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Impacts on Human Health Potentially Caused by Exposure to an Unprecedented Ostreopsis spp Bloom in the Bay of Biscay, French Basque Coast

Paradis Camille [1, *], Chomerat Nicolas [2], Vaucel Jules-Antoine [1], Antajan Elvire [3], Labes Patrice [4], Rappoport Marc [5], Labadie Magali [1]

[1] Centre Anti-Poison de Nouvelle-Aquitaine, Bordeaux University Hospital, 33076, Bordeaux, France
[2] Ifremer, LITTORAL, 29900 Concarneau, France
[3] Ifremer, LITTORAL, 33120 Arcachon, France
[4] Urgences SAMU-SMUR, Centre Hospitalier de la Côte Basque, 64100, Bayonne, France
[5] Médecine interne, Saint-Palais Hospital - Donapaleuko Ospitalea, 64120, Saint-Palais, France

* Corresponding author : Camille Paradis, email address : camille.paradis@chu-bordeaux.fr

Abstract :

Introduction

In recent years, climate change and human activity have modified marine biotopes, including the widening distribution of harmful algal blooms (HABs). Bloom events predominated by microalgae of the genus Ostreopsis have been described on the French Mediterranean coast, but in 2021 an unprecedented bloom occurred on the French Basque coast. The objective of this study is to describe the health impact of the Ostreopsis spp bloom that occurred on the French Basque coast in 2021.

Methods

A historical cohort was conducted, including cases of possible exposure to Ostreopsis spp registered at the Centre Antipoison de Nouvelle-Aquitaine between July 1 and September 30, 2021.

Results

Of 674 patients with possible toxicity due to Ostreopsis spp, 96.9% had bathed in contaminated waters. Most of them developed respiratory tract symptoms (64.4% of patients). The time to the onset of symptoms was <6 h for 73.6% of 174 short-term (<24 h) exposed patients. The median duration of symptoms was 7.5 days for occupational (e.g., lifeguards and surfing instructors) and 3 days for recreational exposures. There were no severe cases. In total, 3% of the cases were of moderate severity, and 97% were of minor severity, according to the Poisoning Severity Score.

Conclusion

Toxic reactions caused by Ostreopsis spp are mostly benign. The clinical picture is similar to that described following exposures to Ostreopsis cf. ovata blooms in the Mediterranean area since the end of

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the 20th century. Ostreopsis spp are present on the Basque coast. The ecological factors promoting its blooms remain to be clarified.

Keywords : algal bloom, marine toxins, ovatoxin-a, respiratory tract, Ostreopsis, dinoflagellate

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Introduction

Climate change and human activity are adversely affecting the marine biotope, including the widening of the distribution of harmful algal blooms (HABs) [1]. In the 2000s, HABs of the microalgal genus *Ostreopsis* were recorded in several areas of the Mediterranean coast [2,3], including along the Genoese coast in 2005 [4,5], Algerian coast in 2009 [6], Croatian coast [7], Catalan coast and Balearic Islands [8] and in the Tyrrhenian Sea [9], where such events had not been observed previously. Similar observations have been reported from Brazil and New-Zealand [10,11]. Bloom events predominated by *Ostreopsis* spp. have recently been reported in the Atlantic Ocean [12–14]. In 2021, a massive HAB, reported by the present authors, occurred in the waters of French Basque Country [15].

Microalgae of the genus *Ostreopsis* are dinoflagellates (Alveolata) of the order Gonyaulacales and are closely related to other toxic genera, including *Alexandrium* and *Gambierdiscus*, which are also neurotoxin-producers.

In the following, we describe a toxic outbreak of *Ostreopsis* spp. on the French Basque coast, during the summer of 2021, including the features of the HAB and the clinical characteristics of the affected individuals. This outbreak was mentioned in a previous paper, reporting the analytical aspect of the 2021 bloom [15]. During this event, the regional health agency had opened an information page on its website, where press releases and the standardized reporting form were available. The local press also reported on the issue.

