

French National Plan to Fight Lyme and Tick-borne Diseases (2016)

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Translation Note: There are some odd phrases in places in this document because most of the translation has been done using Google translate, with a few tweaks. The original plan (in French) is at:

http://solidarites-sante.gouv.fr/IMG/pdf/plan_lyme_281216_aes_-_2.pdf

1. Context and challenges

Ticks are arthropods that live in natural or man-made environments, benefiting from the passage of a host to settle and feed, whether this host is human or animal (farmed or wild). The presence of ticks seems to be expanding in metropolitan areas.

Ticks are likely to transmit, during their blood meal, viruses, bacteria or parasites causing different diseases (eg Lyme disease, tick-borne encephalitis, Rickettsioses). The spread of tick-borne diseases is therefore the result of multiple factors, due to the evolution of the environments hosting them, to climate change, to the more frequent practice of human contact with nature in periurban areas (walking, gardening ...), the presence of wild animals ...

Lyme disease is today the subject of many debates and controversies, because of its polymorphism, diagnostic difficulties and difficulties in taking care of late forms. More generally, all tick-borne diseases are controversial, given the lack of specific knowledge about the pathogens they carry and that can be transmitted to humans.

That is why the Minister of Social Affairs and Health wanted a plan to fight against Lyme disease and tick-borne diseases. Its purpose is to respond concretely to legitimate concerns expressed by citizens.

2. The National Plan to Fight Tick-borne Diseases

The development of the plan is the result of open exchanges with the French Federation against Tick-borne Diseases (FFMVT) and other patient associations, administrations, health safety agencies, regional health agencies and professionals (research teams, health professionals, veterinarians, professionals in charge of wood and forest maintenance ...). Its implementation will require gradually involving new partners, particularly to disseminate information or implement recommendations (health professionals, communities, ...).

The national plan to fight against tick-borne diseases is part of an evolutionary process: it includes actions to assess the situation and plans to re-evaluate the relevance of the actions, the need to amend them, or even the need to evolve, remove, or add to them. The plan is not fixed, it will be continually subject to adaptation in the framework of the governance that will be put in place.

The plan aims to develop knowledge about tick-borne diseases in order to improve patient control and care measures, as well as to implement immediate and concrete prevention, diagnosis and treatment measures to meet the care needs of patients. **It revolves around five strategic areas:**

Strategic Area 1 - Improve Vector Surveillance and Tick Control Measures in a One Health Approach

Several research teams are working to improve knowledge of tick distribution, pathogen prevalence in tick populations, and key factors for predicting tick density. These are essential elements for risk assessment. It will therefore be necessary to unify these initiatives to develop a mapping of the risk and distribution of ticks in France, as well as the pathogens they carry. This knowledge will guide prevention and control actions.

In parallel, the National Agency for Food Safety, Environment and Labor (ANSES) will establish a research and development agreement, with the competent authorities, to evaluate the various measures to fight against ticks and identify the most effective against the proliferation of these species. ANSES will also evaluate the effectiveness of repellents in this context.

Finally, the implementation of a computer application for the collection of reports of tick bites by the public will be carried out. The involvement of all relevant partners, including timber and forest workers, will be useful in supporting this work with knowledge and skills on the ground.

Strategic Area 2 - Strengthen surveillance and prevention of tick-borne diseases

The reinforcement by Public Health France of surveillance of tick-borne diseases in all regions of France, including in regions where the incidence of *Borrelia* is low, will make it possible to evaluate the evolution of these pathologies but also to better guide prevention actions. The strengthening of the Sentinelles network throughout the country and the annual analysis of the reasons for hospitalization will help to better understand the regional prevalence and incidence of diseases.

These analyzes will enable the regional health agencies to establish the "vector-borne diseases" component of their regional health plan provided for by the law to modernize our health system, in conjunction with the FFMVT and the associations. The ARS will organize public awareness actions, relying on territorial relays (health professionals, communities, national

education, associations ...). The training of health professionals will also be reinforced in this context, based on specialized care centers, which each ARS will have identified.

Information measures for walkers and hikers on the edge of forests and hiking trails, will be set up in close partnership with the National Forestry Office (ONF) and the National Office of Hunting and Wildlife (ONCFS).

To support these different actions, Public Health France is responsible for developing information tools on tick-borne diseases, on different media (eg posters, leaflets, digital ...), and in close contact with associations and professional organizations in the forest sector.

The CNAMTS is also mobilized to disseminate this information to policyholders and health professionals.

Strategic Area 3 - Improve and standardize patient care

To combat the medical wanderings that patients suffer before appropriate care is offered, it is essential to improve and standardize the etiological assessment and management of patients, using a multidisciplinary approach.

The development of a national protocol for diagnosis and care (PNDS) of infections transmitted by ticks will be entrusted to the High Health Authority (HAS) in close connection with the SPILF and all disciplines concerned (neurology, dermatology, rheumatology, cardiology, microbiology, immunology ...) both in France and abroad. It will involve associations and the FFMVT in its work to take into account their feelings and the problems that patients face.

The implementation of this PNDS will be ensured in particular by specialized care centers which will be designated in each region by the ARS. Appropriate care channels will be organized, in conjunction with first-line professionals, to provide local and quality care for patients.

