UK Health Security Agency

# The epidemiology and clinical characteristics of Argentine haemorrhagic fever

## A rapid systematic review

# Contents

# Main messages

1. This rapid systematic review (search up to 19 June 2024) identified and summarised evidence relating to the epidemiological and clinical characteristics of Argentine haemorrhagic fever (caused by Junin virus).

2. There were 27 included studies: 2 randomised controlled trials (RCTs) from which observational evidence was extracted (1, 2), one prospective cohort study (3), one retrospective cohort study (4), one case control study (5), 2 cross sectional studies (6, 7), one ecological study (8), 18 case series (9 to 26), and one case report (27), conducted between 1964 and 2020. The number of Argentine haemorrhagic fever cases in the studies ranged from one to 217.

3. All of the reported cases of Argentine haemorrhagic fever occurred in Argentina (1 to 26), apart from a single case imported from Argentina to Belgium (27). Within Argentina, cases occurred in the provinces of Buenos Aires, Cordoba, Santa Fe and La Pampa (2, 5, 7, 8, 22, 23), and in some studies cases were noted to have occurred in rural areas (2, 7, 22).

4. Most studies did not report relevant demographic factors, however where reported most cases of Argentine haemorrhagic fever were in adult men. A serological survey of 695 people in 2 rural endemic areas of Argentina in 1976 to 1977 found that the prevalence of infections was significantly higher in men than women (12.0% and 2.2% respectively, $p<0.001$) (7). There was limited evidence on the ethnicity, occupation and vaccine status of cases, and no evidence on socioeconomic status or comorbidities.

5. There was very limited evidence on transmission of Argentine haemorrhagic fever. A single case report of an imported case in Belgium found no confirmed onward transmission of Argentine haemorrhagic fever amongst 137 identified contacts (27).

6. Twenty-four studies described aspects of the clinical presentation of Argentine haemorrhagic fever (1 to 7, 9 to 24, 27), however the evidence was mostly descriptive, and often from case series. Cases were often categorised into mild, moderate and severe forms, according to clinical features such as the duration of fever, and the severity of neurological involvement (2, 5, 10, 14, 16-20, 23).

7. There was some evidence suggesting asymptomatic infection with Junin virus. Two surveys of laboratory workers working with or near Junin virus, reported prevalence of neutralising antibodies to Junin virus with no clinical history of Argentine haemorrhagic fever as 9.4% (12 out of 127) (6) and 4.7% (5 out of 107) (4). It was 3.9% in a further survey of 695 people in rural parts of Cordoba and Buenos Aires provinces (7).

8. Fourteen studies reported evidence on mortality (1 to 3, 7, 9, 11, 12, 14 to 16, 18, 19, 21, 23, 24, 27), but the proportion of cases with Argentine haemorrhagic fever who died varied

markedly between studies from 0 to 80% (9, 21). This was likely to have been affected by factors such as the small sample sizes, different selection criteria for the studies and the clinical care received. It was therefore not possible to accurately establish the mortality rate for cases with Argentine haemorrhagic fever from the available evidence.

9. The majority of the evidence in this review was descriptive and published over 20 years ago. The studies had variable selection criteria, sampling methods and study contexts, and much of the evidence came from case series with small numbers of cases. The epidemiological and clinical characteristics that were described may not be generalisable to populations and contexts outside of those in the included studies.

# Purpose

The purpose of this rapid systematic review was to identify and summarise the available evidence on the epidemiological and clinical characteristics of Argentine haemorrhagic fever (caused by Junin virus), focussing on the following factors:

a. geographic distribution
b. demographics
c. transmission
d. clinical characteristics

The following outcomes were predefined as being of interest to the commissioner of the report.

**Table 1. Outcomes**

| Theme | Outcomes |
|---|---|
| Geographic distribution | • country, region, and time period<br>• rural or urban setting<br>• incidence and prevalence |
| Demographics | • age<br>• sex<br>• ethnicity<br>• socioeconomic status<br>• occupation<br>• comorbidities<br>• Junin virus vaccination status |
| Transmission | • source of infection (including suspected or confirmed)<br>• any evidence of human-to-human transmission<br>• any measure of incubation period |

| Theme | Outcomes |
|---|---|
| | • any measure of infectious period (including transmission period, culture positivity over time, serial interval and generation time, time to peak viral load, time to viral clearance, viral load over time) |
| Clinical characteristics | • symptoms (including proportion asymptomatic)<br>• proportion hospitalised<br>• proportion requiring intensive care<br>• mortality |

Argentine haemorrhagic fever is a zoonotic infectious disease caused by Junin virus (a type of arenavirus), first reported in Argentina in the 1950s.

# Methods

A rapid systematic review was conducted, following streamlined systematic methods to accelerate the review process. A literature search was undertaken to look for relevant primary studies, published or available as preprint, up to 19 June 2024. The reference lists of included studies were screened for relevant papers (backwards citation searching), and studies that had referenced the included studies were also screened (forwards citation searching). Studies on both confirmed and suspected cases of Argentine haemorrhagic fever were eligible for inclusion, and laboratory confirmation of Junin virus was not required.

Screening on title and abstract was undertaken in duplicate by 2 reviewers for 20% of the eligible studies, with the remainder completed by one reviewer. Screening on full text was undertaken by one reviewer and checked by a second. Data extraction was undertaken by one reviewer and checked by a second.

Risk of bias assessment was conducted in duplicate by 2 reviewers for included studies where analytical outcomes were reported, using the quality criteria checklist (28). Risk of bias assessment was not conducted for studies where only descriptive outcomes were reported, however results were interpreted in light of methodological limitations and generalisability.

A protocol was produced before the literature search was conducted, including the review question, the eligibility criteria, and all other methods. Full details of the methodology are provided in the protocol in Annexe A. There were no deviations from the protocol.

# Evidence

In total, 3,204 studies were screened at title and abstract and 44 studies were screened at full text. Of these, 27 studies met the inclusion criteria (1 to 27). The full text for 4 studies could not be retrieved. An additional 666 studies were screened at title and abstract from forwards and backwards citation searching of the reference lists of included studies, but none were relevant to include. No relevant systematic reviews were found during title and abstract screening. The PRISMA diagram showing the flow of studies through this review is available in Annexe B. Studies excluded on full text screening are available with the reasons why in Annexe C. Full details of included studies are available in Annexe D.

There were 2 included RCTs from which observational evidence was extracted (1, 2), one prospective cohort study (3), one retrospective cohort study (4), one case control study (5), 2 cross sectional studies (6, 7), one ecological study (8), 18 case series (9 to 26), and one case report (27). Studies were conducted between 1964 and 2020, though in 9 studies the time period was not reported (9, 12 to 15, 19, 23 to 25). All but 2 of the included studies were published over 20 years ago (1 to 7, 9 to 26). The total number of cases of Argentine haemorrhagic fever in the studies ranged from one to 217 (1, 27). Overlap in the reported cases between studies was likely, but the extent of this could not be determined.

## Geographic distribution

### Country, region, and rural or urban setting

All the reported cases of Argentine haemorrhagic fever in the included studies occurred in Argentina, apart from a single case report in Brussels, Belgium (27). The affected woman in Belgium was thought to have acquired the infection in the city of Perez in the Santa Fe province of Argentina, before travelling to Brussels and becoming unwell.

Seven studies reported aspects of the geographical distribution of Argentine haemorrhagic fever beyond the country location of cases. Five studies described the city or region where cases had occurred (2, 5, 22, 23, 27). A case control study and a case series described 55 and 19 cases respectively, admitted to hospital in the city of Pergamino (5, 23). Observational evidence taken from an RCT provided evidence on 23 cases from a rural 41-county region in the Southern Santa Fe province (2), and a further case series reported on 21 cases from rural, endemic areas near Junin city (22). In all 7 studies, the geographic location of cases was incidentally reported, however describing the geographical distribution of Argentine haemorrhagic fever was not the purpose of the studies and so the described geographical distribution may not be exhaustive.

### Incidence and prevalence

Weissenbacher and others (7) conducted a serological survey between 1976 to 1977 to determine the prevalence of antibodies to Junin virus in 695 people from 2 rural, endemic areas

in Argentina. This included a 5,000 square kilometre area of Cordoba province (population density 3.4 inhabitants per square kilometre), and a 133 square kilometre area of Buenos Aires province (population density 3.0 inhabitants per square kilometre). They defined clinical infection as positive neutralising antibodies and a clinical history of Argentine haemorrhagic fever in the previous 14 years, and asymptomatic infection as positive neutralising antibodies without a clinical history of Argentine haemorrhagic fever. The overall prevalence of antibodies to Junin virus was similar between provinces (12.0% in Cordoba and 11.6% in Buenos Aires, p>0.5), as was the prevalence of clinical infection (7.6% in Cordoba and 9.7% in Buenos Aires, p>0.5). The prevalence of asymptomatic infection was 4.4% in Cordoba and 1.9% in Buenos Aires (p value not reported). Measures of variance for these prevalence estimates were not reported.

Polop and others (8) conducted an ecological study of environmental differences (such as weather and environmental differences) at sites with different incidence of Argentine haemorrhagic fever. To assist with this, they categorised 65 sites in low grassland areas known as the Pampas as either epidemic for Argentine haemorrhagic fever (disease emergence during 1987 to 1991 and relatively high incidence), historic (where the disease was epidemic, but incidence reduced to less than 2 per 10,000 people between 1987 and 1991), and nonendemic (cases not reported). The study did not report whether the incidence thresholds were per year or across the given time period. The sites were in the provinces of Buenos Aires, Cordoba, Santa Fe, and La Pampa. There were 20 epidemic sites, 26 historic sites and 19 nonendemic sites. A full list of these is available in the data extraction for the study in Annexe D. The source of the incidence data for this ecological study was unclear, making it difficult to assess for any risks to its accuracy.

# Demographics

Most studies did not report any demographic factors relevant to the rapid systematic review protocol (1, 3, 8, 10, 12 to 19, 21 to 26).

## Age and sex

Eight studies reported on the age of cases with Argentine haemorrhagic fever. Six studies provided an age range for some or all of their included cases, which ranged from 10 to 79 years (2, 7, 9, 11, 20, 27). Only 3 studies reported the mean age of participants, which was 39 years in a case-control study with 31 cases (5), 40 years in a case series of 67 cases (20), and 38 years in a case series of 12 cases (11).

Five studies reported on the proportion of participants who were male and female, including a case control study with 31 cases, a cross sectional survey of 695 people, and 3 case series with case numbers ranging from 5 to 67 cases (5, 7, 9, 11, 20). Amongst these, the proportion of cases who were male ranged from 60% to 81%. In addition, an RCT was limited to men only (2), and one case report described a single case in a woman (27).

In their serological survey of 695 people described above, Weissenbacher and others reported the distribution of clinical and asymptomatic Junin virus infection by age and sex (7). The prevalence of clinical infection was significantly higher in men than women (12.0% and 2.2% respectively, p<0.01) (7).

Prevalence of clinical infection was highest in men aged 40 to 49 years (14 out of 68, 20.6%) and 70 to 79 years (3 out of 14, 21.4%), and no clinical infection was found in boys aged 0 to 9 years (0%, 0 out of 23).

