World Health Organization

UK Health Security Agency

Oropouche Virus Research & Development Roadmap

21st October 2025

R&DBlueprint

Powering research to prevent epidemics

Executive Summary

Since 2023, there has been an increase in the number of cases of Oropouche disease with a wider geographical distribution than seen previously. In addition to the increase in cases, there have also been reports of complications, including neurological symptoms, and a number of reported deaths. Cases of vertical transmission and adverse outcomes during pregnancy have also been recorded, suggesting changes in the pathogenicity of Oropouche virus. Thus, there is a need for urgent in-depth research.

Following their publication of the Pathogens Prioritization Framework (2024), the World Health Organisation (WHO) Research & Development (R&D) Blueprint Team launched the Collaborative Open Research Consortium (CORC) initiative to support a priority pathogen family approach to outbreak preparedness. The aim of the CORCs is to convene global researchers from across sectors to identify R&D priorities, and to collaborate through sharing of knowledge and harmonisation of protocols and tools.

On behalf of the WHO, the UK Health Security Agency (UKHSA) was appointed to lead the CORC for bunyaviruses, which includes the *Peribunyaviridae* family, of which Oropouche virus is a member. In response to the current outbreak, a meeting of global scientific experts was convened in February 2025 to discuss the status of Oropouche virus research and to identify priorities for countermeasure development. Following the call, participants registered their interest in joining the CORC. Working Groups subsequently drafted this R&D Roadmap, using a modified Delphi approach.

This Roadmap describes research and knowledge gaps under four themes: 1. Vector Research; 2. Virology and Pathogenesis; 3. Serology and Diagnostics; and 4. Animal Models, Vaccines and Therapeutics. This work is supported by an evidence gap map using rapid systematic methods conducted by UKHSA.

The CORC has agreed on 12 priorities for research and development. They are listed below, organised by research theme rather than in order of priority.

37 Top 12 Research & Development Priorities

Vectors and Transmission

- Conduct field studies to identify environmental drivers of host and breeding site preferences and urban spread, integrating climate and ecological data.
- Evaluate the effectiveness of personal protective measures against vector-borne transmission.
- Undertake laboratory-based studies with insect colonies to clarify vector competence, reproduction, and behaviour.

Virology and Pathogenesis

- Implement genomic surveillance of circulating and related variants and develop methods to identify emerging and recombinant viruses.
- Investigate risk factors for severe disease through in vitro and in vivo studies on viral reassortment, dissemination, tissue tropism, pathogenicity, and innate/adaptive immune control.

Serology and Epidemiology

- Perform seroprevalence studies to assess population exposure.
- Identify optimal serological markers to minimise assay cross reactivity and non-specificity, and that can distinguish current from recent and historic infection.

Diagnostics and Correlates of Protection

- Conduct longitudinal analysis of clinical presentation, as well as cellular and humoral responses to define the duration of immune protection.
- Develop rapid point of care diagnostics (for example, lateral flow devices) to detect acute infection in low- and middle-income countries (LMICs).
- Develop reagents and reference materials from endemic regions to establi target profiles for assay development.

Therapeutics and Vaccines

- Develop preclinical models, including challenge models, for evaluating candidate therapeutics and vaccines.
- Advance therapeutic and vaccine candidates for preclinical testing, prioritizing vaccines with cross-strain protection.

Contents

Abbreviations

BUNV	Bunyamwera virus
CNS	Central Nervous System
CORC	Collaborative Open Research Consortium
CSF	Cerebrospinal Fluid
CVV	Cache Valley Virus
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LACV	La Crosse Virus
LMIC	Low- and Middle-Income Country
OROV	Oropouche Virus
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
qPCR	Quantitative Polymerase Chain Reaction
RNA	Ribonucleic Acid
RT-qPCR	Reverse Transcription Quantitative Polymerase Chain Reaction
SBV	Schmallenberg Virus
UKHSA	United Kingdom Health Security Agency
WHO	World Health Organization

73 Introduction

The World Health Organization (WHO) Research and Development (R&D) Blueprint for Epidemics team have initiated a global effort to further pandemic preparedness R&D by employing a pathogen family approach. The goal is to reduce the time required for the development of safe and effective medical countermeasures for epidemics and pandemics. The approach is to move from a pathogen focus to a pathogen family-centric approach, with institutions convening and facilitating global R&D efforts for each family through a Collaborative Open Research Consortium (CORC). The UK Health Security Agency (UKHSA) is coordinating the CORC for prioritised viral families within the *Bunyaviricetes* class, including *Peribunyaviridae*, of which Oropouche virus is notable due to the ongoing outbreak in the Americas. On 21st February 2025, UKHSA convened the first meeting of the *Peribunyaviridae* CORC.

Peribunyaviridae and Oropouche virus

The *Peribunyaviridae* virus family contains eight genera: *Gryffinivirus, Herbevirus, Khurdivirus, Lambavirus, Orthobunyavirus, Lakivirus, Pacuvirus,* and *Shangavirus*. Of these, the *Orthobunyavirus* genus contains the most species responsible for human disease. Bunyamwera virus (BUNV), La Crosse virus (LACV), Cache Valley virus (CVV), and Oropouche virus (OROV) are examples. All are arthropod-borne viruses, transmitted by biting insects, resulting in a febrile illness of varying severity, some also resulting in neurological disease.

