UK Health Security Agency

The epidemiology of Chapare virus

A rapid review

Contents

Main messages

1. The purpose of this rapid review was to identify and summarise evidence relating to the epidemiology of Chapare haemorrhagic fever (search up to 25 July 2023).
2. Five case reports or case series (1 to 5) and one laboratory based experimental study (6) were identified that reported on 10 people with Chapare haemorrhagic fever across 2 outbreaks, the first between 2003 to 2004 (1) and the second between 2019 and 2020 (2 to 6).
3. All 10 reported cases lived in Bolivia, were aged between 7 to 65 years old, and 3 were women, 2 of whom were pregnant. There was no evidence of Chapare haemorrhagic fever cases originating from countries other than Bolivia.
4. At least 5 cases (all agricultural workers or farmers) were suspected to have been infected from exposure to infected rodents or rodent excrement, and at least 4 cases were suspected to have been infected from human-to-human transmission (3 cases, all healthcare workers, attended to infected cases in healthcare settings, one case was a child who appeared to have acquired the virus from their parent). Risk factors for transmission were therefore reported to include environmental and occupational exposure.
5. The rodent reservoir of the virus has not been confirmed, but a potential reservoir has been detected in samples of tissues from small-eared pygmy rice rats (*Oligoryzomys microtis*) (5).
6. All reported cases had persistent arthralgia (joint stiffness), myalgia (muscle aches), nausea and vomiting, and bleeding episodes (mostly bleeding gums), and at least 9 cases had persistent fever, dizziness, fatigue, chills, abdominal pain, and diarrhoea throughout their illness. Neurological symptoms were reported in 5 of the 9 cases in the second outbreak, and at least 2 cases required mechanical ventilation.
7. In one study, Chapare virus was isolated in the semen of a case 86 days following symptom onset, and Chapare virus ribonucleic acid (RNA) was detected 113 days after symptom onset in the semen of the same case. In the same study, Chapare RNA was detected 170 days after symptom onset in both blood and semen of a different case (5). The same study reported evidence to suggest that cases who had recovered from Chapare virus infection developed antibodies in their blood serum, with anti-Chapare virus Immunoglobin M (IgM) and Immunoglobin G (IgG) detectable up to the last blood draw in 3 survivors following resolution of symptoms (24, 170, and 190 days after symptom onset) (5).
8. The incubation period of Chapare virus ranged from 9 days to at least 19 days for the 5 cases with likely human to human transmission. Five of the 10 reported cases (50%) died, ranging from 14 days and 25 days after development of symptoms. Of the 5 cases that survived, the duration of admission at healthcare facilities until discharge ranged from 18 days to 161 days following symptom onset.
9. Only 2 studies reported on the treatment or management of infected cases, which included mechanical ventilation (3) and supportive care (5). Recommendations to prevent hospital transmission of Chapare virus infections included effective supply and

use of personal protective equipment, and training of healthcare workers on the mode of transmission and differential diagnosis of the virus (4).

10. Overall, there were relatively few studies reporting Chapare haemorrhagic fever, with only 10 reported cases, so the information in this review may not be generalisable to any future outbreaks.

Purpose

The purpose of this rapid review was to identify and summarise evidence relating to the epidemiology of Chapare haemorrhagic fever (caused by Chapare virus). All studies summarising outbreaks of haemorrhagic fever caused by Chapare virus in any geographic location were eligible for inclusion. Studies reporting unspecified haemorrhagic fevers occurring in Bolivia were also eligible for inclusion as long as Chapare virus could have been the cause.

This rapid review focused on epidemiological outcomes, including geographic distribution and demographics of cases, clinical presentation, diagnosis, transmission, and management or treatment of Chapare haemorrhagic fever.

Methods

There was one review question:

1. What is the epidemiology of Chapare haemorrhagic fever (caused by Chapare virus), focussing on the following outcomes:

    a. geographic distribution
    b. demographics
    c. transmission (including animal cases and reservoirs)
    d. diagnostic tests
    e. clinical presentation
    f. interventions (treatment and prophylaxis)

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.

A rapid review of the published literature was undertaken, using streamlined systematic methodologies to accelerate the review process (7). A search of Medline, Embase, Latin American and Caribbean Health Sciences Literature (LILACS), medRxiv, and Research Square (via Europe PMC) was undertaken for relevant literature published up to 25 July 2023.

Screening on title and abstract was undertaken in duplicate by 2 reviewers for 20% of potentially relevant studies and the remainder completed by one reviewer. Full text screening and data extraction were undertaken by one reviewer and checked by a second.

As stated in the protocol, risk of bias assessment was not conducted as all included studies were descriptive rather than analytical.

Evidence

In total, title and abstract screening was conducted for 7,683 studies, of which 57 (including one article identified from reference checking) were screened at full text. Of these, 6 studies were identified that provided evidence to answer the review question (see Table C.1). Studies excluded on full text screening, with exclusion reasons, are available in Annexe B.

Two outbreaks of Chapare haemorrhagic fever have been reported in published literature, with evidence available for a total of 10 cases.

Only one study reported on the first outbreak of Chapare haemorrhagic fever in a small cluster of cases in Cochabamba, near the Chapare River in Bolivia, between December 2003 and January 2004 (1). Blood specimens and clinical descriptions were available for only one case.

Four studies reported on the second outbreak, which affected 9 cases in various areas of Bolivia (including La Paz) between May 2019 and January 2020, although 3 of the studies only reported on the first 5 cases (2 to 4), with the fourth study reporting on both the initial 5 cases and the 4 additional cases (5). One further study used specimens from cases in this outbreak to identify and characterise the Chapare virus strain, and was included in this review as it provides information on the diagnosis of Chapare haemorrhagic fever (6).

Geographic distribution

Delgado and others reported the first outbreak of Chapare haemorrhagic fever involving a small cluster of cases from a rural area near the Chapare River, close to Cochabamba in Bolivia (1). The authors reported clinical features of one fatal case and stated that the total number of cases infected were not known to them. The case had no travel history or contact with any case with similar clinical features (1).

The second outbreak of the virus initially involved 5 hospitalised cases from rural and urban areas in the Caranavi province and La Paz department in Bolivia (2 to 5). The index case in this outbreak lived and worked at the rural areas of Guanay municipality, Larecaja province and Alto Beni (3). An additional 4 cases were found from Palos Blanco, Beni, and Caranavi municipalities in Bolivia, through improved surveillance and laboratory testing (5).

