Committee for the Surveillance and Anticipation of Health Risks (COVARS)

Opinion from April 3, 2024

Assessment of the Risks of Major and Exceptional Sanitary Situations for human health in France during the years 2025-2030

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COVARS
Comité de veille et d'anticipation des risques sanitaires

This opinion was sent to the national authorities on April 3rd, 2024

Like the other opinions of the Health Risk Monitoring and Anticipation Committee, this opinion is intended to be made public.

Referral

This opinion responds to the double referral from the Minister of Health and Prevention and the Minister of Higher Education and Research, addressed to COVARS on December 7, 2023:

GOUVERNEMENT
Liberté
Égalité
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Nos Réf. : D-23-022847

Paris, le 07 DEC. 2023

La Ministre de l'Enseignement Supérieur et de la Recherche

Le Ministre de la Santé et de la Prévention

à

Pr Brigitte AUTRAN
Présidente du Comité de veille et d'anticipation des risques sanitaires
COVARS
14, avenue Duquesne
75350 PARIS 07SP

Madame la Présidente,

Les crises sanitaires successives auxquelles la France a été confrontée ces dernières années rendent nécessaire de mettre à jour l'anticipation et la gestion des risques afin d'assurer la protection de la population française, la pérennité du système de santé et la continuité économique du pays lors de la survenue de situations sanitaires exceptionnelles.

La situation nationale et internationale est marquée par de nouvelles épidémies, parfois liées aux changements climatiques majeurs et à une évolution des modes de vie majorant le risque d'importation et de circulation de maladies émergentes. La prise en compte de ces nouveaux risques via une approche globale, portée notamment par le concept de « Une seule santé », nous amène à considérer l'ensemble des facteurs d'émergence des maladies afin d'anticiper au mieux. Aux risques épidémiques s'ajoute les risques d'autres catastrophes naturelles ou d'accidents industriels ainsi que les menaces terroristes découlant du contexte géostratégique mondial instable.

Dès lors, il est de notre responsabilité de promouvoir une approche pluridisciplinaire, intégrée et globale des enjeux sanitaires qui appellent la mise à jour de notre planification sectorielle et gouvernementale, associée à la préparation de notre système sanitaire, en encourageant la collaboration effective et inclusive des organismes d'expertise et de recherche œuvrant en santé humaine, vétérinaire et environnementale.

C'est dans ce contexte de réflexion globale et de renforcement de l'anticipation des risques que nous sollicitons votre expertise afin d'analyser les risques et menaces déjà identifiées et susceptibles d'être à l'origine de situations sanitaires exceptionnelles majeures sur le territoire national dans les 2 à 5 prochaines années, aussi bien en métropole que dans les territoires outre-mer.

L'objectif serait de pouvoir disposer d'une révision des analyses des risques et menaces sanitaires potentielles existantes et prendre en considération dans les prochaines années afin d'adapter nos dispositifs et moyens de réponse dans un contexte de contraintes calendaires et de ressources.

Pour ce faire, vous pourrez prendre en compte les travaux menés par d'autres instances, et notamment le Haut conseil de la santé publique dans le domaine infectieux et environnemental ou encore le secrétariat général de la Défense et de la Sécurité nationale (SGDSN) pour ce qui concerne les travaux de planification gouvernementale déjà réalisés ou projetés. Je tiens toutefois à rappeler que les questions relatives aux risques NRBC et bioterroriste n'ont pas vocation à entrer dans le champ de la présente saisine.

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Nous vous remercions de bien vouloir me remettre votre rapport avant le 31 décembre 2023. Les services de la DGS et de la DGRI se tiennent à votre disposition pour un échange si vous le souhaitez.

Nous vous prions d'agréer, Madame la Présidente, l'expression de notre considération distinguée.

La Ministre de l'Enseignement Supérieur et de la Recherche

Sylvie RETAILLEAU

Le Ministre de la Santé et de la Prévention

Aurélien ROUSSEAU

Hearings and seminars conducted by COVARS

COVARS Seminars on Climate Change and Biodiversity:

- Valérie Masson-Delmotte, co-chair of working group no. 1 of the 6th **IPCC assessment** report and member of the french **High Council for the Climate** (*Haut Conseil pour le Climat*) (17/04/2023)
- Robert Watson, ex-president of the **IPCC**, ex-president of the Millennium Ecosystem Assessment, ex-president of **IPBES** , president of the 7th Global Environment Outlook (GEO-7) of **UNEP** (25/09/2023)

COVARS hearings:

- **Public Health France (***Santé Publique France*) represented by Ms. B. Coignard, Director of Infectious Diseases, L. Huiart , Scientific Director, and Le Barbier, Deputy Director of the Health, Environment and Work Department (07/12/2023)
- Professor J. Farrar, Chief Scientist of the **World Health Organization (WHO)** (14/12/2023)
- The french **National Food Safety Agency** *(ANSES - Agence Nationale de Sécurité Sanitaire de l'Alimentation)* represented by M. Schuler and G. Salvat (18/12/2023)
- The **National Agency for AIDS Research – Emerging Infectious Diseases** *(ANRS-MIE - Agence Nationale de Recherche sur le Sida – Maladies infectieuses émergentes)* , in the presence of Professor Y. Yazdanpanah and H. Raoul, E.d'Ortenzio , A. Pasquet, E Rosenthal, (11/01/2024)
- January 12 2024 and by email: members of the Ecotox Workshop organized by Pr. Giraudoux, from **UMR6249 Chrono-environment laboratory, University of Franche-Comté/CNRS:** PM Badot, N. Bernard, M. Chalot, M. C. Fritsch, H. Gauthier-Manuel, M., D. Gilbert, F. Gimbert, F. Mauny member of the HCSP - environmental risks commission, R. Scheifler
- The french **High Council for Public Health** (*HCSP – Haut Conseil pour la Santé Publique)* in the presence of Professor D. Lepelletier , President, as well as A. Pariente- Khayat , F. Caron, F. Squinazi and B. Pozzetto , S. Urban- Boudjelab , Mr. Sallendre (15/01/2024)
- **The General Secretariat of Defense and National Security** *(SGDSN - Secrétariat général de la Défense et de la Sécurité Nationale)*, represented by MM. JM Philippe, Health Advisor to the Secretary General and L Lachenaud (15/01/2024)
- **The National Research Institute for Agriculture, Food and the Environment** *(INRAE - Institut National de recherche pour l'Agriculture, l'Alimentation et l'Environnement), represented* by MA Coutellec, C. Mougin and S. Pesce (18/01/2024)
- T**he Center for International Cooperation in Agricultural Research for Development** *(CIRAD - Centre de Coopération Internationale en Recherche Agronomique pour le Développement),* in the presence of Elisabeth Claverie de Saint Martin, President and CEO, and Eric Cardinale and Nathalie Vachiery (22/01/2024)
- T**he Research and Development Institute** *(IRD - Institut Recherche et Développement)* represented by Professor Eric Delaporte, M. Sofonea , A. Binot, C. Boulle, members of the management committee of the **ExposUM Institute**[1] (25/01/2024)

- Ms. L. Alter, Director General of **the Health Innovation Agency** *(AIS – Agence d'Innovation en Santé) and responsible* for coordinating the **France 2030 emerging infectious diseases acceleration strategy** *(SA-MIE - stratégie d'accélération maladies infectieuses émergentes de France 2030)* (05/02/2024)

[1]Initiative of the University of Montpellier and its partners aimed at establishing an off-site and open-ended reference institute for the study, training and science-society interaction of the environmental determinants of human health

Executive summary

The Committee for the Surveillance and Anticipation of Health Risks (COVARS) is responding to a request from the Minister of Health and Prevention and the Minister of Research and Higher Education to review the previous analyses of potential sanitary risks likely to cause major and exceptional sanitary situations in the next 2 to 5 years. The scope of the analysis covers both metropolitan France and the overseas territories and includes all risks likely to have a major impact on the organization and life of the country and its health infrastructure but excludes CBRN and bioterrorism risks. The Committee has adopted a "One Health" approach to the exposome, justified both by the geographical dispersion of the French territories and by the universal nature of infectious and environmental risks. In addition, if certain current or emerging infectious threats have a significant power to induce exceptional and major health situations, other chronic dangers affecting all or a significant fraction of the population, such as environmental factors, have also be taken into consideration.

The COVARS consulted numerous French and international organisations and experts and analysed reports and scientific studies published both in the infectious and environmental fields. Several excellent infectious risk maps have been produced in the recent years, including those of the WHO and the French *HCSP* (Haut Conseil de Santé Publique) for human infectious diseases; those of the EFSA and the french *Anses (*Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail) for zoonoses, as well as the analysis of the french *ANRS-MIE* (Agence nationale de recherches sur le SIDA, les Hépatites et les infections émergentes) for research priorities on infectious outbreaks, and other bodies. However, as far as health risks related to the environment and climate changes are concerned, analyses tend to be more fragmentary and to focus on specific areas or categories of risksa (climate, air pollution, carcinogens, endocrine disrupters, pesticides, etc.), a fact preventing an holistic and comprehensive approach to the prioritisation of factors in terms of impact on human health, and a global vision of the infectious and physicochemical exposome. Research recommendations have been made by COVARS to fill this gap.

The COVARS begins with a non-exhaustive inventory of the issues and contexts likely to cause an exceptional health situation, including the mental health of the population, the state of the healthcare system, and the impact of physico-chemical changes. (*Part I - Elements of the health and environmental context*). The COVARS shows that the combination of several acute and chronic risks in the current context of the French health system can transform infectious or environmental risks, a priori considered as moderately high risk, into high risk with a potential to cause a major and exceptional health situation.

The COVARS analysis is based on a working method and rigorous rules recommended by the former AFSSA (former Agence de sécurité sanitaires des aliments) and the ECDC, which have been also previously used by HCSP or ANRS-MIE (***P**art II. Methodology*). A total of 35 infectious diseases were analysed according to 16 criteria relating to epidemiology, clinical aspects, available countermeasures, and systemic impacts on the health system and with psychosocial, economic and ecosystem impacts. On the basis of documents and hearings of experts in each field, the committee then conducted a contradictory, documented, iterative and multidisciplinary internal debate between its experts (infectious disease and primary care clinicians, ecologists, epidemiologists, microbiologists, immunologists, veterinarians, entomologists and specialists in human and social sciences, with representatives of health democracy). Health risks associated with climate change and physico-chemical pollution were studied in parallel, in a separate analysis.

Results of these analyses (*Part III - COVARS risk mapping*) allow COVARS to establish a mapping for the following risks of exceptional sanitary situations in which it estimates that the infections at highest risk are mainly zoonoses, and more particularly **pandemic respiratory infections (zoonotic influenza and new coronaviruses) and arboviruses** (dengue fever and West Nile virus infection), with a different distribution between metropolitan and overseas french territories. The possible occurrence of **disease "X"** is included in this category, as well as acute winter respiratory infections, the recurrent burden of which is expected to decrease in the coming years thanks to available preventive measures. Close to this group, but at a lower

level of risk, are three other vector-borne diseases, including the two arboviruses, **Zika and Chikungunya**, and the **Crimean-Congo haemorrhagic fever** (CCHF), as well as infections caused by **multi-resistant bacteria.** Another group of pathogens which are currently less likely to induce an ESS but are also strongly modulated by environmental (especially climatic) and geopolitical factors, are sexually transmitted or vector-borne diseases, (AIDS, other sexually transmitted diseases, ultra drug-resistant tuberculosis, tick-borne encephalitis, Rift Valley fever, rabies, gastroenteritis, yellow fever, etc.), the distribution of which varies according to territories.

As far as environmental risks are concerned, the major ones are mainly related to or facilitated by **climate change**. Other environmental factors have an equal or even greater impact on health, but this impact, which is generally chronic and more evenly distributed over time, is less visible. **Air pollution**, well quantified and persistent despite recent progress, is a major health risk, about half that of tobacco. The risks associated with **chemical agent**s are less well quantified, in particular because of the very large number of substances and their intermingled effects on humans. For many of these environmental risks, hazards have been identified (occurrence of cancer, cardiovascular, metabolic, endocrine or neurodegenerative diseases) and biomonitoring studies document widespread exposure, the cumulative effects of which could be significant. Furthermore, in the case of an ESS of infectious origin, these environmental factors and their consequences on the incidence of chronic diseases favor the occurrence of infectious pathologies and increase their severity.

COVARS' conclusions do not differ much from those of other organisations, despite a different specific objective, and should be considered in the light of the current, still fragmentary, knowledge of the health risks associated with infections and the environment.

This assessment of risks leads the COVARS to recommend (*Part IV - Response to the referral and recommendations*) to decision-makers to rapidly set up the specific measures for preparedness and prevention of the estimated risks of ESS (already recommended in previous COVARS Advices) and the rapid implementation of the following measures:

- Prevent and prepare for the risks of major health emergencies, without delay and on a scientific and documented basis, at the national level, that includes territorial specificities, and in coordination with European and international authorities. Preparedness and prevention should integrate the research dimension and promote health democracy, by allowing debates on the risks considered as priorities and the most socially acceptable countermeasures.
- Rapidly develop and support major plans for a better synthesis and prioritisation of risks linked to environmental factors of an infectious, biological, chemical, physical or psychosocial nature (disease burden linked to the whole exposome).
- Urgently support ambitious and innovative, interdisciplinary and intersectoral research programs, in an Exposome and One Health approach, at national and European level, to better understand and prepare the prevention and management of health risks associated with infections and environmental factors.
- Recognise the co-benefits of approaching infectious and environmental threats together by controlling and preventing known infectious and environmental risks, both chronic and acute, and the need to build healthy socio-ecosystems by reducing factors such as pollution, biodiversity loss, climate change and emergence.

Contents

Foreword

COVARS was requested to evaluate the risks likely to induce major and exceptional sanitary situations in human health for the next two to five years, taking into account the territorial specificities in mainland France and overseas territories, in a “One health” vision. The scope of the referral includes risks of infectious and environmental origin that are likely to have a very strong impact on the organisation and life of the country and its health infrastructure; but it excludes risks related to industrial, nuclear or chemical accidents or to bioterrorism.

Although infectious and environmental risks cover a vast field of very heterogeneous knowledge[2], these two areas are closely interrelated, since environmental changes favour the transmission of existing pathogens. Moreover, as the history of epidemics shows, three quarters of emerging infectious risks are due to zoonoses[3]. These emergencies have been and continue to be closely linked to environmental changes, climate change, geopolitical destabilisation events and large gatherings or movements of human populations and domestic animals, which are themselves linked to human activities and contribute to environmental and societal changes[4]. Finally, all these infectious and environmental risks cannot be analyzed from the strict perspective of national territory, since the circulation of many infectious agents knows no borders, as we were reminded by the Covid-19 pandemic, and environmental changes affect the entire planet.

Thus, COVARS followed a reading grid of infectious and environmental risks based on the exposome and in a global "One Health" perspective based on the continuum between human, animal and ecosystem health, while focusing the risk analysis on human health and the French national territory.

This opinion differs from the maps previously carried out in France or abroad (the most recent being the HCSP map on infectious agents[5]) both in terms of the objective set and the scope of the analysis. Due to the short deadline set by the Ministers, the aim here was to carry out a synthetic analysis of the main risks of major and exceptional health situation in a "One Health" approach, based on the risk maps carried out to date by French, European and international health and research organisations or climate monitoring agencies. However, the existing maps tend to focus on limited risk categories and do not include a holistic analysis that encompasses infectious, microbiological, environmental as well as psycho-social risks.

Furthermore, despite the classification of carcinogens and endocrine disrupters, to COVARS knowledge, there is no summary of the level of evidence for the health risks linked with the thousands or tens of thousands of factors present in the environment, with rare exceptions[6]. However, these very many factors and their effects, which are persistent for many of them, although less visible due to the non-specificity of their biological and health consequences, tend to accumulate, causing chronic diseases that saturate our health system and make it less resilient to health crises, as well as increasing the risk of infectious emergence and the severity of infections.

In order to respond as efficiently as possible to the Ministers referral, COVARS considered the current context of the French health system, the French population mental health and psychosocial situation caused by or related to sanitary risks, as well as the climatic, environmental and territorial situation of France. Due to time constraints, it was not possible to analyse known factors such as alcohol, diet or

[2] Environmental risks are defined here as all risks caused by elements of the human environment such as physical, chemical and social conditions, and are therefore differentiated from "infectious" risks, although the latter are also part of the environment of human populations

[3] Jones, KE et al (2008) Nature 451, 990–993. https://doi.org/10.1038/nature06536

[4] Romanello et al, 2023. The Lancet 0. https://doi.org/10.1016/S0140-6736(23)01859-7 Mora, C. et al (2022) Nat. Air conditioning. Chang . **12** , 869–875 (2022). https://doi.org/10.1038/s41558-022-01426-1 Jones, KE et al (2008) Nature 451, 990–993. https://doi.org/10.1038/nature06536

[5] HCSP, List of infectious diseases, 10/27/2023: https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1363

[6] Stacy Colzyn et al (2024). Int J Hyg Environ Health. 256:114311. doi : 10.1016/j.ijheh.2023.114311.

sedentary lifestyle, which are unlikely to cause exceptional health situations but whose control could significantly reduce the burden on the health system and constitute an important lever for limiting the risk of future exceptional health situations.

The analysis of threats of infectious origin carried out by COVARS synthesised the data available over the last 10 years and took into account factors that limit or increase the probability of occurrence and impact of these risks of exceptional health situations, such as: **i)** expected or potential population changes (ageing, multimorbidity) and environmental changes (population mobility linked to climate, conflicts) that affect the behaviour and/or ecology of vectors and the introduction or re-introduction of pathologies with an impact on the territory, **ii)** response capacity, particularly due to territorial isolation, especially overseas. These external or "systemic" factors increase the vulnerability of the populations concerned, and consequently of the health system, and can trigger and/or amplify potential health crises. This has allowed COVARS to produce two maps of human health risks that are likely to lead to exceptional and major, or persistent but major, health situations: 1) identified infectious risks, and 2) an assessment, albeit very fragmentary, of the health consequences and burden of disease caused by environmental risks. COVARS also makes recommendations for the preparation and anticipation of these risks in order to limit the potential impact of the identified risks, highlighting the important links between these risk categories.

This mapping thus opens up a perspective that integrates the main threats and makes it possible to identify the main "gaps" in knowledge on the health consequences of these threats, particularly those of an environmental nature. This work should serve as a basis for a future regular review of the analysis of risks and threats of infectious and environmental origin that could lead to exceptional or major health situations on national territory, in the context of international risks and threats, in order to adapt our health system and research agenda into means of prevention, preparedness and response[7], and to analyse in the coming years whether the corpus of actions undertaken makes it possible to reduce the residual risk in a context of time and resource constraints.

[7]OHHLEP, et al. 2023. PLOS Pathogens 19, e1011504. https://doi.org/10.1371/journal.ppat.1011504

I. Issues and elements of health and environment context:

The concept of major and exceptional health situations (see definition in the Methodology section) encompasses all factors of extra-bodily origin that can influence human health, and include biological, physical, chemical agents as well as psychosocial and behavioural factors. The analysis of risks that are likely to provoke such situations on the national territory must be performed in light of diverse contextual elements, including demographics, the state of the health system, or the mental health of the french population.

As most infectious risks, especially emerging ones, are of zoonotic origin, it is also essential to analyse infectious or environmental risks with the potential to trigger an exceptional health situation as part of an integrated and unifying "One Health" approach, recognising that the health of humans, domestic and wild animals, plants and the general environment (including ecosystems) are interconnected and interdependent.[8]

A- Demographic context

Population ageing needs to be analysed into risk projections. The global population aged 60 and over will increase from 1 billion in 2020 to 1.4 billion in 2030[9].
In France, demographic ageing is lower than in most neighbouring countries and less pronounced in the overseas territories, but it has been increasing since the 2010s, with the estimated number of people aged 75 to 84 increasing by 49% between 2020 and 2030[10]. By 2030, there will be more people aged 65 and over than under 20 (Figure 1 below).

Ageing exacerbates communicable and non-communicable diseases and increases the risk and prevalence of comorbidity factors and pathologies[11], in particular acute respiratory infections such as Covid-19, influenza, RSV, but also arboviruses and most infectious diseases. In addition, this demographic aging **causes an increase in the demand for healthcare[12]** and in social isolation.

[8]-Joint statement of the Tripartite Group (FAO, OIE, WHO) and UNEP (2021), Brown TM et al (2006), Am J Public Health, 96(1): 62–72-Brown TM et al (2006) , Am J Public Health, 96(1): 62–72
[9]WHO (2022), Aging and health: https://www.who.int/en/news-room/fact-sheets/detail/ageing-and-health
[10] INSEE (2016) Population projections by 2070; INED (2020), Demographic issues and prospects in France 2020-2050; INSEE (2021), 68.1 million inhabitants in 2070; Toulemon L et al (2022), INED, Population and Societies, number 597; DOI: 10.3917/popsoc.597.0001
[11] HCAAM opinion (2010), Aging, longevity and health insurance
[12]DREES (2017), number 1025: https://drees.solidarites-sante.gouv.fr/sites/default/files/er1025.pdf - https://www.ameli.fr/medecin/actualites/patients-en- ald-without-treating-doctor-the-trend-is-reversing-since-the-launch-of-the-action-plan

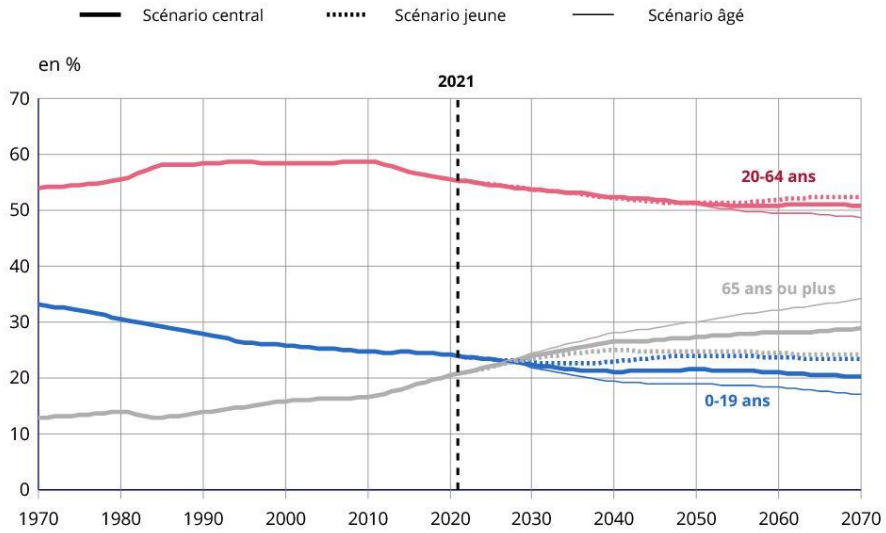

Figure 1: Age structure of the population from 1970 to 2070 according to different scenarios
Source: Insee, population estimates, population projections 2021-2070.

Populations at risk of severe forms in the event of exposure to infectious and environmental risks

Immunosuppression is one of the risk factors for severe forms of most infections and the severely immunocompromised french population has been estimated at around 230,000 people (recent solid organ or bone marrow transplant recipients, patients either dialyzed or under strong immunosuppressive treatment, or treated for certain haematological malignancies[13]). These numbers tend to increase[14].
Other risk factors associated with chronic diseases (especially cardio-respiratory) and obesity also expose people to aggravation of both infectious and environmental risks.*

B- Context of the healthcare system

Health professionals' shortage:

The current difficulties of the French health system, and in particular the professional health workers (PHW) shortage, increase the risk of an exceptional health situation. This shortage of PHW is global[15] and has been described as a "time bomb" by the WHO[16]. In France, according to the French Hospital Federation (FHF), more than 100,000 nurses and nursing assistant positions need to be filled each year[17], and more than 30% of the French population resides in a zone of "medical desertification". Of the 320,000 doctors registered in 2022, only 197,000 practiced regularly[18]; the number of general practitioners decreased by 11% between 2010 and 2022, and 11% of French people over 17 do not have a registered GP[19]. This situation has an impact on the quality of care, as reported in 2021[20], with 6% of bed closures related to nursing shortages,

[13]HAS (2022) Vaccination strategy against Covid-19, anticipation of possible scenarios in fall 2022; Vaccination Strategy Orientation Council, Opinion of April 6, 2021: https://sante.gouv.fr/IMG/pdf/avis_du_cosv_6_avril_2021pdf.pdf
[14] Martinson ML. et al (2024), JAMA. 331(10):880–882. doi: 10.1001/jama.2023.28019
[15] WHO (2020). https://www.who.int/publications/i/item/9789240003279]
[16]WHO (2022), Press release: https://www.who.int/europe/en/news/item/14-09-2022-ticking-timebomb--without-immediate-action--health-and-care -workforce-gaps-in-the-european-region-could-spell-disaster
[17]FHF (2022): https://www.fhf.fr/la-fhf-en-action-renforcer-lattractivite-des-metiers-de-la-sante-et-du-medico-social
[18]National Academy of Medicine (2023): https://www.academie-medecine.fr/wp-content/uploads/2023/04/Rapport-Deserts-medicaux-2023-04-21.pdf
[19]Senate (2022), https://www.senat.fr/rap/r21-589/r21-589-syn.pdf
[20]https://drees.solidarites-sante.gouv.fr/sites/default/files/2021-09/ER1208.pdf
FHF (2022): https://www.fhf.fr/la-fhf-en-action-renforcer-lattractivite-des-metiers-de-la-sante-et-du-medico-social

and partial or total closure of 40% of emergency units[21] in the summer of 2023 [22]. This situation in France is unlikely to evolve in the next 5 years, as medical density is not expected to improve significantly before 2033[23].

Additionally, the surveillance and evaluation of the risks of exceptional health situations should take into account the potential of the veterinary personnel in charge of livestock, which is also decreasing significantly[24]. Furthermore, the community of practitioners involved in the health ecosystem is still insufficiently identified and structured[25].
To this structural fragility of the French health system, the SGDSN (*General Secretariat of Defense and National Security - Secrétariat général de la Défense et de la Sécurité Nationale)* adds the risk of disruption caused, for example, by a violent terrorist or other non-health-related event, to a health system that is totally dependent on electronics and digital technology.

