Clinical manifestations, associated diseases, diagnosis, and treatment of human infections caused by *Erysipelothrix rhusiopathiae*: a systematic review

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Abstract

Introduction ***Erysipelothrix rhusiopathiae*** **is a bacillus that can cause cutaneous and systemic diseases in humans. Studies on the infection caused by this bacterium have been mostly done as case reports. This study aimed to systematically review *E. rhusiopathiae* infection cases published over the last 20 years.**

Methods Science Direct, PubMed, Scopus, Google Scholar, and Web of Science were searched using appropriate keywords to find relevant studies. After assessment of the studies, 57 case reports which surveyed 62 patients were included and their data were collected and analyzed.

Results The majority of cases were adult men living in high-income countries with an animal-related job and/or a history of animal contacts. The number of cases has increased in recent years. The main underlying diseases that were associated with *E. rhusiopathiae* infections include hypertension, diabetes, and alcoholism. The most frequent presentations were fever, pain, local skin lesions, and heart failure/endocarditis. Two patients died, while 60 patients were recovered following antibiotic therapy, mainly with penicillin and ceftriaxone.

Conclusions Altogether, the results indicated that *E. rhusiopathiae* usually infects people who come into contact with animals and causes mild to severe local or systemic infections, especially in those who have underlying diseases. Therefore, accurate and early diagnosis of *E. rhusiopathiae* infections by setting up appropriate laboratory tests is required.

Keywords ***Erysipelothrix rhusiopathiae*****, systematic review, diagnosis, clinical manifestations.**

Introduction

Erysipelothrix rhusiopathiae is a Gram-positive non-spore-forming bacillus that has long been known as an important veterinary and human pathogen.[1] Therefore, infections caused by this bacterium have a considerable impact on the animal industries as well as the human health systems.[1] Given its resistance to environmental conditions, *E. rhusiopathiae* can be found in various environments.[2] From these sources, it can infect a variety of wild and farm animals from fish to swine and turkey by causing erysipelas and other diseases.[3,4] Human infection is mostly linked to occupational exposure to animals or their contaminated products as a zoonotic disease.[3,5,6] In spite of the advances in the animal industries and sanitation that have decreased the incidence of *E. rhusiopathiae* cases, human infections are still occurring as a sporadic disease, in particular for people involved in animal-related businesses. It has been speculated that many cases of *E. rhusiopathiae* infections are not diagnosed because of their similarity to other infections caused by other bacteria or the lack of the laboratory setting for diagnosis of this bacterium as a routine test.[7]

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In humans, three forms of *E. rhusiopathiae* infections have been well-described, namely local cutaneous disease as the most common form (erysipeloid), the generalized cutaneous infection, and septicemia, which is mostly associated with endocarditis.[7] Erysipeloid is a form of cellulitis which has differential diagnosis with other skin infections such as streptococcal and staphylococcal infections. However, studies have reported various manifestations of *E. rhusiopathiae* infections in humans, including arthralgia, septic arthritis, osteoarthritis, intra-abdominal abscess, and central nervous system involvements.[7] On the other hand, little is known about the pathogenesis of *E. rhusiopathiae* infections. However, some virulence factors have been suggested including the presence of the capsule, neuraminidase, hyaluronidase as well as surface proteins which may contribute to infection.[2,8,9]

Given the fact that human infection is mostly sporadic, the majority of the studies about this zoonotic pathogen are case reports. In order to collectively analyze the data on human cases, we aimed to systematically review the published data on diagnosis, treatment, associated diseases, and clinical manifestations of infections caused by *E. rhusiopathiae*.

Methods

Search strategy

Several electronic databases including Science Direct, PubMed, Scopus, Google Scholar, and Web of Science were searched to find published articles on human cases of *E. rhusiopathiae* infections from January 2000 to November 2020. In addition, the references of relevant studies were manually checked and the relevant articles were included. The search was performed using the following keywords: "*Erysipelothrix* spp.", "*Erysipelothrix rhusiopathiae*", "*E. rhusiopathiae*", "erysipeloid", "human", "prevalence", and "case report", alone or in combination with "OR" and/or "AND" operators. The study was designed according to PRISMA [preferred reporting items for systematic reviews and meta-analysis] guidelines.[10]

Inclusion and exclusion criteria

The inclusion criteria of the study were: 1) Studies reporting human cases of *E. rhusiopathiae* infection, 2) Observational studies based on appropriate diagnostic tests (culture, mass spectrometry, and molecular tests), including case-control and cross-sectional studies, 3) Studies published between January 2000 and November 2020.

The exclusion criteria were: 1) Review, letter to editors, and comments without reporting the exact number of human cases of *E. rhusiopathiae* infections, 2) Duplicate publications, conference papers and articles with unavailable full text, 3) Published studies beyond the determined time period of the study, 4) non-English articles.

Data collection and analysis

The following data were collected and recorded from selected studies: first author, year of publication, place of patients' residence, gender, age, job or work, history of animal contact, clinical manifestations, underlying diseases, skin lesions, heart valve involvement, diagnosis methods, treatment, and the disease outcome. The quality assessment of articles and the collected data were independently done by MR and DR and revised by AA to resolve any discrepancies.