Amongst girls and women, prevalence of clinical infection was highest in women aged 40 to 49 years (3 out of 43, 6.9%), and no clinical infection was found in those aged under 30 years (7).

There was no significant difference in prevalence of asymptomatic infections in men compared to women (4.8% and 2.5% respectively, p>0.05) (7). Asymptomatic infection was highest in men aged 30 to 39 years and 70 to 79 years of age (7.1% for both), and for women was highest in 30 to 39 year olds (3.8%).

## Ethnicity

Only one case series reported ethnicity of the cases, where all 12 cases were described as white (11).

## Occupation

There was limited evidence on occupation of affected cases. Two studies surveyed laboratory workers working with or near Junin virus, dividing them into high risk and low risk groups. In one study, high risk groups were those working directly with the virus, whilst low risk groups worked in the same area as the virus (6). In the other, high and low risk groups were not defined (4). Amongst the high-risk laboratory workers, 12 out of 62 (19.4%) (6), and 6 out of 52 (11.5%) (4) had positive serology. Only one of these cases had a history of clinical symptoms of Argentine haemorrhagic fever (4). One study limited participants to men working or residing in rural agricultural areas (2), however no studies specifically addressed the risks of agricultural work.

## Junin virus vaccination status

In an RCT of the effectiveness of a new attenuated Junin virus vaccine candidate, Candid 1, , 23 laboratory-confirmed cases of Argentine haemorrhagic fever occurred amongst 6,500 participants (2). Amongst the cases, 22 had received placebo vaccine and one had received Candid 1 vaccine. Vaccination status was not reported by other studies, and many were conducted before a Junin virus vaccine was introduced.

No evidence was found on socioeconomic status or comorbidities of cases.

# Transmission

## Human-to-human transmission

One case report described the contact tracing that was undertaken for a case of Argentine haemorrhagic fever imported to Belgium (27). The case acquired the infection in Argentina, travelled to Amsterdam in the Netherlands for 4 days via a connecting flight in Madrid, Spain, then travelled by bus to Brussels. She was admitted to hospital unwell in Brussels, but the timing of onset of symptoms relative to her travel was not reported. In total, 137 contacts were identified who were stratified into high risk (77 contacts) and low risk (60 contacts) according to degree of contact with body fluids, and included laboratory personnel, care givers, and sexual and household contacts. No cases of onwards transmission of Argentine haemorrhagic fever were identified, however evidence from contact tracing for a single case may not be generalisable to other cases and settings.

## Infectious period

Three case series reported on viral isolation over time in blood and tissues (24-26). It is possible that the detection of virus over time could relate to infectiousness, however this is not necessarily the case so this evidence should be interpreted with caution. No studies reported on other measures of infectious period such as the transmission period, culture positivity over time, serial interval, generation time, or time to peak viral load.

Ambrosio and others (26) reported on Junin virus isolation in peripheral blood mononuclear cells in a case series of 30 hospitalised cases who were treated with immune plasma. Twenty-eight of the 30 cases had peripheral blood mononuclear cells tested at baseline, and Junin virus was detected in 27 of those. Sixteen of the cases had this test repeated in the recovery phase of illness at days 27 to 43, and no Junin virus was detected. In another case series, 6 cases had their diagnosis confirmed with viral isolation or antibody detection, but Junin virus could not be detected in the blood or liver at the time of death for the 3 cases who died (24). A further case series of 7 fatal cases did find Junin virus in the peripheral blood at postmortem 6 to 14 days after illness onset in 6 of 7 cases, and in the spleen and lymph nodes in all 7 cases (25). The 3 case series provide mixed evidence on whether Junin virus could be detected in the blood and tissues during the recovery phase of the illness, or at time of death.

No evidence was found on the source of infection or incubation period.

# Clinical characteristics

Twenty-four studies reported on aspects of the clinical characteristics of Argentine haemorrhagic fever (1 to 7, 9 to 24, 27).

## Symptoms

The symptoms and signs of cases with Argentine haemorrhagic fever were described in 22 studies. Nine case series described some degree of classification of Argentine haemorrhagic fever cases according to symptom severity. Typically, milder forms of illness were characterised by fever that resolved during the first week of illness, and mild neurological involvement (such as tongue tremor only) (12, 14, 16, 18, 19, 23). Moderate forms of illness were characterised by fever into the second week of illness, and more pronounced neurological involvement such as tongue tremor, reduced or absent reflexes, mental confusion, drowsiness, and balance and co-ordination problems (11, 12, 14, 16, 18, 19, 23). Severe forms of illness were characterised by more severe neurological involvement including reduced muscle tone, absent reflexes, poor balance and co-ordination, seizures, and coma (9, 11, 12, 14, 16, 18, 19, 23). A shock syndrome was noted in some cases who died, though this was not further described (12, 14, 19, 23). There was overlap in the description of symptoms for mild, moderate, and severe forms of the disease. The categorisation of cases is likely to have reflected physician and researcher opinion, and may not be representative of the spread of severity amongst all cases of Argentine haemorrhagic fever. These case series describe individual cases, therefore the findings may not be generalisable to a wider population.

Prospective evidence of the proportions of cases who developed mild, moderate and severe disease was provided by Maiztegui and others, in an RCT of Junin virus vaccine effectiveness (2). Twenty-nine cases of Junin virus detection amongst the 6,500 participants occurred in the following Argentine haemorrhagic fever seasons, of which 19 were clinically diagnosed with mild Argentine haemorrhagic fever, 3 were diagnosed with moderate Argentine haemorrhagic fever, and 2 were diagnosed with severe Argentine haemorrhagic fever. The remaining cases where Junin virus was detected were diagnosed with other febrile illnesses. Definitions of mild, moderate and severe cases were not reported in this study.

One retrospective cohort study and 4 case series reported on other symptoms and signs of Argentine haemorrhagic fever that did not feature in the severity classifications, including malaise, photophobia (aversion to light), headache, retro-ocular pain (pain behind the eyes), loss of appetite, nausea, vomiting, dizziness, muscle pain, low back pain, red eyes, difficulty sleeping, influenza-like-illness, rash, blistering of the mucous membranes, and enlarged lymph nodes (4, 11, 21, 22, 27).

Nine case series described various haemorrhagic (bleeding) problems in cases with Argentine haemorrhagic fever, which ranged from mild to severe. These included petechiae (red spots caused by small bleeding blood vessels), bruising, bleeding gums, nosebleeds, haematomas (a collection of blood outside of the blood vessels), gastrointestinal bleeding, vaginal bleeding, haemoptysis (coughing up blood), and haematuria (blood in the urine) (9 to 12, 17 to 19, 23, 27).

The evidence for additional symptoms and signs including haemorrhagic problems experienced by cases was descriptive in nature, and the proportions of patients with Argentine haemorrhagic fever experiencing each of these symptoms and signs was unclear. The evidence mostly came

from case series which describe individual cases, therefore the findings may not be generalisable to a wider population.

Harrison and others (5) conducted a case control study through a retrospective review of medical records. Amongst 55 people who were admitted with suspected Argentine haemorrhagic fever, 31 were classified as cases due to a 4-fold rise in neutralising antibody titre, and 24 were classified as controls due to negative antibodies. Presence of axillary petechiae (red spots in the armpit caused by small bleeding blood vessels), and absence of upper respiratory tract symptoms, were more common in the cases than controls (18 out of 31 cases, 5 out of 24 controls, p=0.006 and 31 out of 31 cases, 20 out of 31 controls, p=0.03 respectively). Of note, given the controls in this study had been clinically suspected of having Argentine haemorrhagic fever (but without the necessary antibody rise to meet the case definition), it is possible some of the controls were actually cases. This may mean the differences in symptom patterns that were seen do not reflect the true differences between Argentine haemorrhagic fever cases and controls.

One retrospective cohort study and 2 cross sectional studies provided some evidence suggesting asymptomatic infection with Junin virus. In a survey of laboratory workers with no clinical history of Argentine haemorrhagic fever, but who worked directly with or near Junin virus, 12 out of 127 (9.4%) were positive for neutralising antibodies to the virus (6). Similarly, in another survey of 107 laboratory workers working with Junin virus, 6 had positive antibodies, of whom only one reported a history of Argentine haemorrhagic fever symptoms (4). Prevalence of asymptomatic infection (positive for neutralising antibodies but no known history of Argentine haemorrhagic fever) was 3.9% in a survey of 695 people in rural areas of Cordoba and Buenos Aires provinces (7).

One RCT, one case control study, and 5 case series described some aspects of the time course of illness in cases with Argentine haemorrhagic fever. In one case series, clinical improvement was defined as the disappearance of fever and protein in the urine, with a significant increase in circulating white blood cells and platelets, and this occurred on days 9 to 15 amongst 15 non-fatal cases (13). Another case series (48 cases) found patients with mild and moderate severity disease recovered within 2 to 3 weeks of disease onset (19). A case series of 12 fatal cases described neurological symptoms appearing around day 7 of illness, with severe neurological involvement and widespread bleeding in the days preceding death (11). An RCT and a case control study described late onset neurological symptoms in some cases, though further detail was not reported (1, 5). Four cases from case series died within 2 days of admission to hospital (12, 23). Four of 32 patients from another case series died within 9 to 12 days of symptom onset (16). All of this evidence was descriptive in nature and reflects the disease time course seen in individual cases, therefore the findings may not be generalisable to a wider population.

## Hospitalisation and intensive care use

Many studies only included hospitalised cases (5, 10, 12, 15, 21, 22, 24, 27), and in one case report the case received intensive care (27). However, no evidence was found on the

proportions of people with Argentine haemorrhagic fever who required hospitalisation and intensive care.

### Mortality

Fourteen studies reported mortality of cases with Argentine haemorrhagic fever (1 to 3, 9, 12, 14 to 16, 18, 19, 21, 23, 24, 27).

Three of these studies provided prospective evidence of mortality in cases with Argentine haemorrhagic fever. Enria and others (3) conducted a prospective cohort study in 83 cases admitted to hospital with Argentine haemorrhagic fever in the 1982 and 1983 epidemic seasons. All were treated with varying doses of immune plasma, and 3 died (3.6%). Maiztegui and others conducted an RCT investigating the effectiveness of immune plasma treatment, and reported 17 out of 188 (9.0%) laboratory confirmed Argentine haemorrhagic fever cases died, as well as 3 out of 29 (10.3%) clinically diagnosed cases without laboratory confirmation (1). In another RCT, Maiztegui and others assessed the effectiveness of vaccination with Candid 1 compared to placebo vaccination (2). Amongst 6,500 participants who were followed up for one to 2 Argentine haemorrhagic fever seasons, there were 29 cases of Junin virus detected, and one case died (3.4%).

In 10 case series (case numbers ranging from 5 to 48 per series) (9, 12, 14 to 16, 18, 19, 21, 23, 24), the proportion of patients with Argentine haemorrhagic fever who died varied markedly, from 0 to 80% (9, 21). In a single case report, a severely unwell case received intensive care support and survived (27). There were multiple differences between the case series which may have affected the numbers who died. For example, some only included hospitalised patients who may be more ill on average than those who remain in the community (3, 12, 15, 21, 24). Some cases received treatment with immune plasma, which may have influenced their outcome (1, 3, 12, 21). The variation in these case series was too great, and the number of included cases too small, to allow for a meaningful estimate of mortality in cases with Argentine haemorrhagic fever. These case series and case report describe individual cases, therefore the findings may not be generalisable to a wider population.

