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Genetic parameters for resistance to field mortality outbreaks and resistance to a pathogenic strain of *Vibrio splendidus* in *Mytilus edulis*, *Mytilus galloprovincialis* and natural hybrid

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ABSTRACT

Since 2014, abnormal mussel mortality (AMM) outbreaks have occurred along the French Atlantic coasts and mortality rates differed among years and sites (30–100%). Still, the etiology of the AMM is undefined. Our study explores the resistance of two mussel species (*Mytilus edulis* and *Mytilus galloprovincialis*) and natural hybrids (NH) cultivated in France to AMM. One hundred mussel families were produced using six wild mussel populations in January/February 2017. Mussels were tested in two sites, La Floride (LF) and Maison Blanche (MB), in October 2017, and their mortality/growth was recorded until June 2018. AMM was observed at MB during spring 2018, and reached 70%, 43%, and 63%, for *M. edulis*, *M. galloprovincialis*, and NH, respectively, at endpoint. In contrast, mortality was low in LF, reaching 11%, 30%, and 22%, respectively. Heritability for mortality was low to moderate in both sites ranging from 0.12 to 0.37 with higher values in *M. edulis*, intermediate for NH, and the lowest for *M. galloprovincialis*. A significant genotype-by-environment interaction was found for mortality between sites, with low genetic correlations not significantly different from zero (–0.05 to 0.43). In July 2018, mussel families were evaluated under experimental infection using a pathogenic strain of *Vibrio splendidus* isolated during AMM in 2014. The mean mortality after 72 h post-injection was 53%, 22%, and 31% for *M. edulis*, *M. galloprovincialis*, and NH, respectively. The lowest heritability estimates were obtained for NH (0.21) and the highest for *M. galloprovincialis* (0.41), and the genetic correlation between AMM in MB and experimental infection was not significantly different from 0, suggesting that this *Vibrio* strain, is not the major cause of AMM outbreak observed in MB in 2018. Finally, significant genetic variation was observed for growth traits with mostly high heritability (> 0.44) for both species. Interestingly, genetic correlation between mortality and growth was weak and non-significant from zero.

Keywords:

Mussels

Mortality

Heritability

Genetic correlation

Vibrio

Growth

1. Introduction

Aquaculture is playing an effective role in world food security, the development of economic sustainability, and addressing ecosystem challenges (Ren et al., 2022). Aquaculture is by far the primary source of mussels and is responsible for over 90% of total landings (FAO, 2022). The world's total mussel production reached 2.1 million tonnes and it is valued around 4.5 billion USD in 2020 (FAO, 2022). The European Union (EU) represents approximately 25% of the world's production of blue (*M. edulis*) and Mediterranean mussels (*M. galloprovincialis*) in

terms of volume and value (FAO, 2022). In France, both mussel species, as well as their hybrids, are cultivated and production has reached 61,375 t with a commercial value of 160 million USD in 2020 (FAO, 2022). Mussel meat is a high-quality marine protein, low-fat, low-calorie, an excellent source of vitamins, minerals and lower environmental impact than fish species per unit of protein production, so it can justifiably promote as a low-carbon food to the world aquaculture (Avdelas et al., 2021).

French mussel production entirely depends on wild spat collection and it is not sufficient to meet the national demand (Avdelas et al., 2021;

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Prou and Gouletquer, 2002). Bouchot and longline techniques are commonly used for mussel culture and the culture period until marketing lasts 9–15 months, depending on the production area, culture technique, and species. The higher growth rate was observed during spring when the phytoplankton blooms occur, and mussels are mostly marketed from June to January (Prou and Gouletquer, 2002).

Repeated mass mortality episodes of bivalves reduce production, cause economic losses, and negatively impact the ecosystem of natural bivalve populations (Soon and Ransangan, 2019). Massive mortality of various cultured bivalves such as oysters (Degremont et al., 2007; Soon and Zheng, 2020), clams (Ortega et al., 2016), cockles (Burdon et al., 2014; Yurimoto et al., 2014), scallops (Lan et al., 2018; Stokesbury et al., 2007), and mussels (Avdelas et al., 2021; Lupo et al., 2021) have been reported worldwide, and their occurrence seems to increase in the context of global warming. In the case of mussel species, the causes of recent mass mortalities remain largely unknown, as observed in various species such as green-lipped mussels (*Perna canaliculus*) in New Zealand (Ericson et al., 2023), blue mussels (*Mytilus edulis*) in the Netherlands (Capelle et al., 2021), and pheasantshell (*Ortmanniana pectorosa*) in the USA (Putnam et al., 2023).

The sustainability of French mussel farming has become vulnerable since 2014 due to the major mortality outbreaks in particular along the Atlantic coasts. These outbreaks are hereafter referred as abnormal mussel mortality (AMM). Until now, the etiology of AMM outbreaks remains unclear, but it could be linked to pathogens, environmental pollutions, seawater characteristics, mussel characteristics, culture practices, and climate change (Benabdelmouna et al., 2018; Lupo et al., 2021; Polsenaere et al., 2017). The mortality percentages fluctuate among sites and between years; but the peak of mortality outbreaks occurs during spring (Charles et al., 2020a; Degremont et al., 2019). Over the period, one of the proposed causes of mortality could be a pathogenic bacterium in the genus *Vibrio*. Different *V. splendidus* strains were isolated from moribund mussels in France (Ben Cheikh et al., 2016; Benabdelmouna et al., 2018; Lupo and Prou, 2016; Oden et al., 2016; Polsenaere et al., 2017), but their role in AMM are still unknown. Recently, the bacteria *Francisella haliotidica* was identified in *Mytilus* spp. in Normandy and northern Brittany (France) but the authors didn't give any conclusive report on its role in AMM (Charles et al., 2020c). Wide range of studies are going on to figure out the causes of the AMM outbreaks in mussels to propose solutions to reduce the mortalities in mussel farms. In blue mussels (*Mytilus* spp.), genetic abnormalities were found significantly correlated with mortality levels in France (Abdellah et al., 2018). Horizontal transformation of one or several putative causal agents were observed from wild stocks that survived to AMM to wild naïve stocks, and also to hatchery-produced lines (Benabdelmouna et al., 2018). Interestingly, mussel stocks showed significantly different levels of resistance such as *M. edulis* was found slightly more susceptible than *M. galloprovincialis* at the spat stage under laboratory condition (Benabdelmouna et al., 2018). In France, mussel farming consists of *M. edulis*, *M. galloprovincialis*, and their hybrids, distributed from the north of France to Spain. It is crucial to determine the differences in resistance to AMM among species and among populations within species.

Genetic improvement via selective breeding is widely acknowledged as an efficient tool to improve economically important traits including growth rate, disease resistance against specific pathogens, age of sexual maturation, and external coloration for aquaculture species (Degremont et al., 2015a; Gjedrem et al., 2012; Gjedrem and Rye, 2018). Growth and disease resistance rate can usually be improved by 10% to 15% per generation across major farmed molluscs species by using mass or family-based selection (Hollenbeck and Johnston, 2018). The estimation of genetic parameters (heritability and genetic correlation) is the critical step to initiate selective breeding for a trait of interest. Heritability, specifically narrow sense heritability (additive genetic variation) quantifies the potential for genetic improvement of a phenotypic trait, and genetic correlations play an essential role in designing breeding

objectives (Lynch and Walsh, 1998). Genetic variability for phenotypic plasticity is estimated by the genotype by environment interaction, G×E (Becker, 1964; Scheiner and Lyman, 1989), which quantifies the variation of the plastic response among genotypes due to environment changes and it manifests by a change in ranks of families across environments (Gjedrem and Baranski, 2009). Different statistical models are available to compute genetic parameters for survival traits in animal breeding (Forabosco et al., 2009). Linear and threshold models have been widely applied for genetic evaluation of survival data in aquaculture genetics. Compared to linear models, threshold models utilizing a logit link function are better suited for handling binary data. The heritability values obtained from underlying scales in both linear and threshold models have demonstrated good agreement in numerous studies (Odegard et al., 2010b; Prchal et al., 2023). In cases where there is only one observation per animal, genetic analysis on binary trait is often performed using sire-dam threshold models to mitigate biases associated with animal threshold models (Odegard et al., 2010a). However, there is currently no standardized model choice for routine genetic evaluation of survival data in aquaculture breeding programs (Ren et al., 2022). The first estimation of the realized heritability for resistance to AMM was conducted in a single population of *M. edulis*, ranged from 0.55 to 1.15. The over estimation of realized heritability (> 1) suggests the involvement of a single major gene or different origins of control and selected stocks. The variability in realized heritability values is often attributed to the impact of a single generation of mass selection. After one generation of mass selection, there was an increase for survival to AMM by 34–48%. Nonetheless, significant G × E interactions along the French coasts were observed (Degremont et al., 2019). Meanwhile, genetic parameters for the resistance to AMM still need to be obtained for *M. galloprovincialis* as well as natural hybrids.

