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Computerised decision support system towards informing Lyme borreliosis incidence in France

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In Europe, the estimation of Lyme borreliosis (LB) incidence is challenged by its heterogeneous reporting. In France, LB incidence is estimated from cases reported voluntarily to the Sentinelles network through general practitioners (GPs). Here, we explored how a computerised decision support system (CDSS), Antibioclic, with higher GPs participation and country-wide coverage, can inform further LB incidence. We derived the incidence of LB Antibioclic indicators (with either erythema migrans or disseminated disease), surveyed Antibioclic usage for suspect cases seen in GP consultations, and compared those estimates with the Sentinelles network estimations. In 2023, the incidence of Antibioclic LB indicators (290 per 100,000 inhabitants; CI95%, 277–303) was almost five times higher than LB incidence from the Sentinelles network, but sharing similar higher-incidence regions. Antibioclic LB indicators under-estimated the incidence of suspect cases seen in higher-incidence regions, while in lower-risk regions, Antibioclic estimation was closer to observed suspect cases. Refine estimates would benefit from improved follow up over time and space while improving case definition.

Keywords Computerised decision support system (CDSS), Lyme borreliosis, Incidence estimation, Spatial analysis

Lyme borreliosis (LB) is a tick-borne zoonosis caused by the infection with *Borrelia burgdorferi* sensu lato (Bbsl)[1]. Bbsl is transmitted to humans through the bite of an infected *Ixodes* tick, mostly *Ixodes ricinus* in Europe[2]. Its most common clinical symptom is an expanding skin rash called erythema migrans (EM) that starts to develop several days after the tick bite[3]. Initial diagnosis of LB is usually based on clinical signs, notably, through the presence of EM in 60–80% of tick bite cases[1]. For LB cases with disseminated manifestations or in the absence of EM, LB can be diagnosed using direct methods such as culture and PCR to confirm the presence of bacteria, or indirect methods such as ELISA test and Western Blot as the confirmation test to detect the antibodies produced after the infection[4,5].

LB is one of the most common vector-borne disease in Europe[2], yet its incidence estimation is challenged by heterogeneous reporting arising from a combination of mandatory and voluntary reporting, differences in case definition and also testing methods[1,6]. In France, LB is endemic and monitored by the Sentinelles network (*Réseau Sentinelles*) in primary care since 2009[7]. According to the Sentinelles network, annual incidences of LB in France were estimated to vary between 41 and 104 per 100,000 inhabitants from 2009 to 2023 with 59 per 100,000 inhabitants (CI95%, 42–60) in 2023. However, although the Sentinelles network ensures the reliability and quality of the reports, such incidence estimates rely on LB cases reported by general practitioners (GPs) voluntarily registered within the Sentinelles network (hereinafter called Sentinelles GPs), representing around 2% of the registered GPs nationwide (n = 1,135)[8]. Furthermore, their participation in weekly surveillance may be lower, reported on average at 297 GPs per week in 2023[7]. In addition, whilst previous studies have analysed the spatial and seasonal determinants of LB incidence using the Sentinelles network data in combination with animal and environmental data, those previous estimations had limitation in the resolution they used, spatially by using interpolation methods or temporally by providing estimates on an annual or quarterly basis[9,10].

In this context, we aim to improve our knowledge of LB incidence across the country by leveraging information from Antibioclic, a French computerised decision support system (CDSS) used by more than 70% of GPs nationwide.

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Antibioclic (https://antibioclic.com/), implemented in 2011, is an online platform accessible to healthcare professionals including GPs, other physicians, pharmacists, midwifes, and nurses, to assist them in prescribing antibiotics in primary care. In 2018, the number of Antibioclic users was estimated at around 5,000 per day[11]. Antibioclic provides antibiotic prescription recommendations for around 40 health indicators, including LB. Data for Lyme borreliosis indicators, collected each time a user consulted the CDSS LB indicators, have been available since November 2017[11], allowing to study the use of Antibioclic for LB indicators over time. Furthermore, since May 2022, user information (that is, mainly occupation and location of medical practice) has been recorded, enabling better monitoring of direct Antibioclic use by the GP users spatially at postcode level. By December 2023, around 50,000 French GPs were registered within the system[12] out of 89,000 registered Antibioclic users covering all healthcare occupations.

Here, we evaluate the potential of secondary use of CDSS data to provide epidemiological information. We first estimated the incidence of Antibioclic usage for LB indicators and compared them to LB incidence estimates from the Sentinelles network, which is the only surveillance system for LB in primary care in France. We assessed whether Antibioclic CDSS could provide additional insight into LB incidence by using the Sentinelles network as reference. Then, we set up a cross-sectional online study, surveying Antibioclic users, to compare the incidence of Antibioclic usage for LB indicators with reported suspect cases seen in consultations, in order to get a better understanding of Antibioclic use upon cases seen in consultations.

Results

Antibioclic data description

From November 2017 to September 2024 (Fig. 1), over 29 million Antibioclic requests were made, where 75.88% of requests concerned adults (n = 22,326,473) and 24.11% concerned children (n = 7,094,976). The skin and soft tissue infections domain was the 4th most requested domain with a total of 3,923,412 requests (13.3%), where 755,598 requests (3.38%) were related to Lyme borreliosis (LB). Requests for LB indicators were categorised as follows: 59.43% of requests concerned erythema migrans (EM), 31.85% tick bites (TB), and 8.72% disseminated disease (DD) (Supplementary Table 1). From those Lyme requests, 79% (n = 597,236) requests concerned adults and 21% (n = 158,362) concerned children. For Antibioclic LB indicators incidence estimation, we included requests made for EM and DD indicators to make it comparable with the Sentinelles network estimates.

