IR Inter-Research Science Publisher

Diseases of Aquatic Organisms
Volume 163:63–78

Published August 14, 2025
https://doi.org/10.3354/dao03862

Erysipelothrix rhusiopathiae occurrence, epidemiology and vaccine reactions in cetaceans: a thirty-year retrospective based on two global surveys

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ABSTRACT: Erysipelas, an infection caused by *Erysipelothrix rhusiopathiae*, has always been a threat to marine mammal collections. A first global survey (1989–2000) about erysipelas occurrences, covering 1384 animals, reported 69 cases of erysipelas (5%). To better understand the disease epidemiology and vaccine-related reactions, a second survey (2001–2020) was conducted, reaching a 68.6% response rate (140/204 facilities) and including 2267 cetaceans. It reported 108 cases (4.8%), with more than 5 cases annually and a 50% fatality rate. At least 1 case was reported in 40% of responding facilities, all involving non-vaccinated animals or those vaccinated only once or twice. Most facilities began vaccinating after experiencing a case, while fear of adverse fatal anaphylaxis reaction remains the primary reason for avoiding it. Notably, only 1 fatal vaccine reaction was reported in 1989, though procaine penicillin had been co-administered. Adverse reactions were rare and mostly resembled expected inflammatory reactions post vaccination such as anorexia, local swelling or blood changes. These were more frequent with oil-adjuvanted vaccines containing alpha-tocopherol or Amphigen®, and minimal to absent with aluminum hydroxide-based vaccines. Three facilities using the Amphigen®-adjuvanted ER Bac® Plus vaccine (Zoetis) observed transient lethargy and irregular breathing in 8 animals after several vaccinations, of which 1 had been treated. Regional differences in vaccine availability were observed. This 30 yr retrospective study highlights that cetaceans in human care face a greater risk of dying from erysipelas than from vaccine side effects. Furthermore, regular vaccination appears to offer effective protection against this preventable disease.

KEY WORDS: *Erysipelothrix rhusiopathiae* · Epidemiology · Vaccination · Risk assessment · Anaphylactic reaction · Cetacean · Survey

1. INTRODUCTION

Erysipelas is an infectious disease caused by the Gram-positive bacterium *Erysipelothrix rhusiopathiae*. It can affect a wide number of species worldwide including cetaceans, and has always been a threat to marine mammal collections (Ridgway 1972, Wood 1975, Medway 1980). Most of what is known about the disease comes from studies in pigs, where *E. rhusiopathiae* causes significant pathological and economic impact in livestock farming. Interestingly, up to 50% of healthy pigs are reported to be carriers, often harboring the organism in their tonsils (Wood 1975, 1992, Stephenson & Berman 1978, Opriessnig et al. 2020). *Erysipelothrix* species have historically been classified into 26 serotypes and group N, mainly identified as 2 species, *E. rhusiopathiae* and *E. tonsillarum* (Kalf & White 1963, Nørrung & Molin 1991). While survival of the organism in the environment is limited over time, bodily fluids such as urine, feces, saliva or nasal mucus can be an important source of infection by carrier pigs, and animals with acute erysipelas can shed the bacte-

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ria for a long period of time. The bacterium can however survive for several months in frozen tissues, and also in decomposing carcasses or feces when present in a low (<12°C) temperature environment (Wood 1975, Opriessnig & Wood 2012). The bacterium is found to be commensal on the cutaneous slime of both freshwater and saltwater fish (Wood 1975, Bauwens et al. 1992). Transmission mainly occurs through mucosal contact or ingestion of contaminated food and water, though a wound can also serve as a route of entry (Wood 1992). *E. rhusiopathiae* has a zoonotic potential, being an occupational disease in humans through puncture or bite wounds in the skin leading to a cutaneous infection (erysipeloid), but cases of bacteremia and endocarditis have been described (Medway 1980, Suer et al. 1988, Veraldi et al. 2009, Opriessnig et al. 2020).

In most mammals, the clinical disease can present itself as acute septicemia, endocarditis, arthritis or skin lesions (often called 'diamond skin disease' in swine), occurring either alone or in combination (Gyles 1986). Two major forms of the disease can be seen in dolphins. The acute septicemic form is characterized by rapidly occurring death with little to no prior clinical signs and the subacute form may develop with or without the presence of the distinctive grey, diamond- or rhomboid-shaped skin lesions (Geraci et al. 1966, Sweeney & Ridgway 1975, Thurman et al. 1983, Kinsel et al. 1997). A less common vesicular glossitis form has also been described (Bossart & Eimstad 1988). Immediate treatment with antibiotics and general support can lead to recovery if the condition is diagnosed early enough, though this is rarely the case for the acute form (Thurman et al. 1983, Calle et al. 1993, Gearhart et al. 2005).

Erysipelas vaccines are commonly used in pigs (Wood 1992, Opriessnig & Wood 2012). Commercial erysipelas vaccines are predominantly developed from serotype 1 and/or serotype 2 strains, with serotype 1 typically used in attenuated vaccines and serotype 2 more often found in bacterins formulations (Opriessnig et al. 2020). Protection against *E. rhusiopathiae* is not serotype-specific though cross-protection between strains has been demonstrated (Takahashi et al. 1984). This is largely attributed to surface protective antigen (Spa) proteins on the surface of the bacteria, which serve as the key immunogenic components (Lachmann & Deicher 1986, Shimoji et al. 1999). There are 3 known Spa types — SpaA, SpaB and SpaC — each exhibiting genetic and antigenic diversity. While homologous protection within the same Spa type is well documented, heterologous protection between different Spa types is inconsistent (To & Nagai 2007, Shimoji et al. 2019).

Vaccination programs to protect cetaceans started in the 1960s (Geraci et al. 1966) and the vaccination strategies to address the infection threat in these animals have varied over the years. Modified live vaccines were first employed but later abandoned due to cases where the vaccine reverted to a virulent form, causing illness and fatalities post vaccination. This prompted the use of live avirulent vaccines and inactivated dead vaccines in cetaceans (Gilmartin et al. 1971, Ridgway 1972, L. Cornell pers. comm.). The administration of the latter has historically caused localized swelling and instances of fatal anaphylactic shock have reportedly been observed upon revaccination (Medway 1980, Sweeney 1986, Dunn 1990). This prompted numerous facilities in the late 1980s to adopt a one-time vaccination strategy or even to halt vaccination efforts entirely (Sweeney 1986, Dunn 1990, J. F. McBain pers. comm.). Some facilities continued vaccination, adapting their protocols as knowledge evolved (Nollens et al. 2016, Lacave et al. 2019). Various preventive measures to minimize adverse effects of vaccination have been implemented over the years, including postponing vaccination due to unsatisfactory blood test results, premedicating with antihistamines for potential allergic reaction (CDC 2018), keeping emergency medication on hand in case of anaphylactic shock and using lifting-floor pools for quick intervention.

Although reported as extremely rare, a severe allergic reaction like anaphylaxis can be a critical concern in a vaccination protocol and is among the most serious vaccine-associated adverse events (Bohlke et al. 2003, McNeil & DeStefano 2018, McLendon & Sternard 2023). The vaccine components that may cause allergic reactions can be related to either the antigen or added antibiotics, animal proteins, adjuvant, stabilizer or preservative in the vaccine (Mignault & Mitchell 1953, Bohlke et al. 2003, Leventhal et al. 2012, McNeil & DeStefano 2018). Adjuvants form a key component of inactivated and subunit vaccines, acting to potentiate and provide longer immunity (Burakova et al. 2018). Vaccines using aluminum hydroxide and aluminum phosphate as adjuvants, and produced as water-based suspensions, have had a safe profile in the last 6 decades in human and animal vaccinology; however, frequent revaccinations are needed (Burakova et al. 2018). Hypersensitivity to aluminum is rare though it has been documented in humans (Leventhal et al. 2012), with the most common presentation being painful and/or pruritic nodules at the injection site. However, no immediate hypersensitivity reactions to these adjuvants have been documented in humans (McNeil & DeStefano 2018). Oil-based emulsions, such as AS03 (composed of alpha-tocopherol, squalene and polysorbate 80), are also frequently used in veterinary vaccines and can induce a strong local inflammatory reaction, but sometimes also systemic symptoms like fever, headache, malaise and nausea (Stills 2005, Oda et al. 2006, Petrovsky 2008, Garçon et al. 2012).

