Oropouche virus disease across Latin America during the 2023–2025 epidemic: a multi-country case series

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Summary

Background **The 2023–2025 epidemic of Oropouche virus (OROV) disease across Latin America raised public health concerns due to its expansion into previously unaffected regions, alongside reports of increased clinical severity and vertical transmission.**

Methods **We conducted a multi-country case series to characterise the clinical presentation, disease course, outcomes, and virological features of OROV disease during the 2023–2025 epidemic. Analyses were descriptive.**

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Findings We describe 2716 OROV disease cases reported between January 31st, 2024, and November 4th, 2025, across ten states in Brazil, Panama, and Peru. Median age was 38 years (IQR 25–51); 1379/2716 (51%) were female. Most common symptoms were fever (89%), headache (88%), and myalgia (59%), followed by retro-orbital pain (47%). One-fourth of participants reported symptoms' duration beyond one week. Most cases were mild (2542/2716; 94%), although severe manifestations and one death occurred. Haemorrhagic manifestations were reported in 41/2716 (2%), and 7/2716 (<1%) developed severe disease temporally associated with OROV infection. Among 108 pregnant women, 15 (14%) had adverse pregnancy outcomes, including abortions, preterm births, stillbirths, and symptomatic newborns; no congenital malformations were observed. Older age, comorbidities, warning signs, and laboratory abnormalities were more frequently observed among participants with complications. Prolonged RNA detection beyond seven days was observed in serum and urine.

Interpretation Although most OROV disease cases were mild, severe disease and adverse pregnancy outcomes occur and may be under-recognised. These findings support the need for improved clinical recognition, risk stratification, and diagnostics, particularly for high-risk groups, and highlight priorities for surveillance and future research.

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Keywords: Oropouche; Oropouche virus; OROV; Case series; Arboviral diseases; Emerging viral diseases

Introduction

Oropouche virus disease, also known as Oropouche fever, is an emerging zoonotic arboviral illness caused by Oropouche virus (OROV; species *Orthobunyavirus oropoucheense*), an *Orthobunyavirus* primarily transmitted to humans through *Culicoides paraensis* biting midges.[1] First identified in Trinidad and Tobago in 1955, and subsequently recognised as endemic in the Amazon basin, OROV has caused recurrent outbreaks of acute febrile illness across tropical and subtropical regions of Latin America, with an increase in incidence and geographical distribution over the past several decades.[1] Before the emergence of chikungunya virus (CHIKV), and Zika virus (ZIKV) from 2013 onwards, OROV was considered one of the most important vector-borne diseases in the region and the arbovirus with the second highest incidence in Brazil, after dengue virus (DENV).[1]

Between late 2023 and 2025, Latin America has experienced the largest laboratory-confirmed OROV outbreak,[2] linked to the spread of a novel reassortant OROV lineage ($OROV_{BR\text{-}2015\text{-}2024}$) beyond the Amazon region.[3,4] The epidemic has been characterised by a wide geographical expansion into previously unaffected regions and by the recognition of unprecedented severe clinical presentations,[2] leading the World Health Organization (WHO) to declare OROV a high regional public health risk in August 2024.[5] During this period, more than 29,000 confirmed cases were reported across eleven countries in Central and South America and the Caribbean, with additional imported cases identified in North America and Europe.[6,7]

Oropouche typically presents as an acute, self-limiting febrile illness,[8,9] with clinical features that overlap with other co-circulating arboviruses, such as dengue, Zika, and chikungunya, challenging diagnosis and leading to substantial underreporting. Haemorrhagic and neurological manifestations had been described in previous outbreaks.[10–15] However, during the 2023–2025 epidemic, increased clinical severity has been reported, including reports of deaths,[16] adverse pregnancy outcomes, and congenital disease linked to vertical transmission.[17–20] Despite growing recognition of OROV as an emerging public health threat, the clinical spectrum, risk factors for severity, and incidence of severe outcomes during the 2023–2025 epidemic have not been thoroughly described. Existing evidence largely focuses on surveillance and epidemiological dynamic, describes small cohorts, or is restricted to specific regions or disease complications.[21–24]

To address these gaps, we established a multi-country research network across Latin America to comprehensively characterise the clinical presentation, disease course, outcomes, and virological features of OROV disease during the 2023–2025 epidemic.