The main objective of this study was to estimate genetic parameters for growth and resistance to AMM of *M. edulis*, *M. galloprovincialis* and natural hybrids in France using several wild populations. In addition, we investigated the potential involvement of one of the strain of *V. splendidus* in AMM outbreaks.

2. Material and methods

2.1. Biological material

Six wild mussel populations were sampled in fall 2016 along the French coasts (Fig. 1A; Table 1). From Simon et al. (2020), two populations were considered as pure *M. galloprovincialis* (BIA and MOG), one was hybrid (YEU_002), while the three others were pure *M. edulis* (WIM, YEU_001, and OLE-PON) (Table 1). In addition, species (*M. edulis*, *M. galloprovincialis*, and hybrid) of each population were confirmed using KASPTM array method, as all parents used to produce the families were sampled and genotyped (Supplementary Fig. S1 and Supplementary Table S1). Each population was transferred to the Ifremer hatchery in La Tremblade and maintained in separate tanks to avoid horizontal transmission of putative causal agents of mortality between populations, as observed in Benabdelmouna et al. (2018). Unheated UV-treated and filtered seawater (400 L per hour) was enriched with a cultured phytoplankton diet (*Isochrysis galbana*, *Tetraselmis suecica*, and *Skeletonema costatum*) to favour gametogenesis.

2.2. Hatchery and nursery production of mussels

Two sets of crosses (set 1 and set 2) were performed, each containing 50 full-sib families. The first set occurred in January 2017, and the second set in February 2017. For each set, mussels of three populations were induced to spawn, YEU_002, YEU_001, and OLE-PON for the set 1, and BIA, WIM, and MOG for the set 2 (Table 1). For each population, 100 mussels were individually placed in a 400 mL beaker, and spawning was triggered alternating cold (10 °C) and warm seawater (20 °C). Depending of the ripeness of the mussels and the sex ratio, 4, 11 and 10

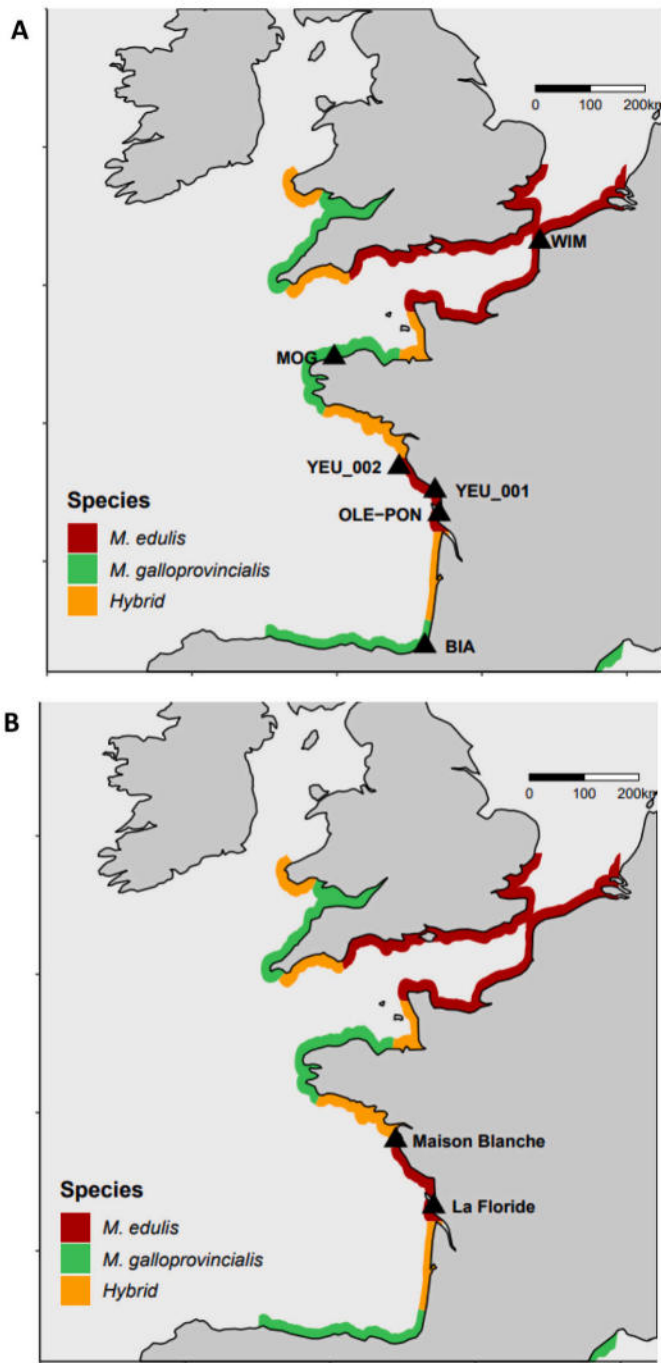


Fig. 1. Origin of the wild population used to produce families (A) and experimental testing sites (B). Each colour represents the distribution of mussel species around the coast (Red: *M. edulis*; Green: *M. galloprovincialis*; Yellow: Hybrid) (The map was constructed based on information provided in the paper, Simon et al., 2020). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

males were used for OLE-PON, YEU_001, and YEU_002 for set 1, respectively, while it was 10, 6, and 9 for BIA, MOG, and WIM for set 2. Within population, each male was mated to two females. In total, 50 half-sib families, each containing two full-sib families were produced. These 100 full-sib families consist of 48 pure *M. edulis* families, 20 hybrid families, and 32 pure *M. galloprovincialis* families, as detailed in Table 1.

Each family was grown separately in 30 L tank filled with filtered and UV-treated seawater at 20 °C. Seawater was changed three times per

week, and larvae were fed daily with a mixture of algae (*I. galbana*, *Chaetoceros gracilis*, *S. costatum*). Larval density was established at 10 larvae mL⁻¹ on day 1 post-fertilization and then progressively reduced to 5 and 3 larvae mL⁻¹ on days 7 and 14 post-fertilization, respectively. At the pediveliger stage, the larvae were then transferred into 150-µm sieve-bottomed trays in 120 L tank to accomplish their metamorphosis using flow-through UV-treated seawater enriched with a mixture of four algal species routinely produced at the hatchery (*I. galbana*, *C. gracilis*, *T. suecica*, and *S. costatum*). Each 120 L tank contained seven or eight families. The sieves were washed daily and changed regularly depending on spat growth. When spat reached 1 cm, they were transferred in our nursery in Bouin in April and in May 2017 for the set 1 and the set 2, respectively. For each family, 1000 spat were maintained in 15 L SEAPA© baskets, and all families were raised in a 20 m³ concrete raceway until their deployment in the field which occurred in October 2017. During this step, flow-through UV-treated seawater was enriched with *S. costatum*.