Due to limited research on erysipelas epidemiology in cetaceans, and to better understand (1) changes in disease prevalence over time, (2) the effectiveness of vaccination and (3) concerns about fatal vaccine reactions, 2 global surveys were conducted. The first survey (1989–2000) examined cases in cetaceans under human care and found that all reported cases occurred in unvaccinated animals or those vaccinated only once, often years prior. No cases were reported in animals vaccinated regularly. These findings strongly supported the benefits of vaccination but did not define a protective antibody threshold (Boehm et al. 2000, Sitt et al. 2010). Despite further studies over the next 2 decades confirming the protective effect of vaccination (Nollens et al. 2016, Lacave et al. 2019), concerns remain. Fear of adverse reactions — especially fatal anaphylaxis — and the perception that erysipelas is rare still deters many facilities from vaccinating. In some cases, the risk of vaccination is viewed as greater than the disease itself (Walsh et al. 2005, Sitt et al. 2010). Therefore, a more in-depth second global epidemiological survey, covering the period from 2001 to 2020 and incorporating specific questions on vaccine types and reactions, was distributed.

The surveys provided data on erysipelas occurrence in managed cetacean populations, global vaccination status, infection rates in non-vaccinated versus vaccinated animals, vaccine types and protocols, and reported adverse reactions. These data were analyzed to assess disease prevalence, vaccination effectiveness and concerns regarding fatal adverse reactions.

2. MATERIALS AND METHODS

For both surveys, the questionnaires covered the species and numbers of cetaceans held in the facility during the time span of the respective study, whether cases occurred (fatal vs. non-fatal), the diagnostic and treatment methods, and whether vaccination was or is performed. Regular vaccination was categorized as either yearly or bi-yearly vaccination after booster at 3 to 4 wk post primary vaccination. No information about the type of vaccine, reactions or the reasons for not vaccinating was requested during the 1st survey (Text S1 in the Supplement at www.int-res.com/articles/suppl/d163p063_supp.pdf), but additional information was provided by a few facilities. For the 2nd survey (Text S2), questions pertaining to the type of vaccine and the frequency of vaccination, whether reactions occurred and of what kind, the reasons for vaccinating, not vaccinating or having stopped, and the species of fish offered and their quality control were added. Several questions had a few cascading sub-questions asking for further details.

For the 1st survey, covering the years 1989 to 2000, the questionnaire was distributed globally in 2000; for the 2nd survey, which addressed 2001 to 2020, it was distributed between 2020 and 2021, with a link to an online questionnaire. All contacted individuals and facilities that did not answer in the first 3 mo were sent 2 to 3 reminders in the following year, often in a personalized way. For the latter survey, the questionnaire was translated into Spanish, and veterinarians experienced in marine mammal medicine who were native speakers of Japanese, Chinese and Russian offered additional translations to reach a wider audience and increase the response rate. Most answers were followed up by e-mails and personal communications for more details in the subsequent 2 yr.

As respondents may belong to subgroups that differ from the total surveyed population, and because selection bias related to representativeness could potentially outweigh or significantly affect the overall response rate or survey information (Cook et al. 2000, Fincham 2008, Stratton 2012), the results were also divided into 6 geographical regions: (1) North America, (2) Western Europe, (3) Eastern Europe and Russia, (4) Asia and the Pacific, (5) Africa and the Middle East, and (6) the Caribbean and Latin America.

The different facilities of a single corporate company were counted individually. Cases from stranding networks and/or stranded mammals in rehabilitation were not included in the results though often reported in answers to the questionnaire.

While participants were asked to provide their contact and facility reference to the authors to prevent overlapping information, they were assured that the presentation of the results would be done anonymously.

3. RESULTS

3.1. Cases and vaccination status

The response rate for the 1st survey was 67.4% (97 out of 144 facilities contacted), representing 1384 animals, while the 2nd survey achieved a response rate of 68.6%

(140 out of 204 facilities), totaling 2267 animals. The percentage of responses to the surveys on a regional level and animal numbers are represented in Figs. 1 & 2.

Globally, 38 facilities (39%) experienced solitary or multiple erysipelas cases in their collection between 1989 and 2000, while 32 facilities (33%) implemented vaccination (Fig. 3a,b). During the period from 2001 to 2020 (2nd survey), 56 facilities (40%) faced erysipelas cases, and 32 facilities (23%) vaccinated their animals (Fig. 3c,d). These were not always the same facilities that were vaccinating during the 1st survey. The regional distribution of facilities with erysipelas cases is represented in Fig. 4.

Table 1 provides an overview of global erysipelas occurrences, with 69 cases reported between 1989 and 2000 (1st survey) and 108 cases between 2001 and 2020 (2nd survey), along with diagnostic methods, animals affected and their vaccination status. No case occurred in regularly vaccinated animals. Six cases were reported for the 1st survey in animals vaccinated once years before and 63 cases in animals that had never been vaccinated. For the 2nd survey, 2 cases were reported in animals vaccinated twice, 2 cases in animals vaccinated once and 104 cases in animals that had never been vaccinated. Table 2 details the regional distribution of erysipelas cases, including fatal and non-fatal outcomes, vaccination status and incidence rates of affected animals, while Fig. 5 presents a visual distribution of the evolution of the cases per region between both surveys.

The species distribution of the surveyed population and respective cases for both surveys are detailed in Table S1.

3.2. Vaccinating and non-vaccinating facilities

The global count of vaccinating facilities at the conclusion of each survey, along with the reasons for choosing vaccination and the respective vaccination schedules are shown in Table 3. The age of first vaccination for animals entering a vaccination program varies between 3 mo and 2.5 yr when born in human care. The vaccines used during the 2nd survey period, with information on their composition, are summarized in Table 4. They were used off-label. The global number of non-vaccinating facilities at the end of each respective survey, with the reasons for non-vaccination provided in the 2nd survey, are shown in Table 5. In the 2nd survey, some veterinarians stated that vaccination was unnecessary, citing the absence of cases at their facility; however, many of them were