The Health Insurance will contribute to the dissemination of the outcome and PNDS to health professionals. It will ensure its dissemination to medical advisers to harmonize the management of severe forms when requests for exemption of user fees in the context of off-list conditions.

The HAS will be asked in parallel to evaluate any examinations or acts that are not already registered in the nomenclature. As part of the referral to the Minister established in June 2016, the HAS may propose medical criteria for the admission of Lyme disease in the list of ALD and recommend the acts and benefits necessary for the management of this disease.

Finally, work will be carried out with the relevant services to determine the extent to which the Lyme disease-related general disease and farm disease tables can be harmonized and the recognition procedures simplified.

Strategic Area 4 - Improve diagnostic tests available

A significant controversy continues to exist regarding existing diagnostic tests.

Thus, ANSM and CNR will continue to evaluate the performance of kits already available on the market, techniques and skills of medical biology laboratories as part of a national quality control in 2016-2017. This will include promoting the use of the best available tests and ensuring the proper interpretation of the results by the laboratories of medical biology.

Strategic Area 5 - Mobilize research on tick-borne diseases

French research is fully mobilized on tick-borne diseases within the framework of the AVIESAN and ALLEnvi Alliances. AVIESAN identified three priority needs in terms of research:

- the development of new diagnostic tools;
- a better understanding of the pathophysiology of the disease;
- the establishment of a prospective cohort of patients suspected to have Lyme disease.

In this context, French research will support work to develop new diagnostic tools and a better understanding of the transmission and pathology of the disease benefiting from new technologies in the field, while collaborating closely with research laboratories including those in animal health, relying on the One Health concept.

For example, two projects proposed by a community of interdisciplinary academic researchers and clinicians will be funded by the ANR by the end of 2016. The Diabolyc project "Diagnosis Borreliosis of Lyme Cutané", coordinated by EA 7290 and the LSMBO / UMR7138 / IPHC at the Strasbourg site, aims to develop a tool for late diagnosis of Lyme disease using mass spectrometry. The "OH! Ticks" project coordinated by the UMR BIPAR (INRA / ANSES / EnVA) in the Paris region, includes a global research study on the pathophysiology of Lyme disease and aims to know all the pathogens transmitted to humans by ticks, in particular *Ixodes ricinus*, to make the diagnosis.

Finally, a national cohort will be set up to better follow patients over time and improve our knowledge of tick-borne diseases. This cohort could include patients in the PNDS. At the organizational level, the implementation of this cohort will be able to rely on a network of clinicians and benefit from AVIESAN expertise in the field of cohorts.

These strategic areas are composed of 15 actions, which are detailed in the next chapter. Some of these actions will require territorial variation by the regional health agencies as part of their future regional health plans, of which one will be devoted to vector-borne diseases (Article L. 1434-3 of the CSP).

The governance of the plan

A driver is identified for each of the actions contained in the plan. It is up to each driver to identify and involve the relevant partners to contribute to the realization of the action. Some of these contributors are already identified. In particular, the patient associations and the FFMVT will be closely involved in carrying out certain actions, particularly in Strategic Areas 2 and 3.

A steering committee, chaired by the Director General of Health, will meet once a quarter and bring together the drivers of actions, including the DSS, DGOS, ANSES, Public Health France, the ANSM, the HAS, the SPILF and AVIESAN, as well as a representative of the ARS. Twice a year, this steering committee will also host the patient associations and the FFMVT.

The objective of this steering committee is to take stock of the progress of the work and to identify and validate the new actions to be implemented.

Setting up a resource center

To facilitate monitoring of the implementation of the plan and facilitate access for health professionals and patients to reliable information tailored to their needs, the website of the Ministry of Health will develop a special folder dedicated to this plan.

This site will summarize the various documents available and will update in particular the rights of users and access to care, particularly in terms of procedure and compensation.

A European and international dimension to take into account

The fight against tick-borne diseases is not just a national issue. The increase of cases in many countries, especially European ones, implies that many teams are working on this subject.

France will bring the issue of vector-borne diseases to the various European and even international bodies concerned. This will involve both sharing information on epidemiological data or control measures implemented by the different states, but also, as far as possible, developing European research projects or harmonizing patient care practices.

France will also support any initiative aimed at setting up a European reference network on tick-bite diseases.

3. List of Plan Actions

Strategic Area 1: Improve Vector Surveillance and Tick Control Measures in a One Health Approach

Action 1 - Strengthen the surveillance of different ticks in the territory

Action 2 - Improve our knowledge of tick ecology and identify the most effective control measures

Action 3 - Test the effectiveness of tick repellents and specify how they are used, especially for workers

Strategic Area 2 – Strengthen surveillance and prevention of tick-borne diseases

Action 4 - To generalize throughout the country the surveillance of diseases transmitted by ticks

Action 5 - Develop information on protective measures on the edge of forests and hiking trails

Action 6 - Integrate a vector disease component into regional health plans and other regional or local health policies

Action 7 - Develop prevention messages and supports, in association with associations and taking into account the results of participatory and behavioural sciences.