Method

The study was based on a prospective cohort, using information received by medical professionals of the Centre Antipoison de Nouvelle-Aquitaine along three month; regarding potential cases of exposure to *Ostreopsis* spp. the Basque coast. Cases likely to be exposed to

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Ostreopsis spp. were reported spontaneously by telephone or email to the Regional Poison Control Center (Centre Antipoison de Nouvelle-Aquitaine), the Regional Health Agency, the Emergency Medical Aid Service (Service d'Aide Médicale Urgente [SAMU]), and on-call doctors (SOS Médecins) via the French Public Health Agency (Santé Publique France [SpF]), between July 1st and September 30th 2021. All cases were registered by the Poison Control Center (PCC) and recorded in France's national database of poisoning cases using the common information system of the French PCCs (SICAP), which registers cases of possible exposure collected by the eight PCCs in the French network. The database is authorized by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés [CNIL], accreditation no. 747735). Individual patient consent was not required for this study according to French law regarding retrospective research conforming with MR-003 (*Journal Officiel de la République Française [JORF] no. 0160 du 13 juillet 2018. texte no. 109* [16]).

Age, sex, medical history, symptoms, time of arrival at the beach, the beach or beaches frequented by the patient, the nature of the activity (e.g., swimming, walking, or surfing), recreational or occupational exposure, route of exposure (inhalation and/or cutaneous or oral), duration of exposure, ingestion of seafood products, metallic taste of the water, nature and duration of the symptoms, medical consultation and severity were recorded.

Cases were documented using a standardized questionnaire filled in either by the patients or by the physician, lifeguard, surfing instructor, etc. (Figure 1). This questionnaire was drawn up at the very start of the epidemic by the poison control center and the medical services of the regional health agency. It was used to systematically collect the data required for the epidemiological study. It was applied prospectively (when the person filling it in was not from the poison control center) or extensively when the person contacted the poison control center, as the data in the questionnaire are at least those collected at the time of a call to the poison control center.

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The severity of the intoxication was estimated according to the Poisoning Severity Score (PSS); a standardized and generally applicable scheme for grading the severity of poisoning allows a qualitative evaluation of morbidity and facilitates comparability of data. PSS includes five severity grades; PSS 0 (no symptoms related to the poisoning), 1 (minor symptoms), 2 (moderate symptoms), 3 (severe symptoms) and 4 (fatal poisoning) [17].

All patients were followed up 1–2 months after their intoxication. No report, granted compensation of any kind.

All patients who developed at least one symptom were included. The exclusion criteria were: a positive COVID-19 test, symptoms prior to arrival on the coast, duplicates, enquiries, cases without clinical information, and cases unrelated to *Ostreopsis* spp. possible exposure.

We calculated the frequencies of symptoms in the study population, as well as the medians of symptom onset times and duration. Statistical comparisons between different subgroups were made using a Fisher's exact test, Chi-2 test and Student t test.

Results

The Centre Antipoison de Nouvelle-Aquitaine received 830 reports during the 2021 season. 137 patients were excluded: 40 duplicates, 5 non-medical records, 2 reports concerning the Mediterranean, 1 patient tested positive for COVID-19, 85 reports without information on symptoms and 9 cases unrelated to possible *Ostreopsis* spp. exposure. Of these 688 reports, 674 were symptomatic (14 asymptomatic), and these are the ones included in the analysis.

For the entire study population and the context of potential exposure, 584 (86.6%) patients were exposed recreationally. In addition, 90 (13.4%) patients were exposed occupationally. When exposed in a professional context, there were 75 lifeguards (93%) and 6 beachfront restaurant staff (7%).

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The global sex ratio (m:f) was 1.22 (sex known for 597 patients). More specifically, in the population exposed recreationally, the sex ratio was 1.0 (sex known for 510 patients) and 4.8 for professionals (sex known for 87 patients). The difference between the two groups is statistically significant with $p < 0.001$.

The global median age was 28 years, with interquartile range [18.0; 44.8] (age known for 492 patient). More precisely; in the population exposed recreationally, median age was 30.3 [16.0; 46.5] (age known for 411 patients) and 24.0 [21.0; 30.2] for professionals (sex known for 81 patients). The difference between the two groups is statistically significant with $p < 0.001$.

Three hundred seventy five patients (63.8%) had been swimming, 258 (43.9%) had been resting/walking on the beach or nearby, 142 (24.1%) had been surfing and other exposures involved 24 patients (4.1%). The activities were known for 588 patients and may be multiple (e.g. swimming + surfing). In contrast, 99 patients had a single activity; 52 patients (8.8%) swam, 24 patients (4.1%) surfed, 22 patients (3.7%) rested/walked on the page or its surroundings and 1 patient (1%) did other activities.

