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**Encephalitis in HIV-negative immunodeficient patients: a prospective multicentre study, France, 2016 to 2019**

Sophie Landré¹, Florence Ader¹, Olivier Epaillard²-⁴, Pierre Tattevin⁵-⁶, Jean Paul Stahl⁵-⁶, Alexandra Mailles³-⁶, on behalf of the Steering committee and Investigators⁷

1. University Claude Bernard Lyon 1, Hospices Civils de Lyon, Infectious disease department, Lyon, France
2. Centre International de Recherche en Infectiologie (CIRI), Inserm 1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, École Normale Supérieure de Lyon, Univ Lyon, France
3. ESCMID Study Group on the infections of the Brain (ESGIB), Basel, Switzerland
4. University Grenoble Alpes, Infectious diseases department, Grenoble, France
5. Infectious diseases department, CHU Pontchaillou, Rennes, France
6. Santé Publique France, Saint-Maurice, France
7. The members of the Scientific committee and the investigators are listed in the Acknowledgments section

Correspondence: Sophie Landre (sophie.landre@chu-lyon.fr)

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Background: Data on infectious encephalitis in immunodeficient (ID) individuals are scarce. This population may present with atypical clinical symptoms, be infected by uncommon pathogens and develop poor outcomes. Aim: We aimed to describe the epidemiology of infectious encephalitis among HIV-negative ID patients. Methods: Patients from the ENCEIF (Étude Nationale de Cohorte des Encéphalites Infectieuses en France) prospective cohort meeting criteria for infectious encephalitis between January 2016 and December 2019 were included. We compared clinical presentation, magnetic resonance imaging (MRI) results, biological results, infection causes and outcome of ID patients with immunocompetent (IC) patients using Pearson’s chi-squared test and Student’s t-test. We carried out logistic regression to assess the role of immunodeficiency as risk factor for poor outcome. Results: ID patients (n = 58) were older (mean 72 vs 59 years), had higher prevalence of diabetes (26% vs 12%), pre-existing neurological disorders (12% vs 5%) and higher case-fatality rate (23.6% vs 5.6%) compared to IC patients (n = 436). Varicella zoster virus was the primary cause of encephalitis in ID patients (this aetiology was more frequent in ID patients (25.9%) than in IC patients (11.5%)), with herpes simplex virus second (22.4% in ID patients vs 27.3% in IC patients). Immunodeficiency was an independent risk factor for death or major sequelae (odds ratio: 3.41, 95%CI: 1.70–6.85). Conclusions: Varicella zoster virus is the most frequent cause of infectious encephalitis in ID patients. Immunodeficiency is a major risk factor for poor outcome. ID encephalitis patients should benefit from stringent investigation of cause and early empiric treatment.

**Introduction**
Infectious encephalitis is a rare disease with an estimated incidence of 7.3 per 100,000 persons per year in the United States (US) between 2000 and 2010 [1]. It has a high case-fatality rate (CFR) (around 10%) and neurological sequelae are frequent; 3 years after hospital discharge, 32% of patients presented severe or moderate sequelae [2,3]. Encephalitis can be challenging to diagnose considering the clinical overlap with other neurological conditions. The cause of encephalitis can be even more difficult to determine due to the variety of possible involved pathogens [4,5].

The life expectancy of immunodeficient (ID) populations is increasing as new indications for immunosuppressive treatments are validated and management of onco-hematological disorders or transplantations improves, leading to increased life expectancy and risk of complications from infections. In central nervous system infections, ID patients may display atypical clinical presentation, and since they are sensitive to infections that usually do not affect immunocompetent patients (opportunistic infections), they may develop a more severe outcome [6].

Previous studies on encephalitis in ID patients mostly included patients with acquired immunodeficiency syndrome due to human immunodeficiency virus (HIV). To date, to the best of our knowledge, no survey of a prospective cohort of encephalitis in HIV-negative ID patients has been reported.

Our objective was to evaluate differences in infectious encephalitis between non-HIV-related ID patients and immunocompetent (IC) patients enrolled in the ENCEIF
cohort (Etude Nationale de Cohorte des Encéphalites Infectieuses en France), a prospective multicentre cohort of infectious encephalitis in France [7]. We included clinical presentation, the causative agent of encephalitis, biological results, magnetic resonance imaging (MRI) results, treatment and outcome.

