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Infectious diseases in oyster aquaculture require a new integrated approach

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Emerging diseases pose a recurrent threat to bivalve aquaculture. Recently, massive mortality events in the Pacific oyster *Crassostrea gigas* associated with the detection of a microvariant of the ostreid herpesvirus 1 (OsHV-1 μ Var) have been reported in Europe, Australia and New Zealand. Although the spread of disease is often viewed as a governance failure, we suggest that the development of protective measures for bivalve farming is presently held back by the lack of key scientific knowledge. In this paper, we explore the case for an integrated approach to study the management of bivalve disease, using OsHV-1 as a case study. Reconsidering the key issues by incorporating multidisciplinary science could provide a holistic understanding of OsHV-1 and increase the benefit of research to policymakers.

1. Introduction

Mollusc production is increasing and has become one of the largest aquaculture activities worldwide. Molluscs are the second most abundant and valuable farmed seafood [1]. Oysters make the largest contribution, with 4.7 million tonnes per year harvested. As a result, oyster farming is an important socio-economic and cultural activity in the coastal zone. However, because it relies on natural environments, oyster farming is presently facing various risks and limiting factors, among which infectious diseases have been prominent throughout history [2–6].

In Europe, oyster farming started during the seventeenth century. This activity relied on the native species *Ostrea edulis* [2,5,6]. During the nineteenth century, unexplained mortalities, overfishing and accidental introductions of parasites such as *Marteilia refringens* and *Bonamia ostreae* led to population decline and local extinctions. In France, *O. edulis* was replaced by the Portuguese oyster *Crassostrea angulata* in 1925, but this species was wiped out by a disease caused by an iridovirus around 1970 [7]. Then Pacific oyster *Crassostrea gigas* was introduced into several European countries during the 1960s and 1970s and it became well established along the NW European coastline where this species is often considered as 'invasive' [6].

Since 2008, massive mortality events in *C. gigas* oysters have been reported in almost all farming areas in France [8–11]. These mortality events are associated with the infection of oysters with a newly described genotype (μ Var) of ostreid herpesvirus 1 (OsHV-1) [12]. The geographical distribution of OsHV-1 μ Var has expanded along the European coastline from Portugal, Spain and Italy to Ireland and up to southern Norway [13–21], and closely related variants of OsHV-1 have been detected from mortality events in Pacific oysters in Australia [22,23], New Zealand [24] and Asia [25]. A causal relationship between OsHV-1 μ Var and oyster mortality has been established epidemiologically and through experimental transmission using OsHV-1 μ Var purified from affected oysters [21,23,26,27]. The OsHV-1 virus now poses a major challenge for Pacific oyster production around the world.

In Europe, OsHV-1 spread rapidly across borders despite the existence of regulatory frameworks at international and national levels to control movements of live animals for aquaculture and trade [28–31]. In New Zealand, but not Australia, translocation of oysters was the reason for national spread [23,27]. The spread of bivalve diseases is therefore often viewed as a governance failure. However, there are uncertainties about the source of the virus, and shortcomings in the development of specific protective measures for oyster farming are partly due to the lack of key scientific knowledge about OsHV-1 risk factors.

As a comprehensive treatment of all bivalve diseases is not possible, this paper focuses on OsHV-1 and its main host, the oyster *C. gigas*. The impact OsHV-1 has on oyster production is an example of the challenges and possible solutions for disease control in aquaculture species. In §2, we review the present understanding of risk factors for OsHV-1 spread in oyster populations. We then identify knowledge gaps and research that are crucial for disease management. Then, in §3, we review principles of disease management and their application to OsHV-1. We focus on the lack of predictive tools and cohesive guidelines for managing and protecting stocks in shellfish farming areas. In §4, we identify priorities for future work to improve disease risk management. In §5, we conclude this review with the introduction of ecosystem-based management for bivalve aquaculture which includes marine-borne diseases.