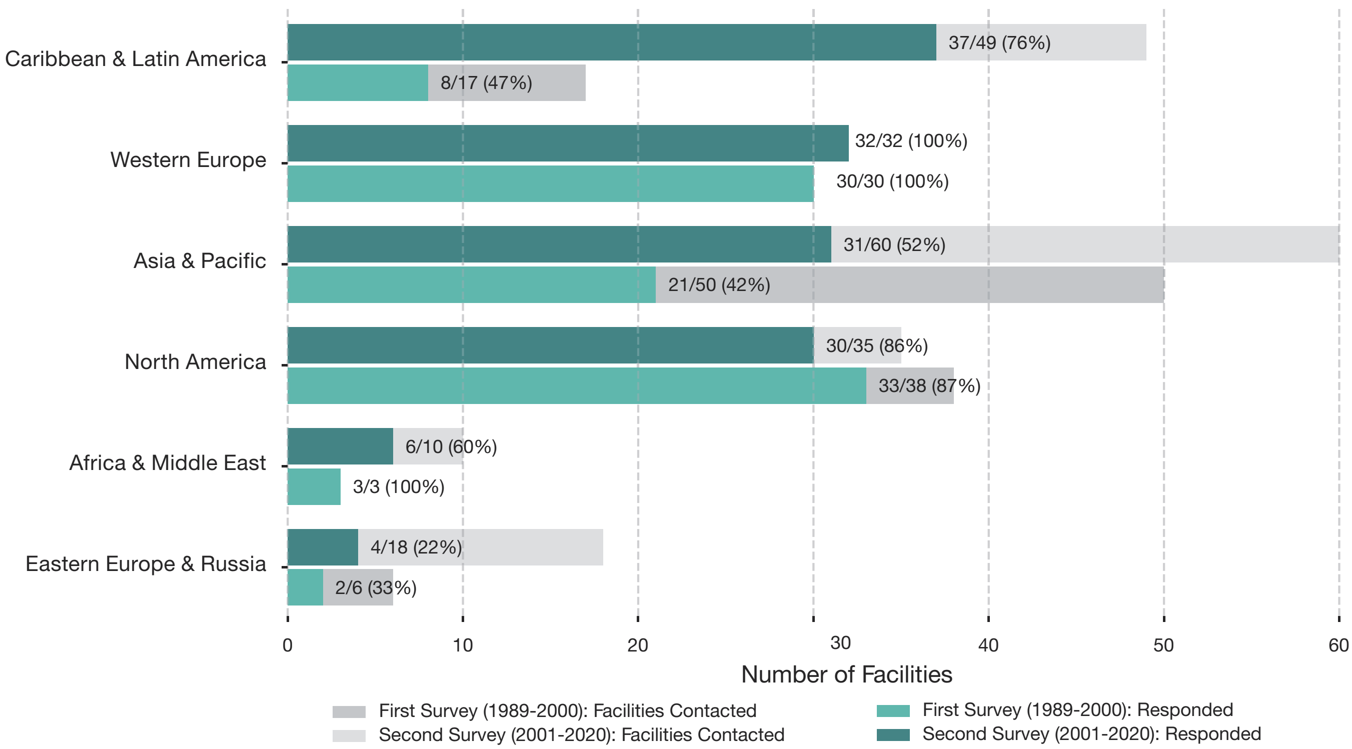

Fig. 1. Comparison of survey participation rate and regional distribution of responding facilities between the 1st and 2nd survey. The graphic is organized by descending order of response based on the results of the 2nd survey

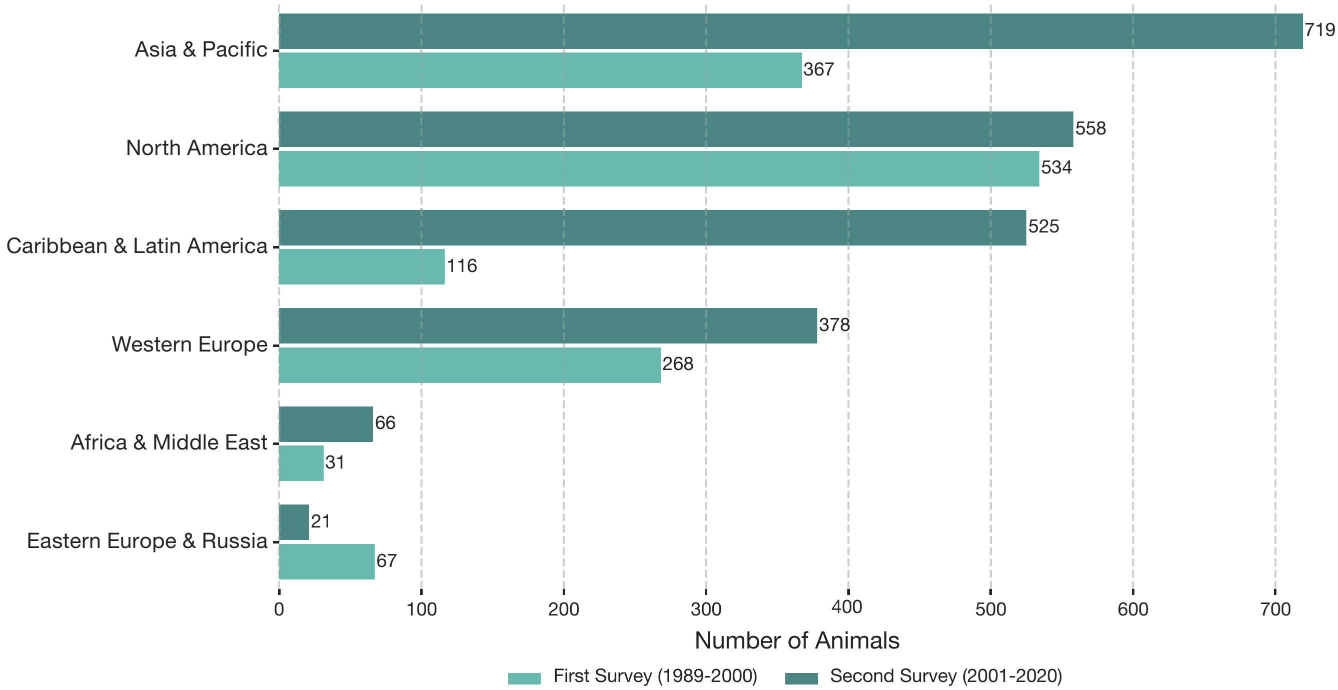

Fig. 2. Total number of animals represented per region in each survey. The graphic is displayed in descending order based on the total animal count from the 2nd survey

younger veterinarians unaware of previous cases reported by their predecessors during the 1st survey. Some facilities (n = 4) vaccinate individual animals in their population, because these are on loan from facilities requesting vaccination, but do not vaccinate their own. They were considered non-vaccinating facilities. One of these facilities experienced a non-fatal case in one of their non-vaccinated animals. In the year after the survey, at least 4 other non-vaccinating parks experienced a total of 2 fatal and 3 non-fatal cases. These latter cases were not taken into consideration in these results.

Fig. 6 presents the regional breakdown of vaccinating and non-vaccinating facilities at the conclusion of each survey period, along with the specific vaccines reported in the 2nd survey.

3.3. Vaccination reactions

In the 2nd survey (2001—2020), 11 facilities reported post-vaccination reactions in several of their animals, while 21 reported no adverse reactions (Table 6). No or minimal reactions were observed while using a vaccine with an aluminum hydroxide adjuvant. No fatal anaphylactic shock was reported. No information was gathered regarding vaccination through catching versus under behavioral control.

The amount of information received about the types of fish used, their handling and specifically their quality control was too much for the scope of this survey and we intend to analyze it in another study.

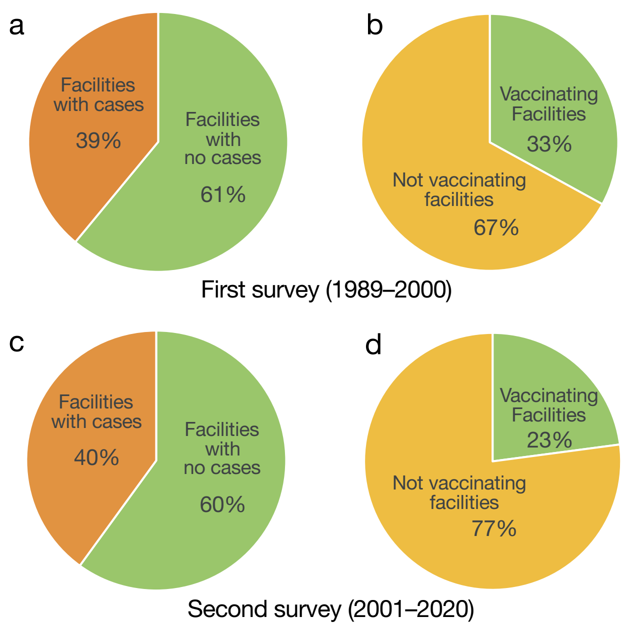

Fig. 3. A global comparison of the percentage of facilities with reported cases and vaccination rates for the (a,b) 1st and (c,d) 2nd survey periods