Methods

Study design and participants

We conducted a multi-country case series of paediatric and adult patients with autochthonous Oropouche virus disease diagnosed in Latin America between January 31st, 2024, and November 4th, 2025 to describe their clinical presentation, disease course, outcomes, and virological features. Researchers at the Fundação de Medicina Tropical Doutor Heitor Vieira Dourado (FMT-HVD) (Brazil) and the Barcelona Institute for Global Health (ISGlobal) (Spain) engaged investigators

Research in context

Evidence before this study

Scientific literature on Oropouche virus (OROV) disease began in 1961, when OROV was first associated with clinical illness during an outbreak in Belém, Brazil. Since then, two distinct periods can be recognised: before and since 2023. Before 2023, evidence was largely based on small outbreak reports from the Amazon region, where the disease is endemic, and sporadic cases reported in non-endemic areas of Brazil, French Guiana, and Colombia. Between 2023 and 2025, unprecedented outbreaks were reported across Central and South America and the Caribbean, including transmission in non-endemic areas and the first reports of deaths and vertical transmission associated with OROV infection. We searched PubMed for articles published from database inception to Dec 31, 2025, using the search terms "Oropouche" AND "OROV", without language restrictions. Publications from the 2023–2025 epidemic have predominantly focused on genomic and epidemiological investigations, as well as small case series restricted to specific geographic areas, populations, or complications. Regarding complications, adverse pregnancy outcomes have been reported in both endemic and non-endemic areas of Brazil, including one stillbirth in Ceará; three infants born with microcephaly, arthrogryposis, and other congenital malformations in Acre; one spontaneous abortion and one live birth with corpus callosum dysgenesis in Espírito Santo; and one abortion and three stillbirths in Pernambuco. Neurological involvement has also been associated with OROV infection, including 43 Guillain-Barré syndrome (GBS) cases reported in Cuba; as well as one GBS case and five cases of encephalitis in Bahía (Brazil). Two fatal cases have also been reported in Bahia in previously healthy women who rapidly progressed to haemorrhagic complications with liver and kidney involvement, coagulopathy, and thrombocytopaenia, ultimately leading to death.

Added value of this study

This multi-country case series provides the largest clinical description of OROV disease reported to date, including 2716 cases from endemic and newly affected areas during the 2023–2025 epidemic. Beyond routine surveillance data, the study includes granular clinical, laboratory, virological, and follow-up data, allowing a more comprehensive characterisation of the clinical spectrum, complications (including seven cases of severe disease temporally associated with OROV infection), outcomes (including 25 hospitalisations and one death), and prolonged viral RNA detection. It also includes the largest reported cohort of pregnant women with OROV disease to date and expands the available evidence describing adverse pregnancy outcomes documented among 15/108 women infected during pregnancy, including abortions, preterm births, stillbirths, and symptomatic newborns. Finally, the study identifies demographic, clinical, and laboratory characteristics more frequently observed among participants with complications, generating hypotheses for future prospective studies.

Implications of all the available evidence

Overall, our findings provide important insights into the clinical spectrum of OROV disease and show that prolonged disease and severe clinical manifestations can occur, although most infections were mild and self-limiting. These observations support improved case detection and surveillance to better characterise the burden and outcomes of OROV disease. The adverse pregnancy outcomes observed in this series contribute to the growing evidence describing clinically relevant maternal–foetal complications among individuals with OROV infection during pregnancy, while further studies are needed to determine their frequency and causal relationship. The clinical and laboratory characteristics more frequently observed among participants with complications provide hypothesis for future studies evaluating potential markers of disease severity. Overall, our results highlight important priorities for future research on pathogenesis, viral kinetics, and determinants of severity in this re-emerging arboviral disease.

in countries reporting the highest numbers of autochthonous OROV cases based on data from the Pan American Health Organization (PAHO) and World Health Organization (WHO) records (Bolivia, Brazil, Colombia, Cuba, Ecuador, Panama, Peru) to establish a regional collaborative network. Eight sites in ten states from Brazil, Panama, and Peru agreed to participate (details in Supplementary Appendix) and contributed data to our convenience-sample case series.