Strategic Area 3 – Improve and standardize patient care

Action 8 - Develop a national diagnostic and care protocol (PNDS) for tick-borne diseases

Action 9 - Designate specialized care centers in the regions

Action 10 - Evaluate whether to include Lyme disease in the list of long-term conditions (ALD)

Strategic Area 4 – Improve diagnostic tests available

Action 11 - Strengthen quality control of medical biology laboratories and quality control of test records

Action 12 - Evaluating the performance of currently marketed tests

Strategic Area 5 – Mobilize research on tick-borne diseases

Action 13 - Develop new vector-based post-exposure diagnostic tools based on new technologies, including the use of veterinary diagnostic methods

Action 14 - Conduct studies on the epidemiology and pathophysiology of tick-borne diseases

Action 15 - Establish a cohort of prospective patient follow-up research suspects of Lyme disease

4. Strategic Area 1 – Improve Vector Surveillance and Tick Control Measures in a One Health Approach

Action 1 – Strengthen the surveillance of different ticks in the territory

Context

Knowledge of the distribution area of vectors, the prevalence of pathogens in vector populations and the main factors for predicting tick density are essential for risk assessment.

Several research actions are underway in the framework of the surveillance of emerging diseases in connection with global warming. Among these actions, there is a project developed by INRA whose objective is to evaluate the activity of ticks (*Ixodes ricinus* mainly) in different regions of France with a collection of ticks every month of the year. Other teams from INRA, ANSES and EnvA are studying the vectorial competence of *Ixodes ricinus* for the transmission of different pathogens in laboratory level 2 and level 3 (*Anaplasma phagocytophilum*, *Bartonella henselae*), or in the field by collecting ticks in different regions of France and detection of pathogens carried, using different techniques allowing the surveillance of 59 pathogens vectorized by ticks.

If there is a lot of work in this area, global coordination seems necessary in order to initiate a more comprehensive tick surveillance.

Description of the action

It will develop a mapping of the risk of distribution of ticks in France and the pathogens they carry. For this, it is necessary to establish, initially, the state of knowledge on the distribution of ticks, in particular *Ixodes ricinus* (main vector of Lyme borreliosis and tick-borne encephalitis), *Dermacentor* sp. and *Hyalomma marginatum* (main vector of Crimean Congo haemorrhagic fever virus), and the prevalence of infection for the purpose of developing a risk map. This action should lead to proposals aimed at identifying and filling the main gaps in this field, through field studies and modeling work, or even through the use of participatory sciences.

In parallel, a mobile application for the collection of reports of tick bites by the public will be carried out inspired by the site www.signalement-moustique.fr and the models of the sites proposed in other European countries.

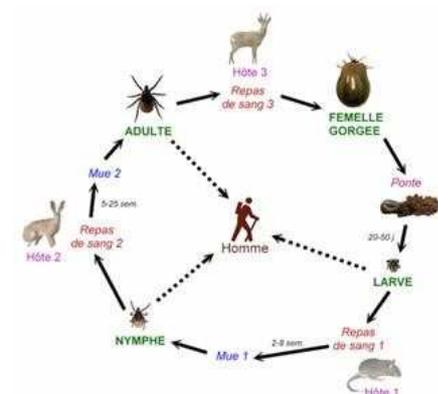
Drivers and partners of the action

- Driver: ANSES - CNEV
- Partners: Réseau « Tiques maladies à tiques », INRA, CIRAD, CNR Borrélia, DGAL, ONF et ONCFS, FNCofOR, CNPF, FNB, FNEDT, Francesylva

Outcomes

- ▶ First mapping will be released end of April 2017
- ▶ Scoping analysis for the tick bite reporting site: April 2017
- ▶ The establishment of the tick bites reporting site if possible in the spring of 2017
- ▶ Gradual establishment of a global surveillance system for ticks from 2018

Action 2 - Improve our knowledge of tick ecology and identify the most effective control measure



Context

The proliferation of big game seems favorable to the multiplication of ticks. Livestock and companion animals are also hosts, allowing the tick to complete its complete cycle (blood meal required to allow larvae to nymphs and nymphs to be transformed into adults and for spawning), that must be protected. Better knowledge of the hosts and the environmental factors responsible for the proliferation of ticks as well as their biology will make it possible to evaluate the existing modes of struggle or to identify new ones. The maintenance of forest areas (silico-synetic balance) or

gardens, as well as the protection of farm animals are probably avenues to explore. It is in fact, to act on the environmental factors influencing the abundance of ticks in the landscape, preserving or restoring ecological balances.

Description of the action

ANSES will set up a committee of scientific experts (CES) and develop a research and development agreement (CRD), integrating several partners, to study the vector ecology on the one hand and to identify the means of struggle and their effectiveness on the other hand. In particular, collaboration could be envisaged with professional forestry organizations and hunters, notably the NFB and ONCFS.

The aim of this action is to evaluate the knowledge available on tick control, whether through environmental actions (eg recommendations for the maintenance of woods and forests, but also the paths and paths, installation of barriers far from hedgerows and bushes to limit contamination of livestock ...), or by the implementation of innovative actions (eg vaccination against ticks of animals).

Driver and partners

- Driver: ANSES - CNEV.
- Partners: DEB, DGAL, le Réseau « Tiques maladies à tiques », INRA, ONCFS...

Outcomes

- ▶ Establishment of a CRD in January 2017
- ▶ Preparation of a summary report on the existing measures and their effectiveness end 2017

Action 3 - Test the effectiveness of repellents against ticks and specify how they are used, especially for workers

Context

Evaluation by ANSES of the dossiers submitted in the regulatory framework for products claiming repulsive action against ticks systematically includes an evaluation of their effectiveness, as well as risk assessments for humans – particularly forest and environmental workers, all contributing to the definition of employment conditions.