The exposure was *via* respiratory and cutaneous routes (including people who have swum) in 96.3%, while 3.7% were *via* the respiratory route only (patient with a single exposure circumstance of resting or walking without swimming).

Respiratory tract symptoms affected 64.4% of the patients, experiencing a cough and symptoms of rhinopharyngitis (e.g., sore throat and rhinorrhea). Other symptoms included breathing discomfort (32.0%), eye pain (29.7%), fever (27.2%), and/or headache (26.1%). Few of our patients (8.8%), developed cutaneous symptoms of toxicity (Table 1). Associated symptoms included hyperthermia (27%), headaches (26%), myalgia (10.7%) and chills (3.3%).

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Details of symptom onset time were available for 344 patients and 174 were acutely exposed (<24h). For patients with acute exposure, it was less than 6 hours for 124 patients (73.6%) and between 6 and 12 hours for 16 patients (9.2%) after exposure (Table 1).

Occupational exposures resulted in more symptoms (median of 7) than recreational exposures (median of 5). The duration of symptoms was also significantly ($p < 0.001$) longer in patients with occupational than recreational exposures (median of 7.5 vs. 3 days).

Of the exposed patients, 150 (22%) performed a COVID-19 test, which in all cases was negative.

We had medical history information (at least one history or no history) for 384 patients (57% of total included patients). Among them, 150 (39%) had at least one medical history (diabetes, hypertension, or asthma…etc. alone or in combination), and among these 12 (3%) were of PSS2 severity ($p < 0.05$).

A medical consultation related to symptoms of the intoxication was sought by 146 patients (22%). Two patients were hospitalized. one for pneumonia, and the other for an asthma attack; both recovered.

The first was a 71-year-old man with a history of atrial fibrillation and a COVID-19 infection in October of the previous year. He had been vaccinated for COVID-19 and his PCR test was negative. The patient was admitted to hospital for 10 days with radiographic evidence of lobar pneumonia, which progressed favourably on probabilistic antibiotic therapy. No aetiology was found. The second patient was a 16-year-old girl with a history of asthma and allergies. She stayed in hospital for less than a week for a flu-like syndrome accompanied by persistent fever. The fever finally lasted 13 days. The young patient had handled and dissected macroalgae on the beach. A local erythema was noted and she rapidly presented a clinical picture similar to that of the other patients. No aetiology was found at the time of hospitalisation, and the chest X-ray was normal, as was EBV serology. The COVID-19 test was also negative.

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There were no cases of high severity (PSS3); in 22 patients (3%) the intoxication was of moderate severity (PSS2), whereas in the majority (n = 652, 97%) it was of minor severity (PSS1).

Discussion

Exposure is not easily defined. We do not have environmental analyses for each possible exposure case. Nevertheless, given that *Ostreopsis* spp. was detected in variable concentrations at least once on each beach during this epidemic, we considered that exposure to *Ostreopsis* spp. was likely or at least possible under the conditions of inclusion. Moreover, it is impossible to exclude exposure, given the variability of concentrations during the same day and that the analyses were not daily in 2021.

The vast majority of patients were exposed recreationally. They were holidaymakers and residents who frequented the beaches in the study area. The region is very popular, with a large touristic affluence at this time of year. The coast is particularly popular as a surfing spot, which may also explain the high proportion of patients exposed in this way. For the part of the population exposed professionally, this mainly concerns lifeguards, which is to be expected since the study period overlaps with the beach surveillance period. It should also be noted that employees of seafront restaurants were also probably exposed to *Ostreopsis* spp.; furthermore, this was a population of interest for a study linking the biology of *Ostreopsis* spp. and the epidemiological aspect of exposure to these algae [18]. On the Basque Coast, the lifeguard population is currently the focus of interest for the PCC and occupational health services.

The slight male predominance observed in the overall population is in reality explained by the proportion of exposed professionals, who are almost 5 times more likely to be men.

The overall age of the patients covers a relatively wide range, but is compatible with that of beach users. However, it should be mentioned that the median age of those exposed

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occupationally is lower, with a very narrow range. This is due to the fact that this population is almost entirely made up of lifeguards, who are relatively young and in good physical condition to be able to practise their profession.