Methods

Enrolment of patients
The ENCEF Cohort has previously been described elsewhere [7,8]. Patients with suspected infectious encephalitis matching the stringent case definition adapted from Venkatesan et al. [9] and admitted to one of the 62 hospital units throughout metropolitan France between 1 January 2016 and 31 December 2019 were included in this study. Investigators were encouraged to apply the French Infectious Diseases Society guidelines when investigating encephalitis aetiology [10].

Data collection
Investigators collected demographic data, as well as data on comorbidities, ongoing treatment, clinical presentation (fever > 38.0°C, confusion, coma, septic shock, hallucination), encephalitis causative agent, biological results, MRI findings described by the local radiologist, treatment and outcome. Glasgow outcome scale (GOS) was used to assess the global functioning of patients at discharge: a poor outcome was defined as a GOS of 1 to 3 (death, neurovegetative state or major sequelae) [11]. We defined immunodeficiency as having: (i) an active cancer; (ii) ongoing chemotherapy within the past year; (iii) undergone a solid organ or haematopoietic stem cell transplantation; (iv) a haematological malignancy; (v) a myelodysplastic syndrome; or (vi) undergoing immunosuppressive treatment.

Statistical analysis
The variables collected for both groups of patients were described using medians and interquartile range (IQR) for quantitative variables and numbers and percentage for qualitative variables. In the univariate analysis, variables were compared using Pearson’s chi-squared test and Student’s t-test (using odd ratios (OR) and 95% confidence intervals (CI)). Risk factors for poor outcome were assessed with multivariable analysis using a logistic regression model. All variables associated with a poor outcome in the univariate analysis with a p value < 0.20 were included in an initial multivariable logistic regression model. The variable selection was performed according to a backward-stepwise procedure. The causative agent and immunodeficiency were retained in the model irrespective of the significance of their association with the dependent variable (encephalitis outcome). The goodness-of-fit of the final model was evaluated by the Hosmer-Lemeshow test [12].

Data were computed using Voozanoo version 3 (Epiconcept, Paris, France) and analysed using Stata statistical software, version 16.0 (Stata Corp, College Station, US).

Results

Patient characteristics
The ENCEF cohort enrolled 494 patients, of whom 58 (11.7%) matched the criteria for ID patients (Table 1). The median age of ID patients was 72 years old (IQR: 68–78), 37 (64%) were male and 21 (36%) were female. Compared with IC patients (n = 436), ID patients were
older (mean 72 years vs 59 years, p < 0.001), were more prone to diabetes (26% (15/58) vs 12% (52/433), p = 0.004), and had more pre-existing neurological disorders (12% (7/58) vs 5% (22/433), p = 0.003). Sex ratio and distribution of educational background levels were similar.

**Encephalitis causative agents**

Varicella zoster virus (VZV) was the primary cause of encephalitis in ID patients (25.9% vs 11.5% in IC patients, p = 0.002) (Table 2). Herpes simplex virus (HSV) was the second most common cause in ID patients (22.4%) but did not significantly differ to IC patients (27.3%). *Listeria monocytogenes* was the third most common cause of infectious encephalitis in ID patients (10.3% in ID vs 3.9% in IC, p = 0.03). Human herpes virus 6 (HHV-6) and John Cunningham (JC) polyomavirus infections were identified in ID patients only. The proportion of cases without an infectious agent identified was lower in ID patients than in IC patients (12.1% vs 37.4%, p = 0.0001).

**Clinical data**

Clinical presentation, including frequency of fever at admission, did not differ between ID and IC patients (Table 3).

Magnetic resonance imaging was performed equally often in both groups (81.2%, 354 /436 IC patients and 79.3%, 46 /58 ID patients). However, due to missing data, MRI results of only 34 ID patients and 230 IC patients were included in this study. The prevalence of haemorrhagic lesions was higher in ID patients (23.5%, 8/34) than IC patients (12.6%, 29/230, but...
this difference did not reach statistical significance (p = 0.09). No specific clinical presentation or MRI findings were associated with a specific cause of infection in ID patients.

The distribution of white blood cell (WBC) count/mm³ in cerebrospinal fluid (CSF) was significantly different in ID and IC patients (p = 0.03). A median WBC count of 45/mm³ (IQR: 6–183) was reported for ID patients, and a median WBC count of 80/mm³ (IQR: 22–268) for IC patients. The absence of biological meningitis, defined as a CSF WBC count < 5/mm³, was more common in ID patients (23.6%, 13/55) than in IC patients (8.9%, 38/423) (p = 0.005).

