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A Computerized Decision Support System (CDSS) for Antibiotic Prescription in Primary Care: Implementation, Adoption and Sustainable Use in the Era of Extended Antimicrobial Resistance

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► To cite this version:

Tristan Delory, Pauline Jeanmougin, Sylvie Lariven, Jean-Pierre Aubert, Nathan Peiffer-Smadja, et al.. A Computerized Decision Support System (CDSS) for Antibiotic Prescription in Primary Care: Implementation, Adoption and Sustainable Use in the Era of Extended Antimicrobial Resistance. *Journal of Antimicrobial Chemotherapy*, 2020, pp.dkaa167. 10.1093/jac/dkaa167 . hal-03888699

HAL Id: hal-03888699

<https://hal.sorbonne-universite.fr/hal-03888699>

Submitted on 30 Jan 2023

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1 **Title (200 characters): 197 / 200**

2 **A computerized decision support system (CDSS) for antibiotic prescribing in primary care - *Antibioclie*:**
3 **implementation, adoption and sustainable use in the era of extended antimicrobial resistance.**

4 **Short title (70 characters): 64 / 70**

5 *Antibioclie* - a CDSS for antibiotic prescribing in primary care.

6 **Word count: 3382/3500** excluding Figures, Tables and their legends

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28 **Synopsis – 308 / 250 words**

29 **Background**

30 To describe the implementation and use of a CDSS for antibiotic prescribing in primary care in France(*Antibiocllic*).

31 The CDSS targets 37 infectious diseases and is freely available on a website since 2011.

32 **Methods**

33 Description and implementation of the architecture of a CDSS for antibiotic prescription in general practice.

34 Analysis of the queries performed between 2012 and 2018 on the CDSS by GPs. Analysis of 2 cross-sectional
35 studies performed in users in 2014 and 2019.

36 **Results**

37 The number of queries increased from a median of 796/day [IQR,578–989] in 2012 to 11,125/day [5,592–12,505]
38 in 2018. Unique users increased from 414/day [245–494] in 2012 to 5,365/day [2,891–5,769] in 2018. Time to
39 perform a query was 2 minutes [1·9–2·1]. Among 3,542,347 queries in 2018, 78% were for adults. Six situations
40 accounted for $\geq 50\%$ of queries: cystitis; acute otitis media; acute sinusitis; community-acquired pneumoniae, sore
41 throat and pyelonephritis. Queries concerned pathologies for which antibiotic prescription was systematic (63·7%),
42 was conditional on additional clinical steps (34·5%), or was not recommended (1·8%). Most users (81%) were
43 GPs, with median age 38-years [31–52] and 58% female. Among GP users, a large majority (96%) reported using
44 the CDSS during the consultation, with 24% systematically using *Antibiocllic* to initiate an antibiotic course and
45 93% having followed the CDSS recommendation for the latest prescription. Most GPs were comfortable using the
46 the CDSS in front of a patient.

47 **Conclusions**

48 *Antibiocllic* has been adopted and is widely used in primary care in France. Its interoperability could allow an
49 adaptation and implementation in other countries.

50 INTRODUCTION

51 Worldwide, inappropriate use of antibiotics has led to an increase in Antimicrobial Resistance (AMR).^{1,2} From
52 2007 to 2015, the burden of AMR has more than doubled in Europe and became equivalent to the cumulative
53 burden of influenza, tuberculosis and HIV.² Despite having implemented AMR national action plans (NAPs) since
54 2001, antibiotic prescription is still very high in France compared to most of high-income countries.^{1,3} As in other
55 European countries, approximately ninety percent of the antibiotic prescription are written in primary care, and
56 71% of all prescriptions by general practitioners (GPs).^{4,5} Other primary care physicians (dentists, paediatricians,
57 dermatologists, ...) account for a 19% of all prescriptions and the rest is written in the hospital.⁴ In 2016, it was
58 estimated that a French GP was initiating an antibiotic course every 6 consultations, corresponding to a 16.7%
59 antibiotic prescribing rate per consultation and 29.9 defined daily dose (DDD) per 1,000 habitants per day.⁶

60 One of the ways to prevent the spread of AMR is to reduce the overall volume and improve the appropriateness of
61 prescribed antibiotics.^{5,7,8} In 2018, the French Ministry of Health has set an objective of 25% reduction of overall
62 antibiotic consumption by 2022.⁷ Since 2011, French primary care GPs have been eligible to a voluntary-based
63 pay for performance (P4P) scheme to decrease their antibiotic consumption. The P4P objectives are: 1) to initiate
64 less than 20 antibiotic therapy for 100 patients between 16 and 65-years, and 2) to reach less than 32% use of
65 broad-spectrum antibiotics for initiated antibiotic therapy – *i.e.* amoxicillin-clavulanic acid, 3rd generation
66 cephalosporins, or fluoroquinolones. Similar interventions have been conducted in Europe, such as the National
67 Health System (NHS) Quality Premium (QP) in England in 2015/2016. A recent evaluation of the NHS Quality
68 Premium through an interrupted time series analysis shown a 3% relative reduction of antibiotic prescribing for
69 respiratory tract infections (RTI) after its implementation.⁹

70 The efficacy of information campaigns on antibiotic consumption reduction is mitigated in Europe.¹⁰ Multifaceted
71 approaches have been associated with decreased antibiotic prescribing, especially in RTI.^{10,11} Involvement of
72 patients through shared decision-making with clinicians for antibiotic prescription has also been shown effective
73 in the short-term, in RTI.¹² New technologies such as computerized decision support systems (CDSS) for
74 antimicrobial prescribing could be effective and induce prolonged impact on practices.¹¹ CDSS are linking clinical
75 observations to knowledge base, at the point-of-care, and might have the ability to support clinical decision-making
76 and improve antimicrobial prescription.¹³ This has been mainly demonstrated in hospital settings, where
77 implementation of antimicrobial stewardship programs (ASP) is high, as compared to primary care.^{8,13,14} Few
78 studies of heterogeneous design and quality have been conducted on CDSS in primary care.^{11,15,16} In a recent
79 review, out of 58 CDSS, 18 had been specifically developed for primary care.¹⁵ Of those, 11 were using syndromic