There was no evidence of Chapare haemorrhagic fever cases originating from countries other than Bolivia.

Demographics

The case involved in the first outbreak was a 22 year old man who worked as a tailor and farmer (1).

The second outbreak involved 3 women and 6 men. The reported ages of the initial 5 cases varied between studies. The age ranges were stated as 21 to 64 years (3), 25 to 65 years (5), 21 to 65 years (4), and 22 to 65 years (2). The 4 additional cases were aged between 7 and 47 years old. Two of these cases were pregnant women (5 and 16 weeks gestation, 27 and 29 years old respectively) (5). Five of the cases were agricultural workers or farmers (including the index case), 3 were healthcare workers, and one was a child of a case (2 to 5).

Transmission

Of the 10 reported cases, 5 (all agricultural workers or farmers) were suspected to have acquired infection via zoonotic transmission, potentially through exposure to infected rodents or rodent excrement.

The remaining 5 cases were likely infected from contact with other human cases, including 3 healthcare workers who attended to other cases, a child who appeared to have acquired the virus from their parent, and an agricultural worker who shared a household with a case, and visited them in hospital, becoming symptomatic shortly afterwards (1 to 5).

Risk factors for transmission were reported to include environmental exposure to infected rodents or their excrement, and occupational exposures such as farming and healthcare (3, 5).

Rodent reservoir

The rodent reservoir of Chapare virus has not been confirmed (1, 3). However, Loayza Mafayle and others reported that Chapare virus RNA was detected in samples of tissues obtained from 9 out of 31 rodents captured in Caranavi and Guanay in July 2019, reporting that the test positive rodent species were small-eared pygmy rice rats (*Oligoryzomys microtis*) (5).

Differential diagnosis and diagnostic tests

In the 5 studies reporting on differential diagnoses, different infections were considered, including yellow fever, dengue fever, Bolivian haemorrhagic fever caused by Machupo virus, hantavirus, zika virus, chikungunya virus, and leptospirosis (1 to 3, 5, 6).

In the first outbreak, Delgado and others reported successful isolation of the Chapare virus strain from blood samples of the first confirmed case during the acute febrile phase of the illness

(1). The authors reported that Chapare virus was most closely related genetically to the Sabiá virus (identified in Brazil), but with some differences in parts of the genetic code (1).

During the second outbreak, Morales-Betoulle and others designed primers and probes to develop specific real-time reverse transcription-polymerase chain reaction (rRT-PCR) assays (6). In the 5 included studies reporting on diagnostic tests, the rRT-PCR was used to detect the Chapare virus RNA (1 to 3, 5, 6). Diagnostic specimens included whole blood sera, saliva, urine samples, nasopharyngeal and oropharyngeal swabs, bronchoalveolar-lavage fluid, semen, and tracheal aspirates (1 to 3, 5, 6).

Viral persistence after recovery

Two of the included studies looked at viral persistence following recovery from Chapare virus infection (2, 5). Cossaboom and others reported detection of Chapare virus RNA in blood, saliva, and semen samples of 2 cases, though the authors did not specify the period between symptom onset or resolution and detection of the virus (2). Loayza Mafayle and others isolated Chapare virus in semen 86 days following symptom onset in one case, and detected Chapare virus RNA at 113 days after symptom onset in the semen of the same case and 170 days after symptom onset in the blood and semen of another case (5).

Seroconversion

Loayza Mafayle and others reported evidence to suggest that cases who had recovered from Chapare virus infection developed detectable antibodies, with anti-Chapare virus IgM and IgG detectable in 3 survivors following resolution of symptoms (5).

Clinical presentation

All reported cases had persistent arthralgia, myalgia, nausea and vomiting, and bleeding episodes (mostly bleeding gums), and at least 9 of the 10 cases had persistent fever, dizziness, fatigue, chills, abdominal pain, and diarrhoea throughout their illness (1, 3, 5). Neurological symptoms were reported in 5 of the 9 cases in the second outbreak, and at least 2 cases required mechanical ventilation (5). Five of the infected cases in the second outbreak had thrombocytopenia, leukopenia, elevated aminotransferase levels, and anaemia (5). Some cases required blood transfusions (5), and one study suggested that the time of illness onset to bleeding manifestation ranged from immediately after exposure to 13 days (4).

The incubation period of Chapare virus ranged from 9 days to at least 19 days for the 5 cases with likely human to human transmission (2, 5). Five of the 10 reported cases (50%) died, ranging from 14 days and 25 days after development of symptoms (1, 3, 5). Of the 5 cases that survived, the duration of admission at healthcare facilities until discharge ranged from 18 days to 161 days following symptom onset (4, 5). None of the included studies explored the association between death and case demographic characteristics.

Interventions

Three of the included studies reported on treatment or management of cases with Chapare haemorrhagic fever (3 to 5). Two studies reported providing mechanical ventilation (3) and supportive care (5) to infected cases, but no further details were given.

Toledo and others suggested interventions to prevent transmission of the virus in hospital settings, and these included providing adequate supply of personal protective equipment, and appropriate training of healthcare workers on the differential diagnosis and mode of transmission of Chapare virus, as well as training on appropriate use of personal protective equipment (4).

Inequalities

Given the limited number of cases of Chapare haemorrhagic fever, there was insufficient evidence to determine whether inequalities existed, for example differences between social, vulnerable, or ethnic groups. However, most cases were agricultural workers, farmers, or worked in healthcare, meaning people who have occupations that put them in contact with animal or human sources of the virus appear to be at greater risk, although the small number of cases makes it difficult to draw any generalisable conclusions.

Individuals of varied age (from 7 to 65 years) and sex were affected, including pregnant women, although there was no evidence to determine whether the virus could be transmitted from mother to foetus during pregnancy.

Limitations

This evidence summary was conducted at pace following streamlined methodology, and data extraction was conducted by one reviewer and checked by a second reviewer, meaning relevant studies or information may have been missed. Additionally, while studies reporting on both Chapare haemorrhagic fever, and Bolivian haemorrhagic fever not known to be caused by Machupo virus, were considered for inclusion in this rapid review, some relevant cases may have been missed as it is difficult to distinguish clinically between Bolivian haemorrhagic fevers caused by Chapare and Machupo viruses (8).