Specificities of Overseas Territories:

As early as 2014, the Cour des Comptes warned that "the overseas departments share health problems, often of a particular nature and scale". In addition to the institutional difficulties common to the French territories in Europe, there is an extreme diversity of risks and specific difficulties characterised by greater vulnerability, linked to:

- ***Greater poverty:*** According to INSEE, in 2017 more than 30% of the population lived below the poverty line in Martinique and Guadeloupe, 42% in Réunion, 53% in Guyana and even 77% in Mayotte, compared to 15% in a Metropolitan France[26].
- ***The highest prevalence of several risk factors and co-morbidities:*** including severe obesity, which affects 18 to 30% of the overseas population, compared with 17% in metropolitan France, and is associated risk factors: diabetes (around 10% in Mayotte, the French Indies, New Caledonia, 14% in Reunion and 22% in French Polynesia, compared with 5% in metropolitan France), hypertension (between 39 and 45% in Guadeloupe, Martinique, Mayotte and Reunion, compared with 31% in the French population). A particular point is sickle cell anaemia, a common genetic disease (1/300) in the West Indies, which is associated with a higher severity of several diseases such as dengue or COVID-19[27].
- ***Compliance with public health policy*** is sometimes less important than in France, as was the case during the Covid-19 crisis.
- ***The structural weakness of the health system,*** particularly in intensive care units. In 2018, there were 80 and 218 doctors per 100,000 inhabitants in Mayotte and Guyana respectively, compared with 338 doctors per 100,000 inhabitants in metropolitan France. There is also a lack of molecular diagnostic capacity. The situation in Guyana and Mayotte could lead to the health reserve being called upon in the event of a major and exceptional health situation, as was the case during the Covid-19 crisis[28].
- ***Geographic Isolation of French islands,*** on top of geographic proximity to major pathogens in neighbouring countries, can generate a high economic cost when major epidemics arise, such as during the Chikungunya epidemics at La Réunion or during the Covid-19 crisis[29].

[21]SFMU (2023) : https://www.sfmu.org/fr/actualites/actualites-de-l-urgences/plus-de-160-services-d-urgence-fermes-au-minis-une-viens-durant-l-ete-enquete-samu-urgences-de-france-/new_id/69282
[22]Roussel, M. et al (2023). JAMA Internal Medicine 183(12): 1378.
[23]Senate (2022): https://www.senat.fr/rap/r21-589/r21-589-syn.pdf
[24]National demographic observatory of the veterinary profession (2023): https://www.veterinaire.fr/system/files/files/2023-12/ATLAS-NATIONAL-2023%20V07122024.pdf
[25]Giraudoux, P. et al. CABI One Health 2022. https://doi.org/10.1079/cabionehealth.2022.0006
[26] Insee (2020): https://www.insee.fr/fr/statistiques/4622377
[27]SpF (2012, updated 2021): https://www.santepubliquefrance.fr/regions/ocean-indien/documents/article/2012/la-drepanocytose-dans-les-departements-francais-d-outre-mer- antilles-guiana-la-reunion-mayotte-.-descriptive-data-and-organization-of-the-prison -in-charge
[28]SPILF (2022): https://www.infectiologie.com/fr/covid-19-les-outre-mer-a-bout-de-souffle.html
[29]Senate information report (2021) : https://www.senat.fr/rap/r21-177/r21-177_mono.html

However, in the Réunion Island, New Caledonia, French Polynesia, Guyana and Mayotte, population ageing is less pronounced, with only 1 to 5% of the population over 75 years of age, which can partially offset the effects of excess morbidity/mortality associated with other risk factors.

Special case of Mayotte : This department has the highest population density in overseas France, the highest growth rate and significant migratory flows, with 310,000 inhabitants in 2022 on 376 km2. In 2019, half of the population was under 17. Since 2016, Mayotte, where 77% of the population is living below the national poverty level (2018 data) and 29% of households do not have access to running water, has suffered from a severe water crisis due to an exceptional drought, the dilapidation of the distribution network, the increase in consumption (+20% in four years) and massive deforestation. From 2020, the frequency of occasional water restrictions increased, becoming almost year-round during the dry season and requiring the supply of bottled water from the end of 2023.
The archipelago is exposed to frequent and devastating tropical cyclones. Exposure to epidemics of arboviruses and zoonoses is also high, with mosquito vectors such as *Aedes Albopictus*, which is present in this territory since the 1990s. The development of competent mosquitoes is favoured by anarchic land-use planning, ruminant farming close to human populations, significant rainfall, and intense animal movement (legal and illegal production).
The 2018-2019 Rift Valley Fever (RVF) outbreak caused food insecurity due to a 20% drop in milk production (see Chapter III). The cholera outbreak in the Comoros , exposed Mayotte, where four simported cases have been reported since 18 March 2024[30].

Risks of stock-outs of essential medicines:

These risks apply not only to antibiotics or paracetamol, but to all therapeutic areas. Despite recommendations for the correct use of medicines[31], the risk remains, partly linked to economic models for medicines production and supply chains (deregulation of the generic market, globalised or even unique production chains, regulatory constraints, etc.). This situation has the potential of transforming normally controlled pathologies into exceptional health situations.

Antibiotic therapy and antimicrobial resistance:

For 10 years, antimicrobial resistance has been the subject of numerous reports (Carlet in 2012[32]) and plans (Obama in 2013 in the USA[33] and the WHO in 2016[34]) alerting political decision-makers, caregivers and the general public of the risk of loss of effectiveness of antibiotics and the threat of a “post-antibiotic era”. High-income countries, such as France, still perceive this threat as a silent epidemic, limited to very fragile patients after complex care pathways[35], in whom emerging highly resistant bacterial or fungal infection is very often associated with serious co-morbidities.

[30]ARS Mayotte, Press release of March 19, 2024: https://www.mayotte.ars.sante.fr/identification-dun-premier-cas-de-cholera-mayotte
[31] HAS (2023): https://www.has-sante.fr/jcms/c_2615258/fr/xi-le-bon-usage-du-medicament-et-des-therapeutiques-non-medicamenteuses; ANSM (2023): https://ansm.sante.fr/dossiers-thematiques/bon-usage-du-medicament ; Ministry of Labor, Health and Solidarity (2016, updated 2022): https://sante.gouv.fr/soins-et-entreprises/medicaments/le-bon-usage-des-medicaments/article/quelques -rules-for-proper-use-of-medications
[32]Carlet J and Le Coz P. (2016) Mines Paris Tech, https://sante.gouv.fr/IMG/pdf/rapport_antibiotics.pdf M
[33] Office of the Assistant Secretary for Planning and Evaluation (2020), National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020-2025: https://aspe.hhs.gov/reports/national-action-plan-combating-antibiotic-resistant -bacteria-2020-2025
[34] WHO (2016), Global action plan to combat antimicrobial resistance: https://www.who.int/en/publications-detail/9789241509763
[35] WHO (2014) Antimicrobial resistance – global report on surveillance, accessible here: https://www.who.int/publications/i/item/9789241564748

However, antimicrobial resistance is a real French and global threat, of a "One Health" nature, reflecting the overuse and misuse of antibiotics, particularly in human medicine, but also in agriculture, which spread in soil and water and, together with climatic stress, contribute to the disruption of microbial ecology[36].
The WHO reports a 15% increase in certain antibiotic-resistant infections in 2020 compared to 2017[37.] Resistance rates of more than 50% have been observed for bacteria responsible not only for potentially deadly hospital infections (particularly *Klebsiella pneumoniae* or *Acinetobacter spp*), but also for common sexually transmitted infections (STIs) such as gonorrhoea (due to *Neisseria gonorrhoeae* resistant to ciprofloxacin) or urinary tract infections (due to *E. coli* resistant to ampicillin, cotrimoxazole and fluoroquinolones). If this growth is mainly observed in low- and middle-income countries[38], some reports point to the excessive use of antibiotics in France, which is 63% higher than in Germany and 27% higher than in the UK, making France the 4th highest user of antibiotics in Europe[39](Figure 2).

Despite the excellent french surveillance and numerous measures to promote correct use and encouraging development, the One Health synthesis from Santé publique France (SpF) on antimicrobial resistance shows that antimicrobial resistance in *Escherichia coli* in France[40](figure 2), particularly in young children, is independent of the Covid-19 epidemic, as the same is not observed in Germany and the UK.

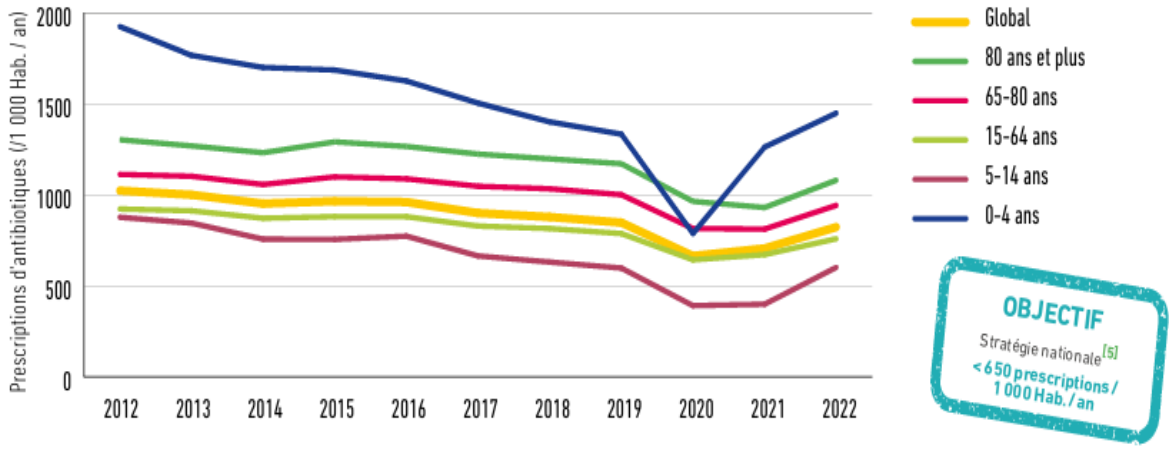

Figure 2: Antibiotic prescriptions by age group and for the total population in France, 2012-2020/ Source: Public Health France (SNDS data)

In addition, the WHO estimates that 10% of the 500,000 new cases of multidrug-resistant tuberculosis observed worldwide each year are associated with ultra-resistant strains known as XDR, the definition of which has been revised by the WHO to be more restrictive[41]. Their treatment, which requires very long courses of expensive anti-tuberculosis drugs with numerous side effects, is often inaccessible to the majority of patients, resulting in very high transmissibility and mortality. In France, the new WHO definition has reduced the proportion of XDR strains reported by the national Reference Center (CNR) from 37 to 6 between 2017 and 2021[42] and SpF highlighted in 2021 that the populations most affected were people who

[36]-Godeau, C. et al (2020). American Journal of Infection Control 48, 702–704. https://doi.org/10.1016/j.ajic.2019.10.003 - Rocchi , S. et al (2021) Medical Mycology (Vol. 59, Issue 7, pp. 741–743) https://doi.org /10.1093/mmy/myab007
[37]WHO (2022): https://www.who.int/news/item/09-12-2022-report-signals-increasing-resistance-to-antibiotics-in-bacterial-infections-in-humans-and-need -for-better-data
[38] WHO (2022), Global antimicrobial resistance and use surveillance system (GLASS) report,: https://www.who.int/publications/i/item/9789240062702 ; OECD (2018), Stopping Antibiotic Resistance in France: https://www.oecd.org/fr/france/Stopping-l-antibior%C3%A9sistance-en-France.pdf
[39]- Public Health France (2022),: https://www.santepubliquefrance.fr/les-actualites/2022/consommation-d-antibiotics-et-prevention-de-l-antibioresistance-en-france-en-2021-ou -are we
-ANSM (2023), Antibiotic consumption in France from 2000 to 2020
[40] Public Health France (2023), The resumption of antibiotic consumption in the urban sector is confirmed in 2022 https://www.santepubliquefrance.fr/presse/2023/la-reprise-de-la-consommation-d-antibiotics-en-secteur-de-ville-se-confirme-en-2022
[41]WHO (2022), Global tuberculosis report 2022. *Geneva*
[42] Veziris N, et al (2021) Eur Respir J 58:2100641

were homeless, detained or born outside of France[43]. While the incidence of XDR-TB remains low worldwide, 60% of cases in 2018 came from the WHO European Region (7 889 cases), mainly from Ukraine, Belarus and Russia, and 27% from South-East Asia (3 580), an increase of 16% compared with 2017. Ukraine reported the third highest number of XDR-TB cases in 2019[44].

C- Mental health of the French population

Since the Covid-19 pandemic, there has been a marked deterioration in the mental health of the French population, which has highlighted the need to monitor the prevalence of mental health among young people. This is particularly the case among young people: SpF's Enabee study (2022)[45] of 30,000 children showed that 13% of school children aged 6 to 11 have at least one probable mental health disorder. Additionally, the use of emergency care for mood disorders, suicidal thoughts and gestures increased in 2021 and 2022 among 11-24 year olds[46]. Among 18-24 year olds, depressive syndromes will affect 20.8% in 2021, compared to 11.7% in 2017. The situation is similar internationally, with almost 32% of 18-24 year olds suffering from mental disorders (+11 points compared to the total population).
Epidemics such as avian influenza also have an impact on the mental health of breeders by affecting the domestic animal world (e.g. the impact of measures to completely eliminate contaminated flocks)[47], or they can fuel public fears about the environment by decimating wildlife and highlighting the virus's adaptation to mammals and the increased risk of transmission to humans[48].

D- General public communication on health crises and infodemics

In an exceptional health situation, communication of public health risks and benefits is based on messages that are often complex and poorly understood. The phenomenon **of infodemics**[49,] highlighted as a major risk by the WHO in particular is defined as the spread of "fake news" and rumours, i.e. false, misleading or unverifiable information, on socio-digital networks and alternative distribution channels in a health crisis situation[50]. This misinformation relates to the safety and harmlessness of countermeasures, their effectiveness or their public health interest and is a source of disinformation.[51] This has a significant negative impact on adherence to health recommendations and the adoption of risk reduction behaviours (WHO, 2020[52]). These difficulties particularly affect the most vulnerable sections of the population, as has happened in the case of compliance with vaccination against Covid-19.
Finally, health risks affecting young children (such as the poisoning of 10,000 children in Berlin in 2012 by contaminated strawberries served in school canteens[53]) can have a societal and media impact of particular

[43] https://www.santepubliquefrance.fr/les-actualites/2023/tuberculose-en-france-les-chiffres-2021
[44] Pavlenko E, et al. (2018) Int J Tuberc Lung Dis 22:197e205. https://doi.org/10.5588/ijtld.17.0254
[45]Public Health France (2023): https://www.santepubliquefrance.fr/presse/2023/sante-mentale-premiers-resultats-de-l-etude-enabee-chez-les-enfants-de-6-a-11 -years-of-school-from-cp-to-cm2
[46]Public Health France (2023): https://www.santepubliquefrance.fr/presse/2023/sante-mentale-des-jeunes-des-conseils-pour-prendre-soin-de-sa-sante-mentale
[47]The major impact During the great epizootic of foot and mouth disease in cattle in England was above all social, with lasting psychological consequences for the breeders who had to endure the sight of thousands of corpses.
[48]Kat Kerlin (2024): https://www.ucdavis.edu/climate/news/avian-influenza-virus-adapting-spread-marine-mammals
[49] Neologism developed by G. Eysenbach and taken up by the WHO to designate the rapid spread of rumors and false information which increasingly accompanies epidemics of infectious diseases.
[50]European Center for Disease Prevention and Control/ECDC (2021). Technical Report: Countering online vaccine misinformation in the EU/EEA. Stockholm: ECDC.
[51]Do Nascimento, IJB et al (2022). Bulletin of the World Health Organization, 100(9), 544 .; Chowdhury, N. et al (2023). Journal of Public Health, 31(4), 553-573.
[52]WHO (2020) An ad hoc WHO technical consultation managing the COVID-19 infodemic: call for action, 7-8 April 2020. Geneva; Roozenbeek , J. et al (2020). Royal Society open science, 7(10), 201199.
[53]Libération (2012): https://www.liberation.fr/planete/2012/10/08/l-allemagne-met-sous-surveillance-de-fraises-surgelees-importationes-de-chine_851717/

magnitude. If serious risks affecting children's health can trigger panic effects, they can also lead to massive acceptance of prevention measures[54].

E- Environmental and climatic factors affecting human health

Climate change

Climate change is real. In France, the average temperature is 1.9 degrees higher (2013-2022) than in the pre-industrial era, and the increase is likely to exceed 2.2°C by 2050[55]. Climate change increases the frequency and severity of extreme weather events, such as heat waves, hurricanes, coastal flooding, intense and prolonged droughts in summer and increased rainfall and flooding in other seasons, as well as the risk of fires[56]. The overseas departments and territories are particularly affected by extreme climatic events: the hottest periods in France since measurements began in 1967 were recorded during the dry season in the Réunion Island, Martinique and Guadeloupe, with episodes of Saharan dust and low winds exacerbating the heat and of severe drought (such as in Mayotte), increasing the risk of exposure to infectious diseases from contaminated water.
In 2023, 5,000 heat-related deaths were estimated to occur (75% of which will be among the over-75s), of which just under a third will be due to heatwaves[57].

Atmospheric pollution

Atmospheric pollution is a leading cause of environment-related mortality worldwide[58], responsible for 7 million deaths per year[59]. In France, around 40,000 deaths are attributed to air pollution by fine particles (see Table 2), with underlying causes such as chronic respiratory diseases (lung cancer, chronic obstructive pulmonary diseases (COPD), asthma .....), cardiovascular diseases (heart attacks, hypertension, strokes) and aggravation of respiratory infections. Exposure could also lead to developmental problems and neurodegenerative diseases[60]. The diagram below, established as part of the Air Quality Report in France in 2022, highlights recent French improvements but also areas of persistence of certain pollutants, in particular ozone, and summarizes the main health consequences associated with pollution and climate change.

[54]https://sante.gouv.fr/actualites/actualites-du-ministere/article/contre-la-bronchiolite-un-traitement-preventif-et-des-gestes-simples
[55]MTECT, 2024. https://www.ecologie.gouv.fr/sites/default/files/document-reference-TRACC.pdf Haut Conseil pour le Climat (2023). General public report 2023: recognize the emergency, commit the means
[56]- Vicedo -Cabrera, AM et al (2021) Nat. Air conditioning. Chang. 11, 492–500. https://doi.org/10.1038/s41558-021-01058-x ; Météo-France, 2023: https://meteofrance.com/le-changement-climatique/observer-le-changement-climatique/changement-climatique-et-feux-de-forets - https://www.ipcc.ch/report/ar6/wg1/downloads/report/IPCC_AR6_WGI_SPM.pdf
[57]DeSouza. et al (2024). Nature Reviews Microbiology , 1-16.; Public Health France (2024): https://www.santepubliquefrance.fr/determinants-de-sante/climat/fortes-chaleurs-canicule/documents/bulletin-national/canicule-et-sante.-bulletin-de-sante- public-summer-2023 review
[58] Landrigan PJ (2017) The Lancet Public Health 2(1): e4–e5.
[59]WHO Global Air Quality Guidelines (2021); WHO (2023) https://www.who.int/news-room/feature-stories/detail/air-pollution--the-invisible-health-threat
[60]MTECT (2023) https://www.statistiques.developpement-durable.gouv.fr/bilan-de-la-qualite-de-lair-exterieur-en-france-en-2022

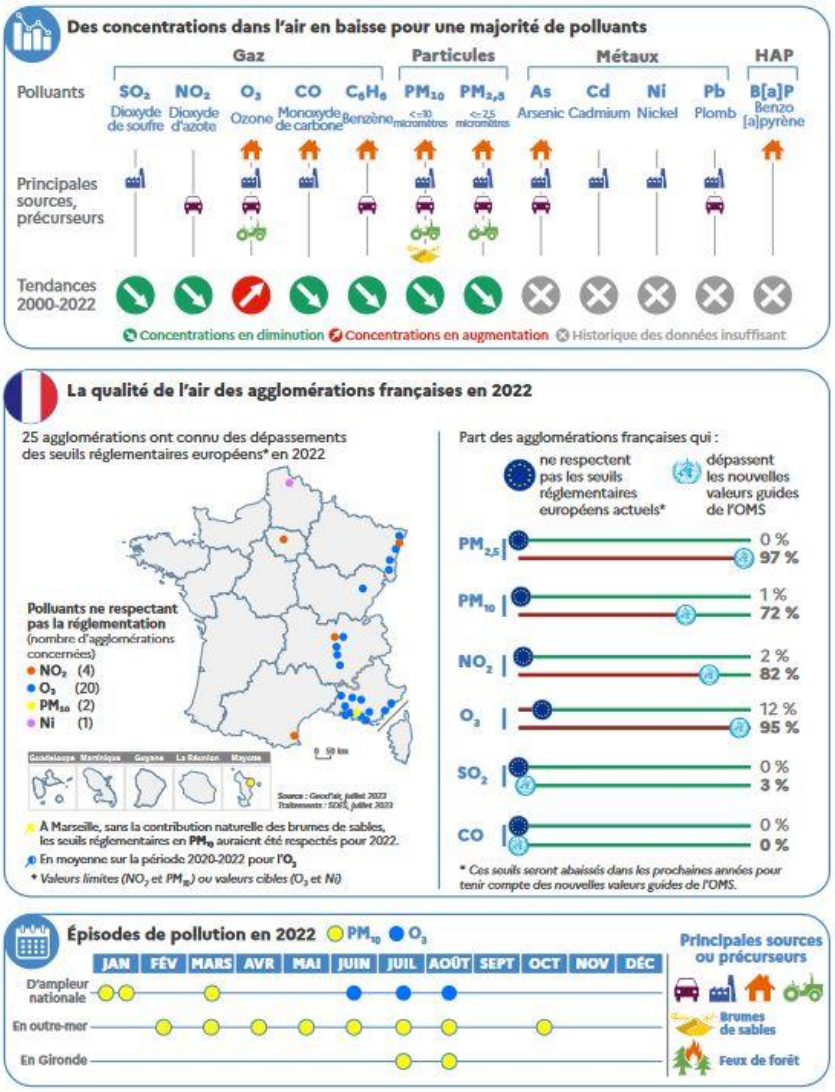

Figure 3 - The "Air quality report - 2022" [61]

Pollution by chemical agents:

Chemical pollution is a major threat to the environment and to human health. Contamination of the environment by chemical substances of anthropogenic origin is found in all environments: air, sea, land and in the food chain. It is also present in the human body[62], as documented by biomonitoring studies[63]. More than 23,000 substances are marketed in the European Union, but this figure only includes substances produced above a certain tonnage and excludes pharmaceuticals, pesticides and cosmetics. In 2021, around 350,000 chemical substances have been manufacturd worldwide, with an average of 3 new substances being registered every day[64].

The WHO has published a list of the 10 major pollutants (figure below):

[61] MTECT (2023): https://www.statistiques.developpement-durable.gouv.fr/bilan-de-la-qualite-de-lair-exterieur-en-france-en-2022
[62]https://www.anses.fr/fr/content/les-études-de-lalimentation-totale-eat
[63]https://www.santepubliquefrance.fr/biosurveillance- humaine/expositions-environnementelles-les-principales-etudes-de-biosurveillance-et-d-impregnation-menees-par-sante-publique-france
[64] WHO (2019), The WHO recommended Classification of Pesticides by Hazard and Guidelines to classification

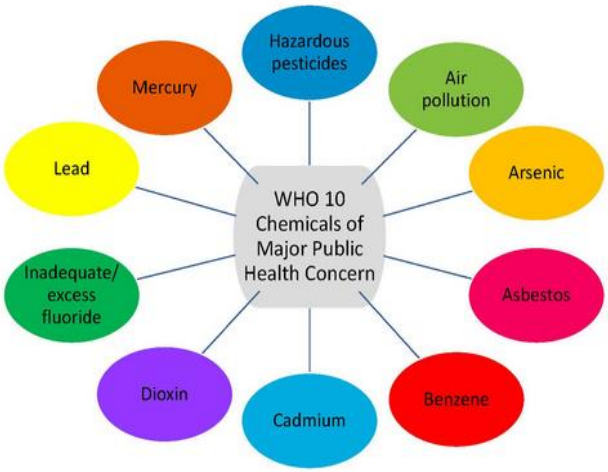

Figure 4: WHO list of 10 major pollutants (2019)

In France, the collective expertise of Inserm in 2013[65] and of INRAE and IFREMER in 2022[66] have clarified the human health risks associated with pesticides and the impact on biodiversity and ecosystems of plant protection products (PPP), of which 55,000 to 70,000 tonnes are sold annually in France (mainland and overseas), including those used in organic agricultural and bio-control. A study carried out in mainland France on several species of small wild mammals shows the presence of 32 to 65 pesticide residues per individual (including 13 to 26 products banned or restricted for use and 18 to 41 currently used)[67], illustrating the contamination of agricultural ecosystems and the cumulative importance of past spraying of substances now banned (such as chlordecone in the West Indies). In addition, this pollution affects the quality of water, in particular through nitrates[68]: between 1980 and 2021, 12,600 drinking water catchments have been closed and 40.7% of catchments will be abandoned due to deterioration in quality and excessive nitrate or pesticide levels[69].

The European Union has proposed a list of the main classes of health and environmental hazards, which are essentially described in the CLP Directive[70], and which includes in particular: carcinogens, mutagens, reprotoxic agents, endocrine disruptors, etc.

Urbanisation and pollution

Urbanisation, with its consequences in terms of population density, increased social inequalities, loss of biodiversity, vulnerability to climate change, environments favourable to only a few animal species (birds, rodents, arthropod vectors), concentrates and increases certain health risks for humans, such as the occurrence of exceptional infectious events and the emergence and transmission of human and zoonotic diseases[71]. Conversely, urbanisation can be seen as a factor that makes it easier to detect and manage an exceptional infectious event by bringing together health services and skills.