2. Risk factors for OsHV-1 transmission: current knowledge and research gaps

Infection starts when viral particles come into contact with susceptible hosts. Viral particles can enter the host via suspension feeding and are directed towards the digestive gland and the haemolymphatic system. OsHV-1 is detected in haemocytes 6 h following exposure of naive oysters in laboratory cohabitation studies, and these cells then transport the virus to target organs [26]. Infected cells transcribe viral genes, which leads to replication and release of the virus into the cytoplasm within 2–3 days [32,33]. The minimum infective dose, an important parameter for evaluating the potential for spread of viruses in their natural environment, is currently unknown for natural infections with OsHV-1. Nevertheless, experimental studies under laboratory conditions reveal a threshold dose and a dose–response effect on mortality [34]. Like other herpesviruses, latent and subclinical (or sublethal) OsHV-1 infections are able to persist in hosts [32,33]. In this case, virus reactivation can occur several weeks to months following initial exposure [35], viral particles are shed into the water column [26] and dispersal to new hosts occurs via water currents [10]. Infected oysters can survive and OsHV-1 then becomes undetectable in their tissues [10,23,36–38]. Factors leading to progressive infection, latency or persistence, and possible clearance from the host are unknown.

Epizootics caused by OsHV-1 occur every spring when seawater temperature is between 16°C and 24°C in Europe [10,39–41]. In Australia and New Zealand, the permissive temperature range is not yet defined, although outbreaks have been observed between 23°C and 26°C in Australia [22,23]. In France, infection occurs a few days before the onset of mass mortality while seawater temperature is below 16°C [41,42]. Although temperature sets the start and

the end of the epizootics in Europe, it does not influence the magnitude of the mortality event [39].

The distance over which infection can be transmitted is limited by the interaction of hydrodynamics with viral shedding and decay rates [43]. Decay rates of marine viruses and persistence outside the host vary with environmental parameters such as seawater temperature, salinity, solar radiation, natural bacterial communities, suspended particulates and grazing [44,45]. Dispersal also depends on whether OsHV-1 is free-living in the water column or adsorbed to suspended particulates as previously suggested [46–48]. OsHV-1 persistence outside the host has not been investigated in Europe, so its potential for long-distance dispersal there is currently unknown. However, persistence of infective viruses in seawater can be short-lived as for other herpesviridae. In Australia, spat exposed to infected seawater previously aged for 48 h show no mortality [47]. Experimental transmission studies confirmed that survival of the Australian strain of OsHV-1 μ Var in seawater in a laboratory environment is unlikely after 2 days [49].

In the laboratory, OsHV-1-induced mortality is positively correlated with the neighbouring biomass of infectious animals and negatively correlated with seawater renewal, two parameters that influence the concentration of infective particles [42]. This is consistent with density-dependent transmission, i.e. larger and denser populations have increased contact between infectious and susceptible individuals [50]. However, the transmission model and host density thresholds, above which OsHV-1 can spread and be maintained in a host population and below which it might be mitigated, need further investigation before disease management scenarios can be envisaged [51,52].

The risk of exposure to OsHV-1 is determined in part by immersion time for those oysters cultivated in the intertidal zone. Manipulation of immersion time by raising the growing height above sea bottom has a major effect in adult oysters, reducing mortalities by 50% [23,36]. Improved survival at high intertidal height can be explained by a lower immersion time leading to a lower exposure to viral particles in the water or a reduction of host metabolic rates which in turn reduce replication rate of the virus [21].

Little is known about the role of other animal species in OsHV-1 transmission. Indeed, knowledge about the transmission of bivalve pathogens has been gained from experiments or models in which hosts and pathogens are considered in an ‘ecological vacuum’ [53]. In reality, hosts exist within diverse ecological communities, and ecological interactions undoubtedly influence the transmission and impact of pathogens [54]. For example, sentinel oysters deployed in mussel farms are less likely to die during an OsHV-1 outbreak than those put in oyster farms or empty areas, suggesting that mussels reduced the infection pressure on susceptible oysters [55]. Similarly, a large population of Sydney rock oysters possibly reduces the exposure of nearby Pacific oysters to OsHV-1, leading to a delay in the onset of a mortality event [23]. Effects of pathogens can be diluted when bivalve hosts are considered within a community of abundant alternative hosts with reduced susceptibility. Conversely, alternative hosts can act as reservoir for pathogens. The antagonistic effects of dilution and reservoirs have received much attention in disease ecology and need further consideration for managing pathogens in oyster farms.

