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Characteristics and Variability of Porcine Reproductive and Respiratory Syndrome Virus Strains: Implications for Virulence and Control - A Scoping Review

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"Characteristics and Variability of Porcine Reproductive and Respiratory Syndrome Virus Strains: Implications for Virulence and Control - A Scoping Review"

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Research Article

Additional Declarations: No competing interests reported.

Abstract

Background

Porcine reproductive and respiratory syndrome virus (PRRSV) is the responsible agent of one of the most important diseases in the pig industry and is distributed worldwide. There are two main classifications of the virus, PRRSV 1 and PRRSV 2, the first common in Europe and the second in the United States and China. The major challenge in controlling the agent is the significant variation in the strains, which limits the efficiency of vaccines and control measures. We examined peer-reviewed literature to investigate the characteristics and distinctions among various strains and identify the attributes enabling the virus to thrive within pig herds.

We searched the PubMed, Scopus, and Web of Science databases between July and August 2022. We identified 2,847 articles published between 2012 and 2022 and evaluated their eligibility based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines. Thirty-one articles were finally selected, analysed, and compared to extract and systematise as many factors that account for PRRSV virulence as possible.

Results/conclusions

The selected studies focused on experimental models of PRRSV infection that compared the virulence and pathogenic characteristics of different strains in different age groups. These studies aimed to identify differences in disease development, transmission, and host susceptibility between breeding-age and young pigs. By comparing different parameters, we provided insights into the varying virulence of PRRSV strains. Future research aims to monitor markers that can help understand the complex interactions between the host, pathogen, and environment, improve animal health, and effectively control the consequences of PRRSV infection.

Background

Porcine reproductive and respiratory syndrome virus (PRRSV) is a significant swine disease with a global impact, causing reproductive failures such as mummification, stillbirth, late-term abortion, delayed return to oestrus, and respiratory disorders in growing pigs. Infected pigs usually exhibit poor growth performance and increased susceptibility to co or secondary infections (1, 2), resulting in substantial economic costs and losses for the swine industry (3–5).

The causal agent of PRRSV is a single-stranded positive-sense RNA virus belonging to the family *Arteriviridae*, and it is divided into two main genotypes: PRRSV-1, of European origin, and PRRSV-2, of North American origin (2, 6). The genome of PRRSV is approximately 15 kilobases in length, and it contains at least ten overlapping open reading frames (ORFs) that encode structural and nonstructural proteins. These proteins play an essential role in the adaptations and diversity of distinct strains (7, 8).

Extensive genetic variation and diversity are commonly recognised issues for controlling clinical PRRS (9). Managing the clinical symptoms of PRRSV can be difficult due to its vast genetic variation and diversity (9). Typically, outbreaks caused by endemic strains result in lower mortality and morbidity losses. However, occasional outbreaks of more severe forms of PRRSV can result in significant economic losses due to associated morbidity and mortality (10–12).

The measure of severity or intensity of a disease caused by a virus is known as virulence (13). Multiple factors influence the virulence of different PRRSV strains, including host genetics, viral genetics, environment, and co-occurring infections (14), resulting in a wide range of clinical and histopathological manifestations.

Experimental infection models provide a method for assessing, in a controlled environment, the disease severity and progression by looking at factors such as viral loads, seroconversion, and postinfection consequences that can reflect the strain's nature (15). This understanding is crucial for farmers and veterinarians to manage the disease effectively, allowing them to detect and control outbreaks and implement effective biosecurity measures for their livestock (16).

This study aims to compare and analyse disease progression and manifestation across different PRRSV strains used in experimental infection models, particularly identifying their interactions to uncover general patterns that may be evaluated through different classifications. The outcomes help to inform the development of effective prevention and control strategies for this economically significant swine disease.

Results

1. Selection process and selected studies overview

The selection strategy followed the PRISMA guidelines, as shown in Fig. 1. We reviewed 2,847 studies from three databases: PubMed, Scopus and Web of Science. After excluding duplicates, preprints and conference proceedings, the titles and abstracts of the identified articles were examined to assess their relevance and inclusion criteria. Of the 113 manuscripts, 82 were excluded as irrelevant to the selection framework. The 31 articles that met the inclusion criteria were selected.

The 31 studies contained 77 isolates sourced from 12 countries, as shown in Fig. 2. Samples were obtained from farms where animals showed clinical symptoms of a disease, and the strains responsible for the disease were isolated. In some cases, up to three strains were detected on a single farm, as observed by Jiang et al. (17).

Up to 54% (n = 17) of the studies originated from China, where mutations of PRRSV-2 are prevalent. Meanwhile, investigations conducted in South Korea revealed a diverse range of strains of both PRRSV-1 and PRRSV-2. It was observed that many strains recombine and travel across different countries, as does the pig trade. This was the case for field isolates from Austria in European outbreaks, which shared genetic and phylogenetic similarities with the South Korean strain KNU-97 (18).