[65]Inserm (2013), Pesticides: effects on health: https://www.inserm.fr/expertise-collective/pesticides-effects-sur-sante/
[66]INRAE/Ifremer collective scientific expertise (2022): https://www.inrae.fr/actualites/impacts-produits-phytopharmaceutiques-biodiversite-services-ecosystemiques-resultats-lexpertise-scientifique-collective-inrae-ifremer
[67]Fritsch, C. et al (2022). Sci Rep 12, 15904. https://doi.org/10.1038/s41598-022-19959-y
[68]Deliberate note No. Ae 2023-N-08 adopted during the meeting of November 23, 2023
[69]https://www.lagrandeconversation.com/ecologie/programmes-daction-nitrates-les-resultats-ne-sont-a-la-hauteur-ni-des-expectations-ni-des-jeux/
[70]Classification, Labeling, Packaging, CE n°1272/2008
[71] Events due to air and water pollution being more endemic and continuing to grow (for the moment)

II. Methodology

A- Existing risk maps analysed by COVARS

In order to respond to the referral, COVARS analysed numerous mapping or assessment documents relating to specific risks in various areas, namely:

1- **Assessments of health risks linked to infections:** (see table in annex 1 for a tabular comparison of the classifications made by these different assessments)

In France :

- **HCSP list of infectious diseases** in human health[72]: this priority list was developed as part of the current revision of the WHO Blueprint and classifies 95 entities (diseases or groups of infectious diseases). (See table in Annex 2)
- **Prioritisation of non-food zoonoses by the 2009 InVS**[73] (See table in annex 2): This InVS analysis aimed to "provide epidemiological arguments justifying the measures to be taken to prevent and control the occurrence or spread of diseases", and defined a series of pathogens "most likely to be the cause of significant pathologies in terms of public health".
- **ANSES list of priority animal diseases**[74] : this list was drawn up in 2012 by prioritizing 103 animal diseases present in metropolitan France.
- **ANRS-MIE list of priority pathogens or families of emerging pathogens** (2022)[75] on which to focus France's preparation efforts for future health crises linked to emerging infections (see annex 2)
- **CIRAD's analysis of infectious risks** in the context of research and surveillance activities and regional health networks in which CIRAD participates (CaribVET and One Health Indian Ocean) for overseas territories[76].

In Europe and Internationally :

- **ECDC document on emerging infectious risks for Europe** (in preparation) (Foresight project[77])
- **WHO List of prioritisation of Diseases and Pathogens for R&D** in **Public Health Emergencies** (2018)[78], revised in 2021 and currently under review (update expected in 2024[79]).
- **Institute for Health classifications, Metrics and Evaluation (IHME**), an independent research centre at the University of Washington School of Medicine in Seattle (United States), partner of WHO Regional office for Europe, which publishes its burden of disease analyses in scientific journals[80]

[72]HCSP, List of infectious diseases, 10/27/2023: https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1363
[73]Health Monitoring Institute (2009), Definition of priorities in the field of non-food zoonoses
[74]Anses (2012), Hierarchy of 103 animal diseases present in the ruminant, equine, pig, poultry and rabbit sectors in mainland France: https://www.anses.fr/fr/system/files/SANT2010sa0280Ra.pdf ; Anses (2012), Methodology for prioritizing animal diseases; application to exotic pathogens for mainland France: https://www.anses.fr/fr/system/files/SANT2008sa0390Ra.pdf; Anses (2012) https://www.anses.fr/fr/system/files/SANT2010sa0280Ra.pdf ; Anses (2024) relating to "Crimean-Congo hemorrhagic fever": https://urldefense.com/v3/__https://www.anses.fr/fr/system/files/SABA2023SA0194.pdf_;
[75]ANRS-MIE (2022), List of priority pathogens, accessible here: https://www.infectiologie.com/UserFiles/File/renarci/liste-des-pathogenes-prioritaires-rech-mie-2023-2.pdf
[76]COVARS hearing of January 22, 2024
[77]ECDC (2020): https://www.ecdc.europa.eu/en/publications-data/single-programming-document-2020-2022
[78]WHO (2018): https://cdn.who.int/media/docs/default-source/blue-print/2018-annual-review-of-diseases-prioritized-under-the-research-and-development-blueprint .pdf?sfvrsn=4c22e36_2 ; -WHO (2023) https://www.who.int/teams/blueprint/who-r-and-d-blueprint-for-epidemics
[79]WHO (2022), Press release, WHO to identify pathogens that could cause future outbreaks and pandemics, available here : https://www.who.int/news/item/21-11-2022-who-to-identify- pathogens-that-could-cause-future-outbreaks-and-pandemics
[80]Vos, T. et al (2020), Lancet. 396(10258):1204-1222; Murray, CJL et al (2020), Lancet 396(10258): 1223–1249.

- **EFSA List (2023)** "Prioritisation of zoonotic diseases for coordinated surveillance systems under the One Health approach for transboundary pathogens that threaten the Union"[81] (see table in annex 2 for the complete classification)
- **List of the Belgian Presidency of the European Union,** " Health priorities ", of which one pillar is the prevention of infectious diseases[82]
- **Priority list of the Dutch government**[83], which classifies only influenza and emerging respiratory viruses as a major infectious risk.
- **Priority list of zoonotic diseases of the United States** produced by the CDC (Center for Disease Control and Prevention), DOI (Department of the Interior), and USDA (Department of Agriculture)[84].

2- Mapping of environmental health risks:

In addition to numerous scientific articles, COVARS has considered and reviewed the following documents on the health risks associated with climate change, pollution and the spread of chemical substances in the environment:

France:

- **ANSES** analyses of heavy metals, cadmium, nitrates, pesticides, PFAS, antibiotics and other pharmaceuticals[85]
- **SpF** analyses related to climate change, especially heat waves[86]
- The **report on outdoor air quality in France 2022-23**[87]
- The report of the **High Council on Climate (HCC)**[88]
- The National Health-Environment Plans of **the PNSE 4** (2021-2025)[89] and the **HCSP** report[90],
- **The collective expertise of INSERM** on pesticides[91] updated in 2021 [92], and of **INRAE and IFREMER** on the impact of plant protection products[93]
- The report of the **National Academy of Medicine** (2020) on the impact of climate change on human and animal health[94], the white paper of the Academy of Medicine foundation on chemical pollution of the environment and public health[95], and the press release from the Hepta-academic conference of 15 June 2022 "One health: microbes and antibiotic resistance"[96]

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[81]European Food Safety Authority (EFSA); Berezowski J et al (2023) EFSA J. 2023 Mar 3;21(3):e 07853. doi : 10.2903/j.efsa.2023.7853. PMID: 36875865; PMCID: PMC9982565.

[82]Health Belgium (2024) EU2024BE; https://www.health.belgium.be/en/health-priorities-belgian-council-presidency

[83] Dutch National Network of Safety and Security Analysts, National Risk Assessment of the Kingdom of the Netherlands 2022: https://www.government.nl/documents/reports/2022/09/26/national-risk-assessment-of-the- kingdom-of-the-netherlands-2022

[84]https://www.cdc.gov/onehealth/pdfs/OHZDP_Workshop_Flyer_508.pdf

[85]ANSES (2020),: https://www.anses.fr/fr/system/files/REACH2019SA0221.pdf ; ANSES (2018): https://www.anses.fr/fr/content/avis-de-lanses-relatif-%C3%A0-l%E2%80%99%C3%A9valuation-des-substances-inscriptiones- in-the-2018-work-program ; ANSES (2019): https://www.anses.fr/fr/system/files/VSR2015SA0140.pdf ; ANSES (2022): https://www.anses.fr/fr/system/files/ERCA2020SA0106Ra.pdf

[86]Public Health France (2023): https://www.santepubliquefrance.fr/determinants-de-sante/climat/fortes-chaleurs-canicule/documents/bulletin-national/canicule-et-sante-exces-de-mortalite.- update-as-of-october-4-2023

[87]MTECT (2023): https://www.statistiques.developpement-durable.gouv.fr/bilan-de-la-qualite-de-lair-exterieur-en-france-en-2022

[88]HCC (2024) Accelerating the climate transition with a low-carbon, resilient and just food system.

[89]Press release (2021): https://sante.gouv.fr/archives/archives-presse/archives-communiques-de-presse/article/le-politique-lance-le-4eme-plan-national-sante-environnement

[90]HCSP (2022), Global evaluation of national health-environment plans (2004-2019): https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1223

[91]Inserm (2013), Pesticides: effects on health: https://www.inserm.fr/expertise-collective/pesticides-effects-sur-sante/

[92]INSERM, 2021. Pesticides: Effects on health. New data. EDP Sciences, Paris.

[93]INRAE/Ifremer collective scientific expertise (2022): https://www.inrae.fr/actualites/impacts-produits-phytopharmaceutiques-biodiversite-services-ecosystemiques-resultats-lexpertise-scientifique-collective-inrae-ifremer

[94]https://www.academie-medecine.fr/wp-content/uploads/2021/01/RAPPORT-Climat-et-sante%CC%81-2020-12-02-apr%C3%A8s-vote-version-d%C3%A9finitive-sign%C3%A9.pdf

[95]Foundation of the Academy of Medicine (2021); http://fam.fr/debats-de-la-fam/glossaire-exposome

[96]National Academy of Medicine (2022): https://www.academie-medecine.fr/synthese-et-conclusions-du-colloque-hepta-academique-du-15-juin-2022-une-seule-sante-les- microbes-and-antibioresistance-in-share/

- The report of the **National Assembly** on the lack of control of the impact of phytosanitary products on human and environmental health[97]
- The note from the **Environmental Authority** on nitrate action programmes[98]

In Europe or Internationally :

- **European Environment Agency** (EAE) : exposure and health risks associated with certain air pollutants[99]
- **EU JRC Technical Report (2024)**: Drought in the Mediterranean Region[100]
- **WHO** [101]and **PAHO** [102], and the WHO pesticide classification[103]
- **World Economic Forum (WEF)** : prospective analyses of the impact of climate change on human health[104]
- **IHME** (see above)
- **Lancet Countdown** on the links between climate change and human health[105] and various scientific references[106]
- **United Kingdom:** HECC analysis (*Health effects of Climate change*) by the Security Agency[107]
- **Minderoo -Monaco Commission** on plastics and human health[108]
- **IPCC:** Sixth Assessment Report[109]
- **IARC** (WHO): identification of carcinogens[110]

COVARS also reviewed documents on public health and research responses to these threats:

- **COP28 Declaration on Climate and health**[111]
- **CNRS** research recommendations in its outlook document on ecology and the environment[112]
- **WHO** analyses/statements[113]

[97]National Assembly, December 14, 2023, Investigation report number 2000, https://www.assemblee-nationale.fr/dyn/16/rapports/cepestici/l16b2000-t1_rapport-enquete

[98]Environmental Authority (2023), deliberate note from the Environmental Authority relating to nitrate action programs

[99] European Environment Agency (2023), ETC HE report 2023/7: https://www.eionet.europa.eu/etcs/etc-he/products/etc-he-products/etc-he-reports/etc-he-report -2023-7-health-risk-assessment-of-air-pollution-assessing-the-environmental-burden-of-disease-in-europe-in-2021

[100]European Commission. Joint Research Center. (2024). Drought in the Mediterranean region: January 2024: GDO analytical report. Office Publications. https://doi.org/10.2760/384093

[101]WHO (2018): https://iris.who.int/bitstream/handle/10665/276332/A71_10-en.pdf?sequence=1&isAllowed=y

[102]PAHO (2022), Climate Change and Health: https://www.paho.org/en/topics/climate-change-and-health

[103]WHO (2019), The WHO recommended Classification of Pesticides by Hazard and Guidelines to classification

[104]World Economic Forum (2024), https://www3.weforum.org/docs/WEF_Quantifying_the_Impact_of_Climate_Change_on_Human_Health_2024.pdf ; World Economic Forum (2023), The Global Riks report 2023, [18th] edition

[105]- Romanello , M. et al (2023 *).* Lancet 402 (10419): 2346–2394; Di Napoli, C. et al (2022). BMC Public Health 22, 663. https://doi.org/10.1186/s12889-022-13055-6 ; Wong, C. (2024). Nature. https://doi.org/10.1038/d41586-023-04077-0

[106]- Naidu, R. et al (2021). Environment International 156:106616; Fuller R et al (2022) Lancet Planet Health . 6(6):e535-e547. doi :10.1016/S2542-5196(22)00090-0. Epub 2022 May 18; Tang, FHM et al (2021) Nat. Geosci . 14, 206–210. https://doi.org/10.1038/s41561-021-00712-5 ; Hill, W. et al (2023) Nature **616** , 159–167. https://doi.org/10.1038/s41586-023-05874-3 ; Fritsch, C. et al (2022) Sci Rep 12, 15904. https://doi.org/10.1038/s41598-022-19959-y ; Mancini, M. et al (2023) Environmental Health Perspectives 131, 107008. https://doi.org/10.1289/EHP12634 ; Stacy Colzyn et al (2024). Int J Hyg Environ Health. 256:114311. doi :10.1016/j.ijheh.2023.114311 . ; Abbasi, K. et al (2023). BMJ (p.p2355). BMJ. https://doi.org/10.1136/bmj.p2355 ; Rocklöv J. et al (2023), The Lancet Regional Health – Europe, 2023; 32: 100701; Haines, A., & Ebi , K. (2019 New England Journal of Medicine 380(3): 263–273; Dobson, AP et al (2020). Science 369, 379–381. https://doi.org/ 10.1126/science.abc3189

[107]UK Health Security Agency (2023), Fourth Health Effects of Climate Change, available here : https://www.gov.uk/government/publications/climate-change-health-effects-in-the-uk ; UK Health security Agency (2023), HECC in th UK, State of Evidence 2023: https://assets.publishing.service.gov.uk/media/659ff6a93308d200131fbe78/HECC-report-2023-overview.pdf

[108] Landrigan PJ et al (2023), Ann Glob Health . 2023 Mar 21;89(1):23. doi :10.5334/aogh.4056.

[109] IPCC (Intergovernmental Panel on Climate Change) February 28, 2022, sixth report, “Impacts, adaptation and vulnerability”

[110] https://monographs.iarc.who.int/fr/agents-classes-par-les-monographies-du-circ-2/)

[111]https://reliefweb.int/report/world/cop28-uae-declaration-climate-and-health

[112]CNRS (2023): https://www.inee.cnrs.fr/fr/prospectives-cnrs-ecologie-environnement-2023

[113]WHO (2023): https://www.who.int/publications/i/item/9789240083196 ; WHO: https://www.who.int/europe/fr/news/item/03-12-2023-statement-cop28-climate-change-is-causing-suffering-death-and-destruction-concerted-climate- action-is-our-only-hope-for-survival

B- Semantic clarifications and definitions used in this notice

For the *Direction Générale de la Santé* (General directorate of health)[114], the notion of *major and exceptional health situations having an impact on healthcare provision* encompasses all **situations likely to lead to an immediate and unforeseeable increase in demand for healthcare or disruption to the organisation of healthcare provision**. These situations may result from an acute kinetic event (epidemic or climatic event of exceptional magnitude) for which the initial management measures prove insufficient, or reflect a massive influx of patients due to an external event, or a major disruption to the healthcare system. The emergency plan called *ORSAN* (and its AMAVI component) can be triggered to enable the ARS (*Regional Health Agencies*) to mobilise the entire healthcare offer in the outpatient, hospital and medico-social sectors[115] .
Major and exceptional health situations can also be caused by slower kinetic events. Thus, for the ANSES representatives interviewed by COVARS, *a "major health situation" can be explained either by the scale of the health impact or by the difficulties in taking action (such as characterising a chemical risk due to the large number of chemical substances[116]) or mitigating a known risk due to the absence of, or poor compliance with, countermeasures.*

For the purposes of this referral, despite the difficulty of quantifying the term "major", COVARS considers **a health situation to be exceptional and major if it includes one or more of the following criteria:**

- Major impact on the national or regional healthcare system,
- Major clinical impact in the general population (in terms of mortality, morbidity, DALYs and speed of contamination of the population, etc.),
- Major impact on a specific population (e.g. populations in a given geographical area or with a specific risk factor, etc.).
- Major psychological impacts on the general population (such as in the cases of a highly contagious and exotic disease such as Ebola)
- Non-major but significant and permanent impacts, particularly on eco-systems, which may be aggravated by external environmental or geopolitical factors.

Nevertheless, it is necessary to clarify the semantics of the terms used in this document:

- **Hazard**: defined here as a potential threat that may give rise to a health risk if adverse effects are identified and assessed in relation to its source[117] .
- **Risk:** defined here as **the combination of the probability of occurrence of a given hazard and the magnitude of its consequences**. It therefore depends on the hazard, the population's exposure and vulnerability, society's ability to implement an effective (appropriate and accepted) response, and the combination of factors where the hazard and the magnitude of the threat are not - or insufficiently - known. “Risk” is therefore intrinsically linked to the **potential** for **harm**[118] of an external factor and to the uncertainty of the occurrence of the undesirable event on human health.
- **Consequences**: the term is used here to refer to all the criteria assessed for a given hazard, including its capacity to spread, severity, lethality, morbidity and severity, **in the context of access to care and the availability of countermeasures** in France.
- **Systemic impact:** this refers to any systemic fallout from a given risk, whether it concerns the healthcare system, the ecosystem, or economic or psychosocial fallout.
- **Pathogen, substance and situation X:** The COVARS map includes unknown risks that have not yet been identified because they are unpredictable and linked to :

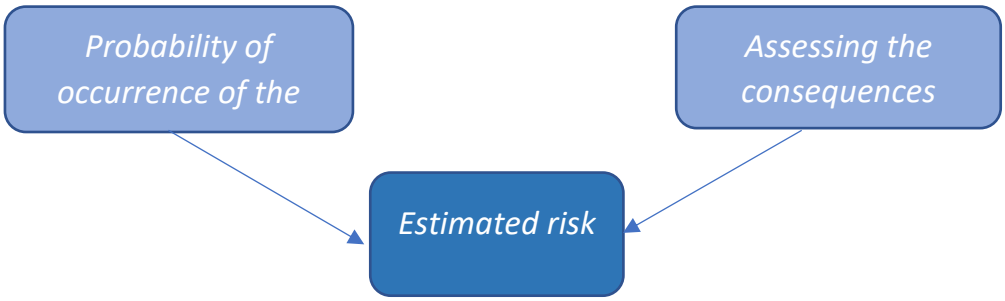
[114] Ministère des solidarités et de la santé (2019), Guide d'aide à la préparation et à la gestion des tensions hospitalières et des situations sanitaires exceptionnelles: https://sante.gouv.fr/IMG/pdf/guide_situation_sanitaire_exceptionnelle.pdf
[115] Decree 2024-8 of 3 January 2024 on the preparation and response of the healthcare system to deal with exceptional health situations
[116] Naidu et al 2021. Environment International 156, 106616. https://doi.org/10.1016/j.envint.2021.106616
[117] Setbon, Médecine et Sciences 1204 n° 11, vol. 16, November 2000
[118] EPA (2023), Human Health Risk Assessment: https://www.epa.gov/risk/human-health-risk-assessment

- A ***pathogen X,*** suggesting an unknown/unexpected infectious agent with the potential to cause major and exceptional health situations.
- *A* ***substance X*** whose mode of action may be potentiated under new conditions such as extreme heat or hydric stress (the risk of causing an exceptional health situation is nevertheless low).
- The term ***situation X is used*** to describe an unknown/unexpected physical or chemical event.

The response to these hazards "X" must be able to be provided by all the composite elements of the specific responses provided for all other health emergencies caused by an identified pathogen or substance. This matrix of response and understanding of risk must cover the needs of any unexpected pathogen or health emergency situation linked to non-infectious events.

C- COVARS working method and stages

COVARS drew on the methodologies and best practices used in prioritising infectious diseases and the risk analysis methods recommended by AFFSA[119] and ECDC[120], as illustrated in the diagram below:



The following procedure was followed:

1- **Creation of a COVARS multidisciplinary working group** comprising 2 epidemiologists, 3 microbiologists, 3 clinicians, 2 immunologists, 2 veterinary surgeons, 1 entomologist, 2 specialists in human and social sciences (SHS) and 2 representatives of health democracy.

2 - **Analysis of existing maps** in France and internationally and their objectives (see chapter III), as well as methodological documents.

3 - **Hearings with** health agencies and bodies, national safety structures, research bodies with a strong international and overseas involvement in medical and agro-environmental research, and leading French and foreign figures in these fields (full list of hearings on page 3).

4 - **Identification of infectious and environmental risks to be included in the analysis.**

5 - **Integration of the specific nature of overseas France** for each risk.

6 - **Discussion and summary by the full committee**.

[119] Afssa. 2008. A qualitative method for estimating animal health risk. https://www.anses.fr/fr/system/files/SANT-Ra-MethodeRisque.pdf.
[120] ECDC (2017): https://www.ecdc.europa.eu/sites/default/files/documents/Tool-for-disease-priority-ranking_handbook-update-dec-18.pdf ; ECDC (2015) : https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/emerging-infectious-disease-threats-best-practices-ranking.pdf ; Rigaud M et al (2024) Environ Health. 23(1):13. doi: 10.1186/s12940-023-01039-x

For infectious risks:

A specific methodology was applied for infectious risks, based on the methods for prioritising health risks in human and animal health used by the ANSES, the CDC, the HCSP and the ANRS-MIE, and partly based on those of the ECDC (referenced above), mainly using the Multi-Criteria Decision Analysis (MCDA) method. The following steps were followed:

- **Identification of 35 infectious diseases to be analysed.**

- **Identification of a series of 16 criteria,** most of which have been, at least partially, used in the WHO, HCSP, InVS, Anses, USDA and WHO maps, allowing some degree of comparability in the analyses. Adaptation of these criteria to the scope of the Ministers' referral, including the temporality (2 to 5 years) as well as the dynamics of the risk linked to environmental changes and geopolitical risks. These criteria cover 4 different dimensions: the likelihood/probability of the risk occurrence, its clinical characteristics, its potential impact in 3 distinct areas (health, societal, economic) over the defined period, and the existence of countermeasures:

- ***Epidemiological potential over the next 5 years :***
  - Estimate of the Probability of occurrence: This is the presence or potential introduction or emergence and autochthonous circulation of a pathogen with inter-human transmission potential.
  - Estimate of the potential increase in the risk of emergence, introduction or spread in relation to environmental risks (climate change, pollution and loss of biodiversity) or geopolitical risks.
  - Geographical expansion and epidemic potential, taking into account the mode of transmission and the evolutionary potential of the pathogen.
- ***Individual clinical criteria,*** considered in the context of access to care and adequate treatment on the national territory and not as criteria of the intrinsic clinical severity of the diseases (For example: context of access to antiretrovirals for HIV, to antibiotics and intensive care units for meningitis, leptospirosis, viral haemorrhagic fevers (VHF)...):
  - Morbidity
  - Individual lethality
  - Lethality and morbidity in high-risk groups
  - Post-infectious syndrome or sequelae after recovery from the infection.
- ***Criteria for countermeasures and preparedness to exceptional health situations :***
  - Lack of availability or feasibility (and difficulties in implementation) of pharmaceutical and non-pharmaceutical *control* countermeasures
  - Lack of availability or feasibility (and difficulties in implementation) of pharmaceutical and non-pharmaceutical *preventive* countermeasures
  - Resistance to antimicrobials or vector control measures
  - Absence of plans or regulations at regional, national, European or international level

The existence or absence of countermeasures is of prime importance in this analysis, highlighting the areas for improvement and for the production and sharing of knowledge or means of combating the disease that need to be speeded up as part of the preparation process. The existence of countermeasures (pharmaceutical or otherwise) can reduce the health impact of a hazard, but it can also increase the political and societal impact, insofar as the societal acceptability of a hazard whose consequences could have been avoided by implementing appropriate measures may be lower (as in the case of the measles epidemic in the UK).

- ***Systemic impacts :***
  - Impact of the disease on the healthcare system (primary care facilities, inequalities in access)
  - Psychosocial impact of the disease (mental health/risks of stigmatisation and discrimination, rumours and misinformation, social isolation)

- Economic impact of the disease (DALY[121] , impact on sick leave, tourism, the livestock industry, etc.)
- Impact of the disease on ecosystems
- Impact of control measures (economic, societal and environmental)

- **For each of the diseases, rating of the criteria according to 5 risk levels** in order to graduate their potential to generate a major and exceptional health situation: Major (rating of 5), High (4), Medium (3), Low (2), Negligible (1). This assessment has been made within the COVARS' collective expertise and integrates the point of view of scientists and external personalities auditioned by the committee. It was carried out according to the principle of adversarial debate between COVARS members, each of whom, whatever his or her discipline, used documented arguments to justify his or her rating for each criterion and hazard, in order to reach a certain consensus for each level of risk. This analysis was carried out in two stages: a 1st series of analyses, initially by pairs of experts form the working group, reviewed by the whole working group and then by the whole of COVARS, followed by a 2nd phase of rereading in pairs and by the working group and a final validation by COVARS. Variations intrinsic to the nature or strains of the pathogen are reflected in the "minimum" and "maximum" ratings assigned to each risk; these ranges translate either the fluctuation of risk depending on the territory or target population, as well as sometimes divergent perceptions of risk levels between COVARS' members. In calculating the average consequences, no weighting was assigned, as the different types of criteria are considered to be of equal importance.

- **Generation of tables and figures based on the ratings for each disease:**
  - **Risk intensity tables** for France as a whole, the Hexagon/Corsica and the French overseas territories, for each risk and criterion, showing only, as a precautionary measure, the maximum rating assigned to each criterion.
  - **Scatterplot describing the Relationships between Probability of Occurrence and Consequences:** for each disease, a **score of the probability of occurrence has been calculated from negligible (1) to major (5)** (on the abscissa). The average of the **consequences** (on the ordinate) includes 3 series of criteria:
    - *Epidemiological*: expansion criterion/epidemic potential. The "risk of increase" criterion is represented by grey arrows (environmental risk factor: climate and biodiversity) or black arrows (geopolitical risk factor) if it is greater than or equal to 4.
    - *Clinical*: The average of the clinical criteria is the average of 4 criteria with a weighting of 0.5 for post-infectious syndromes/sequelae.
    - *Countermeasures*: The average of the countermeasures criteria is the average of 4 criteria with a weighting of 0.5 for the absence of a specific prevention plan.
  - **Radar Chart of the impacts**: The average of the 5 impact criteria (on the healthcare system, psychosocial impact, economic impact of the disease, impact on ecosystems weighted at 0.5, and impact of control measures) represented for the main risks identified in the form of a radar chart.