To analyze the trend of cases frequency over years, linear regression was drawn by Microsoft Excel data analysis ToolPak (version 2007). P values of <0.05 were considered significant.

Results

Literature search

Using the literature search, a total of 145 records were found, of which 11 were excluded because they were duplicates. Fifty-eight studies were excluded because they did not report *E. rhusiopathiae* infections, or were not case reports/case series. Of the 76 remaining studies, 19 articles were excluded because their full texts were not available or not in English. Finally, 57 case reports (or case series) which surveyed 62 unique patients were included (Figure 1).

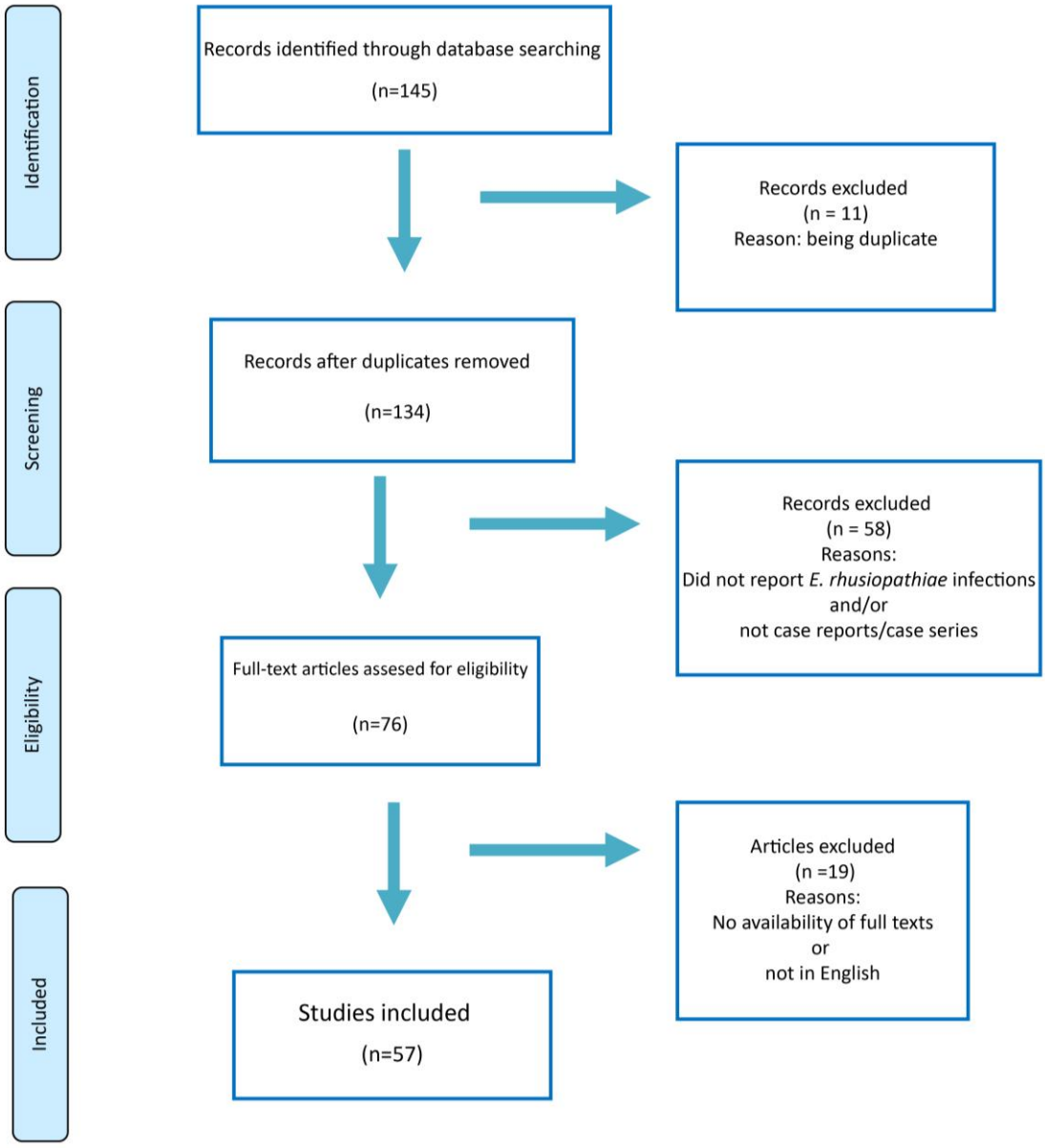


Figure 1. Flowchart of the study selection

Reported cases general data

The data of the included studies are shown in Table 1. Of 62 cases, 47 patients (75.8%) were male and 15 patients (24.2%) were female. Their average age was 54.16 years, and the majority of cases were adults (19-59 years) (58.1%). The job of 30 patients (48.4%) was not clearly determined, the other 32 patients mainly had jobs that involved direct contact with animals as follows: nine (14.5%) were farmers, six (9.7%) had a fish/seafood-related job, two (3.2%) were butchers and 15 (16.1%) had jobs but with no clear relation to animals (Figure 2).