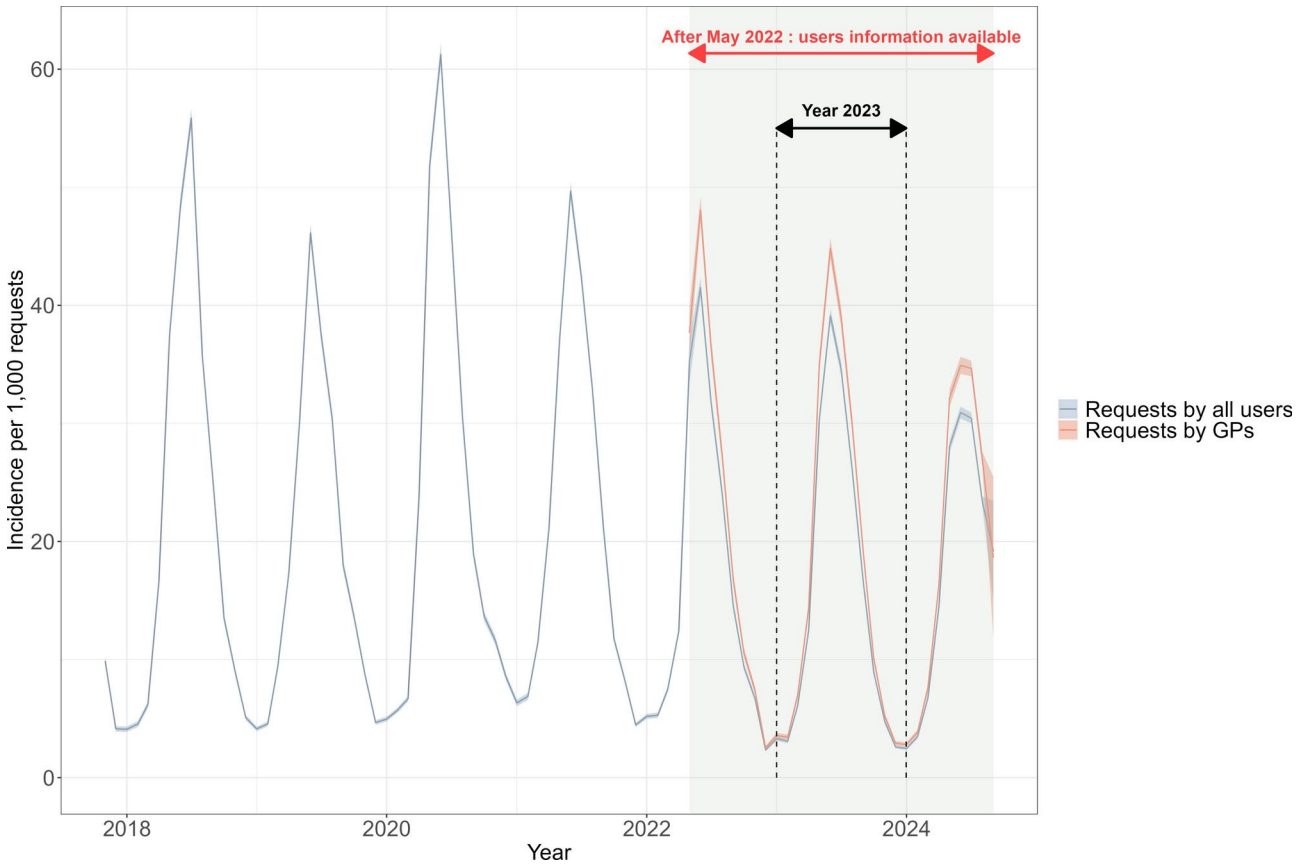


Fig. 1. Monthly incidence estimation of Antibioclic requests (CDSS usage) for Lyme indicators (EM and DD combined). The grey line corresponds to the incidence of Lyme requests from all users and the red line corresponds to the incidence of Lyme requests made by GPs. From May 2022 onwards, the user information was available as represented by the shaded area with red double arrow. The black dashed lines and double arrow represent the full year of 2023.

It is important to note that a request corresponded to an online form filled by users when they consult Antibioclic for any health indicators for any reasons (e.g., during patient consultation, and to gain knowledge about antibiotic prescription guidelines for LB). This implies that some Antibioclic requests might not involve a case seen in consultation. Furthermore, from November 2017 to April 2022, an Antibioclic request was defined as a single CDSS usage, by a health practitioner, on specific day and time. From May 2022, an Antibioclic request was defined by an identified health practitioner, on a specific day and time, and at a specific location (at postcode level).

Prior to May 2022 (Fig. 1), metadata on Antibioclic users and requests (date, time, and IP address) were scarce, precluding targeted data analysis. From May 2022 onwards, date and time of the requests, as well as age, sex, medical specialty, IP addresses, and the postcode of medical practice of the users became available. Between 1 May 2022 and 1 September 2024, a total of 10,930,507 Antibioclic requests were made. Among them, 223,116 (2.04%) were considered duplicates, considering that they were created by the same user for the same indicator within 5 min. Furthermore, during this period, 58.44% (n = 6,257,918) requests were made by 36,089 French GPs over 35 years old. Among these requests, 98.5% were made by GPs in non-hospital-based practice, and 1.5% by GPs in hospital-based practice. For our study, we consider only non-hospital-based (primary care) GPs, who overall created 104,613 Lyme requests (EM and DD), corresponding to 1.7% of total requests made by registered non-hospital-based French GPs (Supplementary Fig. 1). We excluded GPs under 35 years old to exclude young GPs not yet established (see *Methods* for details).

Antibioclic lyme indicators requests, temporal assessment, 2017–2024

We estimated Antibioclic usage through requests made for LB indicators between November 2017 and September 2024. To mirror Lyme (EM and DD) incidence estimation by the Sentinelles network, we considered the requests for Lyme with EM and DD indicators by primary care general practitioners (GPs) (see *Methods* for details).

In 2017–2024, the monthly incidence of Antibioclic usage for LB indicators (expressed per 1,000 requests, as in Delory et al. 2024[13]) exhibited a seasonal pattern (Fig. 1, grey line) with higher incidences reported from late March—early April to October, with peaks around mid-June. During the whole study period, the highest peak was estimated at 61 per 1,000 requests (CI95%, 60–62) in June 2020. From May 2022 onwards (Fig. 1, red double arrow), the availability of user information allowed to estimate incidence of Antibioclic usage by GPs (Fig. 1, red line). For both requests made by all users and by GPs, the yearly incidence peak showed a declining trend from 2020 onwards.

The year 2023 is the sole full year for which complete user information is available (Fig. 1, black double arrow), allowing to estimate the incidence per 100,000 inhabitants from GPs reports, and spatially. Therefore, the year 2023 was used for the spatial assessment, for the comparison with the Sentinelles network, and as a benchmark year to estimate incidence per 100,000 inhabitants before 2023 (i.e., for the period 2018–2022).

Antibioclic lyme indicators requests, spatial assessment, 2023

In 2023, the number of GPs participating in Antibioclic was 29,448, corresponding to 46.5% of the registered GPs in mainland France and Corsica. The 2023 annual incidence of Antibioclic usage for LB indicators was estimated at 290 requests per 100,000 inhabitants (CI95%, 277–303). This estimate varied across regions with higher incidences found in central and northeastern France (Fig. 2a). In these regions, the annual incidence estimation of this indicator peaked at 495 per 100,000 inh. in Limousin, 487 per 100,000 inh. in Auvergne, and 480 per 100,000 inh. in Alsace (Fig. 2b).

In June 2023, a peak month for LB, the national incidence of Antibioclic usage for LB indicators was estimated at 55 per 100,000 inhabitants (CI95%, 49–61), ranging from 35 (CI95%, 30–39) in Provence-Alpes-Côte d'Azur to 98 (CI95%, 80–117) per 100,000 inhabitants in Limousin. The incidence in June 2023 accounted for 18.9% of the annual incidence in 2023. At the regional level, this proportion varied from 16.2% in Provence-Alpes-Côte d'Azur to 25.2% in Corsica (Fig. 2b).