## Critical appraisal

Formal risk of bias assessment was conducted for the 2 studies that had analytical outcomes, using the QCC risk of bias tool (5, 7). This included a case control study, and a cross-sectional study. For both studies it was unclear how participants were selected for the studies, causing a risk of selection bias where the participants in the studies do not reflect the broader population at risk of Argentine haemorrhagic fever. In addition, the associations that were measured were not controlled for potential confounding factors, and it is possible other factors were responsible for the results. For example, one study compared the prevalence of infection with Junin virus between men and women, different age groups, and in 2 different endemic areas in Argentina. For the latter, these areas may not be directly comparable due to differences in other factors such as sex, age, and ethnicity of the population. Caution is therefore needed in interpreting the

association between sex, age, endemic area, and the risk of infection (7), and in interpreting the association of specific clinical signs and symptoms with Argentine haemorrhagic fever (5). Only one of the studies reported on its funding or sponsorship, but it was unclear whether this would have caused bias in any outcomes (7).

Most evidence included in this review was descriptive, which has a number of limitations. It is not possible to report with certainty whether any of the described characteristics are specifically associated with Argentine haemorrhagic fever, or whether they have occurred by chance or been caused by the way cases or populations were selected. Most of the included evidence came from case series, which describe individual cases and therefore the findings may not be generalisable to a wider population.

# Health inequalities

There was very limited evidence enabling exploration of health inequalities in relation to the research question, and the majority of the included studies did not report any relevant demographic factors. Some evidence was available describing the age and sex of cases with Argentine haemorrhagic fever. Where reported, most cases were male, and in adults rather than children (5, 7, 9, 11, 20). Serological survey data suggested that this could reflect a true difference in prevalence between the groups rather than underreporting in certain groups (7). However, this was based on a single cross sectional study with some risks of bias identified in the methodological approach, and therefore caution is warranted in interpreting the findings. No studies explored reasons why there may be a difference in antibody prevalence between men and women, or between different age groups. For other relevant demographic factors there was either limited evidence (ethnicity, occupation and Junin virus vaccination status), or no evidence (socioeconomic status and comorbidities). All of the described cases occurred in Argentina, in the provinces of Buenos Aires, Cordoba, Santa Fe and La Pampa, apart from a single case imported to Belgium.

# Limitations

This rapid systematic review used streamlined systematic methods to accelerate the review process. Sources of evidence searched included databases of peer-reviewed and preprint research, but only 20% of studies were screened in duplicate, so it is possible relevant evidence may have been missed.

This review included studies with a wide variety of selection criteria, sampling methods, and study contexts. These factors will have affected the epidemiological and clinical characteristics that were reported, therefore they may not reflect the characteristics of cases with Argentine haemorrhagic fever across the general population. For example, many of the studies were conducted in hospital settings where cases may be more unwell on average than those in the community, and may receive treatments which influence outcomes. The way cases were

selected was often not reported, which introduces a risk of selection bias where the participants in the studies do not represent the wider population.

The majority of the included evidence was descriptive. It is therefore not possible to report with certainty whether any of the described characteristics are specifically associated with Argentine haemorrhagic fever. In addition, whilst there were a large number of included studies (27), for many of the studies there were only small amounts of data relevant to this review which could be extracted, and this was often reported incidentally rather than being the primary focus of the studies.

Many of the included studies were case series which described the epidemiological or clinical features of Argentine haemorrhagic fever in a limited number of individuals, and all the cases apart from one occurred in Argentina. These findings may not be generalisable to people and settings outside of those found in the included studies.

Most of the included studies were published over 20 years ago, and it is possible that the epidemiological and clinical characteristics of Argentine haemorrhagic fever have changed since that time. For example, the geographic distribution of the disease may have altered over time, or the introduction of vaccination or treatments could have altered incidence and outcomes.

# Evidence gaps

Good quality evidence was lacking on all outcomes, but in particular there was very limited evidence on ethnicity, occupation and Junin virus vaccination status amongst people with Argentine haemorrhagic fever, and no evidence on socioeconomic status or comorbidities. There was also very limited evidence on transmission of Argentine haemorrhagic fever. Only a single study addressed contact tracing following a case. Three studies described viral isolation over time in the blood and tissues of cases, and no evidence on other measures of infectious period was found. No evidence was found on source of infection, or the incubation period.

# Conclusion

This rapid systematic review contains mostly descriptive evidence on the epidemiological and clinical characteristics of Argentine haemorrhagic fever. There were 27 included studies, however for many of the studies only small amounts of information relevant to this review were available.

All of the described cases occurred in Argentina, apart from a single case imported from Argentina to Belgium. Demographic factors were not reported in most of the studies, but where reported most cases occurred in adult men. Serological survey data suggested that this could reflect a true difference in prevalence between the sex and age groups rather than underreporting in certain groups, however this was based on a single cross sectional study with some risks of bias identified in the methodological approach, and therefore caution is warranted in interpreting the findings. There was limited available evidence on other demographic characteristics.

Evidence on transmission was very limited. Contact tracing for a single case report was described with no confirmed human-to-human transmission amongst 137 identified contacts. Viral detection over time in blood and tissues was reported in 3 case series, with mixed evidence on whether Junin virus could be detected in the recovery phase of the illness, or at time of death, however viral detection in blood and tissues may not equate to infectiousness.

A wide variety of symptoms in people with Argentine haemorrhagic fever were reported in the included studies, and many studies categorised the cases into mild, moderate, or severe depending on the duration of fever and the severity of neurological involvement. Evidence from 3 serological surveys (2 in laboratory workers working with or near Junin virus, and one in people living in rural parts of Cordoba and Buenos Aires provinces) was suggestive of some asymptomatic infection with Junin virus. The prevalence of positive neutralising antibodies to Junin virus and no clinical history of Argentine haemorrhagic fever was between 3.9% and 9.4% of those surveyed, which could reflect previous asymptomatic infection. The proportion of cases with Argentine haemorrhagic fever who died varied markedly between studies (from 0 to 80%), and was likely to have been affected factors such as the small numbers of cases in many of the studies, different selection criteria for the studies and the clinical care received. It was therefore not possible to accurately establish the mortality rate for cases with Argentine haemorrhagic fever from the available evidence.

The selection criteria of the included studies was likely to have affected the epidemiological and clinical characteristics that were reported. In addition, many of the included studies were case series with small numbers of cases, and the way in which cases were selected was not commonly reported. These issues mean that the evidence may not be generalisable to people and settings outside of those found in the included studies. In addition, most of the included studies were published over 20 years ago, and it is possible that the epidemiological and clinical characteristics of Argentine haemorrhagic fever have changed since that time.

# Acknowledgment

We would like to thank colleagues within the All Hazards Public Health Response division who either reviewed or input into aspects of the review.

# Disclaimer

UKHSA's rapid systematic reviews and evidence summaries aim to provide the best available evidence to decision makers in a timely and accessible way, based on published peer-reviewed scientific papers, and papers on preprint servers. Please note that the reviews:

- use accelerated methods and may not be representative of the whole body of evidence publicly available
- have undergone an internal independent peer review but not an external peer review
- are only valid as of the date stated on the review

In the event that this evidence summary is shared externally, please note additionally, to the greatest extent possible under any applicable law, that UKHSA accepts no liability for any claim, loss or damage arising out of, or connected with the use of, this review by the recipient or any third party including that arising or resulting from any reliance placed on, or any conclusions drawn from, the review.

# References


1. Maiztegui JI and others. 'Efficacy of immune plasma in treatment of Argentine haemorrhagic fever and association between treatment and a late neurological syndrome' Lancet 1979: volume 2, issue 8154, pages 1,216 to 1,217
2. Maiztegui JI and others. 'Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. AHF Study Group' Journal of Infectious Diseases 1998: volume 177, issue 2, pages 277 to 283
3. Enria DA and others. 'Importance of dose of neutralising antibodies in treatment of Argentine haemorrhagic fever with immune plasma' Lancet 1984: volume 2, issue 8397, pages 255 to 256
4. Weissenbacher MC and others. 'Serological survey to detect subclinical Junin virus infection in laboratory personnel' Journal of Medical Virology 1980: volume 6, issue 3, pages 223 to 226
5. Harrison LH and others. 'Clinical case definitions for Argentine hemorrhagic fever' Clinical Infectious Diseases 1999: volume 28, issue 5, pages 1,091 to 1,094
6. Weissenbacher MC and others. 'Inapparent infections with Junin virus among laboratory workers' Journal of Infectious Diseases 1978: volume 137, issue 3, pages 309 to 313
7. Weissenbacher MC and others. 'Junin virus activity in two rural populations of the Argentine hemorrhagic fever (AHF) endemic area' Journal of Medical Virology 1983: volume 12, issue 4, pages 273 to 280
8. Polop F and others. 'On the relationship between the environmental history and the epidemiological situation of Argentine hemorrhagic fever' Ecological Research 2008: volume 23, issue 1, pages 217 to 225
9. Maiztegui JI and others. 'Ultrastructural and immunohistochemical studies in five cases of Argentine hemorrhagic fever' Journal of Infectious Diseases 1975: volume 132, issue 1, pages 35 to 53
10. Cummins D and others. 'A plasma inhibitor of platelet aggregation in patients with Argentine hemorrhagic fever' American Journal of Tropical Medicine & Hygiene 1990: volume 42, issue 5, pages 470 to 475
11. Elsner B and others. 'Pathology of 12 fatal cases of Argentine hemorrhagic fever' American Journal of Tropical Medicine & Hygiene 1973: volume 22, issue 2, pages 229 to 236
12. Heller MV and others. 'Early markers of blood coagulation and fibrinolysis activation in Argentine hemorrhagic fever' Journal of Thrombosis and Haemostasis 1995: volume 73, issue 3, pages 368 and 373
13. Cossio PM and others. 'Immunofluorescent anti-Junin virus antibodies in Argentine hemorrhagic fever' Intervirology 1979: volume 12, issue 1, pages 26 to 31
14. de Bracco MM and others. 'Argentine hemorrhagic fever. Alterations of the complement system and anti-Junin-virus humoral response' New England Journal of Medicine 1978: volume 299, issue 5, pages 216 to 221
15. Ambrosio AM and others. 'Peripheral blood leukocytes of patients with Argentine hemorrhagic fever as effectors of antibody-dependent cell-cytotoxicity' Journal of Medical Virology 1992: volume 37, issue 3, pages 232 to 236
16. Molinas FC and others. 'Coagulation studies in Argentine hemorrhagic fever' Journal of Infectious Diseases 1981: volume 143, issue 1, pages 1 to 6
17. Molinas FC, Maiztegui JI. 'Factor VIII: C and factor VIII R: Ag in Argentine hemorrhagic fever' Journal of Thrombosis and Haemostasis 1981: volume 46, issue 2, pages 525 to 527