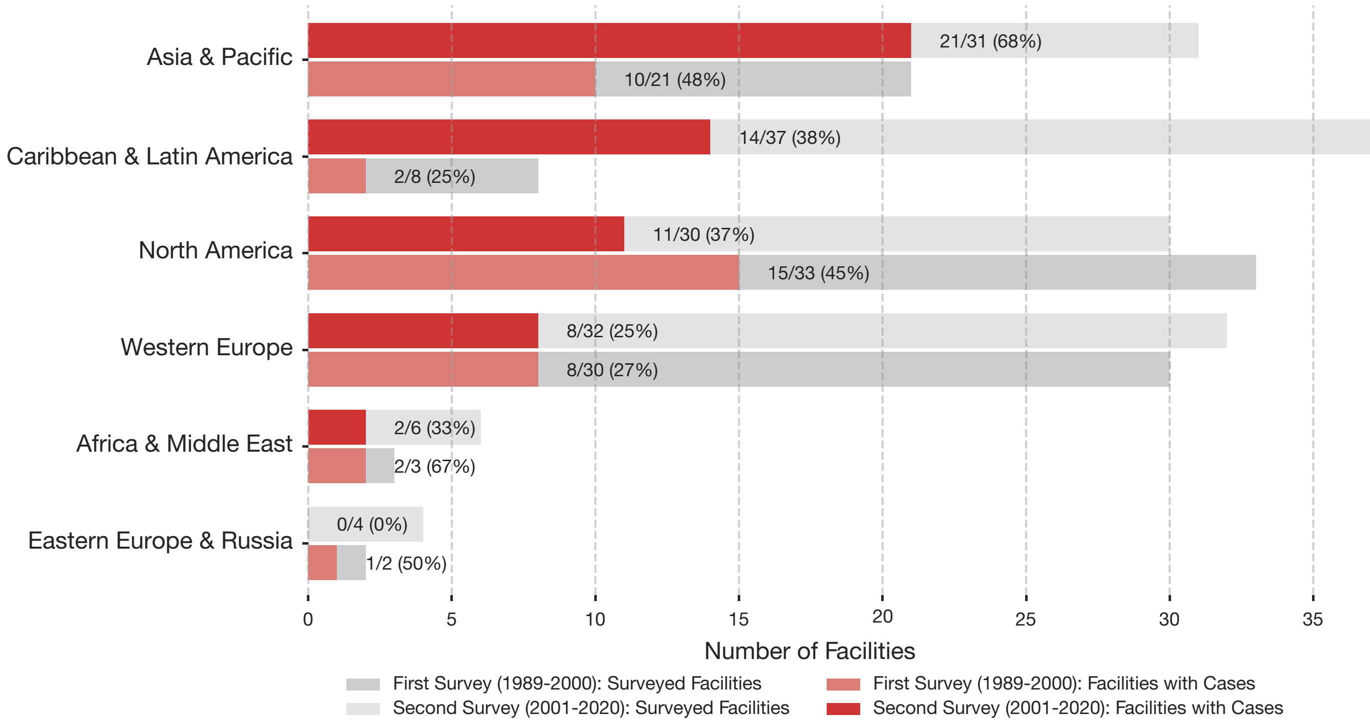

Fig. 4. Regional distribution of facilities with reported cases during each surveyed period. The graphic is displayed in descending order of affected facilities recorded in the 2nd survey

4. DISCUSSION

The 2 surveys and the analysis of the results can be considered as a descriptive observational epidemiologic study with analytic components (DiPietro 2010). The data obtained contribute to a broader scientific understanding of how *Erysipelothrix rhusiopathiae* exposure affects the cetacean population held in human care and the resulting outcomes. The results of the 2nd survey will be analyzed more thoroughly in terms of vaccines and reactions in this discussion, as this survey is more recent and more detailed, though the results will be considered in parallel with those obtained in the 1st survey 20 yr previously. The discussion will successively address (1) response rate and participating facility distribution, (2) erysipelas cases, (3) vaccines and vaccination, (4) vaccination reactions, and (5) efficacy and protection of vaccination.

4.1. Response rate and participating facilities distribution

Response rate and sample size are very important elements for validating scientific surveys as a poor response rate may yield selection bias, thus resulting in misleading information about the issues covered in a survey (Shih & Fan 2008, Stratton 2012). The larger the study sample, the lower the risk of errors in the reported results. The respective response rates of 67.4 and 68.6% for the 1st and 2nd surveys represent a high motivation of the participants to complete the surveys and provide very valid results to understand the erysipelas situation in the population of cetaceans held in human care (Cook et al. 2000, Fincham 2008, Shih & Fan 2008, Short et al. 2015, Cleave 2020)

For the 2nd survey, most of the facilities (92.8%) were equally distributed among (1) North America, (2) Western Europe, (3) Asia and the Pacific, and (4) the Caribbean and Latin America (Fig. 1). These 4 regions also represented 96.2% of the animals (Fig. 2). Though Asia and the Pacific had the highest number of animals overall, only about 50% of the contacted parks returned the questionnaire, very likely underestimating the erysipelas situation in that area of the world. Nevertheless, the results of these 4 regions allowed a good analysis. The remaining 7.2% were distributed between Africa and the Middle East and Eastern Europe and Russia.

4.2. Erysipelas cases

In 2000, it was reported that losses from *E. rhusiopathiae* used to be worse in the past and that improvements in animal husbandry had decreased incidence (Boehm et al. 2000). However, both surveys showed

Table 1. Global erysipelas occurrences, diagnostic methods, animals affected and relative vaccination status

	1st survey (1989–2000) (n = 1384 animals)	2nd survey (2001–2020) (n = 2267 animals)
Total erysipelas cases	69 (5%)	108 (4.8%)
Fatal cases	22 (31.9%)	52 (48.2%)
Adult animals	19	45
Calves	3	7
Nursing but not yet eating (2 to 8 mo)	2	4
Nursing and also eating (≤1 yr)	1	3
Diagnostic methods		
Isolation (post-mortem cultures)	19	20
Isolation (hemoculture and post-mortem cultures)		15
Isolation (hemoculture and fine-needle aspirates)		5
Isolation (hemoculture)		3
Confirmation by PCR		3
Presence of rhomboid lesions and rise in antibody titer	1	
Presence of rhomboid lesions only	1	
Following clinical report, acute septicemia and (hemorrhagic) aspects of all organs at necropsy	1	6
Vaccination status		
Never vaccinated	21 (95.5%)	49 (94.2%)
Vaccinated once	1[a]	2[b]
Vaccinated twice		1[c]
Non fatal cases	47 (68.1%)	56 (51.8%)
Adult animal	46[d]	55
Calves	1	1
Nursing but not yet eating (7 d)	1[e]	
Nursing and also eating (≤1 yr)		1
Diagnostic methods		
Isolation (hemoculture and/or fine-needle aspirates)	12	22
Presence of rhomboid lesions and rise in antibody titer	4	0
Presence of rhomboid lesions, leucopenia/leucocytosis and clinical picture	3	8
Presence of rhomboid lesions only	23	22
Sero-conversion in paired sera without rhomboid lesions	2	4
Following clinical findings (and rhomboid lesions in other animal)	1	
Incidental findings (isolation at necropsy—unrelated death cause)	2[d,e]	
Vaccination status		
Never vaccinated	42 (89.4%)	55 (98.2%)
Vaccinated once	5[a]	
Vaccinated twice		1[a]

[a]Years before; [b]At 3 to 4 wk previously and 10 yr previously; [c]At 3 and 2 mo before death; [d]Including 1 incidental isolation at necropsy — unrelated death cause (twisted bowel); [e]Incidental isolation at necropsy — unrelated death cause (trauma)

similar results in percentage of facilities and animals affected (Table 1, Figs. 3 & 4). Erysipelas is still as present in the population of cetaceans held in human care in 2020, with more than 5 animals infected per year and more than 1 out of every 3 facilities having had a case during the last 20 yr. But while the fatal cases represented about 1/3 (31.9%) of the total cases in the 1st survey, they reached nearly 50% in the 2nd survey (Table 1, Fig. 5). From the analysis of the data provided in the questionnaires, no reason for this higher mortality outcome could be identified.