The incidence comparison between LB-related Antibioclic (AB) usage and LB cases reported to the Sentinelles network (SN) by region in 2023 is presented in Fig. 3. The LB incidence by SN was estimated from reported cases seen in general practice and validated cases by a multidisciplinary independent committee[7]. On the other hand, the incidence of LB-related Antibioclic usage is based on LB-related requests made by primary care GPs to the CDSS. The difference in these two incidence estimates, presented as an AB/SN ratio, varied from 2 to 36 across regions. We applied an exponential decay model and found an exponential relationship between the AB/SN ratio and incidence from the Sentinelles network. That is, higher ratio values were found in lower-risk regions, marked with low LB incidence by the Sentinelles network, and the AB/SN ratio decreased as the incidence from the Sentinelles network increased (Fig. 3b).

Retrospective estimation of incidence of antibioclic lyme indicator, 2018–2022

In 2023, the incidence of LB cases reported to the Sentinelles network was estimated at 59 per 100,000 inhabitants (CI95%, 50–68), with the incidence of Antibioclic usage for LB indicators (290 per 100,000 inhabitants; CI95%, 277–303) being 4.9 times higher. To compare the incidence of LB-related Antibioclic usage and LB cases reported to the Sentinelles network, both expressed per 100,000 inhabitants, for the period 2018–2022, we used the 2023 year as a benchmark. This approach allowed us to estimate the number of Antibioclic requests made by GP in previous years and estimate the incidence of Antibioclic usage for LB indicators per 100,000 inhabitants (see *Methods* for details). This resulted in the annual incidence of LB-related Antibioclic usage in 2018–2022 estimated between 256 (CI95%, 244–267) and 435 (CI95%, 416–454) per 100,000 inhabitants. These estimates were between 4 to 6 times higher than the incidence of LB cases reported to the Sentinelles network (Fig. 4).

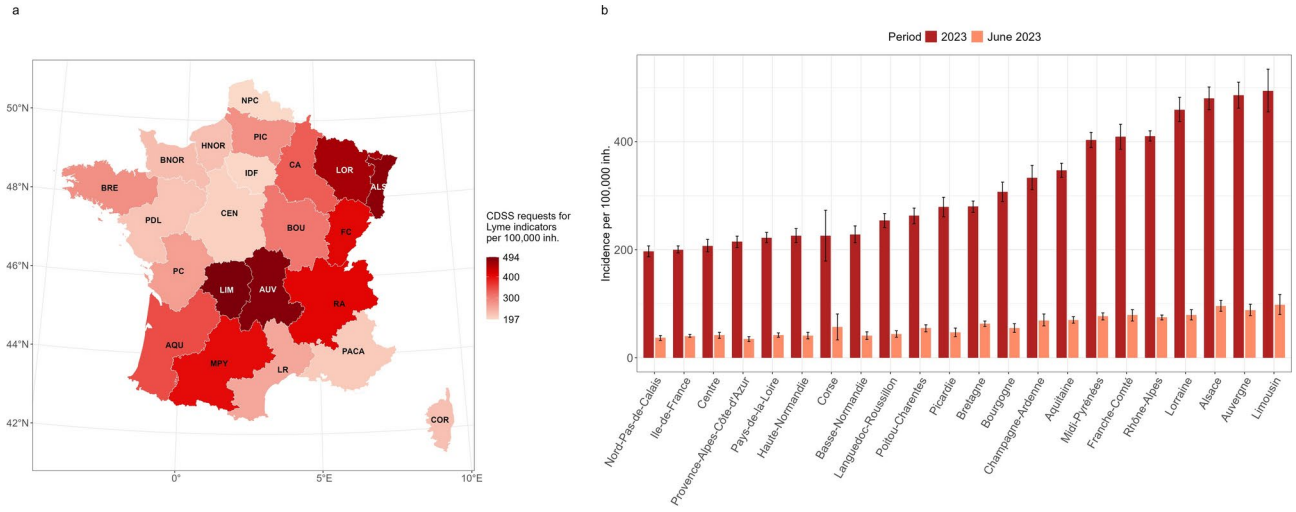


Fig. 2. Incidence of Antibioclic requests (CDSS usage) for Lyme indicators, in France in 2023 per 100,000 inhabitants. (**a**) Map of annual incidence per region. The map was generated using R version 4.4.1 (https://cran.r-project.org/) and R packages: *ggplot2* (https://ggplot2.tidyverse.org/) and *sf* (https://r-spatial.github.io/sf/), in Rstudio version 2024.09.1 (https://posit.co/download/rstudio-desktop/). (**b**) Barplot of regional incidence with CI (per 100,000 inhabitants), ordered from lowest to highest incidence. Dark red bars correspond to the whole period of 2023 and light red bars correspond to the month of June 2023 (peak month). ALS = Alsace; AQU = Aquitaine; AUV = Auvergne; BNOR = Basse-Normandie; BOU = Bourgogne; BRE = Bretagne; CEN = Centre; CA = Champagne-Ardenne; COR = Corse; FC = Franche-Comté; HNOR = Haute-Normandie; IDF = Ile-de-France; LR = Languedoc-Roussillon; LIM = Limousin; LOR = Lorraine; MPY = Midi-Pyrénées; NPC = Nord-Pas-de-Calais; PDL = Pays de la Loire; PIC = Picardie; PC = Poitou–Charentes; PACA = Provence-Alpes-Côte d'Azur; RA = Rhône-Alpes.