OROV belongs in the Simbu serogroup of the *Peribunyaviridae* family within the *Orthobunyavirus* genus and is named after Vega de Oropouche in Trinidad and Tobago where the virus was first detected in 1955. Oropouche fever is an infectious tropical disease caused by OROV that can infect humans via biting midges and some types of mosquitoes.

Oropouche fever presents as a febrile disease. Although this can be debilitating in the short term, those infected often recover with no severe long-term consequences. Symptoms include fever, headache, chills, myalgia, and arthralgia, and typically last less than a week, but many cases of relapse are reported.

While OROV can cause severe disease, particularly in elderly or immunosuppressed individuals, deaths associated with infection are rare. However, during the outbreak in 2024 in Brazil, two OROV-associated deaths were reported, as were one foetal death and several instances of microcephaly in newborns. Due to the common clinical signs, Oropouche fever is often mistaken for dengue, chikungunya, Zika virus, or malaria infection, and is therefore likely under-reported.

The outbreak in 2024 was highlighted by the WHO as an outbreak of concern due to the number of cases, many of which occurred in areas where OROV transmission had not been reported previously, and the associated increased risk to human health.

CORC Objectives and approach

The CORC initiative aims to establish a network of international research consortia focused on priority pathogen families. This concept builds on the WHO's scientific framework for pandemic research preparedness and leverages global scientific expertise to enhance our collective ability to detect, prevent, and respond to emerging pathogen threats.

A key objective for each CORC is collaborative development of comprehensive research roadmaps for their assigned pathogen families. R&D roadmaps will identify research gaps and serve as a framework to underpin strategic goals, research priority areas, and activities to accelerate R&D of the medical countermeasures for each of these priority diseases, from basic research through to late-stage development, licensure, and early use of products.

On 21st February 2025, UKHSA on behalf of the WHO led a virtual CORC meeting to discuss topics relevant to Oropouche fever research and the development of countermeasures: public health and vector research; virology and pathogenesis; diagnostics and serology; preclinical models and vaccine/therapeutic development. The full agenda is attached (Annex I). The meeting was attended by 96 participants including experts presenting on the topics listed above. The aim of the meeting was to review the current status of research and available

countermeasures with a view to identifying gaps and R&D priorities.

Participants were invited to register to join CORC working groups on each of the meeting themes. A modified Delphi-like approach was employed to prioritise research questions using Google Forms and to collaboratively draft this document via Google Documents. 54 experts contributed to the roadmap, with 31% from institutions residing in LMICs. The UKHSA CORC team facilitated each review round, compiled content, and drafted the final document.

Research and Knowledge Gaps

1. Vector Research

1.1 Vector Competence

Vector competence refers to a vector's ability to acquire, replicate, and transmit a specific pathogen. Understanding vector competence enables the development and delivery of targeted vector control strategies and surveillance necessary to determine or predict geographic and seasonal risk.

1.1.1 Research and/or Knowledge Gaps

It is important to understand the vector ecology of OROV transmission, including in a geographic context. Transmission in humans occurs mainly through the biting midge *Culicoides paraensis*, although other arthropods, such as mosquitoes, are thought to play a role. However, little is known about the breadth of competent vector species or the potential for switching vector species in different geographic environments (e.g., rural *vs.* urban/peri-urban).

The knowledge of the *Culicoides* fauna is still limited in many places, especially in regions with high diversity. Several neotropical countries have unknown fauna. Reviews and analyses that include the most abundant and easily identifiable species can help the surveillance teams, as was done in the Pan American Health Organization (PAHO) manual for the Americas (Operational document for the identification of Culicoides Latreille (Diptera: Ceratopogonidae)).

Laboratory-reared biting midges enable vector research. However, there are few laboratory-colonised midge species available, and those available may not represent vector competence for endemic species in outbreak settings. All colonised species are from Nearctic areas, except one Palearctic species (Culicoides nubeculosus) which is not of any veterinary of public health relevance. No neotropical species are laboratory colonised. Efforts to colonise further species, such as *Culicoides paraensis* and *Culicoides insignis*, could support research, especially as these species are implicated in recent outbreaks.

Gräf's work (Gräf, 2025, PMID: 39557055) showed that Oropouche cases were 3–9 times more frequent in small municipalities and also that banana plantations were positively correlated with OROV cases (Expansion of Oropouche virus in non-endemic Brazilian regions: analysis of genomic characterisation and ecological drivers). These observations suggest the spread of virus is compatible with the ecological conditions of development of *C. paraensis*. No data from Brazil indicate vectoring by other species of *Culicoides*. This does not rule out the need for studies on other species that are equally abundant in certain areas.

1.1.2 Key Needs

- To support OROV research, laboratories require access to colonised *Culicoides paraensis* midges that originate from species collected in endemic regions. Challenges around sustaining laboratory colonies need to be considered; for example, wild populations transplanted into a laboratory setting often have difficulty feeding and mating.
- To integrate vector distribution data with other environmental data (e.g., rainfall, temperature, vegetation, moisture, humidity, wind direction, and land use) collected in parallel. This research could also be broadened to include species native to regions beyond the Americas (e.g., European *Culicoides*). Challenges around sustaining laboratory colonies also need to be considered; for example, wild populations transplanted into a laboratory setting have difficulty feeding and mating.
- To conduct studies in relevant species of arthropods (e.g. *Culex* and *Aedes* mosquitoes or *Coquillettidia spp*.) to assess vector competence and transmission capabilities are required. Live in vivo challenges would be the gold standard, but meaningful understanding of replication can be achieved in cell lines derived from arthropod species. This information will be crucial to supply data to epidemiologists and disease modellers looking to predict outbreaks.
- To define the larval habits of *Culicoides* to improve existing traps.