Thirty-seven (59.7%) patients had a history of contacts with animals or animal products while seven patients (11.3%) had no apparent contacts with animals/animal products, and contacts with animals had not been specified for 18 cases (29.0%). Of 37 patients with a history of animal contact, 11 cases had contact with aquatic animals, four cases with pets, three cases with

Table 1. The data of included studies

No.	Author-year	Place	Gender	Age (years)	Job/career	Animal contact	Having underlying morbidities	Manifestation			Diagnosis method	Involved heart valve	Surgery (heart valve replacement)	Antibiotic therapy	Outcome	Reference
								Erysipeloid	Spread skin lesions	Systemic/ Other diseases*						
1	Alawdah-2016	USA	M	12	-	+	-	-	+	+	Culture-mass spectrometry	-	-	+	R	12
2	Altibi-2019	USA	M	61	Farmer	+	+	-	-	+	Culture	+	AV	+	R	13
3	Andrychowski-2012	Poland	M	62	Farmer	+	+	+	-	+	Culture	-	-	+	R	14
4	Artz-2001	Germany	M	46	Butcher	+	+	+	-	+	Culture	+	AV	+	R	15
5	Asimaki-2017	Switzerland	M	72	-	+	+	-	-	+	Culture	-	-	+	R	16
16	Balkhair-2019	Oman	M	51	Farmer	+	-	+	-	+	16S rRNA PCR	+	MV	+	R	17
7	Basu-2013	-	M	50	-	-	-	-	-	+	-	+	MV	-	R	18
8	Bîrlutiu-2015	Romania	M	54	-	-	+	-	-	+	Culture	-	-	+	R	19
9	Boo-2003	Ireland	M	37	Farmer	+	+	+	-	+	Culture	+	AV	+	R	20
10	Boyd-2014	USA	F	14	-	-	+	+	-	+	Culture	-	-	+	R	21
11	Campbell-2013	USA	M	51	Mechanic/homeless	-	+	-	-	+	-	+	AV	+	R	22
12	Carson-2005	USA	M	54	Unemployed	-	+	-	-	+	Culture	+	-	-	D	23
13	Cascio-2012	Italy	F	53	-	-	+	-	+	+	Culture	-	-	+	R	24
14	Cooke-2006	UK	M	47	Fishmonger	+	-	-	-	+	Culture	-	-	+	R	25
15	Denes-2015	France	M	38	Farmer	+	-	-	-	+	Culture, mass spectrometry, 16S sequencing	-	-	+	R	26
16	Drekonja-2013	USA	M	59	Veteran	+	+	+	-	+	Culture	-	-	+	R	27
17	Feasi-2010	Italy	M	42	-	-	+	-	-	+	Culture	-	-	+	R	28
18	Feasi-2018	Italy	F	45	-	-	+	-	-	+	Culture	-	-	+	R	29
19	Gazeau-2017	France	M	82	-	-	+	-	-	+	Culture	-	-	+	R	30

No.	Author-year	Place	Gender	Age (years)	Job/career	Animal contact	Having underlying morbidities	Manifestation			Diagnosis method	Involved heart valve	Surgery (heart valve replacement)	Antibiotic therapy	Outcome	Reference
								Erysipeloid	Spread skin lesions	Systemic/ Other diseases*						
20	Groeschel-2019	Canada	F	69	Artist	+	+	+	-	+	Culture, 16S sequencing	-	-	+	R	31
21	Harada-2011	Japan	M	40	-	-	-	-	+	+	Culture, PCR	+	-	-	-	32
22	Hardman-2004	UK	M	49	Bricklayer	-	+	+	-	+	Culture	-	-	+	R	33
23	Hocqueloux-2010	France	F	68	-	+	+	+	-	+	Culture, 16S sequencing	-	-	+	R	34
24	Hofseth-2017	Norway	M	52	Transportation businessman	+	+	+	-	+	Culture	-	-	+	R	35
25	Hornak-2019	USA	M	52	Seafood packager	+	+	-	-	+	Culture	+	AV	+	R	36
26			M	63	Fisherman	+	+	-	-	+	Culture	-	-	+	R	
27	Hua-2015	China	M	65	-	-	+	-	-	+	Culture	+	AV/MV	+	R	37
28	Huang-2008	China	M	50	Farmer	+	+	-	-	+	Culture, DNA sequence analysis	+	AV	+	R	38
29	Jean-2019	USA	M	59	-	+	+	+	-	+	Culture	+	-	+	R	39
30	Joo-2011	South Korea	F	56	-	-	+	-	-	+	Culture, Vitek-II system	+	MV	+	R	40
31	Kaya-2013	Turkey	F	44	-	+	+	-	-	+	Culture	+	MV	+	R	41
32	Kichloo-2013	USA	M	64	Toy manufacturer	+	+	-	-	+	Culture	-	-	+	R	42
33	Kim-2007	South Korea	M	47	Manufacturer	-	-	-	-	+	Culture, Vitek-II system	-	-	+	R	43
34	Kobayashi-2019	Japan	F	52	-	+	-	+	-	+	Culture, Vitek-II system, 16S rRNA sequencing	-	-	+	R	44
35	Liu-2017	China	M	49	Fish handler	+	-	-	+	+	Culture, Vitek-II system	-	-	+	R	45
36	Lorenz-2018	USA	M	48	-	+	+	-	-	+	Culture	-	-	+	R	46