The percentage of erysipelas cases reported in the population may not reflect the situation exactly. Indeed, in epidemiology, the incidence of a disease is commonly defined as the percentage of individuals getting the disease during a specified time period in a population at risk (Tenny & Hoffman 2023). No case occurred in regularly vaccinated animals, supporting the protective effect of vaccination. Hence, the part of the population that is vaccinated is no longer at risk, and as such, the incidence of infection in the population over the last 20 yr is likely much higher than 4.8%. However, the questionnaire did not allow specific determination of how many animals were vaccinated, but only whether a facility vaccinates or not and whether an affected animal was vaccinated or

Table 2. Regional distribution of erysipelas cases, including fatal and non-fatal outcome, vaccination status, and incidence rates of affected animals, during the 1st (1980–2000, n = 1384, 69 cases) and the 2nd (2001–2020, n = 2267, 108 cases) surveys

	North America		Western Europe		Asia and Pacific		Caribbean and Latin America		Africa and Middle-East		Eastern Europe and Russia	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Animals	534 (38.6%)	558 (24.6%)	268 (19.4%)	378 (16.7%)	367 (26.5%)	719 (31.7%)	116 (8.4%)	525 (23.2%)	31 (2.2%)	66 (2.9%)	67 (4.8%)	21 (0.9%)
Erysipelas cases	23 (33.3%)	24 (22.2%)	14 (20.3%)	11 (10.2%)	23 (33.3%)	52 (48.2%)	3 (4.4%)	19 (17.6%)	5 (7.2%)	2 (1.9%)	1 (1.5%)	0
Fatal	9	11	9	10	3	23	0	8	0	0	1	
Not vaccinated	7	11	7	9	3	22		8			1	
Animal vaccinated once	2[a]		2[c]	1[c]								
Animal vaccinated twice						1[d]						
Non-fatal	14	13	5	1	20	29	3	11	5	2	0	
Not vaccinated	14	12	4	1	20	28	3	11	4	2		
Animal vaccinated once		1[b]	1[c]						1[c]			
Animal vaccinated twice						1[c]						
Incidence rate of affected animals (%)	4.3	4.4	5.2	2.9	6.3	7.2	2.6	3.6	16.1	3	1.5	0

[a]Two years and many years before; [b]Primovaccination 3 to 4 wk before; [c]Many years before; [d]At 3 and 2 mo before death

not. Also, clinical infections with *E. rhusiopathiae* could be underestimated as clinical samples submitted for investigations, during active disease or post mortem, are generally from animals being treated with antibiotics, thus strongly decreasing or potentially eliminating the chance of isolating the bacteria.

Interestingly, cases were also identified in nursing calves which were not yet eating fish (Table 1). This agrees with previous statements that contamination can occur not only through uptake of infected fish but also via other routes, such as contaminated water, cutaneous injuries or arthropod vectors (Geraci et al. 1966, Wood 1992).

Cases were reported in all regions of the world during both surveys except in the Eastern Europe and Russia region during the 2nd survey (Table 2, Fig. 4). However, with only 4 facilities and 21 animals all belonging to the same Russian corporation group, we can hypothesize that the results may be biased. This Russian group, which did not participate in the 1st survey, did however report having had a case in the late 1990s.

While participation levels from facilities in North America and Western Europe were similar in both surveys, participation from Asia and the Pacific rose by 50% and the Caribbean and Latin America region saw a fourfold increase, likely due to the growing number of new facilities established in the region over the past 2 decades (Fig. 1). Since the 1st survey, the proportion of facilities with cases has remained largely unchanged in Western Europe, declined in North America and increased in both Asia and the Pacific and the Caribbean and Latin America (Fig. 4). If we look at the evolution of cases between the 1st and the 2nd survey proportionally, North America still has the same incidence rate in its population, while the rate in Western Europe and Africa and the Middle East has dropped and those in Asia and the Pacific and the Caribbean and Latin America have risen (Table 2). More facilities and animals were affected in Asia and the Pacific, and fewer in Western Europe. At this point, it is not possible to determine objectively whether this difference stems from management (the overall institutional strategies and policies governing animal operations) or from husbandry (the daily care and maintenance of the animals), as no objective evaluation of either has been conducted to date in the marine mammal field.

4.3. Vaccines and vaccination

Swine erysipelas vaccine availability varies globally (Opriessnig et al. 2020), further supporting the divi-