18. Molinas FC and others. 'Plasminogen abnormalities in patients with Argentine hemorrhagic fever' Thrombosis Research 1987: volume 48, issue 6, pages 713 to 720
19. Marta RF and others. 'Relationship between hematopoietic growth factors levels and hematological parameters in Argentine hemorrhagic fever' American Journal of Hematology 2000: volume 64, issue 1, pages 1 to 6
20. del Carmen Saavedra M and others. 'IgG subclasses in human immune response to wild and attenuated (vaccine) Junin virus infection' Journal of Medical Virology 2003: volume 69, issue 3, pages 447 to 450
21. Levis SC and others. 'Endogenous interferon in Argentine hemorrhagic fever' Journal of Infectious Diseases 1984: volume 149, issue 3, pages 428 to 43
22. Ruggiero HA and others. 'Argentine hemorrhagic fever: early diagnosis by immunofluorescence' Archives of Virology 1981: volume 70, issue 2, pages 165 to 168
23. Marta RF and others. 'Proinflammatory cytokines and elastase-alpha-1-antitrypsin in Argentine hemorrhagic fever' American Journal of Tropical Medicine and Hygiene 1999: volume 60, issue 1, pages 85 to 89
24. Enria DA and others. 'Tolerance and antiviral effect of ribavirin in patients with Argentine hemorrhagic fever' Antiviral Research 1987: volume 7, issue 6, pages 353 to 359
25. Gonzalez PH and others. 'Lymphatic tissue in Argentine hemorrhagic fever. Pathologic features' Archives of Pathology & Laboratory Medicine 1980: volume 104, issue 5, pages 250 to 254
26. Ambrosio AM and others. 'Junin virus isolation from lympho-mononuclear cells of patients with Argentine hemorrhagic fever' Intervirology 1986: volume 25, issue 2, pages 97 to 102
27. Veliziotis I and others. 'Clinical Management of Argentine Hemorrhagic Fever using Ribavirin and Favipiravir, Belgium, 2020' Emerging Infectious Diseases 2020: volume 26, issue 7, pages 1,562 to 1,566
28. Duval D and others. 'Critical appraisal in rapid systematic reviews of COVID-19 studies: implementation of the Quality Criteria Checklist (QCC)' Systematic Reviews 2023: volume 12, issue 1, page 55

# Annexe A. Protocol

## Review question

The review question is:

1. What are the epidemiological and clinical characteristics of Argentine haemorrhagic fever, focussing on the following outcomes:

a. geographic distribution
b. demographics
c. transmission
d. clinical characteristics

A search for primary evidence to answer this review question will be conducted up to 19 June 2024.

Both suspected and confirmed cases of Argentine haemorrhagic fever in humans will be included.

## Eligibility criteria

**Table A.1 Inclusion and exclusion criteria**

| | Included | Excluded |
|---|---|---|
| Population | Humans | Animals (except in the context of transmission to humans) |
| Context | All | |
| Settings | All | |
| Intervention or exposure | Argentine haemorrhagic fever, caused by Junin virus (both confirmed and suspected, laboratory confirmation of Junin virus not required) | |
| Outcomes | Geographic distribution:<br>• country, region, and time period<br>• rural or urban setting<br>• incidence and prevalence<br><br>Demographics:<br>• age<br>• sex | |

| | Included | Excluded |
|---|---|---|
| | • ethnicity<br>• socioeconomic status<br>• occupation<br>• comorbidities<br>• Junin virus vaccination status<br><br>Transmission:<br><br>• source of infection (including suspected or confirmed)<br>• any evidence of human-to-human transmission<br>• any measure of incubation period<br>• any measure of infectious period (including transmission period, culture positivity over time, serial interval and generation time, time to peak viral load, time to viral clearance, viral load over time)<br><br>Clinical characteristics:<br><br>• symptoms (including proportion asymptomatic)<br>• proportion hospitalised<br>• proportion requiring intensive care<br>• mortality | |
| Language | English | Any other language |
| Date of publication | Up to 19 June 2024 | |
| Study design | Interventional trials, including:<br><br>• randomised controlled trials<br>• non-randomised controlled trials<br>• single-arm studies<br>• quasi-experimental studies<br><br>Where interventional trials are included only the relevant observational data will be extracted, not intervention effect (post-intervention data will be excluded). | • reviews (all types)<br>• modelling studies<br>• laboratory studies<br>• qualitative studies<br>• animal studies (except in the context of transmission to humans) |

| | Included | Excluded |
|---|---|---|
| | Observational studies:<br>• cohort studies<br>• case-control studies<br>• cross-sectional studies<br>• case series<br>• case reports<br>• ecological studies | |
| Publication type | Published and preprint | • editorials<br>• grey literature including guidelines<br>• conference abstracts<br>• letters |

For this review, the definitions used are:

- incubation period: the time between contracting an infection and symptom onset
- infectious period: the timeframe when an individual may transmit the infection to others (including but not limited to transmission period, culture positivity over time, serial interval and generation time, time to peak viral load, time to viral clearance, and viral load over time)
- serial interval: the time between symptom onset in an initial case and symptom onset in those to whom the infection is passed
- generation time: the time between infection in an initial case and infection in those to whom the infection is passed

# Identification of studies

The following databases and trial registries will be searched for studies published up to 19 June 2024: Ovid Medline, Embase, Scopus, Web of Science Preprint Citation Index and Latin American and Caribbean Health Sciences Literature (LILACS). The search strategy is presented below.

Studies that are included at full text will be used as seed papers for backwards and forwards citation searching. Citation searching will be carried out using Lens.org, via CitationChaser. In addition, any relevant systematic reviews identified during screening will be used as seed papers for backwards citation searching only, again via CitationChaser. Citation details of all papers used as seed for citation searching will be reported in the review.

# Screening

Title and abstract screening will be undertaken in duplicate by 2 reviewers for at least 20% of the eligible studies, with the remainder completed by one reviewer. Disagreement will be resolved by discussion or with involvement of a third reviewer where necessary. References found through citation searching will be screened by one reviewer.

Screening on full text will be undertaken by one reviewer and checked by a second.

# Data extraction

Summary information for each study will be extracted and reported in tabular form. Information to be extracted will include study setting, study period, study design, participant demographics (including age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status), results, and any relevant contextual data. This will be undertaken by one reviewer and checked by a second.

# Risk of bias assessment

As the studies are expected to be descriptive rather than analytical, risk of bias assessment may not be performed. If analytical studies are present, the quality criteria checklist will be used to assess risk of bias (28). This will be completed by one reviewer and checked by a second.

# Synthesis

If data is presented in a consistent format between studies, a narrative synthesis will be produced to describe the results from this review. The number of studies, the number of participants in each study, effect size and variance and a summary of the risk of bias across studies will be summarised and presented. Alternatively, if studies present methodological differences that would make synthesis inappropriate, a narrative summary of each study will be provided.

# Health inequalities

No specific populations were stipulated for subgroup analysis in this review. However, geographic distribution and demographic factors including age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status will be summarised.

# Search strategy

## Ovid MEDLINE(R) ALL (1946 to 19 June 2024)

1. (Arenaviruses, New World/ or Hemorrhagic Fevers, Viral/ or Hemorrhagic Fever, American/ or Arenaviridae Infections/) and (Argentina/ or exp South America/ or argentin*.tw,kf.) (390)
2. *Arenaviruses, New World/ (430)
3. *Hemorrhagic Fever, American/ (393)
4. *Arenaviridae Infections/ (488)
5. Junin virus/ (245)
6. (argentin* and (arenavir* or mammarenavir* or h?emorrhagic or h?emorhagic)).tw,kf. (490)
7. (south america* and (arenavir* or mammarenavir* or h?emorrhagic or h?emorhagic)).tw,kf. (343)
8. junin.tw,kf. (916)
9. JUNV.tw,kf. (162)
10. o'higgin* disease*.tw,kf. (3)
11. stubble disease*.tw,kf. (4)
12. mal de los rastrojos.tw,kf. (1)
13. or/1-12 (2056)

## Embase (1974 to 19 June 2024)

1. (mammarenavirus/ or arenaviridae/ or new world arenavirus/ or hemorrhagic fever/ or american hemorrhagic fever/ or arenavirus infection/) and (Argentina/ or exp South America/ or argentin*.tw,kf.) (204)
2. argentine hemorrhagic fever/ (193)
3. *new world arenavirus/ (24)
4. *american hemorrhagic fever/ (9)
5. *arenavirus infection/ (155)
6. junin virus/ (580)
7. (argentin* and (arenavir* or mammarenavir* or h?emorrhagic or h?emorhagic)).tw,kf. (570)
8. (south america* and (arenavir* or mammarenavir* or h?emorrhagic or h?emorhagic)).tw,kf. (421)
9. junin.tw,kf. (949)
10. JUNV.tw,kf. (183)
11. o'higgin* disease*.tw,kf. (0)
12. stubble disease*.tw,kf. (2)
13. mal de los rastrojos.tw,kf. (1)
14. or/1-13 (1858)

## Scopus

TITLE-ABS-KEY ( ( argentin* AND ( arenavir* OR mammarenavir* OR h*emorrhagic OR h*emorhagic) ) ) OR TITLE-ABS-KEY ( ( “south america*” AND ( arenavir* OR mammarenavir* OR h*emorrhagic OR h*emorhagic) ) ) OR TITLE-ABS-KEY ( junin W/7 ( virus OR viral OR infection* OR fever* OR disease* OR illness* ) ) OR TITLE-ABS-KEY ( junv ) OR TITLE-ABS-KEY ( "o'higgin* disease*" ) OR TITLE-ABS-KEY ( "stubble disease*" OR “mal de los rastrojos”)

## Web of Science Preprint Citation index (1990 – 12 June 2024)

TS=( ( argentin* AND ( arenavir* OR mammarenavir* OR h*emorrhagic OR h*emorhagic) ) ) OR TS=( ( “south america*” AND ( arenavir* OR mammarenavir* OR h?emorrhagic OR h?emorhagic) ) ) OR TS=( junin NEAR/7 ( virus OR viral OR infection* OR fever* OR disease* OR illness* ) ) OR TS=( junv ) OR TS=( "o'higgin* disease*" ) OR TS=( "stubble disease*" OR “mal de los rastrojos”)

8 results

## LILACs (1982 – 12 June 2024)

Date of search: 20 June 2024

(south America* OR argentin*) AND (hemorrhagic OR haemorrhagic))

46 results

(junin OR JUNV)