After excluding patients with early diagnoses through direct microbiological examination of their CSF, namely patients with L. monocytogenes and tuberculosis, acyclovir was less frequently prescribed to ID patients (76.0%, 38/50) than IC patients (92.7%, 371/401), (p = 0.0001). Of note, all patients with a final diagnosis of encephalitis caused by HSV or VZV had received acyclovir as empirical treatment. The proportion of patients who received a high dose of acyclovir (15 mg/kg/8 hours) was similar in both groups (24.6%, 90/366 IC patients vs 36.1%, 13/36 ID patients, p = 0.13).

Outcomes
In-hospital CFR was significantly higher in ID patients (23.6%) than in IC patients (5.6%), p < 0.001. Causes of infectious encephalitis in non-survivor ID patients were: VZV (n = 4), HSV (n = 2), IC virus (n = 2), L. monocytogenes (n = 1), Epstein-Barr virus (n = 1), and Cryptococcus neoformans (n = 1), no causative agent was identified for two ID patients. Major sequelae at discharge were more frequent in ID patients (20%) than in IC patients (94%), p = 0.001 (Table 4).

In the final multivariable model, non-HIV-related immunodeficiency, age, coma and abnormal MRI findings were independently associated with poor outcome (Table 5). Having no causative agent identified was independently associated with a good outcome. The model goodness-of-fit was 0.84.

Discussion
The main findings of this multicentre, prospective cohort study on infectious encephalitis in HIV-negative ID patients are as follows: (i) ID patients with infectious encephalitis were older and had a higher prevalence of diabetes and pre-existing neurological disorders than IC patients; (ii) VZV was the primary cause of infectious encephalitis in ID patients; (iii) poor outcome was 2.7 times more frequent in ID patients (41.4%) than in IC patients (15.4%); (iv) having an immunodeficiency is an independent risk factor for death or major sequelae

### Table 2

<table>
<thead>
<tr>
<th>Causative agent</th>
<th>Immunodeficient patients</th>
<th>Immunocompetent patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 58</td>
<td>N = 416</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>VZV</td>
<td>15</td>
<td>25.9</td>
<td>50</td>
</tr>
<tr>
<td>HSV</td>
<td>13</td>
<td>22.4</td>
<td>119</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>6</td>
<td>10.3</td>
<td>17</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>TBE virus</td>
<td>2</td>
<td>3.4</td>
<td>24</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>EBV</td>
<td>2</td>
<td>3.4</td>
<td>4</td>
</tr>
<tr>
<td>CMV</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HHV6</td>
<td>2</td>
<td>3.4</td>
<td>0</td>
</tr>
<tr>
<td>JC virus</td>
<td>3</td>
<td>5.2</td>
<td>0</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>3</td>
<td>5.2</td>
<td>1</td>
</tr>
<tr>
<td>Other causes²</td>
<td>5</td>
<td>17.2</td>
<td>35</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>12.1</td>
<td>163</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; EBV = Epstein-Barr virus; ENCEIF: Etude Nationale de Cohorte des Encéphalites Infectieuses en France; HHV6 = human herpes virus 6; HSV = herpes simplex virus; JC virus = John Cunningham virus; NA: not applicable; TBE = tick borne encephalitis; VZV = varicella zoster virus.

² Other causative agents: among immunocompetent patients: enterovirus (n = 5), Mycoplasma pneumoniae (n = 4), measles virus (n = 3), West Nile virus (n = 3), Capnocytophaga canimorsus (n = 2), Leptospira spp. (n = 2), Japanese encephalitis virus (n = 2), Tropheryma whippelii (n = 2), Anaplasma phagocytophilum (n = 1), Chikungunya virus (n = 1), Coxiella burnetii (n = 1), Legionella pneumophila (n = 1), Borrelia burgdorferi (n = 1), Human parvovirus B19 (n = 1), Treponema pallidum (n = 1), Toscana virus (n = 1), Francisella tulorensis (n = 1), HIV (n = 1), Zika virus (n = 1), Rickettsia spp. (n = 1).

Other causative agents among immunodeficient patients: Borrelia burgdorferi (n = 2), West Nile virus (n = 1), Bartonella spp. (n = 1), enterovirus (n = 1).
in HIV-negative patients with infectious encephalitis. The older age of ID patients with encephalitis was expected, since the prevalence of ID conditions increase with age. However, ID patients, representing 11.7% of the ENCEIF cohort, had a similar clinical presentation to IC patients.

The distribution of infectious causes of encephalitis differed between the two groups. Among ID patients, the most frequent causative agent was VZV (26%), followed by HSV (22%), as opposed to IC patients, wherein HSV was the most frequent cause identified (27%) and VZV the second (11%).