2.3. Field testing

Families were deployed in two sites in October 2017, in our experimental farm at La Floride in the Marennes-Oléron Bay, just in front of the Ifremer hatchery (45°48'12" N, 1°9'18" W) and in a mussel farm in Maison Blanche (46°59'53.7" N 2°12'17.0" W, Fig. 1B). AMM occurs every year since 2014 in Maison Blanche, while it was only observed in 2016 in La Floride (Degremont et al., 2019). Both sites were located in intertidal area, meaning that mussels emerged during spring tides. At Maison Blanche, all the families were placed into one large bag. Inside the large bag, families were kept separately using a soft mesh bag containing 20 mussels per family with a tag indicating the family name (individual weight around 1.5 g). This was replicated five times, and each large bag was attached to one wooden pole, as mussels are cultivated on rows of wooden poles, called "bouchots" at this site. Mortality was recorded from one of the replicates in February 2018 by bringing the mussels in our laboratory. Subsequently, the mussels did not return in the field, but were discarded. Same protocol was done in April 2018. Finally, the three last bags were recorded at endpoint in June 2018, as mussels are commonly harvested in that period of the year at Maison Blanche. For the site of La Floride, same protocol was used except that 50 mussels were tested per replicate, four replicates were used in total, two replicate bags were recorded at endpoint, and that bags were attached on a rack. Finally, growth parameters were recorded for 30 mussels per family and per site at endpoint, or lower if the mortality rate was too high. Traits recorded were total body weight, total length, shell width, height, weight and dry flesh weight.

2.4. Experimental infection

In July 2018, two experimental infections (EI_1 and EI_2) were conducted using naive mussels kept in our secured facilities to investigate their resistance to one pathogenic strain of *V. splendidus* isolated from moribund mussels collected during AMM in 2014 (strain 14/053 2 T1). For each experiment, 25 full-sib families per set of crosses were randomly sampled, and 30 mussels per family were injected with the *V. splendidus*. Previously, bacteria were grown overnight in Zobell (peptone 4 g/L, yeast extract 1 g/L, Tris-HCl buffer 0.5 g/L, ferric citrate 0.1 g/L, in artificial sterile seawater ASSW (2.3% (w/v) NaCl, 20 mM KCl, 5 mM MgSO₄, 2 mM CaCl₂, pH 7.6) at 20 °C with constant agitation (80 rpm). Cells were washed twice with ASSW and centrifuged at 1200g for 10 min. The supernatant was discarded and the resulting pellet was resuspended in ASSW to obtain an OD_{600nm} of 1 corresponding for this bacteria to 10⁹ CFU/mL. Bacterial purity and concentration was checked by plating this suspension on Zobell agar. Mussels (mean weight around 5 g) were previously anesthetized using MgCl₂ (50 g per L), and 50 µL (10⁹ bacteria/mL) of bacterial solution was injected into the muscle. Then, ten injected mussels per family, and so all the 50 families, were

Table 1

The origin of the wild populations representing different mussel species (*M. edulis*, *M. galloprovincialis* and their hybrid) used to produce full-sib families.

Species	Site	Pop	Lat	Long	NFF	SC
<i>M. edulis</i>	Wimereux	WIM	50.787049	1.599753	18	2
<i>M. edulis</i>	Ile Oléron	OLE-PON	45.85367	-1.18099	8	1
<i>M. edulis</i>	Pertuis Breton	YEU_001	46.27844	-1.29464	22	1
Natural hybrid	Ile d'Yeu	YEU_002	46.70556	-2.28672	20	1
<i>M. galloprovincialis</i>	Moguéric	MOG	48.692257	-4.076711	12	2
<i>M. galloprovincialis</i>	Biarritz	BIA	43.46715	-1.57612	20	2

Pop: Population name; Lat: Latitude; Long: Longitude; NFF: Number of Full-sib families; SC: Set of Crosses.

hold in one 120 L tank containing UV-filtered seawater. Three replicate tanks were used and, in each tank, water recirculation was maintained using a TECO® pump (Ravenna, Italy), which also maintained the seawater temperature at 17 °C. Dead mussels were counted and removed daily up to 72 h post-injection.

2.5. Statistical analysis

The initial analysis for mortality involved a binomial logistic regression in the Glimmix procedure in SAS®9.4 to systematically evaluate individual effects, interactions, and variations within the specified factors (Littell et al., 2002).

ASReml version 4.2 (Gilmour et al., 2021) was used to fit linear (animal) models and threshold (sire-dam) models to estimate the genetic variances and genetic correlations of the mortality using a Residual Maximum Likelihood (REML) method. Genetic variances of growth traits and their correlation with survival were assessed using linear (animal) models. Among species, genetic parameters of mortality in each environment (Maison Blanche, La Floride, and experimental infection) at endpoint were estimated with the following linear mixed animal model on observed scale:

$$Y = X\beta + Z\alpha + e \quad (1)$$

where Y is the binary mortality outcome at the end of testing period (0 = dead, 1 = alive) of mussel, β is the vector of fixed effects, including set of crosses (set 1, set 2), population origins (OLE_PON, WIM, YEU_001, YEU_002, BIA, MOG), species (*M. edulis*, *M. galloprovincialis*, natural hybrid), and replication of the experimental infection (EI_1 and EI_2). α is the vector of additive genetic effect of the animal, assumed to be distributed as $\alpha \sim N(0, A\sigma_a^2)$, where A is the relationship matrix derived from pedigree for all animals, and σ_a^2 is a matrix of additive genetic variance. e is the vector of random residuals, assumed to be distributed as $e \sim N(0, I\sigma_e^2)$, where I is an identity matrix and σ_e^2 is a matrix of the residual variance. X and Z are known incidence matrices relating observations to the fixed and random effects mentioned above.

Within species, the same model terms were used except that population and/or set were dropped for *M. galloprovincialis* (only in set 2), and natural hybrids (only in set 1, and only one population). The common environmental effect due to separate larval rearing, was treated as a random effect common to each full-sib family. However, this effect was excluded from mortality analyses due to its minimal genetic variance.

The heritability estimation on observed scale have been transformed to the liability scale by using the threshold transformation of Dempster and Lerner (1950).

Similarly, the variance components of mortality were also estimated by using a threshold (probit) sire-dam model assuming an underlying normal distributed liability:

$$Pr(Y = 1) = \Phi(X\beta + Z\alpha + e) \quad (2)$$

where Y is the binary mortality outcome (0 = dead, 1 = alive) of mussel, $\Phi(\cdot)$ is the cumulative standard normal distribution and the residual variance fixed to 1 (Odegard et al., 2010a). The other parameters are as described above.

Genetic correlations for mortality between different growing sites (LF and MB), and between growing sites and experimental infection were estimated from bivariate linear mixed animal models, defined as follows.

$$\begin{bmatrix} y_1 \\ y_2 \end{bmatrix} = \begin{bmatrix} X & 0 \\ 0 & X \end{bmatrix} \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} + \begin{bmatrix} Z & 0 \\ 0 & Z \end{bmatrix} \begin{bmatrix} \alpha_1 \\ \alpha_2 \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \end{bmatrix} \quad (3)$$

where the symbols represent the same vectors as described in the Eq. (1), and the subscripts 1 and 2 are the same traits recorded in two environments. For quantifying the G × E interactions and estimating the genetic correlation (r_g), mortality in each environment was considered as two different traits in a bivariate analysis. Because one animal could be tested only in one environment, there was no environmental (residual) correlation between the mortality, and the residual covariance was set to zero in the bivariate analysis (James, 2009).

Finally, a multivariate animal model was fitted to estimate the (co) variance for growth traits and mortality at endpoint in Maison Blanche and in La Floride as follows:

$$Y = X\beta + Z\alpha + e \quad (4)$$

where Y are the vectors of phenotypes of growth traits (total body weight, total length, width, height, shell weight, dry flesh weight), and the other symbols represent the same vectors as described in the Eq. (1). Both vector of α and e are assumed to be multivariate normal distribution with mean zero and variances as

$$\text{Var} \begin{bmatrix} \alpha \\ e \end{bmatrix} = \begin{bmatrix} A\sigma_a^2 & 0 \\ 0 & I\sigma_e^2 \end{bmatrix}$$

here, σ_a^2 and σ_e^2 are the random additive genetic variances and residual variances, respectively. A is the numerator relationship matrix based on pedigree information, and I represent an identity matrix. The common environmental variance was ignored from this model due to large confounding effect with genetic variance.

2.5.1. Heritability and genetic correlations

For Eqs. (1) and (4), heritability (h^2) was estimated as follows:

$$h^2 = \frac{\sigma_a^2}{\sigma_a^2 + \sigma_e^2}$$

where σ_a^2 is the genetic additive variance, and σ_e^2 is the residual variance. Total phenotypic variance (σ_p^2) was calculated as the sum of random additive genetic variance (σ_a^2) and random residual components (σ_e^2).