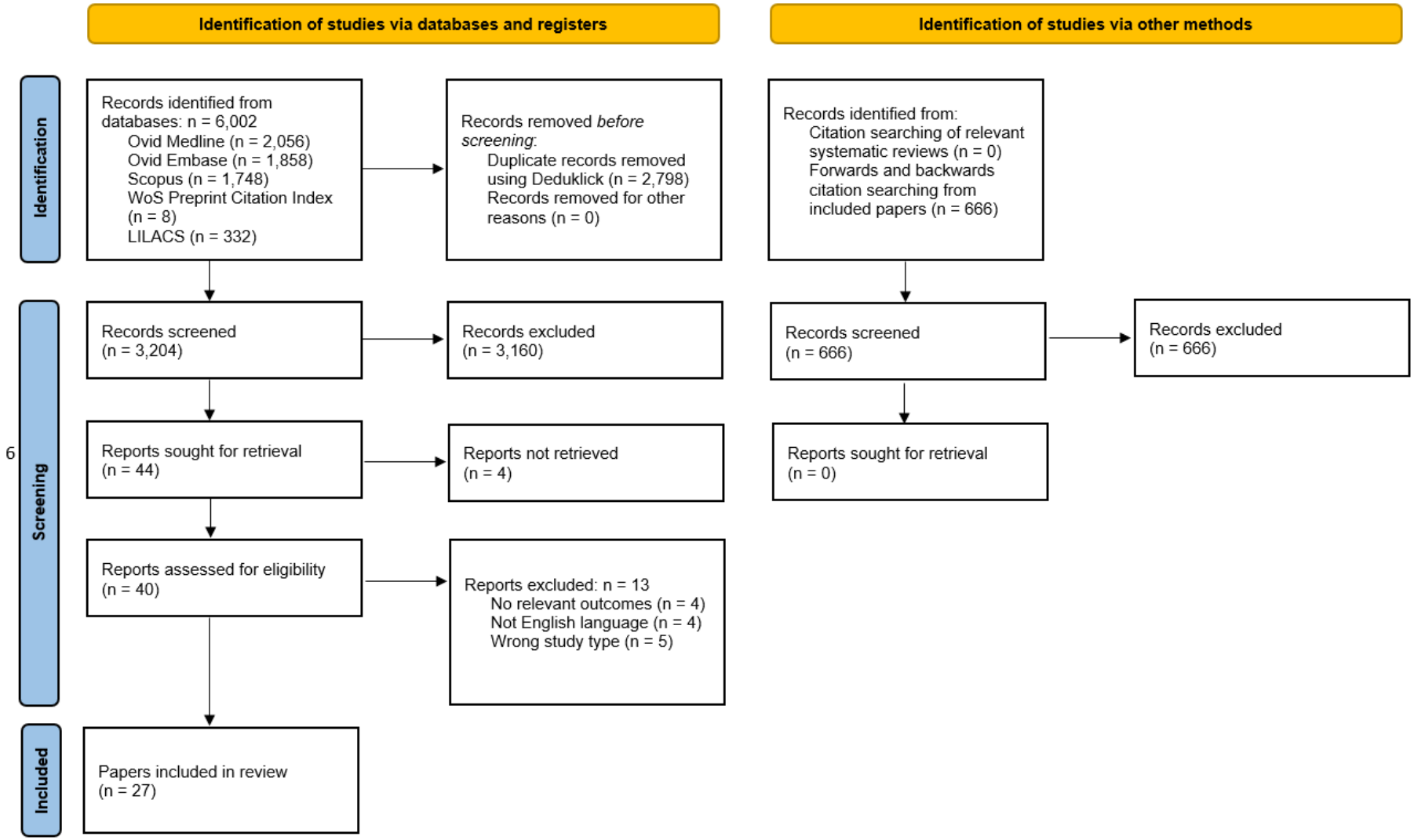
284 results

(stubble disease OR mal de los rastrojos OR o'higgin* disease)

2 results

# Annexe B. Study selection flowchart

**Figure B.1. PRISMA diagram**



**Text version of Figure B.1. PRISMA diagram**

A PRISMA diagram showing the flow of studies through this review, ultimately including 28 studies.

From identification of studies via databases and registers, n=6,002 records were identified from databases:

- Ovid Medline (n = 2,056)
- Ovid Embase (n = 1,858)
- Scopus (n = 1,748)
- WoS Preprint Citation Index (n = 8)
- LILACS (n = 332)

From these, records removed before screening:

- duplicate records removed using Deduklick (n=2,798)
- records removed for other reasons (n=0)

n=3,204 records screened, of which n=3,160 were excluded, leaving n=44 papers sought for retrieval, of which n=4 were not retrieved.

n=666 studies were identified from other methods. All were identified via forward and backwards citation searching of included papers, of which all were excluded at title and abstract screening.

Of the n=40 papers assessed for eligibility, n=13 reports were excluded:

- no relevant outcomes (n = 4)
- not English language (n = 4)
- wrong study type (n = 5)

Overall, n=27 papers were included in the review.

# Annexe C. Excluded full texts

## No relevant outcomes (4 studies)

Ambrosio AN and others. 'Immune response to vaccination against Argentine hemorrhagic fever in an area where different arenaviruses coexist' Viral Immunology 2006: volume 19, issue 2, pages 196 to 201

Cossio P and others. 'Ultrastructural and immunohistochemical study of the human kidney in Argentine haemorrhagic fever' Virchows Archiv A, Pathological Anatomy and Histology 1975: volume 368, issue 1, page 1 to 9

Goni SE and others. 'Viral diversity of Junin virus field strains' Virus Research 2011: volume 160, issue 1, pages 150 to 158

Vallejos DA and others. 'Lymphocyte subsets alteration in patients with Argentine hemorrhagic fever' Journal of Medical Virology 1989: volume 27, issue 2, pages 160 to 163

## Not English language (4 studies)

García Gili MI and others. 'Fiebre hemorrágica Argentina: comunicación de dos casos en zona no endémica' Medicina (B.Aires) 2023: volume 83, issue 1, pages 129 to 132

Mastrangelo A and others. 'Quali-quantitative study of the social variables defining transmission scenarios of argentine hemorrhagic fever in the provinces of Buenos Aires and Santa Fe, 2001 to 2010' Salud Colectiva 2014: volume 10, issue 2, pages 171 to 184

Melcon MO and others. 'Argentine hemorrhagic fever: neurological complications' Neurologia Argentina 2022: volume 14, pages 13 to 25

Weissenbacher MC and others. 'Actividad del virus Junin en humanos y roedores de áreas no endémicas de la provincia de Buenos Aires' Medicina (B.Aires) 1985: volume 45, issue 3, pages 263 to 268

## Wrong study type (5 studies)

Enria D and others. 'Current status of the treatment of Argentine hemorrhagic fever' Medical Microbiology and Immunology 1986: volume 175, issue 2, pages 173 to 176

Heller MV and others. 'Increased tumor necrosis factor-alpha levels in Argentine hemorrhagic fever' Journal of Infectious Diseases 1992: volume 166, issue 5, pages 1,203 to 1,204

Maiztegui JI. 'Clinical and epidemiological patterns of Argentine haemorrhagic fever' Bulletin of the World Health Organization 1975: volume 52, issue 4, pages 567 to 575

Maiztegui J and others. ‘Progressive extension of the endemic area and changing incidence of Argentine hemorrhagic fever’ Medical Microbiology and Immunology 1986: volume 175, issue 2, pages 149 to 152

Molinas FC and others. 'Hemostasis and the complement system in Argentine hemorrhagic fever' Reviews of Infectious Diseases 1989: volume 11, pages S762 to 770