All included studies reporting on people with Chapare haemorrhagic fever were case reports or case series, and formal risk of bias appraisal was not performed as they were descriptive rather than analytical. However, although 4 studies reported on the same cases, the ages of individual cases were not consistently reported between studies, implying some level of conflicting information or reporting.

Overall, there were relatively few studies reporting Chapare haemorrhagic fever, with only 10 reported cases, so the information in this review may not be generalisable to future outbreaks.

Evidence gaps

The included studies reported on 10 cases across the 2 known outbreaks of Chapare haemorrhagic fever. Due to the low number of infected cases, there is limited evidence about disease transmission, any potential rodent reservoir, the incubation period, and progression of symptoms. There is also limited evidence on protective immunity following recovery or potential long-term complications in people infected with the virus.

There is no evidence of association between case outcomes (death or recovery) and case demographic characteristics. It is also unknown whether Chapare virus can be transmitted from mother to foetus in pregnant cases.

Conclusion

In total, 6 studies provided evidence on the epidemiology of Chapare virus, reporting on 2 outbreaks, the first in 2003 to 2004 with one case, and the second in 2019 to 2020 with 9 cases. The reported cases were from Cochabamba, near the Chapare River, the Caranavi province, La Paz, Palos Blanco, and Beni municipalities in Bolivia. There was no evidence of Chapare virus cases originating from countries other than Bolivia.

Of the 10 reported cases, 3 were women (2 of whom were pregnant). The age range of cases was from 7 to 65 years old. Six cases were agricultural workers or farmers, who may have been infected through exposure to infected rodents or, in one case, through exposure to a case they lived with and visited in hospital. Three cases were healthcare workers who attended to infected cases. The rodent reservoir of the virus has not been confirmed, but a potential reservoir has been detected in samples of tissues from small-eared pygmy rice rats (*Oligoryzomys microtis*).

All reported cases had persistent arthralgia (joint stiffness), myalgia (muscle aches), nausea and vomiting, and bleeding episodes (mostly bleeding gums), and at least 9 cases had persistent fever, dizziness, fatigue, chills, abdominal pain, and diarrhoea throughout their illness. Neurological symptoms were reported in 5 of the 9 cases in the second outbreak, and some cases were given mechanical ventilation for airway protection.

There was limited evidence of approaches to treat or manage infected cases, with only 2 studies reporting the provision of mechanical ventilation and supportive care.

Recommendations to prevent transmission of Chapare virus infections in hospital settings included effective supply and use of personal protective equipment, and training of healthcare workers on the mode of transmission and differential diagnosis of the virus.

The incubation period of Chapare virus ranged from 9 days to at least 19 days for the cases with known exposure dates. Five of the 10 reported cases (50%) died, ranging from 14 days and 25 days after development of symptoms. Of the 5 cases that survived, the duration of admission at healthcare facilities until discharge ranged from 18 days to 161 days following symptom onset.

Overall, however, there were relatively few studies reporting Chapare haemorrhagic fever, with only 10 reported cases, so the information in this review may not be generalisable to future outbreaks.

Acknowledgment

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

Disclaimer

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

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

In the event that this evidence review 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 evidence summary.

References

1. Delgado S and others. 'Chapare virus, a newly discovered arenavirus isolated from a fatal hemorrhagic fever case in Bolivia' PLoS Pathogens 2008: volume 4, issue 4, page e1000047
2. Cossaboom C and others. 'Re-emergence of chapare hemorrhagic fever in Bolivia, 2019' American Journal of Tropical Medicine and Hygiene 2020: volume 103, page 436
3. Escalera-Antezana JP and others. 'Clinical features of fatal cases of Chapare virus hemorrhagic fever originating from rural La Paz, Bolivia, 2019: a cluster analysis' Travel Medicine and Infectious Disease 2020: volume 36, page 101,589
4. Toledo J and others. 'Public health implications of a new world arenavirus outbreak that occurred in Bolivia, 2019'. Travel Medicine and Infectious Disease 2021: volume 43, page 102,124
5. Loayza Mafayle R and others. 'Chapare hemorrhagic fever and virus detection in rodents in Bolivia in 2019' New England Journal of Medicine 2022: volume 386, issue 24, pages 2,283 to 2,294
6. Morales-Betoulle M and others. 'Detection and characterization of a novel strain of Chapare virus during an outbreak of viral hemorrhagic fever in Bolivia, 2019' International Journal of Infectious Diseases 2020: volume 101, pages 263 to 264
7. Tricco AC and others. 'Rapid reviews to strengthen health policy and systems: a practical guide' 2017
8. Cajimat MN and others. 'Genetic diversity among Bolivian arenaviruses' Virus Research 2009: volume 140, issue 1, pages 24 to 31

Annexe A. Protocol

Review question

There is one review question:

1. What is the epidemiology of Chapare haemorrhagic fever (caused by Chapare virus), focussing on the following outcomes:

a. geographic distribution
b. demographics
c. transmission (including animal cases and reservoirs)
d. diagnostic tests
e. clinical presentation
f. interventions (treatment and prophylaxis)

A search for primary evidence to answer these review questions will be conducted up to 25 July 2023.

All studies summarising outbreaks of Chapare haemorrhagic fever caused by Chapare virus in any geographic location will be included. To be included, cases must be diagnosed with, or strongly suspected to have, Chapare haemorrhagic fever or Bolivian haemorrhagic (fever not known to be caused by Machupo virus). Unspecified haemorrhagic fevers occurring in Bolivia will also be included as long as Chapare virus could have been the cause.

Eligibility criteria

	Included	**Excluded**
Population	All	Animals (except in the context of transmission)
Settings	Bolivia (for unspecified haemorrhagic fevers), all (for Bolivian and Chapare haemorrhagic fevers)	Other countries (for unspecified haemorrhagic fevers)
Context	All	
Intervention or exposure	Chapare haemorrhagic fever, caused by Chapare virus (diagnosed or strongly suspected), or Bolivian haemorrhagic fever not known to be caused by Machupo virus	Machupo virus (another cause of Bolivian haemorrhagic fever), other infections

	Included	Excluded
Outcomes	Epidemiology of Chapare virus, including: • geographic distribution • demographics • transmission (including animal cases and reservoirs) • diagnostic tests • clinical presentation • interventions (treatment and prophylaxis)	Non-clinical or non-epidemiological outcomes, for example phylogenetic analyses
Language	English	Non-English language studies
Date of publication	Up to 25 July 2023	
Study design	• interventional studies • observational studies (cohorts, case control, and cross-sectional studies, as well as case reports and series)	• systematic or narrative reviews • guidelines • opinion pieces • modelling studies • laboratory studies • ecological studies
Publication type	Published and preprint	

Identification of studies

We will search OVID Medline, OVID Embase, Latin American and Caribbean Health Sciences Literature (LILACs), medRxiv, and Research Square (via Europe PMC) for studies published before 25 July 2023. The search strategy will be checked by another information specialist.