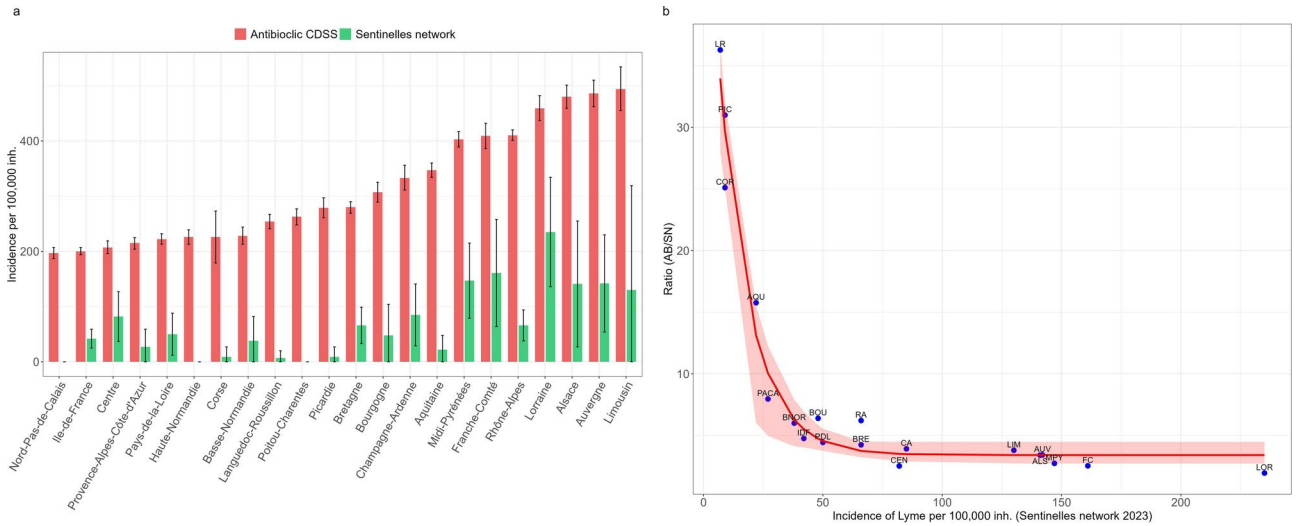


Fig. 3. Comparison of Antibioclic LB requests (AB) and the Sentinelles network Lyme incidence (SN) estimates by region in 2023. (**a**) Barplot showing LB incidence estimated by region from both systems, from lower to higher AB incidence. Red bars correspond to incidence of LB requests from Antibioclic indicator and green bars correspond to incidence of LB cases from the Sentinelles network. (**b**) Relation between AB/SN ratio and Lyme incidence from Sentinelles network in different regions. ALS = Alsace; AQU = Aquitaine; AUV = Auvergne; BNOR = Basse-Normandie; BOU = Bourgogne; BRE = Bretagne; CEN = Centre; CA = Champagne-Ardenne; COR = Corse; FC = Franche-Comté; HNOR = Haute-Normandie; IDF = Ile-de-France; LR = Languedoc-Roussillon; LIM = Limousin; LOR = Lorraine; MPY = Midi-Pyrénées; NPC = Nord-Pas-de-Calais; PDL = Pays de la Loire; PIC = Picardie; PC = Poitou–Charentes; PACA = Provence-Alpes-Côte d'Azur; RA = Rhône-Alpes.