The magnitude of OsHV-1-induced mortality is potentially influenced by host factors such as age, genetic

background, life-history traits and physiological status of oysters [21]. For instance, mortality is much lower in adults than in juveniles [10,17,23,33,36,40,42,56,57], reflecting natural resistance to the disease [10,56], possibly conferred by the maturation of the immune system [33,58]. However, OsHV-1 reference strain has already been detected in subclinical infections in adults [59], raising the question as to what factors trigger viral persistence and reactivation in apparently healthy oysters. Adult oysters can act as carriers and reservoirs of the virus and promote OsHV-1 transmission horizontally (from host-to-host) or vertically (from adults to their progenies) [59,60]. Although larvae are highly susceptible to the reference strain of OsHV-1 [61,62], little attention has been paid to this aspect since the emergence of the μ Var genotype. Nevertheless, given the long-distance dispersal of bivalve larvae, the infectious status of adult oysters and oyster larvae needs to be examined in the wild, as does their role as potential reservoirs/carriers of OsHV-1.

Selection for resistance to summer mortality in which the OsHV-1 reference strain was involved, leading to 'resistant' and 'susceptible' lines, still conferred an advantage to offspring exposed to OsHV-1 μ Var [38,63–65]. Nevertheless, trade-offs between OsHV-1 resistance and other traits, including resistance to other pathogens and their role in maintaining the virus in the host population, require further assessment. Furthermore, selection for disease resistance could have unintended effects on other commercial traits.

Wild oysters are exposed to disease risks in an unpredictable way, whereas in hatcheries and nurseries they can be protected using prophylactic methods [47,66]. In France, the risk of OsHV-1 spread is much higher for wild oysters collected in infected areas than for those from hatcheries and nurseries [42]. Accordingly, OsHV-1 outbreaks often start in wild oysters, followed by those from nurseries [67,68]. Therefore OsHV-1 will unlikely be eliminated at sites where stocks of oysters are self-recruiting. However, in areas where there is no natural recruitment, OsHV-1 impact could be reduced by ceasing restocking [69]. This was observed for four consecutive years in a small bay area in France where the Pacific oyster does not recruit and growers use animals from nurseries only (P Glize 2014, personal communication). Although wild oyster populations often coexist with and even outnumber farmed animals in oyster farm ecosystems, knowledge of diseases in wild oysters lags far behind that in farmed animals. Therefore, the role of wild oysters as putative reservoirs of OsHV-1 and the impact of OsHV-1 on their population dynamics deserve investigation.

Local differences in energetic reserves of oysters, partly caused by variation in food quality, play a significant role in the spatial and temporal dynamics of OsHV-1-induced mortality [37]. In particular, the relative contribution of diatoms to the diet of oysters is positively correlated with their energetic reserves, which in turn decreases the risk of mortality. Overall, well-fed oysters with high levels of energetic reserves are more resistant to OsHV-1 disease [10,37]. Nevertheless, there is a need for more fundamental information on the physiology of the host in relation to viral infection. For instance, the impact of oyster growing conditions on their receptivity to the virus and on the rate of virus proliferation has never been studied. Expression and replication of several viruses infecting eukaryotic cells could depend on the cell cycle of their host, whereas other viruses are independent of their host's cell cycle [70]. Although scientists and growers observed that OsHV-1 disease risk seems to increase in fast-

growing oysters as opposed to slow-growers, this question remains unanswered.

As this overview has illustrated, a great deal of work has been done on the relationship between *C. gigas* and OsHV-1 but information gaps remain. These gaps concern the definition of reservoirs and wild animal carriers of OsHV-1, minimum infective dose, persistence outside the host and potential for long-distance dispersal as a function of environmental factors. Such parameters are critical for building epidemiological models and evaluating the effectiveness of disease management scenarios [51].

3. Principles of control of marine diseases: relevance to OsHV-1

Disease management relies on establishment and maintenance of disease freedom or control of established diseases or both. The World Organisation for Animal Health (OIE) provides guidance and standards to control aquatic animal diseases [71]. These consist of disease eradication, limitation of spread and prevention of disease introduction. The eradication of diseases of molluscs is rarely attempted because host populations cannot be completely removed from open-water systems [72]. Indeed, oyster farming systems range from highly controlled hatcheries to wild coastal areas where cultivated oysters are near wild populations. However, to pursue these objectives, several management actions such as chemotherapy and vaccination, culling of host populations, movement regulations and biosecurity measures, and zoning and compartmentalization are used. Although these guidelines are desirable, they generally cannot be applied in marine habitats mainly because of their greater openness and connectivity compared with terrestrial ecosystems [73].