1.2 Animal Reservoirs and OROV Transmission

Understanding animal reservoirs for OROV transmission will clarify how the virus persists in non-human hosts and how it transitions to human outbreaks. Surveillance in reservoir species can act as an early warning system for potential human outbreaks. Identifying key reservoirs that can serve as ongoing sources of infection can assist in directing targeted control measures, but also help predict emergence risk in new areas where reservoir species may be present.

1.2.1 Research and/or Knowledge Gaps

It is vital to understand the OROV transmission cycle in forest, rural, periurban, and densely populated urban areas. Animal reservoirs may be a factor in OROV's transmission into urban areas and so must be understood to implement effective control measures.

To date, most studies on vertebrate reservoir diversity have been limited to the Amazon Basin. With OROV transmission expanding beyond this region, it is essential to investigate other potential reservoirs – both domestic and sylvatic – in diverse environments.

1.2.2 Key Needs

- To conduct sero-surveillance studies to sample animal species that are involved or have the potential to be involved in the OROV transmission cycle. The output of this research will provide a greater understanding of OROV transmission routes.

1.3 Ecology and Exposure

In order to fully understand the role of vectors in disease transmission, there is a need for an in-depth understanding of vector ecology. Factors such as deforestation, urban expansion, certain types of agricultural activity, and other socio-economic factors may play vital roles in driving OROV transmission.

1.3.1 Research and/or Knowledge Gaps

There are several different kinds of biogeographic regions associated with Oropouche fever outbreaks, which highlights the need for more in-depth analysis of the conditions present during periods of OROV transmission.

Studies have shown *Culicoides spp*. biting occurs more commonly in

rural areas rather than urban settings. It is important to investigate other possible *C. paraensis* breeding sites to predict the spread of Oropouche fever to other areas. Previous studies point to the presence of agricultural crops as a relevant factor for the development of this species, but we still do not know what the possible breeding sites and ecological drivers would be in more urban environments.

1.3.2 Key Needs

- To collect, analyse, and disseminate data from previous outbreaks to lead to a broader understanding of the risk locations of where biting has taken place previously.
- To conduct vector ecology studies of biting midges to establish seasonal changes, review climatic aspects, dispersal, rates of natural infection, host preference, anthropogenic factors, virus evolution, and associated changes to pathogenicity and transmission.

1.4 Vector Management

Targeted and effective vector management is essential for safeguarding human health by preventing vector-borne disease outbreaks, reducing disease incidence and burden on healthcare systems. Several technical, environmental, social, and operational considerations are required during the development of vector control strategies, including vector biology and behaviour, environmental and ecological impacts, insecticide resistance, cost and resources, policy, and monitoring and evaluation.

1.4.1 Research and/or Knowledge Gaps

With the widespread expansion of OROV into new environments and the increasing number of exposed individuals, it is crucial to have updated information on the most effective vector control tools that national programs can implement. Additionally, understanding the extent to which personal protective measures (e.g. repellents) provide protection is essential for guiding appropriate public health recommendations.

1.4.2 Key Needs

- To understand effectiveness of insecticides, a contemporary systematic literature review is needed along with new laboratory insecticide tests using

relevant midge and mosquito colonies and field-collected insects.

- To confirm the role of *Wolbachia* as a means of OROV control. As there are already releases of *Wolbachia* transinfected mosquitoes in South America, this could be used as a control measure for OROV, taking advantage of the existing infrastructure. *Wolbachia* has been found in colonised *Culicoides sonorensis* and in field-caught *Culicoides spp*, and *Wolbachia* in *Culicoides* cell lines have been shown to inhibit the replication of *Orbiviruses*.
- To evaluate adapting control strategies to exposure routes (e.g., if biting occurs in houses, consider repellent, fine-mesh bed, window and door nets, given the midges are considerably smaller than mosquitoes, electric fences, and fans, comparing effectiveness with the treatment of breeding sites).
- To evaluate community empowerment initiatives coupled with the implementation of vector control strategies tailored to local behaviours and context.

2 Virology and Pathogenesis

2.1 Innate, Humoral and Cellular Host Immune Response

Clinical infection and disease can present with varying degrees of severity, from asymptomatic or a non-specific febrile illness to a range of symptoms including headache, myalgia, rash, arthralgia, and neurological complications. The latter can include aseptic meningitis, and there is a strong temporal association with Guillain-Barre syndrome. Oropouche fever may have a biphasic natural history with a recurrence of symptoms after initial resolution. Vertical transmission has also been associated with miscarriage and stillbirth.

Understanding the immune response to OROV is important to develop optimal supportive care strategies, identify therapeutic targets for development of novel therapeutics or repurposing of existing drugs and for targeted prevention strategies to prevent severe disease. The protective role of humoral and cellular components of the host immune response has not been described in humans, and the protective role of previous OROV exposure against reinfection and the duration of protective immunity remain unknown.

2.1.1 Research and/or Knowledge Gaps

Understanding the immune response to OROV is important to stratify the risk of infection/reinfection and/or disease and to underpin the development of therapeutics and vaccines. We lack a full understanding of the natural history of acute infection, including why there may be transient symptom resolution followed by recurrence of fever and other systemic symptoms, which may be immunologically or virally mediated.