For the sire-dam models (Eq. (2)), the sire-dam variance is expected to correspond to ¼ of the total genetic additive variance, heritability estimation were estimated according to Odegard et al. (2010a) as follows:

$$h^2 = \frac{4\sigma_{sd}^2}{2\sigma_{sd}^2 + \sigma_e^2}$$

where σ_{sd}^2 is the sire-dam additive genetic variance, and σ_e^2 is the residual variance, fixed to 1 in case of Probit model.

The genetic correlations (r_{xy}) among traits were calculated according to (Lynch and Walsh, 1998)

$$r_{xy} = \frac{\sigma_{ax,ay}}{\sigma_{ax}^2 \sigma_{ay}^2}$$

where $\sigma_{ax,ay}$ is the additive genetic covariance between x and y, σ_{ax}^2 corresponds to the additive genetic variance of x and σ_{ay}^2 corresponds to the additive genetic variance of y.

3. Results

3.1. Mortality in growing sites (LF and MB)

Mean mortality per species was low, ranging from 1 to 6%, in La Floride in February 2018 (Fig. 2A), while it was slightly higher in Maison Blanche, reaching 13% for *M. edulis* and natural hybrids, and 5% for *M. galloprovincialis* (Fig. 2B). In April 2018, mean mortality remained below 10% for *M. edulis* and hybrids, and reached 27% for *M. galloprovincialis* in La Floride. In contrast, *M. edulis* had the highest

mortality (47%) in Maison Blanche, intermediate for hybrids (37%), and the lowest for *M. galloprovincialis* (23%). At endpoint, a significant site by species interaction was observed ($p < 0.0001$). For each species, mussels tested in Maison Blanche showed significant higher mortality than those deployed in La Floride ($p < 0.0001$). Within site, significant differences in mortality were observed among species with the highest mortality for *M. edulis* (70%), followed by hybrid (63%), and lowest for *M. galloprovincialis* (43%) in Maison Blanche ($p < 0.0001$) (Table 2; Fig. 2B). Significant differences in mortality were also noted among species at the endpoint in La Floride ($p < 0.0001$) but with the highest mortality for *M. galloprovincialis* (30%), intermediate for hybrids (23%) and the lowest for *M. edulis* (11%) (Table 2; Fig. 2A). The population-level descriptive statistics by species, including mortality data, are presented in Supplementary Table S2 and Fig. S2. Within species and within site, the population factor was not significant for *M. edulis* ($p > 0.47$ and $p > 0.09$) and *M. galloprovincialis* ($p = 0.55$ and $p = 0.85$) in La Floride and Maison Blanche, respectively.

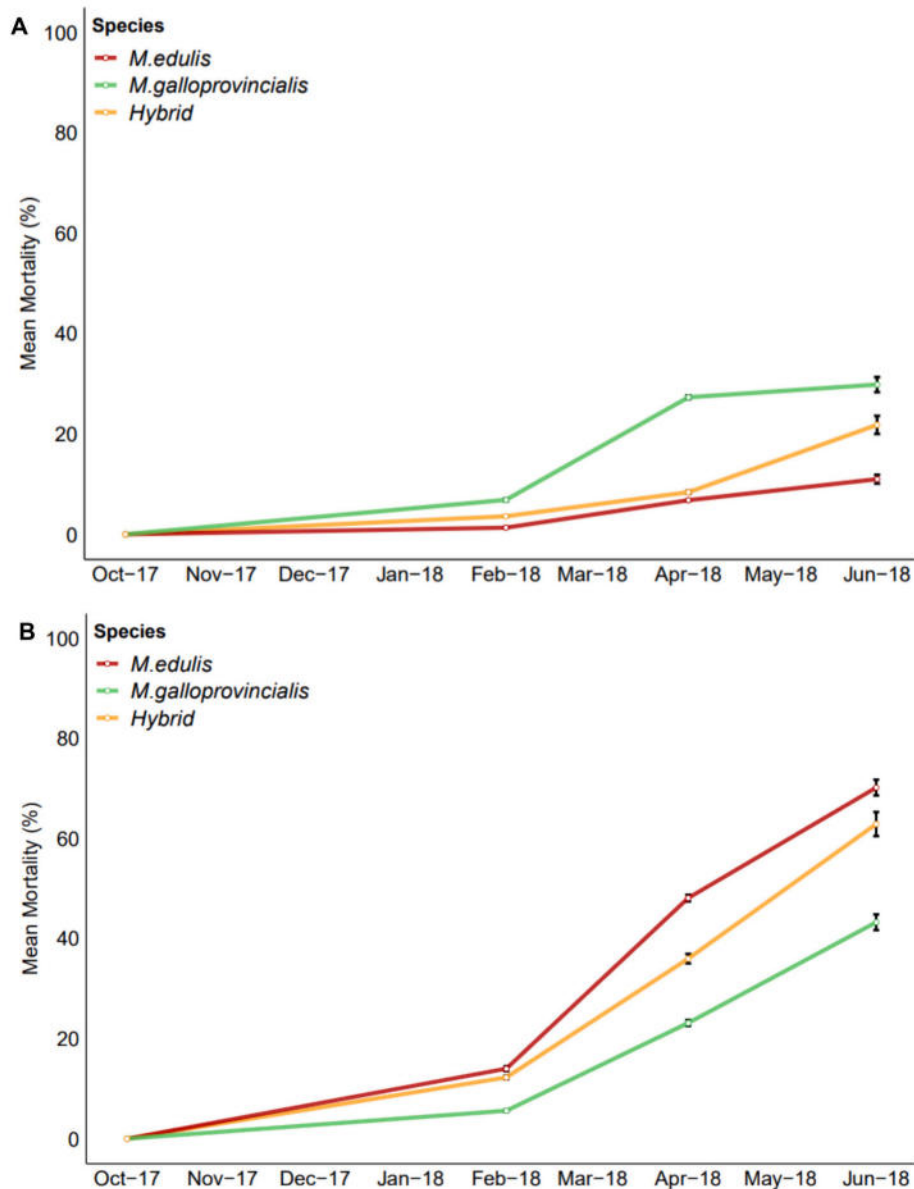


Fig. 2. Mean mortality among families (\pm SE) per species in La Floride (A) and Maison Blanche (B). Colour represents the mussel species (Red: *M. edulis*; Green: *M. galloprovincialis*; Yellow: Hybrid). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2

Summary statistics of mortalities (%) among families for each species and across species in Maison Blanche, La Floride and experimental infection at endpoint in June 2018.

Site	Species	N	Mean	StdDev	Stderr	Min	Max	CV
Maison Blanche	<i>M. edulis</i>	48	70.20	18.90	1.57	30	95	26.92
	<i>M. galloprovincialis</i>	32	43.28	15.57	1.58	20	67	35.98
	Natural hybrid	20	62.91	18.80	2.42	22	88	29.88
	Across species	100	60.13	21.43	1.23	20	95	35.64
La Floride	<i>M. edulis</i>	48	11.00	8.56	0.87	1	26	77.83
	<i>M. galloprovincialis</i>	32	29.85	12.05	1.50	15	53	40.37
	Natural hybrid	20	22.82	11.43	1.80	9	35	52.38
	Across species	100	19.20	13.30	0.94	1	53	69.28
Experimental Infection	<i>M. edulis</i>	48	52.54	25.22	2.03	16	90	47.99
	<i>M. galloprovincialis</i>	32	22.25	19.34	1.91	3	70	86.90
	Natural hybrid	20	31.42	22.13	2.78	13	63	70.42
	Across species	100	38.64	26.64	1.49	3	90	68.95

N: number of full-sib families.

3.2. Growth in growing sites

Mean phenotypic values of growth traits at endpoint varied among sites and species as shown in Tables 3 and 4. The interaction between sites and species was highly significant for all traits except total length and shell length (Supplementary Table S3).