2. Summary characteristics of selected studies

Seventy-nine experimental animal groups were included in the 31 studies selected. Among these groups, 23 were infected with PRRSV type 1, and 54 were infected with PRRSV type 2. Interestingly, two groups were simultaneously infected with both types in a dual infection scenario (19, 20). Across all the studies, researchers analysed a total of 77 different strains.

Four studies were conducted to compare the features of type 1 and type 2 infections. Specifically, two studies examined the effects of these infections in piglets and gilts simultaneously (19, 20). The other two studies focused on separate groups, analysing the differences between type 1 and type 2 infections in piglets and gilts (21, 22). The main characteristics of the strains, including survival percentage, seroconversion and the peak of viremia (measured in days postinoculation, days postinfection [DPI]), presence of antibodies (represented by the S/P ratio, which provides a numerical value indicating the strength of the sample's response compared to the positive control, with a higher ratio indicating a more robust response), and viral load (measured as log10 copies of PRRSV RNA/ml), are summarised in Table 1. Furthermore, a comprehensive description and details of the selected studies, strains, and classification can be found in the supplementary material.

Table 1
Summary characteristics of the selected studies.

PRRSV type	Survival percentage[1]	Seroconversion (DPI)	Antibodies (S/P ratio)	Viral Load (Log10 copies RNA/ml)	Peak viremia (DPI)	References
1	< 40	≤ 10	-	4−6	≤ 10	(5*,20*,23) *2
1	40−60	-	-	4−6	≤ 10	(4,5*,24,25)
1	> 70	> 10	< 1	4−6	-	(22*)
1	> 70	-	1−2	4−6	≤ 10	(18,26)
1	> 70	≤ 10	> 2	< 4	≤ 10	(21,23,27)
1	> 70	≤ 10	-	4−6	≤ 10	(18,19,21,26−28)
2	< 40	≤ 10		4−6	> 10	(9,25)
2	< 40	-	1−2	6−8	≤ 10	(17,24,29)
2	40−60	≤ 10	< 1	6−8	≤ 10	(4,17,30)
2	40−60	≤ 10	1−2	> 8	≤ 10	(31)
2	40−60	-	-	4−6	≤ 10	(18,32*)
2	> 70	> 10	< 1	> 8	≤ 10	(30)
2	> 70	> 10	-	< 4	≤ 10	(9,32*,33)
2	> 70	≤ 10	< 1	4−6	≤ 10	(25,33)
2	> 70	≤ 10	> 2	4−6	≤ 10	(9,25,29,34−36)
2	> 70	≤ 10	1−2	> 8	≤ 10	(37,38)
2	> 70	≤ 10	1−2	4−6	≤ 10	(22*,32*,33,37,39,40)
2	> 70	≤ 10	1−2	6−8	≤ 10	(19,31,41,42)
2	> 70	No[3]	No	4−6	> 10	(29,34)
2	> 70	-	> 2	4−6	> 10	(9,29,35,36,43,44)
2	> 70	-	-	4−6	≤ 10	(9,29,35)

[1] In the case of gilts, the survival rate is measured with the liveborn litter.

[2] * Symbol refers to gilts in the study

[3] Animals with seronegative serostatus for the antibody

Comparative studies examining the virulence and clinical manifestations of type 1 and type 2 PRRSV showed that in terms of reproductive failure, pregnant gilts infected with either type 1 or type 2 PRRSV exhibited premature farrowing compared to uninfected gilts, with no significant differences observed in terms of virulence associated with reproductive failure (20, 22).

The Jeong et al. (20) study involved pregnant gilts infected with type 1 or 2 PRRSV alone or dually infected with both types. Pregnant gilts infected with type 1 PRRSV alone exhibited higher genomic copies of type 1 PRRSV and more type 1 PRRSV-positive cells in stillborn foetuses and live-born piglets than gilts dually infected with both types. In contrast, pregnant gilts infected with type 2 PRRSV alone did not show a significant difference in genomic copies of type 2 PRRSV compared to dually infected gilts. Moreover, no significant differences in type 2 PRRSV-positive cells were observed in the tissues of stillborn foetuses and live-born piglets.

In weaned pigs, PRRSV type 2 was found to exhibit higher virulence than PRRSV type 1, inducing more severe pulmonary pathology and broader distribution of the virus in the body and resulting in higher levels of oral excretion compared to PRRSV type 1 (19, 36).

Overall, the reviewed studies showed a variety of clinical manifestations. On the one hand, strains classified as highly pathogenic for their ability to cause high fever, high morbidity and mortality (31), such as rJXwn06, JXA1-like HP-PRRSV type 2 (29, 35), and the recombinant strain WestSib13 from Lena PRRSV-1 (23), replicated more in serum, produced higher temperatures, and mortalities higher than 80% in piglets, leading to a classification of "severe" for the clinical signs categories. On the other hand, other strains showed asymptomatic infections, particularly in sows (26, 32), or mild respiratory signs in piglets (21), which led to a "mild" classification in our clinical sign categories.