No.	Author-year	Place	Gender	Age (years)	Job/career	Animal contact	Having underlying morbidities	Manifestation			Diagnosis method	Involved heart valve	Surgery (heart valve replacement)	Antibiotic therapy	Outcome	Reference
								Erysipeloid	Spread skin lesions	Systemic/ Other diseases*						
37	Meric-2012	Turkey	M	43	Stockyard worker	+	+	-	-	+	Culture, Vitek-II system	-	-	+	R	47
38	Miura-2013	Japan	F	42	School worker	-	+	+	-	+	Culture	+	AV	+	R	48
39	Mukhopadhyay-2012	India	M	5	-	-	-	+	-	+	Culture, Vitek-II system	-	-	+	R	49
40	Nielsen-2018	Norway	M	59	Ship worker	+	+	-	-	+	Culture-MALDITOF	+	AV	+	R	50
41	Özkalaycı-2019	Turkey	M	77	-	-	+	-	-	+	Culture, Vitek-II system	+	-	+	R	51
42	Principe-2016	Italy	M	74	-	-	+	+	+	+	Culture-MALDITOF	-	-	+	R	52
43	Rihana-2018	USA	M	49	-	+	+	+	-	+	Culture	-	-	+	R	53
44	Romney-2001	USA	F	67	-	+	+	-	-	+	Culture	+	-	+	R	54
45	Ruiz-2003	USA	M	76	-	-	+	-	-	+	Culture	+	-	+	R	55
46	Ko-2003	South Korea	F	63	Fisherwoman	+	+	+	-	+	Culture	+	-	+	R	56
47	Sharifuddin-2020	Malaysia	F	57	Housewife	+	-	-	-	+	Culture	-	-	+	R	57
48	Shin-2010	South Korea	M	50	Salesman	+	+	+	-	+	Culture, Vitek-II system	-	-	+	R	58
49	Shivaprakasha-2007	India	M	37	Cinematographer	-	+	-	-	+	Culture	+	-	+	R	59
50	Simionescu-2003	USA	F	70	-	-	+	+	-	+	Culture	-	-	+	R	60
51	Sinclair-2013	Australia	M	39	Medical scientist	+	+	-	-	+	Culture	-	-	-	R	61
52	Surrun-2008	Singapore	F	67	-	+	+	-	-	+	Culture	-	-	+	R	62
53	Tan-2016	USA	M	74	-	+	+	+	-	+	Culture	-	-	+	R	63
54			M	91	Farmer	+	+	-	-	+	Culture	-	-	+	R	
55			F	58	-	+	+	-	-	+	Culture	-	-	+	R	
56			M	72	-	-	+	-	-	+	Culture	+	-	+	R	
57			M	57	-	+	+	-	-	+	Culture	-	-	+	R	

No.	Author-year	Place	Gender	Age (years)	Job/career	Animal contact	Having underlying morbidities	Manifestation			Diagnosis method	Involved heart valve	Surgery (heart valve replacement)	Antibiotic therapy	Outcome	Reference
								Erysipeloid	Spread skin lesions	Systemic/ Other diseases*						
58	Traer-2008	UK	M	76	Worker in tanning factory	+	+	-	-	+	Culture	-	-	+	R	[64]
59	Upapan-2014	Thailand	M	62	Farmer	+	+	-	-	+	Culture	-	-	+	R	[65]
60	Vallianatos-2003	Greece	M	18	Student	-	+	-	-	+	Culture	-	-	+	R	[66]
61	Volard-2016	France	M	60	Retired (former gardener)	-	+	-	-	+	Culture	-	-	+	R	[67]
62	Yamamoto-2008	Japan	M	58	-	-	-	-	+	+	Culture, 16S rRNA sequencing	+	Tricuspid	+	D	[68]

farm animals, eight cases with animal products, and 11 cases with multiple animals (Figure 2).

Of 57 studies, 20 were from Asia, 19 from Europe, 16 from North America, one from Australia, and one without specified region. Based on World Bank data,[11] the countries were divided into four groups as follows: high-income, upper middle income, lower middle income, and low income. Applying this classification, most of our studied cases (82.3%) had been reported in high-income countries (Figure 2). The number of cases in each country is also depicted in Figure 3.

Reported cases over years

We studied all published case reports from January 2000 until November 2020. The first case report was published in 2001, followed by the increase of published reports afterward. This increase was statistically significant as indicated by linear regression analysis (R^2=0.111, p value=0.019).