Overall, mussels reared in Maison Blanche had a higher growth than those tested in La Floride ($p < 0.0001$). Within site, natural hybrid had the highest mean value of all growth traits, except the dry flesh weight, in La Floride, and the highest mean value of growth for shell traits in Maison Blanche, while *M. galloprovincialis* had the lowest growth in both sites (Tables 3 and 4). Interestingly, *M. edulis* had the highest mean value of dry flesh weight irrespective of sites.

3.3. Experimental bacterial infection

Mortality rates at 72 h post-injection showed a significant difference between experimental infections 1 and 2, with rates of 49% for EI_1 and 29% for EI_2 ($p < 0.0001$). Significant differences in mortality were observed among species, with 53%, 31%, and 22% for *M. edulis*, natural hybrids, and *M. galloprovincialis*, respectively ($p < 0.0001$, Table 2). Susceptibility to the strain of *V. splendidus* among mussel populations showed contrasting results between species. For *M. galloprovincialis*, both populations showed similar susceptibility to the bacteria (21% for MOG, and 24% for BIA) ($p = 0.56$), while for *M. edulis*, the WIM population (61%) showed a significant higher susceptibility than the OLE_PON (38%) and YEU_001 (50%) populations (Supplementary Table S2). The families showed variability in mortality rate upon

exposure to *V. splendidus*, ranging from 16 to 90% for *M. edulis*, 3 to 70% for *M. galloprovincialis*, and from 13 to 63% for hybrids (Table 2; Supplementary Fig. S3).

3.4. Genetic parameters

3.4.1. Heritability estimates for mortality and growth

Heritability estimates for the mortality of *M. edulis*, *M. galloprovincialis*, and natural hybrid were low in La Floride, ranging from 0.12 to 0.17 using linear and threshold models (Table 5). Higher estimates were observed in Maison Blanche where AMM occurs, with values ranging from 0.16 to 0.37 (Table 5). The genetic variance for susceptibility to *V. splendidus* was low to moderate, with heritability values ranging from 0.15 in natural hybrids to 0.41 in *M. galloprovincialis* (Table 5).

Heritability estimates for total body weight, shell length, shell width, shell height, shell weight, and flesh dry weight were high for *M. edulis*, *M. galloprovincialis*, and natural hybrid (> 0.44) in La Floride (Table 6). Similar trends followed in Maison Blanche (> 0.62 , Table 6). The multivariate models did not converge for shell weight for *M. edulis*; width for *M. galloprovincialis*; height for natural hybrid in La Floride and for shell weight in Maison Blanche for all species, so it was removed from the model before genetic analysis.

3.4.2. Genetic correlations

Genetic correlation for the resistance to mortality between the two growing sites were -0.05 , 0.43 , 0.21 and 0.14 for *M. edulis*, *M. galloprovincialis*, natural hybrid, and across species, respectively

Table 3

Summary statistics of growth traits among families for each species in La Floride at endpoint (June).

Species	Traits	Unit	N	Mean	StdDev	Stderr	Min	Max	CV (%)
<i>M. edulis</i>	TW	g	48	2.61	0.97	0.03	0.88	7.31	37.33
	TL	mm	48	32.17	3.95	0.13	22.70	45.86	12.28
	W	mm	48	16.77	2.02	0.07	12.01	23.87	12.09
	H	mm	48	12.13	1.65	0.05	7.15	19.89	13.65
	SW	g	48	1.16	0.40	0.01	0.39	2.99	34.34
	DFW	g	48	0.45	0.21	0.01	0.09	1.52	46.91
	<i>M. galloprovincialis</i>	TW	g	32	1.57	0.58	0.02	0.48	4.16
TL		mm	32	28.37	4.02	0.13	18.76	41.53	14.16
W		mm	32	15.50	2.22	0.07	9.89	22.79	14.32
H		mm	32	9.86	1.40	0.05	5.75	14.43	14.25
SW		g	32	0.76	0.29	0.01	0.26	1.99	38.45
DFW		g	32	0.25	0.14	0.01	0.04	1.22	56.53
Natural hybrid		TW	g	20	2.67	1.04	0.05	0.79	7.16
	TL	mm	20	34.25	4.83	0.25	23.59	49.67	14.10
	W	mm	20	18.04	2.47	0.13	12.55	25.75	13.70
	H	mm	20	12.56	1.86	0.09	8.74	19.59	14.82
	SW	g	20	1.37	0.55	0.03	0.48	3.77	40.56
	DFW	g	20	0.43	0.21	0.01	0.07	1.23	49.94

TW: Total weight; TL: Total Length; W: Width; H: Height; SW: Shell Weight; DFW: Dry Flesh Weight; N: number of full-sib families.

Table 4

Summary statistics of growth traits among families for each species in Maison Blanche at endpoint (June).

Species	Traits	Unit	N	Mean	StdDev	Stderr	Min	Max	CV (%)
<i>M. edulis</i>	TW	g	48	3.49	1.34	0.05	0.78	8.75	38.49
	TL	mm	48	33.79	4.12	0.14	16.02	47.75	12.19
	W	mm	48	17.65	1.97	0.07	12.26	23.55	11.18
	H	mm	48	13.61	1.82	0.06	7.59	19.78	13.38
	SW	g	48	1.49	0.51	0.02	0.40	3.94	34.53
<i>M. galloprovincialis</i>	DFW	g	48	0.95	0.38	0.01	0.18	2.67	39.73
	TW	g	32	2.04	0.92	0.03	0.41	10.65	45.17
	TL	mm	32	29.49	4.01	0.13	20.40	47.28	13.60
	W	mm	32	16.39	2.31	0.07	9.16	26.88	14.09
	H	mm	32	11.30	1.64	0.05	6.42	18.84	14.58
Natural hybrid	SW	g	32	1.01	0.38	0.01	0.30	3.48	37.89
	DFW	g	32	0.51	0.27	0.01	0.04	3.03	53.93
	TW	g	20	3.32	1.51	0.07	0.90	12.97	45.38
	TL	mm	20	34.70	5.07	0.25	22.21	51.36	14.63
	W	mm	20	18.28	2.69	0.13	12.20	28.99	14.75
Natural hybrid	H	mm	20	13.72	2.21	0.10	7.80	22.84	16.16
	SW	g	20	1.62	0.70	0.03	0.47	4.85	43.43
	DFW	g	20	0.84	0.39	0.02	0.10	2.57	46.86

TW: Total weight; TL: Total Length; W: Width; H: Height; SW: Shell Weight; DFW: Dry Flesh Weight; N: number of full-sib families.

Table 5Estimated endpoint heritability of mortality (\pm SE) in La Floride, Maison Blanche and experimental infection.

Species/sites	La Floride		Maison Blanche		Experimental infection	
	LM ¹	SD ²	LM ¹	SD ²	LM ¹	SD ²
<i>M. edulis</i>	0.17	0.17	0.37 \pm	0.34	0.20	0.20
	\pm 0.06	\pm 0.05	0.09	\pm 0.07	\pm 0.06	\pm 0.06
<i>M. galloprovincialis</i>	0.12	0.12	0.16 \pm	0.16	0.41	0.38
	\pm 0.03	\pm 0.04	0.06	\pm 0.05	\pm 0.14	\pm 0.13
Natural hybrid	0.16	0.15	0.26 \pm	0.25	0.21	0.15
	\pm 0.06	\pm 0.06	0.10	\pm 0.09	\pm 0.10	\pm 0.09
Across species	0.15	0.14	0.26 \pm	0.26	0.23	0.23
	\pm 0.02	\pm 0.03	0.05	\pm 0.04	\pm 0.05	\pm 0.05

¹ LM: Linear Model.² SD: Sire Dam model on underlying scale.**Table 6**

Heritability of growth traits for testing sites (La Floride and Maison Blanche) at end point (June).

