223 tool allows for maintaining a standard approach for data collection, identification of people
224 with epilepsy, measure of concept, etc. The few numbers of tools developed on this
225 continent could also be explained by the availability of tools in French or English versions,
226 already designed in high-income countries (Cramer et al., 1998; Picot et al., 2004). Indeed,
227 several tools developed in LMICs have already been created in some high-income countries
228 (e.g. Spanish QOLIE-10, U.S. English QOLIE-31, French NDDI-E, Italian LAEP, Danish PATE)
229 (Cramer et al., 1998; Jensen & Dam, 1992; Micoulaud-Franchi et al., 2015; Romoli et al.,
230 2018; Viteri et al., 2008). However, cultural adaptation of a tool is an important step in
231 making it applicable to a population according to its cultural context (Guillemin et al., 1993).
232 After their development and validation process, some tools had low usage ratios. This could
233 be explained by tools that were not valued after their development. Equally, the use of the
234 tools without valorization of the results by a scientific article may also underestimate the
235 number of uses that were sought by citation method.

236 Over the last twenty years, the development of different topics of tools shows that
237 medical care workers are increasingly moving toward a global management of patients with
238 epilepsy. Epilepsy is a complex disease whose quality of life does not only depend on seizure
239 control, but also on the presence of comorbidities, side effects of medication or stigma
240 (Micoulaud-Franchi` et al., 2017; Mroueh et al., 2020). In recent years, self-management
241 tools are being developed with the vision to involve the patient in the management of the
242 disease (Pandey et al., 2019).

243 Some countries have developed many tools, as Brazil (n=14) and China (n=19). This
244 allows to provide various culturally adapted tools on different topics, targeting different
245 populations such as children and/or adolescents and/or adults (e.g. QOLIE31 and QOLIE-AD-
246 48), suitable for a study location. Despite multiple tools to measure the same concept may
247 limit the reproducibility and comparability between studies, they have been developed
248 according to criteria on which researchers base their choice of survey instruments.
249 Additionally, Brazil and China are two upper-middle income countries, which may explain
250 the large number of tools, as development and validation is a costly and time-consuming
251 process (Boateng et al., 2018). They can be LMICs with research priorities and high research
252 investments (Kwan et al., 2015; Morán-Mariños et al., 2020; The World Bank. 2021).

253 Recommendations have been created to assist in the development and validation of
254 tools (Boateng et al., 2018), as well as for cultural adaptation, which remains an important
255 step and does not only consist of a translation but a global re-validation (Guillemin et al,
256 1993; Beaton et al, 2000). Overall, the development and validation processes are
257 heterogeneous. However, the steps of translation, back-translation and reliability
258 assessment were found for most tools. For future validations, it would be interesting to be
259 informed about the methods used during validations of the tool in other versions (e.g., Thai,
260 Brazilian, Serbian, Indian, Bulgarian versions of QOLIE-31) and try to base on them to be as
261 reproducible as possible (e.g., pretest, number of subjects needed, study population, types
262 of validations, gold standard, etc.). Also, many of these validations have been done in
263 hospital-based, except for some screening tools and general population attitude scales. The
264 affected-case versus unaffected-control design was mostly used. However, patients in the
265 hospital often have more severe forms and are more likely to be positive to the test, which
266 may overestimate the sensitivity (Giuliano et al., 2019; Mulherin & Miller, 2002). Field

267 validation is more complex, costly and time consuming. It requires a screening of a large
268 sample of the population including in rural areas, where specialists are rare and yet
269 necessary to confirm the diagnosis in a second step (Giuliano et al., 2017; Ngugi et al., 2012;
270 Placencia et al., 1992). Therefore, for screening tools, field validation provides more accurate
271 psychometric values and allows a better estimation of the prevalence of the disease during
272 prevalence studies in the general population (Giuliano et al., 2019). After the development
273 and validation stages, it would be interesting to train primary care professionals to use these
274 tools. The objective is to promote better access to care to improve the management of
275 people with epilepsy at the primary care level (Konipo et al., 2021; Sham et al., 2020).