Underlying diseases of the reported cases

Regarding the underlying morbidity of the patients, 12 cases had no/not-stated underlying morbidities while the rest of the cases (50 patients) had underlying conditions associated with *E. rhusiopathiae* infections (Figure 4). These underlying morbidities included hypertension (14 cases), diabetes (12 cases), alcoholism (11 cases), arthritis/musculoskeletal diseases (10 cases), heart diseases (10 cases), pulmonary diseases (eight cases), immunosuppression/autoimmune diseases (seven cases), kidney/urinary tract diseases (six cases), surgery (five cases), hepatitis (five cases), hyperlipidemia (five cases), gastroenteric diseases (five cases), smoking/substance abuse (five cases), neurological diseases (four cases), liver diseases (three cases), cancer/carcinoma (three cases), dermatitis/skin diseases (two cases), wound/laceration/trauma (two cases), mental diseases (two cases), bacterial infection (two cases), viral infection (one case), fungal infection (one case), anemia (one case), and obesity (one case) (Figure 4).

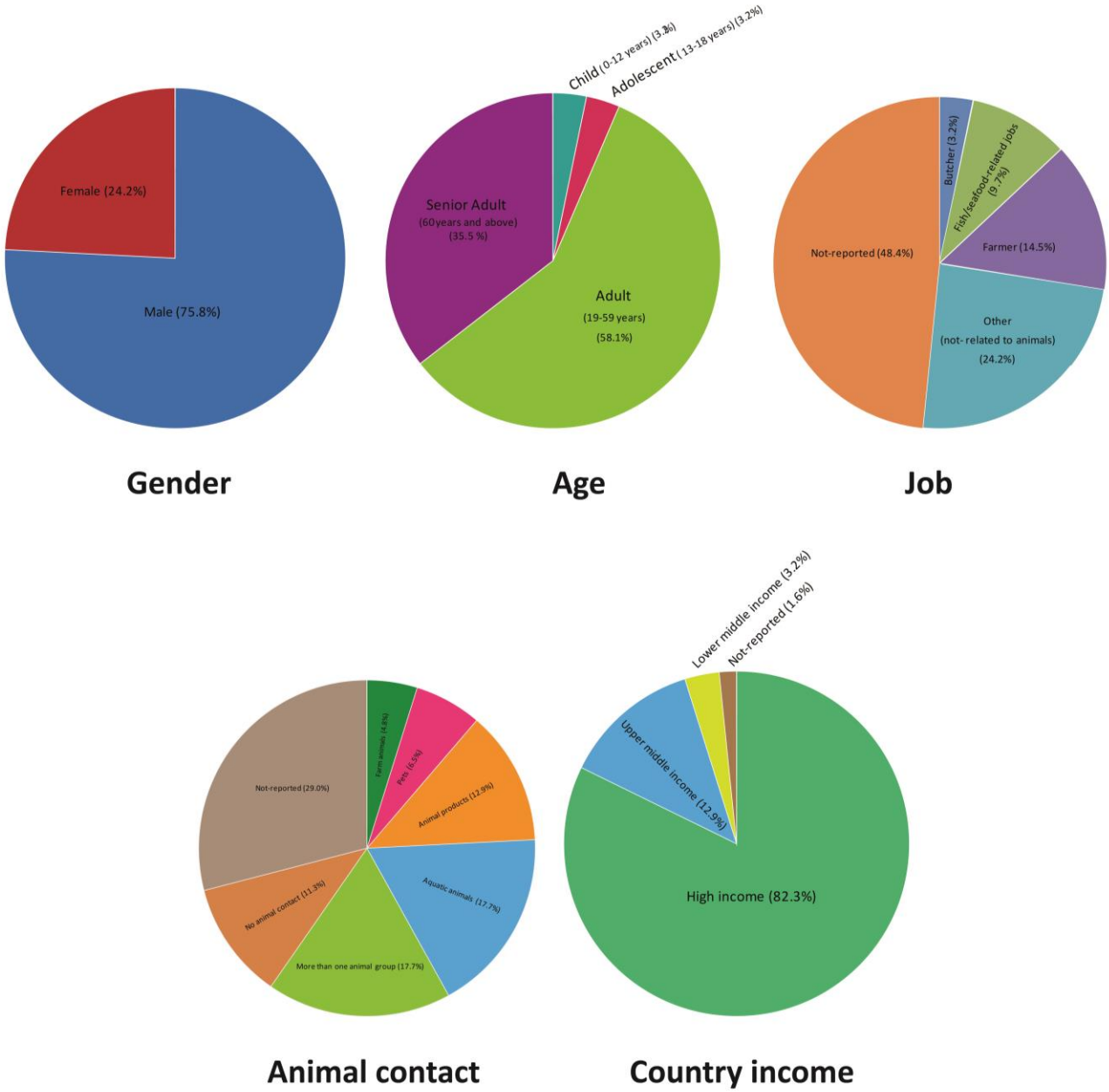
Manifestations of *E. rhusiopathiae* infections

The overall manifestations of *E. rhusiopathiae* infections reported by studies are shown in Figure 6. These manifestations could be divided into nine groups as follows: skin involvement, cardiovascular involvement, pulmonary involvement, urinary tract involvement, gastrointestinal tract involvement, musculoskeletal involvement, blood disorders, general signs/other symptoms, and other organ diseases (Figure 5). The most frequent complications were fever (35 cases), pain (20 cases), local skin lesions (erysipeloid) (18 cases), and heart failure/endocarditis (18 cases) (Figure 5).