The first antibody detection ranged between six and 14 days after infection, with < 0.4–6 S/P ratio levels. The most frequently reported values were seroconversion at seven (36.7%) and ten days (32.6%) postinoculation (DPI), with the peak occurring at 14 days (18 strains/56.3%) for PRRSV-2 and 28 days for PRRSV-1 (3 strains/33.3%). An exception was described in (34), where one group displayed clinical signs, and analysis tissues were PRRSV-positive; however, these animals remained seronegative throughout the experiment.

The association between viral load and the clinical signs and lesion categories is shown in Fig. 3. The viral loads ranged between 2.5 and 9 log 10 copies/ml. Higher viral loads were generally associated with moderate clinical signs and lesions. Viral titres below 4 log 10 copies/ml typically indicated mild clinical signs and lesion category levels. In contrast, titers above 6 log 10 copies/ml suggested a moderate to severe level of clinical signs and lesion categories. In two studies, the viral titres reached 9 logs 10 copies/ml for the MB6 strain (PRRSV-2 HP-PRRSV northern, sublineage 8.7) (31) and the recombinant strain FJNP2017 (PRRSV-2, lineage 8.7, recombinant strain that contains genetic elements from both the JXA1-like strain and the NADC30-like strain) (37).

PRRSV-1 and PRRSV-2 typically result in detectable viral titres three days following infection, with the peak occurring between 2 and 14 days post-exposure to the virus and generally seven days post-infection (Fig. 4). Mild clinical signs were observed at the peak viral titre approximately six days after infection or later, while moderate and severe clinical signs occurred earlier.

Discussion

This scoping review aims to provide a comprehensive overview of the selected experimental infection studies to identify and summarise the different characteristics of PRRSV strains. Our study covers 77 isolates from 12 countries, demonstrating the significant differences between strains and their impact, including different clinical manifestations and other characteristics associated with the disease.

PRRSV is categorised into two phylogenetic clades: PRRSV type 1 and PRRSV type 2. The identification of these clades originated from Europe and North America. To understand disease transmission and epidemiology, scientists often analyse the genetic similarities between PRRSV isolates (45, 46). Comparative studies and coinfection analysis can be particularly useful in countries where PRRSV 1 and PRRSV 2 constantly cocirculate in pig farms (20, 47).

Regarding comparative studies of type 1 and type 2 PRRSV, type 2 PRRSV generally exhibits higher virulence in inducing pulmonary pathology and viral distribution in weaned pigs (19, 36). However, despite type 2 PRRSV replication being more efficient in dually infected pregnant gilts, neither PRRSV type exacerbated reproductive failure in gilts already dually infected with both types (20), suggesting that the severity of reproductive failure is similar between dual infection (type 1 and type 2 PRRSV) and single infection (type 1 or type 2 PRRSV).

The severity of PRRSV infection varies depending on the route of viral exposure. The virus explicitly targets alveolar macrophages in the lungs of infected pigs, but it can also infect other cells in the monocyte/macrophage lineage, including subsets of macrophages found in lymph nodes, spleen, and pulmonary intravascular macrophages. Moreover, the virus can infect intravascular macrophages in the placenta and umbilical cord (48, 49).

Overall, it is important to interpret these findings cautiously, as the virulence of PRRSV can vary significantly between strains and other factors, such as immune responses, environmental conditions, and transmission routes.

The clinical presentation of PRRSV infection can vary depending on the age of the affected animals. In pregnant gilts, the clinical signs are strongly influenced by the stage of gestation. The infection can lead to embryonic death during early gestation, while mid-gestation does not cause reproductive failure. However, infection during late gestation can consistently result in transplacental infection and clinical manifestations (32). In piglets, it can cause both systemic and respiratory effects. These include weight loss, fever ranging from 39°C to 41.5°C, lethargy, reduced appetite, diarrhoea, respiratory distress, pneumonia, and laboured breathing. Coughing and sneezing may be observed early at the onset of

infection, indicating that the virus can replicate in the nasal mucosa, with a higher likelihood of spreading to other pigs via the airborne route (27).

While high fever typically corresponds with more severe clinical signs, one study reported contrasting results with the pattern in Fig. 3. Yuzhakov et al.(23) found that their novel WestSib13 isolate, despite being highly pathogenic with high levels of viraemia, did not induce fever in infected animals. Notably, this study observed mortality in all animals under study, which could indicate a lack of systemic inflammatory response and a fever-free mortality pattern after infection. Cases such as this show how critical clinical signs such as fever, anorexia or depression are for early disease detection.

In addition to clinical signs, the development and extension of lesions were directly related to the virulence of PRRSV (Fig. 3). PRRSV primarily targets pigs' immune and respiratory systems, infecting the cells of the lungs and lymph nodes. The distribution of the virus in the lungs is the most critical evaluation criterion for determining the virulence of PRRSV. More virulent strains replicate faster and induce more severe interstitial pneumonia, regardless of their genotype (21). In cases of greater virulence, lesions can be seen in other organs, such as the thymus, kidneys, and heart; for instance, Do et al. (31) observed PRRSV in cardiac myocytes, cerebrum and cerebellum.