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In many cases there was more than one risk factor (e.g., surfing and then resting on the beach). Thus, in the vast majority of cases the exposure routes were combined cutaneous and respiratory routes excluding the oral route (see Limits section). Exposures solely via the respiratory route, such as walking on the beach but not swimming, were rare (3.7%) but the resulting symptomatology was the same as that of patients who had been swimming [2]. With the available information, food-borne poisonings are unlikely but cannot be discarded given that toxicological tests were not conducted.

The symptoms involved the nose and the throat, the respiratory system, and the eyes were the most commonly occurring and have been described in previous cases of *Ostreopsis* spp. intoxication in the Mediterranean. The respiratory symptoms could have resulted not only from the toxin but also from the presence of large quantities of heterologous proteins in the respiratory system following the inhalation of contaminated spray [19]. Overall, the symptoms presented by the patients were consistent with a previous Mediterranean outbreak of *Ostreopsis* spp. [2]. Although *Ostreopsis* spp. exposure may cause rhabdomyolysis in humans and mice

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[20], no patients underwent creatine phosphokinase testing. Therefore, it was not possible to determine whether any of the 10.7% of patients with mylagia, also had rhabdomyolysis.

The time to onset of symptoms was less than 6 hours in the clear majority of cases (nearly three quarters), although a few patients had a later onset. It should be pointed out, however, that the sample of patients for whom we had this information was relatively small. Data from patients with sub-acute exposure (more than 24 hours and less than 90 days) were not used for these calculations because they were generally difficult to use; in particular because these patients generally reported later, generating a significant memory bias for the time of onset of symptoms. In other series, symptoms appeared within < 4 h of exposure in the vast majority of patients. However, we used the time of arrival at the beach as a reference for dating exposure, while some patients may have reached the beach and started by resting before swimming or surfing, for example. These activities may have their own levels of exposure, which could modify the delay in the onset of symptoms. In addition, the concentrations of *Ostreopsis* spp. vary greatly during the course of a single day, particularly in relation to the tides. The duration of exposure was difficult to define. While the duration was typically very short (one swim), in a few cases there may have been multiple exposures during the same day, in which case the daily variation in algal concentrations may have played a role [21]. As cases of subacute exposure mostly involved patients with occupational exposures, for the latter group the duration was defined as equivalent to the contractual working time.

The number of symptoms reported by occupationally exposed patients was greater than that of recreationally exposed patients. This seems to be compatible with the fact that these patients are potentially exposed to higher doses of algae because they are longer exposed. With the same observations, the median duration of the four most common symptoms was about 2 days. However, for subacute exposures (e.g., those in the occupational setting), the duration of symptoms was longer, ranging from twice as long for the most common symptoms and up to 7

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days for breathing discomfort. This longer duration of symptoms could be explained by the fact that these patients are by nature exposed for more extended periods.

Information on the patient's medical history was collected for the majority of patients. It should be highlighted that patients who had at least one medical history (no matter which one) compared to those who had none; had significantly more severe clinical pictures ($p < 0.05$).

A medical consultation was necessary in 22% of cases, a proportion that still seems significant given the potential number of people exposed on Basque beaches during the summer. It is important to be aware of the pressure this can put on health professionals in the area and on hospitals, which already have to manage a higher flow of patients due to the seasonal influx of tourists.

To date, 11 *Ostreopsis* species have been taxonomically described, but molecular data suggest cryptic diversity and some ribotypes are as yet undescribed [22,23]. Among the 11 species are those able to synthesize palytoxin (PLTX) analogs, notably ovatoxins (OVTXs), which are synthesized by *Ostreopsis* cf. *ovata*, and ostreocins, synthesized by *Ostreopsis siamensis* [24–26]. The link between taxonomy and toxicity is unclear. For example, strains belonging to *Ostreopsis.* cf. *ovata*, a species detected worldwide, vary from non-toxic to highly toxic [1].

