World Health Organization

Study Protocol

Longitudinal Observational Study of the Natural History of Andes Virus Infection Following Exposure in a Shipboard Outbreak

Short Title: Natural History of Andes Virus Infection in a Shipboard Outbreak (**NAVIS**)

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Why NAVIS?

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Transmission Uncertainties

Person-to-person transmission timing and infectiousness remain unsufficiently characterized, challenging outbreak response decisions.

Early Detection Challenges

RT-qPCR detects viral RNA before symptoms, but the presymptomatic phase varies widely among individuals.

Evidence-Informed Policies

NAVIS will generate data to support risk-based public health measures that balance effectiveness with social and economic impacts.

Proactive Outbreak Response

The study addresses the need for early actionable knowledge before interventions or vaccines are widely available.

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NAVIS Protocol Overview

- This is a **longitudinal observational cohort study** enrolling individuals with a defined exposure to Andes Virus (ANDV) after a shipboard outbreak who are confined or quarantined. Ideally **prospective**, but **retrospective** data inclusion will be allowed.
- Subjects are followed from **enrolment (E0)** until they become **PCR-positive (P0)** and then through acute illness defined by **symptom onset (S0)**, and **convalescence**. Epidemiological information from their **exposure (X0)** is also collected.
- The overarching goal is to **delineate the natural history and the virologic and immunologic mechanisms and consequences of infection** with sampling intensity matched to biological inflection points.
- Clinical care is not directed by the protocol. **All medical decisions remain under treating clinicians**.
- This protocol remains **observational and purposely low-intensity** because it does not direct clinical care, and uses a trigger-based, phase-adaptive tier structure that limits biospecimen collection to fixed, low-frequency schedules.
- Participation **does not restrict or prevent enrollment** in **other Hantavirus-related emergency responses or interventional clinical trials.**

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Inclusion criteria

1. **No age restriction.**
2. **Persons diagnosed with Andes virus in association with the current outbreak linked to the MV Hondius**
3. **Exposure to Andes Virus (ANDV).** Participants must meet at least one of the following criteria prior to screening or symptom onset:
   - **a. Direct physical exposure to a person with ANDV infection**
     - History of direct physical contact with a confirmed case or their bodily fluids (e.g., saliva, respiratory secretions).
     - Reported intimate contact, including kissing or sexual activity, with a confirmed case.
     - Documented sharing of personal items, such as eating utensils, drinking containers, or non-disposable medical equipment.
   - **b. Environmental and proximity exposure to a person with ANDV infection**
     - Prolonged presence in an enclosed or poorly ventilated shared airspace. *Note: defined as cumulative exposure of 15 minutes or more within a 24-hour period in a confined space, or shared occupancy of an enclosed environment for more than 2 hours.*
     - Co-habitation in the same household, room, or cabin (e.g., maritime or shared residential settings).
     - Documented proximity during long-haul travel exceeding 4 hours. *Note: Proximity is defined as sitting in an adjacent seat, defined as the same row or within two rows in front or behind. Long haul travel includes flight, bus, car or train*
   - **c. Occupational or caregiving exposure**
     - Provision of direct healthcare or personal care to a person with ANDV infection without the consistent use of recommended Personal Protective Equipment (PPE).
     - Direct handling of potentially contaminated fomites, such as soiled linens, clothing, or bedding used by a confirmed case.
4. **Ability to comply with confinement sampling and follow-up procedures.**
5. **Informed consent** by participant, parent, or surrogate where allowed and applicable.