However, specific prospective and synthetic work for all means of "chemical" control against ticks could be conducted. This work would complement the elements relating to the other means of control, referred to in Action 2.

Description of the action

If ANSES generally bases its evaluation on the studies provided by veterinarians and the available knowledge, it will set up a research and development agreement (CRD) with the institutions able to use experimental tests to measure the effectiveness of the biocidal products.

Driver and partners

- Driver: ANSES
- Partners: DGPR, CNEV

Outcomes

- ▶ Dissemination of an initial list of repellents effective against ticks end of 2016
- ▶ Establishment of a CRD in January 2017
- ▶ Preparation of a summary report on the existing measures and their effectiveness end 2017

5. Strategic Area 2 – Strengthen surveillance and prevention of tick-borne diseases

Action 4 – To generalize all over the country the surveillance of diseases transmitted by ticks

Context

Many surveillance actions have been conducted in France and Europe for several years. In France, the epidemiological surveillance currently in place includes:

- ▶ the long-term surveillance implemented with the Sentinelles Network since 2009. It allows estimation of the national incidence of the disease and its trends over time. It also describes the main socio-demographic and clinical characteristics of patients;
- ▶ specific incidence studies carried out by ANSP and CNR between 2001 and 2015 in the Aquitaine, Alsace, Franche-Comté, Limousin and Rhône-Alpes regions. These studies make it possible to estimate the regional and sub-regional impacts;
- ▶ The medicalization of information systems program (PMSI) makes it possible to evaluate the weight of the disease in France in terms of hospitalization, its trends and its geographical variations. It is particularly relevant for neuroborreliosis.

Overall between 2009 and 2014, the national incidence of Lyme borreliosis remained stable, varying between 41 and 55 cases / 100,000 per year in France. However, these data show large regional disparities estimated between 232 / 100,000 cases in Alsace and 24 / 100,000 cases in Aquitaine between 2001 and 2012.

In view of the increase in cases observed in some countries, the reinforcement and generalization of surveillance studies of tick-borne diseases should make it possible to objectify the actual health situation in the territory.

Description of the action

- ▶ Strengthen the monitoring implemented by the Sentinelles network throughout the country;
- ▶ Conduct an annual analysis of PMSI data to track national and regional trends in rates and reasons for hospitalization;
- ▶ Finalize the regional impact studies implemented in Alsace and Franche Comté and compare the results with the other monitoring systems put in place. Evaluate the opportunity to extend these studies to other regions.

Driver and partners

- Driver: Santé Publique France
- Partners: CNR Borrelia, ARS, réseau Sentinelles

Outcomes

- ▶ Consolidated data of the Sentinelles network: January 2017
- ▶ Analysis of the PMSI data: January 2017 and then annually
- ▶ Results of regional impact studies: end of 2016 - beginning of 2017

Action 5 - Develop information on protective measures on the edge of forests and hiking trails

Context

Ticks live in forests, woods, tall grass but also in mountains and in private or public gardens, that is to say in wooded and humid places where the temperature is between 7° C and 25° C. In this case, the ticks remain active and represent a danger all year long. Below 7° C or above 25° C, ticks will not move and hide in the ground, below the ground or under vegetation to protect themselves from these temperatures. They live mainly in temperate regions.

In addition, ticks feed mainly on the blood of wild animals, from rodents to deer, climbing on their prey up to 1.5 meters above ground level.

In this context, the risk of a tick bite is higher in forests or hiking trails, as well as in peri-urban gardens. It is therefore appropriate to target public awareness actions that use these spaces, especially forests.

Description of the action

In this context, Public Health France and the NFB will develop a partnership to develop information materials (information boards, leaflets) for walkers or hikers in forests or hiking trails. This first phase of design, after an inventory of what exists, will be conducted in close association with the associations.

Then, these panels will be gradually deployed on the edge of public forests managed by the NFB, including the 1300 state forests, like the actions implemented in some forests of the Grand Est region. Subsequently, as part of a partnership with FNCoFor, these measures could be extended to communal forests. Finally, the information materials developed by Public Health France can be made available to private forest managers so that they can also develop targeted information.

At the same time, complementary national partnerships will be sought, in particular the professional organizations of the forest sector, the federations of hunters or hikers, in order to develop information campaigns for these target audiences. Specific awareness campaigns, in the form of entertainment, games, and other activities in forest houses or in forest communes will also be considered.

Finally, preventive actions may also be implemented for forest workers, closely linked to Public Health France, the NFB and the MSA.

The CNAMTS will participate in the dissemination of this information to the insured (amelisante.fr) and to health professionals. The CCMSA will participate in the dissemination to the agricultural insured.

Driver and partners

- Driver: Santé Publique France
- Partners: Associations, ARS, ONF, ONCFS, FNCoFoR, CNPF, FNB, FNEDT, Francesylva, CNAMTS, CCMSA, le réseau mutualiste

Outcomes

- Establishment of working groups: November 2016
- Review of existing documents: 4th quarter 2016
- Design and availability of documents: 1st quarter 2017
- Deployment in state forests in 2017, then progressive deployment in other forests

Action 6 - Integrate a vector disease component into regional health plans and other regional and local policies

Context

Law No. 2016-41 of January 26, 2016 to modernize our health system provides that future regional health plans include "if necessary, a component dedicated to the implementation of actions to raise awareness among the population and training health professionals to limit possible contamination by vector-borne diseases".