- **Identification of the risks with the highest and intermediate potential to generate an exceptional health situation.** On the scatterplots, those are the diseases with a probability of occurrence and an average consequence both above 3 (red box: highest risk) or above 2.5 (orange box: intermediate risk).

- **Discussion and comparison of the COVARS classification with identified maps of other agencies.**

[121] DALYs (Disability-Adjusted Life Years) express the impact of a disease in years of life lost. A year can be lost through premature mortality or through living with a disability (morbidity). Mortality is measured in years of life lost out of the life expectancy, by age group and sex, of the population under consideration (YLL - *years of life lost*) and morbidity by the number of years lived with a disability (YLD - *years lost due to disability*).

III. Estimation of the risks of major Exceptional Sanitary situations by COVARS

COVARS consulted some fifty French and international reports and documents, as well as leading scientific articles. Apart from rare exceptions such as the interdisciplinary and cross-sectional assessments carried out by the Netherlands[122], the IHME[123] and the WEF[124,] COVARS did not find any systematic, forward-looking and holistic analyses integrating both infectious and environmental risks, as well as their resulting psycho-social consequencesh . For France, COVARS has analysed the prioritisation lists drawn up by the HCSP, Anses, SpF[125]

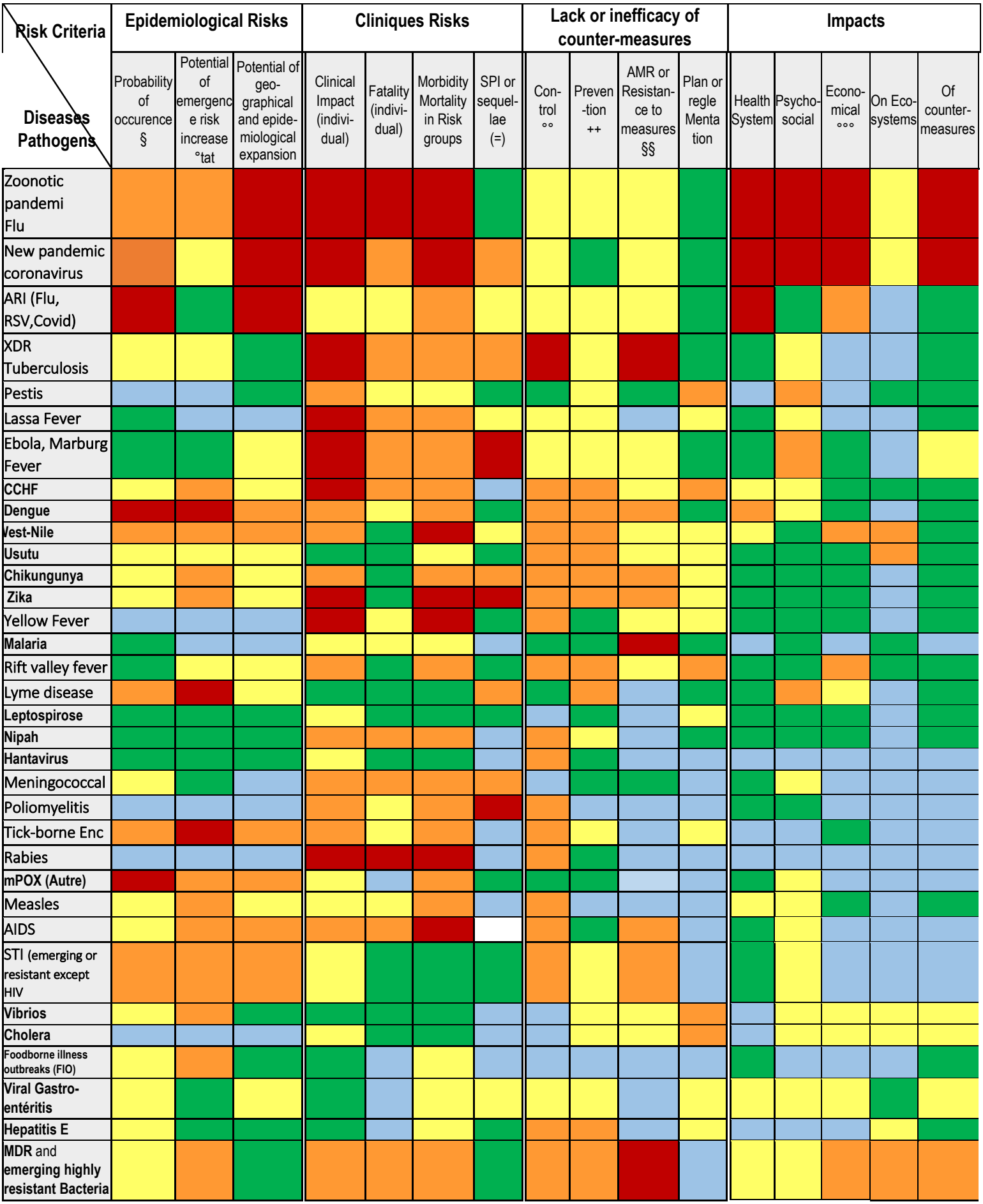
A- Risks of exceptional sanitary situations risk analyses estimated by COVARS on the basis of existing maps

1- Infectious diseases

COVARS has performed an in-depth analysis of 35 prioritized infectious diseases selected from the reports mentionned above, according to the 16 criteria described in part 2 (Methodology). The risk levels of 34 of these 35 infectious diseases were analysed according to 4 sets of criteria and estimated on a scale of 1 (negligible) to 5 (major), using the rigorous, referenced methodology aforementioned. Some infectious diseases with the potential to generate a major and exceptional health situation are emerging ones, while others are re-emerging or are due to endemic pathogens with the potential to evolve and whose impact on the healthcare system is already measurable. It should be noted that the Creutzfeld-Jakob disease is rated separately because it does not meet all the criteria analysed.
Each criterion was graded on a 5 level scale for each of the 34 diseases taking into account access to countermeasures available in France. These ratings allowed to establish scores and to draw risk intensity tables which are shown for France in **Table 1**, and separately for mainland France, Corsica and the French overseas territories (Tables 1b and 1c in Appendices 3B and 3C).

Table 1 ***: Synthesis of the risk intensities de risque for France in link with 34 infectious diseases established by COVARS along the 4 series of 16 criteria analysed*** (next page)

[122] National Network of Safety and Security Analysts 2022: https://www.government.nl/documents/reports/2022/09/26/national-risk-assessment-of-the-kingdom-of-the-netherlands-2022
[123] Institute for Health Metrics and Evaluation (2019) https://www.healthdata.org/research-analysis/gbd.
[124] World Economic Forum (2024), https://www3.weforum.org/docs/WEF_Quantifying_the_Impact_of_Climate_Change_on_Human_Health_2024.pdf ; World Economic Forum (2023), The Global Riks report 2023, 18th edition
[125] Denys S., Barouki R.(2021), Annales des Mines - Responsabilité et environnement, 2024/4 (N° 104), p. 32-35. DOI : 10.3917/re1.104.0032; Carlson, C.J. et al (2022) *Nature* 607, 555-562; Mora C. et al (2022). Nat Clim Chang. 2022,12(9):869-875. doi: 10.1038/s41558-022-01426-1; Hermanns K et al.


Risk Criteria
Diseases Pathogens
Epidemiological Risks
Cliniques Risks
Lack or inefficacy of counter-measures
Impacts
Probability of occurence §
Potential of emergence risk increase °tat
Potential of geo-graphical and epide-miological expansion
Clinical Impact (indivi-dual)
Fatality (indivi-dual)
Morbidity Mortality in Risk groups
SPI or sequel-lae (=)
Con-trol °°
Preven -tion ++
AMR or Resistan-ce to measures §§
Plan or regle Menta tion
Health System
Psycho-social
Econo-mical °°°
On Eco-systems
Of counter-measures
Zoonotic pandemi Flu
New pandemic coronavirus
ARI (Flu, RSV,Covid)
XDR Tuberculosis
Pestis
Lassa Fever
Ebola, Marburg Fever
CCHF
Dengue
Vest-Nile
Usutu
Chikungunya
Zika
Yellow Fever
Malaria
Rift valley fever
Lyme disease
Leptospirose
Nipah
Hantavirus
Meningococcal
Poliomyelitis
Tick-borne Enc
Rabies
mPOX (Autre)
Measles
AIDS
STI (emerging or resistant except HIV
Vibrios
Cholera
Foodborne illness outbreaks (FIO)
Viral Gastro-entéritis
Hepatitis E
MDR and emerging highly resistant Bacteria

Légende du tableau 1 :
§ Présence ou potentiel d'introduction ou d'émergence ou de circulation autochtone
° Potentiel d'augmentation du risque d'émergence ou d'introduction/extension lié au changement climatique, à la pollution, à la perte de biodiversité
** Potentiel d'extension géographique et épidémique intégrant le mode de transmission et le potentiel évolutif de l'agent*
= Syndrome Post-Infectieux (SPI) ou séquelles
°° Indisponibilité ou impossibilité de mise en oeuvre des contre-mesures pharmaceutiques ou non pharmaceutiques pour le contrôle
++ Indisponibilité ou impossibilité de mise en oeuvre des contre-mesures pharmaceutiques ou non pharmaceutiques pour la prévention
*** Absence de plan ou de réglementation régionale, nationale ou internationale*
! Impact social incluant (santé mentale, risque de stigmatisation, etc.)
°°° Impacts économiques (Arrêtés de travail, tourisme, secteur animalier)
+++ Impact des contre-mesures (économiques, sociétales, environnementales)

Intensité des risques : majeur (rouge, note de 5), élevé (orange, 4), moyen (jaune, 3), faible (vert, 2), négligeable (bleu, 1). A noter que les maladies apparaissent dans l'ordre suivant : infections respiratoires (jusqu'à la Peste), fièvres hémorragiques virales (jusqu'au CCHF), maladies à transmission vectorielle (jusqu'à l'Hantavirus), infections neurologiques (jusqu'à la Rage), infections muco-cutanées. (jusqu'aux « autres IST »), les infections digestives (jusqu'aux bactéries multirésistantes et aux bactéries émergentes hautement pathogènes).

A noter que le graphique représente les valeurs maximales attribuées à chacun des risques

Based on these risk intensity ratings, a further analysis was made by generating scatter plots showing together the **probability score of occurrence and the average clinical and epidemiological consequences**, [see Figure 5 below, which presents the risk analysis for Hexagon-Corsica and Overseas France respectively, and appendices 5 and 6 for maps of emerging pathogens and those already present in France].

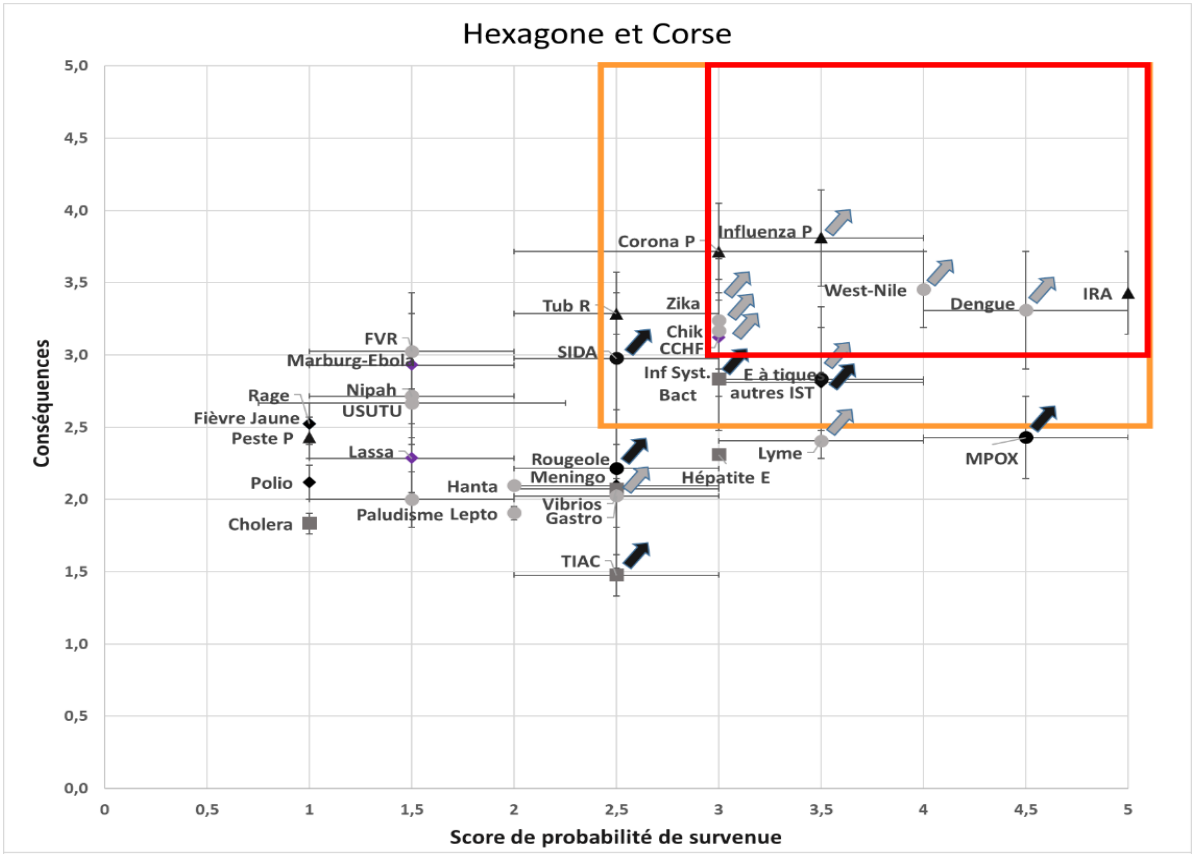
On these scatter plots, the "consequences" are an average of three types of criteria:
- *Epidemiological*: expansion criteria/epidemic potential. Note that a high "risk of increase" criterion, greater than or equal to 4, is represented by grey arrows (environmental risk factor: climate and biodiversity) or black arrows (geopolitical and population risk factor).
- *Clinical*: The average of the 4 clinical criteria (described in part 2 – methodology), with a weighting of 0.5 for post-infectious syndromes/sequelae.
- *Countermeasures*: The average of the 4 countermeasures criteria (described in part 2 – methodology) with a weighting of 0.5 for the absence of a plan.

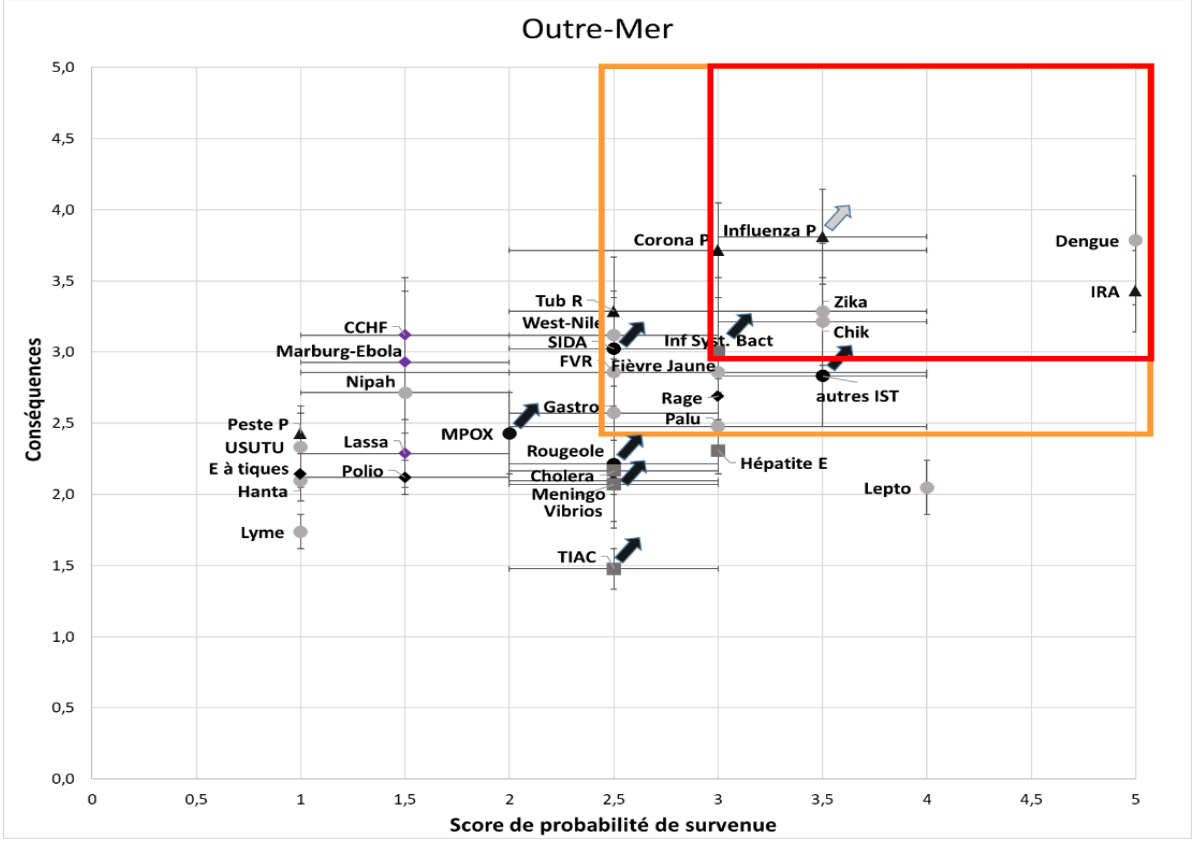
On the scatter plots, the diseases with the highest levels (greater than or equal to 3) **for both probability of occurrence and average consequences have the highest potential of generating an exceptional sanitary situation are represented within the red square**. . The diseases with an “intermediate” potential of generating an exceptional sanitary situation are rated between 2.5 and 3 for both the probability of occurrence and the average consequences and are identified in the orange square and .

Importantly, while Table 1 (risk intensity table) represents the maximum values for each of the criteria, Figure 5 below shows the margins of variation in the experts' estimates. In addition, the criterion of risk fluctuation as a function of the dynamics of environmental, geopolitical and population factors is also taken into account for each of these diseases.

Figure 5: Estimated likelihood of occurrence of infectious diseases and their average consequences, taking into account territories and factors of environmental or geopolitical origin

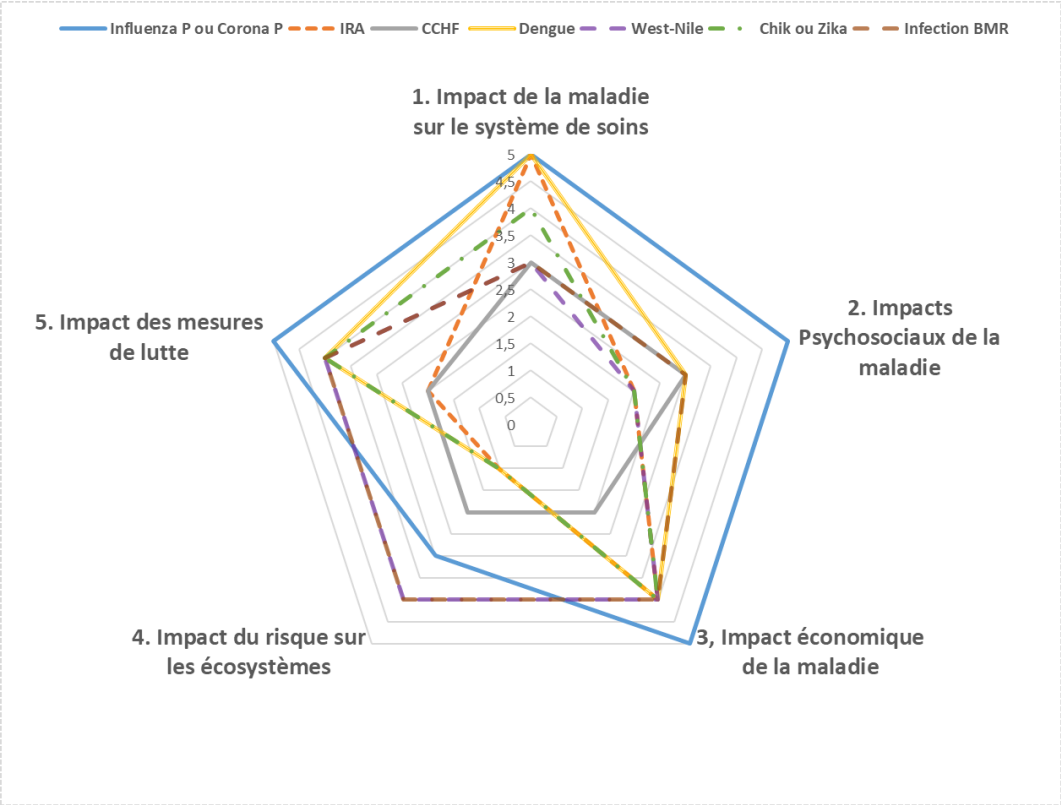
Legend: Diseases with a major or a moderate potential of generating an exceptional health situation, respectively;
Margins of variation of the estimate by the COVARS experts represented for each point.
Arrows: represent a high or major "risk of increase" linked to environmental risk factors (grey) or geopolitical risk factors (black);
Markers for vector-borne diseases (grey circle) and other diseases using a syndromic approach (black triangle: respiratory infections; purple diamond: viral haemorrhagic fevers; black diamond: neurological infections; black circle: mucocutaneous infections; dark grey square: digestive infections).





Based on these estimates, the COVARS wanted to illustrate the potential **impact of the diseases with the highest potential of generating an exceptional sanitary situation** (see Figure 5) on the healthcare system, the ecosystem and of psycho-social and economic nature. Figure 6 below shows that emerging respiratory infections have the greatest potential impact.

Figure 6: Estimated impact of the 6 infectious diseases considered to be at highest risk of SES *(*the graph shows the maximum values assigned to each risk).



These analyses enable us to propose a classification into 3 main groups according to their risk of inducing exceptional health situations over a period of 2 to 5 years, differentiating between the risk in France and that in the overseas territories.

1-1- Diseases most likely to cause SES :

The diseases with an estimated high potential of generating a major and exceptional sanitary situation, shown in the red square in Figure 5, can be grouped into 4 groups: emerging respiratory infections, certain arboviroses, acute respiratory infections and Disease X:

- **Emerging respiratory virus infections with high pandemic potential:** despite a relatively moderate probability of occurrence, these infections have very strong clinical and epidemiological consequences, as well as strong systemic impacts on the healthcare system and of socio-economic nature. The COVARS estimated that the risk of occurrence and dissemination within 2 to 5 years was slightly higher for zoonotic influenza than for a new Coronavirus because :
  - **The highly pathogenic avian influenza virus (HPAI)** is currently endemic in many parts of the world, including France, and the frequency of new sporadic cases in terrestrial mammals, including humans, marine mammals and recently domestic mammals as cattle, has been increasing for several years worldwide (see COVARS' Advice

of the 8th June 2023[126]). Currently, more than 48 species of mammals infected with the H5N1 virus have been reported by 26 countries, and the number of infected animals has been rising sharply since 2020 compared with the previous decade. Transmission between mammals, mainly through close contact and ingestion of infected birds, appears to be linked to mutations that allow H5N1 to adapt to mammals[127] . It should be stressed, however, that despite the very high human mortality rate of these zoonotic influenza viruses, no human-to-human transmission has been observed to date, but the effectiveness of the vaccines and antiviral treatments available remains uncertain. [128]

- **A new emerging coronavirus is possible but might** lead to a more limited risk of exceptional health situations due to : **i)** the possibility of epidemics of a smaller scale than that of Covid-19, although with a higher mortality rate, such as SARS-CoV responsible in 2002-04 for around 8,000 cases and a mortality rate of 10% to 50%, or MERS-CoV responsible since 2012 for just over 2,600 cases in 28 countries[129] **ii)** a potentially limited severity in the event of a Beta-CoronaV close to SARS-CoV, and **iii)** the achievements of the Covid-19 pandemic which demonstrated the protective efficacy of vaccines directed against the spike in coronaviruses and the ability to rapidly develop appropriate vaccines and on a large scale. Nevertheless, the Covid-19 pandemic shows that the risks of exceptional health situations linked to these 2 diseases differ little. Ongoing surveillance and research are essential to mitigate the risk of a global pandemic.

- **Arboviruses transmitted by mosquitoes :**
  - **Dengue fever:** France's overseas tropical territories are highly exposed to the intense global circulation of dengue virus in tropical zones, creating severe epidemics with the rank of exceptional sanitary situations (as recently in French Guiana and the Caribbean). The existence of 4 viral serotypes offering no cross-protection, the abundance of the *Aedes aegypti* vector and the mixing of populations are responsible for the recurrence of dengue epidemics in tropical environments. In mainland France, in addition to the frequent imported cases, native cases are increasing due to the spread of the *Aedes albopictus* vector and climatic and environmental changes, creating an objective risk of summer epidemic spread. The Olympic Games in the summer of 2024 are an example of the increased risk of imported cases and spreading in France. In addition, the risk of exceptional health situations due to Dengue fever is increasing in mainland France, as the COVARS pointed out in a previous Opinion[130] , due a lower level of preparedness for Dengue fever epidemics than in the French overseas territories.
  - **WNV infection in mainland France**: circulation of the West Nile virus in avian populations is endemo-epidemic in Europe and mainland France, increasing the likelihood of human epidemics, with the Culex mosquito vectors present throughout the country. The potential for epidemic spread is considered to be lower than that of dengue virus, but the severity of this disease in around 20% of cases, the risk of transmission via blood products and organ donations, and the potential for extreme severity in immunocompromised recipients, mean that this infection has the potential of inducing an exceptional sanitary situation. The health and economic impact on equidae and the environmental impact on birds should also be taken into account. (See COVARS Opinion on the WNV virus)
  - In the French **overseas territories,** the epidemic risks associated with the **other Aedes arboviruses** (Zika and Chikungunya) should not be overlooked, even if their potential for recurrence (strongly linked to population immunity) is lower than that of Dengue in the absence of viral serotype diversity. The risks of importation and autochthonous spread in mainland France have been estimated to be lower than for Dengue fever.