80 approach to assist the practitioner for pulmonary and/or urinary tract infections (UTI). None of the CDSS covered
81 all the infectious situations that are frequently encountered by GPs.^{5,17} The impact at prescriber level was not
82 consistently measured and none was tailored to demonstrate an effect on patients' hospitalization rate, or
83 mortality.¹⁵ Rawson *et al.* highlighted that when CDSS failed to demonstrate their primary outcome it was often
84 related to a low uptake and a poor adherence to generated advice. Qualitative studies have shown that ease of use
85 and integration into daily clinical practice workflow, with no impact on consultation time nor negative
86 consequence for patient relationship, were key factors in improving CDSS uptake.^{18,19} In addition, physicians have
87 to follow the recommendations issued by the CDSS in order to improve antibiotic prescribing. According to the
88 WHO, the main challenge in tackling AMR is the successful implementation of policies.⁵ Many innovations in
89 healthcare have been abandoned after their initial evaluation because of insufficient work on their implementation,
90 and adoption.²⁰ The non-adoption, abandonment, scale-up, spread and sustainability (NASS) framework for digital
91 technologies shows that the adoption of an innovation in healthcare is a dynamic process related to many factors
92 from the micro to the macro level.²⁰

93 In 2011, a French multidisciplinary team involving academic and non-academic GPs, infectious disease specialists
94 and engineers co-designed a guideline-based CDSS focusing on GPs' antibiotic prescribing in primary care –
95 *Antibiocliv*.²¹ The aim of *Antibiocliv* was to improve the quality of antimicrobial prescribing in primary care, but
96 to date, no high quality evaluation of its impact has been performed. Herein we describe the implementation,
97 adoption and sustainable use of *Antibiocliv* from 2012 to 2018, and provide future perspectives for development.

98 **METHODS**

99 **Description of the CDSS**

100 *Antibiocllic* – <http://www.antibiocllic.com> – is a French CDSS for antibiotic prescribing in primary care developed
101 and released in October 2011.²¹ Initial advertising was limited to an article in a French family medicine journal.²¹
102 Since then, advertising is performed in medicine faculties to GP residents. Several communications or posters
103 were also presented in French family medicine and infectious diseases congress (see acknowledgement section).
104 It was co-designed by the *Antibiocllic* steering committee, a team of academic and non-academic GPs, ID
105 specialists, and engineers (IT). *Antibiocllic* is a stand-alone web application and is not integrated into electronic
106 health records (EHR). Since 2017 a smartphone application has been available. *Antibiocllic* access and use is free
107 of charge, does not require registration and is granted to any healthcare professional or service user 24/24-7/7.

108 ***Task-Network Model of Antibiocllic decision tree***

109 A systematic method was used to transform the clinical practice guidelines (CPG) from the French National
110 Authority for Health (HAS) or the French Infectious Diseases Society (SPILF) into computer interpretable
111 guidelines (CIG). We used a semi-formal decision-tree, implementing a Task-Network Model (TNM) where
112 antibiotic prescription is described as a process with a set of predefined tasks and rules to obtain a decision.²² The
113 tasks of the TNM includes :

114 *Data entry: for describing a clinical case*

115 *Required criteria*

- 116
- 117 • Anatomical domain related to the pathology/infectious disease
 - 118 • Name of the pathology/infectious disease
 - 119 • Age group of the patient: adult versus children

119 *Optional criteria*

- 120
- 121 • Specific conditions that might impact choice of antibiotic therapy and drug-drug interactions:
122 pregnancy (if adult), breastfeeding (if adult), and chronic kidney failure.
 - 123 • Other specific condition related to the pathology/infectious disease, such as the CRB-65 score for
124 community acquired pneumoniae (CAP), or the result of Point-of-Care testing for group A
streptococci in sore throat.