Within this framework, Regional Health Agencies (ARS), especially those located in areas where the incidence of tick-borne diseases is important, will set multi-year targets to develop public awareness actions on the prevention of tick-borne diseases and information of professionals to diagnosis and management of tick-borne diseases.

These actions will be developed by the ARS in consultation with the patient associations and the FFMVT within the framework of regional health democracy bodies. They will be adapted to the local context and may also be integrated into other regional or local policy elements, such as the regional health environment plan or local health contracts.

Description of the action

The public awareness actions developed will be complementary to those mentioned in Action 5 and will require the development of partnerships to identify channels of dissemination, particularly with local authorities and the National Education. The ARS will be able to rely on the public awareness documents prepared by Public Health France. The use of civic service volunteers may be considered in particular to carry out specific awareness-raising actions in the most exposed areas.

In terms of information for health professionals, the ARS will also be able to rely on documents produced by Public Health France. It will be important to ensure that health professionals are aware of methods for the diagnosis and treatment of tick-borne diseases. The CNAMTS will notably participate in the dissemination of these materials to policyholders (ameli-sante.fr) and health professionals, CCMISA to agricultural policyholders (MSA.fr). To this end, the ARS will rely on the specialized care centers mentioned in Action 9, which will be responsible in particular for disseminating information and organizing training activities for health professionals in the region. in a logic of increased city-hospital coordination.

Driver and partners

- Driver: ARS
- Partners: Santé Publique France, CNAMTS, CCMISA, Education nationale, Agence du service civique, associations de patients...

Outcomes

- Design Awareness and Information Materials: January 2017
- Development of regional health plans: 2017
- Establishment of public awareness and training of health professionals: from 2017

Action 7 – To evolve the messages and supports of prevention, in association with the associations and taking into account the results of the participative and behavioral sciences

Context

Scientific results as such are important, but may have little impact without effective communication to the general public. In the specific case of tick-borne diseases, there is

considerable debate about the importance of these diseases at the moment, and the result is growing concern about the danger of ticks. Better understanding of the social perception of risk and the behavior of both the public and the professionals must make it possible to adapt the messages of sensitization or their modes of diffusion.

Description of the action

In this context, Public Health France introduced into the 2016 health barometer questions on ticks and Lyme borreliosis. This survey asked a sample of 15,000 people aged 15 to 75 eight questions about their exposure to risk, the prevention behaviors adopted, knowledge about the illness and its severity, and their feelings about the information. The results of this study will be available in early 2017 and can contribute to the development, adaptation and dissemination of prevention messages.

At the same time, work with associations and participatory science work with teams of researchers will help to involve citizens in the prevention of tick-borne diseases.

Thus Public Health France will take into account the results of these various initiatives to gradually rehabilitate messages and information media, in connection with associations.

Driver and partners

- Driver: Santé Publique France
- Partners: associations de patients, ANSES – INRA, EHESP...

Outcomes

- ▶ Dissemination of health barometer results: 1st half of 2017
- ▶ Establishment of a working group to revise the documents: 2nd semester 2017
- ▶ Adaptation of prevention media: early 2018

6. Strategic Area 3 – Improve and standardize patient care

Action 8 - Develop a national diagnostic and care protocol (PNDS) for tick-borne diseases

Context

In its report on Lyme borreliosis in 2014, the High Council of Public Health concludes that "it seems clear that there is a significant number of patients with chronic and disabling symptoms labelled 'Lyme disease' without certainty due to negative biological tests, or the persistence of antibodies against *B. burgdorferi sensu lato* distorting their interpretation. Probably some could have Lyme disease, escaping the biological tests. But one can also think that a large number of them could suffer from an infection related to other microorganisms carried by ticks and transmitted by them on the occasion of a tick bite" or other pathologies.

In this context, in the case of chronic and disabling symptoms resulting from a tick bite and in case of negativity of the test on Lyme disease, patients are today deprived to establish a reliable diagnosis of the disease they suffer and that they are offered appropriate treatment. This favors medical wandering or even resorting to non validated tests.

Thus, it seems essential today to develop an extended and standardized diagnostic assessment and to improve and standardize the medical care of patients with a goal of equity in terms of access to diagnosis, treatment and comprehensive care of sick people.

In this respect, like the existing mechanisms for rare diseases, the development of a national protocol for diagnosis and care (PNDS) is an essential element of quality care, particularly in order to limit the medical wandering of patients.

Description of the action

The HAS is commissioned to develop a national protocol for diagnosis and care (PNDS) in a collegial and multidisciplinary way in close connection with the SPILF and with the support of other scholarly societies concerned (neurology, dermatology, rheumatology, cardiology, microbiology ...) . HAS will also involve any person it deems useful, including representatives of patient associations to define its objectives.

These rules of good practice will provide patients with an optimal response in terms of diagnosis, treatment and follow-up between health professionals. The drafting of this PNDS will follow the methodology defined by the Haute Autorité de Santé (HAS) and will include a standardized etiological assessment in the form of an algorithm, describing precisely the list of examinations necessary to establish an etiological and differential diagnosis for patients with late forms of Lyme borreliosis.