Secondary bacterial infections were also observed, and the visualisation of lesions, such as extensive, severe pneumonia accompanied by suppurative or fibrinous bronchopneumonia in the lung, may be indicative of the involvement of secondary infections, with pathogens such as *B. bronchiseptica* and *H. parasuis* (29, 33). The presence of nasal pathogens such as B. *bronchiseptica* and *Chlamydia suis* can cause intense sneezing, facilitating the virus's spread.

PRRSV seroconversion and viral load can vary depending on the strain involved, route of infection, and host immune response. The dynamics of the viral load imply an increase rapidly following infection, reaching a peak and then declining as the host immune system responds and begins to control the infection. Han, Seo, Oh, et al. (21) reported that a more virulent strain of PRRSV exhibited better in vivo replication and higher serum viral loads. Ruedas-Torres et al. (13) suggested that a 2 log 10 copies/mL difference in viral loads could be used as a parameter to identify significantly virulent strains. Similarly, in this study (Fig. 3), viral loads over 6 log 10 copies/mL were observed in animals with a moderate to severe classification of clinical signs.

The seroconversion times in this study were consistent with those reported by Mateu and Díaz (50), who found that some pigs developed circulating antibodies against PRRSV as early as five–seven days post-infection, with all animals seroconverting by day 14 (Fig. 4). Virulent PRRSV strains elicit rapid and efficient humoral antibody responses, resulting in higher serum viral loads (37). However, there is often a balance between the severity of clinical symptoms and the evolutionary mechanism of avoiding host mortality.

Another characteristic mentioned in the studies is the description of recombinant strains. Recombination is a crucial mechanism that provides advantages in replication potential and survival (14, 43). PRRSV

recombination is important in increasing transmissibility, adaptation to different organ targets, and escape from immune recognition (4, 40). Additionally, PRRSV recombination patterns in the field are becoming increasingly complex, with different strains from the same lineage showing different recombination patterns and lineages recombining with each other (39), including attenuated strains from modified live vaccines (MLVs) (27, 44). This has made the identification of specific genomic determinants of virulence elusive and multifaceted (33).

This scoping review summarises the literature on PRRSV virulence and pathogenicity characteristics in the last decade. Overall, this review found that the identified virulence characteristics of PRRSV are broadly consistent with those previously described in the literature. However, some studies described particular characteristics, such as nonseroconversion as a result of the infection (34) or mortality with the absence of fever as a clinical sign (23), among others, highlighting the host–pathogen relationship's complexity. The clinical symptoms of PRRSV infection observed in the field can be influenced by several factors, including genetic susceptibility, environmental factors, immune status, management practices, virus strains, and coinfections with other pathogens. The studies analysed have shown that the mild clinical disease observed could be due to the use of pigs with very high health and hygienic status, which helps avoid the exaggeration of secondary infections and contributes to fewer evident clinical signs, as commonly observed in conventional pigs (26).

This review highlights features that may facilitate early detection, particularly given the different manifestations of PRRSV according to age groups. As with all types of infectious diseases, it is essential to emphasise the role of biosecurity and good practices to prevent the development of new strains or the emergence of virulent strains in a pig farm. It is crucial to be vigilant for early signs such as fever, coughing, and sneezing and to conduct serological analyses to confirm and isolate infected animals or make informed decisions regarding their management.

Conclusions

Recognition of virulent strains showed moderate to high clinical sign scores, high mortality rates above 20%, fever above 39.5°C, clinical respiratory signs, lesions in the lungs and other organs, high viral loads above 6 logs 10 copies/mL, and early seroconversion before seven days post-infection.

Virulent strains of PRRSV have adapted to enhance transmissibility through clinical signs that promote virus shedding in short periods. This evolution has resulted in highly pathogenic and virulent strains that prevail in certain regions.

Therefore, new-generation studies covering a wide range of PRRSV strains and different methodological techniques are required to better understand the differences between the different strains and their dynamics and possible impacts on animal health and food safety.

Methods

Search strategy and inclusion criteria

The present study was conducted to identify studies of induced diseases to analyse the parameters that account for the progress and virulence of the disease produced by PRRSV. The methods for this review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.

PubMed, Scopus and Web of Science were used for the search and selection of articles during July and August 2022 using the following keywords, titles or abstract terms: "PRRSV" OR "porcine reproductive and respiratory syndrome virus" AND" "pathogenicity" OR "replicati*" OR "transmissi*" OR "virulen*".

The truncated search term replicati* was used to capture articles containing the terms replicative, replication and transmissi* was used to capture articles containing transmission, transmissive and virulen* was used to capture the concept of virulent and virulence—the Boolean operators "OR" and "AND" combined subheadings and search terms.

