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### ► **To cite this version:**

P. Letertre-Gibert, Gwenaël Vourc'h, Isabelle Lebert, Magalie René-Martellet, V. Corbin-Valdenaire, et al.. Lyme Snap: a feasibility study of on-line declarations of erythema migrans in a rural area of France. *Ticks and Tick-borne Diseases*, 2020, 11, 10.1016/j.ttbdis.2019.101301 . hal-02503295

**HAL Id: hal-02503295**

**<https://hal.science/hal-02503295>**

Submitted on 21 Dec 2021

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1 **Lyme Snap: a feasibility study of on-line declarations of erythema migrans in a rural area of**  
2 **France.**

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25 **ABSTRACT**

26 The incidence of Lyme borreliosis remains a matter of debate, but it can be estimated using  
27 the incidence of erythema migrans (EM), which is pathognomonic of the first phase. The aim  
28 of this prospective pilot study was to assess the feasibility of the on-line declaration of EM in  
29 rural areas where the incidence of Lyme borreliosis was previously estimated at 85 per  
30 100,000 inhabitants per year.

31 The study was limited to a rural area (Les Combrailles, Auvergne) of approximately 52,800  
32 inhabitants and was preceded by an information campaign for the inhabitants and the  
33 healthcare professionals. Patients who sent a photo of the suspected EM by email or MMS  
34 message between April 2017 and April 2018 and who accepted to answer a questionnaire  
35 were included in the study. Two physicians then evaluated the quality of the photographs and  
36 the probability of EM. In parallel, the number of EM seen by physicians and pharmacists in the  
37 area over the given period was recorded.

38 Out of the 113 emails and MMS messages received, 73 people were outside of the trial area  
39 or period and 9 did not complete the questionnaire. The photos of the remaining 31 people  
40 were analysed. The median age was 51.5 years old ([38-58] IQR) and 18 (58%) were women.  
41 Seven people (25%) stated that they did not have a smartphone and in 9 cases (29%) the photo  
42 was sent by a third party. The quality of the photos was considered very good in 22 (71%)  
43 cases, good in 7 (23%) cases, and average in 2 (6%) cases. The probability of EM was  
44 determined to be strong or possible in 12 (38%) cases, i.e. an estimated incidence of 22.7 per  
45 100,000 inhabitants. Over the study period, 40 physicians and 20 pharmacists were contacted  
46 on a monthly basis. A median of 5 physicians [3 ;7] and 4 pharmacists [3 ;7] answered each  
47 month for a total of 18 and 36 declared EM respectively. The EM (strong probability/possible)  
48 collected by on-line declaration and those declared by healthcare professionals were all sent  
49 between April and October 2017. The total time spent on the information campaign and  
50 collection has been estimated at 265 hours (divided between 10 people) for an overall cost of  
51 10,669 Euros.

52 The incidence of EM recorded by on-line self-declaration in our study seems to be lower than  
53 in previous studies, the under-reporting was probably linked to the low use of new  
54 technologies in the rural areas. Increasing the human resources and finances appears difficult  
55 to achieve in practice over a longer time period but the development of an application for the  
56 automatic recognition of EM could be one method for a more exhaustive collection in the long  
57 term and at lower cost.

58 **INTRODUCTION**

59 Lyme borreliosis (LB), caused by *Borrelia burgdorferi* sensu lato in Europe and transmitted by  
60 ticks of the genus *Ixodes*, has become a public health problem. The controversy surrounding  
61 the disease is notably fuelled by a debate concerning its actual incidence. Although the  
62 infections linked to tick bites are probably an emerging problem, the uncertainty regarding  
63 the incidence of LB is an obstacle to the knowledge of its evolution over time and of its  
64 importance in terms of public health (Paules et al., 2018; Rosenberg et al., 2018). Moreover,  
65 knowledge of the areas at risk is an important element in the diagnosis, which is based on a  
66 clinical, biological and epidemiological triad (Shapiro and Wormser, 2018). It also allows better  
67 targeting of preventative actions.

68 The assessment of the incidence of LB in France is currently based on the National Reference  
69 Centre as well as the Sentinelles network (voluntary report by general practitioners), which is  
70 coordinated by the Institut de Veille Sanitaire (InVS), and has been active since 2009. The  
71 diagnosis of LB is based on the EUCLB clinical and biological criteria (Stanek et al., 2011). A  
72 significant increase in the French national incidence was seen in 2016, with a median of 84  
73 cases [40-79] per 100,000 inhabitants, up to 105 in Auvergne, the region of our study (Fournier  
74 et al., 2018; Septfons et al., 2019). This increase could be attributed to the start of the national  
75 plan against LB, with awareness-raising measures for the general public and healthcare  
76 professionals (Ministère des Solidarités et de la Santé, 2016). However, it cannot be excluded  
77 that the incidence is truly increasing.