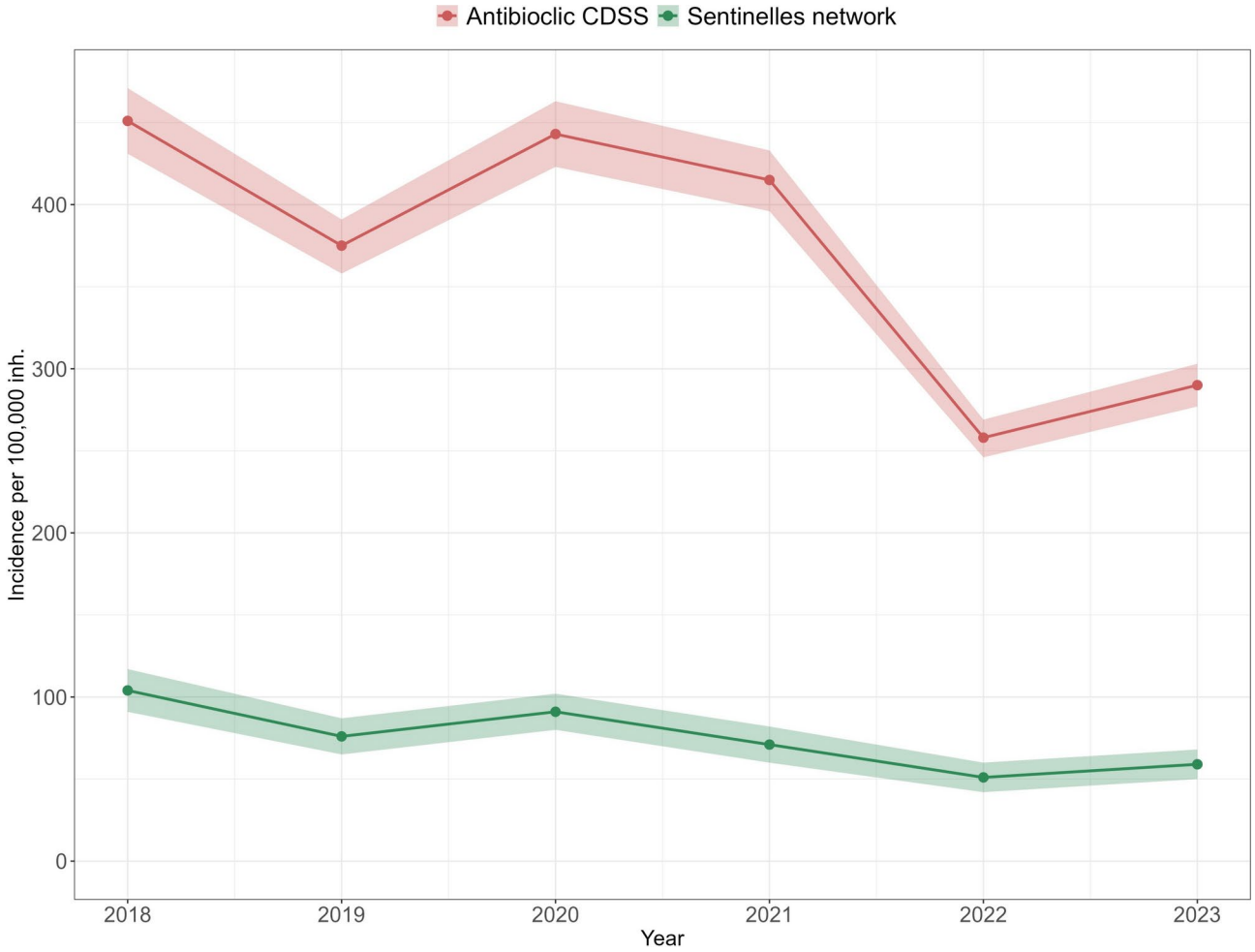


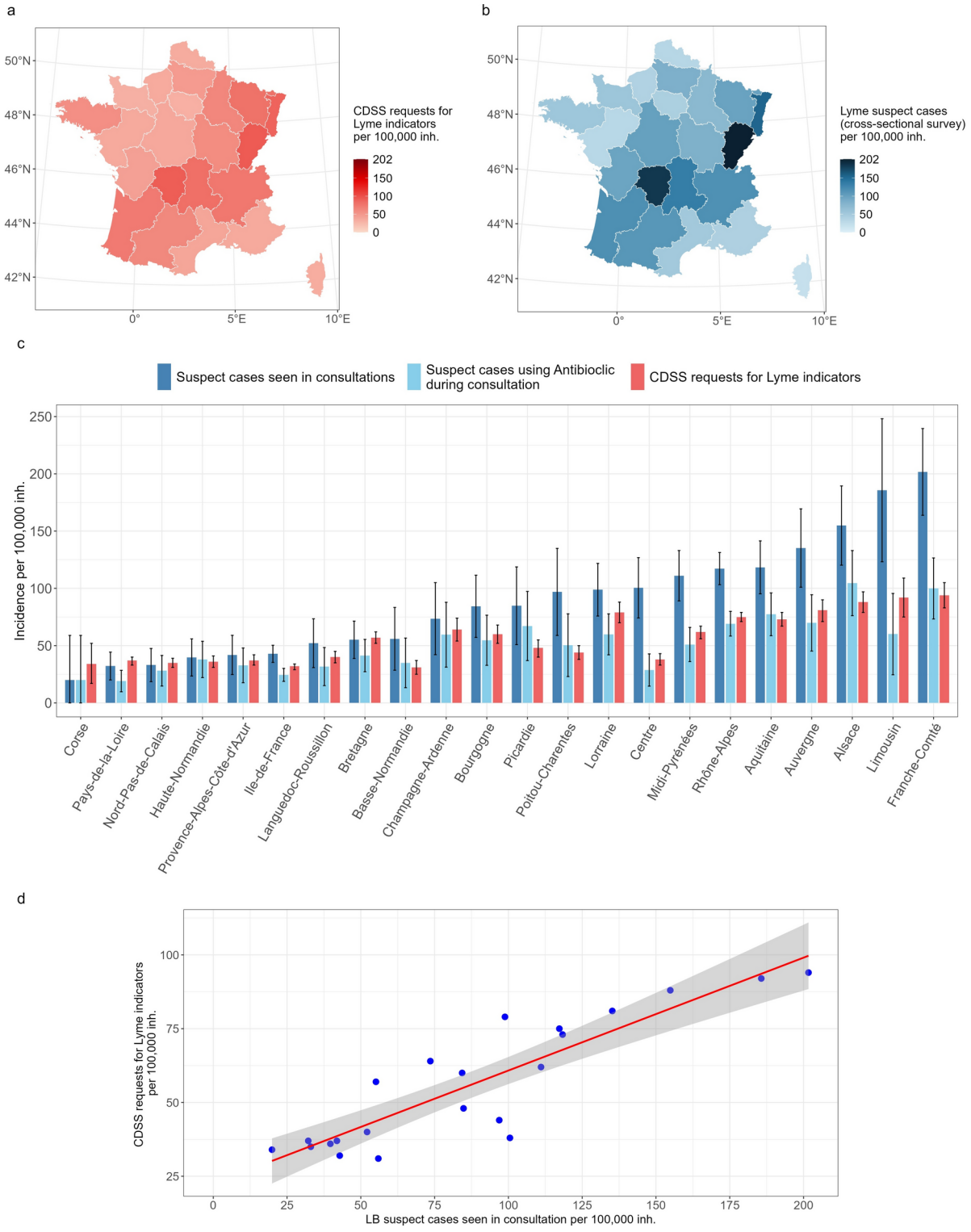
Fig. 4. Comparison of annual incidences between Antibioclic LB requests (red line) and the Sentinelles network LB incidence (green line) from 2018 to 2023, per 100,000 inhabitants.

Antibioclic cross-sectional study

We set up a cross-sectional study that surveyed Antibioclic users online, to estimate the incidence of reported Antibioclic usage for LB suspect cases seen in consultations during the month of June 2024 (see *Methods* for study protocol). Overall, 38,206 Antibioclic users were invited for the online survey and 3,243 users participated, including GPs and other health professionals, and resulting in 8.49% participation rate for all users. The survey participants' profession-based characteristics were similar to Antibioclic participants recorded in June 2024, but with higher median of age (42 [IQR, 35–55]) for survey participants (Supplementary Table 2). Among the respondents, 62.6% of them were females (n = 1,759) and 37.4% were males (n = 1,052). The majority (76.1%) of the respondents were GPs, while the rest were specialists (8%), pharmacists (7.9%), and other health professionals (2.6%). Since the number of GPs invited to the survey among the overall invited participants (n = 38,206) was untracked, we could not estimate survey participation rate among GPs. Nevertheless, the percentage of GPs who responded to the survey among all Antibioclic GP users varied from 3.6% to 11.5% across regions (Supplementary Table 3), and the regional distribution of GPs respondents was similar to the regional distribution of Antibioclic GP users (Supplementary Table 4).

From the survey, a total of 1,306 suspicions of Lyme borreliosis, either erythema migrans or disseminated disease, were reported from 1,451 GPs over 35 years old (Supplementary Fig. 2). Among them, 32.2% GPs (n = 468) reported that they used Antibioclic for at least one suspected LB case over the surveyed month. These GPs used Antibioclic for 57.6% of these suspected LB consultations (n = 752). The incidence of Antibioclic usage for LB suspicions reported in the survey was estimated at 45 per 100,000 inhabitants (CI95%, 30–61). This level was similar to the incidence of LB-related Antibioclic usage recorded in the CDSS for the same month (51 per 100,000 inhabitants; CI95%, 46–56) but lower than the incidence of consultations for LB suspicions (76 per 100,000 inhabitants; CI95%, 57–96) in June 2024.

Despite the difference between the Antibioclic LB indicators in CDSS (51 per 100,000 inhabitants) and the consultations reported for LB suspect cases in the survey (76 per 100,000 inhabitants), the regional incidences showed similar pattern, with the highest incidence found in Franche Comté, Limousin, and Alsace regions (Fig. 5a-c). In addition, the incidence of Antibioclic LB requests in June 2024 was similar to the period of June



2023 (55 per 100,000) (Fig. 2b, light red bars) and ranged from 31 (CI95%, 25–37) in Basse-Normandie to 94 (CI95%, 83–105) per 100,000 inhabitants in Franche-Comté (Fig. 5c, red bars).

The Pearson correlation analysis showed a positive correlation between regional incidence of Antibioclic usage in CDSS for LB indicators and consultations for LB suspect cases reported in the survey, with a coefficient of 0.89 (CI95%, 0.75–0.95). The linear regression analysis provided an R^2 value of 0.79 (Fig. 5d). Furthermore, the relation between the incidence of LB suspect cases seen in consultations and the proportion of survey participants per region was presented in Supplementary Fig. 3, showing a linear relationship where the incidence of suspect cases tended to increase with the increased proportion of participants ($R^2 = 0.40$).

◀**Fig. 5**. Comparison of incidence between Antibioclic LB requests and survey results, June 2024. (**a**) Map of regional incidence of Lyme Antibioclic requests submitted to CDSS (per 100,000 inhabitants) in France. The map was generated using R version 4.4.1 (https://cran.r-project.org/) and R packages: *ggplot2* (https://ggplot2.tidyverse.org/) and *sf* (https://r-spatial.github.io/sf/), in Rstudio version 2024.09.1 (https://posit.co/download/rstudio-desktop/). (**b**) Map of the regional incidence of Lyme suspect cases seen in consultations (per 100,000 inhabitants) in France, from the survey. The map was generated using R version 4.4.1 (https://cran.r-project.org/) and R packages: *ggplot2* (https://ggplot2.tidyverse.org/) and *sf* (https://r-spatial.github.io/sf/), in Rstudio version 2024.09.1 (https://posit.co/download/rstudio-desktop/). (**c**) Barplot of regional incidence with CI95% (per 100,000 inhabitants): dark blue bars correspond to incidence of Lyme suspect cases seen in consultations, light blue bars correspond to incidence of Lyme suspect cases where GPs consulted Antibioclic during consultation, and red bars correspond to the incidence of Lyme Antibioclic requests. (d) Scatter plot of the relation between the incidence of Lyme suspect cases and Lyme Antibioclic requests.