The PNDS will therefore make it possible to propose a complete diagnosis (standardized assessment) to any person presenting chronic symptoms occurring after a tick bite, evoking an infection linked to this vectorial exposure and to optimize and harmonize etiological management and adapted monitoring of these diseases throughout the country.

The Health Insurance will contribute to the dissemination of the PNDS to social protection organizations and health professionals. It will ensure its dissemination to medical advisers to harmonize the management of severe forms when requests for exemption of user fees in the context of off-list conditions. It will take charge of the examinations proposed in this standardized report which are not yet registered in the nomenclatures if the scientific data are sufficient, and after the opinion of the Commission of acts of medical biology.

Driver and partners

- Driver: HAS - SPILF
- Partners: CNAMTS, CCMSA, ARS, DGOS, concerned scholarly societies, Council of the Order of Physicians, patient associations and FFMVT

Outcomes

- ▶ Development of a scoping note of the PNDS: December 2016
- ▶ Validation of the PNDS (including the standardized balance sheet): June 2017
- ▶ Broadcast and training: 2nd semester 2017

Action 9 - Designate specialized care centers in the regions

Context

The fight against medical wandering suffered by some patients involves both the development of the national screening and care program (PNDS) in order to standardize the principles of care of these patients but also by setting up adapted care pathways in the regions to ensure the proper implementation of these principles.

Description of the action

In this respect, the ARS will set up adapted care pathways in each region and in a logic of increased city-hospital coordination. They will raise awareness of health professionals of the first resort to the management of patients bitten by a tick, in application of the PNDS. They will define, as appropriate, a specific role for multi-disciplinary health centres.

Finally they will designate in each region, specialized centers of care, in connection with the URPS. These specialized centers will implement national diagnostics and care examinations and treatment protocols to provide clinical support for recourse, particularly through the organization of multidisciplinary synthesis or consultation meetings (RCP).

Driver and partners

- Driver: ARS
- Partners: URPS, DGOS

Outcomes

- ▶ Instruction to the ARS for the designation of specialized centers from the publication of the PNDS: 3rd quarter 2017
- ▶ Designation of specialized care centers in the regions: 4th quarter 2017

Action 10 – To evaluate the advisability of including Lyme disease in the list of long-term conditions (ALD)

Context

Lyme disease in its primary form is a condition usually curable in a few weeks. Its inclusion on the list of long-term conditions does not seem necessary.

On the other hand, the secondary and tertiary forms could be inscribed because their neurological or rheumatological manifestations can lead to long and expensive treatments (IV antibiotic therapy in case of arthritis or prolonged functional rehabilitation in case of polyneuropathies for example).

Currently, a patient with severe forms of Lyme disease may be exempted from co-payment under off-label ALD if the treatment is of a predictable duration of more than 6 months and is particularly costly because of cost or frequency of acts, benefits and treatments.

Description of the action

The Minister of Social Affairs and Health has referred to HAS in June 2016 to propose medical criteria for the admission of Lyme disease in the list of ALD and recommends the acts and services necessary for the management of this disease. According to the opinion of the HAS, this affection could be inscribed in the list of long-term conditions (L.160-14 3rd of the CSS) by ministerial decree.

In the meantime, the Health Insurance will ensure the dissemination of the PNDS to medical advisers to harmonize the management of severe forms when requests for exemption from co-payment for off-list conditions.

Driver and partners

- Driver: DSS, CNAMTS
- Partners: HAS

Outcomes

- ▶ referral to the HAS conducted in June 2016
- ▶ Proposal of criteria by the HAS after the elaboration of the PNDS

7. Strategic Area 4 – Improve diagnostic tests available

Action 11 – Strengthen quality control of medical biology laboratories and quality control of test records

Context

To prepare the report of the HCSP published in December 2014, the ANSM had established a situation of the reagents by recording the data provided by the manufacturers in the leaflets of the tests marketed: composition, method of assay, analytes assayed, matrices used, performances (sensitivity and specificity in particular). In its review, the HCSP report noted deficiencies in the leaflets and in the reagent performance data provided by the manufacturers. As a result of this report, ANSM carried out a first quality control of medical biology laboratories (LBM). In particular, this control highlighted the need to improve biologists' information on the interpretation of a screening result based on the clinic and epidemiological data, which led to the development of departmental recommendations at the national level biologists and doctors published in 2016.

At the same time, the ANSM launched a check of the test records present on the national market so that the manufacturers of the tests respond to the nonconformities or remarks noted for their various reagents during the first report drawn up within the framework of the work of the HCSP. The report of this survey is expected at the end of 2016.

Description of the action

This control of the test records is currently in progress and concerns 40 reagents including 34 reagents ELISA technique. The aim is to check that they meet the requirements of the European Directive 98/79 / EC and the remarks made by the HCSP in 2014. The report is expected at the end of 2016.

A new national quality control operation will be carried out by ANSM in 2017 with LBMs to verify the quality of the analytical results provided by the laboratories and also the quality of the interpretation with regard to the clinical context.

Driver and partners

- Driver: ANSM
- Partners: CNR

Outcomes

- ▶ Report on the control of the notices of tests present on the market: end of 2016
- ▶ Establishment of the CNQ in 2017 and transmission of a summary report: end of 2017

Action 12 - Evaluate the performance of currently marketed tests

Context

On the regulatory side, reagents for the diagnosis of Lyme borreliosis have the status of in vitro diagnostic medical devices (IVDDM) and are CE marked in accordance with European Directive 98/79 / EC. They are placed on the market under the responsibility of the manufacturer. This is a self-certification, except for self-diagnostic tests.