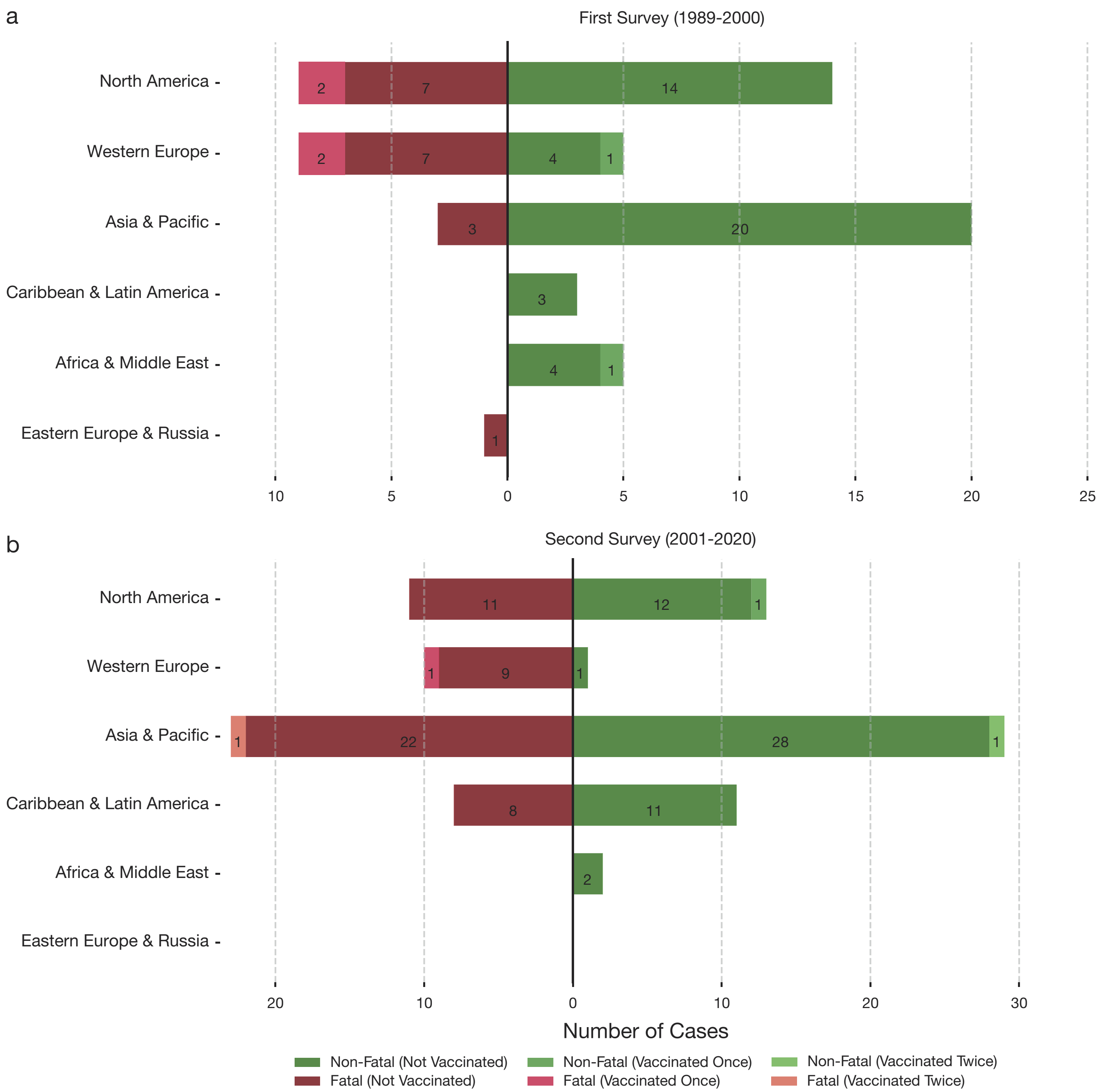

Fig. 5. Fatal and non-fatal cases across regions, with their respective vaccination status. Results are presented to facilitate comparison between the (a) 1st (1989—2000) and (b) 2nd (2001—2020) survey for each region

sion of the results into 6 regions for better analysis (Tables 4 & 6). While 25% of non-vaccinating facilities cite vaccine unavailability, they refer only to ER Bac® Plus, which is registered solely in the USA (Tables 4 & 5). It has however been used in several European facilities via a special permit for investigation issued to 1 facility. Aluminum hydroxide-based vaccines, like Eryseng and Eryvac, are widely available, including in the EU, Mexico, China and Australia (Opriessnig et al. 2020, Wang et al. 2021, European Medicines Agency 2023). However, access remains challenging in some Muslim countries.

The results of the 2nd survey, conducted 20 yr after the 1st survey, revealed a global decline in vaccinating facilities from 31 to 23%, although the North America region saw a strong increase in facilities vaccinating

Table 3. Global count of vaccinating facilities at the conclusion of each survey, along with the motivations for choosing vaccination and the respective vaccination schedules

	By 2000	By 2020
Total number of facilities still operating	96	133
Total number of facilities vaccinating	30 (31%)	30 (22.6%)
Never had a case, but as preventive measure	14	9
Because of a fatal case in the time-span of the 1st survey (or previously)	6	3
Because of a fatal case in the time-span of the 2nd survey		17
Because of a non-fatal case in the time-span of the 2nd survey		1
Not specified	10	0
Schedule of vaccination		
Vaccinating sporadically	9	1
Vaccinating once	9[a]	3[b]
Vaccinating twice	0	1[c]
Vaccinating once per year[d]	9[e]	21
Vaccinating twice per year[d]	3	4
Number of facilities considering and/or planning to start vaccination	2	1[f]
Facilities having closed		7
Vaccinating		2
Not vaccinating		5[g]

[a]Vaccination (1) between 6 and 12 mo of age, (2) ±6 mo after collection from the wild or (3) once at 1.5 yr of age; [b]Between 4 and 8 mo of age; [c]With 1 mo interval; [d]Post primovaccination and booster at 3 to 4 wk; [e]One facility was using a live-vaccine for their yearly booster after primovaccination with an inactivated vaccine; [f]One facility originally answered not vaccinating because it never experienced a case but then experienced a fatal case after having answered; [g]One facility would vaccinate if they still had cetaceans

by 2020 compared to previously (Table 3, Fig. 6). This is likely related to presentations about several acute fatal and non-fatal erysipelas cases at the beginning of this millennium (Chittick et al. 2003, Gearhart et al. 2005) and the subsequent presentations and publications of results obtained with ER Bac® Plus (Nollens et al. 2005, 2013, 2016, Walsh et al. 2005, Sitt et al. 2010). The major drop in vaccinating facilities occurred in Western Europe, where this is mainly related to the discontinuation of the Eurovac Ery vaccine in 2006, followed by the discontinuation of the Ruvax vaccine in 2019, both for commercial reasons following European regulations in company merger procedures (European Commission competition cases, version 2024)[1], together with the 'non-availability' of the ER Bac® Plus vaccine in Europe. The proportion of facilities vaccinating in Asia and the Pacific remained constant. For 70% of the vaccinating facilities, the loss of an animal to erysipelas was the main incentive to start a vaccination program (Table 3).

[1]CaseNoIV/M.1681AkzoNobel/HoechstRousselVet. Notification of 06.10.1999 pursuant to Article 4 of Council Regulation No 4064/89, 1999. https://competition-cases.ec.europa.eu/search?search=case%201681&caseInstrument=M&caseTitleOrCompanyName=HOECHST%20ROUSSEL%20VET&sortField=relevance&sortOrder=DESC (Version 14 Aug 2024).

Most vaccinating facilities follow a schedule of a primovaccination, a booster after 3 to 4 wk, and annual revaccination, though a small number consider that a one-time vaccination provides full protection (Table 3). However, results from both surveys have shown that fatal and non-fatal cases have occurred in animals vaccinated only once or twice (Tables 1 & 2, Fig. 5). This aligns with findings that antibodies from natural erysipelas infection are short-lived and that at least 3 vaccinations are required to achieve antibody levels significantly higher than in non-vaccinated animals (Nollens et al. 2016, Lacave et al. 2019).

4.4. Vaccination reactions

Two thirds of the vaccinating facilities reported no reaction to vaccination in the 20 yr span of the 2nd survey (Table 6). The majority vaccinated on a regular base, either once or twice per year. No reaction was ever reported when using Eurovac Ery, Eryseng, Eryvac or Ruvax. All these vaccines have aluminum hydroxide as adjuvant (Table 4). The loss of appetite reported at 1 facility, where various vaccines had been used over the years and ER Bac® Plus was being administered at the time of the survey, is likely a normal vaccination reaction. In contrast, at the other

Table 4. Vaccines administered during the 2nd survey, sorted by adjuvant type and including details of their composition. na: not available

Vaccine	Adjuvant	Preservative	Serotype	Strain	Authorization holder
Eurovac Ery[a]	Aluminum hydroxide	None	2	Br 12-92	Eurovet Animal Health BV, The Netherlands
Eryseng®	Aluminum hydroxide	None	2	R32E11	Hipra SA, Spain
Ruvax® Vet[a]	Aluminum hydroxide	Thiomersal	2	na	Boehringer Ingelheim Int
Erysorb Plus[b]	Aluminum hydroxide	Thiomersal	1 and 2	P15/10, CN3342 and CN3461	Intervet, UK
Eryvac	Aluminum hydroxide	Thiomersal	1 and 2	na	Zoetis Australia Pty, Ltd.
Porcilis Ery	Alpha-tocopherol	Formaldehyde	2	M2	MSD Animal Health Co. Ltd.
ER Bac® Plus	Amphigen®	Thiomersal and EDTA	2	CN3342	Zoetis Inc., USA

[a]Discontinued for commercial reasons (European company merger regulations); [b]Withdrawn from the market on 12 November 2008

Table 5. Global number of non-vaccinating facilities at the end of each respective survey, with reasons for non-vaccination provided for the 2nd survey

	By 2000	By 2020
Total number of facilities still operating	96	133
Total number of facilities not vaccinating	66 (68.8%)	103 (77.4%)
Fear of (fatal) anaphylactic reaction and reported high rates of vaccine reactions		48 (36%)
Experienced a fatal anaphylactic reaction during the survey		0
Experienced a fatal anaphylactic reaction prior to the survey		1
Experienced non-fatal anaphylactic reaction prior to the survey		1
Experienced reaction during the survey		1[a]
Stopped but never experienced a reaction		8
Never vaccinated		37
Vaccine not available or not legal[b]		25 (18.8%)
No or rare cases — not a priority — not important		16 (12%)
Stopped because of local reactions and animals going off food		2
Good water, fish quality and good husbandry sufficient		3
Stopped because no rise in hemagglutination titer		1
No scientific evidence about efficacy of vaccination		1
Has never been discussed in the facility		2
Not specified		5

[a]Reported as a possible case of anaphylaxis; [b]Only referring to ER Bac® Plus

facility with anorexia post vaccination, all animals received doses from the same vaccine vial within a month and the possibility of handling contamination cannot be ruled out. The facility reporting loss of appetite together with local reactions was using Erysorb Plus, albeit many years previously. Together with Eryvac®, this differs from the other vaccines in that it contains both serotype 1 and 2 bacterins. This vaccine is no longer manufactured.