125 *Outcome: Guidelines to assist the physician*

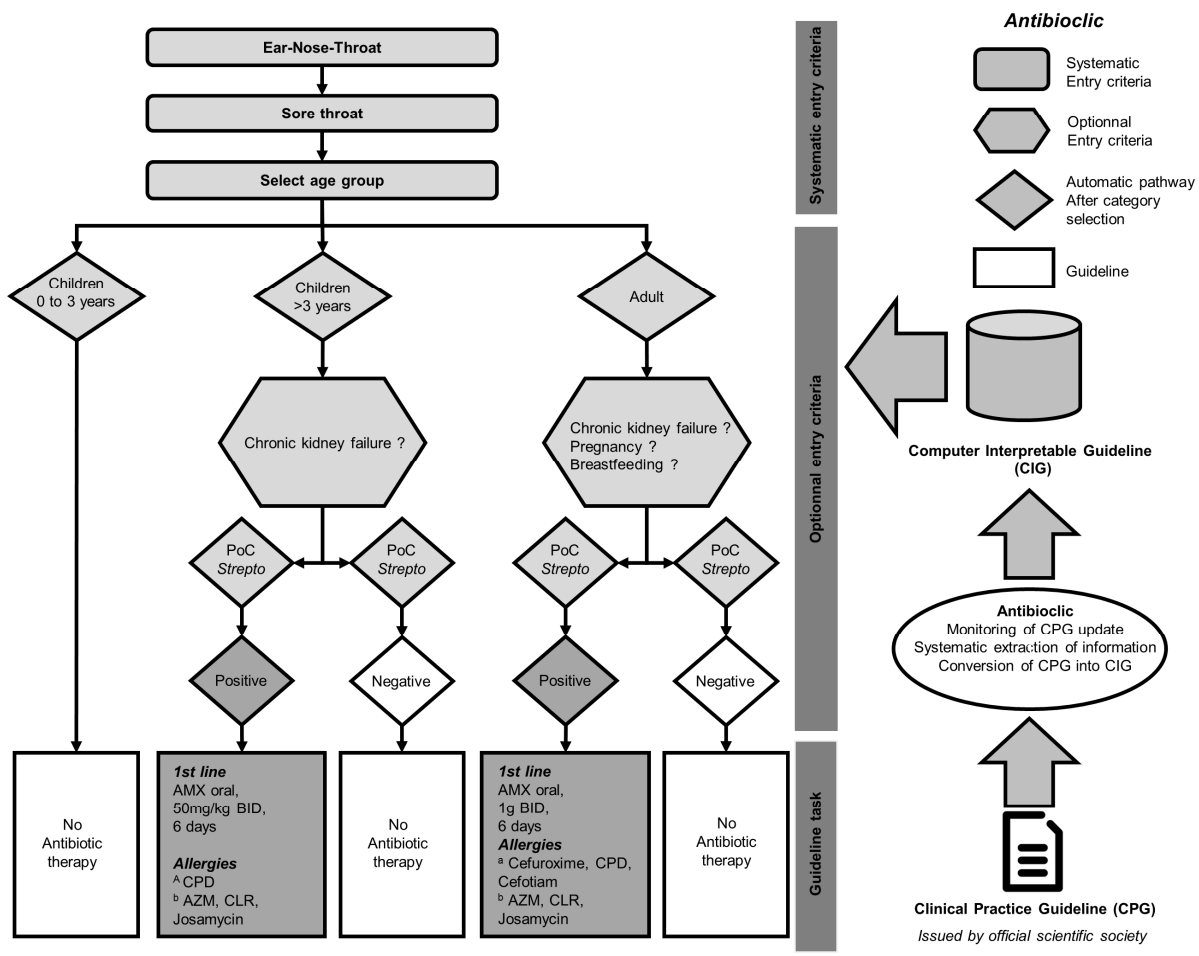
- 126 • Depending on the pathology, antibiotic prescription can be necessary, conditional or not
127 recommended (Table 1).
 - 128 ○ Necessary prescription implies that an antibiotic treatment is always necessary but its choice
129 depends on modifiers (= patient's characteristics).
 - 130 ○ Conditional prescription implies that an antibiotic treatment may be necessary according to
131 modifiers (patient's characteristics) and/or the outcome of additional steps like a POC test.
 - 132 ○ Not recommended prescription implies that no antibiotic treatment should be prescribed.
- 133 • In any case, *Antibiocliv* displays:
 - 134 ○ Link to the CPG
 - 135 ○ Date of the version update
- 136 • If an antibiotic is recommended, *Antibiocliv* displays:
 - 137 ○ List of the recommended International Nonproprietary Name (INN), route of administration,
138 dosage, and duration of recommended antibiotics
 - 139 ○ Alternatives in case of allergies
- 140 • When CPGs did not prioritize one antibiotic over others, *Antibiocliv* steering committee chose a
141 common recommendation for the preferred first line regimen. The decision is based on a systematic
142 rule: 1) to prefer the molecule with the shortest treatment duration; 2) the least side effects; 3) and
143 the narrowest spectrum.

144 ***Reliability***

145 To ensure that *Antibiocliv* follows official guidelines, a partnership with the French National College of Academic
146 General Practitioners (CNGE) and the SPILF, has been developed. Each Society designed a representative member
147 in the steering committee. The steering committee is monitoring official updates of national guidelines for each
148 pathology/infectious disease. When national guidelines are issued or updated, the CDSS recommendations are
149 updated accordingly by the steering committee using the TNM described above. From 2011 to end of 2018, the
150 median rate of guidelines update was 3 [IQR, 2-4].

151 Service users can also contact the steering committee through a dedicated e-mail address.

152 Figure 1 represents the conversion of a CPG to a CIG using the example of sore throat.



153

154 *PoC Strepto = Point-of-Care test result for presence of group A streptococci.*

155 *The steering committee extracts knowledge from clinical practice guideline (CPG) using a systematic procedure.*

156 *CPGs are converted in computer interpretable guidelines (CIG) using the Task-Network Model (TNM) of*

157 *Antibiotic – i.e. the extracted information is allocated to boxes in the decision-tree. The physician then selects*

158 *the characteristics of the patient among lists or categories. After completing all the entry criteria, a guideline task*

159 *is displayed. Standard abbreviations for antibiotics: AMX = amoxicillin, CPD = cefpodoxime, AZM =*

160 *azithromycin, CLR = clarithromycin.*

161 **Figure 1: Antibiotic Task-Network Model for CPG to CIG conversion – the example of sore throat**

162 **Ethics, policies and funding**

163 *Antibiotic is a non-profit organization and is not linked by pharmaceuticals companies for the contents of the*

164 *CDSS or funding. The steering committee members are volunteers and funding is obtained from competitive call*

165 for tenders from universities, the French health authorities or learned societies. Conflicts of interest of individual
166 steering committee members are disclosed on the web site.

167 None of the collected data is shared with private companies. Confidentiality policy is fulfilling with European
168 General Data Protection Regulation. The study has been approved by the ethics committee of the CNGE (N°
169 16051997).

170 Results of the study will be made available on the CDSS website.

171 ***Patient and Public Involvement***

172 This research was done without patient or public involvement. Before publication, the results of this study were
173 not disseminated to patients or the public.

174 **Data collection on the use of the CDSS**

175 ***Routine use***

176 We used automated data collection by the Internet Service Providers (ISP) for our website to describe 1) date and
177 time of request; 2) approximate geolocation based on the Internet Protocol (IP) address (In France, the accuracy
178 of geolocation is 46% at the level of city within 10 km radius, and 76% at level of region.) Due to changes of ISP
179 over the years, these data were available from week 42 of year 2011 to week 52 of year 2012, then from 2015 on.

180 We also used data logged specifically in our system regarding the details of the queries to the CDSS. These data
181 allow determining the pages seen by a user, as well as the duration of interaction with the system. We described
182 the nature of queries and the characteristics of user interactions over time. Due to change of ISP, these data were
183 available from week 42 of year 2011 to week 52 of year 2012 then from week 42 of year 2017 on.