This finding might suggest increasing the dose of acyclovir from 10 mg/kg/8 hours to 15 mg/kg/8 hours for the empirical treatment of encephalitis in HIV-negative ID patients before identifying the causative agent. However, although VZV is less susceptible to acyclovir than HSV in vitro [13], there are no data showing that a higher dose is more effective than a lower one, and there has been no clinical trial so far. Moreover, weighing the benefits and risks advocates against the systematic use of high-dose acyclovir for empirical treatment of encephalitis, given the dose-dependent renal and neurological toxicity of acyclovir [14]. Hence, most international guidelines recommend a dose of 10 mg/kg/8 hours acyclovir for empirical treatment of encephalitis, except when the probability of VZV encephalitis is high [10,15].

Our finding that VZV is the most frequent cause of encephalitis in HIV-negative ID patients has consequences: (i) the criteria for the use of high-dose acyclovir in this population may be different than for IC patients (i.e. consider high-dose in the presence of any suggestive clinical or imaging findings as haemorrhagic lesions) [16-18]; (ii) the results of CSF PCR tests for both HSV and VZV should be obtained as soon as possible in ID encephalitis patients to adjust the antiviral treatment if needed [10].

The apparent lower rate of acyclovir prescription in ID patients in this study raises concerns, given that HSV and VZV remain the most frequent pathogens responsible for encephalitis in this population, and given the strong association between early treatment with acyclovir and outcome [10,15]. However, none of the patients in this study with an apparent absence of acyclovir were later diagnosed with HSV and VZV.

As expected, *L. monocytogenes* was significantly more frequent among ID patients than IC patients.

Other opportunistic pathogens associated with severe immunodeficiency were found in our study, namely HHV-6, JC polyomavirus, and *C. neoformans*. Human herpes virus 6 may be responsible for encephalitis only in ID patients [19], and was identified in one allogeneic haematopoietic stem cell transplant recipient and one patient receiving long-term corticosteroid treatment in our cohort. Human herpes virus 6 integration was ruled out in those two cases. We diagnosed three cases of JC polyomavirus encephalitis: two patients with lymphoma treated with chemotherapy, and one heart transplant recipient who recently received rituximab treatment [20]. The two cases of Epstein-Barr virus encephalitis occurred in kidney transplant recipients in our cohort.

Encephalitis of unknown cause was three times less frequent among ID patients (12.1%) than IC patients (37.4%). Although the ENCEIF cohort only enrolled patients with encephalitis presumably of infectious origin, some cases of unknown origin may have been immune or inflammatory encephalitis. In HIV-negative ID patients with a weak immune system due to immunosuppressive treatment and unable to exhibit a strong immune or inflammatory response, encephalitis of inflammatory cause may be less frequent. This hypothesis is supported by our finding that having an encephalitis of unknown cause despite the suspicion of infectious origin was an independent protective factor against poor outcome in our final multivariable model. It is also possible that ID patients were more comprehensively investigated than IC patients. However, our data do not allow us to assess this hypothesis.

Several non-infectious causes of central nervous system disorders may be more common in HIV-negative ID patients, such as posterior reversible encephalopathy syndrome in patients treated with calcineurin inhibitors.
paraneoplastic encephalitis [22], central nervous system inflammation caused by tumour necrosis factor inhibitors [23] or neurologic adverse effects of immune checkpoint inhibitors [24]. Although non-infectious, these patients may fulfill the ENCEIF inclusion criteria (altered mental status > 24 hours, seizures, confusion, focal neurologic deficit, fever, MRI lesions) and could have been enrolled in our cohort.

The fact that 23.6% of ID patients had no biological meningitis (i.e. CSF WBC count < 5/μm³) outlines that suspected encephalitis should not be ruled out with regards to this finding only, especially in HIV-negative ID patients, who may display a lower inflammatory response. This is in agreement with the international case definition [9], where meningitis is only one criterion among others. In line with our findings, a literature review of encephalitis in ID patients found that HSV and VZV encephalitis were associated with lower CSF WBC count than in IC patients [25].

A retrospective case control study on HSV and VZV encephalitis in HIV-negative ID patients (n = 14), with an ID and IC group comparable to our study patients, showed a lower frequency of prodromal symptoms, an overall similar clinical presentation and a much higher CFR (35.7%) in ID patients than in IC patients (6.7%), in agreement with our study. They also found that a low CSF WBC count was associated with death, which may give way to a physio-pathological hypothesis for the severity of encephalitis in ID patients. Their inability to develop an efficient immune response may enable the pathogen to spread in the brain parenchyma [26].