	TW	TL	W	H	SW	DFW
La Floride						
<i>M. edulis</i>	0.65	0.72	0.75	0.58		0.50
	\pm	\pm	\pm	\pm		\pm
<i>M. galloprovincialis</i>	0.13	0.13	0.13	0.12	NC ¹	0.11
	0.72	0.84		0.90	0.78	0.44
Natural hybrid	0.13	0.14	NC ¹	0.14	0.13	0.11
	0.80	0.89	0.84		0.83	0.60
Across species	0.23	0.23	0.23	NC ¹	0.23	0.20
	0.71	0.80	0.76	0.72	0.72	0.49
Maison Blanche	0.08	0.08	0.08	0.08	0.08	0.07
	0.71	0.64	0.70	0.67		0.63
<i>M. edulis</i>	0.11	0.11	0.11	0.11	NC ¹	0.11
	0.80	0.91	0.78	0.78		0.62
<i>M. galloprovincialis</i>	0.14	0.13	0.13	0.13	NC ¹	0.12
	0.90	0.96	0.91	0.90		0.70
Natural hybrid	0.18	0.18	0.18	0.18	NC ¹	0.17
	0.82	0.83	0.79	0.78		0.67
Across species	0.08	0.08	0.08	0.08	NC ¹	0.07

¹ NC: not converged.**Table 7**Genetic correlations for resistance to mortality outbreaks (\pm SE) between environments; La Floride (LF) vs Maison Blanche (MB); La Floride vs Experimental infection (EI) and Maison Blanche vs Experimental infection.

Species	Sites	MB	EI
<i>M. edulis</i>	LF	-0.05 \pm 0.19	-0.08 \pm 0.20
	MB		0.18 \pm 0.19
<i>M. galloprovincialis</i>	LF	0.43 \pm 0.21	-0.05 \pm 0.24
	MB		-0.17 \pm 0.24
Natural hybrid	LF	0.21 \pm 0.29	-0.36 \pm 0.28
	MB		0.02 \pm 0.31
Across species	LF	0.14 \pm 0.13	-0.10 \pm 0.14
	MB		0.08 \pm 0.13

(Table 7). All genetic correlations for the resistance to mortality between one of the growing sites and the experimental infection against *V. splendidus* were low and not significantly different from 0, ranging from -0.36 to 0.18 (Table 7). The phenotypic correlation between sites and experimental infection across species is illustrated in Supplementary Fig. S4.

Across species, genetic correlations between growth traits were positive and high ranging from 0.80 to 0.96 in La Floride, and ranging from 0.77 to 0.95 in Maison Blanche (Table 8). Genetic correlations between resistance to mortality and growth traits were not significantly different from zero in La Floride (0.04 to 0.19), and Maison Blanche (0.02 to 0.11, Table 8). The species-specific genetic correlation for both La Floride and Maison Blanche is presented in Supplementary Tables S4, S5 and S6.

4. Discussion

Developing routine genetic evaluation systems for resistance to mortality outbreaks in the field is an important step for producing robust strains (Ren et al., 2022). The use of such method is particularly relevant in breeding programs for aquaculture species, especially for an unknown causative agent. This is the case of AMM occurring in France since 2014 as reported by Benabdelmouna et al. (2018), which lead to drastic production and economic loss in 2014 and 2016. So, it is an important initiative to evaluate the genetic variability of resistance to AMM of the mussel stocks and species cultivated in France, in order to sustain the mussel production.

Our major objective was to investigate the genetic parameters of the resistance to AMM in mussels to assess whether selective breeding to enhance survival could be achieved in the two main mussel species cultivated in France. Additionally, resistance of the mussels were also

Table 8

Genetic correlations across species between growth traits and between growth traits and resistance to mortality in La Floride (above the diagonal) and in Maison Blanche (below the diagonal).

La Floride/ Maison Blanche	TW	TL	W	H	SW	DFW	M
TW		0.86 ±	0.85 ±	0.81 ±	0.85 ±	0.86 ±	0.11 ±
		0.03	0.03	0.04	0.03	0.04	0.15
TL	0.89 ±		0.96 ±	0.91 ±	0.91 ±	0.87 ±	0.13 ±
	0.02		0.01	0.02	0.02	0.03	0.14
W	0.86 ±	0.95 ±		0.88 ±	0.91 ±	0.87 ±	0.19 ±
	0.03	0.01		0.03	0.02	0.03	0.14
H	0.86 ±	0.92 ±	0.86 ±		0.88 ±	0.80 ±	0.04 ±
	0.03	0.02	0.03		0.03	0.04	0.15
SW						0.80 ±	0.07 ±
						0.05	0.15
DFW	0.84 ±	0.83 ±	0.79 ±	0.77 ±			0.10 ±
	0.03	0.04	0.04	0.04			0.06
M	0.02 ±	0.07 ±	0.11 ±	0.04 ±		0.06 ±	
	0.12	0.12	0.12	0.12		0.12	

TW: Total weight; TL: Total Length; W: Width; H: Height; SW: Shell Weight; DFW: Dry Flesh Weight; M: Mortality.

evaluated against one pathogenic strain of *V. splendidus* isolated during the first mortality outbreak in 2014, in order to estimate its relevance in AMM.

4.1. Resistance to mortality outbreaks in the field

4.1.1. Species and population susceptibility in field site

Species-specific differences in mortality may have important consequences for the distributions and persistence of these mussels (Nicastro et al., 2008; Sherwood and Petraitis, 1998). Strong species by site interaction was found at endpoint in June 2018 suggesting that different causative agents between sites (Fig. 2). Our study is in agreement with results obtained for *M. edulis*, unselected and selected against AMM through a first generation of mass selection, and tested in several environments along the French coasts in 2017 (Degremont et al., 2019). Thus, sites in Vendée and Pays de Loire areas are more likely to be impacted by AMM outbreaks than sites in Charente-Maritime, as described in Pépin et al. (2019). It is interesting to note that in the absence of AMM, *M. galloprovincialis* are less resilient than *M. edulis* in La Floride (Fig. 2A). This could partly explain the patch of pure *M. edulis* in Vendée and Charente-Maritime, whereas it is surrounded by hybrids and then pure *M. galloprovincialis* northern in the Brittany region, and southern in the south of the Nouvelle Aquitaine region (Fig. 1) (Simon et al., 2020). For mussels deployed at Maison Blanche, a site regularly impacted by AMM, *M. edulis* exhibited a higher susceptibility compared to *M. galloprovincialis*, while hybrids were intermediate. Our findings agree in part with prior research conducted at the spat stage under laboratory conditions, which reported a slightly higher mortality in *M. edulis* (20%) compared to *M. galloprovincialis* (16%) (Benabdelmouna et al., 2018). Nevertheless, it is relevant to suggest that in their study, the mortality pattern is different of AMM in field condition as hybrids exhibited higher mortality than *M. edulis* and *M. galloprovincialis*. Consequently, our study represents the first investigation of species-level mortality due to AMM outbreaks in France at the adult stage. Due to the absence of commercial mussel hatchery in France, and so selective breeding program, our results suggest that in sites where recurrent AMM outbreaks occurs, survival can be enhanced by growing *M. galloprovincialis*.

Regardless of the growing sites, our study consistently demonstrated that hybrid mussels exhibited intermediate mortality rates. Natural hybrid populations had a range of admixture proportions observed between the two parental species, *M. edulis* and *M. galloprovincialis* (Simon et al., 2020). It results in a mix of traits and characteristics as observed in *M. trossulus* and *M. galloprovincialis* (Braby and Somero, 2006). Thus, differences in mortality between species with intermediate performances for hybrids strongly supports a genetic basis to AMM in Maison Blanche, as well as to the mortality pattern observed in La Floride. This genetic diversity may confer a level of adaptability and resilience to environmental challenges, potentially explaining intermediate mortality rates observed across different conditions. Further investigations should explore the implications of the genetic diversity within and between mussel species for understanding resistance mechanisms to AMM, as well as the mortality pattern observed in La Floride.

Furthermore, it's worth highlighting that when comparing populations within each species and within each site, we observed no significant variations in mortality at endpoint (Supplementary Fig. S2). This finding strongly implies the absence of local adaptation to mortality events, either AMM or not, irrespective of the geographic origins of these mussel populations. Similar findings were observed in *Ostrea lurida*, where F₂ oysters from three different populations were tested for low salinity tolerance in a controlled laboratory environment, with no significant differences in tolerance levels detected among these populations (Bible and Sanford, 2016). Hughes et al. (2017) conducted a reciprocal transplant experiment with juvenile oysters from six populations at three sites, revealing significant genetic-environment interactions impacting oyster survival and growth, yet there was no evidence for local adaptation. The lack of significant population-based variations in mortality across different geographic origins raises the possibility that these mortality outbreaks could be a recent phenomenon in France.