184 ***Cross-sectional studies***

185 In addition to routine data collection, two cross-sectional studies on *Antibiocliv* users were done in 2014 and 2019.
186 The questionnaires were developed by the steering committee and covered: demographics, medical activity, CDSS
187 usage, and users' compliance with CDSS recommendations. Participation was possible for all *Antibiocliv* website
188 users over a period of 2 months in both years, subject to one answer only for each IP address. No reminders were
189 sent. Data was anonymized before analysis. The questionnaires are available in Table S2. Cross-sectional studies
190 were compliant with the corresponding STROBE guidelines.

191 **Statistical analysis**

192 We computed mean number of queries to the CDSS per time period and according to location. Each unique IP
193 address defined a user. We tabulated the number of queries according to disease, age and items specific to each
194 query. We compared the responses to the survey in 2014 and 2019. Given the large number of participants, we
195 focused on “large” differences (>10%) rather than on statistical significance in these comparisons.

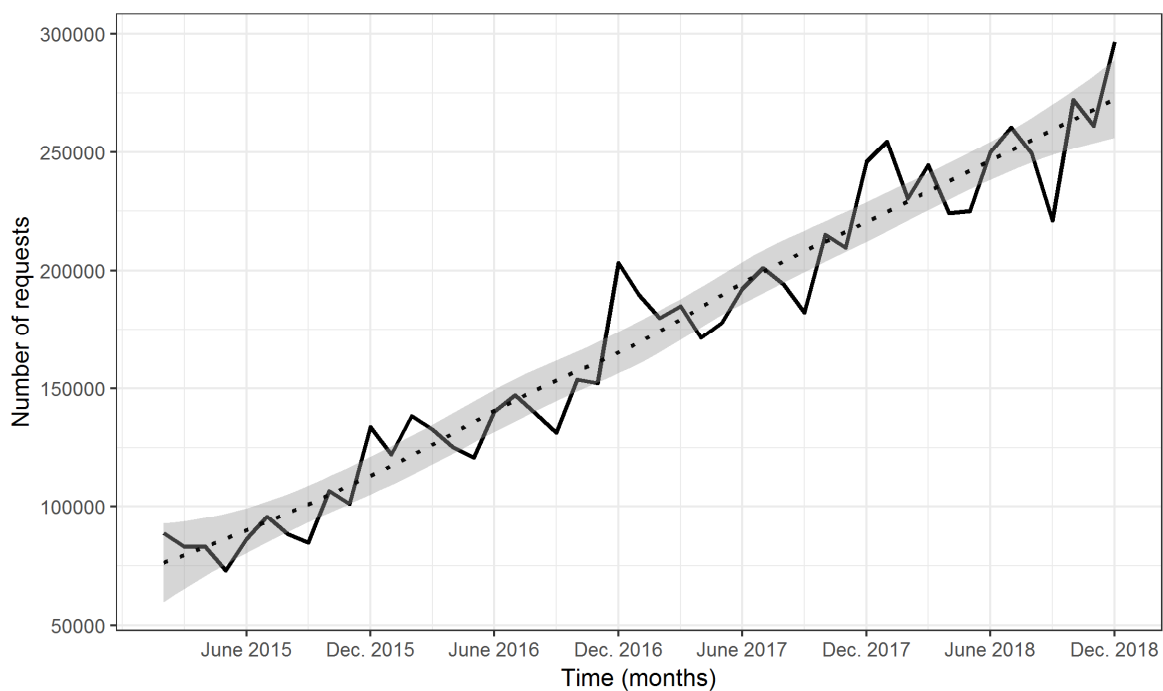
196 Results are reported as frequency and percentages or median and IQR as appropriate. Analysis were performed on
197 R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

198 **RESULTS**

199 *Antibiotic use*

200 The number of queries to the website increased from a total of 369,317 and a median [IQR] of 796 per day [578–
201 989] in 2012, to 3,542,347 and 11,125 per day [5,592–12,505] in 2018 (+1397%). The number of users (unique IP
202 address) increased from 414 [245–494] in 2012 to 5,365 per day [2,891–5,769] in 2018 (+1296%). In 2018, the
203 maximum number users per day was 7,091. The increase in the number of queries did not lead to a saturation effect
204 (Figure 2).

205 The median number of queries per user and per day was 2 [1·8–2·4] over the period 2015-18. The median time
206 per query was 2 minutes [IQR, 1·9–2·1]. The median number of “clicks” to reach the page displaying the
207 recommended action was 4 [IQR, 3–6].