We documented the high severity of encephalitis among ID patients with in-hospital CFR of 23.6%, and a high prevalence of sequelae or persisting symptoms impairing their global functioning at discharge (20%). Immunodeficiency was an independent risk factor of poor outcome with an OR of 3.41 (95% CI: 1.7–6.85), after adjusting for confounding bias. This finding suggests lowering immunosuppression therapy in HIV-negative ID patients presenting with encephalitis when possible, as a part of encephalitis treatment. An increase in age was also associated with poor outcome, in agreement with a previous study [2,4].

Beside susceptibility to severe infection, a secondary explanation for the severity of HSV or VZV encephalitis among ID patients may be acyclovir resistance due to prolonged exposure to valacyclovir, which is used as the primary prophylaxis in several ID conditions, particularly for transplant recipients [27,28].

Finally, prevention strategies should be used where possible. Varicella zoster virus infections could be avoided through pre-immunodeficiency vaccination, and food-borne listeriosis may be prevented in vulnerable patients, for example by informing them about at-risk food and spreading recommendation about preparing meals and respecting best-before dates [29]. These strategies are critical to address with the patient before starting an immunosuppressive treatment, keeping in mind the need for balance between making drastic changes and taking risk-adapted advice to lower the risk of infectious diseases.

The strengths of our study are the prospective design, allowing extensive data collection, the size of our cohort, a multicentric inclusion of patients and high external validity. To the best of our knowledge, this is the first prospective cohort to present the characteristics of infectious encephalitis among a broad spectrum of immunodepressive conditions.

This study has limitations. First, as this cohort was designed to study the clinical features and risk factors of infectious encephalitis in a large population in France, we did not collect extensive data on immune status, such as dose or duration of corticosteroid use or time elapsed since transplantation. Second, since patients were enrolled by infectious disease specialists, neurologists and intensivists, some patients with severe immunodeficiency may not have been enrolled if they were managed in other departments, such as haematology.

### Table 4

**Functional outcome at hospital discharge in HIV-negative immunodeficient and immunocompetent patients with infectious encephalitis, ENCEIF cohort, France 2016–2019 (n = 482)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Immunodeficient patients</th>
<th>Immunocompetent patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 55</td>
<td>N = 427</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n %</td>
</tr>
<tr>
<td>Death</td>
<td>13</td>
<td>23.6</td>
<td>24</td>
</tr>
<tr>
<td>Neuro-vegetative state</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Major sequelae</td>
<td>11</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Moderate sequelae</td>
<td>10</td>
<td>18.2</td>
<td>110</td>
</tr>
<tr>
<td>Minor sequelae</td>
<td>21</td>
<td>38.2</td>
<td>251</td>
</tr>
</tbody>
</table>


Functional outcome is assessed with the Glasgow outcome scale [11].

Outcome data were not available for three immunodeficient patients and nine immunocompetent patients.
TABLE 5
Risk factors for poor outcome from infectious encephalitis in HIV-negative immunodeficient patients from the multivariable analysis, final model, ENCEIF cohort, France 2016–2019 (n = 465)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.02–1.05</td>
<td>&lt;10⁻³</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>3.41</td>
<td>1.70–6.85</td>
<td>10⁻¹</td>
</tr>
<tr>
<td>Coma</td>
<td>6.05</td>
<td>3.31–11.07</td>
<td>&lt;10⁻³</td>
</tr>
<tr>
<td>MRI lesions</td>
<td>3.47</td>
<td>1.86–6.65</td>
<td>&lt;10⁻³</td>
</tr>
<tr>
<td>No causative agent identified</td>
<td>0.47</td>
<td>0.21–0.82</td>
<td>0.012</td>
</tr>
</tbody>
</table>

CI: confidence interval; ENCEIF: Étude Nationale de Cohorte des Encéphalites Infectieuses en France; GOS: Glasgow outcome scale; MRI: magnetic resonance imaging; OR: odds ratio.

Immunocompetent patients were the reference group for OR calculations. ORs were adjusted for immunodeficient patients.

For every 1-year increase in age.

Poor outcome was defined as a GOS of 1 to 3 (death, neurovegetative state or major sequelae).