Screening

Screening on title and abstract 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.

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 will include country, study period, study design, participants, 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. This will be completed by one reviewer and checked by a second.

Synthesis

A narrative synthesis may be written to describe the results from this review.

Variations across populations and subgroups, for example cultural variations or differences between ethnic or social groups will be considered, where evidence is available.

Search strategy

Database: Ovid MEDLINE(R) ALL (1946 to 24 July 2023)

Search strategy

1. Arenaviridae/ or Arenavirus/ or Arenaviruses, New World/ or Arenaviruses, Old World/ (1219)
2. ((Bolivi* or america* or new world* or old world*) and h?emorrhagic fever*).tw,kf. (787)
3. Chapare.tw,kf. (36)
4. (arenavir* or mammarenavir*).tw,kf. (1648)
5. CHAPV.tw,kf. (2)
6. Hemorrhagic Fever, American/ (447)
7. Hemorrhagic Fevers, Viral/ and exp Americas/ (127)
8. CHHF.tw,kf. (19)
9. Arenaviridae Infections/ (669)
10. or/1-9 (3160)
11. h?emorrhagic fever*.ti,kf. (6385)
12. (lassa or dengue or ebola or crimea* or hantavirus* or yellow fever or marburg).ti. not (chapare or bolivi* or america*).tw,kf. (33396)
13. 11 not 12 (3165)
14. 10 or 13 (5804)

Database: Embase (1974 to 20 July 2023)

Search strategy

1. arenaviridae/ or mammarenavirus/ or new world arenavirus/ or old world arenavirus/ (375)
2. ((Bolivi* or america* or new world* or old world*) and h?emorrhagic fever*).tw,kf. (1291)
3. Chapare.tw,kf. (40)
4. (arenavir* or mammarenavir*).tw,kf. (1884)
5. CHAPV.tw,kf. (6)
6. exp American hemorrhagic fever/ (251)
7. virus hemorrhagic fever/ and exp Western Hemisphere/ (210)
8. CHHF.tw,kf. (26)
9. arenavirus infection/ (303)
10. or/1-9 (3424)
11. h?emorrhagic fever*.ti,kf. (7308)
12. (lassa or dengue or ebola or crimea* or hantavirus* or yellow fever or marburg).ti. not (chapare or CHAPV or CHHF or bolivi* or america* or new world* or old world*).tw,kf. (36973)
13. 11 not 12 (3204)
14. 10 or 13 (5966)

Latin American and Caribbean Health Sciences Literature (LILACs) database (search 25 July 2023)

Latin American and Caribbean Health Sciences Literature (LILACs) database

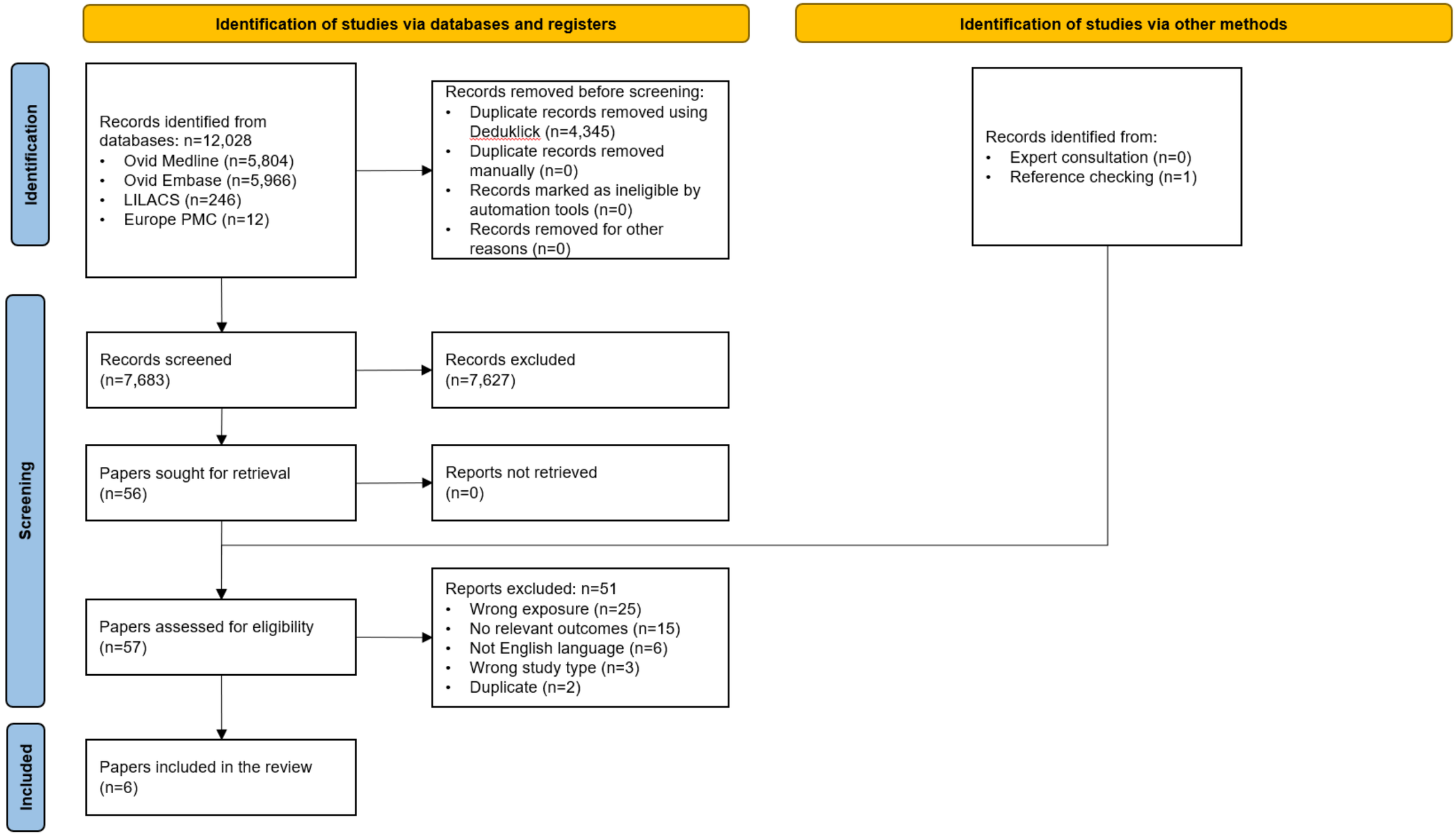
Search in title, abstract and subject fields: (chapare OR hemorrhagic fever OR haemorrhagic fever OR american haemorrhagic fever OR american hemorrhagic fever OR chapv OR chhf OR mammarenavir* OR arenavir*) - 246 results