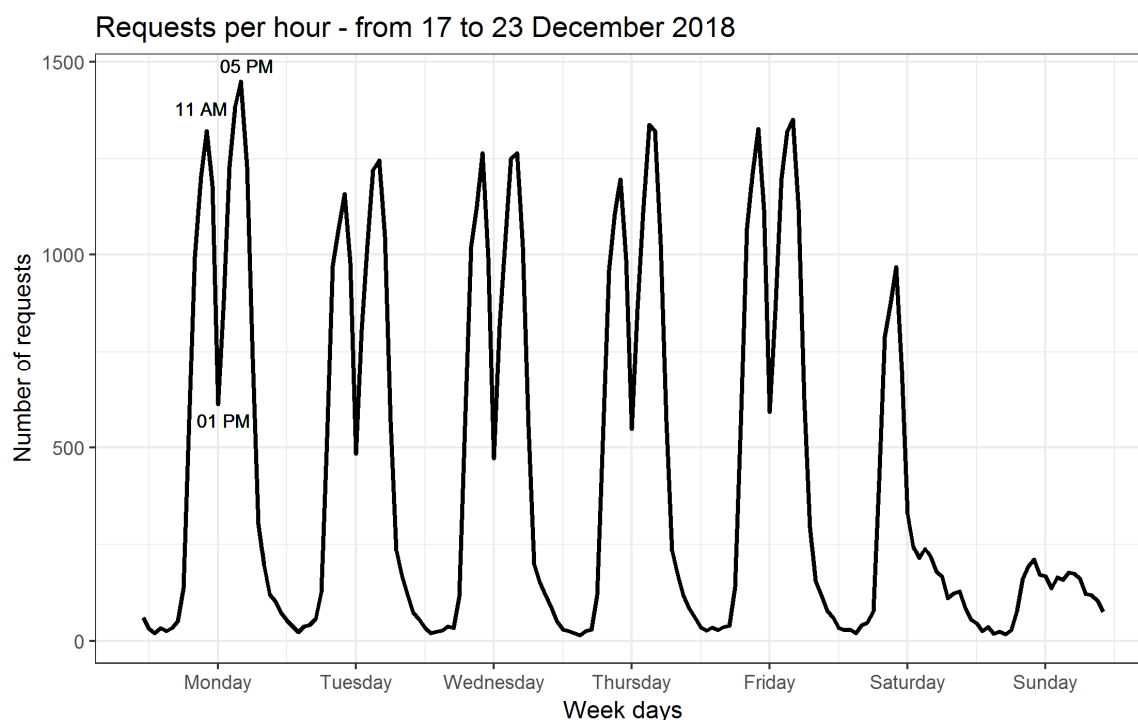
208

209 *The number of queries performed over time in months is represented. The linear tendency is also plotted as a*
210 *dotted line with its confidence interval in grey.*

211 **Figure 2: Number of queries to the Antibiotic system between 2015 and 2018 per month.**

212

213 The pattern of web-site traffic matched GP practice premises opening hours, with fewer queries over the week-
214 end.²³ (Figure 3).



215
216 The number of queries performed over time in hours and according to weekdays of the week 51 of year 2018 is
217 represented. Traffic peaks occur at 11 A.M. and 05 P.M., gaps at 01 P.M.

218 **Figure 3: Number of queries to the Antibiotic CDSS per hour over week 51, year 2018.**

219 Antibiotic users were all over France, with a median of 7,562 queries/100,000 inhabitants [IQR, 6,341–9,222],
220 and a maximum of 12,191 queries/100,000 inhabitants in Paris area, Table S3 and Figure S1.

221 Among the 3,542,347 queries performed in 2018, 2,763,031 (78%) concerned adults. The three most requested
222 anatomical domains in 2018 were: ear-nose-throat infections (ENT) with 968,737 queries (27.3%); UTI with
223 959,393 queries (27.1%); and skin and soft tissues infections with 535,755 queries (15.1%). Six situations
224 accounted for more than half of the total number of queries: cystitis, 504,428 (14.2%); acute otitis media, 410,219
225 (11.6%); acute sinusitis, 340,128 (9.6%); CAP, 327,669 (9.3%), sore throat, 210,954 (6.0%), and pyelonephritis,
226 210,847 (6.0%). The details of queries performed are reported in Table 1. The outcome of the CDSS was that an
227 antibiotic treatment was not recommended for 64,468 queries (1.8%); conditional for 1,223,013 queries (34.5%);
228 and systematic for 2,254,866 queries (63.7%).

Pathology	AB prescribing	Modifiers	N	%
ENT			968,737	27.3%
Acute Otitis Media	Conditional	Age group	410,219	11.6%
Acute sinusitis	Necessary	Age group Location	340,128	9.6%
Sore throat	Conditional	Age group PoC strepto ^a	210,954	6.0%
Rhinopharyngitis	Not recommended		7,436	0.2%
Urinary infections			959,393	27.1%
Cystitis	Necessary	Age group Complication Pregnancy	504,428	14.2%
Pyelonephritis	Necessary	Age group Complication Pregnancy ESBL ^b identification	210,847	6.0%
Masculine Urinary Tract Infection	Necessary	ESBL ^b identification	189,017	5.3%
Orchitis	Necessary		42,312	1.2%
Urinary colonization	Conditional	Pregnancy	12,789	0.4%
Skin and Soft Tissue Infection			535,755	15.1%
Lyme	Necessary	Age group Location / Dissemination	133,766	3.8%
Erysipelas	Necessary		107,455	3.0%
Impetigo	Conditional	Age group Severity	64,994	1.8%
Boil	Conditional	Age group Severity	51,543	1.5%
Paronychia	Conditional	Age group Surgery	51,992	1.5%
Scarlet fever	Conditional	Age group PoC strepto ^a	40,731	1.1%
Mammalian bites	Necessary	Age group	35,576	1.0%
Wound	Conditional	Age group Location / Dissemination	29,101	0.8%

Folliculitis	Not recommended		20,597	0·6%
Respiratory Tract Infections			498,052	14·1%
Community Acquired Pneumonia	Necessary	Age group CRB-65 score Influenza association	327,669	9·3%
COPD exacerbation	Conditional	FEV1 ^c value Purulent sputum	98,767	2·8%
Bronchitis	Not recommended		36,435	1·0%
Pertussis	Necessary		29,158	0·8%
Bronchiolitis	Conditional	Acute Otitis Media Pneumoniae Fever > 38.5°C for 3 days	6,023	0·2%
Sexually Transmitted Infections			292,332	8·3%
Vaginitis	Conditional	Identified pathogen	181,056	5·1%
Urethritis	Necessary	Identified pathogen	60,710	1·7%
Cervicitis	Necessary	Identified pathogen	17,998	0·5%
Salpingitis	Necessary		14,398	0·4%
Syphilis	Necessary		12,731	0·4%
Rectitis	Necessary	Identified pathogen	3,606	0·1%
Lymphogranuloma venereum	Necessary		1,833	0·1%
Digestive infections			269,933	7·6%
Bacterial diarrhea	Necessary	Age group Identified or suspected pathogen	168,642	4·8%
Diverticulitis	Conditional	Immunosuppression ASA ^d score	55,622	1·6%
<i>Helicobacter pylori</i> infection	Necessary	Sensitivity to clarithromycin	25,605	0·7%
Parasitic infection	Necessary	Age group Identified pathogen	20,064	0·6%
Prophylaxis			18,145	0·5%
Endocarditis	Conditional	Age group Location of surgery	9,222	0·3%
Meningococcal meningitis	Necessary	Age group	6,083	0·2%
Tuberculosis	Necessary	Age group	2,840	0·1%

230 ^a PoC strepto = Point-of-Care test for group A streptococci

231 ^b ESBL = Extended Spectrum Beta-Lactamase

232 ^c FEV1 = Forced Expiratory Volume in 1 second

233 ^d ASA score = American Society of Anesthesiologists – Physical status classification system

234 The CDSS can recommend antibiotic prescribing or not, based on conditions. If conditions are impacting decision

235 to recommend antibiotic prescribing, they are represented in the dedicated column.