The genus *Ostreopsis* is epiphytic and grows on macroalgae attached to rocky substrates, but cells are sometimes found in the water column, a result of their detachment from the substrate due to strong wave action. Depending on the substrate, temperature, wind conditions, and water agitation, *Ostreopsis* spp. abundances can increase locally, ranging from a mucilaginous covering on rocks and macroalgae to an extensive brown foam on the water surface [15]. Blooms of *Ostreopsis* spp. are mainly associated with calm waters, higher temperatures, and high nutrient availability [27]. Basque country and North of Spain have rocky

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coasts and increasing surface (and bottom) water temperatures, above 19.5 °C for several months, which is suspected to trigger the blooms.[15]. Contamination of sea spray by the microalga can cause respiratory symptoms in beachgoers [28], including those who do not enter the water. Many patients with symptoms describe a metallic taste to the water. An additional probable route of *Ostreopsis* spp. toxicity is the consumption of contaminated fish and shellfish [29].

The bloom in August was found to contain a mixture of two *Ostreopsis* species, *O.* cf. *siamensis* and *O.* cf. *ovata*, with the latter being more abundant [15]. Previously, however, the only species present on the European Atlantic coast North of Portugal was *O.* cf. *siamensis*. Toxin profiles were also analyzed from samples collected on site and showed a mixture of the PLTX analogs: OVTX-a and OVTX-b. Analyses of a collected and cultured strain of *O.* cf. *ovata* indicated that it was capable of producing OVTX-a, -b, -c, -d, and -e. This toxin profile is similar to the profiles of species found in the Mediterranean. Two other strains of *O.* cf. *siamensis* were collected and cultured, but both were negative for the 20 tested PLTX analogs [15]. It is currently not possible to make the link between patients' symptoms and the toxins produced by *O.* cf. *ovata*, especially because it is not certain whether the symptoms are solely or partly linked to the toxins produced.

The main symptoms observed in our population were oropharyngeal pain, rhinitis and cough (Table 1). Other authors have also described these symptoms in the Mediterranean [2,3,18,30], although their proportions in their populations were different. Gallitelli *et al.* [30] reported a significantly shorter delay in the onset of symptoms than that observed here. However, we considered the start of exposure to be the time of arrival at the beach, which is perhaps a difference in method with this study. Regarding the duration of symptoms, the data seem to be consistent in general (although a little longer) than the Tichadou *et al*. study [2], but are much longer than those found by Gallitelli *et al*., who reported that symptoms generally

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lasted less than 24 hours. Overall, it can be said that the clinical pictures observed in our series of patients are similar to those observed to date in the Mediterranean; however, the onset and duration of symptoms differ somewhat. It is possible that methodological differences in data collection could explain these differences. Interestingly, in the group with occupational exposure, the clinical picture was both longer and more marked.

During the summer of 2022, *O.* cf. *ovata* was again detected on the Atlantic coast, resulting in a large number of calls to the PCC and reports to the Regional Health Agency. Causes of algal blooms in areas where they previously were unknown may include presence of suitable substrate, sea conditions (warming of deep waters, changes in turbulence, salinity, and pH) or meteorological conditions (ambient temperature, light) [1].

This toxic outbreak linked to *Ostreopsis* spp. is an emerging situation and is likely to recur, given the persistence of the identified species in Basque waters. In health terms, an assay of toxins in marine aerosol would be of great interest.

Limits

Our study had several limitations. First, because the number of cases was determined based on voluntary reports. Thus, even if the number of cases is significant, it was likely to have been underestimated; the real number of cases was probably much higher. For example, the large community of surfers along the Basque coast is highly likely to be exposed, but they accounted for fewer than the expected cases, although the local surfing associations reported many cases. Occupational exposures were also probably under-reported, as these seasonal positions are highly sought-after. Some affected workers do not provide information about their health status, likely to avoid losing their job. For example, some of them were reporting that their colleagues were sick, although we did not have their reports. Moreover, exposure is largely inevitable for seaside workers (presence on the beach for surveillance and entry into the water for rescue). It

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is possible that the relatively longer duration of the clinical pictures of occupationally exposed persons can be explained by a more important and repeated exposure.

Second, the main differential diagnosis in this period was COVID-19, although many patients tested negative. For those who were not tested, the occurrence of clustered and simultaneous cases was sufficient to instead suggest *Ostreopsis* spp. intoxication. The number of cases per beach was also recorded in our study, although this was not a reliable parameter because the total number of people visiting a particular beach varied; the time of year was noted as well. In addition, the weather at different beaches may not be the same and people who visited a beach with a lifeguard or surfing instructor may have been encouraged by that person and thus more likely to report *Ostreopsis* spp. intoxication.