Preprints via Europe PMC (search 25 July 2023)

Europe PMC

TITLE_ABS:(chapare OR hemorrhagic fever OR haemorrhagic fever OR american haemorrhagic fever OR american hemorrhagic fever OR chapv OR chhf OR mammarenavir* OR arenavir*) AND filter to Preprints – 12 results

Figure A.1. PRISMA diagram



Text version of Figure A.1. PRISMA diagram

A PRISMA diagram showing the flow of studies through this review, ultimately including 6 studies.

From identification of studies via databases and registers, n=12,028 records identified from databases:

- Ovid Medline (n=5,804)
- Ovid Embase (n=5,966)
- LILACS (Latin American and Caribbean Health Sciences Literature) (n=246)
- Europe PMC (n=12)

From these, records removed before screening:

- duplicate records removed using Deduklick (n=4,345)
- duplicate records removed manually (n=0)
- records marked as ineligible by automation tools (n=0)
- records removed for other reasons (n=0)

n=7,683 records screened, of which n=7,627 were excluded, leaving n=56 papers sought for retrieval, all of which were retrieved.

One study was identified from identification of studies via other methods:

- n=0 studies were identified from expert consultation
- n=1 study identified from reference checking

Of the n=57 papers assessed for eligibility, n=51 reports were excluded:

- Wrong exposure (n=25)
- No relevant outcomes (n=15)
- Not English language (n=6)
- Wrong study type (n=3)
- Duplicate (n=2)

n=6 papers included in the review.

Annexe B. Excluded full texts

Wrong exposure (n=25)

Aguilar PV and others. 'Re-emergence of Bolivian Hemorrhagic Fever, 2007 to 2008' Emerging Infectious Diseases 2009: volume 15, issue 9, pages 1,526 to 1,528

Andrei G and others. 'Molecular approaches for the treatment of hemorrhagic fever virus infections' Antiviral Research 1993: volume 22, issue 1, pages 45 to 75

Anonymous. 'International Notes Bolivian Hemorrhagic fever: El Beni Department, Bolivia, 1994' Morbidity and Mortality Weekly Report 1994: volume 43, issue 50, pages 943 to 946

Anonymous. 'Re-emergence of Bolivian hemorrhagic fever' Epidemiological Bulletin 1994: volume 15, issue 4, pages 4 to 5

Anonymous. 'Bolivian hemorrhagic fever reappears' Bulletin of the Pan American Health Organization 1995: volume 29, issue 2, pages 185 to 186

Anonymous. 'Re-emergence of Bolivian haemorrhagic fever' Weekly Epidemiological Record 1995: volume 70, issue 3, pages 16 to 17

Anonymous. 'Notice to readers update: management of patients with suspected viral hemorrhagic fever' JAMA 1995: volume 274, issue 5, pages 374 to 375

Bell TM and others. 'Pathogenesis of Bolivian hemorrhagic fever in guinea pigs' Veterinary Pathology 2016: volume 53, issue 1, pages 190 to 199

Bell TM and others. 'Pathology of experimental Machupo virus infection, Chicava strain, in cynomolgus macaques (*Macaca fascicularis*) by intramuscular and aerosol exposure' Veterinary Pathology 2015: volume 52, issue 1, pages 26 to 37

Child PL and others. 'Acidophilic bodies: their chemical and physical nature in patients with Bolivian haemorrhagic fever' Archives of Pathology and Laboratory Medicine 1968: volume 85, issue 1, pages 45 to 50

Child PL and others. 'Bolivian hemorrhagic fever: a pathologic description' Archives of Pathology and Laboratory Medicine 1967: volume 83, issue 5, pages 434 to 445

Johnson KM and others. 'On the mode of transmission of Bolivian hemorrhagic fever' Japanese Journal of Medical Science and Biology 1967: volume 20 supplement pages 153 to 159

Johnson KM and others. ‘Virus isolations from human cases of hemorrhagic fever in Bolivia’ Proceedings of the Society for Experimental Biology and Medicine 1965: volume 118, pages 113 to 118

Mackenzie RB and others. ‘Epidemic hemorrhagic fever in Bolivia. I. A preliminary report of the epidemiologic and clinical findings in a new epidemic area in South America' American Journal of Tropical Medicine and Hygiene 1964: volume 13, pages 620 to 625

Patterson M and others. ‘Epidemiology and pathogenesis of Bolivian hemorrhagic fever’ Current Opinion in Virology 2014: volume 5, pages 82 to 90

Peters CJ. ‘Emerging infections: lessons from the viral hemorrhagic fevers’ Transactions of the American Clinical and Climatological Association 2006: volume 117, pages 189 to 196; discussion pages 96 to 97

Peters CJ and others. ‘Hemorrhagic fever in Cochabamba, Bolivia, 1971’ American Journal of Epidemiology 1974: volume 99, issue 6, pages 425 to 433

Pfau CJ. 'Arenaviruses'. University of Texas Medical Branch at Galveston. Fourth Chapter 1996: volume 571,996, page 571,996

Salazar-Bravo J and others. ‘Natural nidality in Bolivian hemorrhagic fever and the systematics of the reservoir species' Infection, Genetics and Evolution 2002: volume 1, issue 3, pages 191 to 199