We included confirmed and probable Oropouche cases, according to the PAHO/WHO case definitions. A confirmed case was defined as a symptomatic individual with an epidemiological link, and a positive result for OROV detection by reverse transcription polymerase chain reaction (RT-PCR) in blood, cerebrospinal fluid (CSF), or other bodily fluid; or antibody seroconversion or increase in antibody titre of at least four-fold in paired samples taken more than 7–10 days apart. A probable case was determined by a single positive Immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) test for OROV. The choice of clinically validated RT-PCR assay for OROV detection was site-specific, depending on local availability and guidelines (Supplementary Appendix). We excluded suspected OROV cases and cases with incomplete essential data.

The study was approved by the Ethics Committees of the Fundação de Medicina Tropical Doutor Heitor Vieira Dourado (CEP/FMT-HVD) (Brazil) (CAAE 86807625.7.0000.0005; 7.527.298) and Hospital Clínic de Barcelona (Spain) (HCB/2024/1121), as well as by local institutional review boards as per each site's local requirement. Written informed consent was obtained from participants enrolled prospectively at participating sites; for routinely collected data, consent procedures followed local regulations.

Data collection and study procedures

Each contributing centre completed a standardised, de-identified case-report form (CRF) to capture variables of interest relevant to OROV disease. The CRF included sociodemographic, epidemiological, clinical, and laboratory information, with particular focus on clinical presentation, virological findings, disease course, complications, and outcomes (Supplementary Appendix). Additionally, for pregnant cases, we specifically included pregnancy clinical data, neonatal outcomes, and laboratory evidence of vertical transmission, when available. CRFs were retrospectively completed at each participating site by local investigators, using data abstracted from observational prospective cohorts, or from routine surveillance notification systems and medical records of patients presenting to hospitals and primary healthcare facilities, according to the local setting. Laboratory confirmation of OROV infection was performed either locally within prospective cohort studies (Amazonas and Rio de Janeiro), or through regional and national reference laboratories following site-specific arboviral surveillance algorithms, including investigation of samples negative for DENV, ZIKV, and CHIKV, retrospective screening of archived samples, and testing of suspected arboviral cases. Sex was collected from clinical records or reported by participants and categorised as female or male. Ethnicity, when available, was self-reported according to country-specific census definitions. Primary outcomes included complications (arthritis, haemorrhagic manifestations, severe disease, organ involvement, adverse pregnancy outcomes) and highest level of care (outpatient management, hospitalisation, ICU admission, death). Outcomes were classified by treating clinicians and reviewed by local and coordinating study teams, informed by routine severity assessment, management decisions, and available evidence on OROV and related arboviral diseases. Cycle threshold (Ct) values and sequencing data were extracted from laboratory records at each participating centre. Pregnancy status was not systematically assessed; maternal and neonatal outcomes were ascertained through clinical follow-up, surveillance systems, and medical record review according to local protocols. All data were de-identified and securely transferred to the coordinating centre for analysis. Site-specific details are provided in the Supplementary Appendix.

Statistical analysis

All analyses were descriptive. Continuous variables were described as median and interquartile range (IQR), and categorical variables were described as counts and percentages using the total sample population as the denominator unless otherwise specified, to avoid overestimation of proportions due to variable availability across sites. We did not impute missing data due to the descriptive objectives of the study and the heterogeneity of data availability across sites. The number of missing observations for each variable is reported in tables and figures. We categorised the presence or absence of clinician-reported complications by organ system. When comparing data across complications, we categorised patients with more than one complication into the most severe form of complication (pregnancy complication, haemorrhagic, arthritis) to avoid double counting. Data were analysed using R software version ≥4.2.1.