276 This study has some limitations. Some tools may not have been included in the
277 review due to indexing problems or no clear mention of tool development and/or validation
278 in the title or abstract during the selection process. The grey literature was excluded in the
279 estimation of use, which may have underestimated the frequency of use. Most screening
280 tools were developed in hospital-based or using an affected-case versus unaffected-control
281 design, that limits the availability of tools applicable to the general population. Quality
282 assessment of the validation studies was not performed due to the different tool themes
283 and the small number of validation study evaluation scales. However, the design process for
284 each tool was compared to a best practice model for tool development and validation
285 (Boateng et al., 2018). For the search strategy, international and local bibliographic
286 databases were investigated. At least Embase, MedLine, Web of Science, and Google Scholar
287 were explored which corresponds to the best combination to scan the most articles
288 according to Bramer et al. (Bramer et al., 2017).

289

290 **5. Conclusion**

291 This study provides an overview to researchers of the tools available in LMICs for
292 investigating epilepsy. It also shows the importance to properly perform the development or
293 cultural adaptation steps, as well as the validation to ensure the quality of the tools. It is also
294 important to value them afterward so that they can be known, available and used.

295

296 **Declaration of conflict of interest**

297 The authors declare that there is no conflict of interest. We confirm that we have read the
298 Journal's position on issues involved in ethical publication and affirm that this report is
299 consistent with those guidelines.

300

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304

305 **Registration**

306 This review has not been registered on PROSPERO.

307

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440 **CAPTIONS**

441 Figure 1: Flowchart of articles

442 Figure 2: Topics of tools developed and validated in low- and middle-income countries for
443 investigation of epilepsy (n=91)

444 Figure 3: Chronology of the development and validation of the tools (n=91)

445 Figure 4: Use of screening tools identified for the investigation of epilepsy in low- and
446 middle-income countries

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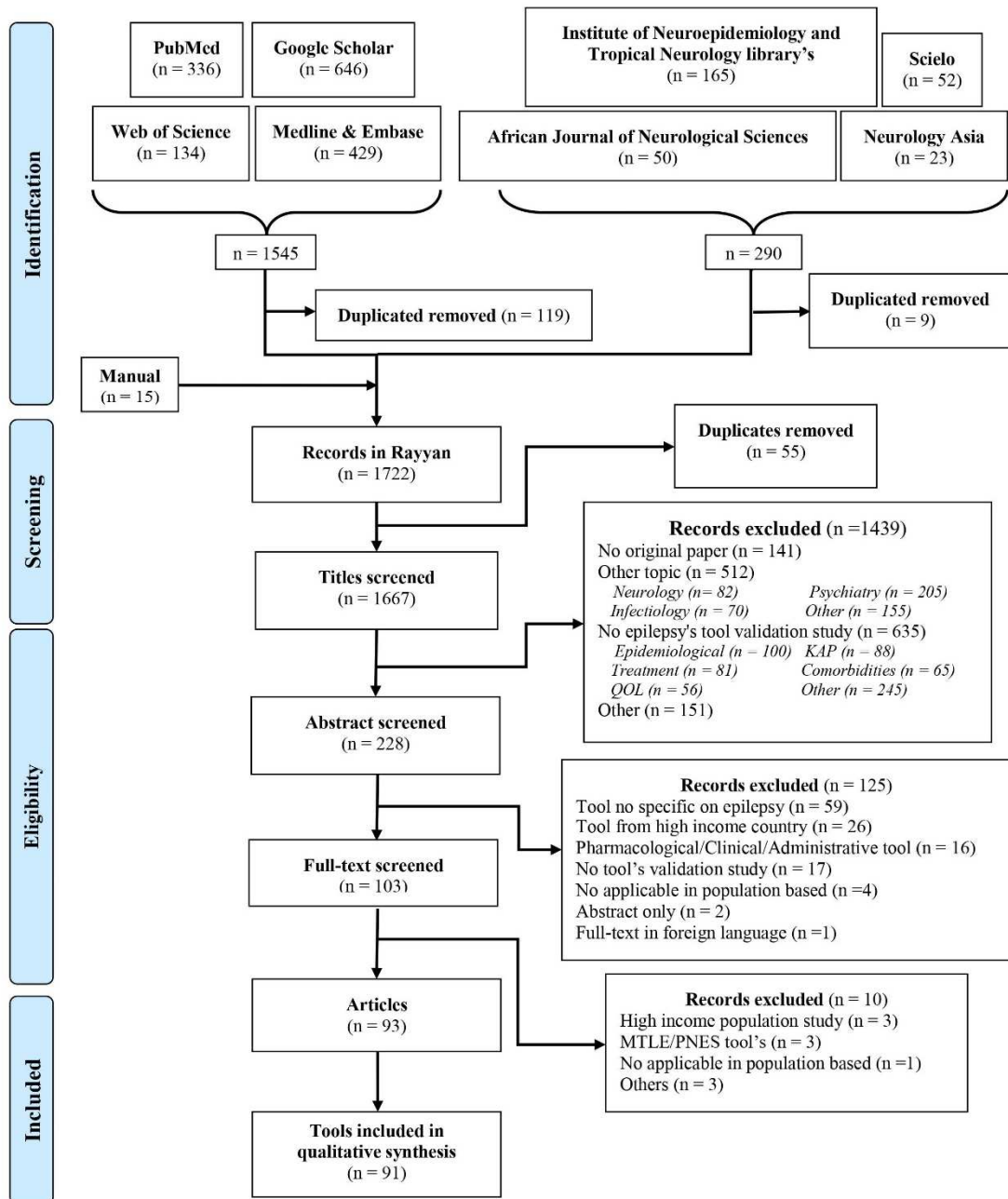
448 Appendix A: Methodology: search strategies