Stinebaugh BJ and others. ‘Bolivian hemorrhagic fever: a report of 4 cases' American Journal of Medicine 1966: volume 40, issue 2, pages 217 to 230

Terrell TG and others. ‘Comparative histopathology of 2 strains of Bolivian hemorrhagic fever virus infections in suckling hamsters'. American Journal of Tropical Medicine and Hygiene 1973: volume 22, issue 6, pages 814 to 818

Vainrub B and others. ‘Latin American hemorrhagic fever’ Infectious Disease Clinics of North America 1994: volume 8, issue 1, pages 47 to 59

Villagra M and others. ‘Bolivian hemorrhagic fever: EI Beni Department, Bolivia, 1994' Jama 1995: volume 273(3), pages 194 to 196

Webb PA and others. ‘The measurement of specific antibodies in Bolivian hemorrhagic fever by neutralization of virus plaques’ Proceedings of the Society for Experimental Biology and Medicine 1969: volume 130, issue 3, pages 1,013 to 1,019

Wiebenga NH and others. ‘Epidemic hemorrhagic fever in Bolivia. II. Demonstration of complement-fixing antibody in patients' sera with Junín virus antigen’ American Journal of Tropical Medicine and Hygiene 1964: volume 13, pages 626 to 628

No relevant outcomes (n=15)

Anonymous. 'Bolivian hemorrhagic fever' JAMA 1967: volume 200, issue 8, pages 716 to 717

Anonymous. 'Viral haemorrhagic fevers' Lancet 1971: volume 2, issue 7,729, pages 858 to 859

Anonymous. ‘Possession, use, and transfer of select agents and toxins; biennial review: final rule’. Federal Register 2012: volume 77, issue 194, pages 61,083 to 61,115

Cajimat MN and others. ‘Genetic diversity among Bolivian arenaviruses’ Virus Research 2009: volume 140, issue 1 to 2, pages 24 to 31

Cardona Maya WD and others. ‘Semen and viruses: significance during the transmission of infections’ Journal of Assisted Reproduction and Genetics 2022: volume 39(10), pages 2,431 to 2,432

Ferrero S and others. ‘Antibody-based inhibition of pathogenic new world hemorrhagic fever mammarenaviruses by steric occlusion of the human transferrin receptor 1 apical domain’ Journal of Virology 2021: volume 95, issue 17, pags e0186820

Fukushi S and others. ‘Serological assays based on recombinant viral proteins for the diagnosis of arenavirus hemorrhagic fevers’ Viruses 2012: volume 4, issue 10, pages 2,097 to 2,114

Malhotra H and others. ‘Codon usage signatures in Sabia and Chapare for host adaptation’ Bioinformation 2021: volume 17, issue 10, pages 891 to 898

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Annexe C. Data extraction table

Table C.1: Overview of epidemiology of Chapare virus

Acronyms used: ARDS = acute respiratory distress syndrome, RT-PCR = reverse-transcriptase polymerase chain reaction; RNA = ribonucleic acid

Study	Methods	Outcome
Cossaboom and others (2) (conference abstract)	**Study type**: Case series **Setting**: The index case reported to a hospital in Caranavi Municipality, Bolivia **Time period**: May 2019 to July 2019 **Population**: 5 cases • case 1 (index case): 65 year old male agricultural worker (died) • case 2: 25 year old medical intern (attended to case 1) (died) • case 3: 22 year old male agricultural worker (spent the night in the hospital with index case) (survived) • case 4: 48 year old ambulance worker (survived) • case 5: 42 year old gastroenterologist (died)	**Geographical distribution:** as described in Escalera-Antezana (3) **Transmission:** • index case: not reported • cases 2 to 5: human-to-human **Clinical presentation:** as described in Escalera-Antezana (3) **Differential diagnosis**: index case suspected of having severe dengue fever **Diagnostic specimen**: blood, saliva, tracheal aspirates, urine, and semen **Diagnostic test**: a novel real-time RT-PCR assay was developed that detected Chapare virus RNA in specimens in cases 2 to 5. Index case was only probable Chapare virus as no specimens were available to test **Reservoir**: unknown, following a limited ecological study **Intervention or management**: not stated **Incubation and fatality periods**: • case 1: unknown when exposed, symptom onset 23 April (incubation period unknown), died 12 May (died 19 days after symptom onset) • case 2: exposed 11 May, symptom onset 20 May (incubation period 9 days), died 4 June (died 24 days after exposure, 15 days after symptom onset) • case 3: exposed 11 May, symptom onset 29 May (incubation period 18 days), discharged 30 June (survived) • case 4: exposed 2 June, symptom onset 18 June (incubation period 16 days), recovered (date not stated, survived) • case 5: exposed 4 June, symptom onset 18 June (incubation period 14 days), died 10 July (died 36 days after exposure, 22 days after symptom onset) **Viral persistence after recovery**: Chapare virus RNA was detected in blood, saliva, urine, and semen of the 2 survivors following recovery.
Delgado and others (1)	**Study type**: Case report **Setting**: Cochabamba, near the Chapare River, Bolivia	**Geographic distribution:** a small cluster of haemorrhagic fever cases in a rural area near the Chapare river close to Cochabamba **Transmission:** no members of case household or other close contacts were reportedly affected, but details on the number of affected cases was unknown