# Annexe D. Data extraction table

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| Ambrosio 1992 (15) | Argentina, study period not reported | Case series | 26 hospitalised cases diagnosed serologically with Argentine haemorrhagic fever (AHF), and treated with immune plasma.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Study of peripheral blood mononuclear cells and polymorphonuclear leucocytes of cases with AHF as effectors of antibody-dependent cell cytotoxicity, using blood samples from cases at 3 time points (admission, 4 days after treatment with immune plasma, and 30 days after clinical onset of disease). Incidentally reported mortality. | Clinical characteristics | 1 out of 26 cases with AHF reported to have died (timepoint of death not reported) |
| Ambrosio 1986 (26) | Argentina, 1982 to 1983 | Case series | 30 hospitalised cases (21 from an epidemic in 1982 and 15 from an epidemic in 1983) who received treatment with immune plasma. 6 additional cases had febrile diseases other than AHF.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Isolation of Junin virus over time by 3 different methods in AHF cases. | Transmission | Prior to immune plasma administration:<br><br>Junin virus was obtained from 27 out of 28 cases by co-cultivation of mononuclear cells, from 16 out of 30 cases by inoculation of blood into suckling mice, and from 14 of 30 cases by culture on Vero cell monolayers.<br><br>16 cases had viraemia measured again after immune plasma treatment (by co-cultivation of mononuclear cells). During the first 3 days after treatment with immune plasma, viraemia was present with decreasing frequency.<br><br>16 cases had samples taken during convalescence from days 27 to 43, where viraemia was not detected (by co-cultivation of mononuclear cells).<br><br>Overall, Junin virus was found in peripheral blood mononuclear cells in the acute phase of the disease, but not during early convalescence. |
| Cossio 1979 (13) | Argentina, study period not reported | Case series | 15 cases diagnosed with AHF and who did not die (diagnostic criteria not reported).<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, Junin virus vaccination status not reported | Investigating the relationship between development of antibodies for Junin virus and clinical improvement. Daily blood samples were taken from the 9th to the 20th day after onset of symptoms. Control group with serum from 15 blood donors, 20 people with connective tissue disease, and 3 patients with lymphochoriomeningitis. Incidentally reported on clinical symptoms of the AHF cases. | Clinical characteristics | Clinical improvement was defined as the disappearance of fever and proteinuria and a significant increase in the number of circulating leucocytes and platelets.<br><br>Day of clinical improvement amongst the 15 cases with AHF ranged from day 9 to 15 after illness onset. |
| Cummins 1990 (10) | Argentina, 1988 | Case series | 10 hospitalised cases with AHF admitted during a 1988 epidemic in Argentina.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Study to determine whether cases with AHF developed a circulating plasma inhibitor of platelet aggregation, through comparison to patients with other acute febrile illness. Incidentally reported on symptoms and disease severity. | Clinical characteristics | 2 cases with AHF were classified as mild, 2 as moderate, and 6 as severe based on the clinical picture and severity of neurological involvement. Further detail on severity classification not reported, and inclusion criteria unclear.<br><br>All cases had petechiae in the mouth. 2 of the patients with severe AHF developed gastrointestinal bleeding. |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| de Bracco 1978 (14) | Country and study period not reported | Case series | 19 cases with AHF, further details not provided.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Study to investigate immunological mechanisms and the role of complement in AHF. Blood collected from cases during the acute phase of the disease, and at 30 and 60 days. Incidentally reported clinical presentation. | Clinical characteristics | 9 cases classified as having a mild clinical form of the disease, 5 as moderate, and 5 as severe. 3 out of 5 of the severe cases died (timepoint not specified).<br><br>Mild clinical form: did not have fever after the first week of illness, protein only excreted in the urine transiently and less than 0.5 grams per litre, and neurological involvement only included tongue tremor.<br><br>Moderate clinical form: fever up to the second week of illness, protein in the urine ranging from 0.5 to 1.5 grams per litre if present in the first week of illness, definite signs of neurological involvement (tremor of the tongue, reduced or absent reflexes, mental confusion, drowsiness, ataxia (poor balance and co-ordination), but without convulsions or coma.<br><br>Severe clinical form: same characteristics as moderate cases with the same or more protein in the urine, and with more severe signs of neurological involvement: severe muscular hypotonia, absent reflexes, ataxia (poor balance and co-ordination), convulsions, and coma. 'Shock syndrome' (not defined) was observed terminally in the cases who died. |
| del Carmen Saavedra 2003 (20) | Argentina, 1984 to 1996 | Case series | 67 cases of AHF selected from 1984 to 1996 epidemics (selection criteria not reported).<br><br>Mean age: 39.5 years, range 10 to 73 years.<br><br>Sex: 70.15% male, 29.85% female.<br><br>Ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | IgG subclass responses in those who received a new attenuated Junin virus vaccine candidate, Candid 1, (24 people) and those with AHF (67 people) were compared using serial blood samples. Demographics and clinical characteristics of AHF cases incidentally reported. | Clinical characteristics | 21 out of 67 had mild AHF, 46 out of 67 had severe AHF (definitions not reported). |
| Elsner 1973 (11) | Argentina, 1964 to 1971 | Case series | 12 autopsied cases of fatal AHF.<br><br>10 out of 12 had virological confirmation of Junin virus, and diagnosis was clinical in the remaining 2.<br><br>Age: ranged from 24 to 63 years, mean 38 years.<br><br>Sex: 8 male, 4 female.<br><br>Ethnicity: all described as white. | Autopsy findings from the records of the Department of Pathology of the Center of Medical Education and Clinical Investigation were reviewed. | Clinical characteristics | All selected cases were in those who died from AHF.<br><br>Symptoms were described for the 12 cases collectively and included: high fever, malaise, photophobia (aversion to light), headache, retro-ocular (behind the eye) pain, loss of appetite, nausea and dizziness. Examination findings included: erythematous exanthema (red rash) to the face, neck and chest, focal haemorrhages (bleeding) in the skin and mucous membranes, congestion and small vesicles of the mouth mucous membranes, and generalised lymphadenopathy (enlarged lymph nodes).<br><br>Amongst the included cases, neurological symptoms appeared on around the 7th day of illness and included ataxia (problems with balance and co-ordination), drowsiness or poor sleep, loss of muscle tone and/or muscular tremor (mainly of the tongue), and intellectual deficit. Cases with more severe neurological involvement had tonic-clonic convulsions and coma. Severe and widespread haemorrhages (bleeding) developed in the days preceding death, including haematemesis (vomiting blood), melaena (digested blood in the stools), nosebleeds, coughing blood, and blood in the urine. Low blood pressure and death followed. |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| | | | Socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | | | Proportion of cases with various pathological findings on autopsy:<br><br>Lung<br>Pulmonary haemorrhage: 7 out of 12<br>Hyaline membrane: 4 out of 12<br>Bronchopneumonia or embolic abscess: 7 out of 12<br><br>Heart<br>Myocarditis: 4 out of 12<br>Pericardial haemorrhages: 4 out of 12<br>Embolic abscess: 1 out of 12<br><br>Kidney<br>Papillary necrosis or haemorrhage: 3 out of 12<br>Pelvic or capsular haemorrhage: 5 out of 12<br>Acute tubular necrosis: 6 out of 12<br><br>Adrenal<br>Haemorrhage: 3 out of 12<br>Pseudotubular formation: 8 out of 12<br><br>Central nervous system<br>Haemorrhage in Virchow Robin space: 5 out of 12<br>Lymphocytic perivascular infiltrate: 3 out of 12<br>Microglial proliferation: 2 out of 12<br><br>Alimentary tract<br>Haemorrhages: 5 out of 12<br>Acute ulcers: 8 out of 12<br><br>Liver<br>Acidophilic bodies: 7 out of 12<br>Intranuclear inclusions: 1 out of 12<br>Focal necrosis: 5 out of 12<br>Subcapsular haemorrhage: 4 out of 12<br>Centrolobular necrosis: 2 out of 12<br><br>Lymph nodes<br>Reticulum cell hyperplasia: 8 out of 12<br>Erythrophagocytosis: 6 out of 12<br><br>Spleen<br>Haemorrhage: 6 out of 12<br>Infarction: 2 out of 12 |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| | | | | | | Bone marrow<br>Erythroid hypoplasia: 6 out of 10<br><br>Presence of fibrin thrombi (liver lung spleen and brain): 3 out of 12 |
| Enria 1984 (3) | Argentina, 1978 to 1983 | Prospective cohort | 83 cases with AHF admitted during epidemics in 1982 and 1983 and treated with varying doses of immune plasma.<br><br>Diagnosis was confirmed with isolation of Junin virus from blood samples or serological conversion.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Aimed to determine the therapeutic dose of immune plasma (neutralising antibodies). Prospective study of 83 cases admitted to the hospital unit (not randomised). The authors also reported on a related retrospective study of 7 cases in their unit who died from AHF and 30 randomly selected survivors, however there were no relevant outcomes from this study. | Clinical characteristics | Mortality rate<br>n=22 cases treated with 1000 to 2000 therapeutic units of neutralising antibodies per kilogram: 9.09% (2 of 22)<br>n=27 cases treated with 2000 to 3000 therapeutic units of neutralising antibodies per kilogram: 3.70% (1 of 27)<br>n=34 cases treated with more than 3000 therapeutic units of neutralising antibodies per kilogram: 0% (0 of 34) |
| Enria 1987 (24) | Argentina, study period not reported | Case series | 7 hospitalised cases with a clinical diagnosis of AHF with symptoms beginning at least 8 days before, of whom 6 were confirmed through either virus isolation from blood, or antibody detection. For one case diagnosis could not be confirmed on laboratory tests. The 6 confirmed cases were treated with ribavirin.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported.<br><br>Inclusion criteria were: male or non-pregnant female, age 15 years or over, not participating in other clinical protocols, and clinical and laboratory findings suggestive of AHF. | Study of the tolerance and antiviral effect of ribavirin in cases with AHF. Ribavirin was given 8 days after the onset of symptoms. A variety of laboratory tests were performed at regular intervals up until day 60, including viral isolation from blood through intracerebral inoculation of white outbred mice. | Clinical characteristics | 4 of the cases are described as being very ill when admitted.<br><br>4 out of 7 cases died at day 14 to 17 of illness, including 1 case not confirmed on laboratory testing, and 3 of the confirmed cases.<br><br>1 case developed a febrile syndrome at day 31 during the recovery period, with abnormal cerebrospinal fluid on lumbar puncture, abnormal auditory evoked responses of the brain stem, but no abnormal neurological signs and symptoms. The authors report the patient did not meet criteria for a late neurological syndrome. They were readmitted and recovered. |
| | | | | | Transmission | Authors report that 3 days after beginning ribavirin treatment all virus isolations were negative, and that Junin virus could not be isolated from the blood or liver at time of death in the 3 fatal cases. |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| Gonzalez 1980 (25) | Argentina, study period not reported | Case series | 7 cases who died of AHF, diagnosis based on clinical symptoms and virus isolation from peripheral blood.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Postmortem examination of 7 cases who died due to AHF. Junin virus isolation performed by inoculation of suckling mice with measures of the numbers dead 14 days later (Reed and Muench method). Postmortems were carried out between 20 minutes and 2 hours after death (auricular blood obtained at the same time). | Transmission | Junin virus detected in peripheral (auricular) blood at post-mortem in 6 out of 7 cases, 6 to 14 days after disease onset.<br><br>Junin virus detected in the spleen at postmortem in 7 out of 7 cases, 6 to 14 days after disease onset.<br><br>Junin virus detected in the lymph nodes at postmortem in 7 out of 7 cases, 6 to 14 days after disease onset. |
| Harrison 1999 (5) | Argentina, 1986 to 1990 | Case control | 55 people with an admission diagnosis of suspected AHF, of which 31 were classified as cases (admission diagnosis of suspected AHF and four-fold rise in neutralising antibody titre) and 24 allocated as controls (admission diagnosis of suspected AHF but without serological evidence of AHF).<br><br>Mean age cases: 39 years<br>Mean age controls: 34 years<br><br>Sex in cases: 81% male<br>Sex in controls: 79% male<br><br>28 out of 31 cases (90%) received treatment with immune plasma.14 out of 24 (58%) controls received treatment with immune plasma.<br><br>Ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Chart review of a random selection of patients admitted to Instituto Nacional de Enfermedades Virales Humanas. Cases were admitted based on a clinical impression of AHF from one of 3 physicians with substantial experience in AHF diagnosis and management. All included patients were clinically suspected to have AHF, but were retrospectively divided into cases and controls based on whether there was positive serology. Comparisons were made of clinical and laboratory features between those assigned as cases and controls, to help inform case definitions for the disease. | Clinical characteristics | Clinical symptoms and signs<br><br>Tremor (hand or tongue): 5 of 31 cases, 1 of 24 controls (p=0.2)<br>Gingival (gum) bleeding: 4 of 31 cases, 0 of 24 controls (p=0.1)<br>Late neurological syndrome: 4 of 31 cases, 0 of 24 controls (p=0.1)<br>Conjunctival injection (eye redness): 28 of 31 cases, 20 of 24 controls (p=0.7)<br>Mouth exanthem (skin changes to mouth): 27 of 31 cases, 17 of 24 controls (p=0.2)<br>Cervical adenopathy (enlarged lymph nodes, neck): 27 of 31 cases, 17 of 24 controls (p=0.2)<br>Axillary petechiae (red spots, armpit): 18 of 31 cases, 5 of 24 controls (p=0.006)<br>Exanthem (rash): 12 of 31 cases, 5 of 24 controls (p=0.2)<br>Low back pain: 20 of 31 cases, 13 of 24 controls (p=0.4)<br>Myalgia (muscle pain): 17 of 31 cases, 14 of 24 controls (p=0.8)<br>Nausea: 14 of 31 cases, 11 of 24 controls (p=1.0)<br>Lack of upper respiratory tract symptoms: 31 of 31 cases, 20 of 24 controls (p=0.03)<br><br>Amongst clinical signs and symptoms, axillary petechiae and a lack of upper respiratory tract symptoms were significantly more common in cases than controls. (Laboratory data not extracted as outside of protocol). |
| | | | | | Geographic distribution | Cases were admitted to hospital in Pergamino, Argentina. |
| Heller 1995 (12) | Argentina, study period not reported | Case series | 14 hospitalised cases with AHF, of which 12 were treated with immune plasma (2 were not treated | Investigated alterations in the blood coagulation and fibrinolytic system of cases with AHF via blood samples collected for 6 consecutive days. | Clinical characteristics | 9 of the AHF cases were categorised as mild, 3 as moderate, and 2 as severe.<br><br>Cases were admitted between days 6 and 9 from symptom onset (classified as onset of fever). |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| | | | with immune plasma as they were admitted after day 9 of onset).<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Incidentally reported disease severity, symptoms, and numbers who died. | | Cases were classified as mild if they had fever during only the first week of illness, and tongue tremor was the only feature of neurological involvement.<br><br>Cases were classified as moderate if fever persisted into the second week of illness, with neurological abnormalities such as underactive or absent reflexes, and mental confusion.<br><br>Cases were classified as severe if they had marked neurological abnormalities such as absent reflexes, low muscle tone, ataxia (balance and co-ordination problems), seizures, and coma. A terminal shock syndrome was observed in fatal cases (not further described).<br><br>Haemorrhagic (bleeding) features amongst the cases were mild only: petechiae (red spots due to bleeding small blood vessels), ecchymosis (bruising), haematomas (collection of blood outside of blood vessels), and bleeding gums. The 2 cases categorised as severe died 24 to 48 hours after admission |
| Levis 1984 (21) | Argentina, 1982 | Case series | 30 hospitalised cases, 28 diagnosed serologically with AHF, through indirect immunofluorescence or neutralisation tests, and 27 treated with immune plasma.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Took serum samples (for endogenous interferon) before and after administration of immune plasma as treatment for AHF (30 cases and 20 controls). | Clinical characteristics | Cases admitted to hospital between 4 and 7 days after symptom onset. Some cases had fevers, chills and backache, however this was assessed in relation to high titres of interferon, and during treatment with immune plasma. All cases survived. |
| Maiztegui 1979 (1) | Argentina, 1974 to 1978 | Randomised controlled trial | 217 study participants, 188 confirmed cases by serological conversion in cases who survived and isolation of junin virus strains from blood or necropsy of those who died. A further 29 cases had a clinical diagnosis of AHF that was not confirmed virologically.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Cases were randomly allocated to receive either 500ml of intravenous immune plasma with antibodies against Junin virus, or normal plasma. Double blind. | Clinical characteristics | Of the 188 confirmed cases, 17 died.<br>Of the 29 cases with a clinical diagnosis that was not confirmed virologically, 3 died.<br>Mortality in each treatment group not extracted as beyond the scope of the review.<br>Of those who survived, 10 relapsed with a neurological syndrome. |
| Maiztegui 1975 (9) | Argentina, study period not reported | Case series | 5 confirmed cases of AHF where disease is endemic in Argentina. | Study of the ultrastructural and immunohistochemical properties of particles from tissues of 5 cases with | Clinical characteristics | Four cases died, one survived.<br><br>4 cases had convulsions (and all died), and one had tremor of hands and tongue (survived).<br>2 cases had hematemesis, 1 of which also had terminal haemoptysis and one with terminal |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| | | | Age: 34 to 63 years<br><br>Sex: 4 male, 1 female<br><br>Ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | AHF. Examined tissues included kidney, liver, spleen, and lymph nodes. | | uterine (womb) bleeding. 2 cases had bleeding gums and nose (1 survived, 1 died), and one had only bleeding gums (died). |