Chemotherapy, defined here as the use of antibiotic drugs, is often used for controlling disease in shrimp and fin-fish aquaculture, but rarely in bivalve farming. Indeed, chemotherapy requires closed or semi-closed farming structures, such as hatcheries, nurseries, ponds or sea-cages to avoid dilution and spillover of the chemical into the wild, whereas bivalve farming is mostly done in open or semi-open environments. Chemotherapy to treat viral diseases in livestock is not common and this has not been developed for fighting viral disease in oysters [74,75].

Although vaccination is routinely used for preventing disease introduction in other types of animal production, this is not suitable for oyster farming. One reason for lack of vaccine-based approaches is that molluscs lack an adaptive immune system and are unable to respond to conventional vaccines [75].

Culling of infected individuals and disposal of dead animals contributes to controlling disease spread and possible eradication. For instance, Norwegian farms that removed dead salmon daily in summer were three-times less likely to suffer an infectious salmon anaemia (ISA) outbreak than farms that removed dead fish less frequently [76]. However, culling of oysters infected with OsHV-1 and disposal of dead animals is not feasible on a day-to-day basis. Indeed, access to oyster stock on farms is constrained by tide level and meteorological conditions, and checking animals every day is neither economic nor practical. Also, infected oysters are not visually detectable due to the absence of clinical signs until just before death. Finally, virus replication

within the host, shedding of viral particles into the environment and spread of dead tissues occurs rapidly, a few days following infection [26,46].

A more proactive approach consists of the culling of susceptible hosts to reduce the local population density enough that it falls below the threshold for disease maintenance [77]. Although the elimination of bivalve diseases from open-water production systems is considered impossible or prohibitively expensive [72], culling has been successful in molluscs [73]. For instance, to mitigate the impact of a polychaete parasite that infested abalone in California, hosts of the most susceptible species and size were removed, reducing transmission of the worms to the surviving gastropods to below the replacement rate until no more infected gastropods were recorded [78]. This approach requires proved density-dependent transmission of the pathogen and knowledge of the host density threshold, above which the pathogen can spread and maintain itself in a host population and below which it can be eradicated.

Movements of live animals can be regulated to limit disease spread and prevent pathogen introduction. In Europe, containment measures based on the restriction of movements of live oysters out of the areas of high mortality have been used to control OsHV-1 as an emerging disease (Reg. EU175/2010). Restrictions on movements of oysters in the UK have contributed to limiting the spread of OsHV-1 in this country [79]. In Australia, the Department of Primary Industries in New South Wales adopted a disease response plan which involved quarantine and prevention of oyster movements from the affected rivers [57]. Other biosecurity measures, such as minimizing the exchanges of stock, personnel and equipment between farming areas help to limit the introduction or the spread of pathogens in finfish [28,80] and are recommended for bivalve farming [57].

Zoning and compartmentalization was introduced by OIE in the Aquatic Animal Health Code to eradicate a disease locally, limit disease spread and prevent pathogen introduction. The essential difference between zoning and compartmentalization is that the recognition of zones is based on geographical boundaries, whereas the recognition of compartments is based on management and biosecurity practices. Using these concepts, countries could eradicate a disease from a part of their territory while the country as a whole is not yet free of the disease. Compartmentalization is ideally suited for closed and semi-closed systems, whereas a mixed approach of zoning and compartmentalization is appropriate for industries which rely on a combination of systems ranging from closed systems to semi-open ones [81], as oyster farming does.

These measures make perfect sense, but their implementation and effectiveness against OsHV-1 is constrained by the lack of data, including epidemiological parameters and mechanism of transmission of OsHV-1 (see §2). These different approaches result in very different responses to intervention strategies. For example, culling could be effective for controlling density-dependent disease but could be counterproductive when pathogens depend on open recruitment. It is therefore important for management that appropriate models be selected [51]. Response plans need to be flexible and updated in real time. For example, there is considerable economic cost and little practical advantage in maintaining local biosecurity measures if the emerging pathogen has already spread widely in an ecosystem [57].