Discussion

Our study investigated the incidence of LB-related requests from a CDSS, Antibioclic, as a proxy to help informing Lyme borreliosis (LB) epidemiology in mainland France and Corsica, benefiting from the system's nationwide coverage with over 50,000 French general practitioners (GPs).

The temporal incidence estimation, expressed per 1,000 requests, demonstrated the seasonality of Lyme borreliosis with higher estimation between April and October. This seasonality is in line with the period of activity of *Ixodes ricinus*[14], which is the primary vector that transmit the bacteria causing LB in France. The risk of getting bitten by *Ixodes ricinus* was reported to increase in May–June and August-September[15]. Similarly, a study by Septfons et al. using the Sentinelles network data, reported an annual peak of diagnosed LB cases in July between 2011 and 2016[16].

In 2023, the incidence of Antibioclic usage for LB indicators was reported at 290 requests per 100,000 inhabitants (CI95%, 277–303), almost five times higher than the 59 LB cases per 100,000 inhabitants reported by the Sentinelles network (CI95%, 50–68). Between 2018 and 2023, annual incidences from Antibioclic usage for LB indicators were approximatively four to six times higher than incidence of LB cases reported by the Sentinelles network. However, despite the difference, the spatial distribution of regional incidences from Antibioclic in 2023 aligned with higher-risk regions as highlighted by the Sentinelles network, in northeastern and central parts of the country, such as Limousin, Auvergne, Alsace, and Lorraine[7]. Furthermore, two serosurveys investigating the presence of *Borrelia burgdorferi* sensu lato (Bbsl) antibodies among forestry workers and conducted over fifteen years apart also found higher seroprevalence in the north eastern part of France[5,14]. The study conducted in 2020 covering northern half of France found a west–east gradient where the seroprevalence in the western area (Basse-Normandie, Bretagne, and Pays-de-la-Loire) was lower than the eastern regions (Alsace, Lorraine, Champagne-Ardenne, Bourgogne, and Franche-Comté)[5], similar to our finding. These higher seroprevalence of Bbsl found in the northeastern regions of France[5,14] might help explain the higher incidence of LB-related Antibioclic requests we estimated in those areas.

The relation between Antibioclic (AB) LB indicators usage and the Sentinelles network (SN) estimates were presented as ratio, which represents the gap between AB and SN regional estimates in 2023. This AB/SN ratio and the Sentinelles network incidence showed an exponential decay relationship, where the ratio was higher in regions with lower LB cases incidence. This could suggest a discrepancy in CDSS use by GPs between regions, depending on their familiarity towards the disease. GPs in lower-risk regions, marked by lower LB incidences from the Sentinelles network, might be less exposed to see potential LB cases in consultations, and thus rely more frequently on Antibioclic for diagnostic and treatment recommendations[17]. Moreover, this gap in incidence estimates may also result from difference in GPs profile between those participating to the Sentinelles network and those using Antibioclic. In this regard, we tried to match as much as possible the profile of Antibioclic GPs to the Sentinelles network ones when estimating the incidence (see *Methods* for explanation). Furthermore, four regions with the lowest incidence from the Sentinelles network (Languedoc-Rousillon, Picardie, Corsica, and Aquitaine) showed the largest gap with Antibioclic with AB/SN ratio of over 15. This might be explained by the presence of ticks, not necessarily *Ixodes*, everywhere in France[18–20]. The bites from these ticks could cause skin reaction that resembles erythema migrans, which might increase the number of consultations related to LB and therefore could increase the incidence of Antibioclic usage for LB indicators.

In addition, the observed discrepancies between Antibioclic and the Sentinelles network estimates might partly result from differences in case definitions, which might impact the sensitivity and specificity of the reported cases. The Sentinelles network validates Lyme cases upon a European case definition[21] and with a multidisciplinary validation committee (see *Methods* for case definition) which might lead to higher specificity but also a possible sampling bias by GPs reporting the cases, and thus results in under-estimation of cases incidence. On the other hand, even when LB-related Antibioclic request was made during consultation, Antibioclic usage depends on GPs' clinical diagnosis which might differ from one GP to another, with some GPs more frequently exposed and trained in conducting LB diagnosis. Moreover, in certain cases, GPs might also consult Antibioclic to prescribe preventive treatment for LB following a tick bite. Similarly, LB suspect cases reported in our cross-sectional survey were based on clinical suspicions without a defined case definition nor a validation process, therefore lowering the specificity of the data we collected online compared to the Sentinelles network. Antibioclic CDSS could potentially capture more LB suspect cases based on clinical diagnosis, with the risk of over-estimating the incidence. For instance, a retrospective study by Perthame et al. analysing over 3,000 Lyme cases from 700 physicians, found that only 60% of Lyme cases were confirmed (n = 2,104) which correspond to LB cases with an EM with at least 5 cm in diameter or positive serology test for disseminated

aspects of the disease[22], supporting the possibility of over-reporting both in Antibioclic system and in our survey among Antibioclic users.

Our cross-sectional survey revealed that Antibioclic was used overall in about half of consultations for LB clinical suspect cases (752 of 1,306 suspect cases) therefore underestimating the observed incidence of suspect cases overall (45 vs 76 per 100,000 inh. in June 2024). In higher-risk regions, in this case marked by higher regional incidence compared to the national incidence of LB suspect cases (regional incidence of suspect cases > 76 per 100,000 inhabitants), we observed a less systematic use of Antibioclic during consultations, in comparison with the number of reported suspect cases. Meanwhile in regions at lower risk (regional incidence of suspect cases < 76 per 100,000 inhabitants), Antibioclic requests estimations were almost similar to LB suspicions seen in consultations, suggesting that Antibioclic may better reflect its usage during consultations in regions with lower incidence of LB suspect cases. Furthermore, reported Antibioclic use from the survey closely aligned with the estimated incidence of Antibioclic LB requests in June 2024 (45 vs 51 per 100,000 inh.). This finding suggests that although Antibioclic requests could be made for informative purposes without an actual case[11], Antibioclic use for this motive might not be as frequent among GPs. However, the overall participation rate among Antibioclic users invited to the survey, which included different healthcare professionals, was low, under 10%. Moreover, we could not estimate the participation rate specifically for GPs, since the number of invited GPs was not available.

Most surveillance systems are prone to underestimation, resulting from under-ascertainment in the community and underreporting by healthcare provider[23]. This might also be the case for the Sentinelles network, considering the voluntary nature of the reporting system. A study conducted in Wisconsin, United States (US), showed a lower estimation of LB incidence from the national surveillance compared to the estimation from the electronic health record (EHR)[24]. Similarly in Germany, from 2013 to 2017, LB incidence from 9 states with mandatory notification was estimated between 26 and 41 cases per 100,000 population[25], while the incidence of medically-attended LB from 2015 to 2019 was estimated higher, ranging from 195.7 to 254.5 per 100,000 population[26]. These findings suggest the needs of additional data sources to help estimating the real burden of LB.