We currently do not understand which biomarkers or symptoms correlate with disease severity (e.g., neurological complications), whether patients will experience long-term neurological sequelae, or whether they are likely to transmit the infection. For example, does the detection of OROV via polymerase chain reaction (PCR) in whole blood (or other bodily fluids) at up to 90 days post-infection correlate with the presence of infectious virus, and what threshold of viral ribonucleic

acid (RNA) correlates with onward human-to-human transmission risk.

Given evidence of live virus shedding in semen, there appears to be a potential risk for sexual transmission, but this has not yet been documented.

Knowing which immunological mechanisms (e.g., neutralising antibodies, T cells, mucosal immunity, restriction factors, etc.) provide protection from or susceptibility to infection/disease will underpin the development of therapeutics, vaccines, and other countermeasures, as well as the identification of specific risk factors associated with disease severity. Understanding amino acid changes associated with decreased susceptibility to these responses will also inform the likelihood of viral immune escape.

There is limited understanding of the risks associated with any potential antibody-dependent enhancement of disease related to sub-neutralising antibody responses during reinfection (or from prior exposure to closely related orthobunya viruses such as Iquitos) and whether this drives the enhanced pathogenesis and severe disease associated with recent outbreaks.

In addition, a greater understanding of the temporal nature of viral shedding and the antibody response over time needs to be established in humans, given evidence of a protective role in mice. Knowledge of how long preexisting immunity lasts and the breadth of protection afforded is essential to understand a population's susceptibility to emergent reassorted strains of OROV.

2.1.2 Key Needs

- To conduct longitudinal studies in endemic countries with well-defined cohorts (based on a clear case definition) with frequent sample collection and (potentially) long-term follow up, incorporating analyses such as quantitative PCR (qPCR), sequencing, and/or virus isolation. Ideally this would include individuals who were proven to be infected but were asymptomatic as controls/comparators.
- To develop biological reference materials, international standards and positive control

sera and sample availability for assay validation.

- To conduct broad and unbiased analyses of different cellular and humoral immune responses in well-defined patients correlated with clinical outcome.
- To understand which innate/intrinsic pathways can restrict infection, which are targets for viral countermeasures, and which can lead to stimulation of effective adaptive immunity.
- To proactively assess viral sequences and antigenic variation that might underpin immune escape in combination with serological data.
- To use preclinical (animal) studies to elucidate immune protection. Animal studies can also investigate bite site immunology and links to infection outcome. Preclinical studies will enable challenge and rechallenge experiments with different cross-isolates/strains of OROV. These studies will also reveal whether enhanced pathogenesis is seen in animals with prior OROV infection that yielded an antibody response. The value of preclinical studies involving permissive animal species is described further below.

2.2 Viral Genomics including Evolutionary Dynamics, Phylogeny and Genome Reassortment

Understanding viral genomics is essential, because the segmented genome of OROV enables reassortment and the emergence of new viruses to which the human host may be susceptible, irrespective of previous infections.

2.2.1 Research and/or Knowledge Gaps

Genomic surveillance of newly emerging variants is a research priority. Further work into the genomic determinants of such differences is key to predicting future outbreak variants.

An emerging strain, which arose through genetic reassortment, OROVBR-2015_2024, is responsible for the epidemic that started in 2024 and is characterised by more severe outcomes. One study (Scachetti, 2024: Reemergence of Oropouche virus between 2023 and 2024 in Brazil) suggested that this strain has a higher replication efficiency in mammalian cells than the prototype BeAn19991 strain (Brazilian OROV prototype), at least

at early time points post-infection. The currently circulating OROV strains seem to be less susceptible to neutralising antibodies elicited by the prototype strain. It is therefore important to understand the virological aspects responsible for potential increases in viral fitness, immune escape, and mechanisms of pathogenesis.

A comprehensive understanding of the molecular evolution of OROV and the genotype-to-phenotype connection is crucial to anticipate the emergence of new strains that could escape immunisation induced by a vaccine strategy.

Understanding the contributions to pathogenesis and transmission of viral genes from emergent isolates will require the use of reverse genetics technologies.
Tracking reassortment/recombination events using current sequencing efforts will also enable accurate monitoring of virus emergence over time and/or phylogeographic location.

2.2.2 Key Needs

- To comprehensively map circulating variants and related viruses to understand the genetic 'drifts' and 'shifts' that are possible.
- To assess in vitro which related viruses could potentially donate genetic material to make viable OROV and to further characterise such genes/viruses.
- To proactively assess the potential for immune escape.
- To develop reverse genetics systems for emergent and reassorted viruses to assess the contributions of individual viral proteins and their variants to pathogenesis and transmission.

2.3 Viral Tropism including Neurotropism and Neuropathogenesis

Orthobunyaviruses generally have restricted host and geographical ranges, and infection may result in different, strain-specific clinical presentations and outcomes in humans. These may be partly explained by the propensity of the virus to bind and infect particular cell types. Tropism can also be defined and examined in the context of the arthropods that are transmitting OROV. Neuropathogenesis is a particular concern in the context of OROV infection.

2.3.1 Research and/or Knowledge Gaps

Knowing which host and/or viral factors underlie central nervous system (CNS) involvement may allow monitoring/screening for risk factors and/or the development of therapies.