449 Appendix B: Description of tools included

450 Appendix C: Description of development and validation processes used for tools included

451 Appendix D: Usage ratio of the tools used after their development

452 Appendix E: Use of screening questionnaires after development and validation (n=8)



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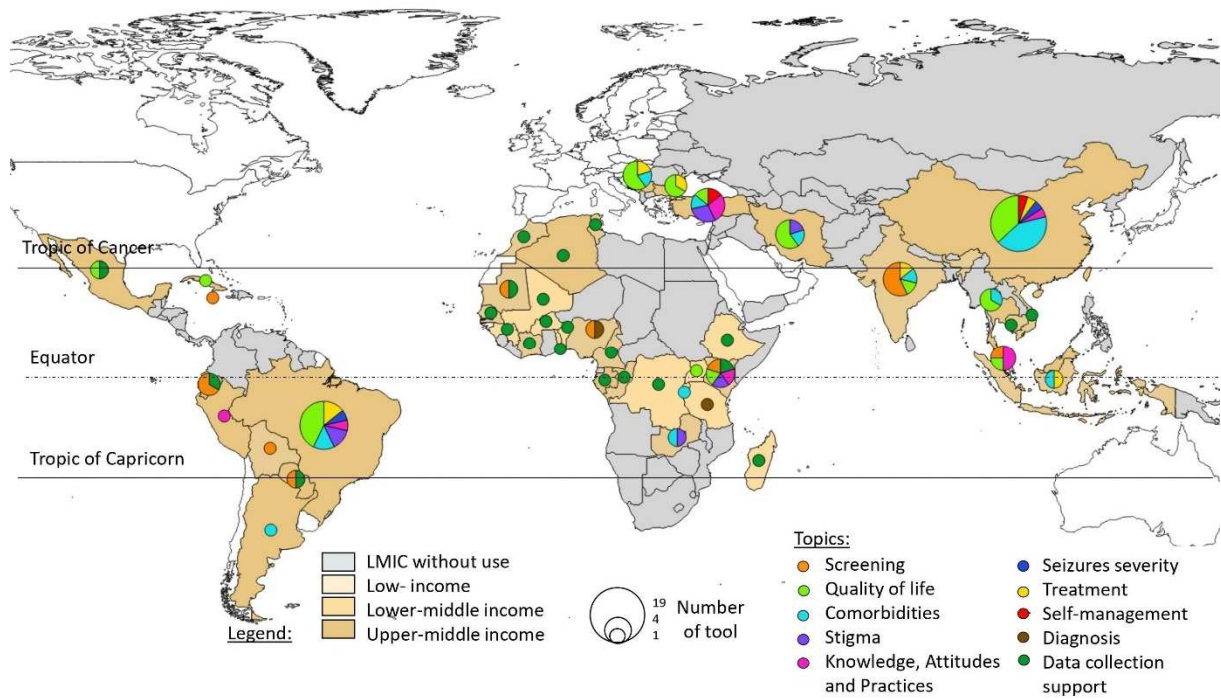
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 462 investigation of epilepsy (n=91)