Study	Methods	Outcome
	Time period: December 2003 to January 2004 **Population**: one case • 22 year old male tailor and farmer with no travel history and no known contact with any case with compatible illness in the 4 weeks prior to disease onset (3 January 2004)	**Clinical presentation:** acute febrile illness, including fever, headache, arthralgia (joint stiffness), myalgia (muscle aches and pains), and vomiting, rapidly progressing to bleeding, shock, and death **Differential diagnosis:** yellow fever, dengue haemorrhagic fever, Machupo virus and other related arenaviruses **Diagnostic specimen**: serum collected on days 4, 7, 9, and 14 after disease onset **Diagnostic test**: RT-PCR and sequence analysis followed by primer walking. Both the day 7 and 9 sera yielded a non-cytopathic virus by growth in Vero E6 cells, identified by immunofluorescent antibody staining with rabbit polyvalent hyperimmune serum raised against South American arenaviruses previously known to cause haemorrhagic fever (that is, Guanarito, Machupo, and Sabiá). Full length virus genome sequences were determined for the virus isolated from day 9 post-haemorrhage onset. The virus was found to be most closely linked to the Sabiá virus (identified in Brazil), but with 26% and 30% nucleotide differences in the complete S and L segments; 26%, 28%, 15% and 22% amino acid differences for the L, Z, N, and GP protein, respectively. **Reservoir**: unknown, following a limited ecological study **Intervention or management**: not stated **Incubation and fatality periods**: unknown when exposed, symptom onset 3 January, died 17 January (died 14 days after symptom onset) **Viral persistence after recovery**: not applicable
Escalera-Antezana and others (3)	**Study type**: Case series **Setting**: Caranavi, Caranavi province, La Paz department, and La Paz capital city, Bolivia **Time period**: May 2019 to June 2019 **Population**: 5 cases (4 men, one woman) • index case: 64 year old male rice and coffee farmer (died) • case 2: 25 year old female medical student (died) • case 3: 45 year old male physician (survived)	**Geographical distribution:** 5 cases hospitalised at rural urban areas in the municipality of Caranavi province in La Paz department, and La Paz capital city, Bolivia **Transmission:** • index case: possible zoonotic exposure (rodent faeces in house) • case 2: human to human transmission (attended to index case) • case 3: human to human transmission (accompanied case 2 in ambulance) • case 4: human to human transmission (attended to case 2) • case 5: human to human transmission (son in law of index case) **Risk factors:** exposure to rodents; occupational exposures such as farming, healthcare **Clinical presentation:** • index case (no RT-PCR): fever, myalgia, retro-orbital pain, abdominal pain, nausea, vomiting, acute respiratory distress syndrome (ARDS), fatigue, dizziness, chills, diarrhoea, sever upper digestive haemorrhage • case 2 (no RT-PCR): fever, chills, dizziness, fatigue, retro-orbital pain, abdominal pain, nausea, vomiting, diarrhoea, thrombocytopenia, and severe upper digestive haemorrhage

Study	Methods	Outcome
	• case 4: 42 year old male gastroenterologist (died) • case 5: 21 year old male, son in law of index case (survived)	• case 3 (RT-PCR positive)*:* fever, chills, dizziness, fatigue, retro-orbital pain, ARDS requiring mechanical ventilation, abdominal pain, vomiting, nausea, diarrhoea, thrombocytopenia, upper digestive haemorrhage, renal and hepatic failure, ataxia, and encephalitis • case 4 (RT-PCR positive): fever, chills, dizziness, fatigue, retro-orbital pain, abdominal pain, ARDS requiring mechanical ventilation, nausea, vomiting, diarrhoea, thrombocytopenia, upper digestive haemorrhage, renal and hepatic failure, ataxia, and encephalitis • case 5 (no RT-PCR): fever, myalgia, arthralgia, and upper digestive haemorrhage **Summary**: • fever: 5 cases • upper digestive haemorrhage: 5 cases • dizziness: 4 cases • fatigue: 4 cases • chills: 4 cases • abdominal pain: 4 cases • nausea: 4 cases • vomiting: 4 cases • diarrhoea: 4 cases • thrombocytopenia: 3 cases • required mechanical ventilation: 3 cases • ARDS: 2 cases • renal failure: 2 cases • hepatic failure: 2 cases • encephalitis: 2 cases • ataxia: 2 cases **Differential diagnosis:** case 2 was initially suspected to have dengue fever **Diagnostic specimen**: not stated **Diagnostic test**: RT-PCR for Chapare mammarenavirus **Reservoir**: not confirmed, although there is a suspicion that species of Oligoryzomys would be related as reservoir of Chapare virus **Intervention and management**: mechanical ventilation, no further information **Incubation and fatality periods**: • index case: died one month after hospitalisation • case 2: incubation period 7 days, died 15 days after symptom onset

Study	Methods	Outcome
		• case 3: incubation period 14 days, survived • case 4: incubation period 12 days, died 25 days after developing symptoms • case 5: survived, but with a tracheostomy and sequelae of the encephalitis (still hospitalised at time of study writing) **Viral persistence after recovery**: not applicable
Loayza Mafayle and others (5)	**Study type**: Case series **Setting**: The municipality of Caranavi and La Paz, Bolivia (initial cases), Palos Blanco municipality, Alto Beni municipality, and Caranavi, Bolivia (additional cases) **Time period**: April 2019 to June 2019 (initial cases), July 2019 and January 2020 (additional cases) **Outbreak**: 2019 to 2020 **Population**: 9 cases (5 initial cases, 4 additional cases) Initial cases: 5 cases (4 male, 1 female): • index case: 65 year old male old Agricultural worker • case 2: 25 year old female medical intern • case 3: 25 year old male agricultural worker • case 4: 48 year old male physician • case 5: 42 year old male physician Additional cases: 4 cases (2 male, 2 female): • case 6: 29 year old female agricultural worker, pregnant at 16 weeks gestation	**Geographical distribution:** initial cases: as described in Escalera-Antezana (3) **Additional cases**: 4 cases were detected in Palos Blanco municipality, Alto Beni municipality, and Caranavi **Transmission:** Initial cases*:* as described in Escalera-Antezana (3), with the additional information that case 3 was an agricultural worker and shared a home with the index case and was in contact with him during his hospitalisation **Additional cases***:* • case 6: unknown environmental exposure in Palos Blancos • case 7: unknown environmental exposure in Alto Beni • case 8: unknown environmental exposure in Caranavi • case 9: unknown environmental exposure or contact with case 8 in Caranavi **Risk factors:** environmental exposure, occupational exposure (for example, farming), exposure to a case **Clinical presentation:** Initial cases, in addition to symptoms described in Escalera-Antezana (3): • index case: gingival haemorrhage • case 2: gingival and vaginal haemorrhage, generalised seizure, haemorrhagic shock • case 3: generalised seizure, confusion, agitation, hemiparesis on left side, haemorrhagic signs (gingival, gastro-intestinal, intracerebral, and injection site bleeding; epistaxis; haematuria; petechiae and ecchymoses), haemorrhagic shock, multi-organ failure, hypoxemic respiratory failure, prolonged neurologic deficits for several months after discharge • case 4: paraparesis, hypoxemic respiratory failure, gingival haemorrhage, confusion, agitation, prolonged muscular and neurologic deficits for several months after discharge • case 5: generalised seizure, confusion, agitation, hyporeflexia of legs, haemorrhagic signs (gingival, gastro-intestinal, and injection site bleeding, petechiae and ecchymoses), multi-organ failure, haemorrhagic shock **Additional cases**: • case 6: fever, headache, myalgia, retro-orbital pain, abdominal pain, vomiting, lethargy, gingival haemorrhage, Icterus, cervical lymphadenopathy, respiratory distress • case 7: headache, retro-orbital pain, arthralgia, myalgia, neurologic deficits, gingival haemorrhage, neurologic deterioration • case 8: headache, epistaxis, malaise, gingival haemorrhage, uncomplicated childbirth • case 9: fever, headache, vomiting, lethargy, gingival haemorrhage