All these measures implicitly rely on the establishment of epidemiological units, i.e. a group of animals that share about the same risk of exposure to a pathogen within a defined area. Definition of epidemiological units requires specific considerations of reservoirs and carriers of the pathogen, the minimum infective dose, pathogen persistence outside the host, potential for long-distance dispersal and hydrodynamic connectivity, as well as host criteria. In Scotland, use of epidemiological units, also called 'disease management areas', has been effective in restricting spread of ISA to a small area [43,82]. Epidemiological units have not yet been defined in bivalve farming in Europe, except for certain areas in UK and Ireland where a surveillance plan for OsHV-1 was designed according to epidemiological units (Commission decision 2011/187/EC extended by the Commission implementing decision 2014/250/EU). In France, disease surveillance areas have been delimited along the coastline according to hydrodynamic, sedimentary and biological criteria. Surveillance areas differ from epidemiological units in that pathogen and host criteria are not taken into account. Therefore, movement regulation of live animals might not be efficient, because pathogen dispersal could take place naturally through the water column between surveillance areas. In New South Wales, Australia, whole estuaries are considered as epidemiological units, and movements of live animals between estuaries are regulated depending on disease risks. Finally, in New Zealand, hydrodynamically modelled epidemiological units are currently being proposed for detection surveys of waterborne diseases [83,84].

The lack of traceability in oyster farming [85] is a major limiting factor for the identification of epizootic sources, routes of spread and application of control measures in many European countries. Movements and traceability in the oyster aquaculture industry are not yet fully applied as suggested by the European Food Safety Agency [11] and in accordance with the requirements of Council Directive 2006/88/EC [21]. The UK and certain areas in Ireland record movements of live oysters as part of their national surveillance programmes regarding OsHV-1. Although measures to record oyster movements are in place in Australia, exhaustive tracking is unlikely. Nevertheless, tracing investigations allow determining that the source of OsHV-1 μ Var for a massive epizootic in the Hawkesbury River was not associated with farmed oysters or farm equipment, leading to the suggestion of an oceanic source [57].

At present, the likelihood of eradicating OsHV-1 is low because the pathogen is present in wild populations, it persists in a subclinical or latent form, costs to the industry are prohibitive, and OsHV-1 is not a notifiable disease for international trade under the mandate of the OIE. Eradication programmes to establish OsHV-1-free areas have never, therefore, been proposed [72]. However, limitation of spread and prevention of introduction of OsHV-1 by movement regulations, biosecurity measures and compartmentalization and zoning are feasible, as previously reported locally in France (P Glize 2014, personal communication), UK [79] and Australia [86]. Finally, mitigation of OsHV-1 disease impacts is currently being achieved by the genetic selection of OsHV-1 disease resistant oysters (see §2). Recently, some breeding programmes have been started in Europe, Australia and New Zealand for improving the resistance of oysters to OsHV-1 disease. Given that the higher survival reported for resistant batches is associated with reduced viral load, replication and shedding on the short-term [87,88],

farming disease resistant oysters could lower OsHV-1 transmission in marine ecosystems, but this latter possibility needs to be investigated over the long-term.

In summary, reducing the infectious pressure in oyster farms by biosecurity measures, movement regulations and zoning based on epidemiological units, use of traceability measures and collaboration among growers to manage risks on a regional basis will be likely to help mitigate current losses and prevent further disease introductions. At present, there is a lack of predictive tools and cohesive guidelines for managing and protecting stocks in a harmonized manner throughout the European community, and indeed elsewhere.

4. Problems and research priorities

To find the best way to remedy the lack of information and find tools to fight marine disease, we will pinpoint the major unsolved problems and priorities for future work. Improving disease risk management is one of the keys to sustainable oyster farming, economic returns and ecosystem health [89]. Practically, if we are to propose counter-measures to overcome this situation and provide new tools to support bivalve farming, we need to identify and prioritize risk factors for disease and to develop predictive modelling of disease transmission. Then, this modelling approach can be used to evaluate the efficiency and acceptability of management scenarios.