| Maiztegui 1998 (2) | Argentina, 1988 to 1990 | Randomised controlled trial | 23 cases meeting the clinical case definition for AHF, of 29 who had evidence of Junin virus infection. 22 of the cases had received placebo, and 1 had received Candid 1 Junin virus vaccination. Overall study size: 6500 participants, of whom 3,255 received vaccine and 3,245 received placebo.<br><br>Sex: male (females were excluded from study)<br><br>Age: 41 years (died), others unknown.<br><br>Ethnicity, socioeconomic status, occupation, and comorbidities not reported.<br><br>Inclusion criteria: healthy, male, aged 15 to 64 years, resided or worked in a rural agricultural area of the 41-county area, no history of AHF, normal baseline blood values, negative for HIV, and no known allergies to vaccine components.<br><br>Exclusion criteria included: underlying medical conditions, history of AHF, and residence outside of study localities. | Prospective, randomised, double blind, controlled trial investigating the efficacy of Candid 1, a new Junin virus vaccine candidate. Healthy volunteers recruited at start of trial, followed up after administration of placebo or vaccine for AHF. Participants were followed up for one to 2 AHF epidemic seasons (Presumed to equate to 1 to 2 years). | Clinical characteristics | Of the 29 with evidence of Junin virus infection, 1 died of AHF. (25 had received placebo, and 4 had received Junin virus vaccine). 19 were diagnosed with mild AHF, 3 moderate and 2 severe (other diagnoses included fever of unknown aetiology, viral hepatitis and mononucleosis). |
| | | | | | Geographic distribution | All participants were from a 41 county region of Southern Santa Fe Province where AHF is endemic. |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| Marta 2000 (19) | Argentina, study period not reported | Case series | 48 cases of AHF confirmed by anti-Junin virus antibodies in serum or Junin virus isolation from those who died.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Study of haematopoietic growth factors serum levels and haematological parameters of 48 AHF cases, with blood samples taken before treatment with immune plasma and where possible on remission at day 30. Incidentally reported disease severity. | Clinical characteristics | Of the 48 cases, 16 were mild, 17 moderate and 15 severe.<br><br>Those classified as mild has fever in the first week of illness and tongue tremor. Moderate cases had fever into the second week and had central nervous system involvement including hyporeflexia or areflexia, mental confusion, drowsiness or ataxia. Severe cases had neurological symptoms such as muscular hypotonia, areflexia, ataxia, seizures and coma.<br><br>All cases had minor haemorrhagic manifestations.<br><br>11 cases died (with terminal shock syndrome, all classed as severe AHF).<br><br>Onset of symptoms was classed as first day of disease, patients were admitted to hospital between 6 and 13 days after onset of symptoms.<br><br>Cases with mild and moderate AHF all recovered within 2 to 3 weeks of disease onset. |
| Marta 1999 (23) | Argentina, study period not reported | Case series | 19 cases with AHF confirmed by anti Junin virus antibodies in serum or Junin virus isolation from those who died.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Study of proinflammatory cytokines and elastase-a-1 antitrypsin in 19 AHF cases, with blood samples taken before treatment with immune plasma and where possible on remission day 30. Incidentally reported disease severity. | Clinical characteristics | Of 19 cases, six were classified as severe, four moderate and nine mild.<br><br>Those classified as mild had fever in the first week of illness and tongue tremor. Moderate cases has fever into the second week and had central nervous system involvement including hyporeflexia or areflexia, mental confusion, drowsiness or ataxia. Severe cases had neurological symptoms such as muscular hypotonia, areflexia, ataxia, seizures and coma.<br><br>Haemorrhagic (bleeding) features were mild, including petechiae (red spots caused by bleeding small blood vessels), ecchymosis (bruising), haematomas (collection of blood outside of blood vessel) and gingival (gum) bleeding.<br><br>3 cases died, all within 2 days of admission to hospital (with terminal shock syndrome).<br><br>Cases were admitted to hospital between 6 and 9 days after onset of fever.<br><br>Cases with mild and moderate AHF all recovered within 2-3 weeks. |
| | | | | | Geographic distribution | All cases were admitted to hospital in Pergamino, Argentina. |
| Molinas 1981 (16) | Argentina, 1977 | Case series | 32 cases of AHF diagnosed by Junin virus isolation or serological conversion.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Study of the profiles of coagulation factors during the course of AHF. Blood samples taken daily between day 6 and 22. Incidentally reported disease severity, symptoms and numbers who died. | Clinical characteristics | 17 mild cases, 9 moderate cases and 6 severe cases. Those with mild AHF had fever during the first week of illness, and tongue tremor. Those with moderate AHF had fever into the second week of disease and had other signs of central nervous system alteration (tremor of tongue, hyporeflexia or areflexia, mental confusion, coma). Symptoms of central nervous system alteration were greater in severe cases with signs and symptoms such as muscular hypotonia, areflexia, ataxia, convulsions and coma.<br><br>Petechiae (red spots caused by bleeding small blood vessels) in the mouth and the axillary (armpit) region were found in 31 of 32 cases. 18 cases had haematuria (blood in urine). In time, some of these cases also bled from the gastrointestinal tract (5 cases) or had heavy menstrual bleeding (5 cases), haemorrhagic gingivitis (bleeding, inflamed gums) (5 cases), or epistaxis (nosebleeds) (4 cases) or haemoptysis (coughing up blood) (1 case). |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| | | | | | | Four cases with severe disease died between day 9 and day 12 of the onset of symptoms. All had symptoms involving the central nervous system. Two also had serious haemorrhagic (bleeding) complications. On the other hand, 2 cases with moderate and another with mild AHF had haemorrhages similar to those of cases who died. |
| Molinas and Maiztegui 1981 (17) | Argentina, 1977 to 1979 | Case series | 35 cases diagnosed via Junin virus isolation and/or serological conversion. 21 were treated with immune plasma, 12 with normal plasma, and 2 did not receive plasma treatment.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, and Junin virus vaccination status not reported. | Study of the profiles of coagulation factors during the course of AHF. Blood samples taken daily between day 6 and 16, and then during convalescence at approximately day 30. Incidentally reported disease severity and symptoms. | Clinical characteristics | 14 mild cases, 7 moderate cases, 5 severe cases (criteria for classification not described).<br><br>Petechiae (red spots caused by bleeding small blood vessels) in the mouth and skin was the most frequent haemorrhagic (bleeding) feature during the acute phase of the disease.<br><br>18 out of 35 cases had haematuria (blood in urine).<br><br>5 out of 35 cases bled from the gastrointestinal tract. |
| Molinas 1987 (18) | Argentina, 1981 to 1985 | Case series | 45 cases with laboratory confirmed AHF.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, Junin virus vaccination status not reported. | Investigated the relationship between plasminogen abnormalities and AHF disease severity. Incidentally reported on disease severity, symptoms, and numbers who died. | Clinical characteristics | 17 mild, 14 moderate, 14 severe cases.<br><br>9 out of 45 died, all from the severe group. 3 had neurological and haemorrhagic (bleeding) features, 6 had severe neurological involvement.<br><br>Mild AHF classified as: tongue tremor as only neurological sign.<br><br>Moderate AHF classified as: tongue tremor, hyporeflexia, areflexia and mental confusion.<br><br>Severe AHF classified as: muscular hypotonia, areflexia, ataxia and coma.<br><br>Petechiae (red spots caused by bleeding small blood vessels) and haemorrhagic gingivitis (inflamed, bleeding gums) were the most common hemorrhagic manifestations.<br><br>2 cases had gastrointestinal bleeding. |
| Polop 2008 (8) | Argentina, 1987 to 1991 | Ecological | The study area was the central region of Argentina, including Buenos Aires, Cordoba, Santa Fe, and La Pampa provinces (which are situated in 'The Pampas': low grassland areas).<br><br>Demographics of people in these areas not reported. | Aimed to determine environmental differences (for example level of vegetation, weather, and so on) at sites with different incidences of AHF In the context of doing this they incidentally categorised regions into different levels of AHF incidence. | Geographic distribution | Regions were categorised as epidemic (disease emergence and relatively high incidence during 1987 to 1991), historical (where the disease was epidemic but incidence had reduced to less than 2 per 10,000 people between 1987 and 1991), and nonendemic (AHF cases not reported). Not reported if the incidence cut offs were per year or for the whole time period given.<br><br>20 epidemic sites, 26 historic sites, and 19 nonendemic sites were assessed.<br><br>Epidemic sites included: Guatimosin, A. Cabral, Ucacha, Villa Neuva, DelCampillo, Uranga, Alcorta, M. Paz, J.B. Molina, S. Pedro, S. Nicolas, Colon, S. Teresa, Carmen, Venado Tuerto, Maggiolo, S. Eduardo, Arteaga, Huanchilla, and La Carlota.<br><br>Historic sites included: 9 de Julio, Ferre, G Pinto, G Arenales, A. Dulce, Baradero, Bragado, Chillar, Chivilcoy, Chacabuco, C Sarmiento, Arrecife, Los Toldos, Azul, Lincoln, Olavarria, Vedia, Tandil, Salto, S. Regina, Zarate, Melo, Rojas, Pergamino, Roberts, and G. Villegas. |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| | | | | | | Nonendemic sites included: Gigena, C. Casare, Chucul, Maciel, Oliveros, S. Jorge, Piamonte, Los Cardos, M. Susana, El Trebol, Galvez, Coronda, C. Pellegrini, C. Rosquin, Saladillo, T. Lauquen, R. Perez, G. Alvear, and C. Tejedo. |
| Ruggiero 1981 (22) | Argentina, 1975 to 1976 | Case series | 21 hospitalised cases positive for AHF confirmed serologically (another 10 patients with fever had other diseases).<br><br>Region: rural endemic areas near Junin city.<br><br>Age, sex, ethnicity, socioeconomic status, occupation, comorbidities, Junin virus vaccination status not reported. | The study investigated an immuno-fluorescent technique used to diagnose AHF from urine samples. Some limited information on geographic distribution and clinical characteristics reported incidentally. | Geographic distribution | All cases were from rural endemic areas near Junin city. |
| | | | | | Clinical characteristics | All hospitalised.<br>Presented with febrile syndrome. |
| Veliziotis 2020 (27) | Belgium, 2020 | Case report | One case of laboratory confirmed AHF in a woman admitted to hospital in Brussels, Belgium. She had been in Argentina, then travelled to Amsterdam in the Netherlands for 4 days via a connecting flight in Madrid, Spain, then travelled by bus to Brussels.<br><br>137 potential contacts were identified (77 high risk, 60 low risk, classified according to degree of contact with body fluids). Contacts included laboratory personnel, care givers, and sexual and household contacts.<br><br>Age: 41 years.<br><br>Sex: female.<br><br>Ethnicity, socioeconomic status, occupation, comorbidities, Junin virus vaccination status not reported. | Description of case and contact tracing. | Clinical characteristics | Hospitalised, admitted to the intensive care unit. Received treatments including: ribavirin, favipavir, broad spectrum antibiotics, voriconazole for probable invasive pulmonary aspergillosis, and filgrastim for persistent neutropenia. Signs and symptoms included: influenza-like-illness for one week before admission. Vomiting up to 4 days before admission. Seizure while in emergency department. Severe haematoma of tongue and epistaxis leading to airway obstruction and need for intubation. Discharged day 50 of admission without any persistent health problems. |
| | | | | | Geographic distribution | The case had come from the city of Perez, Santa Fe province, Argentina (unclear if resident there or visiting). |
| | | | | | Transmission | None of 137 potential contacts developed AHF. |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| Weissenbacher 1980 (4) | Argentina, 1974 to 1978 | Retrospective cohort | 107 laboratory personnel working with attenuated and pathogenic Junin virus from 2 laboratories in Buenos Aires. 52 (37 from laboratory 1, 15 from laboratory 2) regarded as high risk, 56 (all from laboratory 1) classified as low risk.<br><br>Age, sex, ethnicity, socioeconomic status, comorbidities, Junin virus vaccination status not reported | 107 laboratory personnel across 2 laboratories monitored for development of AHF at 2 timepoints 3.5 years apart using serology. Exposed to Junin virus as an occupational hazard. | Clinical characteristics | 1974 serology results<br>High risk personnel laboratory 1: 5 out of 21 had positive serology<br>High risk personnel laboratory 2: 0 out of 9 had positive serology<br>Low risk personnel laboratory 1: 0 out of 37 had positive serology<br>Low risk personnel laboratory 2: 0 out of 2 had positive serology<br><br>1978 serology results<br>High risk personnel laboratory 1: 5 out of 37 had positive serology<br>High risk personnel laboratory 2: 1 out of 15 had positive serology<br>Low risk personnel laboratory 1: 0 out of 56 had positive serology<br>Low risk personnel laboratory 2: none included<br><br>Amongst the 5 cases positive for Junin virus serology from laboratory 1 in 1978, 3 had persistent positive serology from 1974, and 2 had newly positive serology. The 1 case positive for Junin virus serology from laboratory 2 was also a new case. 1 out of the 3 new cases had a history of clinical symptoms including fever, headache, retroocular pain and insomnia. Virus was not obtained from the blood during the acute illness. Full recovery after 1 week. 3 people had positive antibodies in both 1974 and 1978 with no clinical signs.<br><br>Overall: 3 out of 52 high risk laboratory personnel developed new neutralising antibodies to Junin virus, of which 1 had a mild clinical illness and recovered, and 2 did not report any illness. |
| Weissenbacher 1983 (7) | Argentina, 1976 to 1977 | Cross sectional | 695 samples taken from rural people living in Cordoba and around Buenos Aires (endemic areas).<br><br>Age: ranged from 10 to 79 years.<br><br>Sex: 418 males, 277 females.<br><br>Ethnicity, socioeconomic status, occupation, comorbidities, Junin virus vaccination status not reported. | Serological survey to determine the prevalence of those infected with Junin virus across 2 different endemic areas in Argentina. | Geographic distribution | Rural population. 2 areas: 5,000 square kilometre area in the province of Cordoba, population density of 3.4 inhabitants per square kilometre. 133 square kilometre area in the province of Buenos Aires, population density of 3.0 inhabitants per square kilometre.<br><br>Prevalence of Junin virus antibodies:<br>Overall: 83 out of 695 (11.94%)<br>Cordoba: 65 out of 540 (12.03%)<br>Buenos Aires: 18 out of 155 (11.60%)<br><br>Prevalence of clinical infection (positive for neutralising antibodies and gave a history of AHF in preceding 14 years):<br>Overall: 56 out of 695 (8.05%)<br>Cordoba: 41 out of 540 (7.59%)<br>Buenos Aires: 15 out of 155 (9.67%)<br><br>Prevalence of inapparent (asymptomatic) infection (positive for neutralising antibodies but no history of AHF):<br>Overall: 27 out of 695 (3.88%)<br>Cordoba: 24 out of 540 (4.44%)<br>Buenos Aires: 3 out of 155 (1.93%)<br>No significant difference found (p>0.5) between rates of total infections or clinical infections. P value not reported for inapparent infections. |
| | | | | | Clinical characteristics | Prevalence of human Junin virus infection measured by serology in 2 AHF endemic areas: sex and age distribution |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| | | | | | | Males<br>0-9 years old: 23 in total, 0% clinical infection, 0% inapparent infection<br>10-19 years old: 55 in total, 3.6% clinical infection, 1.8% inapparent infection<br>20-29 years old: 71 in total, 8.4% clinical infection, 4.2% inapparent infection<br>30-39 years old: 85 in total, 12.9% clinical infection, 7.05% inapparent infection<br>40-49 years old: 68 in total, 20.6% clinical infection, 5.8% inapparent infection<br>50-59 years old: 64 in total, 12.5% clinical infection, 4.7% inapparent infection<br>60-69 years old: 38 in total, 15.8% clinical infection, 5.3% inapparent infection<br>70-79 years old: 14 in total, 21.4% clinical infection, 7.1% inapparent infection<br>Overall: 418 males participating in study, 11.96% had clinical infection, 4.8% had inapparent infection<br><br>Females<br>0-9 years old: 14 in total, 0% clinical infection, 0% inapparent infection<br>10-19 years old: 51 in total, 0% clinical infection, 0% inapparent infection<br>20-29 years old: 58 in total, 0% clinical infection, 5.2% inapparent infection<br>30-39 years old: 52 in total, 1.9% clinical infection, 3.8% inapparent infection<br>40-49 years old: 43 in total, 6.9% clinical infection, 2.3% inapparent infection<br>50-59 years old: 37 in total, 2.7% clinical infection, 2.7% inapparent infection<br>60-69 years old: 19 in total, 5.3% clinical infection, 0% inapparent infection<br>70-79 years old: 3 in total, 0% clinical infection, 0% inapparent infection<br>Overall: 277 females in total, 2.2% clinical infection, 2.5% inapparent infection<br><br>Significant difference in the prevalence of clinical versus inapparent infections for males ( $p<0.001$)<br>No significant difference in prevalence of clinical versus inapparent infections for females ($p>0.05$)<br>The prevalence of clinical infections was significantly higher in men than women ($p<0.01$). However, no significant difference in prevalence of inapparent infections in men versus women ($p>0.05$).<br><br>The distribution of cases by age group was uniform across the 14 year period, based on reported year of clinical infection.<br><br>Two-thirds of clinical infections occurred in the first half of the 14 year period, based on reported year of clinical infection. |
| Weissenbacher 1978 (6) | Argentina, 1974 to 1975 | Cross sectional | 127 personnel based in 5 different laboratories across Buenos Aires, Cordoba, Pergamino.<br>Divided into 2 groups: group 1 were those who worked directly with Junin virus; group 2 had potential contact with the virus as they carried out their work near the areas where | Serological survey to determine the prevalence of asymptomatic AHF infection of laboratory personnel. Serum samples were studied by neutralisation, complement fixation, and fluorescent antibody tests using Junin virus antibodies. | Clinical characteristics | Group 1: 12 out of 62 (19.4%) positive for neutralising antibodies. None had been to AHF endemic areas.<br><br>Group 2: 0 out of 65 (0%) positive for neutralising antibodies.<br><br>Overall: 12 out of 127 (9.4%) positive for neutralising antibodies.<br>Of note, all the serum samples were negative by complement fixation methods. 6 out of 12 were positive by fluorescent antibody methods. |