236 *Antibiotic users*

237 The number of users taking the online survey was 1,848 in 2014 and 3,621 in 2019. Questionnaires were fulfilled
238 by 1,366 (81%) participants in 2014 and 3207 (98%) in 2019. Overall, 352 (7%) were not medical doctors but
239 most of them (54%) were health professionals (pharmacists, midwives, dentist). Among the 4,607 (93%) who were
240 doctors either in training or registered, 4,016 (81%) were GPs; the other medical specialties included emergency
241 medicine (103), geriatrics (32), paediatrics (20), and gynaecology (11). The median age of the 4,016 GPs was 38-
242 years old [31–52], 2,314 (58%) were women, 3,106 (77%) practiced in group-practices, and 460 (11%) were
243 trainees.

244 The detailed results of the 2 surveys are reported in Table 2. For most questions that were posed on both occasions,
245 the answers were similar (less than 10% change). Most GPs reported using the CDSS during the consultation
246 before prescribing an antibiotic (96%), and 93% reported following *Antibiotic* recommendations. A large majority
247 of users (94%) reported that the CDSS was not extending consultation duration, and that they were comfortable
248 using the CDSS during the consultation. Using *Antibiotic* to update knowledge was less reported over time (83%
249 in 2014 vs. 43% in 2019) – even though 90% of the 2019 reported that the CDSS was improving their knowledge
250 in antibiotic therapy. Users were also fewer to use *Antibiotic* in each situation of antibiotic prescription (35% vs.
251 19%). A substantial portion of GPs (43%) reported using the CDSS to explain to patients why they did not
252 prescribe antibiotics. From 2014 to 2019, the occurrence of a divergence with the recommendations grew smaller
253 in terms of choosing the antibiotic, starting a cure when it was not recommended and extending the duration of the
254 cure. Moreover, 93% of them reported following the CDSS recommendation in their last prescription, even if 20
255 to 30% of them acknowledged disagreements from time to time.

256

257

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261

262 *Table 2. Characteristics of general practitioner users – results of 2014 and 2019 cross-sectional studies*

Characteristic of general practitioners	2014	2019
	N = 1,283	N = 2,733
	N (%), Median [IQR]	N (%), Median [IQR]
Demographics		
Resident	133 (10%)	327 (12%)
If physician, involved in residents training	522 / 1,150 (45%)	856 / 2,406 (36%)
Female	706 (55%)	1,608 (59%)
Median age (years)	37 [30 – 53]	36 [31 – 50]
Group practice ^a	794 (62%)	2,312 (85%)
CDSS impact on consultation		
CDSS is mostly used during the consultation, before antibiotic prescription	1,270 (99%)	2,596 (95%)
Consultation duration is not extended by CDSS use	1,206 (94%)	-
Comfortable with using CDSS in front of a patient	1,100 (86%)	2,299 (84%)
Users are using the CDSS		
To update knowledge	1,059 (83%)	1,168 (43%)
Every time they had to initiate an antibiotic therapy	447 (35%)	525 (19%)
To justify the non-prescription of antibiotic	-	1,176 (43%)
Compliance with CDSS recommendations		
Last antibiotic prescription was as the one recommended by the CDSS	1,191 (93%)	2,552 (93%)
Divergent antibiotic prescription – reasons		
Antibiotic different from the recommended one	366 / 897 (41%)	736 / 2,637 (28%)
Antibiotic initiation while not recommended	356 / 897 (40%)	866 / 2,637 (33%)
Extension of course duration	190 / 897 (21%)	534 / 2,637 (20%)
Other ^b	179 / 897 (20%)	301 / 2,637 (11%)
Users' vision of the CDSS		
Recommendations are reliable ^c	1,155 (90%)	2,401 (88%)
It is independent from pharmaceuticals companies ^c	1,105 (86%)	2,215 (81%)
It helps to improve knowledge in antibiotic therapy ^c	-	2,460 (90%)
It “deskills” the physician ^c	-	289 (11%)

263 ^a Group practice is defined as working in group facilities, medical health center, private or public hospital

264 ^b Other: Antibiotic is not prescribed while it was recommended, the duration is shorter than what was
265 recommended, the posology is different from the recommended one.

266 ^c For these indicators, a 5-points Likert scale was used. Only “I agree” and “I strongly agree” were considered
267 as positive answers in the computation of frequencies.

268 -: question not posed.

269 **DISCUSSION**

270 The number of users of *Antibiocliv* has been steadily increasing over time with no saturation effect. Assuming that
271 a unique IP address represents one user, and that 81% may have been GPs, this corresponds to a maximum of
272 5,700 GPs using *Antibiocliv* daily, or about 10% of the 58,140 registered GPs in primary care.²⁴