78 The rise in the number of smartphones and the development of telemedicine (Boiteux et al.,  
79 2016; Gossec et al., 2017; Gilmore, 2018) makes it possible to consider collection of EM by  
80 self-declaration, based on the sending of digital photographs. This self-declaration is also used  
81 in other epidemiological follow-ups (“Signalement tiques”, ongoing study being carried out by  
82 INRA, Institut National de la Recherche Agronomique). However, the efficacy of this method  
83 can meet with several difficulties, such as reduced diffusion of information and digital tools in  
84 rural areas. The quality of the photography may also prove to be an impediment when trying to  
85 make a confident diagnosis.

86 We therefore wanted to evaluate the feasibility of an on-line declaration of EM for estimating  
87 the incidence of LB via the sending of a digital photo, in a rural area of France (Les Combrailles,  
88 Auvergne), known for having a significant part of the tick population carrying *Borrelia*  
89 *burgdorferi* s.l. (Boyard et al., 2011).

90

91

92 **MATERIALS and METHODS**

93 This was a prospective, non-interventional study evaluating the feasibility of a diagnostic  
94 method, carried out as part of a local Hospital Clinical Research Program (PHRC) and led by  
95 both University Hospital of Clermont-Ferrand and INRA. It received ethics committee approval  
96 within the framework of category 3 of article L.1121-1 given by the decree of February 23,  
97 2017 (registration number 2016-A02068-43). The study was limited to the Combrailles area of  
98 the Puy-de-Dôme department, a rural area of approximately 52,800 inhabitants in the center  
99 of France. It took place over a period of one year, from 1<sup>st</sup> April 2017 to 31<sup>st</sup> March 2018.

100 To raise awareness of the study, an information campaign for the inhabitants and the  
101 healthcare professionals was carried out beforehand, in February and March 2017. It  
102 consisted of repeated letters (paper and electronic) to the general practitioners, pharmacists  
103 and paramedical staff in the area, 3 briefings (2 for the healthcare professionals, 1 for the local  
104 population), posters and flyers in the local shops in the area, articles in the locally printed  
105 press as well as reports on local radio and television (France Bleu Pays d’Auvergne and France  
106 3 Auvergne-Rhône-Alpes). Furthermore, an information website dedicated to the study was  
107 hosted on the INRA website (<https://www6.ara.inra.fr/lyme-combrailles>).

108 In order to participate, a photo of a suspected EM skin lesion had to be sent (by the person  
109 themselves or by a third person) by email or MMS message during the study period. The  
110 patients then had to complete a questionnaire (by email or telephone interview) reporting the  
111 characteristics of the erythema, the possible clinical signs associated and epidemiological and  
112 demographic data. The photos were then embedded in the questionnaire. The inclusion  
113 criteria were the appearance of erythema during the study period with compatible exposure  
114 during the previous month in the Pays des Combrailles area. Patients were not included if they  
115 presented an erythema before the 1<sup>st</sup> April 2017 or after the 31<sup>st</sup> March 2018, or if they had  
116 not stayed in the Combrailles area. After the photo and questionnaire had been received, two  
117 doctors (an infectious disease specialist and a dermatologist) determined the quality of the  
118 photograph and the probability of EM.

119 In parallel to the collection from the general public, the number of EM seen by doctors and  
120 pharmacists in the area (31 physicians and 20 pharmacists) during the study period was  
121 collected by an INRA scientist. Case report forms were provided to these healthcare  
122 professionals and a monthly reminder was sent by email to collect the number of EM  
123 identified. The sending of a photo was not required. An initial delivery of the questionnaire  
124 was made at the start of the month and a reminder was sent at the end of the month to the  
125 doctors and pharmacists that had not replied. Finally, an evaluation of the cost and the time  
126 required for the information campaign and the collection was carried out.

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129 **RESULTS**

130 At the end of the study, 113 emails or MMS messages had been received, including 30  
131 photographs of erythema that appeared in the area and period of the study (Figure 1). Thirty  
132 patients with a median age of 51 years [IQR: 35-58] were included in the study. Their  
133 characteristics are summarised in Table 1.

134 All participants except 2 considered the sending of the photograph to be easy. However, in 8  
135 cases (27%) the photo was sent by a third party (4 by family members, 2 by a pharmacist, 1 by  
136 a nurse and 1 by a doctor). The quality of the photographs was determined to be very good in  
137 22 cases (73%), good in 6 (20%) and average in 2 cases (7%). The results of the joint analysis  
138 of the photograph and questionnaire are summarised in Figure 1. Erythema migrans  
139 probability was determined to be strong or possible in 40% of cases.