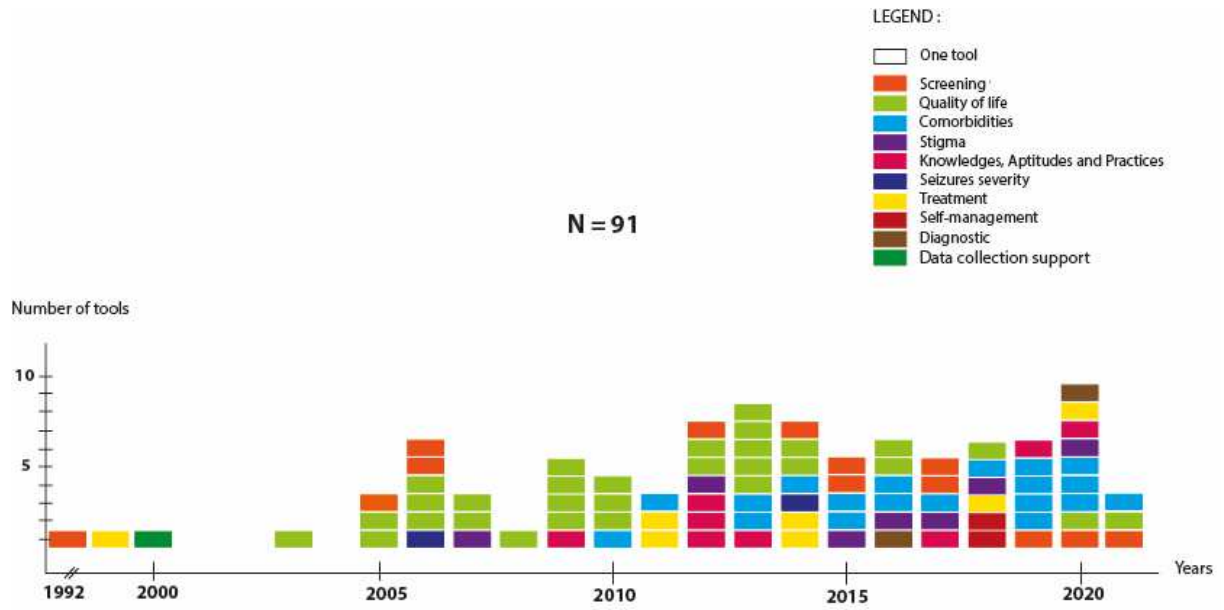
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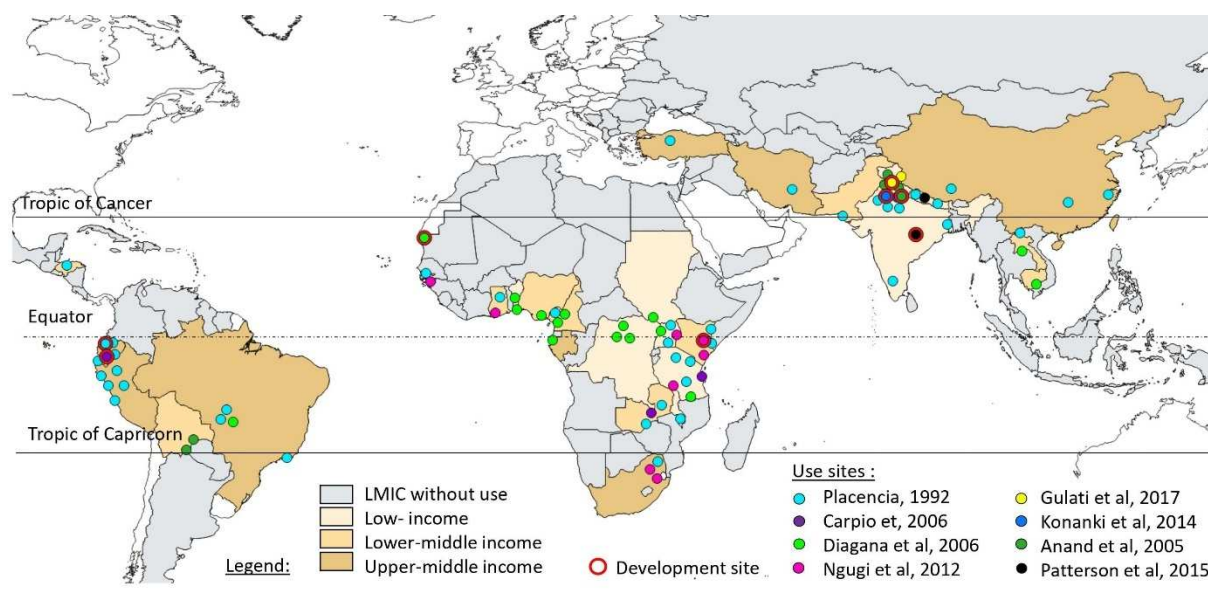
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479 Figure 4: Use of screening tools identified for the investigation of epilepsy in low- and
 480 middle-income countries