Skin lesions and heart valve involvements are two main manifestations of *E. rhusiopathiae* infections. In terms of presence/absence or type of skin lesions, eighteen patients (29%) showed local skin lesions (erysipeloid), three patients (4.9%) showed spread skin lesions, and the remaining 41 (66.1%) patients had non-skin manifestations (Table 1 and Figure 5). Of 62 cases, 23 patients (37.1%) had cardiac valve involvements and 14 of them underwent valve replacement surgery (Table 1). Cases of skin and heart valve involvement are reported in Table 1, while the details of other manifestations for each case are presented in Table S1. Two of 62 patients died (one with heart failure and another without a stated reason) but the rest recovered after treatment (Table 1).

Detection of *E. rhusiopathiae* infections and antibiotics used

The diagnostic methods used by the studies were as follow: the microbiological culture (37 studies, 64.9%), the combination of microbiological culture and Vitek-II System (seven studies, 12.3%), the combination of microbiological culture and molecular techniques (16S rRNA PCR) (six studies, 10.6%), the combination of microbiological culture and mass spectrometry (MALDI-TOF) (three studies, 5.3%), the combination of microbiological culture with molecular techniques and mass spectrometry (one study, 1.7%), and finally the combination of microbiological culture with



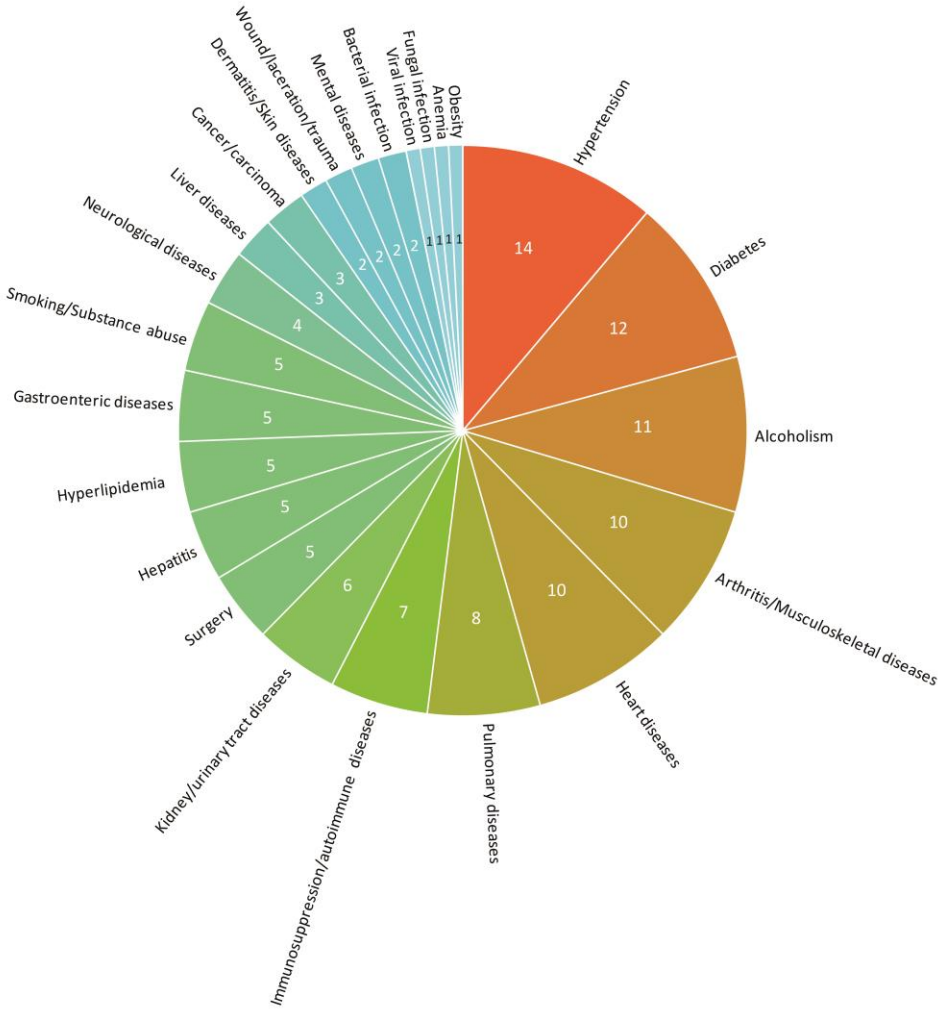
Each pie chart indicates the percentages of one parameter in the 62 included cases.