140 In the 12 probable or possible cases, 10 (83%) appeared in June and July 2017, 2 people did  
141 not notice the tick and in the 10 others, the erythema appeared within a median of 2 days ([1  
142 ;7] IQR) after the bite. Ten people received an antibiotic therapy (6 with amoxicillin, 2 with  
143 doxycycline and 2 could not remember the name).

144 Concerning the questionnaire for professionals, 45 replies were received from 10 different  
145 physicians (out of 40). A median of 5 physicians replied per month [3-7] (participation rate of  
146 10%), for 18 declared cases of EM during the all study. Forty-three replies were received from  
147 8 different pharmacists (out of 20). A median of 4 pharmacists replied per month [3-7]  
148 (participation rate of 20%), for 36 declared EM during the all study. Only 6 of these patients  
149 seen by professionals stated that they were participating in the Lyme Snap study, the  
150 information was missing for the other ones.

151 No EM were declared by the population nor the healthcare professionals after October 2017.  
152 The photographs received were mainly from the north of the Combrailles area.

153 The incidence of EM in the year (probability considered as strong/probably based on the  
154 photos, i.e. 12 per 52,800 inhabitants) was estimated at 22.7 per 100,000 inhabitants per year.

155 The time spent in the briefings, the poster advertising and the information for the healthcare  
156 professionals was estimated at 183 hours (8 people involved), and the time required for the  
157 collection of the information and the classification of the EM (4 people involved) was  
158 estimated at 82 hours. The total cost in terms of human resources amounted to 8,061 Euros.  
159 The cost (travel and material) for the information campaign amounted to 2,608 Euros. The  
160 overall cost was 10,669 Euros.

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162

163 **DISCUSSION**

164 In this study we investigated the feasibility of self-declaring EM in rural areas by sending a  
165 digital photograph of a skin lesion. This method of collecting EM by on-line declaration is  
166 certainly attractive but it faces the problems of feasibility.

167 A study carried out in the same rural area in 2005 and 2006 found an incidence of EM (declared  
168 by the doctors) of 66 to 104 per 100,000 inhabitants (Beytout et al., 2007), which is 3 to 4  
169 times higher than the incidence estimated from the self-declarations in our study. Likewise, in  
170 our study, the number of EM reported by physicians and pharmacists in the same period was  
171 greater than those collected by self-declaration, despite a low rate of participation of  
172 healthcare professionals. However, the diagnoses of EM declared by healthcare professionals  
173 were not verified by our team, which may have resulted in an over-declaration on their part.

174 The possible under-reporting may be linked to several factors: (a) the possible low use of new  
175 technologies in the rural areas could have been the cause of the low number of self-declared  
176 cases. (b) A geographical effect exists with fewer photos received from the southern area, an  
177 area less accessible, with fewer healthcare professionals and with a lower population but also  
178 with a lower known density of ticks. (c) A temporal effect also existed during the study with a  
179 maximum number of photographs received during the 7 first months (April-October).  
180 However, it is difficult to know if this was due to the fact that the information drive was not  
181 repeated (the study then being forgotten), or simply because *Ixodes* ticks are known to be less  
182 active during this period. The information campaign should probably have been repeated  
183 during the study, but with a more significant spending and human mobilisation. A larger scale  
184 study would require repeated information drives and more resources.

185 It is important to note that the majority of the exposures to ticks were due to gardening  
186 activities, an activity usually sparsely highlighted in the prevention strategies, which mostly  
187 targets hikers. However, the people who sent the photographs were mainly inhabitants of the  
188 area and rarely tourists, who would have been less informed of the study.

189 Several factors that could contribute to feasibility issues, particularly in a large-scale study,  
190 have been identified. Firstly, we received many messages and emails that were not related to  
191 EM (mainly chronic aspecific symptoms). Although they underline the need to inform the  
192 public, these messages interfere with the study and significantly increase the workload. Then  
193 again, in the context of a larger study, the human resources needed to sort out and reply to  
194 these inappropriate declarations would be considerable. Furthermore, the call-back for  
195 suspected cases in order to obtain the clinical history data, essential for the analysis of the  
196 photographs, was very time-consuming; And even when the message contained a photograph  
197 of the skin lesion, over half were not EM. The questionnaire was a key element for classifying  
198 the probability of EM based on the significance of the history but effectively required  
199 additional time. This method of collection for the estimation of the incidence of EM is probably  
200 not the most appropriate due to the low number of EM collected, despite the significant

201 human and financial resources. Nevertheless, to date, no other collection method appears to  
202 be satisfactory (Cartter et al., 2018).