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Exclusion criteria

1. Current imprisonment (quarantine does not count).

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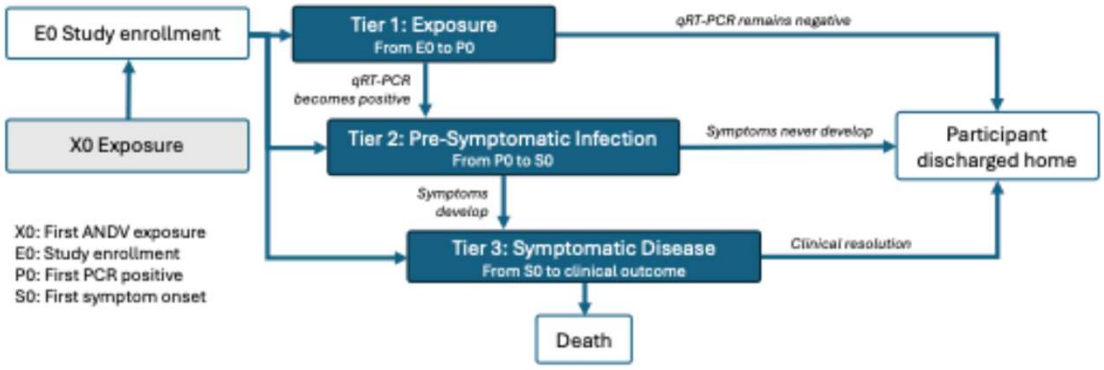
Schedule of Events



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Tier 1. Exposure

From X0 (exposure) to P0 (first PCR positive)

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Test / Assessment	Enrollment (E0)	Time since Exposure (X0)					
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Informed consent	X						
Epidemiological assessment Exposure, contact tracing	X						
Clinical assessments							
Demographics, comorbidities and other relevant pre-existing clinical conditions	X						
Daily clinical monitoring (symptom diary + temperature + SpO_2 + blood pressure + diuresis)	X	Daily	Daily	Daily	Daily	Daily	Daily
Blood Hematology, Coagulation and Biochemistry	X	1×/week	1×/week	1×/week	1×/week	1×/week	1×/week
Virological assessments							
ANDV RT-qPCR in venous blood (EDTA → buffy coat preferred, ± plasma)	X	1×/week	2×/week	2×/week	2×/week	2×/week	1×/week
ANDV RT-qPCR in nasopharingeal swab	X	1×/week	2×/week	2×/week	2×/week	2×/week	1×/week
ANDV RT-qPCR in saliva	X	1×/week	2×/week	2×/week	2×/week	2×/week	1×/week
ANDV RT-qPCR in urine	X	1×/week	2×/week	2×/week	2×/week	2×/week	1×/week
Optional: RT-qPCR in semen	X	none	none	X	none	none	X
Immunological assessments							
Serology (IgM/IgG; serum)	X	1×/week	2×/week	2×/week	2×/week	2×/week	1×/week
Longitudinal immunological panel (Peripheral Blood Mononuclear Cells, PBMCs)	X	1×/week	1×/week	1×/week	1×/week	1×/week	1×/week
Host genetics testing (Opt-in) [a]							
4mL EDTA tube	X	none	none	none	none	none	none

Note: For feasibility, sample shipment and follow-up clarity: 2x / week sampling may be performed on Mondays and Thursdays; 1x / week sampling may be performed on Mondays

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Tier 2. Pre-symptomatic infection

From P0 (first PCR positive) to S0 (first symptom onset)

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Test / Assessment	Enrollment (P0)	Time since first PCR positive (P0)					
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Informed consent [a]	X						
Epidemiological assessment [a] Exposure, contact tracing	X						
Clinical assessments							
Daily clinical monitoring (symptom diary + temperature + SpO_2 + blood pressure + diuresis)	X	Daily	Daily	Daily	Daily	Daily	Daily
Blood Hematology, Coagulation and Biochemistry	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
Virological assessments							
ANDV RT-qPCR in venous blood (EDTA → buffy coat preferred, ± plasma)	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
ANDV RT-qPCR in nasopharingeal swab	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
ANDV RT-qPCR in saliva	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
ANDV RT-qPCR in urine	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
Optional: RT-qPCR in semen	X	none	none	X	none	none	X
Immunological assessments							
Serology (IgM/IgG; serum)	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
Longitudinal immunological panel (Peripheral Blood Mononuclear Cells, PBMCs)	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
Host genetics testing (Opt-in) [a]							
4mL EDTA tube	X	none	none	none	none	none	none

[a] *If not provided before, i.e. the study participant is first enrolled in this phase (Tier 2)*