273 As proposed by Rawson *et al*, we discuss the rationale for development, implementation and assessment of our
274 CDSS.¹⁵ Having physicians follow recommended prescribing policies is a current challenge for the control of
275 AMR.⁵ Adoption of CPGs is often insufficient with up to 40% of patients not receiving the best care.²⁸ CDSS may
276 lead to substantial improvements, though their efficacy in primary care has been variable.²⁸ In this respect,
277 *Antibiocliv* allows GPs to quickly get specialized advice at the time and place of decision making, using 3
278 systematic and 2 optional *entry criteria*. Our system includes the most prevalent situations in primary care and is
279 in line with the situations recently targeted in England by the National Institute for Health and Excellence / Public
280 Health England (NICE/PHE) antimicrobial prescribing guidelines.¹⁷ Furthermore, it includes more situations for
281 antibiotic prescriptions in primary care than other CDSS.^{5,15,16} factors identified as being key of clinical practice
282 improvement.²⁵ To ensure acceptability and integration in the GP workflow, *Antibiocliv* has been co-designed
283 since the beginning by a multidisciplinary team including GPs. This ensured including the CDSS' users perspective
284 – *i.e.* the prescribers – into consideration. We also obtained feedback from users via e-mail and with the repeated
285 cross-sectional studies. With a median time to perform a request of 2 minutes, users reported that it was possible
286 to use *Antibiocliv* during the consultation without extending its duration. Users were also very likely to trust the
287 CDSS recommendations and reported the CDSS as a reliable source to update and improve their knowledge in
288 antibiotic therapy. The more recent *Antibiocliv* smartphone application has already been downloaded 38,170 times
289 as of April 2019, and should further improve availability and timeliness of prescribing information at the point of
290 care. To date, *Antibiocliv* is not integrated into patients' EHR in primary care, but could easily evolve from a semi-
291 formal to a formal CIG.^{22,30} Through collection of individualized data, CDSS recommendations could then be more
292 accurate and individualized.^{22,30} So far, no formal assessment of *Antibiocliv* impact has been made. Several studies
293 have shown that an impact of CDSS on the appropriateness of antibiotic treatment in primary care is possible and
294 mostly linked to the CDSS uptake level.^{15,16} The continued increase in the number of users is therefore good news
295 in this respect. Two small scale studies, independent from the team developing *Antibiocliv*, reported encouraging
296 results on the use of the system. Heslot *et al.* conducted a cross-sectional study among 142 GPs to investigate the
297 impact of *Antibiocliv* use on duration of amoxicillin course in CAP.²⁶ One hundred and twelve (79%) reported
298 using *Antibiocliv* to update their knowledge while 82 (58%) were directly looking at CPGs, 74 (52%) scientific

299 literature, and 48 (34%) the website of the SPILF. Only *Antibiocliv* users had an amoxicillin course duration ≤ 7
300 days ($p < 0.001$).²⁶ Faucal *et al.* prospectively investigated 136 antibiotic prescriptions performed by 19 GPs.²⁷
301 Among the prescriptions, 31 (23%) were performed using *Antibiocliv*.²⁷ The duration of antibiotic therapy was
302 more appropriate to CPGs in case of *Antibiocliv* use (81% versus 51%, $p = 0.038$).²⁷ Since *Antibiocliv* use is
303 volunteer and self-initiated, a selection bias may be present in the participants described in these studies.^{26,27}
304 Physicians using *Antibiocliv* may have a lower and more appropriate baseline antibiotic prescription level. This is
305 suggested by the characteristics of the population surveyed in the cross-sectional studies that we conducted. Heslot
306 *et al.* and Faucal *et al.* studies were conducted between our cross-sectional surveys and might have biased the
307 conduction or the interpretation of our surveys. In order to better estimate the impact of *Antibiocliv*, we are
308 currently conducting a large scale observational study, comparing antibiotic prescribing and patient outcomes
309 between all CDSS users and a control group of GPs. A social science perspective is also under way to understand
310 how prescribers use the CDSS and how it may change clinical decision-making.

311 Secondary use of the data collected using this CDSS could provide information on the epidemiology of common
312 infectious diseases in primary care. Collected data could be integrated in AMR NAPs surveillance system.^{5,14} This
313 would be of particular interest for microbiological data such as the level of resistance in UTI.⁵ But such attempts
314 would have to be handled carefully. For example, CAP queries were more frequent than COPD exacerbation and
315 bronchitis, when the epidemiology of these conditions would suggest otherwise. It may be that users consult the
316 the CDSS less frequently in situations where antibiotic prescription is not recommended (e.g. bronchitis) or that
317 were already encountered before. This might lead to an under- use/reporting for those type of infections. In France,
318 GPs in primary care are taking care of 92 to 97 patients per week, and antibiotic prescription rate is around
319 16.7%.^{6,29} Over 3.5 millions of queries were performed on *Antibiocliv* in 2018 and the median number of queries
320 per day per users was stable at 2 [1.8–2.4]. Assuming a constant number of weekly patients across GPs and that
321 each request corresponded to a situation in which an antibiotic could have been initiated, the rate of antibiotic
322 prescribing would range between 14.4 and 15.2% in CDSS users.²⁹ These results support the fact that queries have
323 been performed to manage real patients.

324 As of now, the design of the platform did not allow collecting the details of antibiotic prescription. This choice
325 was made to improve user experience and ease its uptake.²⁵ Therefore, our study uses the analysis of queries as a
326 surrogate marker for antibiotic prescription. It is not possible to differentiate situations in which a request has been
327 performed for a real patient from queries unrelated to patient's care. However, queries analysis shows a clear
328 correlation with the daily medical activity of GP in primary care, supporting that they are made at point of care.²³

329 In *Antibioctic*, patients' interface and involvement are lacking. We plan to develop it through a collaboration with
330 health authorities, in order to improve patient education regarding AMR and the shared decision making between
331 patients and physicians.^{5,22}

332 Finally, considering the international reach of AMR, and *Antibioctic*' interoperability, we believe that *Antibioctic*
333 could be shared and adapted internationally. LMICs, where the rate of CPG development is low, data on ASP
334 development and implementation are scarce, AMR is high and antibiotic consumption has been consistently
335 increasing over the last 16-years could be prime targets for intervention.^{3,31,32} In such settings, implementation and
336 promotion of an adapted version of *Antibioctic* through multilateral collaboration, could be an inexpensive and
337 easy way to avoid effort in *de novo* CPG development, and effectively support the implementation and adoption
338 of integrated CDSS in primary care, at the point-of-care.^{14,28,31-33}

339 In conclusion, *Antibioctic* was designed using a simple and systematic approach to convert CPG into CIG from
340 the primary care physician perspective. *Antibioctic* allows a quick access to antibiotic prescribing
341 recommendations for a large panel of primary care infectious diseases in accordance with up-to-date official CPGs.
342 This study demonstrates that *Antibioctic* has been successfully implemented and adopted by French GPs with data
343 supporting a sustainable use and a continuous increase of users. *Antibioctic* might have a positive impact on users'
344 prescription, antibiotic consumption, AMR and patients' care. In an era where AMR is increasing while therapeutic
345 innovation is rare, such systems should be promoted and developed in a global collaborative approach.