203 Since the quality of the photographs received during the study was very good, it is possible to  
204 envisage an automatic recognition application for EM combined with a few short questions in  
205 order to assess the probability of EM. This technique, which has already been validated for  
206 the diagnosis of melanoma, could help with diagnosis but also with an epidemiological  
207 collection while limiting, after the implementation phase of the application, the financial and  
208 human cost.

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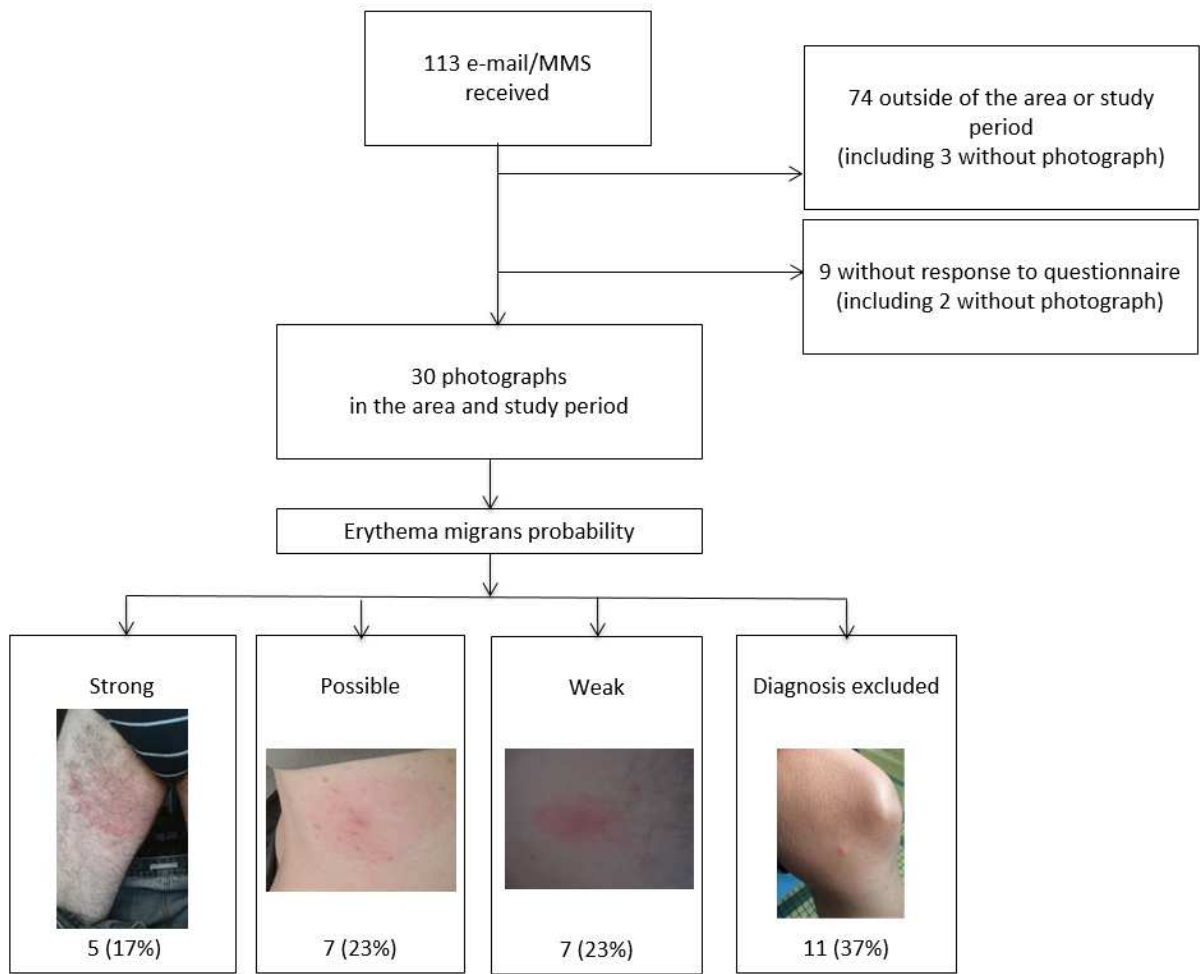
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266 Figure 1. Study workflow.

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268

Characteristics	Number (%)
Women n (%)	18 (60%)
Link with the Combrailles area n (%)	
Home	28 (94%)
Strictly professional	1 (3%)
Leisure/tourist	1 (3%)
Activity at the time of the bite n (%)	
Gardening	18 (61%)
Hiking/biking	6 (20%)
Animal care	2 (6 %)
Unknown	4 (13%)
Owned a smartphone n (%)	26 (87%)
Photograph sent by a third party n (%)	8 (27%)

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270 Table 1. *Characteristics of the included patients (n=30)*

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