[126] COVARS Notice of 8 June 2023: https://sante.gouv.fr/IMG/pdf/avis_du_covars_du_8_juin_2023_-_risque_sanitaire_lie_a_l_iahp_et_la_grippe_aviaire.pdf
[127] Plaza PI et al (2024), Emerging Infectious Diseases, 30 (3)
[128] On 1er April 2024, the CDC reported a human case of HPAI A(H5N1) in a cattle farmer in the USA that was not serious, following a 1er case in 2021: https://urldefense.com/v3/__https://www.cdc.gov/media/releases/2024/p0401-avian-flu.html__;!!FiWPmuqhD5aF3oDTQnc!l_kEW2ijBpZHSec7OZ5E_Dm9zMwB__6J-3VBLuKSWo6Oay6bUPvMk9rAIsxyUUgkkWAQtvrL_qMquX9OpMJO8flCuK-Jpw$
[129] https://www.ecdc.europa.eu/en/middle-east-respiratory-syndrome-coronavirus-mers-cov-situation-update
[130] COVARS Avis du du 3 avril 2023 relatif aux risques sanitaires de la dengue et autres arboviroses à aedes : https://www.enseignementsup-recherche.gouv.fr/sites/default/files/2023-04/avis-du-covars-du-3-avril-2023---risques-sanitaires-de-la-dengue-du-zika-et-du-chikungunya-en-lien-avec-le-changement-climatique-27356.pdf

- In addition, the risk of exceptional sanitary situations linked to yellow fever, particularly in French Guiana, is estimated to be more moderate due to the effectiveness of the vaccine.

- **ARIs:** While they collectively still represent a medical burden that is a source of major recurring health situations each winter, **this risk should fall significantly over the next 2 to 5 years** thanks to the introduction and support of effective means of prevention, not only against Covid-19 and influenza, but also against severe RSV infections. Indeed, the use of preventive treatment for severe RSV infection in infants with the antibody Nirsevimab, successfully introduced in France in autumn 2023, or the possibility of using a preventive vaccine for severe RSV infections in elderly people as soon as possible, combined with a sustained public policy of preventing respiratory infections through strong vaccination campaigns (followed by healthcare professionals and the general public) and prevention (barrier measures including masks and ventilation of premises), should reduce the burden of these infections[131].

- **Disease X,** which characterises an emerging pathogen that is currently unknown. The known emergence factors indicate that it will probably be a zoonosis and that its emergence could be linked to human activities and their climatic and environmental impacts. There is a significant risk that at the time of emergence there will be few countermeasures, be it pharmaceutical or non-pharmaceutical, which will accentuate the impact on the healthcare system and society. The level of risk can only be assessed by assimilating it to the risk levels defined for known emerging pathogens/diseases, adapting this level according to the accumulation of knowledge. It is therefore impossible to position a point representing "disease X" on the scatter plots, as is the case for other known pathologies, but this pathogen X must be considered to be located a priori within the high-risk framework (red frame in Figure 5). Its level of risk will evolve as data on epidemiology, pathogenicity and the ability to mobilise effective countermeasures accumulates.
  In addition, a serious Disease X occurring and/or of particular severity in **children** would immediately be classified as an absolute health emergency, triggering a major societal impact**.**

1-2- Pathogens with a more moderate risk of inducing exceptional health situations :

Certain diseases (represented within the orange square on figure 5) are at intermediate risk of generating an exceptional health situation but are particularly likely to increase in relation to environmental factors (global warming in particular) and population factors (environmental, geo-political and tourist migrations), as illustrated by the grey and black arrows respectively in Figure 5, with :

- **Vector-borne diseases :**
  - **In mainland France: infections transmitted** mainly by **ticks,** the distribution of which varies from one region to another:
    - **Crimean-Congo haemorrhagic fever:** The COVARS has deemed CCHF to be the viral haemorrhagic fever most likely to induce exceptional health situations in France, particularly in mainland France and Corsica, albeit at a moderate level of risk, but emblematic between emergence, anthropocene and climate disruption. This zoonosis, caused by the highly pathogenic CCHFV RNA virus classified as a group P4 MOT agent, infects humans accidentally. It is transmitted by a variety of ticks, including *Hyalomma marginatum*, natural reservoirs of the pathogen that preferentially infect small mammals (rodents and lagomorphs) or birds, as well as large mammals (canines, deer, ungulates) that serve as asymptomatic amplifying hosts. CCHF is also transmitted to humans through contact with the fluids of infected animals, so there is a high risk for farmers, veterinarians, people in contact with infected livestock carcasses (e.g. at calendar

[131] Covars, Note of 14 December 2023 on stepping up the campaign to prevent Covid-19 and acute respiratory infections: https://sante.gouv.fr/IMG/pdf/avis-14-decembre-2023-covars-campagne-de-prevention-de-covid-et-infections-respiratoires-aigues.pdf

community events), healthcare staff and slaughterhouse workers. Climate change and other factors, such as the transport of livestock, are increasing the geographical distribution of the tick and the risk of CCHF emergence, particularly in the south of France and Corsica.

In Europe, 13 human cases were observed in Spain[132] (including 2 deaths) between 2016 and 2023, where a seroprevalence of 1% was observed among blood donors in the affected regions. The viruses were related to strains from Africa and Eastern Mediterranean Europe, illustrating the diversity and mobility of import routes. These cases have however not had a critical societal impact on in Spain, which should not detract from the efforts of participatory science in risk management. In France, if no human cases have yet been reported, a high rate of seropositivity in animals in Corsica has been detected (13% in cattle, 2-3% in sheep and goats) and there has been 2 outbreaks of infected ticks in 2023 in the Eastern Pyrenees among cattle and in Corsica. Therefore, new outbreaks of viral circulation can be expected in urban and peri-urban areas in the south of France, as well as sporadic cases, due to the endemic nature of the disease[133].

The human lethality rate if this disease is high, at around 20%. In the absence of any specific treatment, vaccine or therapeutic antibody, standard care is based on supportive care supplemented by compassionate antiviral treatment (ribavirin under the aegis of the ANSM, or even favipiravir). In France, as with other group 4 pathogens, a reactive monitoring procedure has been put in place (management of an unexpected symptomatic case of low probability) and anticipation of management in secure conditions (DGS/COREB, national ESR-REB).

- **Tick-borne encephalitis (TBE):** TBE is likely to induce an exceptional health situation in France at a moderate level of risk. It is caused by the TBEV arbovirus, the most common in Central and Eastern Europe, a flavivirus transmitted by ticks of the genus Ixodes. The number of human cases has been rising in Europe since 2000[134] . Ticks transmit TBEV to rodents, ruminants (goats, cows and sheep) and wildlife (deer, wild boar), which are permissive asymptomatic species. The virus can also be transmitted through the consumption of unpasteurised milk from infected animals, such as in France in 2020 with the infection of 43 humans as a result of the consumption of raw-milk goat's cheese[135] . The virus can also be transmitted via blood products and organ donations, with the potential for extreme severity in immunocompromised recipients. The geographical distribution of TBEV in France is still very poorly known, but it is wider than suggested by mandatory reporting (since 2021). In Western Europe, the *Ixodes ricinus* tick, which is widely distributed in forest environments, requires favourable humidity and temperature. Global climate change is shifting its range northwards, and the period of activity is not unequivocal.

  It is one of the leading causes of encephalitis, which can lead to serious long-term sequelae, with mortality in 0.5 to 3% of cases, despite the fact that around 60% of infections are asymptomatic. A vaccine is recommended for travellers to endemic areas. Forecasts based on mandatory reporting, serological surveys and biometeorological data should guide the forthcoming extension of preventive vaccination to other groups at risk of exposure[136] .

- **In Overseas France,** the main risks are **Arboviruses** transmitted by mosquitoes, in particular :
  - **Rift Valley fever** (RVF): this major emerging arbovirus, with a poorly understood human and animal cycle and an underestimated burden, constitutes a risk despite the absence of human-to-human transmission to date. It is a zoonosis caused by the RVFV virus, a Phlebovirus which infects farmed ruminants (goats, sheep, cattle, camels) and several species of wildlife via mosquito vectors, causing epizootics. Humans are infected

[132] -Baz-Flores, S. et al (2024). In Ticks and Tick-borne Diseases 15 (1): 102281 ; Lorenzo Juanes HM et al (2023) Emerg Infect Dis. 29(2):252-259. doi: 10.3201/eid2902.220677.

[133] Anses (2024) Opinion on "Crimean-Congo haemorrhagic fever" https://www.anses.fr/fr/system/files/SABA2023SA0194.pdf

[134] Bogovic, P. et al. World J Clin Cases, 2015. 3(5): p. 430-41.

[135] Velay, A., et al. Crit Rev Microbiol, 2019. 45(4): p. 472-493.

[136] Gonzalez, G., et al. Frontiers in microbiology, 2022. 13: p. 863725-863725.

mainly through contact with infected animal products and aerosols, but can also be infected by vector transmission. The main epidemics occur in East Africa, including two recent outbreaks in Kenya and Madagascar in 2021, and two in Mayotte, where the 2018-2019 epidemic/epizootic resulted in 142 confirmed human cases and numerous animal outbreaks. Infections are asymptomatic in 60 to 80% of cases, but pauci-symptomatic forms, which are under-notified, may have affected almost 11,000 people[137]. Severe symptomatic forms lead to hepatitis and severe haemostasis defects, sometimes with post-infectious neurological and ocular damage, and abortions in livestock. The health, socio-economic and food consequences also include high mortality in ruminant farms and food insecurity. The determinants of re-emergence involve complex interactions. Several risk factors are involved: climatic changes, animal movements (legal and illegal) and low herd immunity to RVFV[138] .

- **Severe infections caused by multi-resistant bacteria,** which are already present in France but at limited levels – in particular emerging extensively drug-resistant bacteria (eXDR) - are likely to increase in both mainland France. Their seriousness stems from the clinical spectrum of these severe diseases and the lack of therapeutic capacity when these bacteria are resistant to all available antibiotic treatments. Their increase in many low- and middle-income countries is considered by the WHO as a major risk for the years 2030-50. In 2015, the O'Neil report modelled the impact in terms of mortality by 2050: if nothing changes, antimicrobial resistance will become one of the most frequent causes of death, along with cancer and metabolic diseases[139]. Although biomedical research is gaining momentum, the dynamics of antimicrobial resistance are driven by antibiotic misuse and lack of adherence to universal prevention measures, to which environmental factors must be added (see below and chapter I).

- **Emerging STIs** (excluding mPox infection) or **STIs caused by antibiotic-resistant pathogens**: Despite increased screening and diagnosis of STIs and availability of early treatment, the number of gonococci that are ultra-resistant to antibiotics (XDR), particularly ceftriaxone and azithromycin, has risen[140]. The risk increases particularly during large festive gatherings and population mixes, such as those caused by the Olympic Games. Their spread must be contained, in particular by raising awareness among healthcare professionals and the general public.

- **AIDS:** The major effectiveness of antiretroviral (ARV) treatments in the therapeutic control and prevention of HIV infection as well as the excellent quality of care provided in France, must not blind us to the fact that this pandemic is due to a chronic, lifelong infection, which is fatal in almost all cases and for which no spontaneous or ARV-induced cure is possible, requiring lifelong treatment and strict compliance. Although progress in the use of long-lasting ARVs and implants will soon improve compliance, there is no solid hope of a universal therapeutic cure within the next 5 years, and any prolonged interruption of treatment systematically leads to a loss of viral control and an increased risk of transmission. In addition, despite access to ARVs being around 60% worldwide, diagnosis and treatment remain problematic and subject to considerable stigma in many countries, including European ones, and are liable to be called into question during geopolitical or socio-economic upheavals. For example, the Covid-19 pandemic has been associated with a 14% drop in screening in France between 2019 and 2020, followed by a 12% increase in new seropositive cases (from 5,113 to 5,738 per year)[141] between 2020 and 2022, reflecting either a catch-up effect, an increase in infections or a resumption of migratory flows. The same effects have been observed worldwide in connection with the Covid-19 crisis and the decline in financial support for access to treatment[142].

[137] Bastard J. et al (2022) *Commun Med* (Lond). 2(1):163.
[138] Métras R, et al (2020) Proc Natl Acad Sci USA 117: 24567-74; Youssouf H, et al (2020) Emerg Infect Dis 26: 769-72.
[139] O'Neill J. (2016) https://amr review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
[140] Niaré D et al. BEH 24-25 | 12 December 2023 | 515
[141] Cazein F. et al (2023): https://www.santepubliquefrance.fr/maladies-et-traumatismes/infections-sexuellement-transmissibles/vih-sida/documents/communication-congres/depistage-du-vih-et-decouvertes-de-seropositivite2
[142] UNAIDS (2023): http://hivfinancial.unaids.org/hivfinancialdashboards.html); Stover J et al (2021). PLoS Med. 2021;18(10):e1003831.

- **In the French overseas departments and territories,** there are also risks linked to :
  - **Rabies**: this risk is mainly linked to the illegal importation of infected carnivores and the proximity of countries where rabies is endemic (Madagascar and Comoros for Réunion and Mayotte, Brazil and other Latin American countries for French Guiana and the West Indies).
  - **Viral gastro-enteritis**: this mixed risk depends on hygiene and prevention measures (including vaccination for rotavirus) as well as the quality of drinking water treatment. The particular sanitary situation in certain overseas territories, with the presence of shanty towns or areas of the country poorly served by drinking water systems, and a low level of hygiene, makes this risk significant. It is also heightened by the age of the population, with more very young children at risk than in mainland France[143] .

1-3 Conditions considered to have a low potential to trigger an exceptional health situations

These pathologies are not detailed here, but their analysis in relation to the risk of exceptional health situations is shown in Table 1A (Appendix 3A) and Figure 5 above.

In addition, certain diseases and infectious risks have been considered separately, including:

- **Non-conventional pathogens** such as prions, responsible in particular for Creutzfeldt-Jakob disease, whose risk of inducing major and exceptional health situation in France appeared moderate to COVARS in the current context of preventive countermeasures and reglementations.
- **Diversion of pathogens for malicious purposes:** such as poxviruses, the viruses responsible for VHF (Lassa, Ebola, Marburg, CCHF), RVF, the Nipah virus or *Y pestis*, whose risks of diversion for malicious purposes have been assessed as moderate to low. As the risks of bioterrorism are excluded from the scope of the referral, and other pathogens likely to be used for malicious purposes are not analysed in this opinion.

2- Health risks related to physical and chemical factors

To COVARS' knowledge, the hazards associated with physical and chemical factors have not been summarised in a way that is accessible and consistent with the latest scientific knowledge. Summaries do exist for certain categories of specific hazards, in particular carcinogenicity (IARC work on identifying carcinogens[144]); however, very few studies provide simultaneous access to all hazards, including mutagens, reprotoxics, endocrine disruptors, etc. One important source is the list of *substances of very high concern* (SVHC) compiled by the European Chemicals Agency[145] , but it is based to a large extent on regulatory work and procedures and, despite its interest, cannot be seen as perfectly representing the state of the scientific art.

Only certain factors of risks - i.e. the translation of these dangers into years of healthy life lost – have associated estimates available and a well-documented exposure for which robust dose-response relationships exist (tobacco, fine particles, heat, lead, etc.). This knowledge is summarised in the work of the Institute for Health Metrics and Evaluation (IHME) in Seattle; however, it takes into account only a very small fraction of chemical factors.

For its part, COVARS has identified the following main risks:

2-1- Risks associated with climate change

The risks associated with climate change, which are already present throughout France, are **particularly likely to induce a major and exceptional health situation.** The European Environment Agency predicts that peak and

[143] Santé Publique France, Acute gastroenteritis. Bulletin dated 16 January 2024, available here: https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-infectieuses-d-origine-alimentaire/gastro-enterites-aigues/documents/bulletin-national/gastro-enterites-aigues.-bulletin-du-16-janvier-2024

[144] https://monographs.iarc.who.int/fr/agents-classes-par-les-monographies-du-circ-2/)

[145] https://www.echa.europa.eu/candidate-list-table)

continuous increases in temperature and sunshine, combined with photo-oxidising effects, will increase exposure to ozone.

The health risks associated with climate change are either immediate (injuries, malnutrition, respiratory and cardiovascular diseases) or indirect and delayed (stress, trauma, outbreaks of mental illness, etc.), particularly after climatic disasters. The risks of water-borne and food-borne diseases are also increasing.
In France, substantial increases in morbidity and mortality due to climate change are expected as a result of increased exposure to higher temperatures, altered air and water quality, and certain vector-borne diseases, particularly in the OM territories, due to even longer periods of altered temperature and humidity.

- **Heat waves and droughts**: according to INSEE, at least 14% of French people will be exposed to more than 20 abnormally hot days each summer in the coming decades[146] . While the main consequences are severe dehydration due to heatwaves, which are now well known and can be anticipated, particularly with the Heatwave Plan, the clinical consequences of heat peaks and prolonged exposure to high temperatures, whether cardiovascular, metabolic or neurocognitive, are still debated.

- **Flooding**: France will be one of the European countries most at risk from coastal flooding, according to the IPCC, with 900,000 people currently living in areas at risk, rising to 1.7 million by the end of the century. These floods can lead to imbalances in ecosystems, particularly microbial, the consequences of which are still difficult to measure and require research.

- **Water shortages:** According to the WHO, 2 billion people do not have access to drinking water[147], and almost half the world's population experiences a serious water shortage for at least one month a year. In Europe, 17% of the population is at risk of water shortages by 2050[148]. In France, this risk particularly affects the overseas territories, especially **Mayotte**, but also the **southern half of France**. These shortages, which mean that water has to be drawn from the bottom of the water table, expose people to infectious water-borne diseases, particularly viruses responsible for gastro-enteritis or Vibrios, but also toxic diseases, due to abnormal concentrations of pollutants.

- **Extreme weather events**: cyclones and storms, which are becoming increasingly frequent, will pose a particular threat to overseas territories. **Forest fires** in Mediterranean Europe are expected to involve 2,200 to 2,500 km^2 of forest, putting the region among the most at-risk areas according to the WEF, and are expected to cause an additional 300,000 deaths worldwide by 2050. As well as causing violent deaths, these fires release large quantities of fine particles and ozone, further exposing people to the risks of atmospheric pollution, particularly respiratory pathologies.

The desire to make cities healthier and more habitable, particularly by revegetation and the creation of green spaces, should reduce the health risks associated with urbanisation, namely air pollution, heat islands, exposure to UV rays, noise pollution and the loss of biodiversity, as well as improving the well-being of residents.
However, we must also anticipate the negative impacts of uncontrolled revegetation, such as the closure of air circulation corridors, the establishment and increase in animal species and arthropod vectors carrying infectious agents for humans, which could initiate or reveal outbreaks or even **epidemics of vector-borne diseases** (dengue fever, West Nile virus fever, tick-borne diseases, leishmaniosis) or **non-vector-borne diseases** such as leptospirosis[149] . In addition, the general increase in urbanisation and hygiene[150] has gone hand in hand with an increase in **allergies**, the

[146] https://www.insee.fr/fr/statistiques/6522912
[147]https://www.who.int/fr/news-room/fact-sheets/detail/climate-change-and-health
[148] WWF (2022) https://wwf.panda.org/wwf_news/?6214416/17-of-Europes-population-faces-high-risk-of-water-scarcity-by-2050
[149] In particular: urban parks favouring concentration and contact between coypu and the population; rats proliferate because of the food resources involuntarily made available, becoming reservoirs of certain diseases. For birds, possible concentration at feeding points, bodies of water in parks, etc.
[150] Depner, M. et al (2020). Nat Med 26, 1766-1775. https://doi.org/10.1038/s41591-020-1095-x; Vuitton, D.A., Dalphin, J.-C. (2017). Engineering 3, 98-109. https://doi.org/10.1016/J.ENG.2017.01.019 ; Kirjavainen, P.V. et al (2019) Nat Med 25, 1089-1095. https://doi.org/10.1038/s41591-019-0469-4

prevalence of which has risen from 5% to around 25% of the population since the 1950s, particularly respiratory allergies linked to allergens of plant origin and air pollution[151] .

2-2- Risks associated with pollutants[152]

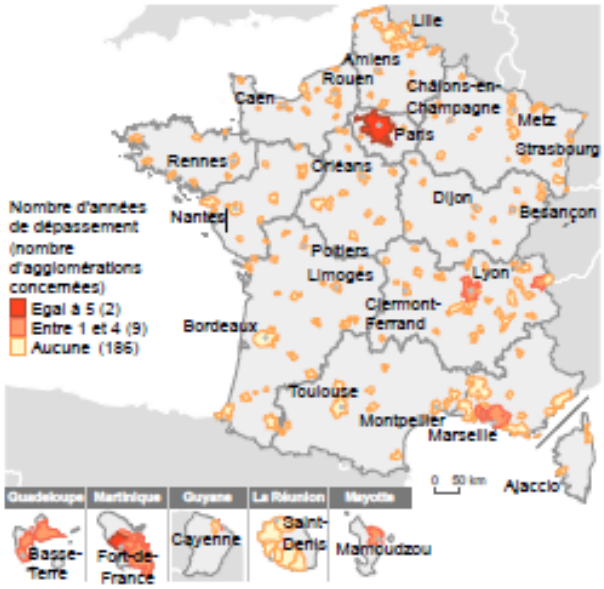
While these exposures do not in themselves give rise to a risk of major and exceptional health situations, apart from industrial accidents, they do constitute a groundswell that is increasingly affecting the overall health situation in France and worldwide. Combined exposure to atmospheric pollutants and chemical agents aggravates a number of pathologies and is strongly associated with a growing rate of cancers, particularly in young people, and with reproductive disorders. In addition, many of these pollutants exacerbate infectious risks, as has been demonstrated for Covid-19[153]. However, the respective impact of these pollutants on the associated diseases is difficult to measure because of the many interactions of the factors involved.
COVARS has summarised the main health risks induced by these pollutants below.

Air pollution :

The health risks associated with air pollution are the best documented, no doubt due to the ease with which pollutants can be measured and the fact that exposure is mainly via the respiratory tract. The European "zero pollution action plan" aims to reduce the number of deaths due to air pollution by 55% by 2030 compared with 2005, particularly in relation to fine particles. Many sectors have reduced these pollutants, with the exception of maritime transport, whose emissions of atmospheric pollutants remain above regulatory thresholds, according to the European Environment Agency (EEA).
In France, despite a nationwide drop in concentrations of $PM_{2.5}$ and most other air pollutants in 2022[154] **, the main French conurbations are still exposed to levels above the regulatory thresholds**: Ile-de-France (nitrogen dioxide), Lyon region and Rhône valley (nitrogen dioxide and ozone), PACA region (ozone and PM10), Alsace (nitrogen dioxide and ozone), Hauts de France (Nickel). In addition, 2022 was marked by several nationwide episodes of ozone pollution in mainland France and by local pollution episodes linked to sand fog. The health risks caused by this pollution will therefore continue for the next 5 years.

[151] Hanski, I. et al (2012) PNAS 109, 8334-8339. https://doi.org/10.1073/pnas.1205624109
[152] Naidu, R., et al (2021). Environment International 156, 106616. https://doi.org/10.1016/j.envint.2021.106616 ANSES (2019), avis relatif à l'Exposition au cadmium (CAS n°7440-43-9,: https://www.anses.fr/fr/system/files/VSR2015SA0140.pdf; European Environment Agency (2024) ETC HE Report 2023/7: Health Risk Assessment of Air Pollution: assessing the environmental burden of disease in Europe in 2021: https://www.eea.europa.eu/data-and-maps/data/external/etc-he-report-2023-7-1 ; ANSES (2023), actualisation des données relatives aux substances phytopharmaceutiques de la famille des SDHI : https://www.anses.fr/fr/system/files/VSR2019SA0202Ra.pdf ; Inserm (2013), Pesticides : effets sur la santé : https://www.inserm.fr/expertise-collective/pesticides-effets-sur-sante/ ; Fritsch, C. et al (2022).. Sci Rep 12, 15904. https://doi.org/10.1038/s41598-022-19959-y ; Tang, F.H.M. et al (2021) Nat. Geosci. 14, 206-210. https://doi.org/10.1038/s41561-021-00712-5
[153] Chen Z. (2022), American Journal of Respiratory and Critical Care Medicine 20 Sept, 2022 DOI: 10.1164/rccm.202206-1123LE
[154] MTECT (2023)https://www.statistiques.developpement-durable.gouv.fr/bilan-de-la-qualite-de-lair-exterieur-en-france-en-2022

Carte 3b : PM_{10} (période 2015-2022)



Map showing the distribution of fine particles in France (From: Report on Air Quality in France 2022)

These risks and associated pathologies, linked in particular to **Fine Particles ($PM_{2.5/10}$), Nitrogen Dioxide (NO2) and Ozone (O3),** are described in Table 2 below.