Moreover, as shown in Table 1, some of the symptoms were not described using medical terminology since many surveys were filled out secondarily by lifeguards, surfing instructors, or by the patients themselves. For example, "unspecified breathing discomfort" rather than "dyspnea" was recorded when the latter was not described by a physician on site. We chose not to over-interpret these symptoms.

Besides, the description of this toxic epidemic is based on voluntary reports with symptoms chronologically and comparatively compatible with *Ostreopsis* spp. intoxication. It is true that these clinical pictures are not specific.

Then, the route of oral exposure was difficult to determine. Indeed, patients who had been swimming might have ingested small amounts of seawater, but this seemed too inconsistent to consider it an oral route. Nevertheless, we considered that only patients who had eaten seafood or indicated that they had involuntarily ingested a significant amount of seawater (e.g., surfers) were orally exposed.

Also, given the study design there may have been recall bias at the follow-up by telephone, conducted at least 4 weeks after the initial exposure.

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Conclusion

The vast majority of *Ostreopsis* spp. possible exposure and intoxications are mild, resulting in upper and lower respiratory tract symptoms. Symptoms are generally mild, rarely require hospital care, and generally resolve within a few days. Occupational exposures in seaside workers may be more severe or more persistent. To date, this is the first description of a toxic epidemic potentially caused by *Ostreopsis* spp. on the French Atlantic coast. Additional studies are needed to more accurately assess the health impact of *Ostreopsis* spp. exposures and to understand the mechanisms behind the blooms.

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Authors contributions

Study concept and design : CP, NC, ML

Data acquisition : CP, EA, PL, MR, ML

Data analysis : CP, JAV

Drafting and critical revision of the manuscript : CP, NC, ML

Approval of final manuscript : CP, NC, JAV, EA, PL, MR, ML

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Disclosure

None

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OSTREOPSIS MICRO-ALGAE

Form for reporting symptoms after potential exposure

To be sent to the Regional Health Agency (ARS) focal point by e-mail _____@ars.sante.fr or by fax to 05 67

DATE : __ /__ / 2021

CONTACT

□ Doctor □ Pharmacist □ Nurse
□ Lifeguard □ Private individual
□ Other .....
Name: .....
Phone .....

PATIENT Last name: ..... First name: .....
Sex □ M □ F Date of birth: _ _/ _ _/ _ _ _ _
Phone (preferably mobile): .....
Postcode of usual residence: _ _ _ _ _
Professional working on the beach: □ yes □ no

BEACH VISITED MAX 48H BEFORE ONSET OF SYMPTOMS (see bottom of page if more than one)

Date ..... /...../ 2021 Approximate time(s): from .....h..... to h.....
Municipality Name: ..... **Postal code:** _ _ _ _ _ **Name Beach:**.....
Swimming □ Yes □ No **Water activity** □ Yes □ No **Fishing on the beach** □ Yes □ No
Walking, resting □ Yes □ No **Other: ...**
Unusual smell of water: □ Yes, specify..... □ No
Unusual taste of water: □ Yes, metallic □ Yes, other..... □ No
Unusual appearance of water: □ Yes, colour..... □ Yes, "slimy" water □ Yes, other..... □ No

Other sick person(s) among people who visited the beach together: .....

CONSUMPTION OF SEAFOOD HARVESTED ON THE BASQUE COAST 48 HOURS BEFORE THE ONSET OF SYMPTOMS (RECREATIONAL FISHING)

Products concerned:
Date of consumption..... / ..... / 2021 Approximate time(s): from .....h..... to h.....
Date of fishing/harvest of products consumed: ..... / ..... / 2021
Municipality where the products were caught/harvested: ..... **Postal code:** _ _ _ _ _ **Name of the beach, place:** .....
Other sick person(s) among those who consumed the same products: .....

PATIENT SYMPTOMS

□ Sore throat □ Cough □ Respiratory discomfort □ Nasal irritation (rhinitis, itching)
□ Runny nose □ Nosebleed □ Nausea □ Headache □ Fever
□ Itchy or runny eyes □ Skin rash □ Itchy skin
□ Other(s): .....