Conclusion
Immunodeficient patients with infectious encephalitis are at high risk of death or major sequelae. While HIV-negative ID patients have been shown to be similar to IC patients in terms of clinical presentation and MRI results, the prevalence of meningitis was lower in ID patients. Varicella zoster virus, HSV and L. monocytogenes were the most frequent causes of infectious encephalitis among ID patients. Although investigating the causative agent should include rare and more ID-oriented pathogens, looking for the common pathogens responsible for infectious encephalitis in IC patients remains essential. Diagnosis and treatment algorithms, with empirical acyclovir, need to be carried out with the same stringency as with IC patients.

Ethical statement
In accordance with French regulation, we obtained informed non-opposition consent for the use of medical data from all patients or from relatives responsible for legal matters, or from the attending physician for patients with consciousness disorders. In the latter case, non-opposition to the use of medical data had to be confirmed by patients once they were able to. This study was approved by the French National Ethics Committee (CNIL, No. 915148, authorisation obtained 20 October 2015).

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Investigators

Sophie Abgrall (Paris), Laurent Argaud (Lyon), Xavier Argemi (Strasbourg), Guillaume Baille (Lille), Aurélie Baldolli (Caen), Sarah Benghanem (Paris), Kevin Bertrand (Perpignan), Charlotte Biron (Nantes), Genievela Blanchet-Fourcade (Narbonne), Mathieu Blot (Dijon), Elisabeth Botelho-Nevers (Saint-Etienne), Frédéric Bourdain (Paris), David Boutouille (Nantes), Cédric Bruel (Paris), Fabrice Brunelle (Versailles), Rodolphe Buzele (Saint-brieuc), Etienne Canoï (Paris), Philippe Casenave (Libourne), Bernard Castan (Périgueux), Charles Cazanave (Bordeaux), Céline Cazorla (Saint-Etienne), Thibaut Challan Belval (Annemasse), Pascal Chavanet (Dijon), Catherine Chirouze (Besançon), Tomasz Chroboczek (Villefranche sur Saone), Daniel Da Silva (Saint-Denis), Thomas De Broucker (Saint-Denis), Arnaud De La Blanchardière (Caen), Eric Denes (Limoges), Colin Deschanvres (Nantes), Aurélien Dinh (Paris), Olivier Epaulard (Grenoble), Pierre Fillatre (Saint-brieuc), Emmanuel Forestier (Chambéry), Thibault Frasse (Alès), Benjamin Gaborit (Nantes), Amandine Gagneux-Brunon (Saint-Etienne), Nicolas Gaillard (Montpellier), Arnaud Galbois (Quincy sous Sénart), François Goehringer (Nancy), Simon Gravier (Colmar), Valentin Greigert (Colmar), Isabelle Guet (Rouen), Thomas Guimard (La Roche sur Yon), Carole Henry (Saint-Denis), Maxime Bentzen (Reims), Jean-Etienne Herbrecht (Strasbourg), Snejana Jurici (Perpignan), Solene Kerneis (Paris), Marion Le Maréchal (Grenoble), Gwenael Le Moal (Poitiers), Raphael Lecomte (Nantes), François-Vicier Lesure (Paris), Olivier Lesueur (La Rochelle), Guillaume Louis (Metz), Rafael Mahieu (Angers), Alain Makinson (Montpellier), Guillaume Marc (Saint-Nazaire), Alexandre Maria (Montpellier), Nathalie Marin (Paris), Guillaume Martin-Blondel (Toulouse), Martin Martinot (Colmar), Philippe Mateu (Charleville-Mézière), Morgan Matt (Paris), Laurence Maulin (Aix-en-Provence), Frédéric Mechai (Paris), Eugénie Mutez (Lille), Nathalie Pansu (Montpellier), Solene Patrat-Delon (Rennes), Patricia Pavese (Grenoble), Véronique Pelonde-Ermée (Fort de France), Isabelle Pierre (Grenoble), Emilie Piet (Anneycy), Dimitri Psimaras (Paris), Mathilde Puges (Bordeaux), Sylvain Rheims (Lyon), Aurélie Richard-Morns (Lyon), Vincent Roubeau (Paris), Yvon Ruch (Strasbourg), Jean-Paul Stahl (Grenoble), Pierre Tattevin (Rennes), Jean-Marie Turmel (Fort de France), Louise Tyvaert (Nancy), Marc-Olivier Vareil (Bayonne), Adrien Wang (Suresnes), Heidi Wille (Bayonne), Mathieu Zuber (Paris).

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None declared.

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Statistical analysis, manuscript redaction: SL; AM.

Expert opinion and final proofreading: FA; OE; PT; JPS; AM.

References