We restricted our search to articles published between 2012 and 2022 and only included English articles. The term "PRRS" was excluded from our search because it has a common meaning: "pattern recognition receptors (PRRs)." The final search results were exported into Zotero Software (51). From the total results obtained (n = 2847), we removed duplicates (n = 1924) and contents that were not relevant to the disease/methodology (n = 370) or the selection criteria (n = 440), and the screening of returned search results based on the title and abstract was conducted.

Articles were excluded if they did not pertain to PRRSV, were descriptive about the virus but were not related to it, did not describe animal challenge studies of virus strains or had no full text available. A full manuscript review was conducted of the selected articles. The eligibility criteria were defined using the Population, Intervention, Comparator, Outcome (PICO) framework.

We included studies that addressed the characteristics of the virus and its relationship with the development of the disease, considering pathogenicity (interpreted through clinical and associated lesions), immune response (interpreted as seroconversion rate), recombination (described in the studies), and replication capacity (measured as viral load). In terms of clinical signs and associated lesions, we categorised them into three groups based on their magnitude: mild, moderate, and severe. These categories provide a helpful framework for evaluating the severity of PRRSV infections and their relationship to clinical signs and lesions.

Clinical sign categories:

- Mild: described for animals with no fever, no fatalities, and minimal clinical signs.
- Moderate: described for animals with a fever below 40°C, mortalities up to 20%, and moderate clinical signs.
- Severe: described for animals with a persistent fever above 40°C, mortalities over 20%, and major clinical signs.

Lesion categories:

- Mild: described for animals with minor histological lesions, focal interstitial pneumonia, and swollen lymph nodes.
- Moderate: described for animals with edematous swollen lymph nodes, multifocal interstitial pneumonia, lesions in other organs (such as thymic atrophy, heart, kidney, spleen, and throat), and possibly other coinfections.
- Severe: described for animals with severe interstitial pneumonia, lobular or diffuse distribution with monocyte infiltration, cystic lymph nodes, mild nonsuppurative encephalitis, myocarditis, rhinitis, and possible depletion of lymph node germinal centres. Coinfections caused by influenza virus, *Streptococcus suis, Mycoplasma hyopneumoniae*, *Salmonella* choleraesuis, *Haemophilus parasuis*, *Pasteurella multocida*, porcine circovirus, porcine respiratory coronavirus, and *Actinobacillus pleuropneumoniae* were also considered.

Abbreviations

PRRSV
Porcine Reproductive and Respiratory Syndrome virus
PRISMA-ScR
Systematic Reviews and Meta-Analyses Extension for Scoping Reviews guidelines
ORFs
open reading frames
DPI
days post-infection
S/P Ratio
Signal-to-Positive Ratio
log10
Logarithm base 10
RNA/ml
Ribonucleic Acid per
MLVs
modified live vaccines
°C
Degrees Celsius
PICO
Population, Intervention, Comparator, Outcome Framework

Declarations

Ethics approval and consent to participate:

Not applicable

- **Consent for publication**

Not applicable

- **Availability of data and materials**

This scoping review is based on analysing and synthesising literature and publicly available materials. All the data sources referenced in this review are from published articles, reports, and other publicly accessible documents. No additional datasets, software, or materials were generated specifically for this review. Citations to the sources used in this scoping review are provided within the text and listed in the references section. Readers interested in obtaining access to the original articles and materials are encouraged to refer to the cited sources or contact the respective publishers and authors directly. For further information or inquiries regarding the materials referenced in this scoping review, please feel free to contact the corresponding author.

- **Competing interests**

The authors declare no competing interests related to the conduct or publication of this scoping review.

- **Authors' contributions**

NM: Conceptualisation, literature search, data extraction, analysis and interpretation, manuscript drafting and editing.

JP and IDC: Conceptualisation, data interpretation, manuscript revision and editing.

GM and MG: Critical review of the manuscript.

The final manuscript was reviewed and approved by all authors.