2.3.2 Key Needs

- To establish animal models that can aid the identification of mechanisms of virus dissemination/pathology.
- To determine the mechanisms of viral attachment and invasion in different host cell lines and potentially in silico.
- To compare different OROV strains in established in vitro models of the blood-brain barrier.

2.4 Viral Replication Mechanism

The development of preventive measures relies to a large extent on understanding the stages of viral replication, from initial attachment and entry via host cell receptors and co-receptors to shutdown of the host molecular metabolism and takeover by viral mechanisms.

2.4.1 Research and/or Knowledge Gaps

Our understanding of OROV biology remains limited, largely extrapolated from studies of the prototype BUNV and other Orthobunyaviruses.

2.4.2 Key Needs

- To conduct a global analysis of the molecular interactions that occur between OROV and host cells during infection. This would include testing the relevance of entry molecules on host cells, the role of innate immunity and other viral factors associated with immune evasion, identified in previous studies of BUNV and other related Orthobunyaviruses for OROV replication. Such studies should be undertaken in different relevant cell types using different viral isolates. Studies should also be expanded to vector species and reservoirs (e.g., sloths) and cell cultures derived from them.

2.5 Viral Transmission and Pathogenesis

Other *Peribunyaviridae*, including *Schmallenberg virus* (SBV), are known to be vertically transmitted and cause stillbirths and congenital malformations in livestock such as sheep, goats, and cattle. More recently, case reports describing human vertical transmission have been described for OROV infections in pregnant women, and the

potential for the sexual transmission based on the presence of virus in semen and vaginal secretions. This highlights a pressing research need.

2.5.1 Research and/or Knowledge Gaps

Vertical transmission of OROV has been reported based on the detection of OROV genetic material in umbilical cord blood and foetal organ tissue, including brain, liver, kidneys, lungs, heart, and spleen, correlated with maternal infection. The mechanism(s) by which OROV crosses barriers at the maternal-fetal interface is not known. Defining which host and/or virus factors underlie vertical transmission (and when) may allow monitoring/screening for risk factors and/or interventions.

2.5.2 Key Needs

- To study onward transmission risk, which may be linked to viral titres in the blood, with a need to establish thresholds for viral infectivity.
- To conduct longitudinal study of clinical presentation cases, recruiting ideally as wide a range of illness severity as possible to monitor disease progression and outcomes. Accurate estimates of the rate of severe disease and poor foetal outcomes during pregnancy would be very important for public health planning.
- To conduct histopathological analyses of placentas or gestational membranes from OROV-infected mothers to inform the mechanism(s) of vertical transmission.
- To use relevant animal models, explant models, and primary cells to dissect the viral/host factors that underpin vertical transmission.
- To monitor and/or screen at-risk pregnant women and link infection to vertical transmission to establish patient cohorts for follow-up to assess vertical transmission rates and any adverse outcomes.
- To use banked samples (e.g.,vaginal swabs, blood samples, placentas, gestational membranes, umbilical cords) from at-risk regions to determine the impact of OROV on pregnancy prior to 2023. OROV-infected mothers/offspring could be identified using reverse transcription qPCR.

3 Serology and Diagnostics

3.1 Lateral Flow

Improved diagnostics that can be used in LMIC field settings are critical to allow rapid, accurate diagnosis and the implementation of early management and infection control measures. Ideally, these assays would be easy to run and not reliant on a cold chain.

3.1.1 Research and/or Knowledge Gaps

Current diagnostic methods for OROV rely heavily on RT-PCR, which requires adequately equipped laboratories, limiting their use in remote or resource-limited settings. A rapid, field-deployable diagnostic tool (e.g., lateral flow assay or isothermal amplification-based test) would enable early case detection, timely outbreak responses, and improved disease surveillance.

Currently, diagnostic assays are usually performed in reference laboratories and are often undertaken in the context of an epidemic, limiting our understanding of the true burden of disease. A rapid point of care diagnostic assay would allow differentiation from co-circulating febrile illnesses that present with similar symptoms in the clinic (e.g., dengue, chikungunya, or Zika virus infection) and would help establish a clear case definition for OROV. It would also inform the clinical application of any future antiviral or immunomodulatory therapies to treat OROV infection and/or the associated immunopathology.

3.1.2 Key Needs

- To define target product profiles that fulfill desired characteristics and performance criteria.
- To develop reagents and assays to detect OROV antigens during acute infection (e.g., lateral flow devices for testing sera from patients infected with OROV). Initial development will require synthetic samples (e.g., human blood spiked with viral antigens), but validation will require partnerships between scientists and clinicians with access to banked acute-phase samples from patients infected with OROV.
- To establish partnerships between scientists, clinicians, and industry to allow development

beyond research use to the point of regulatory approval.
- To build laboratory capacity to facilitate centralised evaluation of assay performance.
- To focus on sustainable access to commercialised assays at an affordable price.

3.2 Serology and Molecular Diagnostics

Antibody responses play a key role in protection and recovery from viral infections and constitute a cornerstone for the diagnosis of acute and past infections.

3.2.1 Research and/or Knowledge Gaps

OROV fever symptoms are similar to those of other arboviral diseases, leading to frequent misdiagnoses. A multiplex assay incorporating serological markers could improve diagnosis, reduce unnecessary treatments, and provide a clearer epidemiological picture of arboviral co-circulation.