In addition to these outdoor air pollution factors, there is also indoor pollution from **smoking.**

This outdoor and indoor air pollution is responsible for an exacerbation of obstructive respiratory pathologies (asthma, COPD) and of the intensity of respiratory infections; it is also responsible for cardiovascular, neurological, metabolic and reproductive pathologies and bronchopulmonary cancers, particularly in non-smokers. A new carcinogenic mechanism of fine particles at the origin of these cancers has been demonstrated[155] and large British studies[156] show that a previous exposure of 3 years to $PM_{2.5}$ could increase the risk of lung cancer in non smokers

In addition, **the combination of air pollution and climatic factors,** such as rising temperatures and higher concentrations of carbon dioxide and fine particles, is exacerbating exposure to pollens, particularly in connection with the lengthening of pollen seasons and the introduction into towns of plants that emit allergenic pollens, leading to asthma and respiratory **allergies.**

Pollution from chemical agents, including plant protection products (PPPs):

Various collective expert reports[157], including those by the WHO, Anses and INSERM, have established links at different levels of presumption between exposure to PPPs and various pathologies (neurodegenerative, cancer, anxiety-depression disorders, etc.) [158]. Although the use of certain products has been banned for several years (organophosphates in particular), they persist in almost all ecosystem compartments, and French and European control measures and regulations against these agents are often not adopted at the rate required to avoid the consequences, both chronic and acute[159]. Some chemical substances are harmful to humans, particularly in the workplace, during pregnancy and childhood, and to people living near areas where they are spread on land.

[155] Lim EL. et al. Nature. 2023 April 01; 616(7955): 159-167. doi:10.1038/s41586-023-05874-3.
[156] Huang Y, et al. (2021). Am J Respir Crit Care Med. 204: 817-825; Hill W et al (2023) Nature. 616(7955): 159-167; Turner MC, et al (2020). CA Cancer J Clin. 70: 460-479.
[157] Colzyn S. et al (2024). Int J Hyg Environ Health. 256:114311. doi: 10.1016/j.ijheh.2023.114311.
[158] INSERM, 2021. Pesticides: Effects on health. Nouvelles données. EDP Sciences, Paris.
[159] Naidu, R., et al (2021). Environment International 156, 106616. https://doi.org/10.1016/j.envint.2021.106616

In addition to these factors, microplastics are ubiquitous in ecosystems[160] exposing humans through oral ingestion, inhalation and contact, and can be an inert carrier of pathogens[161] . They are detectable in lungs, placentas and blood vessels[162], and an epidemiological link has been shown with various chronic diseases (respiratory, intestinal, hepatic, vascular)[163].

The clinical consequences of these various agents can persist for many years after the withdrawal of certain unauthorised pollutants because of their persistence in the soil and their run-off into water, leading to permanent but diverse excess risks depending on the family of pollutants, which can be regrouped in a syndromic approach:

- **Respiratory diseases:** linked to air pollutants, metals and organic pollutants**,**
- **Cancers:** in addition to the airborne pollutants associated with lung cancer - the 3rd most common cancer in France and the 1st cause of cancer deaths[164] - pesticides (organophosphates), metals, persistent organic pollutants, phenols and fluoroalkylated per/polys,
- **Metabolic and endocrine pathologies** (diabetes and renal pathologies): linked to pesticides (organophosphates), metals, persistent organic pollutants, phenols and fluoroalkylated per/polys,
- **Neurocognitive disorders:** linked to pesticides (organophosphates), metals, persistent organic pollutants, phenols and Per/poly fluoroalkylates
- **Reproductive disorders and foetal development**: particularly in relation to phthalates, but also in relation to pesticides (organophosphates), metals, persistent organic pollutants, phenols and Per/poly fluoroalkylates.
- **Alteration of mental health and eco-anxiety:** all these pollutants converge to induce deleterious consequences on mental health, in the form of "widespread generalised anxiety", "chronic fear of environmental catastrophe" and "experience of a change in the domestic environment perceived negatively", and should not be minimised[165] . Out of 10,000 young people aged 16 to 25 surveyed in ten countries, almost 70% said they were "very worried" or "extremely worried" about climate change[166] .

It is not the aim of the COVARS to draw up an exhaustive list here, but a few significant examples of highly plausible or proven associations between certain factors linked to climate change and environmental physico-chemical agents and certain pathologies are described in the table below (**Table 2)**.

[160] Rillig, M. C. et al (2020). Science 368(6498): 1430-1431). American Association for the Advancement of Science (AAAS). https://doi.org/10.1126/science.abb5979

[161] Zhang, E. et al (2022). Sci Rep 12, 6532. https://doi.org/10.1038/s41598-022-10485-5

[162] Garcia, M. A. (2024). Quantitation and identification of microplastics accumulation in human placental specimens using pyrolysis gas chromatography mass spectrometry. In Toxicological Sciences. Oxford University Press (OUP). https://doi.org/10.1093/toxsci/kfae021

[163] Li, Y. et al (2023). Environ. Health 1, 249-257. https://doi.org/10.1021/envhealth.3c00052

[164] https://www.e-cancer.fr/Professionnels-de-sante/Les-chiffres-du-cancer-en-France/Epidemiologie-des-cancers/Les-cancers-les-plus-frequents/Cancer-du-poumon

[165] American Psychoogical Association, Climate for Health and EcoAmerica (2017): https://www.apa.org/news/press/releases/2017/03/mental-health-climate.pdf

[166] Hickman C. et al (2021), Lancet Planetary Health 5:e863-73

***Table 2** : Snapshot of Clinical effects and sanitary impacts of environemental factors*

Effects and Impacts / Factors		Exposure		Clinical Consequences									Sanitary Impact (Death/year)	Counter-Measures	Ref.
		Frequency in population	Expected Increase	Mental Health	Cancers	Neurolo-gical	Reproduc-tion & child develop-ment	Respira-tory	Metabo lic, endocri ne	Cardio-Vascu-lar°	Exacer-bation of Infections	Fatality			
Climate	Heat waves	+	+										1 000 (2014-2022) 5 000-15 000 (big waves)		213
	Heat (except waves)	+	+										2 600 (2014-2022)		214
	Fires		+												
	Other extreme events		+												215
Other Physical Agents	Noise / UV Radiations	+	P.D.									(UV)		Yes	216
Chemical Agents	**Atmospherical Polluants**														
	Fine Particules ($PM_{2,5}$)		-										40 000	Yes	217
	Nitrogen Oxydes		+/-										7 000	Yes	218
	Ozone		+												219
	VOC (volatile organic compounds)														
	Tobacco		+										75 000	Yes	
	Metals, including														
	Lead	+	-												
	Cadmium	+													220
	Mercury														
	Endocrine disruptors														
	Phtalates		P.D.												221
	Phenols		P.D.												
	PFAS (per- & poly-fluoroalkylés)	(PFOA, PFOS)	P.D.												222
	Pesticides														223
	Organochlorine (DDT, HCB, chlordecone)	+	-												
	Organophos-phates													Yes	224
	Drinking water Polluants														
	Nitrates		+/-											Yes	225
	Trihalomethanes		+				(x)								

Legend and References of Table 2 :

° Cardiovascular complications including haemodynamicalterations and dehydratation due to heat waves ; VOC : Volatil organic compounds ; P.D. : Poorly documented ; The clinical consequences mentionned here-in correspond to a plausible or above level of evidence.

References :

1. Ballester J, Nat Clim Change 2023 ; Pascal M (SpF), 2023 : https://www.santepubliquefrance.fr/determinants-de-sante/climat/fortes-chaleurs-canicule/documents/rapport-synthese/estimation-de-la-fraction-de-la-mortalite-attribuable-a-l-exposition-de-la-population-generale-a-la-chaleur-en-france-metropolitaine.-application-a

2. Pascal M (SpF), 2023 : https://www.santepubliquefrance.fr/determinants-de-sante/climat/fortes-chaleurs-canicule/documents/rapport-synthese/estimation-de-la-fraction-de-la-mortalite-attribuable-a-l-exposition-de-la-population-generale-a-la-chaleur-en-france-metropolitaine.-appl

3. Extreme weather events et santé : IPCC ou Weilnhammer, IJHEH, 2021, https://www.sciencedirect.com/science/article/pii/S1438463921000018

4. https://iris.who.int/handle/10665/279952

5. https://www.santepubliquefrance.fr/determinants-de-sante/pollution-et-sante/air/documents/enquetes-etudes/impact-de-pollution-de-l-air-ambiant-sur-la-mortalite-en-france-metropolitaine.-reduction-en-lien-avec-le-confinement-du-printemps-2020-et-nouvelle

6. Medina (2021), https://www.santepubliquefrance.fr/determinants-de-sante/pollution-et-sante/air/documents/enquetes-etudes/impact-de-pollution-de-l-air-ambiant-sur-la-mortalite-en-france-metropolitaine.-reduction-en-lien-avec-le-confinement-du-printemps-2020-et-nouvelle

7. Ozone : Domingo, One Health 2024 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7615682/

8. Carne, G. et al (2021), Science of The Total Environment 760: 143374; Suciu, N.A. et al (2022) Environmental Science & Health 30, 100392. https://doi.org/10.1016/j.coesh.2022.100392

9. Wang, Y., Qian, H. (2021) Healthcare 9, 603. https://doi.org/10.3390/healthcare9050603

10. eBioMedicine, 2023. Forever chemicals: the persistent effects of perfluoroalkyl and polyfluoroalkyl substances on human health. eBioMedicine 95. https://doi.org/10.1016/j.ebiom.2023.104806 ;
https://www.anses.fr/fr/content/pfas-des-substances-chimiques-dans-le-collimateur ; https://www.savoie.gouv.fr/Actualites/Actualites/Substances-perfluorees-PFAS ; https://www.aria.developpement-durable.gouv.fr/synthese/inventaire-des-incidents-et-accidents-technologiques-survenus-en-2022/ ; https://www.e-cancer.fr/Professionnels-de-sante/Les-chiffres-du-cancer-en-France/Epidemiologie-des-cancers/Les-cancers-les-plus-frequents/Cancer-du-poumon

11. https://www.eea.europa.eu/publications/how-pesticides-impact-human-health ; Expertise collective Inserm sur pesticides et santé, actualisée en 2021

12. https://www.ncbi.nlm.nih.gov/books/NBK222858/

13. Autorité environnementale, 2023. Note délibérée de l'Autorité environnementale

This table does not claim to be exhaustive and simply provides examples of physical and chemical factors present in different environments. It summarises the Effects, Impacts, Exposure and Clinical Consequences of the main environmental factors analysed by the COVARS, based on the leading scientific opinions, reports and articles in the field, but in no way represents an exhaustive list of these factors or their consequences. In particular, it illustrates the many "gaps" in knowledge that still exist in this field.

3- Links between infectious risks and climate and environmental change:

It is artificial to separate infectious and environmental risks. The links between pandemics and environmental crises have been widely demonstrated and, along with human migration, are the cause of the biggest epidemics in history[167] . The **WHO** presents an overview of these risks:

[167] IPCC (2019) Climate Change and Land: an IPCC special report on climate change, desertification, land degradation, sustainable land management, food security, and greenhouse gas fluxes in terrestrial ecosystems; Whitmee, S. et al (2015). Lancet 386(10007): 1973-2028; B. J. McMahon et al (2018) Zoonoses Public Health. 65: 755-765. https://doi.org/10.1111/zph.12489

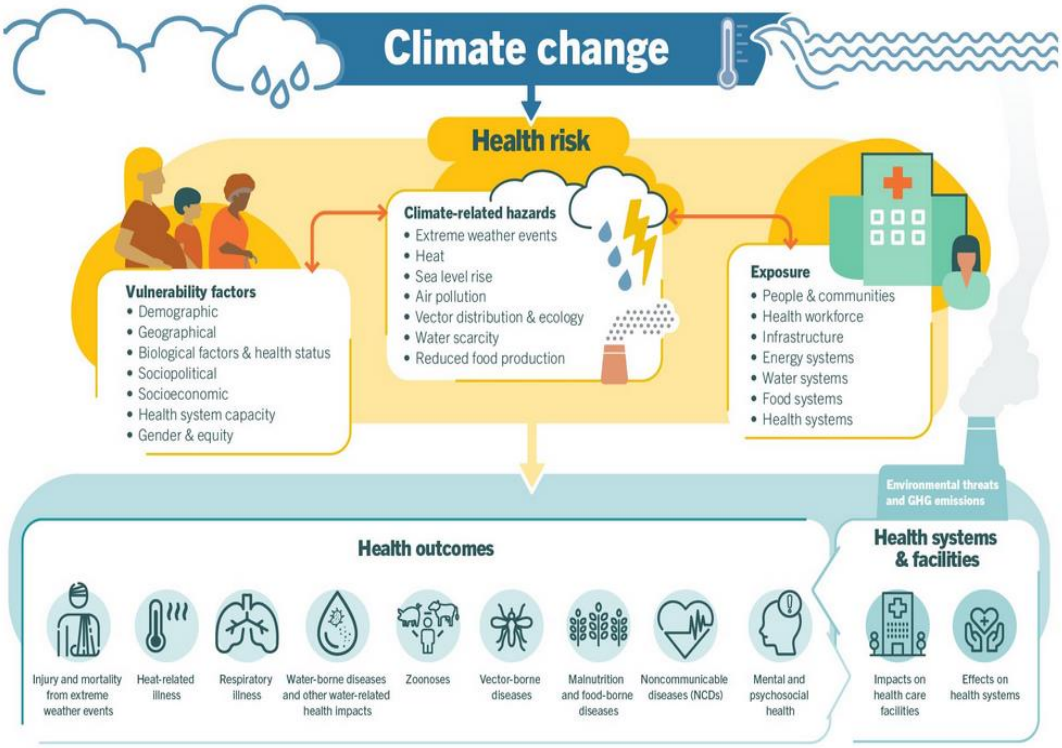


Figure: An overview of climate-sensitive health risks, their exposure pathways and vulnerability factors. Climate change impacts health both directly and indirectly, and is strongly mediated by environmental, social and public health determinants.

- Certain links between infectious and environmental risks are known and expected, in particular :
  - **Vector-borne diseases, arboviroses** and **zoonotic influenza**[168], linked to global warming, elongation of at risk hot seasons and climate change, as set out in the previous COVARS Advices [169]. By 2050, an additional 500 million people will be in a zone exposed to vector-borne diseases, according to the WEF[170] .
  - **Respiratory and gastroenteric infections**: respiratory infections can be exacerbated by air pollution, leading to increased vulnerability in the entire population, more so in children or people with chronic respiratory pathologies, as demonstrated during the Covid-19 pandemic[171]. In addition, climatic disturbances such as flooding can increase the risk of the spread of enteric infectious agents and foodborne infections.
  - **Increase in antibiotic resistance**: linked to climate change and environmental factors**,** particularly in resource-poor countries where antibiotics and resistant bacteria are dispersed into the environment via

[168]Romanello et al (2023) Lancet 402(10419) : 2346-2394.https://doi.org/10.1016/S0140-6736(23)01859-7

[169] COVARS: https://sante.gouv.fr/IMG/pdf/avis_du_covars_du_8_juin_2023_-_risque_sanitaire_lie_a_l_iahp_et_la_grippe_aviaire.pdf; Avis du 3 avril 2023 relatif aux risques sanitaires de la dengue et autres arboviroses à aedes, accessible here: https://www.enseignementsup-recherche.gouv.fr/sites/default/files/2023-04/avis-du-covars-du-3-avril-2023---risques-sanitaires-de-la-dengue-du-zika-et-du-chikungunya-en-lien-avec-le-changement-climatique-27356.pdf; Document de cadrage du 23 décembre 2022 relatif aux maladies à transmission vectorielle (MTV) en France, accessible here: https://sante.gouv.fr/IMG/pdf/covars_document_de_cadrage_du_23.12_2022_sur_les_maladies_a_transmission_vectorielle_mtv_en_france.pdf

[170] World Economic Forum (2024), https://www3.weforum.org/docs/WEF_Quantifying_the_Impact_of_Climate_Change_on_Human_Health_2024.pdf

[171] Denys S., Barouki R.(2021), Annales des Mines - Responsabilité et environnement, 2024/4 (N° 104), p. 32-35. DOI : 10.3917/re1.104.0032 ; HERA-COVID-19 Working Group (2021), Environment International, doi: 10.1016/j.envint.2020.106272; Conticini et al, 2020 ; Wu et al (2020) Science Advances, vol. 6, n°45, eabd4049

waste water[172][173]. Very high levels of antibiotics have been found in rivers around anti-microbial production sites in India and China, where the vast majority of these products are manufactured[174]. Globalisation and the massive increase in population movements are contributing to the dispersal of these BHRe. Today, a clone of *Escherichia coli, a* very common digestive bacterium carried by all humans, ST 167, has become resistant to all antibiotics, including the most recent, and is dispersed throughout the world in waste water and by dirty hands. In Europe, France seems to be[175]. Efforts to ensure proper use of antibiotics must continue to be directed at the health care workers and patients, with behavioural approaches helping to define new levers for action, in order to[176]

- Other less well-known risks are linked to :
    - **The effects of global warming and changes in water levels,** which can increase exposure to pathogens and biological invasions;

    - **loss of biodiversity** as a result of human activity and pollution :

Most of the risk of the emergence of zoonotic diseases associated with wildlife is linked to contacts between highly biodiverse ecosystems (rich in microbes) and highly intensive animal production systems (genetically poor and homogenous, and therefore more vulnerable to pathogens) and/or high human concentrations[177].

The loss of biodiversity results in a simplification of ecosystems, leading, among other things, to their reduced robustness and greater instability, which encourages an increase in the size of populations of opportunistic species. These species take advantage of the ecological niches left empty by the more specialised species that are the first to disappear. These opportunistic species can be indigenous or exotic, and sometimes invasive[178][179]. A higher population biomass of a particular species, reservoir or vector (rodent, mosquito, mite, etc.), can increase exposure to certain pathogens (arboviruses, leptospires, hantaviruses, historically Yersinia pestis, etc.).

Controlling the nuisance caused by these species, whether directly (bites, damage to stored foodstuffs, etc.) or indirectly through the pathogens they carry, increases the risk of **resistance** if chemical agents are used, for example in vector control using insecticides. These phenomena, combined with the impact of their use on non-target species and the consequent even greater reduction in biodiversity, can lead to a long-term loss of control of these infectious agents and be the source of the emergence of known or unknown agents (**Disease X**).

4- Particular risks in Overseas territories :

Analysis of the risks affecting the overseas territories takes account different aggravating factors (climate, economic and health levels), of introduction and transmission (permeable borders, closer animal-human contacts) and shows specific risks:

- The introduction of pathogens such as **HPAI** in the American territories, **RVF** in the Indian Ocean territories, and recurring risks (**dengue fever, Zika, Chikungunya, yellow fever and malaria,** particularly in French Guiana for the two latters).

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[172] WHO (2022), Press release: Report highlights rise in antibiotic resistance in human bacterial infections and the need for more robust data: https://www.who.int/fr/news/item/09-12-2022-report-signals-increasing-resistance-to-antibiotics-in-bacterial-infections-in-humans-and-need-for-better-data ; Li, W. et al. (2023) Lancet Reg. Health West. Pac. 30, 100628; MacFadden, D. R., et al (2018) Nature Clim. Change 8, 510-514; McGough, S. F., et al (2020) Euro Surveill. 25, 1900414; Brumfield, K. D. et al. mBio 14, e01476-23 (2023)

[173] Sikder et al (2024) Water Environ Res 96(2):e10987. doi: 10.1002/wer.10987

[174] Arum N et al (2022). Indian J Med Microbiol. 40(3):374-377. doi: 10.1016/j.ijmmb.2022.05.010.

[175] Huang J, et al. Commun Biol. 2024 Jan 6;7(1):51. doi: 10.1038/s42003-023-05745-7.

[176] Bonmarin I. et al (2023). Bull Épidémiol Hebd.(22-23):480-7. http://beh.santepubliquefrance.fr/beh/2023/22-23/2023_22-23_5.html

[177] IPBES, 2020. https://doi.org/10.5281/zenodo.4147317

[178] Ostfeld, R.S., Keesing, F. (2020). Nature 584(7821) : 346-347.

[179] Keesing, F. et al (2010). Nature 468, 647-652.

- Environmental: such as sargassum in the French West Indies, sand dust in the desert, organochlorines, moulds specific to the French West Indies or the exploitation of natural resources (nickel in New Caledonia), which can generate classic effects if the soil is polluted.

It is also important to highlight the particular case of **Mayotte**, where major epidemic risks - including almost all the diseases analysed, such as cholera (with currently 3 imported cases), plague and polio, which have been virtually forgotten in France - are combined with food, infectious and toxicological risks linked to climate change, particularly drought.

5- Psychosocial risks and socio-economic factors

In addition to the risks of deteriorating mental health, particularly in connection with eco-anxiety, exceptional health situations entail a range of psychosocial and socio-economic risks, as demonstrated by the Covid-19 pandemic. The study of contemporary epidemics and pandemics has highlighted contradictory psychosocial dynamics in the response of populations to threats to health or the environment, with the concomitant observation of phenomena of over- and under-reaction, at the cognitive, emotional and behavioural levels, as shown by the work of S. Taylor:

Sous-réaction	Réaction « médiane »	Sur-réaction
- Apathie - Minimisation et dénégation du risque - Production ou promotion de récits alternatifs sur la nature et l'origine du risque (dont théories du complot) - Recherche et stigmatisation de « bouc-émissaires » - Recherche et promotion de traitements alternatifs	- Stress et inquiétude - Recherche d'informations - Recherche de soutien social - Renforcement de la coopération sociale - Altruisme et entraide - **Adoption de mesures de précaution ou de prévention** - Maintien des schémas d'organisation - Introspection, méditation, pratiques religieuses, etc.	- Panique - Recherche compulsive d'informations - Isolement, fuite et exode - Constitution de stock de précaution (nourriture, essence, produits hygiéniques, etc.) - Recherche et stigmatisation des non-observants - Maintien de précautions inutiles

Table: Typology of the most frequent psychosocial responses to major and exceptional health situations[180]

Some threats are more anxiety-provoking than others, as shown by risk psychology research modelling the emotional, social and behavioural responses of European and North American populations on the basis of a small number of perceptual criteria: sensitivity to unfamiliar and uncertain health threats is heightened as soon as they are discovered and publicised, as is sensitivity to threats that are more difficult to control or prevent at an individual level.
A cognitive risk map, drawn up by *Slovic et al,* helps us to understand people's sensitivity to certain threats and their relative indifference to others (see Figure 8 below). The location of eco-toxicity-related diseases in the upper-right quadrant of this map illustrates the greater attention paid by contemporary societies to these threats, compared with older ones such as smoking or air pollution. However, as the experiences of HIV and Covid-19 have shown, the development of effective therapeutic or preventive treatments can contribute to a trivialisation of the risk, as well as to a significant and rapid demobilisation of the populations exposed, whereas the epidemiological situation warrants the maintenance of a minimum level of vigilance.

[180] Taylor, S. (2019). The psychology of pandemics: Preparing for the next global outbreak of infectious disease. Cambridge Scholars Publishing.

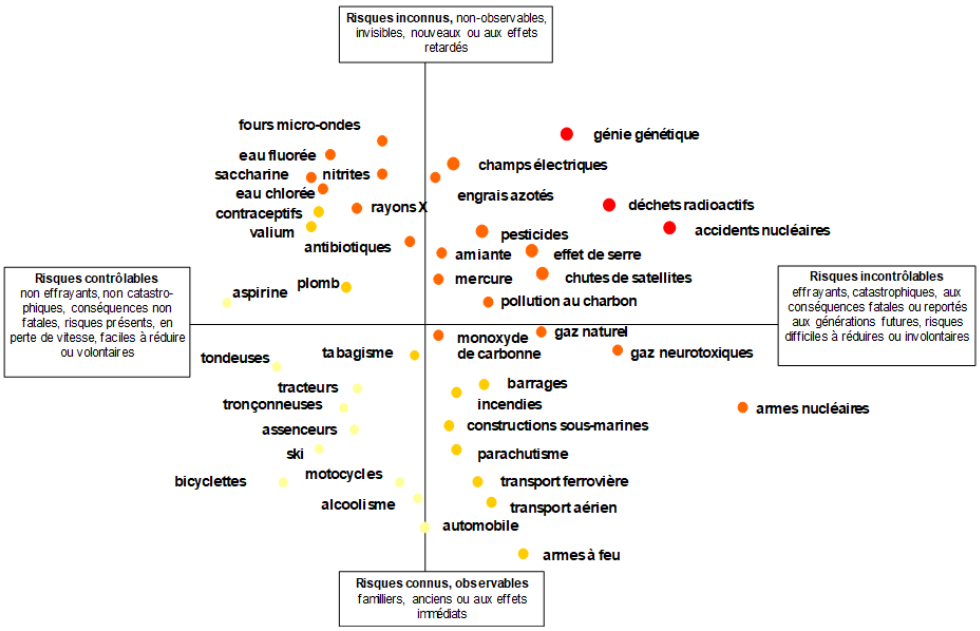


Figure 8. Cognitive risk map[181]

Finally, exceptional health situations tend to exacerbate the phenomena of **'structural' social inequalities** in health, although this is less well documented in the field of emerging diseases than in that of chronic diseases[182]. For example, the EPICOV study showed that persistent and obvious social disparities existed in France throughout the anti-Covid19 vaccination campaign, despite the fact that the vaccines were free and accessible[183]. These recent observations are a reminder of the importance of a "proportionate universalism" approach in the design of the prevention to exceptional health situations and control policies and programmes, i.e. the need to pay particular attention to the most vulnerable socio-economic and socio-cultural groups.

The major and exceptional health situations risks identified by the COVARS in the current state of our knowledge are essentially linked to: 1) on the infectious side, zoonotic pandemic respiratory viruses and certain arboviroses, to which must be added the risk of a currently unknown "Disease X", and 2) on the environmental side, acute events induced by climate change, while stressing that 3) health risks linked to physico-chemical pollution are a source of major but permanent health situations, and that 4) these infectious and environmental risks are closely linked.

The COVARS is fully aware of the potential limitations of this assessment, covering a wide range of risks analysed in a short space of time, and which has produced a hierarchy that meets the objective set by the referral. The results are subject to change as new knowledge emerges.

B- Discussion

[181] Slovic, P. (1987). Perception of risk. *Science*, *236*(4799), 280-285.
[182] Cohen, J. M. et al (2007). Journal of Epidemiology & Community Health, *61*(12), 1021-1027; Noppert, G. A. et al (2017). J Epidemiol Community Health, 71(4), 350-355.
[183] Bajos, N. (2022). PLoS One, 17(1), e0262192.