(a) Identifying and prioritizing risk factors

Although several risk factors for OsHV-1 transmission have been identified, many gaps remain in our knowledge (see §2). Indeed, the effects of environmental factors, such as salinity, pH, nutrients and biotic communities, and host parameters, such as genetic background, on OsHV-1 transmission in the oyster ecosystem need further investigation. Also, it is urgent to identify the reservoirs of OsHV-1, if these exist.

Spatial epidemiology, i.e. the description and analysis of geographical variations in disease with respect to environmental factors, allows understanding of factors that govern the spatial pattern and rate of spread of diseases [90,91]. One approach is to deploy specific pathogen-free individuals that are standardized as much as possible at specific locations as sentinels for infection, morbidity or abnormal mortality [92], and to correlate disease incidence and location features. Recently, large-scale sentinel oyster monitoring in the Mediterranean Thau lagoon gave a comprehensive view of the spread of OsHV-1 and related mortality in relation to host energetic reserves, trophic environment and surrounding farming practices [37,55]. Similarly, in Australia, sentinels were used to understand the temporal dynamics of the first exposure to OsHV-1 in a previously disease-free estuary [57].

More broadly, sentinel oyster monitoring coupled with habitat mapping, i.e. mapping of biotic (e.g. species composition and abundance) and abiotic parameters (depth, substratum, current, temperature, salinity, etc.), is a promising avenue for identifying and prioritizing disease risk factors and for identifying reservoirs. Indeed, correlation analyses between disease incidence and the presence of a given species could indicate a putative reservoir host (positive correlation) or an alternative host with reduced receptivity (negative correlation). This spatially explicit approach would benefit from tools and methods used in ecosystem management. Habitat mapping plays an important role in marine spatial planning

with respect to some environmental and socio-economic issues [93]. Some of these issues could be linked to epidemiological risks, e.g. health of marine ecosystems, impact of human activities, role of coastal zone habitat in population dynamics of commercially exploited species, population- and community-level impacts of contaminants, habitat changes in the coastal zone and climate change processes.

Retrospective analyses of spatial and temporal dynamics in epizootics can also be used for characterizing spatial variation in disease risk [91]. The most common procedure is to construct distribution maps of disease and environmental factors that might influence it, including reservoirs and vectors. Then, factors that are most strongly associated with the distribution of the disease are projected to either other areas or future times to make predictions about disease risks beyond the current map. Although such risk maps have been established recently for several vertebrates diseases [91], they have rarely been used for aquatic animals. The only available examples are pancreas disease risk maps of Norwegian Atlantic salmon farming sites [94] and *Mikrocytos mackini* risk maps of French oyster populations [95].

A complementary approach to spatial and temporal monitoring of sentinel oysters consists of retrospective analyses of epizootics based on farmer questionnaire surveys as recently done in Ireland for OsHV-1 in oysters [28]. This approach is a first step towards integrating the industry into the research framework, which generally results in a better understanding and acceptance of the science, making it more likely to be considered by end-users and to influence policy decisions.

(b) Building epidemiological models

Predictive modelling can provide a better understanding and potentially prevent future disease events [50]. A key factor influencing epidemiological patterns is the transmission from infected to susceptible hosts [96], which needs to be integrated in such models but in an environmentally realistic manner. Transmission is strongly dependent on the environment, so the processes behind transmission in aquatic environments could be substantially different to those in terrestrial environments [73], making it potentially inappropriate to simply apply approaches developed for terrestrial systems. In marine systems, water transmits free-moving pathogens between hydrodynamically connected farms [97] and infection can begin without the presence of an infected host within a healthy population. A modified discrete time susceptible–infected–recovered (SIR) type model is therefore needed, representing farm units linked by a hydrodynamic model that allows for between-farm transmission [51,98].

Hydro-epidemiological modelling is still in its infancy for bivalve disease. For instance, the relationship between host density, pathogen dilution and disease risk using a compartmental model coupled with a three-dimensional hydrodynamic model is currently being investigated for bivalve diseases [99]. Also, an approach combining the compartmental epidemiological dynamic models of the SIR type with three-dimensional hydrodynamic models is currently underway for *Vibrio aestuarianus*, a bacterial pathogen of *C. gigas*, and for OsHV-1. These models rely on the definition of key parameters such as minimum infective dose, viral shedding and decay rate for OsHV-1, which can be obtained experimentally [100]. Although these models require considerable amounts of data for accurate parametrization, they

clearly identify gaps in the available data and thus remain a priority for research [101].