Given their high genetic similarity (with some shared segments), there may be cross-reactivity of serological reagents developed against OROV, Iquitos virus, Perdões virus, and Madre de Dios virus. However, it has been shown that prior infection with historical OROV isolates does not provide cross-protection against the newly circulating AM0088 2023 isolate (Scachetti, 2025: Re-emergence of Oropouche virus between 2023 and 2024 in Brazil: an observational epidemiological study).

It will be important to differentiate among these infections to monitor the association between infection genotype and clinical outcome and to understand the capacity for cross-protection. Serological and/or PCR/sequencing methodologies should be developed and standardised for this purpose.

Understanding immune response dynamics is essential for serological surveillance and vaccine development. Differentiating between acute and past infections can guide public health interventions, particularly in endemic areas where repeated exposure is common. Seroprevalence studies carried out before and after outbreaks are essential to determine the level of asymptomatic or oligosymptomatic cases in endemic and non-endemic areas.

There are no widely available international reference materials for OROV. This deficiency prevents the standardisation and rigorous comparison of data generated using different serological assays.

Similarly, there are no widely available banks of sera or cells/tissues from patients with acute or convalescent OROV infection to conduct validation studies. The lack of such resources impedes the development, validation, and rigorous comparison of new diagnostic tests to detect host antibody responses, viral antigens, and/or viral nucleic acids. It also complicates the comparison of assay sensitivities such as viral loads across different sites, even when using the same established PCR-based diagnostic assay.

3.2.2 Key Needs

- To define target product profiles that fulfill desired characteristics and performance criteria.
- To develop reference materials that allow comparisons of assay performance, which will support the development and validation of serological and molecular assays.
- To facilitate the equitable availability of clinical samples via collaborations with clinical colleagues in endemic areas, that can be made available through repositories/biobanks, facilitating validation studies and the development of assays to regulatory standards.
- To conduct experimental animal studies that generate convalescent sera with known infection histories and to use synthetic viral genetic elements to support initial assay development. The availability of well-characterised viral isolates and human sera and their development into international reference materials will support assay standardisation.
- To establish routine RT-PCR testing and serosurveillance for OROV infection in endemic areas, using standardised and well-validated serology assays, to distinguish between active infection, past infection, and reinfection.
- To build laboratory capacity to facilitate centralised evaluation of assay performance.
- To focus on sustainable access to commercialised assays at an affordable price.

3.3 Sample Collection

There is limited data on OROV persistence in bodily fluids. Understanding viral kinetics in various sample types can optimize diagnostic testing algorithms and improve case detection at different stages of infection. This is particularly important for neurological cases, where cerebrospinal fluid (CSF) sampling may be required.

Determination of the ideal sample type for testing is essential to ensure diagnostic accuracy and to determine how long a patient remains infectious (e.g., live virus in semen may be associated with prolonged infectivity via sexual transmission). Ease of collection is also a key consideration (e.g., blood versus urine).

3.3.1 Research and/or Knowledge Gaps

Anecdotal reports suggest that serum is inferior to whole blood and that urine is a less invasive alternative to blood for the diagnosis of OROV. Comparisons of matched blood, serum, and urine samples from acute-phase patients across multiple time points (longitudinal studies) are required to determine where and when OROV can be most readily detected as a prelude to establishing the most sensitive/convenient diagnostic assay.

3.3.2 Key Needs

- To perform animal studies to determine potential sites of viral persistence/replication.
- To collect and catalogue relevant clinical samples in an opportunistic and minimally invasive manner.
- To analyse samples across multiple sites using standardised and fully validated diagnostic assays.

3.4 Capacity Building

The establishment and maintenance of laboratory infrastructure is key to conducting studies that are relevant to endemic needs. The effect of strengthening public institutions will lead to improved evidence-based policymaking. In the longer term, greater laboratory capacity could generate a virtuous feedback loop with increasing investment and sustainable development of capabilities/infrastructure.

3.4.1 Research and/or Knowledge Gaps

Many LMICs face challenges in conducting serological and diagnostic prevalence studies due to limited laboratory infrastructure, a lack of standardized assays, insufficient funding, and shortages of trained personnel. Supporting these countries through technology transfer, workforce training, the development of affordable and field-adapted serological assays, and the establishment of regional reference laboratories can improve surveillance and outbreak preparedness. Fostering collaborative research networks and data-sharing platforms will enhance global understanding of OROV epidemiology and guide effective public health interventions.

3.4.2 Key Needs

- To build long-term equitable partnerships between scientists and clinicians studying OROV and co-circulating arboviruses.
- To support exchange visits and collaborative research projects to enable two-way learning, strengthen research capacity, ensure the delivery of relevant research, and provide streamlined pathways to impact.
- To develop reference materials and standardised assays in collaboration with colleagues in OROV endemic areas and to ensure their relevance and accessibility.
- To support collaborations between researchers in endemic areas and to make best use of existing technical and human resources by providing funding and by lowering barriers for sharing and movement of both researchers and clinical samples.
- To develop awareness training for front-line healthcare staff, field sampling teams, and laboratory staff.
- To provide e-learning/hybrid training material on international best practices, protocols, and diagnostic capabilities (i.e., newly validated test kits).

4 Animal Models, Vaccines and Therapeutics

4.1 Animal Models

Despite the rise of animal replacement technologies (e.g. organoids), many immunological and pathological issues can only be addressed in whole organisms. We therefore need to know which animal models most accurately recapitulate the key features of human infection with OROV. Models of vertical transmission are particularly important in this context, given reports of foetal infection during the 2024 outbreak in Brazil.