Figure 2. The general data of reported *E. rhusiopathiae* cases

Country	Case No.
Australia	1
Canada	1
China	3
France	4
Germany	1
Greece	1
India	2
Ireland	1
Italy	4
Japan	4
Malaysia	1
Norway	2
Oman	1
Poland	1
Romania	1
Singapore	1
South Korea	4
Switzerland	1
Thailand	1
Turkey	3
United Kingdom	3
United States	20

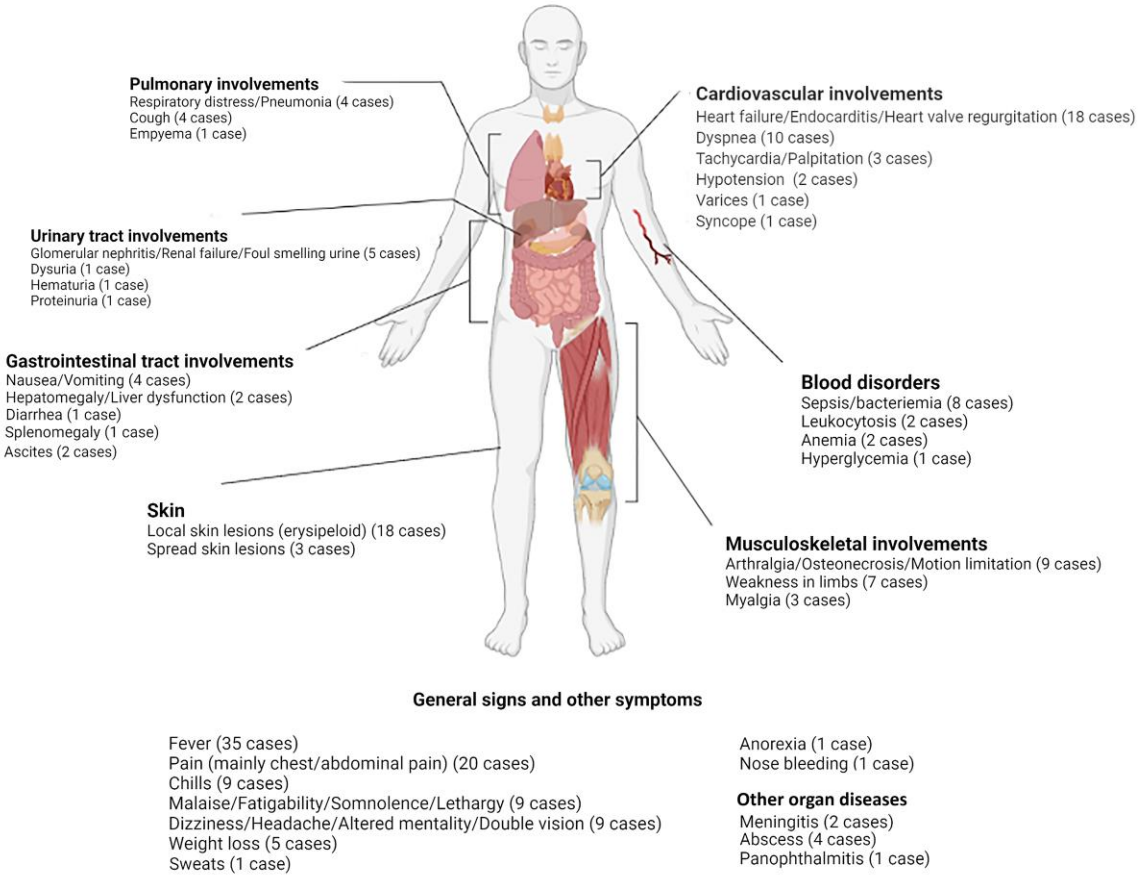
The map shows the number of *E. rhusiopathiae* cases reported in different countries of the world.

Figure 3. The place of *E. rhusiopathiae* reported cases



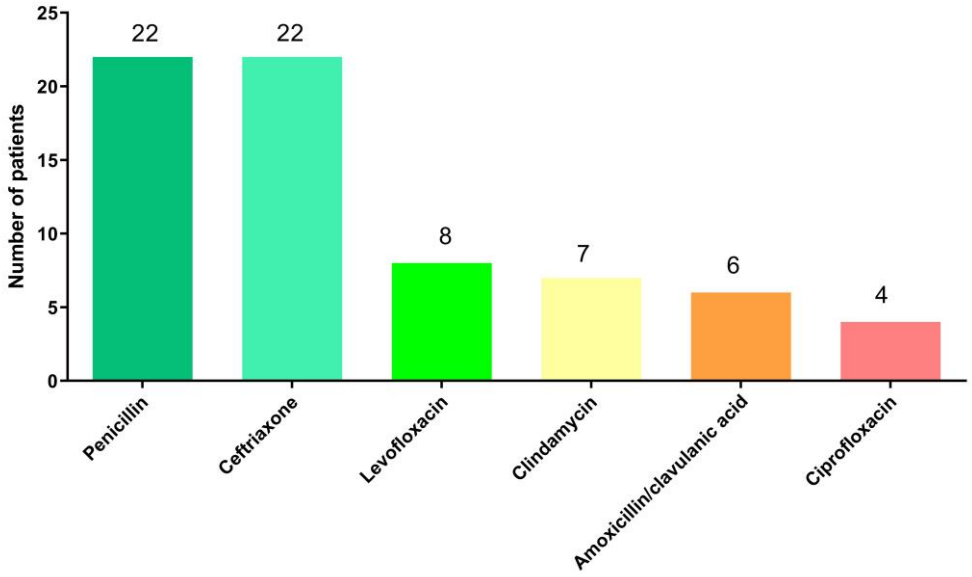
Of 62 evaluated patients, 12 cases had no/not-stated co-morbidities while the rest of the cases (50 patients) had underlying morbidities (shown with numbers in each part of the pie chart).