Role of the funding source

This work received no funding.

Results

Demographic and epidemiological characteristics

We describe 2716 OROV disease cases reported across eight sites in ten states or provinces in Brazil, Panama, and Peru during the 2023–2025 epidemic, representing 9.3% of all autochthonous cases, in countries accounting for 96% of OROV cases reported globally during this period. Most (94%) were reported in Brazil, including 48% from Espírito Santo, 18% from Ceará, 16% from Paraíba, 9% from Pernambuco, 2% from Amazonas, 2% from Rio de Janeiro, and <1% from Minas Gerais and São Paulo states. 2% of cases were from Panama (Darién), and 4% from Peru (Alto Amazonas) (Fig. 1, Tables S1 and S2). Overall, 61% of cases were reported in 2024 and 39% in 2025. Across sites, OROV positivity ranged from 3% to 71% among patients investigated for acute febrile illness and suspected arboviral disease during the respective outbreak periods (Table S3); country-level cumulative incidence during 2024–2025 was 12.08, 4.96, and 16.29 cases per 100,000 population in Brazil, Peru and Panama, respectively (Figure S1).

The demographic and epidemiological characteristics are described in Table 1. The median age was 38 years (IQR 25–51), with most cases occurring in adults aged 18–<40 years (41%) and 40–<65 (39%). 1379/2716 (51%) participants were female, of whom 108 had a known pregnancy at the time of OROV diagnosis. 11% had at least one reported comorbidity, most commonly hypertension (9%) and diabetes mellitus (3%). All participants tested negative by RT-PCR for DENV, ZIKV, and CHIKV, except for a small number of cases with confirmed coinfections, including dengue in 23