4.1.1 Research and/or Knowledge Gaps

Immune-competent adult mice infected with OROV do not exhibit disease, whereas hamsters do. Hamsters may therefore be superior for studies of immune protection during horizontal transmission. However, we lack the reagents to dissect many features of immunity in hamsters. Vertical transmission can only be studied in mice at the present time. A recent study, however, has also shown that several non-human primate species are susceptible to OROV infection, that are clinically asymptomatic but nonetheless immunostimulatory, potentially mimicking the human situation more closely (Oropouche virus efficiently replicates and is immunostimulatory in vivo in nonhuman primate species).

4.1.2 Key Needs

- To develop and validate reagents (e.g., antibodies that identify common immune subsets and activation markers) for the hamster model (the current gold standard for disease characterisation).
- To develop models of vertical transmission in rodents for comparison with human pathology during pregnancy.
- To develop non-human primate models to confirm and extend findings in rodent models and to test promising candidate therapeutics, vaccines, and other countermeasures in a setting conducive to reliable translation.

4.2 Immunology

Understanding the role of the immune system is critical for the development of medical countermeasures to protect against OROV.

4.2.1 Research and/or Knowledge Gaps

The epitope specificity of neutralising and non-neutralising (Fc-mediated) antibody responses after infection is largely unknown, hindering our understanding of immune escape and cross-protective immunity against novel reassortant strains of OROV. Such knowledge is essential for the development of novel vaccines and therapeutics.

Similarly, little is known about the role of NK cells and T cells as determinants of protection against OROV infection and/or disease, a limitation that impedes the rational construction of a vaccine that could fare better in the face of an escaped or partially escaped antibody response. A comprehensive view of the immune response will help guide strategies to provide optimal long-term protection against novel and mutated strains of OROV.

4.2.2 Key Needs

- To conduct epitope mapping and structural work on broad panels of non-overlapping neutralising and non-neutralising antibodies and to map the specificity of OROV-reactive T cells.
- To dissect immune responses to infection in immune-competent animal models and clinical samples from patients with known disease severity.
- To identify the correlates of protection from reinfection (e.g., the role of neutralising antibodies quantified relative to an international reference material and/or the abundance, characteristics, and specificity of OROV-reactive T cells).
- To study immunopathology in animals that show signs of OROV disease, again comparing with markers of immunopathology observed in severe clinical cases. Understanding immunopathology could allow the informed use of existing immunomodulatory therapies (e.g., steroids) to reduce disease severity and improve patient outcomes.

4.3 Vaccine and Therapeutic Development

Vaccines play a key role in outbreak preparedness and management at the population level, with the potential to reduce disease severity, transmission rates, and healthcare/socioeconomic burden. Therapeutic interventions can also

reduce disease morbidity and mortality.

4.3.1 Research and/or Knowledge Gaps

Currently, there are no OROV-specific vaccines or therapeutics licensed for use, highlighting a clear gap in our ability to respond to future outbreaks of OROV.

Moreover, there is potential for the emergence of new strains containing mutations that reduce susceptibility to natural or vaccine-induced immunity, indicating a need not only to develop broadly protective vaccines but also to identify additional therapeutic options (e.g., by screening small molecules and repurposing existing antiviral drugs).

4.3.2 Key Needs

- To conduct in-depth analyses of immune protection in small animal models, preferably using immune-competent animals that are susceptible to pathology.
- To compare the pathogenesis and immune control of reassortants versus archetypal strains in the context of vaccination.
- To assess vaccine platforms that generate durable immunity, bearing in mind ease of manufacture and distribution.
- To develop reagents enabling high-throughput screening of existing and novel drugs for therapeutic efficacy (e.g., tagged viruses, replicon systems, and/or reporter cells).
- To perform preclinical immunisation trials in animal models using different immunogen and adjuvant formulations, measuring antibody and cellular responses, protection against challenge, and the durability of immune protection.
- To compare vaccine responses in animals with established correlates of protection to prioritise the most promising vaccine platforms. Relevant animal models should be used to determine whether maternal immunisation can prevent vertical transmission. The use of different historical OROV isolates and related viruses (e.g. Iquitos virus, Perdões virus, and Madre de Dios virus) should also be considered in order to measure and potentially improve cross-protection.
- To create accurate representations of immune

profiles in endemic regions, where clinical trials need to take place.

- To use international reference reagents to standardise the reporting of serological data, enabling realistic predictions of vaccine immunogenicity/efficacy.

Supporting Evidence

As part of the Bunyaviricetes CORC, an evidence gap map (EGM) was commissioned in February 2025 from the UKHSA Science Evidence Review team in the Research, Evidence and Knowledge division (UK Health Security Agency | Evidence gap map Oropouche Virus). The purpose of the EGM, which follows rapid systematic methods, was to identify and categorize the available evidence on Oropouche virus to inform research prioritization. The corresponding report summarizes the findings (Oropouche virus: a rapid evidence gap map - GOV.UK). It highlights that the available evidence is restricted to a relatively low number of primary studies (< 270), the majority on epidemiology and surveillance in endemic regions. Of 269 studies, 233 reported data and findings from South America or Central America and the Caribbean, with none from Africa, reflecting the geographical epidemiology of Oropouche virus and also the absence of a global R&D effort. Critically, evidence gaps were identified for medical countermeasures for Oropouche virus (particularly experimental studies in humans), correlates of immune protection in the host, and public health and social measures to control the virus. The conclusions of the EGM were consistent and overlapped with the key findings in this roadmap.