The state of the art on the biological diagnosis of Lyme borreliosis is currently defined by the recommendations of the EUCALB (European Union Concerted Action on Lyme Borreliosis) European Consensus / ESGBOR (European Study Group on Lyme Borreliosis). In the field of biological diagnosis, these European recommendations give guidelines on the expected performance of the tests. They recommend for evaluating the performance of a reagent:

- ▶ assess the level of seroprevalence in the population where the test will be used;
- ▶ to evaluate cross reactions with patients with antibodies known to interfere in the detection of Lyme borreliosis (eg syphilis, Epstein Barr Virus, Cytomegalovirus ...);
- ▶ establish sensitivity with clinically confirmed cases of Lyme borreliosis at different stages;
- ▶ to establish specificity on at least 100 sera samples from healthy donors. The value for ELISA tests must be at least 90% and for Western Blots (WB) at least 95%.

Description of the action

In this context, the National Reference Center (CNR) carries out a technical evaluation of the tests, in connection with the ANSM. This will be an evaluation of the quality and performance of the tests put on the market, in application of the European recommendations. This analysis will specify the criteria for inclusion of patients and the stage of the disease. The results of this evaluation will be made public and communicated to the laboratories to promote the best performing tests.

The question of the place of rapid tests and the usefulness of a self-test can also be reevaluated on this occasion.

Driver and partners

- Driver: CNR
- Partners: ANSM

Outcomes

- ▶ Western-Blot test performance evaluation report: last quarter 2016
- ▶ Elisa test performance evaluation report: last quarter in 2017

8. Strategic Area 5 – Mobilize research on tick-borne diseases

Action 13 – Develop new vector-based post-exposure diagnostic tools based on new technologies, including the use of veterinary diagnostic methods

Context

A significant controversy continues to exist regarding existing diagnostic tests. In this context, French research could focus on the development of new diagnostic tools that are radically different from what is currently proposed by benefiting from new advanced technologies and by developing collaborations with animal health research laboratories.

Indeed, ANSES is developing new high-throughput tools (microfluidic PCRs) to better detect and characterize arthropod vector-borne pathogens. Today 59 pathogens vectorized by European distribution ticks (bacteria, parasites and viruses) can be detected in 96 samples of ticks (or mammals or human blood) in a single manipulation.

Description of the action

It will be a question of unifying the projects which will make it possible to optimize the diagnosis in the man of the different diseases transmitted by the ticks, by using the knowledge acquired in all the fields (human health / animal). Currently, the Institut Pasteur in Paris is developing sequencing projects and the University of Strasbourg is developing and evaluating new techniques, including mass spectrometry. This university research team has recently benefited from ANR funding in this context to implement the Diabolyc project, whose goal is to develop a targeted proteomic approach of mass spectrometry to detect markers of active infection in disseminated infections. The development of large-scale transportable diagnostic tests (which can be done in a town / country office) may also be considered.

Thus, the Ministry of Health has contacted AVIESAN to coordinate the various research teams working on this issue (Institut Pasteur, CNR, ANSES, IHU, CNR, University of Strasbourg ...).

In order to increase the chances of success, it will also be necessary to evaluate the feasibility of extending this approach to a European level or to encourage public-private partnerships so that innovations can then be turned into a common diagnostic tool. This action could thus be eligible for the investment program for the future (PIA).

Driver and partners

- Driver: AVIESAN
- Partners: Institut Pasteur, ANSES, CNR, IHU, ANR, CNRS, Université de Strasbourg

Outcomes

- ▶ Reference to AVIESAN: 3rd quarter 2016
- ▶ Launch of works: 2017

Action 14 – Conduct studies on the epidemiology and pathophysiology of tick-borne diseases

Context

Since a certain number of patients could suffer from an infection linked to other microorganisms carried by ticks and transmitted by them during an injection, it seems essential to know all the pathogens transmitted to humans by ticks, in particular *Ixodes ricinus*, to make the diagnosis.

In this context, the project "OH! Ticks", which associates many partners (INRA / ANSES / EnVA, IP, APHP, INSERM, CNRS, IHU ...), is based on the One Health approach. This one is essential for a better knowledge of the modes of transmission of this disease and factors that explain the increasing incidence of tick-bite-related diseases. This project takes into account the human and veterinary aspects of tick-borne diseases and is funded by the ANR.

Description of the action

The Ministry of Social Affairs and Health, the Ministry of Research, the AVIESAN and AllEnvi alliances, the funding agencies will encourage and support research aimed at increasing the knowledge of the epidemiology and pathophysiology of tick-borne diseases.

The scientific objectives aim to:

- ▶ detect, identify and isolate new, unknown or unexpected microorganisms from samples of patients and animals suffering from unexplained syndromes after tick bites ;
- ▶ to inform the pathogenicity of these microorganisms; in particular, to demonstrate the link between the presence of the transmitted microorganism, the pathology and the bite by the tick;
- ▶ demonstrate the competence of ticks to transmit these agents ;
- ▶ provide concrete evidence for better management of tick-borne diseases, including developing tools that can be used to develop diagnostic tests;
- ▶ to conduct studies on epidemiology.