Previously, health insurance claims data in the US has been used to estimate the incidence of clinician-diagnosed LB between 2005 and 2010. They showed similar epidemiological pattern but with higher incidence estimate for claims data compared to US surveillance (106.6 vs 9.4 cases per 100,000 persons per year)[27], which was in line with our findings. In another study, Antibioclic has been used to help informing the epidemiological pattern of community-acquired pneumonia (CAP), where they managed to capture the emergence of CAP in 2023, yet without surveying GPs on actual cases seen in practice[13].

Despite the gap between Antibioclic LB-related requests and LB suspect cases reported from the survey, our study suggests that their spatial variations at regional level were similar to those observed by the Sentinelles network, showing higher Antibioclic activity in regions with higher LB incidence reported by the Sentinelles network. In the Sentinelles network, certain regions show fluctuations in incidence between years, especially in regions with higher incidences. It will be important to investigate in the future whether Antibioclic data will have similar regional variations, covering more years to capture regional trends over time, and thus enable a more robust spatial and temporal comparison with the Sentinelles network.

To summarise, our analysis revealed a higher annual incidence estimation from Antibioclic compared to the Sentinelles network. However, Antibioclic LB indicators captured similar trends of Lyme incidence over time and space, at regional level. Antibioclic along with cross-sectional survey could offer an estimation of the number of consultations for LB suspect cases, which could represent the upper bound limit of LB incidence, while LB incidence estimation from the Sentinelles network could represent the lower bound estimate. This demonstrates a potential secondary use of CDSS to help inform LB activity in France, as a complement to the Sentinelles network, by capturing LB cases signal in areas that might be missed or not covered by the Sentinelles network. Consequently, integrating multiple data sources is an option to explore further to improve LB epidemiology in France. Nevertheless, improved estimation of LB incidence using CDSS would benefit from further data and research collected on the system, as well as implementation of LB case definition to improve specificity of the clinical diagnosis by CDSS users. Finally, since September 2024, Antibioclic CDSS has been recording systematically information on purpose usage to help assess better suspect cases.

Methods

Antibioclic data

Antibioclic CDSS has a wide coverage across France, with over 50% of French general practitioners (GPs) registered in the system. Antibioclic data were collected every time the user consulted the system by filling out an online requests form for a targeted pathology, where the user could detail the specific indicator or symptom of the disease, the patient's age group, and specific health conditions. However, Antibioclic use is not limited to receive treatment recommendations during patient consultations, but it can also be used for informative purpose. Consequently, Antibioclic request made for a health indicator does not necessarily correspond to a case seen in consultation. Since its release in late 2011, Antibioclic has collected data on 37 health indicators grouped in seven anatomical domains[11], and as of September 2024, Antibioclic included additional indicators up to over 40 health indicators, grouped in nine different anatomical domains (Supplementary Fig. 4). Our study focused on Lyme borreliosis (LB) indicators, which is classified within skin and soft tissue infections domain.

Antibioclic online survey to compare CDSS use with activity in consultations, June 2024

We conducted a survey on Antibioclic users to understand Antibioclic usage frequency related to Lyme indicators and to estimate incidence of LB suspicious cases seen in consultations. Lyme indicators generally peaked in June according to 2017–2023 Antibioclic data. Therefore, the questionnaire was sent in July 2024 to investigate the

peak month of June 2024. The survey invitation was addressed to a subset of Antibioclic users who have agreed to participate to research studies.

The questionnaire consisted of a set of questions regarding the users and their practice: i) how many cases of tick bites, suspicions of erythema migrans (EM), and suspicions of Lyme borreliosis disseminated disease (DD) they received during the month of June 2024, ii) whether they consulted Antibioclic for any of those consultations, and iii) for how many of Lyme-related consultations they used Antibioclic. For DD indicator, we also asked whether the patient had a positive serology test result.

Using these data, we estimated i) the incidence of Lyme suspect cases (EM + DD) seen in consultations by GPs in June 2024, ii) Antibioclic usage percentage reported by GPs during consultations, and iii) the incidence of consultations for Lyme suspect cases (EM + DD) for which GPs reported to use Antibioclic. We compared those estimates (i and iii) with Antibioclic requests for LB indicator submitted to the CDSS for that same period (June 2024), and for June 2023, as a benchmark for between-year comparison.

Antibioclic incidence estimation, in time and space

For incidence estimation and to enable the comparison with the Sentinelles network, we only considered Lyme requests with EM or DD indicators, created by non-hospital-based GPs over 35 years old in mainland France and Corsica. The number of GPs registered within Antibioclic system was higher than the number of registered French GPs, which might be caused by the presence of young GPs not yet established. In France, the mean age for GPs to establish their practice is estimated at 35 years[28]. Therefore, we limited the incidence estimation to include only GPs that are 35 years old or older. The incidence of Antibioclic usage for LB indicators was estimated based on the weekly number of Lyme requests made per participating Antibioclic GPs, and adjusted by the number of registered GPs and population size. However, for the incidence of suspect cases from the survey in June 2024, the incidence was estimated directly for the whole month, based on the number of suspect cases and participating GPs in that month. In addition, we excluded GPs under 35 years old from the survey to enable comparison with the Antibioclic request data.

The annual incidence of Antibioclic usage for LB indicators per 100,000 inhabitants in France (I^1) was obtained from the weekly regional incidences ($I_{r,w}$). To estimate this weekly regional incidence, we first calculated the $R_{r,w}$ which was the number of Lyme requests made per participating GPs in region r and week w (Eq. 1). Then, we estimated the total number of Lyme requests ($L_{r,w}$) by multiplying $R_{r,w}$ to the number of registered French GPs in the region (Eq. 2), and also estimated the confidence interval for $L_{r,w}$ (Eq. 3). Later, we adjusted $L_{r,w}$ with the number of populations of the region to obtain the weekly regional incidence ($I_{r,w}$) per 100,000 inhabitants (Eq. 4). We summed up the weekly regional incidences to get the annual regional incidences (I_r) (Eq. 5). Finally, we obtained the annual national incidence (I^1) from the weighted sum of regional incidence based on the population size (Eq. 6).

$$R_{r,w} = \frac{N_{r,w}}{m_{r,w}} \tag{1}$$

$$L_{r,w} = R_{r,w} \cdot M_r \tag{2}$$

$$CI = R_{r,w}M_r \pm 1.96M_r\sqrt{var(R_{r,w})} \tag{3}$$

$$I_{r,w} = \frac{L_{r,w}}{P_r} \cdot 100{,}000 \tag{4}$$

$$I_r = \sum I_{r,w} \tag{5}$$

$$I^1 = \sum (I_r \frac{P_r}{P_{FR}}) \tag{6}$$

In the equations, $\boldsymbol{N_{r,w}}$ corresponds to the number of Lyme requests by GP over 35 years old in region r and week w, $\boldsymbol{m_{r,w}}$ corresponds to the number of participating Antibioclic GPs over 35 years old (for any health indicators) in region r and week w, $\boldsymbol{M_r}$ corresponds to the number of registered GPs in region r exercising in the liberal exclusive and mixed sectors, $\boldsymbol{P_r}$ corresponds to the population size of the region r, and $\boldsymbol{P_{FR}}$ corresponds to national French population in 2022, collected from INSEE (*Institut national de la statistique et des études économiques*; https://www.insee.fr/fr/accueil)[29]. The number of registered GPs per region (M_r) corresponded to the number in 2023 and was obtained from DREES (*Direction de la recherche, des études, de l'évaluation et des statistiques*; https://drees.shinyapps.io/demographie-ps/)[30].