- **Funding**

- **Acknowledgements**

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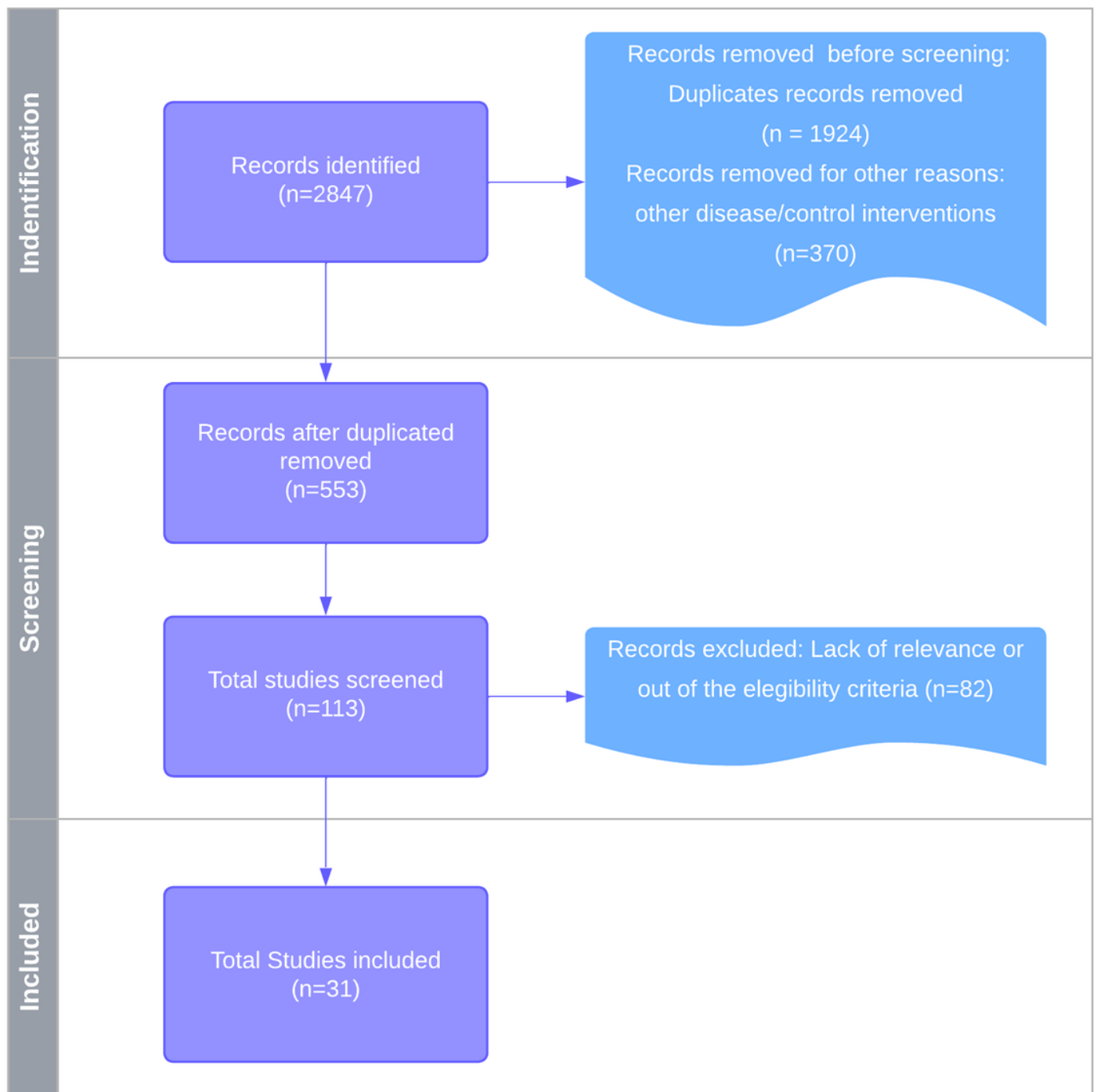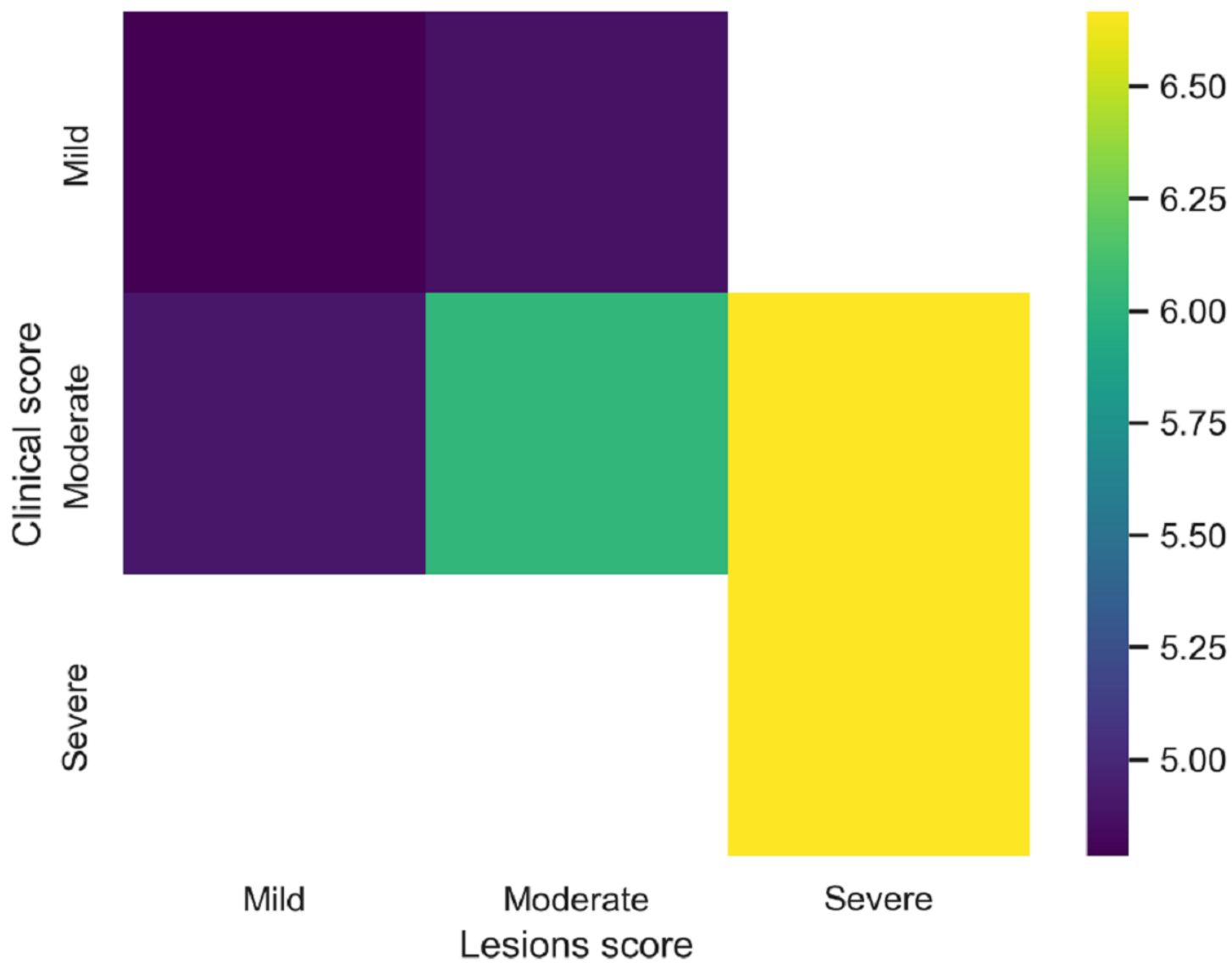
Figures