Driver and partners

- Driver: AVIESAN / INRA
- Partners: ANR, ANSES, Inserm, Institut Pasteur, IHU, ICAREB, APHP, HAS,

Outcomes

- ▶ Launch of the project "OH! Ticks" in 2017 and deadline in 2021

Action 15 – Set up a cohort of prospective research to follow patients suspected of Lyme disease

Context

Cohort studies consist of observing the occurrence of health events over time within a defined population. This type of study is based on the follow-up of subjects participating according to a pre-established protocol and aims to describe the circumstances of occurrence and the evolution of diseases. They are mainly developed from a research perspective.

The cohort is thus the type of observational study most likely to quantify and determine the existence and form of an association between risk factors and exposure or pathology. They have become an irreplaceable tool for studying the health effects of infrequent exposures or those that can not be evaluated correctly retrospectively.

The establishment of a prospective cohort of patients with acute infection following a tick bite:

- ▶ to ensure the longitudinal follow-up of these patients;
- ▶ to deepen knowledge on the pathophysiology of tick-borne diseases;
- ▶ to anticipate the disorders that accompany the chronic phase of the infection;
- ▶ accelerate research on the molecular and cellular mechanisms underlying the onset of the chronic syndrome.

In addition, the establishment of a prospective cohort would also allow the development of ancillary studies in Human and Social Sciences to inform the experience of patients with Lyme.

Several sub-studies of more fundamental research can be grafted on this clinical cohort (immunology, genetics, inflammation ...) while benefiting from potential funding from the ANR.

The prospective cohort therefore seems to be a particularly suitable tool to monitor this type of patient for a long time and also to look at the real place of chronic manifestations.

Description of the action

The first step will be to build clinical databases and biological sample collection developed by teams of clinicians in several regions by strengthening these initiatives through a single, coordinated and interactive base between the different hospital centers.

The Ministries of Health, Research and the AVIESAN Alliance will encourage research and hospital teams to share a methodological and management center. The setting up of a prospective cohort should also lead to a rationalization of the care of patients. This cohort of prospective research will be dedicated to the follow-up of patients exposed to tick bites including cases of Lyme, SPPT (persistent polymorphic symptom after tick bite), cured patients. It will include humanities and social aspects to better know and analyze the experience of patients.

This cohort will include the setting up of biobanks and will include patients in charge of specialized regional care centers.

Its implementation will be based on cohort initiatives in hospitals, under the coordination of AVIESAN.

Driver and partners

- Driver: AVIESAN
- Partners: DGS, DGOS

Outcomes:

- ▶ Call for projects in 2017

List of Acronyms Used

ANR	Agence nationale de recherche
ANSM	Agence nationale de sécurité du médicament et des produits de santé
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail
APHP	Assistance publique des Hôpitaux de Paris
ARS	Agence régionale de santé
ASC	Agence du service civique
ALLENVI	Alliance nationale de recherche pour l'environnement
AVIESAN	Alliance nationale pour les sciences de la vie et de la santé
BL	Borrélieuse de Lyme
CCMAS	Caisse centrale de la mutualité sociale agricole
CES	Comité d'experts scientifiques
CNAMTS	Caisse nationale d'assurance maladies
CNEV	Centre national d'expertise des vecteurs
CNPF	Centre national de la propriété française
CNR	Centre national de référence
CNRS	Centre national de la recherche scientifique
CNQ	Contrôle national de qualité
CRD	Convention de recherche et de développement
DEB	Direction de l'eau et de la biodiversité (Ministère de l'environnement, de l'énergie et de la mer)
DEPR	Direction de l'évaluation des produits réglementés de l'ANSES
DGAI	Direction générale de l'alimentation (Ministère de l'agriculture)
DGALN	Direction Générale de l'aménagement, du logement, et de la nature (Ministère de l'environnement, de l'énergie et de la mer)
DGPR	Direction générale de la prévention des risques (Ministère de l'environnement, de l'énergie et de la mer)
DGS	Direction générale de la santé
DGOS	Direction générale de l'Offre de soins
DMAT	Direction de la modernisation et de l'action territoriale (Ministère de l'intérieur)
DSS	Direction de la Sécurité sociale
FFMVT	Fédération Française contre les Maladies Vectorielles à Tiques
FNB	Fédération nationale du bois
FNCoFor	Fédération nationale des Communes forestières
FNEDT	Fédération Nationale Entrepreneurs Des Territoires
Francesylva	Fédération des Forestiers privés de France
HAS	Haute Autorité de Santé
IHU	Institut hospitalo-universitaire
INRA	Institut national de recherche agronomique
INSERM	Institut national de la santé et de la recherche médicale
IP	Institut Pasteur
LBM	laboratoire de biologie médicale
LNR	Laboratoire national de référence
MSA	Mutualité sociale agricole
ONCFS	Office national de la chasse et de la faune sauvage
ONF	Office national des forêts
PHRC	Programme hospitalier de recherche clinique
SpFrance	Santé Publique France - Agence nationale de santé publique (ANSP)
SPILF	Société des pathologies infectieuses de langue française
SPPT	Sémiologie polymorphe persistante après piqûre de tique
TBE	Encéphalite à tiques
URPS	Union régionale des professionnels de santé