Classification of infectious risks

The priority ranking of pandemic respiratory infections, certain arboviruses and disease "X" is consistent with all existing classifications : A comparison of the COVARS analysis with the main existing French risk maps shows a great deal of convergence, with only a few differences reflecting different risk analysis objectives.
In particular: **The HCSP**'s list[184] has assessed 95 diseases or groups of infectious diseases using partly different criteria from COVARS, with ten diseases classified as priority ones: 1) viral haemorrhagic fevers, 2) seasonal acute respiratory infections excluding influenza, 3) arboviruses, 4) zoonotic influenza, 5) seasonal influenza, 6) emerging coronavirus infections, 7) other ARIs, 8) Creutzfeld-Jakob disease, 9) multi-drug-resistant infections and 10) emerging multi-drug-resistant bacteria (MDRB). Unlike the HCSP, the COVARS has broken down entities such as "haemorrhagic fevers" and "arboviruses" into their various components and analysed the specific risks in mainland France and the French overseas territories. In addition, the differences in risk ratings may reflect the highly multidisciplinary composition of COVARS, which differs from the medical composition of the HCSP. As a result, it appears that :

- **There is a great deal of convergence in terms of major risks, particularly in terms of the relative positioning of the risks of zoonotic influenza and emerging coronaviruses, as well as arboviruses** and ARIs. However, COVARS considers that this latter risk should decrease in the coming years with the application of preventive countermeasures.
- **There are a few differences, particularly for viral haemorrhagic fevers (VHF):** COVARS considered them to be at lower risk of major and exceptional health situations in France due to their lower probability of occurrence in France, their lower potential for transmission and in the context of a level of preparedness and access to modern healthcare capacities throughout the French territories, despite their major epidemic and re-emergence potential subject to environmental and anthropogenic factors. These zoonoses are caused by highly pathogenic viruses that are highly transmissible between humans, with a lethality rate of 10% to 80%, and can lead to catastrophic epidemics that can be anticipated and are often contained, even though they can have an international impact. Societal perception of the risk (real or assumed) is important, and is linked to breakdowns in social peace, as in Africa during the HFV epidemic crises of 2014-20. This applies in particular to the following fevers: i) *Ebola and Marburg*, 10-20% of forms of which are pauci- or asymptomatic; the Ebola epidemics of 2013-2016 and 2018-2020 led to considerable progress in terms of diagnosis, treatment and vaccine prophylaxis; ii) *Lassa,* for which no candidate vaccine under development has yet been licensed[185]. The classification of these pathogens as group P4 indicates the major level of security required for pre- and analytical measures on contaminated samples, and for the management and care of suspected or confirmed patients in the high-security units of RSEs with a national mission for Epidemic and Biological Risk (EBR) in France.

The COVARS' analyses are also in line with those carried out by **InVS**[186] in 2009, which classified vector-borne diseases such as Chikungunya, Dengue fever and Crimean-Congo fever as priorities (see table in Appendix 2), although they were positioned differently depending on the region.

For the overseas territories, the COVARS analysis is partly consistent with the analysis proposed at the **CIRAD** hearing[187]: a high risk for pandemic influenza and dengue fever, a medium risk for West Nile, Zika and Chikungunya virus infections, Leptospirosis and RVF, in Mayotte, a low risk for rabies and negligible for Nipah and Ebola virus

[184] HCSP, List of infectious diseases, 27/10/2023: https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1363
[185] Malvy D et al. in: Molecular Medical Microbiology, Ed. Yi-Wei Tang et al, (vol. 4), 2024 Elsevier Ltd, Part 19, p. 2281-2311); Coulborn RM, et al. Lancet Infect Dis. 2024 Feb 7:S1473-3099(23)00819-8. doi: 10.1016/S1473-3099(23)00819-8).
[186] Institut de Veille sanitaire (2009), Definition of priorities in the field of non-food zoonoses
[187] COVARS hearing on 22 January 2024

infections.[188]. For mainland France, CIRAD envisaged a high risk for West Nile virus, Dengue fever, pandemic influenza and CCHF, a medium risk for Chikungunya and Zika virus infection, and a low risk for RVF.

Finally, the **WHO**'*s* 2018 priority list of diseases and pathogens in emergency situations[189], revised in 2021, included, like the COVARS list, emerging acute respiratory viruses, FHV and arboviruses, to which were added Nipah virus infections and disease X.

The list of research priorities of the **ANRS-MIE**[190] on pathogen families linked to emergencies also converges with the COVARS major and exceptional health situations prioritisation list. The ANRS-MIE identifies 12 priority virus families, including various viruses responsible for FHV and vector-borne diseases, coronaviruses and influenza viruses in particular (see table in appendix 2, pages 61-62).

Of note, the COVARS map incorporates the main infectious risks arising from large gatherings and influxes of people from all over the world, such as the **2024 Olympic and Paralympic Games**, including : 1) imported cases of Arboviruses and their risk of dissemination during the summer period of activity of the mosquito vectors, 2) a "Disease X" or even 3) highly contagious or severe diseases that are usually absent from the French territory, 4) the increased risk linked to STIs, HIV/AIDS and the mPox virus, and 5) collective food poisoning (CFT) and other individual food-borne infections.

In addition, there are specific points to be highlighted in relation to infectious major and exceptional health situations risks:

- **Risks associated with zoonoses:** among the major risks of emerging diseases, the COVARS analysis highlights 8 risks of zoonotic viral infection (zoonotic influenza and new pandemic coronavirus, West Nile virus, Crimean-Congo fever, Rift Valley virus, Yellow fever, Rabies, the other 4 being transmitted by mosquitoes which are also vectors of zoonotic and animal diseases (Dengue, Zika, Chikungunya, Malaria)). These results converge with the analysis carried out by Anses and in the USA, which prioritised 8 zoonoses (IA virus, salmonellosis, West Nile, plague, emerging coronaviruses, rabies and brucellosis).[191] They are in line with publications showing that 75% of emerging infectious diseases in humans have an animal origin[192], illustrating the fact that all these major health risks are directly linked to interactions between humans, animals, vectors and the environment in the context of global change, particularly climate change.
- **Risks of nosocomial transmission:** This criterion has been included in the risk criteria analysed by the COVARS, particularly at the level of prevention plans for infections that can be transmitted via the respiratory or digestive tract (such as BHRe), as well as via the bloodstream (CCHF and HIV). The risks of transfusion or of transmission and induction of severe pathologies by organ donation are major for HIV, but also significant for many pathogens (WNV virus and arboviroses, TBE and rabies in particular), requiring the reinforcement or even the establishment of prevention plans.

- **Risks associated with gain-of-function experiments and laboratory accidents**: The questions that arose during the outbreak of SARS-CoV-2 about the possibility of a genetically manipulated virus in the level 4 biosafety laboratory in Wuhan, the epicentre of the COVID-19 pandemic, make it necessary to maintain a high level of surveillance and control over scientific work that may be carried out on viruses with a high pandemic potential. The importance of research to understand the mechanisms of adaptation of a zoonotic virus to humans, and to control of the risk of a human epidemic emerging, must be weighed up. Such research must be very strictly supervised, avoiding as far as

[188] COVARS hearing on 22 January 2024
[189] WHO (2018), Annual review of diseases prioritized under the Research and Development Blueprint, meeting report: https://cdn.who.int/media/docs/default-source/blue-print/2018-annual-review-of-diseases-prioritized-under-the-research-and-development-blueprint.pdf?sfvrsn=4c22e36_2; WHO (2023) R&D Blueprint for Epidemics - Targeting research on diseases of greatest Epidemic and Pandemic threat, available here: https://www.who.int/teams/blueprint/who-r-and-d-blueprint-for-epidemics
[190] https://www.infectiologie.com/UserFiles/File/renarci/liste-des-pathogenes-prioritaires-rech-mie-2023-2.pdf
[191] US CDC, DOI, USDA (2022), One Health Zoonotic Disease https://www.cdc.gov/onehealth/pdfs/OHZDP_Workshop_Flyer_508.pdf
[192] Jones et al, (2008) Nature.451: 990-3).

possible the production of infectious viruses, and strictly limited to high security L4 laboratories with reinforced and supervised maintenance.

Classification of environmental risks

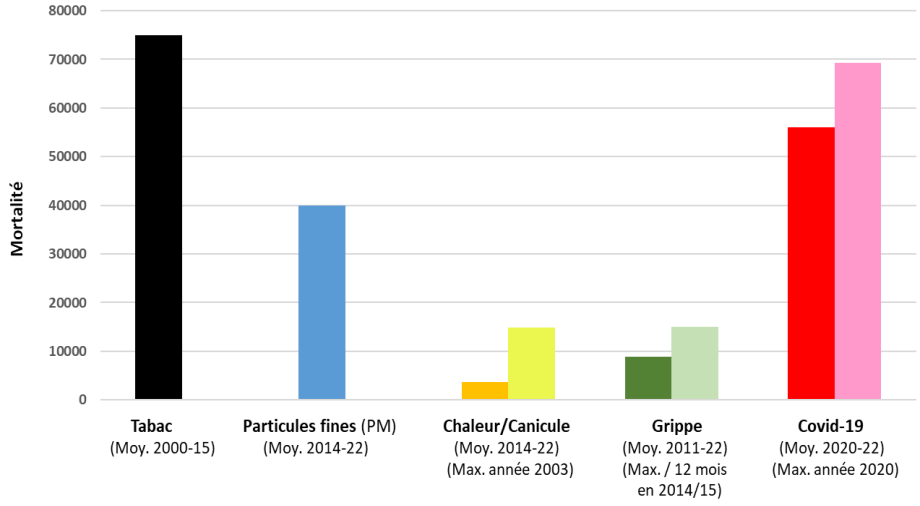
The question of the links between exposure to pesticides and diseases is becoming increasingly complex and a matter of growing scientific concern, particularly with regards to the indirect effects of certain pesticides on human health through their impact on ecosystems. The interdependence involved needs to be studied and integrated to a greater extent, in the same way as the social and economic aspects, in order to inform decision-making when developing public policies, as highlighted in 2012 by the Inserm collective expertise on pesticides[193] .

The health risks attributed to climate change and to ecotoxicity due to air pollution and chemical and plant health pollutants are artificially distinguished, but there is a continuum and additive effects between these agents, global warming and health effects. The complexity of these cumulative effects makes any precise analysis of environment-related health risks difficult, apart from those of global warming and air pollution, which are easier to identify.

To illustrate the need to take into account both the health risks associated with infectious agents and environmental factors, the COVARS has summarised below the mortality data associated with several of these risks. Figure 9 shows the same orders of magnitude for reported 12-month mortality linked to exposures: 1) permanent, such as to tobacco or fine particles close to those of peak mortality due to Covid-19, 2) seasonal, such as heatwaves or influenza.

Figure 9: Examples of mortality linked to environmental and infectious factors

5Mortality expressed as the average number of deaths per year over the time periods indicated, and as the number observed over a 1-year period for peaks[194] .



These latest data illustrate the need to consider not only infectious risks in the list of risks likely to lead to major exceptional health situations, or even major but non-exceptional health situations.

[193] Inserm (2013), Pesticides: health effects; available here: https://www.inserm.fr/expertise-collective/pesticides-effets-sur-sante/

[194] Sources for the graph: Tobacco: Bonaldi C et al. Bull. Epidemiol. Hebd. 2019, 15, 278-84; PM: Medina S. report. SpF; Heat: SpF bilan 2014-22 ; Influenza: SpF: bilan 2011-22 and Lemaitre M et al. Influenza Other Respir. Viruses 2022, 16(4) 717-25; Covid-19: 2020-21: CépiDC and 2022: Insee.

This difficulty in drawing up a rigorous map underlines the low level of knowledge in this area in France and around the world, and the urgent need to support major research efforts into the health risks associated with this multi-exposure or Exposome and above all multidisciplinary and multi-sector partnerships between the fields of human, animal, plant and ecosystem health.

In Summary :

The risk analysis of Exceptional Sanitary Situations (ESS) performed by COVARS in the current state of knowledge and for the next 2 to 5 years in France, allows to estimate the following main risks in the fields of :

- **Infectious diseases,** these risks are strongly modulated by environnemental factors (climate notably) and geopolitical changes :
  - **Risks of major ESS will be mainly due to:**
    - **pandemic respiratory infections** (**zoonotic Flu and new coronavirus**)
    - **arboviroses** : **dengue in the overseas mostly** but also **in** metropolitan France, and **West-Nile virus infection i**n metropolitan France.
    - **Disease « X »**
    - **Acute respiratory infections,** the burden of which should decrease with application of preventative measures,
  - **A close, though lesser, level of risk** linked to :
    - V**ectorial diseases :** transmitted by : i) mosquitoes : Zika and Chikungunya, particularly overseas, ii) ticks : **hemorragic Crimee-Congo fever** (HCCF) in metropolitan France,
    - Severe i**nfections due to multi-resistant bacterias**.
  - A lesser but still notable risk linked to sexually-transmitted or vector-borne diseases (AIDS, other STIs, XDR-tuberculosis, tick-borne encephalitis, Rift valley fever, rabies, gastro-enteritis...), with distinct distribution according to territories.
- **Environnemental Factors,** such as :
  - **Risks of major ESS : mainly linked to climate changes.**
  - **Health impacts** of air and chemical agents pollution**,** which are chronic and diffuse, but as important, if not more, and favoring and increasing the severity of most infectious diseases.

IV- Recommendations

Assessing the risks of a Major and Exceptional Sanitary Situation means understanding and monitoring them upstream in order to prevent them, so as to be able to detect and treat them as early as possible in the crisis.
As a result of this work, COVARS recommends:

A- Rapidly implement Prevention and Response Preparedness measures for major and exceptional health situations risks.

The prevention and preparation of major and exceptional health situations risks assessed by the COVARS in relation to infectious diseases have been detailed in previous Advices of the committee, and require for the next 5 years in the current French context :

- **the health care system**: to strengthen the health care system **before the crisis hits,** so that it is not overwhelmed by slight health risks, and to take and strengthen all preventive measures to limit the burden of disease,
- **mental health,** particularly among young people, and the risks of infodemia in crisis situations: to strengthen studies in the social sciences and humanities and the preventive management of psychological disorders.

Concerning the diseases with a high potential of triggering an exceptional health situation, recommendations have been detailed in previous COVARS Advices and require in particular for**:**

- **Pandemic zoonotic influenza**: monitoring inter-mammalian and inter-species transmission events, and recombination (pig/avian virus), improving prediction models, and researching, innovating and preparing vaccines and treatments.[195]
- **Pandemic coronavirus infections**: monitoring animal reservoirs, developing eco-epidemiology, maintaining and developing research into prevention, treatment and social and human sciences in particular.[196]
- **Dengue**: develop: i) LAV alternatives, in particular using TIS and boosted TIS methods, ii) antiviral treatments, iii) management and monitoring tools for operators, iv) and strengthen vector risk modelling work. [197]
- **West Nile infection:** supporting research and integrated One Health surveillance, monitoring ecosystems where reservoirs, vectors and exposure sites and conditions live, improving or developing specific viral diagnostic tests in mosquitoes, developing antivirals, etc.
- **ARIs**: Prevent ARI through vaccination by providing consistent and transparent information to healthcare professionals and the general public, and by organising and facilitating the vaccination process[198] .
- For all these risks: preparing for the prevention of **psycho-social risks**.

For diseases with a more moderate risk of exceptional health situation:

- **CCHF, TBE and FVR**: develop eco-epidemiological and sociological work to estimate the risk of emergence in animals and humans, develop work on the competence and dispersion of the vectors present by integrating the effects of climate change (targeted surveillance and participative approach), step up research into antiviral treatments**.**
- **Antimicrobial resistance**: strengthening prevention and training programmes to limit the use of antibiotics,

[195] https://sante.gouv.fr/IMG/pdf/avis_du_covars_du_8_juin_2023_-_risque_sanitaire_lie_a_l_iahp_et_la_grippe_aviaire.pdf
[196]https://sante.gouv.fr/IMG/pdf/avis_du_covars_du_20.10.2022_sur_le_covid-19.pdf
[197]https://www.enseignementsup-recherche.gouv.fr/sites/default/files/2023-04/avis-du-covars-du-3-avril-2023---risques-sanitaires-de-la-dengue-du-zika-et-du-chikungunya-en-lien-avec-le-changement-climatique-27356.pdf
https://sante.gouv.fr/IMG/pdf/covars_document_de_cadrage_du_23.12_2022_sur_les_maladies_a_transmission_vectorielle_mtv_en_france.pdf
[198] https://sante.gouv.fr/IMG/pdf/avis-14-decembre-2023-covars-campagne-de-prevention-de-covid-et-infections-respiratoires-aigues.pdf

- **STIs**: strengthening early detection and treatment programmes, and prevention and public information programmes,
- **HIV/AIDS**: maintaining access to universal treatment and increasing the level of information available to young people.

More generally, preventing and preparing for major and exceptional health situations requires a "One Health" vision, at the local, national and international level, integrating the stages of knowledge acquisition/research, biomonitoring of people, wildlife and the environment, understanding the dynamics of exposure and implementing relevant interventions:

- **Anticipate/prepare for the inter-crisis period** by organising, preparing and installing tools through basic and clinical research, development of innovative diagnostic capabilities and non-pharmaceutical and pharmaceutical response elements, in order to have the capacity to use responses in real time at the start of a crisis,
- **Support and strengthen surveillance systems** at national and international level (see below) in all their dimensions (epidemiological, microbiological, etc.) to guarantee optimal capacity to detect, characterise and measure the impact of major and exceptional health situations, and to facilitate the feedback, matching and sharing of data in a reactive manner, as well as the capacity to scale up an activity in times of crisis, both at the level of surveillance agencies and reference centres and laboratories.
- **Organising collective support** for **the health response and the fight against infodemia**, by building **mutual trust between the public, scientists and politicians** and by taking into account social, economic, environmental and political factors. Transparency in the decision-making process is essential to ensure that the risk is appropriate and understood, integrating a holistic vision of the response. The quality of support for the response requires an understanding of science and of responses to the crisis based on rational elements. This acculturation, which concerns decision-makers, healthcare professionals and the general public alike, requires a long-term approach involving the introduction of public health and climate education into healthcare training and throughout school curricula, and transparent exchanges between scientists, political decision-makers, associations with specific expertise and the general public**.**
- **Take into account the vulnerability** of certain regions and populations at risk, with a view to ensuring equal access to healthcare throughout the country, particularly in French overseas territories, by preparing early interventions targeted at vulnerable populations, and in particular by strengthening the resilience of vulnerable communities.
- **Integrate climate change, pollution and the biodiversity crisis** with health issues in all sectors, promoting preventive and adaptive behaviour.
- **Evaluate and analyse the response and its temporality**: to determine whether the residual risk of the impact is lowered by prevention or preparation for the risk and whether the temporality of the response to an effective major and exceptional health situations concerns the short and long term.
- **Integrate research into all stages of** a health crisis (prevention, preparation, management) to produce the knowledge needed to better prevent other major and exceptional health situations.

B- Carry out urgent intersectoral research on the health risks induced by environmental changes

Efforts are already underway in France with PEPRs on emerging pathogens, coordinated by ANRS-MIE, and on zoonoses with the Prezode PEPR, coordinated by INRAe, IRD and CIRAD.
However there is still an **urgent need to strengthen** this research and prepare ambitious **multidisciplinary and cross-sectoral** programmes, bringing together health and environmental research. The setting up of **the new Programme Agencies** is an opportunity not to be missed to strengthen these programmes, provided working in “silos” is avoided : the "health", "agriculture-food, natural resources" and "biodiversity and sustainable society" agencies must work together for One Health and Exposome approaches, following in particular the recommendations of several national research bodies:

- **ANRS-MIE**[199] on a family approach to pathogens likely to emerge, involving fundamental, clinical and societal research,
- **IRD** and **CIRAD**'s "Research-Action" projects, particularly at local level, to better understand and control animal-human transmission cycles within the ecosystem and to increase the participation of society, based on international collaboration, particularly with countries in the South where zoonotic emergencies are major.
- **Inserm report** on pesticides from 2013[200] stressing the importance of periodically re-evaluating knowledge in this field, as **strong presumptions of links between certain pathologies and exposure to pesticides** should guide public action towards better protection of the population,
- **INRAe and IFREMER:** stressing the need for long-term monitoring and research to establish links between the **exposome and health**, through stable calls for tender,
- **CNRS**[201] with 3 scientific priorities until 2030: i) **understanding** the mechanisms by which pathogens and hosts evolve, and the effects of anthropogenic changes on pathogen emergence; ii) **searching the links** between socio-ecosystems and chronic non-infectious diseases; iii) **setting up long-term monitoring** of population health and facilitating access to large databases and tools for managing, analysing, modelling and interpreting data.

In light of the major and exceptional sanitary situations risks identified, the COVARS recommends:

- **Improving French researchers' access to integrated health surveillance and research databases, and developing projects involving the human and social sciences,** subjects that will be addressed in future COVARS opinions.
- **Plan major cross-sectoral and integrated lines of research, enabling a holistic approach to major and exceptional health situations risks,** taking into account the need for a **One Health** vision and the **'Exposome'** concept**,** in particular by :
    - Identifying the different factors involved in the emergence process,
    - The study of the Resistome (antimicrobial resistance and other resistances),
    - The study of health risks due to pollution by chemical pollutants (including plant protection products) and its health impact.

The complexity of exposure to risks of composite origin and the difficulty of identifying truly significant associations and the mechanisms of action involved, mean that these programmes need to be significantly strengthened, with both short- and long-term issues at stake, and innovative methodologies need to be developed to produce new series of reliable data.

These research programmes should be seen as an integral part of preparing for health risks (including major and exceptional health situations), some of them should be supported for longer than the usual funding periods, and should be conducted in France and at European level.

C- Multilateral organisation of the Preparation

Health risks of infectious and environmental origin know no borders for the most part, even if they do have territorial specificities, and require urgent preparedness actions which, to be fully effective, must be thought out, financed and carried out not only on a French scale but also on a multilateral scale:

- **In Europe** :
    - **Strengthening One Health and Exposome international health monitoring,** in particular at SpF in conjunction not only with the ECDC, but also with the national animal health epidemio-surveillance platform (PNESA) and animal and human health research bodies, to ensure **strong interaction between research and monitoring** of major health risks, as well as methods for early detection of emerging diseases (health databases, informal information searches on the Web, visualisation methods, modelling, diagnostics, etc.**).**

[199] ANRS-MIE (2022), List of priority pathogens, available here: https://www.infectiologie.com/UserFiles/File/renarci/liste-des-pathogenes-prioritaires-rech-mie-2023-2.pdf
[200] Inserm (2013), Pesticides: health effects; available here: https://www.inserm.fr/expertise-collective/pesticides-effets-sur-sante/
[201] CNRS (2023) Prospectives écologie et environnement, available here: https://www.inee.cnrs.fr/fr/prospectives-cnrs-ecologie-environnement-2023

- **Propose a European framework for the co-production of indicators**[202] in order to support **risk reduction and monitoring** policies and gain a better understanding of climate-related areas of vulnerability at the interface between humans, animals and the environment by :
  - The co-development of early warning and response systems to assess the costs and benefits of climate change adaptation policies, improve the resilience of health systems at regional, national and international levels, and define new opportunities for action,
  - A strong commitment at all levels to a "One Health" vision
  - An improvement in knowledge levels.
- **Strengthen European initiatives for an integrated approach to human and animal health,** climate, ecotoxicity and biodiversity, in particular :
  - The Task Force of European health agencies (European Environment Agency (EEA), European Centre for Disease Prevention and Control (ECDC), European Chemicals Agency (ECHA), European Medicines Agency (EMA)) set up to strengthen their scientific recommendations as part of an integrated One Health approach.
  - DG HERA (European Health Emergency Response and Preparedness Authority), which was very useful during the Covid-19 crisis, but is still very much focused on human health and needs to open up to a One Health vision of infectious and environmental risks.

- **Internationally :**

There is an urgent need to strengthen the coordination of preparedness for major health, infectious and environmental risks and to support initiatives such as:

- **The WHO**, which is coordinating the negotiation of an agreement on the prevention of pandemics[203] and has set up the Alliance for Transformative Action on Climate and Health (ATACH), to define a common agenda of rapid and far-reaching priority actions at all levels, to collect reliable and relevant data, to set up quality indicators for the actions taken, to finance needs and to share knowledge.
- **Taking health into account at the COPs,** with the first health day at COP 28 on climate and the declaration on climate and health signed by 143 countries committed to integrating climate and health within a One Health framework for mutual benefit[204], and the biodiversity COPs which, since COP 15, have included a debate on One Health[205]. It is vital to encourage these two COPs to work together on the climate-biodiversity-health nexus.
- **France:** which launched the international Prezode initiative (Preventing zoonotic disease emergence).

[202] J Rocklov et al (2023) The Lancet Regional Health - Europe 32: 100701 https://doi.org/10.1016/j.lanepe.2023.100701
[203] Revised draft of the negotiating text of the WHO Pandemic Agreement https://apps.who.int/gb/inb/pdf_files/inb9/A_inb9_3-en.pdf
[204] https://www.who.int/publications/m/item/cop28-uae-declaration-on-climate-and-health
[205] https://ici.radio-canada.ca/nouvelle/1941908/cop15-sante-bienfaits-biodiversite-cadre-mondial-negociations-montreal

V- Conclusions and outlook

This initial analysis of major and exceptional sanitary situations risks over the next 5 years in France enables COVARS to propose **short-term responses (2-5 years)** to infectious risks, mainly linked to zoonoses, and to environmental factors, mainly linked to climate change and atmospheric pollution, without minimising the permanent chemical health risks which are more difficult to quantify. These analyses converge with the conclusions of other organisations working for different objectives, and should be considered in the light of current knowledge, which is still fragmentary, on health risks linked to infections and above all to the environment. The COVARS' assessment of major and exceptional health situations risks should help to identify the objectives of:

- **Pandemic preparedness and contingency planning for epidemic emergencies,** with frequent updates serving as an essential benchmark for preparing emergency and crisis plans.
- **Protection against environmental risks and physical and chemical pollution.**
- **Research, to better prepare for crises** by stepping up scientific examination of psycho-social risks in the various territories, classes of pathogens likely to induce major and exceptional health situations, prevention and treatment measures and mechanisms of resistance to these countermeasures, as well as the effects and mechanisms of action of chemical products on health.
- **Public policy**, to support decisions on a rational and scientific basis, enabling effective major and exceptional health situations **prevention** measures to be implemented.
- **Communicating and raising awareness** of risks among the general public, healthcare professionals and public policy decision-makers, thereby encouraging greater support for risk preparedness and faster response in the event of an emergency.