The 4 facilities reporting fever, anorexia and swollen injection site use Porcilis Ery, an alpha-tocopherol oil-based adjuvanted vaccine. One of these facilities reported that almost all of their beluga population had strong secondary reactions to the vaccine and though reactions have also occurred in some dolphins, these were less intense. The remaining facility experiencing comparable reactions used ER Bac® Plus. The reactions were observed exclusively in their beluga population but were also linked to blood abnormalities and long-term morbidity in some individuals, for up to several years. There are previous reports of higher rates of adverse reactions in beluga (Dunn 1990) and further investigation of the immune system of these animals is warranted. However, both Porcilis

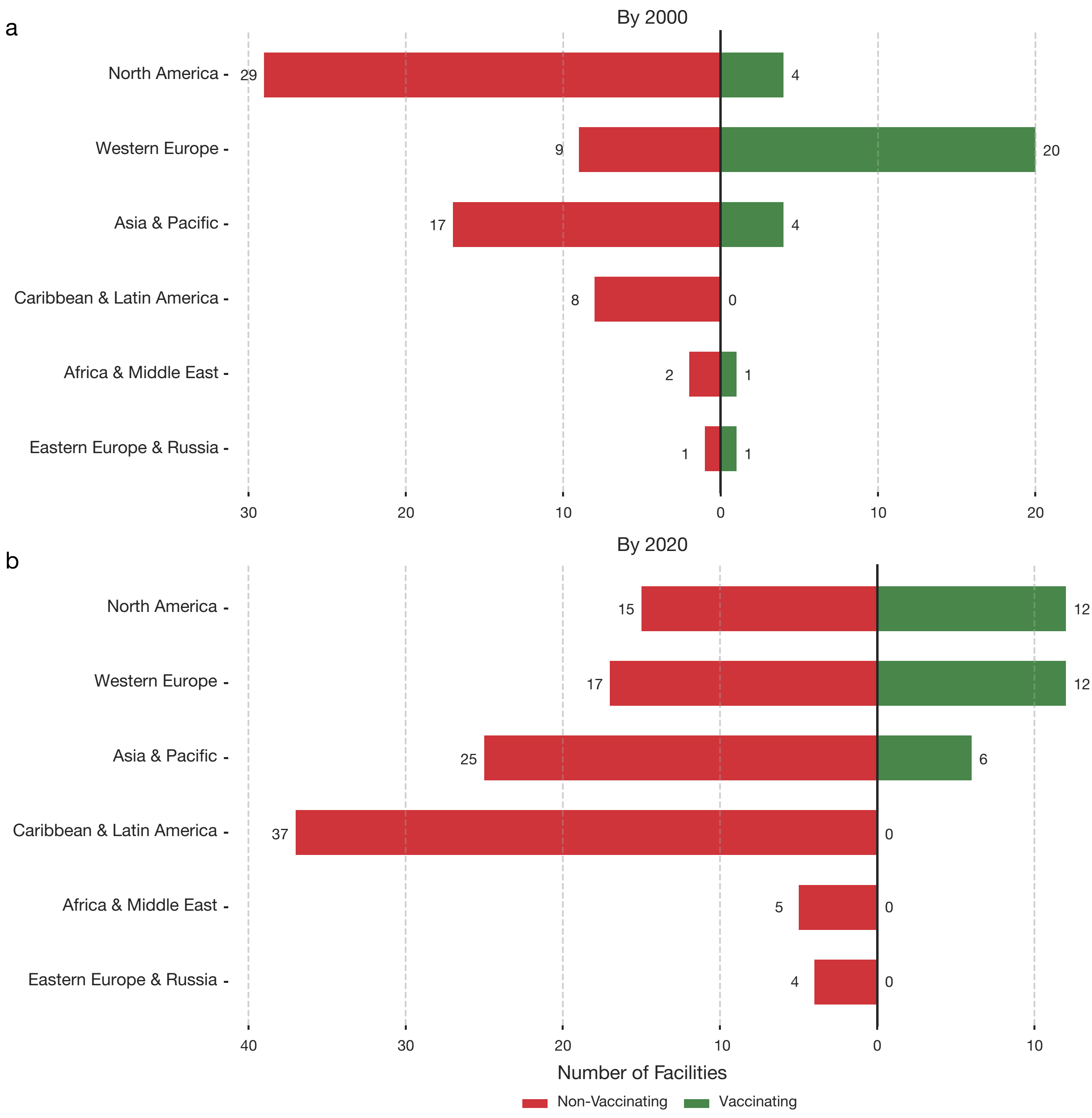

Fig. 6. Comparison of vaccinating versus non-vaccinating facilities across regions at the conclusion of each survey period: (a) by 2000 for the 1st survey and (b) by 2020 for the 2nd survey. In 2020, all North American facilities used ER Bac® Plus. In Western Europe half of the facilities used ER Bac® Plus and half used Eryseng. In Asia and the Pacific, 1 facility reported using Eryvac and 5 facilities used Porcilis Ery

Ery and ER Bac® Plus are oil-emulsion vaccines which are reported to yield strong local irritation, typically resulting in severe injection pain and inflammation due to tissue damage, though the Amphigen® adjuvant used in the latter reportedly contains less oil compared to classical oil adjuvants, in order to reduce reactions. While not life-threatening, these local reactions can lead to significant morbidity, such as local abscesses that sometimes require surgical drainage. Systemic reactions may also occur and persist for weeks (Stills 2005, Petrovsky 2015, Burakova et al. 2018).

Table 6. Described reactions during the 2nd survey

	Facilities	Animals	Vaccine	Adjuvant	Preservative
Described reactions to vaccination					
Anaphylactic shock and death	0				
Transient lethargy or excitement, irregular breathing and/or some listing	3[a]	8[b,c]	ER Bac® Plus	Amphigen®	Thiomersal and EDTA
Not treated, over in a few minutes to a few hours		7			
With nausea/vomiting		4			
Treated and normal eating/behavior within 1 h		1[d]			
Fever, anorexia or loss of appetite, swollen injection site, blood changes[e]	1[f]	Several	ER Bac® Plus	Amphigen®	Thiomersal and EDTA
Fever, anorexia or loss of appetite, swollen injection site	4[g]	Several	Porcilis Ery	Alpha-tocopherol	Formaldehyde
Loss of appetite — swollen injection site	1	Several	Erysorb Plus	Aluminum hydroxide	Thiomersal
Loss of appetite	2[a,h]	Several	ER Bac® Plus	Amphigen®	Thiomersal and EDTA
No reaction post vaccination	21[i]				

[a]Yearly vaccination; [b]Between their 4th and 11th vaccination; [c]Two facilities interrupted vaccinating the animals that showed an adverse reaction in the subsequent years; 1 facility with 1 case stopped all vaccination; [d]Corticosteroids and antihistamines; considered a possible anaphylactic reaction; [e]Mainly a rise in leucocytes and inflammatory parameters; [f]Only in their beluga population; [g]One facility reported the reactions occurred only in their beluga population; [h]One facility reported that loss of appetite rarely lasted more than 48 h, the other had a case of 8 out of 12 animals off food for 2 to 7 d post-vaccination but all had been vaccinated within a month from the same vial; [i]None of the animals from these 21 facilities—with the whole array of vaccines used—showed a reaction