Figure 1

PRISMA flow chart of the manuscript selection process for analysis of the PRRSV virulence characteristics.
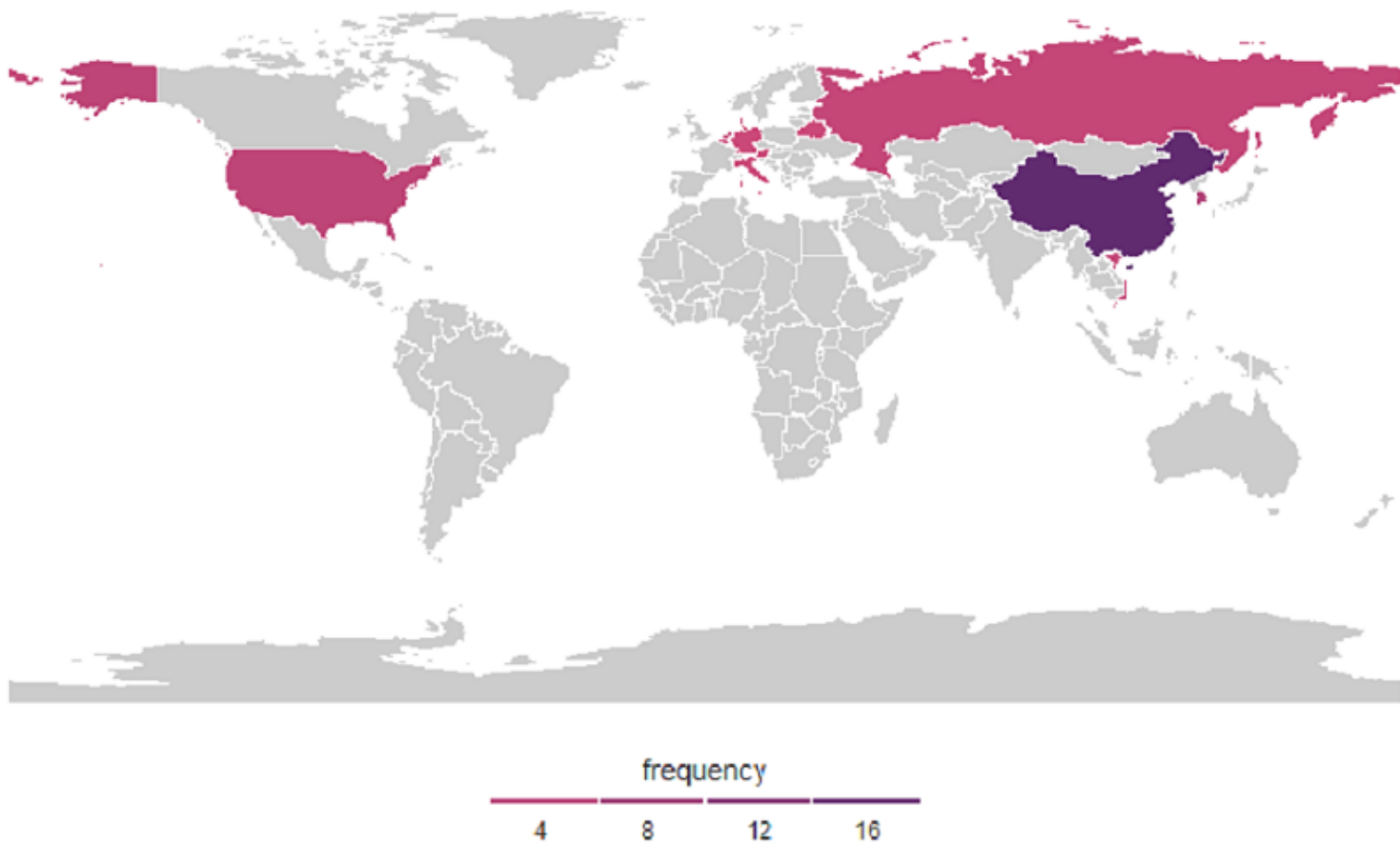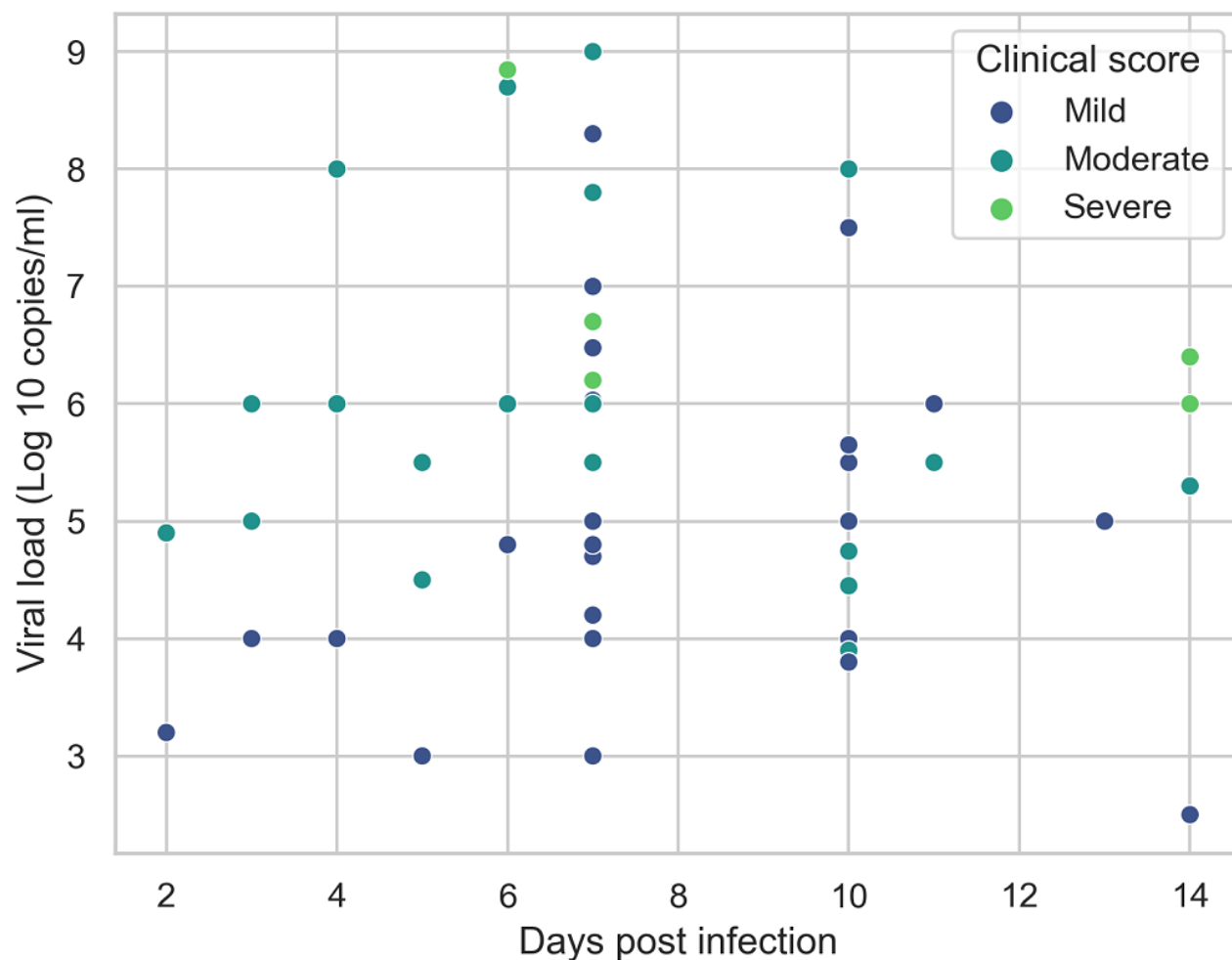
Figure 2

Source map that includes the frequency and origin of the strains under analysis.

Figure 3

Relationship between clinical and histopathological signs and viral titers (log10 copies/mL).

Figure 4

Maximum levels of viremia (log10 copies/mL) per DPI, according to the categorisation of clinical signs.

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