Since metadata on users were available from May 2022 onwards (Fig. 1, red double arrow), the annual incidence (calendar year) of Antibioclic usage for LB indicators per 100,000 inhabitants in France was calculated for 2023 (Fig. 1, black double arrow). For the previous years (2018–2022), the available information was the total number of requests and the number of Lyme requests by all users (i.e., those data did not allow to distinguish GPs from other users, neither allowing to locate users). Thus, for 2018–2022, we applied another incidence estimation method allowing to estimate the incidence, referred as I^2, accounting for the proportion of Lyme requests per 1,000 requests, as in Delory et al., 2024[13]:

$$I^2 = \frac{N}{T} \cdot 1{,}000 \tag{7}$$

where $\boldsymbol{N}$ corresponds to the number of Lyme requests over a period of time and $\boldsymbol{T}$ corresponds to the total number of requests of that same period.

To compare those 2018–2022 incidences with the Sentinelles network estimates expressed per 100,000 inhabitants, we applied Bayesian inference using information in 2023 as priors using *rjags* package[31] in R 4.4.1[32] to re-estimate annual incidence of Antibioclic usage for LB indicators per 100,000 inhabitants (I^1) for 2018–2022.

For the year 2023, we calculated the proportion of all requests and LB requests made by GPs over those made by all users, to infer the number of all requests (N_{all}) and Lyme requests (N_{lb}) made by GPs in each of the previous years (2018–2022). In addition, we calculated the average number of requests (all indicators) made per participating GPs in 2023 and this number was considered to be stable over years. This average number of requests per GPs and the estimated number of all requests by GPs (N_{all}) allowed us to obtain the number of participating GPs (m) for each year (2018–2022). Using the estimated number of LB requests (N_{lb}) by GPs and participating GPs (m) for 2018 to 2022, we estimated the annual incidence per 100,000 inhabitants as per Eq. (1) to (6), but calculated directly for the whole year and at national level, and we named it I^{1b} incidence. We also calculated the I^{1b} for 2023 using the observed Antibioclic data. Finally, we compared the incidence calculated directly per year (I^{1b}) with the one calculated by considering weekly and regional data (I^1) in 2023, in order to adjust the I^{1b} in 2018 to 2022 into I^1.

We presented the relation between LB-related Antibioclic (AB) usage incidence and the Sentinelles network (SN) LB incidence as AB/SN ratio and applied exponential decay model at regional level between AB/SN ratio and regional incidences from the Sentinelles network. Regions with zero reported LB case in the Sentinelles network (Haute Normandie, Nord-Pas-de-Calais, and Poitou Charentes)[7] were excluded from the model.

All data analysis and visualisations were performed in Rstudio version 2024.09.1[33], using R 4.4.1[32] and R packages such as *dplyr*, *tidyr*, *ggplot2*, *purrr*, *lubridate*, *forcats*, *sf*, *gt*, and *gridExtra*[34–42].

Lyme incidence by the sentinelles network

To compare with Antibioclic incidence estimates, we used the annual incidences from the Sentinelles network of cases seen in general practice available at https://www.sentiweb.fr/, at both national and regional levels[7,43]. Sentinelles GPs across France report the number of cases, or absence of cases, in a weekly basis for multiple health indicators, and later validated by a group of experts to ensure the validation of cases. LB is included in the surveillance of the Sentinelles network since 2009, and is defined with the presence of either erythema migrans or at least one clinical manifestation (neurological, articular, cutaneous, or cardiac) that has been tested positive with both ELISA and Western Blot, referring to the case definition by the European Study Group for Lyme borreliosis (ESGBOR)[21].

The Sentinelles network estimated LB cases incidence based on the number of reported cases and adjusted by weekly participation and surveillance period of each GP[44]. The incidence rate of Lyme borreliosis in 2023 was estimated at 59 per 100,000 inhabitants (CI95%, 50–68) from 177 validated Lyme borreliosis cases. These cases included 175 cases of erythema migrans and 2 cases with disseminated manifestations.

Ethics statement

Data collected during requests performed to the CDSS are filled by physicians and do not allow the identification of patients. A summary of the collected information is published in Delory et al.[11]. We are not accessing health records, and the data collection process ensures that we cannot identify patients. The data collected are considered anonymised and are not categorised as pseudo-anonymised health data. According to French regulation (https://www.cnil.fr/fr/quest-ce-ce-quune-donnee-de-sante), we are not enrolling patients and we are analysing requests. Thereby, we have to follow the French regulation aligned with the EU GDPR (https://gdpr-info.eu/). Antibioclic confidentiality policy details all the data that are collected and how we can analyse them: https://antibioclic.com/p/politique-de-confidentialite.

Under the French regulation ('Jardé' law N°2012–300 of March 5, 2012: https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000025441587), surveying healthcare professionals about their practices is classified as 'Non-RIPH' (not involving the human person) and does not require ethical approval; only GDPR regulations apply.

Data availability

Requests for Lyme borreliosis (LB) Sentinelles network data can be addressed to rs-data@sentiweb.fr. Requests for Antibioclic data can be addressed to contact.antibioclic@gmail.com.

Code availability

The code for estimating incidence on this study is available in SI.

Received: 10 February 2025; Accepted: 23 April 2025
Published online: 03 May 2025

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Acknowledgements

I.E.S. is funded by a Sorbonne Université PhD fellowship. This study was conducted under the Agence Nationale de la Recherche JCJC MoZArt project (www.mozartonehealth.com), grant number ANR-22-CE35-0003. We are grateful to Antibioclic for providing the data, to all Antibioclic users, and to those who participated in the online survey. We are also grateful to Réseau Sentinelles, for providing the Lyme borreliosis incidence data. We thank Benoît Jaulhac and Pierre-Yves Böelle for their valuable discussion.

Author contributions

I.E.S., J.L.B., T.D., and R.M. contributed to the study conception. J.L.B. and T.D. collated the Antibioclic data and the online survey. T.L. calculated the incidence of LB cases from the Sentinelles network data. I.E.S. performed the analysis. I.E.S., J.L.B., C.B., T.L., Y.K., T.D., and R.M. interpreted the results. I.E.S. and R.M. wrote the initial draft. All authors read and approved the final manuscript.

Funding
Sorbonne Université and Agence Nationale de la Recherche grant number ANR-22-CE35-0003.

Declarations

Competing interests
Raphaëlle Métras is an Editorial Board Member in a nature portfolio journal (Communications Medicine). All other authors declare no financial or non-financial competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-99896-8.

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