Figure 4. The underlying morbidities of the patients infected by *E. rhusiopathiae*



The number of occurring times has been shown with numbers in parentheses in front of each clinical manifestation.

Figure 5. The categories of clinical manifestations of the patients infected by *E. rhusiopathiae*



The six most frequent antibiotics used are shown. The number of times for each antibiotic has been shown with numbers on the bars.

Figure 6. The most frequent antibiotics used to treat *E. rhusiopathiae* infections

molecular techniques and Vitek-II System (one study, 1.7%). Two studies (3.5%) did not report diagnostic methods (Table 1).

Antibiotics were used to treat *E. rhusiopathiae* infections in 57 patients while for five patients antibiotics were either not used or not reported (Table 1). The most frequently used antibiotics were penicillin and ceftriaxone (each in 22 patients) followed by levofloxacin (eight patients), clindamycin (seven patients), amoxicillin/clavulanic acid (six patients), ciprofloxacin (four patients), imipenem/cilastatin (two patients), gentamicin (two patients), ampicillin/sulbactam (two patients), piperacillin/tazobactam (two patients), and cephalosporin, rifampicin, vancomycin, moxifloxacin, doxycycline, ofloxacin, teicoplanin, oxacillin, daptomycin, ceftazidime, cefazolin, and meropenem each for one patient (Table S2). The most frequently used antibiotics are shown in Figure 6.

Discussion

Although *E. rhusiopathiae* infection in humans is not a common infection, it can occur as a sporadic disease and, as our results indicated, the number of cases have increased in recent years. Sporadic infection with this bacterium needs to be accurately diagnosed at early stages otherwise severe complications including heart failure may occur. Our results showed that most human cases of *E. rhusiopathiae* infection have been reported from developed and high-income countries, probably due to the better laboratory settings for the diagnosis of this infection. This may explain the underestimated cases of human infections caused by *E. rhusiopathiae* in developing and undeveloped countries.

It has been shown that *E. rhusiopathiae* infection mainly occurs in people involved in animal-related jobs.[1,5,7] Our results indicated that people with jobs/works with exposure to animals or animal products are more prone to *E. rhusiopathiae* infections. Aquatic animals (mostly fishes) and farm animals are likely the two most common types of sources for *E. rhusiopathiae*. This bacterium usually infects humans via wounds/injuries in non-protected areas of hands and feet in case of contact with bacterial sources. Furthermore, regardless of the jobs/work of people, the majority of the *E. rhusiopathiae* patients had declared previous contacts with animals, highlighting the significance of animal contacts in the transmission of *E. rhusiopathiae* infection. Although animal contacts appear the main transmission route of *E. rhusiopathiae*, this bacterium also presents in many environmental sources and can accidentally infect people. Therefore, practicing personal sanitation and protection is essential to prevent this infection in case of exposure to contaminated sources. The majority of human *E. rhusiopathiae* cases were adult men, which can be explained by the fact that men are more exposed to bacterial sources (animals and animal products) due to their jobs/works.

Although the unequivocal relationship of personal health background and probability of systemic *E. rhusiopathiae* infection needs more studies, the majority of human cases in our study had at least a comorbid health background that seems to be an associated condition with *E. rhusiopathiae* infections. People with these comorbidities may be more susceptible to systemic *E. rhusiopathiae* infections, in particular those with hypertension, diabetes, and alcoholism.

The clinical manifestations of human *E. rhusiopathiae* infections indicated a range of systemic and local signs and symptoms. For instance, only 21 out of 62 cases (34%) had skin lesions and 41 cases (66%) had non-skin lesions but presented systemic manifestations. The wide range of clinical manifestations indicates that the signs and symptoms should be cautiously assessed for the diagnosis of *E. rhusiopathiae* infection. The most severe complication of *E. rhusiopathiae* infection is the involvement of heart valves found in 23 cases (37.1%) in our study. This highlights the importance of early diagnosis of *E. rhusiopathiae* infections. Given the difficulty of clinical diagnosis of *E. rhusiopathiae* infections based on signs and symptoms, setting up proper laboratory-diagnosed tests for accurate identification of this bacterium is essential.

In terms of treatment, almost all *E. rhusiopathiae* cases recovered following antibiotic therapy or combined with heart valve replacement surgery. The most common antibiotics used were penicillin and/or ceftriaxone alone or in combination with other antibiotics.

Conclusions

In conclusion, the majority of *E. rhusiopathiae* infections with local cutaneous lesions are self-limited. However, in some patients with underlying diseases, local infections may spread through the body and cause severe systemic infections mostly with cardiac valve involvement and other complications. Given the varying manifestations and complications of this infection, it is hard to be clinically diagnosed without the aid of laboratory testing. Therefore, medical diagnostic laboratories should be appropriately set up to test samples of patients who are suspected to have *E. rhusiopathiae* infections.

Authors' contributions statement: MR and AA contributed in the study conceptualization, methodology, data curation, writing - review & editing. DR contributed to the study methodology and data curation. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

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