Note: For feasibility, sample shipment and follow-up clarity: 2x / week sampling may be performed on Mondays and Thursdays; 1x / week sampling may be performed on Mondays

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Tier 3. Symptomatic Disease

From S0 (first symptom onset) to clinical outcome

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Test / Assessment	Enrollment (S0)	Time since first Symptoms (S0)					
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Informed consent *	X						
Epidemiological assessment * Exposure, contact tracing	X						
Clinical assessments							
Daily clinical monitoring (symptom diary + temperature + SpO_2 + blood pressure + diuresis)	X	Daily	Daily	Daily	Daily	Daily	Daily
Blood Hematology, Coagulation and Biochemistry	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
Virological assessments							
ANDV RT-qPCR in venous blood (EDTA → buffy coat preferred, ± plasma)	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
ANDV RT-qPCR in nasopharingeal swab	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
ANDV RT-qPCR in saliva	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
ANDV RT-qPCR in urine	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
Optional: RT-qPCR in semen	X	none	none	X	none	none	X
Immunological assessments							
Serology (IgM/IgG; serum)	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
Longitudinal immunological panel (Peripheral Blood Mononuclear Cells, PBMCs)	X	2×/week	2×/week	2×/week	2×/week	1×/week	1×/week
Host genetics testing (Opt-in) *							
4mL EDTA tube	X	none	none	none	none	none	none

** If not provided before, i.e. the study participant is first enrolled in this phase (Tier 3)*

Note: For feasibility, sample shipment and follow-up clarity: 2x / week sampling may be performed on Mondays and Thursdays; 1x / week sampling may be performed on Mondays

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Laboratory research

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Host genetics Opt-in substudy

1. Lead: Dr. Kenneth Baillie, University of Edinburgh

Advanced Research Laboratory Investigations

- *To be performed in proficient research labs within the NAVIS Network.*
- *For NAVIS sites **without access to such investigations locall**y, they are also **available at the irsiCaixa Research Institute, Badalona, Spain**, upon request. Contact persons: Dr. Julià Blanco, jblanco@irsicaixa.es, and Dr Núria Izquierdo-Useros: nizquierdo@irsicaixa.es*

1. Andes Virus Neutralization Assays
2. T-cell Immunity against Andes Virus
3. Andes Virus isolation from clinical samples
4. Antiviral activity against Andes Virus
5. Andes Virus Whole Genome Sequencing

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Data sharing and publications

- After the study has ended and its results have been reported, anonymized, deidentified data sharing will occur as per the Policy Statement on Data Sharing by the World Health Organization*.
- The final data sets will be available to principal investigators on the dedicated site (ISARIC) during and after the study results are published.
- There will be group authorship recognizing the contribution of all national and local investigators and guided by the International Committee of Medical Journal Editors (ICMJE) criteria and recommendations.
- A writing committee will consist of the protocol group as listed in the protocol – publication will include all international and national collaborators whose team, in the view of the national principal investigator, contributed substantially towards the trial, in line with ICMJE policy.
- The results of the study will be presented at conferences held in each country and each of the partner countries, as well as at international conferences.
- All principal investigators and teams will be kept informed about timelines to report and publish data – there will be no publication or dissemination without permission from the protocol team.
- Agreement not to make public or otherwise disseminate any results of the study until these have been formally published, with group authorship recognizing the contribution of all national and local investigators, unless permission is received from the protocol group ahead of time.

*World Health Organization. New WHO policy requires sharing of all research data. 16 September 2022. https://www.who.int/news/item/16-09-2022-new-who-policy-requires-sharing-of-all-research-data.
* http://www.icmje.org/#author

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Key take aways

Trigger-based Adaptive Framework
NAVIS uses a phase-adaptive framework to align data collection with key biological events during outbreaks.

Addressing Key Outbreak Uncertainties
NAVIS will provide insights on presymptomatic transmission, infectious period, and severity predictors critical for containment.

Embedded Observational Research
NAVIS demonstrates embedding quality observational research into emergency response without disrupting patient care.

Scalable and Ethical Model
NAVIS offers a scalable, ethically proportionate model for outbreak science to support global health decisions.

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