Three facilities reported more serious reactions of transient lethargy and irregular breathing in 8 animals, all post ER Bac® Plus booster vaccinations, with nausea and vomiting in 4 cases, of which 1 received immediate treatment for a suspected hypersensitivity allergic reaction. A case is considered as possible or probable anaphylaxis depending on the number of organ systems involved, e.g. mucocutaneous, respiratory, cardiovascular and/or gastrointestinal (Bohlke et al. 2003). According to the suggested algorithm, 3 dolphins which were reported in the 2nd survey as having irregular breathing and vomiting immediately after vaccination — but which were not treated — would be classified as possible cases of anaphylaxis, although these remain questionable (2 systems were involved but no treatment given). In contrast, the 1 dolphin that did receive treatment would be considered a probable case of anaphylaxis (2 systems involved and treatment administered). For the other 4 animals, an anaphylactic reaction is unlikely, as only 1 system was involved, no treatment was given and all returned to normal within minutes. Transient post-injection pain or an inflammatory reaction are more plausible explanations.

Nearly half of the non-vaccinating facilities cited fear of severe vaccination reactions — including fatal anaphylaxis — as their main reason, with many stating that these risks could equal or exceed those of erysipelas infection itself (Table 5). Though fatal cases have occurred in the past following revaccination with live vaccine, none of the studies that were referenced to support the belief that numerous cases of fatal anaphylactic reaction have occurred after using inactivated vaccine showed such results (Gilmartin et al. 1971, Ridgway 1972, Colgrove 1975). Historically, 2 cases of anaphylaxis reaction in *Tursiops truncatus* have been reported, in 1988 and 1989, both upon third booster vaccination with the older American CEVA vaccine. The non-fatal case was reversed with corticosteroids and epinephrin (J. F. McBain pers. comm.) (Text S3). The fatal anaphylactic reaction was documented in a dolphin which had already been vaccinated with 0.5 ml of the CEVA erysipelas vaccine in 1983 and again in 1984. In 1989, the animal received a 3rd dose (2 ml) of the same vaccine alongside 3 ml of procaine penicillin. Following vaccination, the dolphin initially re-beached and ate a few fish, but later became disoriented, thrashed and drowned (E. D. Jensen pers. comm.). Two cases of non-fatal anaphylaxis also occurred in beluga whales upon booster vaccination with a killed bacterin in the early 1980s. Reactions were reversed by intravenous administration of epinephrine (Dunn 1990). Adverse reactions to erysipelas vaccination in cetaceans, while infrequent, may be perceived with greater concern than in other species, where inflammatory responses are considered normal and acceptable. The survey results confirmed a generally low frequency of adverse reactions overall, with a single fatal anaphylactic case dating back to 1989. Although several reported reactions suggest the potential for hypersensitivity reactions upon revaccination, it remains unclear whether the trigger lies in the antigen, adjuvant or specifically in the co-administration of another product such as procaine penicillin in the fatal case or certain adjuvants in other cases. No adverse events have been reported with Eurovac or Eryseng, both aluminum hydroxide-based and preservative-free, leading several facilities in Europe to revert to these types of adjuvant-based formulation in 2017, after prior use of ER Bac® Plus for several years (Lacave et al. 2019).

These reports may offer a skewed representation of expected reactions post vaccination due to the diversity of vaccine types used. The varying composition of the 7 vaccines administered during the 2nd survey period, particularly differences in adjuvants and preservatives, raise important questions about their potential role in adverse reactions.

4.5. Efficacy and protection of vaccination

Several veterinarians reported that very little or no rise in antibodies could be observed post-vaccination, and that the efficacy of vaccination had not been proven. Antibody detection and monitoring of their kinetics over time are key to evaluating vaccine-induced immunity. Agglutination assays, though cost-effective and commonly used in cetaceans, lack sensitivity and may cross-react with other organisms (Van Poucke 1994). Enzyme-linked immunosorbent assays and indirect immunofluorescence assays have become the preferred methods due to their higher specificity and sensitivity (Melero et al. 2016, Lacave et al. 2019).

While dolphin antibodies produced post-vaccination have shown protective effects in earlier mouse challenge studies (Hermans 1997, Lacave et al. 2001), an increase in antibody levels does not confirm protective immunity. Seroconversion may result from exposure to the vaccine, *Erysipelothrix* spp., or similar organisms. Determining a protective titer would require live-pathogen challenge studies which, although they have been performed in the past (L. Cornell pers. comm.), are no longer ethically or realistically feasible in cetaceans.

Early studies suggested that biannual vaccination was necessary to maintain antibody levels (Gilmartin et al. 1971, Lacave et al. 2001); however, later findings indicate that yearly vaccination, following an initial dose and a 1 mo booster, is sufficient. Longer intervals may be possible after several years of regular vaccination (Nollens et al. 2016, Lacave et al. 2019).

Most of the swine vaccines contain strains of serotypes 1 and/or 2 (Opriessnig et al. 2020). More serotypes of *E. rhusiopathiae* have been identified in dolphins in addition to serotype 2 (Terasawa et al. 2001), namely a serotype partially identical to serotype 5 (Lacave et al. 2001), serotype 5 (Takahashi et al. 2008), serotype 6 (Kinuta et al. 1984, Tagaki et al. 1987) and a serotype partially identical to serotypes 15 and 21 (Lacave et al. 2001). Only a few studies on cross-protection in dolphins with commercial swine vaccines have been undertaken (Lacave et al. 2001) and it is not known whether these vaccines induce protection against all types of *E. rhusiopathiae* isolates yielding disease in dolphins. No deaths occurred in regularly vaccinated animals during both surveys.

5. CONCLUSIONS

This retrospective analysis highlights that cetaceans in managed care remain at significant risk of fatal *Erysipelothrix rhusiopathiae* infection. Over the last 2 surveyed decades, more than 5 cetaceans per year have been affected by *E. rhusiopathiae*, with a 50% fatality rate, and cases were reported in over one-third of the facilities. All cases occurred in non-vaccinated animals, animals vaccinated once and, in 2 instances, in animals vaccinated twice. Facilities that began vaccinating did so after experiencing losses, while fear of adverse vaccine reactions, particularly fatal anaphylaxis, remains the primary reason for avoiding it. However, while immediate hypersensitivity reaction is always a concern during vaccination, only 1 fatal reaction was documented in 1989. Adverse events were rare and mostly resembled expected inflammatory reactions post vaccination. These were more frequent with oil-based adjuvanted vaccines and minimal to absent with aluminum hydroxide-based products. Geographic variation in vaccine use corresponded to differences in side-effect profiles, particularly with adjuvant types. Vaccination remains one of the most crucial strategies for preventing potentially fatal infectious diseases and it requires a balanced evaluation of its protective benefits versus potential adverse effects. Importantly, facilities adhering to regular vaccination schedules reported no cases of erysipelas, reaffirming vaccination as the most effective preventive measure currently available.

Acknowledgements. The authors thank all the facilities which participated in the surveys and followed up with additional communications. Special thanks go to Dr. Fumio Terasawa for the Japanese translation and Dr. Jen I-Fan for the Chinese translation of the survey, which greatly helped in its distribution and in facilitating communication with regional veterinarians. The authors also express their appreciation to their Russian collaborator, who prefers to remain anonymous. Lastly, the authors gratefully acknowledge Gilles Maene for his valuable contributions in the design of the bar plots.

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Editorial responsibility: Stephen Raverty, Abbotsford, British Columbia, Canada
Reviewed by: B. Biancani and 2 anonymous referees

Submitted: October 9, 2024
Accepted: May 28, 2025
Proofs received from author(s): August 8, 2025