Date of onset of symptoms: ..... / ..... / 2021 Time of onset of symptoms: .....h..... Duration of symptoms: □ Ongoing □ Completed, duration: .....

COVID-19 vaccination: □ Not vaccinated □ Vaccination in progress □ Complete vaccination **Negative COVID-19 test less than 72h**: □ Yes, RT-PCR □ Yes, antigenic □ No

HEALTHCARE PATHWAY

□ First aid station □ Pharmacist □ Nurse
□ Doctor □ Emergency □ Other: .....

ADDITIONAL INFORMATION

- Attendance at other beach(s) within 48 hours prior to symptoms (specify commune and range): .....
- Other environmental information (strong wind blowing from the sea to the land, strong swell,...): .....
- Other health information (history of Covid-19 (date), other history,...): .....

Figure 1. Reporting form used during the epidemic.

Table 1. Time and duration of onset of different types of symptoms (only symptoms that concerned more than 5% of patients).

		Time of onset		Duration of the symptom	
	Number (percentage)	Number reporting	Median [IQR[a]] in h	Number reporting	Median [IQR] in d
All symptoms	674 (100%)	344 (51%)	6 [2 ; 16]	416 (61.7%)	3 [1 ; 10]
Skin symptoms	59 (8.8%)	32 (54%)	8 [0.9 ; 22.9]	30 (51%)	4 [1 ; 10.8]
Skin manifestations	58 (8.6%)	31 (53%)	8 [1 ; 23]	29 (50%)	4 [1 ; 12]
Digestive symptoms	125 (18.5%)	56 (0.44)	7 [4.7 ; 19.5]	68 (54%)	3 [1 ; 7]
Nausea	88 (13.1%)	44 (50%)	6.5 [4.5 ; 21]	49 (56%)	2 [1 ; 7]
General symptoms	245 (36.4%)	135 (55%)	5 [2 ;17]	168 (69%)	3 [1 ; 7]
Hyperthermia	186 (27.6%)	103 (55%)	5 [2 ;16]	121 (65%)	2 [2 ;5]
Asthenia	78 (11.6%)	42 (54%)	7 [3.2 ; 22.1]	58 (74%)	6 [3 ; 10]
Muscle symptoms	74 (11%)	40 (54%)	8.2 [4.5 ; 21]	43 (72%)	4 [2 ; 6.8]
Myalgia	72 (11%)	39 (54%)	8.5 [4.75 ; 21]	42 (58%)	4 [2 ; 6.8]
Neurological symptoms	179 (26.6%)	88 (49%)	8 [5 ; 24]	112 (62%)	3 [1.8 ; 6]
Headaches	176 (26%)	86 (48%)	8 [5 ; 24]	110 (63%)	3 [2 ; 6]
Ophthalmic symptoms	199 (30%)	87 (44%)	5 [2 ; 11.8]	98 (49%)	4 [2 ; 10]
Eye pain	199 (30%)	87 (44%)	5 [2 ; 11.8]	96 (48%)	3 [1.8 ; 7]
ENT symptoms	580 (86%)	297 (51%)	5 [2 ; 12]	345 (59%)	3 [1 ; 7]
Oropharyngeal pain	448 (66%)	239 (53%)	6 [2.2 ; 15]	257 (57%)	3 [1 ; 7]
Rhinitis	443 (66%)	225 (51%)	6 [2 ; 16]	265 (60%)	3 [1 ; 7]
Epistaxis	39 (5.8%)	22 (56%)	5 [1.5 ; 7.8]	23 (59%)	5 [1.5 ; 7]
Respiratory symptoms	504 (75%)	118 (23%)	6 [2 ; 12.5]	312 (62%)	3 [1 ; 10]
Cough	438 (65%)	247 (56%)	6 [2 ; 12]	283 (65%)	3 [1 ; 7]
Unspecified respiratory discomfort	215 (32%)	118 (55%)	6 [2 ; 12]	127 (59%)	3 [1 ; 7]
Expectoration	43 (6.4%)	19 (44%)	5 [5 ; 10.5]	21 (48%)	7 [3 ; 7]
Anosmia	2 (0.3%)	0 (0%)	–	1 (50%)	3

[a]IQR: interquartile range.