4.1.2. Genetic parameters

Our study represents the first report of heritability estimates for resistance to mortality outbreaks in *M. edulis*, *M. galloprovincialis* and natural hybrids in France. In a site where AMM was observed, moderate narrow-sense heritabilities (Table 5) indicate that selective breeding will enhance resistance to AMM in both mussel species. Notably, the highest heritability was observed in *M. edulis* (0.34), intermediate for hybrids (0.25) and the lowest for *M. galloprovincialis* (0.16) on an underlying scale. This finding aligns with a previous study by Degremont et al. (2019), which also highlighted substantial genetic variation in *M. edulis* related to improved survival against AMM outbreaks in France, with an increase of 34–48% after one generation of mass selection. Lower heritability estimates for resistance to mortality was observed for mussels tested in La Floride, ranging from 0.12 to 0.17, with the same ranking among species. Unfortunately, to our knowledge, studies estimating heritability for mortality in mussel species are scarce, and none have compared several mussel species tested in the same environment yet. Mallet et al. (1986) reported similar heritability values for survival to those estimated in La Floride, ranging from 0 to 0.15 in adults in *M. edulis*. Similarly, heritability of heat tolerance among veligers was extremely low in Zebra mussels (Elderkin et al., 2004). Nevertheless, our heritability estimates can be compared with other bivalves, such as in *C. gigas* with similar values for summer survival (0.12–0.28) and survival in a field environmental condition (0.16–0.43), or the Caribbean scallop (*Argopecten nucleus*) that exhibited a low heritability (0.20) for survival after nine months of cultivation in natural marine conditions (Barros et al., 2018; Chi et al., 2022; Ernande et al., 2004).

4.1.3. Genetic correlation between growing sites

Genetic correlation between mortality recorded in MB and LF, was low and non-significantly different from 0 across all mussel species (0.14), as well as for each species (Table 7). Consequently, AMM at MB and mortality at LF are different traits, and selection to improve resistance to AMM should neither increase nor decrease the resistance to

mortality event in La Floride within or among species. Similar results were found when survival was assessed across different testing sites, showing no significant genetic correlation (strong family re-ranking) for survival in Nile tilapia (Luan et al., 2008), Yesso scallop (Wu et al., 2022), and Pacific oyster (De Melo et al., 2018). Selective breeding program to enhance resistance to mortality events in mussel species should be developed for each environment. It also suggests that the causative factors contributing to mortality outbreaks in the field may vary, emphasizing the need for further research to unravel these complexities.

4.1.4. Kinetics of mortality

Most of the mortality occurred during the spring in each site (Fig. 2). This period correspond to the spawning season in mussel species in France as activation of the gonad generally starts before winter and gametogenesis takes place over winter (Kamermans et al., 2013). Usually, mussels species undergo several spawning peaks during the spring either in *M. edulis* or *M. galloprovincialis* (Bouquet et al., 2019; Villalba, 1995). Along the French coasts in 2018, a massive spawning was observed late April (Bouquet et al., 2019). This step is well known that it compromises their immune defences, leaving them more susceptible to stressors during the subsequent post-spawning stage (Li et al., 2007). Such physiological demands may contribute to a state of weakened resilience among mussels, potentially playing a role in mass mortality events in France (Benabdelmouna et al., 2018; Charles et al., 2020a; Degremont et al., 2019). It ultimately shows that a spawning event could render mussels more susceptible in both sites, with many associated risk factors contributing to mass mortality outbreaks in Maison Blanche during the spring.

4.2. Genetic parameters for growth and its relationship with resistance to mortality events

The heritability estimates for growth traits were high in both sites for all mussel species (Tables 6 and 7). Heritability estimates for growth-related traits have been explored in several mussel species tested in various environment, including *M. galloprovincialis* (Nguyen et al., 2014) ranges from 0.23 to 0.64, *M. edulis* (Mallet et al., 1986; Stromgren and Nielsen, 1989) exhibits a range of 0.2 to 0.9, *M. chilensis* (Gutiérrez et al., 2017) shows a range of 0.29 to 0.71, Greenshell™ mussel *Perna canaliculus* (Hess et al., 2018) demonstrates a range of 0.41 to 0.92, and the purple freshwater pearl mussel *Hyriopsis cumingii* (Hu et al., 2021) displays a range of 0.24 to 0.49. Notably, our study identified higher genetic variation for growth traits than previous findings in mussel species, which underscore the potential for enhancing growth traits in each mussel species used in our study through selective breeding. Meanwhile, these high estimates could be substantially inflated by common environmental effects, stemming from the separate rearing of families over an extended period of approximately 7 months (Gallardo et al., 2010; Pham et al., 2021). The practical challenges of mitigating common environmental effects, such as early communal rearing require genetic markers to identify parentage among all recorded mussels as performed in Nguyen et al. (2014).

The growth traits showed high positive genetic correlations, which is consistent with previous report in *P. canaliculus* (Hess et al., 2018) and *C. gigas* (Jourdan et al., 2023). Thus, selective breeding program focusing on total body weight would undeniably also increase other morphometric and weight traits. Indeed, some genes are likely to be common between growth traits. Interestingly, genetic correlations between mortality and growth traits at both growing sites were low and non-significantly different from 0 suggesting that these traits are likely controlled by different, unlinked sets of genes. Previous reports suggest that similar findings between growth and survival in oysters (Chi et al., 2022; Chi et al., 2021; Degremont et al., 2007), rainbow trout (Silverstein et al., 2009), black tiger prawn (Kenway et al., 2006), and whiteleg shrimp (Zhang et al., 2017). As a result, increase resistance to mortality

event, either AMM or not, in *M. edulis* and *M. galloprovincialis* would not have an antagonistic impact on growth traits.

4.3. Genetic parameters for experimental infection

Bacterial diseases caused in particularly by members of the genus *Vibrio* infects larval, juvenile, and adult molluscs and induced mortalities in numerous bivalve species including oysters, mussels, abalones, clams, and scallops (Beaz-Hidalgo et al., 2010; Ben Cheikh et al., 2017; Paillard et al., 2004; Travers et al., 2015). In line with these findings, previous results have suggested that *V. splendidus* may be potential pathogens involved in AMM outbreaks (Oden et al., 2016; Polsenaere et al., 2017). High level of phenotypic variation among families for resistance to *V. splendidus* was observed for each species, with the cumulative mean mortality rate ranging from 3 to 90%. Thus, both species, as well as natural hybrids were susceptible to this strain of *V. splendidus*. To our knowledge, our study is the first to investigate mussel resistance to pathogens using hatchery-produced mussels. This is an important point to note, as the use of mussels from different origins sampled in the wild could be highly biased due to the lack of information on mortality prior to sampling. Other studies investigated difference in virulence among isolates from cultures mussels in mortality events (Oden et al., 2016; Yang et al., 2020). Low to moderate heritability was estimated (Table 5) indicating that genetic basis of disease resistance against *V. splendidus* is available in *M. edulis*, *M. galloprovincialis* and natural hybrids. In contrast with heritability in field condition, *M. galloprovincialis* had higher heritability than *M. edulis* and hybrids. Heritabilities of resistance to vibriosis in natural outbreaks were found to be low to moderate (h^2 ranging from 0.04 to 0.21) and significantly different from zero in Chinese tongue sole, *Cynoglossus semilaevis* (Hu et al., 2020). Similar findings have been reported for genetic analysis of survival data in experimental challenge tests on aquaculture species, salmon (Barria et al., 2019; Yanez et al., 2016); Tilapia (Joshi et al., 2021); catfish (Vu et al., 2019), and oysters (Azema et al., 2017; Degremont et al., 2015b; Zhai et al., 2021).