Once epidemiological models are available, they can be used for evaluating effectiveness, i.e. benefits of disease control scenarios on health, as previously reported in terrestrial animals [102,103]. For instance, epidemiological modelling coupled with hydrodynamics made it possible to investigate the effect of several measures such as increasing distances between farms and reducing farm size on disease risk in salmon [98,104]. Therefore, epidemiological models can prove useful for testing the effectiveness of disease control scenarios in oyster-farm ecosystems.

(c) Measuring efficiency and acceptability of disease control scenarios

We must consider the economic and social costs of managing disease. The economic impacts of disease are felt in terms of lost productivity, culled animals, trade restriction and control and compensation costs. Investigation of (i) efficiency, which relates the cost of disease control measures to the benefits, and (ii) acceptability, which is the willingness of persons and organizations to put into action disease control measures, are prerequisites for their applications. Efficiency can be obtained using *ex-ante* benefit–cost analyses to assess whether the value of expected profits would exceed the cost of a disease control scenario as reported for finfish diseases [105,106]. Acceptability can be estimated with participation rates obtained from survey questionnaires to stakeholders. Considering that the effectiveness of disease control strategies relies on a collaboration between neighbouring farms [89,98], acceptability of disease control should be measured in the largest possible proportion of growers that participate in long-term activities.

The perception of oyster farmers of recent disease mortality outbreaks of oysters and their consequences on their production areas, business and professional organization is the subject of ongoing study in France [107]. This type of work is a first step towards identification of acceptable disease control scenarios. Acceptability can differ locally depending on historical and cultural background, so acceptability analyses will be needed in areas of different countries.

5. Final thought: an integrated approach to marine disease

In the current context of global change and accelerating emergence of marine diseases [108,109], understanding epidemiology is crucial to propose efficient and acceptable management scenario to growers and consumers. This objective requires an integrated approach that encompasses the ecosystem and the social aspects of drivers, impacts and regulation of disease. This integrative approach falls under the umbrella

of ecosystem-based management, i.e. an integrated approach to management that considers the entire ecosystem, including humans [110,111]. Indeed, the objective of ecosystem-based management is to maintain an ecosystem in a sustainable, healthy, productive and resilient condition so that it can provide the services humans want and need. An ecosystem approach to animal health has already been proposed in terrestrial and freshwater ecosystems [112].

Implementing ecosystem-based management in the marine environment requires marine spatial planning, i.e. the process of analysing and allocating the spatial and temporal distribution of human activities to achieve ecological, economic and social objectives [113]. At present, countries that have adopted spatial planning of bivalve farming rely on the ‘production carrying capacity’, which consists of predicting the maximum sustainable yield of cultured bivalves based on the physical carrying capacity and the magnitude of primary production [114,115]. Although this approach has some merits, spatial planning of bivalve aquaculture based on production carrying capacity ignores disease risk, and this is obvious in the history of oyster farming [2–4]. Therefore, spatial planning of bivalve aquaculture should consider zoning and compartmentalization, minimum separation distances between farms, firebreaks between aquaculture zones and density regulation of susceptible hosts to limit disease spread and emergence of still more virulent pathogens.

Recently, the sustainable aquaculture concept has led to an assessment of carrying capacity by ecosystem structure and function [114,116]. This ‘ecological carrying capacity’ is defined as the level of culture that can be supported without leading to significant changes to ecological processes, species, populations or communities in the farm environment. Although it is not explicitly stated, disease risk is considered to be a factor influencing the ecological carrying capacity of a marine ecosystem [114,116]. However, ecological carrying capacity is typically calculated using ecosystem modelling techniques [115,117] in which disease epidemiology is not taken into account. Using ecological–epidemiological carrying capacity models for marine spatial planning of bivalve aquaculture is a laudable goal that would permit implementation of disease mitigation measures prior to reaching an unacceptable ecological state.

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