Study	Methods	Outcome
	• case 7: 47 year old male agricultural worker • case 8: 27 year old female agricultural worker, pregnant at 5 weeks gestation • case 9: 7 year old male, son of case 8	**Laboratory findings**: anaemia, leukopenia, thrombocytopenia, elevated aminotransferase levels, coagulopathy, acute kidney injury **Differential diagnosis:** the specimens were first tested for hantavirus, Machupo virus, dengue virus, yellow fever virus, chikungunya virus, Zika viruses, and Leptospira, which were all negative. Possible hospital acquired infection was suspected in at least 3 of the initial cases (the medical intern, and the 2 physicians) **Diagnostic specimen**: whole blood serum, urine samples, nasopharyngeal and oropharyngeal swabs, bronchoalveolar-lavage fluid, and conjunctiva and semen specimens **Diagnostic test**: real-time quantitative RT-PCR assays targeting the L and S segments of Chapare virus were designed and used to test specimens obtained from humans and rodents. Virus isolation was attempted with the use of Vero E6 cells, and serologic testing was performed with the use of Junín, Machupo and Chapare virus antigens **Reservoir**: Chapare virus RNA was detected in samples of tissues obtained from 9 out of 31 rodents captured in Caranavi and Guanay between 7 and 9 July 2019. Chapare virus-positive rodent species were identified as small-eared pygmy rice rats (*Oligoryzomys microtis*), with the use of cytochrome b sequences for *Oligoryzomys microtis*. **Intervention and management**: supportive care, no further details reported **Incubation and fatality periods:** • index case: exposure date unknown, symptom onset 24 April 2019, died 12 May 2019 (died 18 days after symptom onset) • case 2: exposed 11 May 2019, symptom onset 20 May 2019, died 4 June 2019 (incubation period 9 days, died 15 days after symptom onset) • case 3: exposed latest 11 May 2019 (had exposure before then as lived with index case), symptom onset 30 May, discharged 30 June 2019 (incubation period at least 19 days, discharged 31 days after symptom onset) • case 4: exposed 2 June 2019, symptom onset 18 June 2019, discharged 26 November 2019 (incubation period 16 days, discharged 161 days after symptom onset) • case 5: exposed 4 June 2019, symptom onset 20 June 2019, died 10 July 2019 (incubation period 14 days, died 22 days after symptom onset) • case 6: exposure date unknown (no link to initial cases), symptom onset 9 July 2019, died 18 July 2019 (unknown incubation period, died 9 days after symptom onset) • case 7: exposure date unknown, symptom onset 3 December 2019, discharged 5 January 2020 (unknown incubation period, discharged 33 days after symptom onset) • case 8: exposure date unknown, symptom onset 5 December 2019, discharged 29 December 2019 (unknown incubation period, discharged 24 days after symptom onset) • case 9: exposure date unknown, symptom onset 23 December 2019, discharged 10 January 2020 (unknown incubation period, discharged 18 days after symptom onset)

Study	Methods	Outcome
		Virus persistence after recovery: Chapare virus RNA was detectable 113 days (in case 3) and 170 days (in case 4) after symptom onset. Chapare virus was isolated from a semen sample obtained from case 3 at 86 days after symptom onset **Seroconversion**: anti-Chapare virus IgM and IgG seroconversion was detected in Case 3, 4, and Case 7, all of whom recovered
Morales-Betoulle and others (6) (conference abstract)	Experimental (laboratory based)	**Differential diagnosis:** the specimens were first tested for Machupo virus, dengue virus, and yellow fever, which were all negative **Diagnostic specimen**: blood, serum, tracheal aspirates, urine, or semen **Diagnostic approach**: because a viral haemorrhagic fever was suspected, the specimens were first sent to the Viral Special Pathogens Branch at the Centres for Disease Control and Prevention, USA, for testing and identification in the Biosafety Level-4 (BSL4) lab. The molecular assays were then deployed for continued testing in Bolivia. A combination of next generation sequencing and virus isolation were used to characterise the virus as a strain of Chapare virus. Primers and probes were designed to develop specific real-time RT-PCR assays for the S and L segments of the virus.
Toledo and others (4)	**Study type**: Case series **Setting**: Yungas region of Bolivia **Time period**: April 2019 to July 2019 **Population**: 5 cases (4 male, 1 female) • index case: 65 year old farmer • case 2: 25 year old medical doctor • case 3: 21 year old farmer • case 4: 48 year old medical doctor • case 5: 42 year old medical doctor	**Type of transmission:** • index case: zoonotic • case 2: human to human transmission • case 3: zoonotic • case 4: human to human transmission • case 5: human to human transmission **Time of illness onset to bleeding manifestation** (including gastrointestinal bleeding, hematemesis, melena, gingival haemorrhage, epistaxis, or central nervous system bleeding)**:** • index case: 13 days • case 2: 10 days • case 3: 7 days • case 4: 0 days • case 5: 12 days **Time from illness onset to hospital admission:** • index case: 8 days • case 2: 7 days • case 3: 7 days • case 4: 2 days • case 5: 2 days **Duration of admission at healthcare facility until discharge or death:** • index case: 13 days (died)

Study	Methods	Outcome
		• case 2: 15 days (died) • case 3: 30 days (survived) • case 4: 153 days (survived) • case 5: 22 days (died) **Clinical presentation:** as described in Escalera-Antezana (3) **Suggested interventions to prevent transmission of Chapare virus infection in hospital settings:** • having adequate supply of personal protective equipment • healthcare provider training on the differential diagnosis of dengue fever, the routes of arenavirus transmission, and training on appropriate use of personal protective equipment

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

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Published: January 2024
Publishing reference: GOV-16010