More importantly, the genetic correlation between one of the growing sites and experimental infection against *V. splendidus* was non-significantly different from zero within and among species (Table 7). It clearly demonstrates that the family rank varied between environments, indicating strong GxE in mussel species. These results suggest that mass mortality outbreaks result from a combination of multiple causes, including pathogens. More specifically, emergence of pathobiomes (pathogenic agent integrated within its biotic environment) may lead to mortality outbreaks (Meistertzheim et al., 2017). Initial infection by primary pathogens induces immune compromise, enabling subsequent bacteraemia by opportunistic environmental pathogens, including the *V. splendidus* strain. Future investigations of the pathobiomes are required to reveal the causative agent of the outbreaks. The occurrence of mass mortality appears to be intricately influenced by a complex interplay of host, pathogens, and environmental factors. In oyster, Pacific oyster mortality syndrome results from a multifaceted infection process, initiated by the infection of oyster haemocytes with the Ostreid herpesvirus OsHV-1 μ Var progressing to subsequent bacteraemia caused by opportunistic bacteria (De Lorgeril et al., 2018). This finding indicated that even if *V. splendidus* can induce mortality in mussel species, it might not be the main cause of mortality observed in field condition, either in AMM site or for the mortality pattern observed in La Floride in 2018. Oden et al. (2016) identified a strain (M3H) within the *V. splendidus* group using Multi-Locus Sequence Analysis (MLSA) that induced mortality rates of up to 80% in mussels, highlighting its potential pathogenicity. Consequently, selective breeding program to enhance resistance to *V. splendidus* will neither increase resistance to mortality events in any mussel species. Moreover, it's essential to understand that *V. splendidus* related strains (*V. crassostreae* 7T4_12 and *V. splendidus* 3G1_6) were not inherently virulent to mussels, and their pathogenicity depended on mussel physiology, seasonal timing, and the origin of spat recruitment

(Charles et al., 2020b). It will be highly relevant to test other pathogens detected in mortality events to disentangle their role in AMM outbreaks, as *Francisella halioticiada* (Bouras et al., 2023; Charles et al., 2020c) or other *V. splendidus*-related strains (Charles et al., 2020b; Oden et al., 2016). Such experiments could be easily set up through experimental infection with these potential putative causal agents using susceptible and resistant mussel families for each species.

4.3.1. Pathogen specificity and impact

V. splendidus induced mortality in both mussel species and hybrids. The non-significant from zero genetic correlation between AMM site and experimental infection against *V. splendidus* showed this pathogen is not the main pathogen in the AMM outbreak in 2018, but it could be one of the pathogens involved in the mortality outbreak. It is now increasingly accepted that many diseases are caused not by a single pathogen but by a consortium of pathogens and host microflora, the pathobiome. POMS disease in oysters, for example, is caused by a consortium of micro-organisms including the herpes virus OsHV-1 and bacteria from the *Splendidus* or *Harveyi* clades (De Lorgeril et al., 2018; Oyanedel et al., 2023). For AMM, there is currently no consensus on the consortium of micro-organisms that could be involved. Some virulent *V. splendidus* strains were isolated in moribund mussels (Oden et al., 2016; Polsenaere et al., 2017). Some *Francisella halioticiada* strains were also isolated from field mortality and could be implied in field mortality (Bouras et al., 2023; Charles et al., 2020c). Transmissible neoplasia affecting mussel immune cells could also have an influence on mussel physiology (Burioli et al., 2021). Moreover, one can not exclude the implication of non-culturable pathogen. However, as a *V. splendidus* phylogenetically defined group has been isolated from the large majority of moribund individuals sampled on mussel farms, and are virulent toward mussels by injection, this work aimed to assess its level of involvement in the mortalities observed in the field by comparing the evaluation of numerous families in both field and experimental infection which is the best method to figure it out.

4.4. Breeding program implications

Our study represents the first report of heritability estimates for resistance to AMM of commercially important mussel species cultivated in France. Results highlight the potential of selective breeding to enhance resistance to AMM within wild mussel populations. Meanwhile, the significant $G \times E$ interaction observed for mortality, resulting in family re-ranking among *M. edulis*, *M. galloprovincialis*, and hybrids when reared in different environments, suggest to develop selective breeding programs for each environment. Consequently, and due to the strong impact of AMM on profitability of mussel farmers, optimizing selective breeding programs to enhance mussel survival should be prioritized against AMM across. Further studies are needed to test mussel selected families in several AMM sites to validate the present results, although it was found that one selected line against AMM in *M. edulis* had a gain of survival across three sites (Degremont et al., 2019). A strategy involving strong selection for sites experiencing AMM outbreaks, while adjusting the relative selection weight for low mortality sites in *M. edulis*, *M. galloprovincialis*, and hybrids, may reduce the impact of mortality outbreaks by selecting families with the highest breeding values for resistance. However, it's important to note that if mortality is caused by different etiology, the genetic gain for resistance to AMM may be reduced (as indicated by our results) due to the selection of multiple traits. Furthermore, given the unknown pathogens behind AMM outbreaks, there is a risk that different pathogens may appear in different years, leading to inconsistencies in selection programs and potentially lower genetic gain. Nevertheless, selection will then focus on this emergence, to include this new trait in the selective breeding scheme.

4.5. Societal and environmental implications

The recent collapse of the French oyster industry from 2008 to 2010 due to mass mortality outbreak (Girard and Agúndez, 2014) highlights the urgent need to mitigate AMM outbreaks in the mussel industry. In France, the reliance on wild spat collection for mussel production poses significant challenges, including the depletion of local stocks and susceptibility to disease outbreaks (Lupo et al., 2021; Prou and Gouletquer, 2002). Indeed, wild caught spat occurs in sites highly impacted by AMM outbreaks, which are then sold to mussel farmers along the Atlantic coasts and in the Channel. Such strategies, repeated annually, can rapidly spread AMM along the coasts in the near future, potentially threatening to the French mussel farming industry. Despite these risks, there has been limited focus on selecting for resistance to AMM to date, due to hatchery-produced mussels are forbidden for cultivation by some mussel farmers and their representatives. Our study found that wild spat collected from sites where our populations were sampled, and cultured in AMM sites are highly susceptible to AMM outbreaks that leads to only potential solution for sustainable mussel farming in AMM sites is to prioritize the cultivation of wild caught *M. galloprovincialis*. By emphasizing the importance of selective breeding to produce resilient mussel populations, the impact of AMM outbreaks can be mitigated to promote sustainable mussel farming practices in France and also in other countries where *M. edulis* and *M. galloprovincialis* are cultivated.

4.6. Limitations and future directions

Our study focused on selection strategies aimed at enhancing survival until the harvest season in field experiments, with the goal of improving industry profitability. One significant limitation is the uncertainty surrounding the specific pathogen(s) involved. Moreover, there are indications that multiple pathogens could be contributing to the AMM outbreaks. The reliance solely on field tests for selection presents practical difficulties and risks of failure, particularly in complex field environments where infection pressure is uncontrolled and disease outbreaks recorded as AMM which is site and year specific (Lupo et al., 2021; Polsenaere et al., 2017). In our investigation, we performed a challenge test using a strain of *V. splendidus* associated with AMM outbreaks. However, it is necessary to test for other potential pathogens to comprehensively understand the disease dynamics, such as *F. halioticiada*. Furthermore, understanding environmental factors influencing disease outbreaks and contributing to mass mortalities is crucial for developing effective management strategies.

5. Conclusions

Strong species by environment interaction was found, with higher susceptibility to AMM for *M. edulis*, while it has highest resistance to the mortality in La Floride. If AMM generalised among sites in the next future, then *M. galloprovincialis* might offer a substantial benefice to the French mussel farmers, knowing that hatchery-produced mussels are not authorized along the French coasts. Resistance levels remained consistent among populations within species for both mortality patterns in our study. The estimated heritabilities suggest the potential for improving mussel survival in France through selective breeding programs. The weak genetic correlation between mortality in AMM site and experimental infection suggests the tested *V. splendidus* strain may not be the main cause of AMM in France in 2018. Notably, enhancing AMM resistance won't impact growth.

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Munusamy Ajithkumar: Data curation, Formal analysis, Software, Writing – original draft, Writing – review & editing. **Marie Lillehammer:** Software, Supervision, Writing – review & editing. **Marie-Agnès Travers:** Methodology, Writing – review & editing. **Elise Maurouard:** Methodology. **Muhammad Luqman Aslam:** Software, Writing – review & editing. **Lionel Dégremont:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.aquaculture.2024.741034>.

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