346

347 As compared with the results of the French Ministry of Health 2018 study on French medical physicians,
348 *Antibioctic* users seemed younger, with a higher frequency of women, group practices, and involvement in training
349 of residents.^{6,24} Without good quality quantitative study, any observed difference between users and non-users
350 could be linked to the CDSS, or to the users themselves. This also reinforce the need of a standardized framework
351 for evidence-based reporting of CDSS analysis in primary care.¹⁵

352 Preliminary data from the 2019 cross-sectional study suggest that only 11% of surveyed GPs feel "deskilled",
353 while 90% have the impression to improve their knowledge in antibiotic therapy. We are conducting a
354 complementary qualitative analysis in order to further precise the place and role of *Antibioctic* within the medical
355 consultation, its advantages and limitations from the GP's point of view, as well as their needs and expectations
356 for future development. We will particularly consider common and potential unexpected consequences that are
357 feared, such as the risk of "deskilling" physicians who use CDSS routinely, the risk of an automation bias or the

358 risk of decreased interaction between the physician and the patient. A better understanding of how *Antibioctic* is
359 being used will allow to gather valuable data to design and implement future systems and user interface, including
360 systems using artificial intelligence.³⁰

361

362 **ACKNOWLEDGMENT**

363 Partial results of this work were presented at the CMGF (congress of general practice France), the CNGE (congrès
364 du college national des généralistes enseignants), the JNI (journées nationales d’infectiologie), and the RICAI
365 (interdisciplinary meeting of anti-infective chemotherapy):

- 366 - 2011: CMGF (communication); JNI (poster)
- 367 - 2014: CMGF (poster), RICAI (poster and communication)
- 368 - 2015: JNI (poster)
- 369 - 2016: CMGF (poster)
- 370 - 2018: CMGF (poster), JNI (poster) RICAI (poster)

371 We thank all the users for their positive feedback and their participation to the CDSS development.

372 We thank Gunther Groenewege for is help in ergonomics design.

373 We thank the ANTIBIOCLIC+ study group (alphabetical order): Danny Asfari, Isabelle Aubin-Auger, Marion
374 Caseris, Emilie Ferrat, Jean Gaschignard, Kiara Maje, Nathan Moreau, Raphaël Lepeule, Philippe Lesprit, Louise
375 Rossignol, Cécile Souty, Florence Tubach, Yazdan Yazdanpanah.

376 We also thank the Paris Diderot University, the SPILF, the CNGE, the Regional Health Authorities of Ile-de-
377 France (ARS Ile-de-France), and the Health Insurance Agency of Ile-de-France (DRSM Ile-de-France) for their
378 active collaboration.

379

380 **FUNDING**

381 None to declare.

382

383 **TRANSPARENCY DECLARATION**

384 None to declare.

385

386 **AUTHORS CONTRIBUTION**

387 TD: Conceptualization, Funding Acquisition, Project administration, Data Curation, Formal analysis,
388 Visualization, Original Draft Preparation

389 PJ: Conceptualization, Data Curation, Resources, Project administration, Funding Acquisition, Review and editing

390 SL: Conceptualization, Funding Acquisition, Project administration, Review and editing

391 JPA: Conceptualization, Funding Acquisition, Project administration, Software, Review and editing

392 NPS: Review and editing

393 PYB: Review and editing

394 EB: Conceptualization, Funding Acquisition, Project administration, Review and editing

395 FXL: Conceptualization, Funding Acquisition, Project administration, Review and editing

396 JLB: Conceptualization, Funding Acquisition, Project administration, Software, Supervision, Original Draft
397 Preparation

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412 [summaries/averting-the-amr-crisis](http://www.euro.who.int/en/about-us/partners/observatory/publications/policy-briefs-and-summaries/averting-the-amr-crisis).
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- 491

492 **SUPPORTING INFORMATION**

Year	2011 ^a	2012	2013	2014	2015	2016	2017 ^a	2018	2019
Date and time of request ^b	X	X			X	X	X	X	X
IP address ^c	X	X					X	X	X
Details of request according to TNM ^d	X	X					X	X	X

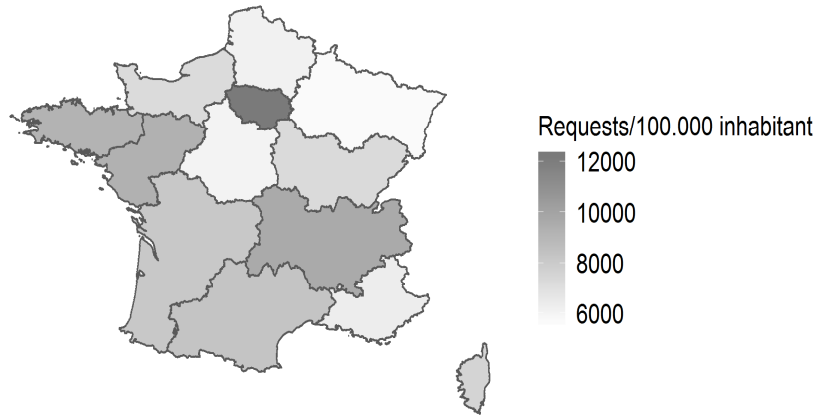
493 ^a Collection process started in week 42 that year.

494 ^b Time is monitored in “hour,minute,second”.

495 ^c Internet Protocol address – allow the geolocation of the request.

496 ^d The request details include the 3 systematic entry criteria and the 2 optional entry criteria.

497 **S1 appendix: Availability of data collected since 2011**



498

499 *For every administrative region of France, the number of queries per 100,000 inhabitants has been calculated*
500 *and plotted on France map. The greyscale gradient corresponds to the level of use.*

501 **S2 Appendix: Number of queries per 100-000 inhabitants over French territory.**