| Study | Country, time period | Study type | Population | Study context and methods | Outcome | Results |
|---|---|---|---|---|---|---|
| | | | Junin virus was used but did not work directly with the virus.<br>Group 1: 62 participants<br>Group 2: 65 participants<br>Participants had no previous clinical history of AHF.<br><br>Age, sex, ethnicity, socioeconomic status, comorbidities, Junin virus vaccination status not reported | | | In a control group with a history of laboratory confirmed AHF, 17 out of 18 participants had positive neutralising antibodies, |

AHF: Argentine haemorrhagic fever, HIV: human immunodeficiency virus, ml: millilitre, RCT: randomised controlled trial.

# Annexe E. Critical appraisal

**Table E1. Critical appraisal of studies with analytical outcomes**

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Harrison and others (5) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No |
| Weissenbacher and others (7) | Yes | Unclear | No | Yes | No | Yes | Yes | Yes | Yes | Unclear |

Q = question. The QCC critical appraisal tool was used.

Q1: Was the research question clearly stated?
Q2: Was the selection of study subjects or patients free from bias?
Q3: Were study groups comparable?
Q4: Was method of handling withdrawals described?
Q5: Was blinding used to prevent introduction of bias?
Q6: Were intervention, therapeutic regimens or exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?
Q7: Were outcomes clearly defined and the measurements valid and reliable?
Q8: Was the statistical analysis appropriate for the study design and type of outcome indicators?
Q9: Are conclusions supported by the results with biases and limitations taken into consideration?
Q10: Is bias due to the study's funding or sponsorship unlikely?

# About the UK Health Security Agency

The UK Health Security Agency (UKHSA) prevents, prepares for and responds to infectious diseases, and environmental hazards, to keep all our communities safe, save lives and protect livelihoods. We provide scientific and operational leadership, working with local, national and international partners to protect the public's health and build the nation's health security capability.

UKHSA is an executive agency, sponsored by the Department of Health and Social Care.



Prepared by: Naomi Carter, Stefano Brini, Serena Carville, Sean Harrison, Jennifer Hill, Mikhailia McIntosh Maman, Georgia Towson

For queries relating to this document, please contact: enquiries@ukhsa.gov.uk

Published: June 2025
Publication reference: GOV-18554 (CPHR027)

Suggested citation: Carter N, Brini S, Carville S, Harrison S, Hill J, Maman McIntosh M, Towson G. The epidemiology and clinical characteristics of Argentine haemorrhagic fever: a rapid systematic review. UKHSA; 2025