Independently of this roadmap, there have been other, recent efforts to review current research and knowledge in response to the current OROV outbreak.

In January 2025, PAHO convened a consultation meeting entitled "Development of a research agenda for the characterization of Oropouche virus and its public health implications". Members of this CORC were also participants in the PAHO consultation which identified research priorities in relation to five predefined themes: vertical transmission, vectors and reservoirs, epidemiology and surveillance, laboratory, and clinical aspects (Oropouche virus research agenda. January 2025. Development of a research agenda for the characterization of Oropouche virus and its public health implications - PAHO/WHO | Pan American Health Organization). Key needs and priorities identified in this Roadmap align with the output of the PAHO

consultation. Distinguishing features of this Roadmap are the focus on 12 top R&D priorities and authorship by the global scientific community, including experts from outside of the Americas. In addition to the priorities highlighted in this report, PAHO recommendations emphasized the importance of personal protection, clarifying the case definitions to aid early diagnosis and management, and longitudinal studies to investigate the risk of vertical transmission.

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Annex I

This annex provides the agenda for the OROV CORC call scheduled on 21st February 2025. The agenda outlines key topics and contributors.

Moderator: Yper Hall

Time	Topic	Speakers
14:00 – 14:10	Welcome and introduction	Ana Maria Henao-Restrepo (WHO) Isabel Oliver (UKHSA) & Yper Hall (UKHSA)
14:10 – 14:20	Situational/epidemiological update regional and country level	Jairo A. Méndez-Rico (PAHO)
Session 1: Public Health and vector research Chair: Isabelle Dietrich (The Pirbright Institute)		
14:20 – 14:30	Entomological studies during the outbreak of Oropouche	Ariamys Companioni Ibanez (IPK, Cuba)
14:30 – 14:40	Arthropod vector research	Horace Cox (Caribbean Public Health Agency)
14:40 – 14:50	Clinical aspects of Oropouche fever and research gaps	Maria Paula Mourão (Universidade do Estado do Amazonas, and Fundação de Medicina Tropical Dr. Heitor Vieira Dourado)
14:50 – 15:05	Panel/Q&A	Jairo A. Méndez-Rico / Maria Paula Mourão / Horace Cox / Ariamys Companioni Ibanez / María Guadalupe Guzmán Tirado (IPK, Cuba)
15:05 – 15:15	Break	
Session 2: Virology and pathogenesis Chair: Ben Brennan (MRC-University of Glasgow Centre for Virus Research)		
15:15 – 15:25	Anti-interferon strategy of orthobunyaviruses	Friedemann Weber (Institute for Virology, Justus Liebig University Giessen)
15:25 – 15:35	Molecular epidemiology of the ongoing Oropouche virus	Felipe Gomes Naveca (Fiocruz)

Time	Topic	Speakers
	outbreak: viral evolution and ecological drivers	
15:35 – 15:45	Non-vector modes of transmission and potential neurotropism of Oropouche virus	David Hamer (Boston University Center on Emerging Infectious Diseases)
15:45 – 16:00	Panel/Q&A	Friedemann Weber / Felipe Gomes Naveca / David Hamer / Neelika Malavige (University of Sri Jayewardenepura) / Pragya D Yadav (NIV)
Session 3: Diagnostics and serology Chair: Amy Hartman (Infectious Disease & Microbiology, University of Pittsburgh)		
16:00 – 16:10	Serological assessment of the immune response during Oropouche virus infection in Brazil	Pritesh Lalwani (FioCruz)
16:10 – 16:20	Protein-based tools to detect and study OROV infection	Stephen Graham (University of Cambridge, UK)
16:20 – 16:30	The development of NIBSC standards and reagents for Oropouche virus by the MHRA Science & Research Group	Emma Bentley (MHRA, UK)
16:30 – 16:45	Panel/Q&A	Pritesh Lalwani / Stephen Graham / Emma Bentley / Massab U Raja (NIH Pakistan) / Mosoka Papa Fallah (Africa CDC) / Tommy Rampling (UKHSA) / Supaporn Wacharapluesadee (Thai Red Cross Emerging Infectious Diseases Clinical Centre)
16:45 – 16:55	Break	
Session 4: Pre-clinical models and vaccine/therapeutic development Chair: Yper Hall (UKHSA)		
16:55 – 17:05	Murine Models of Oropouche Virus Pathogenesis	Natasha Tilston (Indiana University School of Medicine)

Time	Topic	Speakers
17:05 – 17:10	Experimental OROV infection in vivo and ex vivo	Eurico Arruda (University of São Paulo, Brazil)
17:10 – 17:20	Discovery of antiviral compounds against OROV and related initiatives in Brazilian science	Rafael Elias Marques (Centro Nacional de Pesquisa em Energia e Materiais – CNPEM)
17:20 – 17:35	Panel/Q&A	Natasha Tilston / Eurico Arruda / Rafael Elias Marques / Lance Turtle (Liverpool University) / Rafael França (Fiocruz)
Closing		
17:35 – 18:00	Conclusions, Wrap up and Next Steps	Yper Hall /Charlie Dearman (UKHSA)
18:00	Close of meeting	