The goal of prevention must not be limited to the organisation of care, but requires a genuine programme of investment in prevention and research in order to limit the massive human, social and economic costs of dealing with pandemic crises, costs that cannot be reduced simply by anticipating them.

This integrated overview of infectious and environmental risks should lead to more in-depth risk mapping work, linking infectious and environmental risks within the framework of multi-stakeholder workshops, coordinated between agencies and supported by human resources.

This analysis must continue over the longer term: major and exceptional health situations are not just about the acute and sudden emergence of infectious agents, but also include the consequences of progressive evolutionary processes that are often difficult to analyse and for which certain thresholds may prove critical.

This first mapping exercise should be the start of an ongoing process of updating, incorporating the acquisition and development of knowledge, rather than a one-off process, as some countries and international organisations are already doing. The performance of risk mitigation strategies should be monitored throughout the mapping process in order to visualise the preventive measures put in place to reduce the impact or level of risk.

Preventing these major and exceptional health situations means quickly realising the close link between infectious and environmental threats and the potential co-benefits that controlling and preventing known infectious and environmental risks would bring.

Annexes

Annexe 1: Tableau de synthèse des priorisations françaises et de l'OMS de risques infectieux :

Pathologies infectieuses	**OMS**		**HCSP Maladies Infectieuses prioritaires)**	**IRS-MIE** (Pathogènes emergents)
	2018	**2023**		
Echelle	1-10	1-11	1-19	1-16
Fièvres Hémorragiques Virales			**1**	
Ebola, Marburg (FiloVirus)	**2**	**3**	1	7
Lassa (Arenavirus)	**3**	**4**	1	11
Fievre de la vallée du Rift (PhléboV)	**6**	**7**	1	4
Viroses Respiratoires Aigues hors grippe			**2**	
Covid-19 et CoronaV émergents		**1**	**6**	2
MERS & SARS (CoronaV)	**4**	**5**		2
Influenza zoonotique (OrthomyxoV)			**4**	1
Grippe saisonniere (OrthomyxoV)			**5**	1
VRS			**7**	
Arboviroses (dont Dengue)			**3**	
Fièvre hémorragique Crimée-Congo (CCHF) (NairoVirus)	**1**	**2**	1	4
Zika (Flavivirus)	**7**	**8**	3	9
Chikungunya (Togavirus)			3	15
Infection à virus **Nipah** (ParamyxoV)	**5**	**6**	1	
Maladie X	**8**	**9**		
Maladie de Creutzfeld-Jakob			**8**	
Inf systémiques **Multirésistantes**			**9**	
Inf BHRe			**10**	
Infections Invasives à **Méningocoques**			11	
Rage (Rhabdoviroses)			12	
Tuberculose			13	
Infections Invasives à **Pneumocoques**			14	
Peste *(Y. pestis)*			15	
Mycoses invasives			16	
Infections Severes à **Enterobactéries**			17	
Gastro-Enterites (RotaV)			18	
Tuberculose XDR			19	

Annexe 2: Classifications de risques d'autres agences

Classification du HCSP – Source : HCSP, Liste de maladies infectieuses, 27/10/2023

Tableau 4 : résultat du classement des maladies infectieuses (hors maladie X) de M1 à M94. Les couleurs rouge, jaune et verte de fond de trame des cellules sont à mettre en relation avec celles des barres d'histogramme de la Figure 5.

Pathologie	Score total sur une échelle de 0+ à 100	Dissensus entre experts
M1- Fièvres hémorragiques virales (Ebola, Marburg, Lassa, Nipah, Hendra, Arénavirus du nouveau monde, fièvre hémorragique Crimée-Congo, Omsk...)	62,92	3,19
M2- Viroses respiratoires aiguës (hors grippe) : entérovirus, coronavirus saisonniers, virus parainfluenza humains (hPIV 1,2,3,4), rhinovirus humains (hRV A, B, C)	56,97	2,41
M3- Arboviroses transmises par les moustiques : Chikungunya, dengue, fièvre jaune, encéphalite japonaise, fièvre de la vallée du Rift, West Nile, Zika, ...	55,67	2,02
M4- Infections à virus influenza à potentiel zoonotique	55,19	2,58
M5- Grippe saisonnière à virus influenza A et B	53,68	2,11
M6- Infections à coronavirus émergents (SARS, MERS, Covid-19)	49,28	1,57
M7- Infections respiratoires à virus respiratoire syncytial A et B et à métapneumovirus A et B	48,63	2,40
M8- Maladie de Creutzfeldt-Jakob et autres ESST humaines	48,01	1,06
M9- Infections systémiques à bactéries multirésistantes, dont : *Acinetobacter baumannii*, *Burkholderia cepacia*, *Pseudomonas aeruginosa*, ...	46,93	2,12
M10- Infections à bactéries hautement résistantes émergentes (BHRe)	45,45	2,75
M11- Infections invasives à *Neisseria meningitidis*	44,82	1,09
M12- Rage	44,32	1,01
M13- Tuberculose (*Mycobacterium tuberculosis* sensible aux antituberculeux)	43,74	1,59
M14- Pneumococcies invasives	43,33	1,35
M15- Peste (*Yersinia pestis*)	39,84	0,75
M16- Mycoses invasives à levures et à champignons filamenteux : *Candida*, *Aspergillus*	39,55	1,57
M17- Infections graves à *Enterobacterales* (ex-entérobactéries)	38,68	0,34
M18- Gastro-entérites à rotavirus	37,91	0,72
M19- Tuberculose (*Mycobacterium tuberculosis* R-R, MDR et XDR)	37,22	1,58
M20- Tétanos (*Clostridium tetani*)	37,17	0,46
M21- Gastro-entérites virales (hors rotavirus) : astrovirus, norovirus, sapovirus, ...	37,09	1,92
M22- Listériose	36,92	2,17
M23- Infections invasives à *Staphylococcus aureus*	36,80	1,43
M24- Mycoses invasives tropicales : *Blastomyces*, *Coccidioides*, *Histoplasma*, *Cryptococcus* ...	36,14	1,13
M25- Mélioïdose (infections à *Burkholderia pseudomallei*)	35,95	0,64
M26- Rougeole	34,85	2,14
M27- Infections cutanées d'origine aquatique (*V. vulnificus*, *Aeromonas*, *Mycobacterium marinum*, *Shewanella sp.*)	33,61	1,42
M28- Infection à HIV	32,80	1,82
M29- Gastro-entérites alimentaires/toxi-infections alimentaires : *B. cereus*, *Campylobacter sp.*, *Arcobacter*, *C. perfringens*, *E. coli*, S.non typhiques, *Shigella spp.*, *Yersinia sp.*, *Vibrio parahaemolyticus*	32,06	0,86

Classification de l'INVS – Source : Institut de Veille sanitaire (2009), Définition des priorités dans le domaine des zoonoses non alimentaires

Classement des maladies par groupe de priorité – Rapport priorisation des zoonoses 2009

Prioritaires	Importantes	Moyennement importantes
Borréliose de Lyme	Encéphalite à tiques	Anaplasmose humaine
Chikungunya	Fièvre jaune	Babésiose
Dengue	Fièvre Q	Bartonelloses
Fièvre Crimée-Congo	Fièvre de la Vallée du Rift	Ébola
	Psittacose	Fièvre boutonneuse méditerranéenne
	Tularémie	Fièvre hémorragique de Marburg
		Fièvre de Lassa
		Hépatite E
		Rickettsioses (autres)
		Typhus exanthématique

Classification de l'ANRS – Source : https://www.infectiologie.com/UserFiles/File/renarci/liste-des-pathogenes-prioritaires-rech-mie-2023-2.pdf

VIRUS

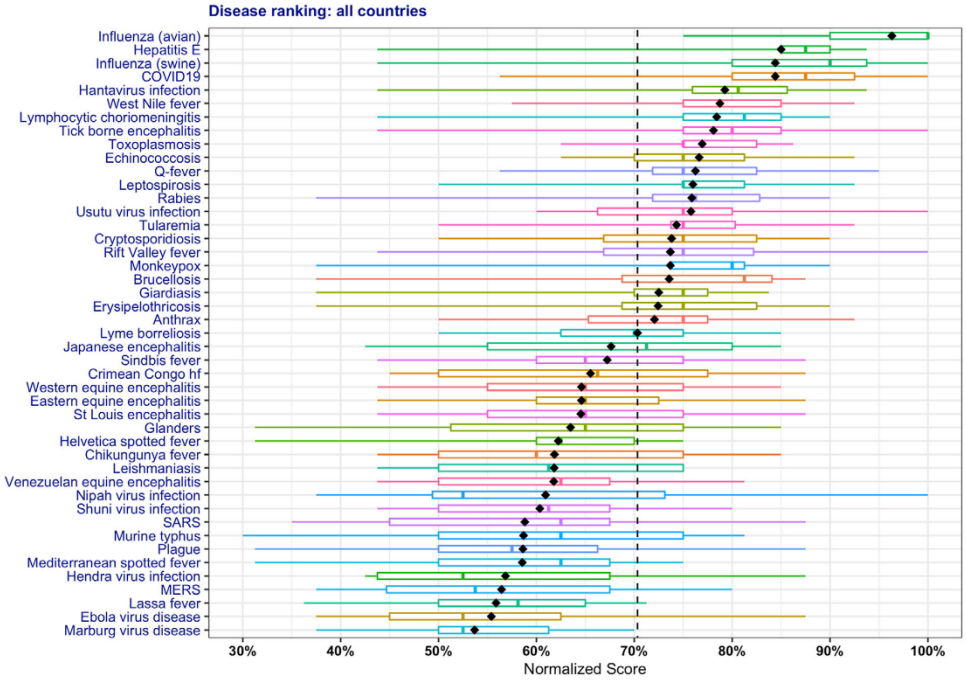
- Arenaviridae : Genus Mammarenvirus (Lassa virus)
- Nairoviridae : Genus Orthonairovirus (Crimean Congo Hemorrhagic Fever virus)
- Phenuiviridae : Genus Phlebovirus (Rift Valley Fever virus)
- Hantaviridae : Genus Orthohantavirus (Andes & Sin Nombre viruses)
- Coronaviridae
- Filoviridae (Ebola & Marburg viruses)
- Flaviviridae : Genus Flavivirus (Zika, Dengue, Fièvre jaune & West Nile viruses)
- Orthomyxoviridae (Influenza viruses)
- Pneumoviridae (RSV)
- Paramyxoviridae (Nipah & parainfluenza viruses)
- PoXviridae (Monkeypox & Camelpox viruses)
- Togaviridae (Chikungunya virus)

BACTERIES

- *Francisella tularensis tularensis*
- *Yersinia pestis*
- *Bacillus anthracis*
- *Burkholderia mallei*

PATHOGENE X

Classification de l'EFSA – Source : European Food Safety Authority (EFSA); Berezowski J et al (2023) Prioritisation of zoonotic diseases for coordinated surveillance systems under the One Health approach for cross-border pathogens that threaten the Union. EFSA J. 2023 Mar 3;21(3):e07853. doi: 10.2903/j.efsa.2023.7853. PMID: 36875865; PMCID: PMC9982565.



Annexe 3 : Tableaux d'intensités des risques liés à 34 maladies infectieuses en fonction de 16 critères : 3A : en Hexagone/Corse : (voir légende en page 67)

Critères de risque / Contaminations/ Pathogènes	*Risques épidémiologiques*			*Risques cliniques*				*Existence de contre-mesures*				*Impact*			
	Possibi-lité de surve-nue §	Potentiel d'augmen-tation du risque d'émer-gence	Expansion géogra-phique et potentiel épidémique*	Impact clinique indivi-duel	Létalité indivi-duelle	Létalité morbidité Groupes à risque	SPI ou séquel-les (=)	Con-trôle °°	Préven-tion ++	AMR ou Résistan-ce aux mesures de lutte	Absence de plan ou règlement **	Systè-me de soins	Psycho-sociaux !	Econo-mique °°°	Sur le écosy tème
Grippe pandémique zoonotique															
Nouveau coronavirus pandémique															
IRA (grippe, VRS, Covid															
Tuberculose XDR															
Peste															
F .de Lassa															
F. Ebola, Marburg															
CCHF															
Dengue															
West-Nile															
Usutu															
Chikungunya															
Zika															
Fièvre Jaune															
Paludisme															
F. Vallée du Rift															
Lyme															
Leptospirose															
Nipah															
Hantavirus															
Méningocoque															
Poliomyélite															
Enc. à tique															
Rage															
mPOX (Autre)															
Rougeole															
SIDA															
IST émergentes ou résistantes hors VIH															
Vibrios															
Cholera															
TIAC															
Gastro-entérites virales															
Hépatite E															
Bactéries MDR et BHR															

3B : en Outremer : : (voir légende en page 62)

Critères de risque / aminations/ nogènes	*Risques épidémiologiques*			*Risques cliniques*				*Existence de contre-mesures*				*Impact*				
	Probabilité de survenue §	Potentiel d'augmentation du risque d'émergence	Expansion géographique et potentiel épidémique*	Impact clinique individuel	Létalité individuelle	létalité et morbidité des groupes à risque	SPI ou séquelles (=)	Contrôle °°	Prévention ++	AMR ou Résistance aux mesures de lutte	Absence de plan ou règlement **	Système de soins	Psychosocial	Economique °°°	Sur les écosystèmes	Des mesures de lutte
e pandémique otique																
eau coronavirus émique																
grippe, VRS,																
rculose																
Lassa																
rburg et Ebola																
ue																
-Nile																
ngunya																
ion Zika																
e Jaune																
isme																
la Vallée du																
liose de Lyme																
spirose																
ion à avirus																
ngocoque																
myélite																
phalite à tiques																
X (autres POX)																
eole																
mergentes ou antes hors VIH																
s																
era																
o-entérites																
tite E																
ries MDR et e																

Légende du tableau 1 :

§ Présence ou potentiel d'introduction ou d'émergence ou de circulation autochtone

° Potentiel d'augmentation du risque d'émergence ou d'introduction/extension lié au changement climatique, à la pollution, à la perte de biodiversité

** Potentiel d'extension géographique et épidémique intégrant le mode de transmission et le potentiel évolutif de l'agent*

= Syndrome Post-Infectieux (SPI) ou séquelles

°° Indisponibilité ou impossibilité de mise en oeuvre des contre-mesures pharmaceutiques ou non pharmaceutiques pour le contrôle

++ Indisponibilité ou impossibilité de mise en oeuvre des contre-mesures pharmaceutiques ou non pharmaceutiques pour la prévention

*** Absence de plan ou de réglementation régionale, nationale ou internationale*

! Impact social incluant (santé mentale, risque de stigmatisation, etc.)

°°° Impacts économiques (Arrêtés de travail, tourisme, secteur animalier)

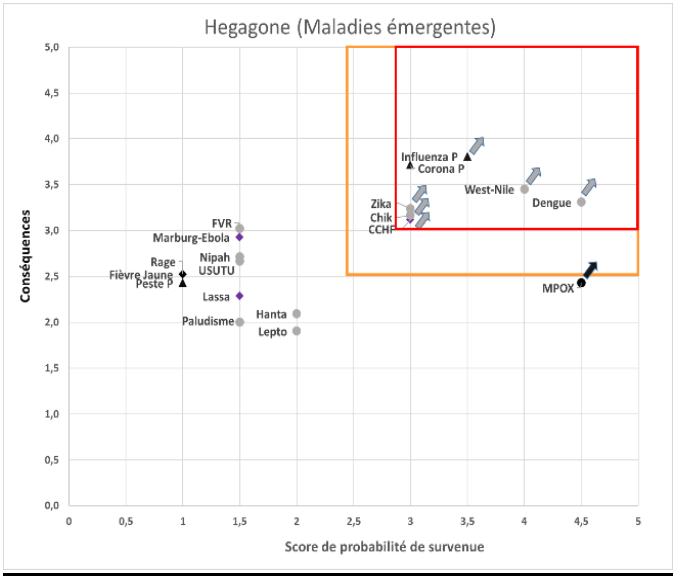
+++ Impact des contre-mesures (économiques, sociétales, environnementales)

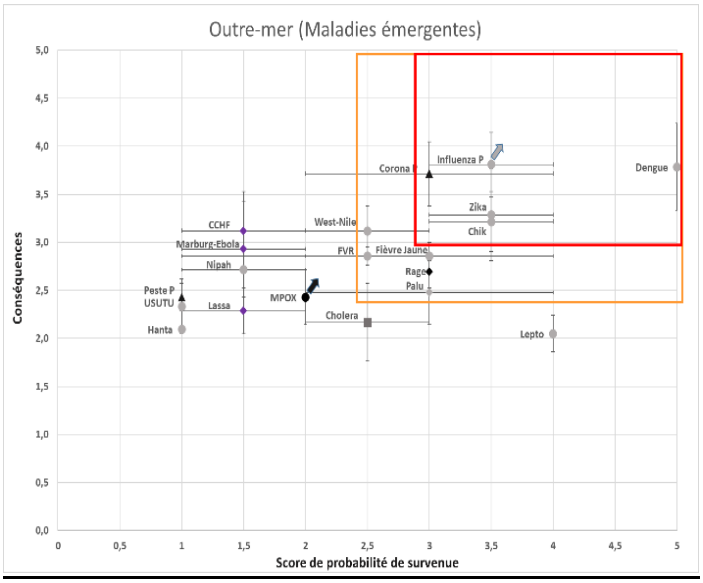
Intensité des risques : majeur (rouge, note de 5), élevé (orange, 4), moyen (jaune, 3), faible (vert, 2), négligeable (bleu, 1). A noter que les maladies apparaissent dans l'ordre suivant : infections respiratoires (jusqu'à la Peste), fièvres hémorragiques virales (jusqu'au CCHF), maladies à transmission vectorielle (jusqu'à l'Hantavirus), infections neurologiques (jusqu'à la Rage), infections muco-cutanées. (jusqu'aux « autres IST »), les infections digestives (jusqu'aux bactéries multirésistantes et aux bactéries émergentes hautement pathogènes).

A noter que le graphique représente les valeurs maximales attribuées à chacun des risques

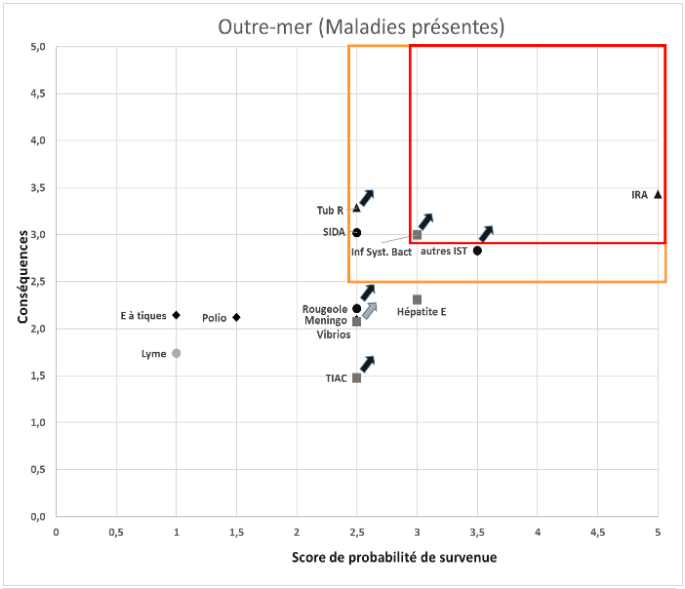
Annexe 4: Score de Probabilité de survenue en fonction des Conséquences des maladies infectieuses pour les :

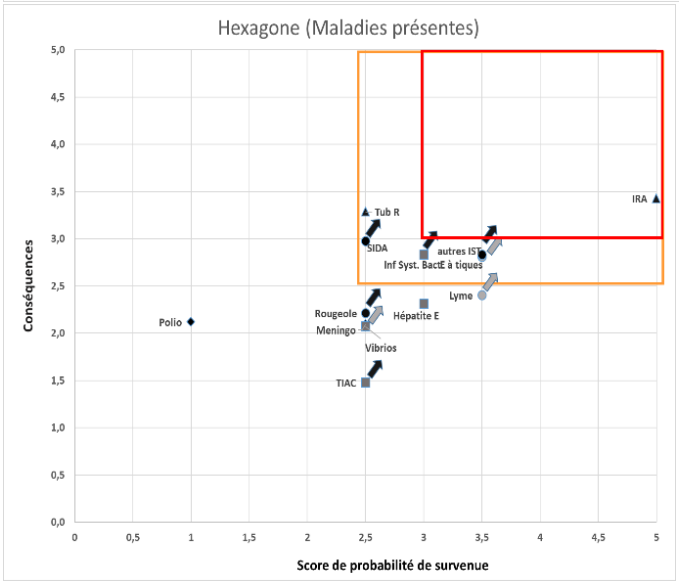
4A : <u>Pathogènes émergents</u>





4B : Pathogènes présents sur le territoire national

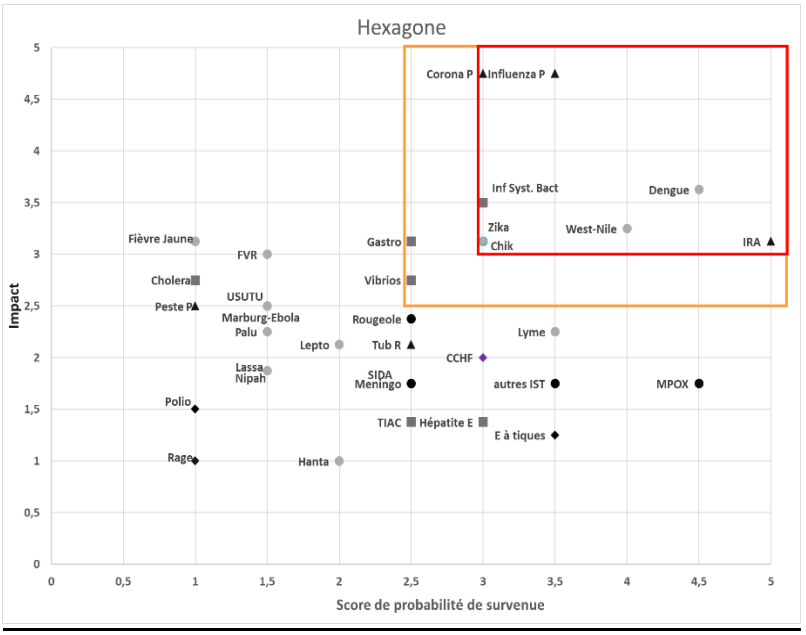


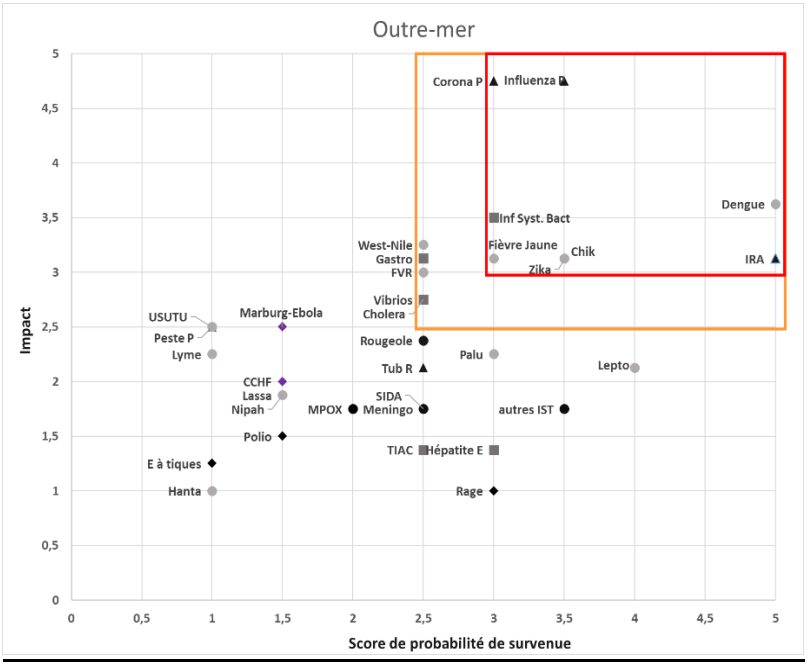


Légende : Les Rectangles Rouges et Oranges identifient les risques Majeurs et modérés de SSE; Les flèches représentent un « risque d'augmentation » élevé ou majeur (grises: facteurs de risque d'origine environnementale, noires: facteurs de risque géopolitique); Les marqueurs permettent de distinguer les maladies à transmission vectorielle (rond gris) et classent les autres maladies infectieuses par approche syndromique (triangle noir pour les infections respiratoires , losange violet pour les Fièvres hémorragiques virales ; losange noir pour les infections neurologiques; rond noir pour les infections cutanéo-muqueuses, carré gris foncé pour les infections digestives

Annexe 5: Score de Probabilité de survenue de maladies infectieuses en fonction de leurs Impacts

(Moyenne des impacts sur le système de soins, sur la situation socio-économique, sur la santé mentale, sur les écosystèmes et également impact des contre-mesures éventuelles sur les écosystèmes)





Légende : Les Rectangles Rouges et Oranges identifient les risques Majeurs et modérés de SSE; Les flèches représentent un « risque d'augmentation » élevé ou majeur (grises: facteurs de risque d'origine environnementale, noires: facteurs de risque géopolitique); Les marqueurs permettent de distinguer les maladies à transmission vectorielle (rond gris) et classent les autres maladies infectieuses par approche syndromique (triangle noir pour les infections respiratoires , losange violet pour les Fièvres hémorragiques virales ; losange noir pour les infections neurologiques; rond noir pour les infections cutanéo-muqueuses, carré gris foncé pour les infections digestives