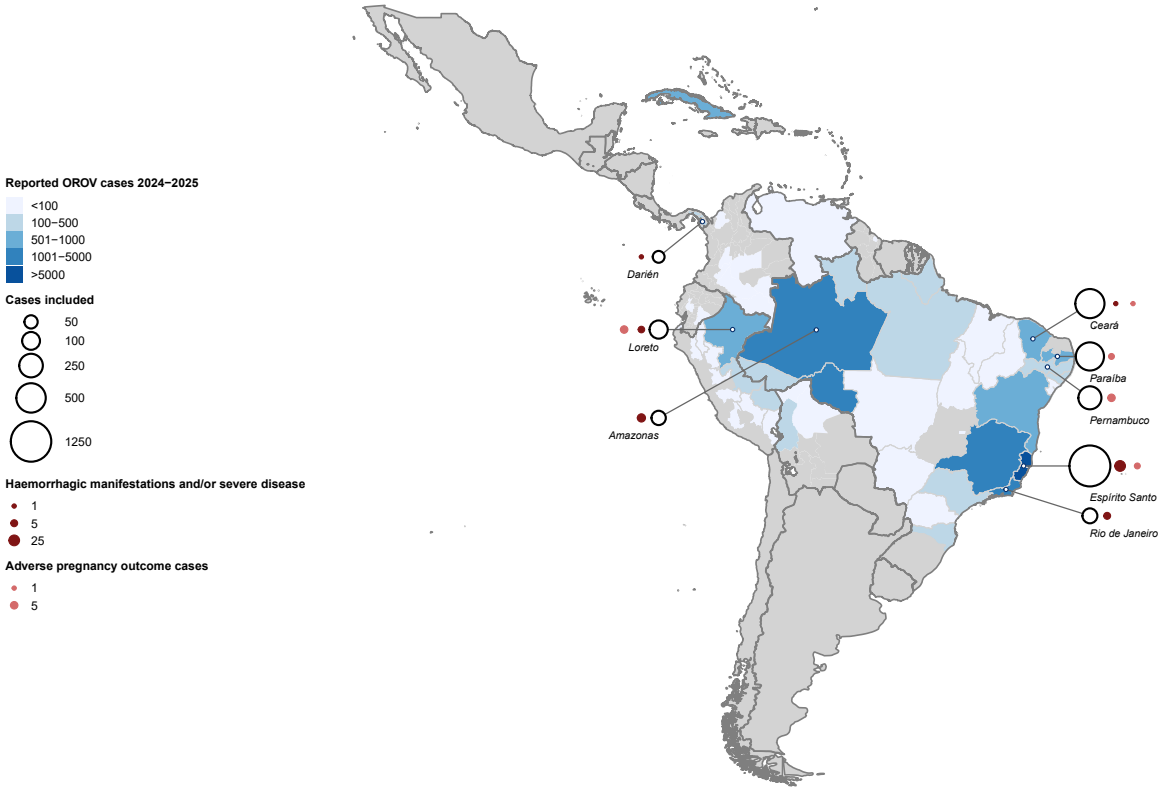


***Fig. 1:* Geographic distribution of Oropouche virus disease cases included in this study**. The map shows the geographic distribution of reported autochthonous OROV disease cases across Latin America (indicated by blue colour gradients), together with the cases included in this study (black circles), cases with haemorrhagic manifestations and/or severe disease temporally associated with OROV infection (red circles), and cases with adverse pregnancy outcomes (pink circles) across eight sites in ten states or provinces in Brazil, Panama, and Peru. We categorised patients with more than one complication into the most severe form of complication (pregnancy complication, haemorrhagic, arthritis). Six patients with more than one complication were categorised as follows: 3 participants with arthritis and haemorrhagic complications as Haemorrhagic, 1 patient with arthritis and pregnancy complication as Pregnancy complication, 2 patients with haemorrhagic complications and pregnancy complications as Pregnancy complications. Data on reported cases are based on PAHO/WHO records derived from national reports, and political administrative boundaries shapefiles were sourced from the public geoBoundaries database.[25,26] In Brazil, these PAHO-reported cases originate from the Ministry of Health, which compiles data entered into the Notifiable Diseases Information System (SINAN). The higher number of cases from Pernambuco reflects additional laboratory-confirmed cases identified at Fiocruz Pernambuco that were not captured through the Unified Health System (SUS) system and therefore not yet included in SINAN.

participants, chikungunya in 18 participants, and malaria in one participant.

Clinical presentation

The most frequently reported symptoms were fever (89%), headache (88%), myalgia (59%), and retro-orbital pain (47%); followed by nausea (33%), and back pain (32%) (Table 2, Figure S2). Arthralgia (19%), and vomiting (14%) were less common, while skin rash (6%), abdominal pain (2%), diarrhoea (2%), and dizziness (2%) were infrequent. Clinical presentation varied by age: adults aged 18–64 years reported the highest frequency of symptoms overall; adults 65 years or older had lower frequencies of fever, headache, and retro-orbital pain, but higher frequencies of myalgia and arthralgia; whereas children more commonly presented with fever and rash (Fig. 2a). Except for fever, symptoms were more common among individuals with comorbidities; whereas pregnant women more frequently reported abdominal pain, nausea, vomiting, and skin rash (Fig. 2b). No relevant differences in clinical presentation were observed between cases from the historically endemic Amazon basin (Amazonas and Loreto) and those from newly affected areas (Ceará, Darién, Espírito Santo, Paraíba, Pernambuco, Rio de Janeiro) (Figure S3). Among 370 participants with available data, the median duration of overall symptoms was three days (IQR 2–7); 86/370 (23%) had symptoms lasting >7 days and the maximum reported duration was 65 days (Figure S4). Recurrent symptoms were reported in 39 of 112 participants with available data.

	Overall N = 2716[a]	Ceará N = 487[a]	Darién N = 47[a]	Espírito Santo N = 1,289[a]	Paraíba N = 439[a]	Pernambuco N = 231[a]	Rio de Janeiro N = 61[a]	Amazonas N = 56[a]	Loreto N = 106[a]
Age (years)									
Median (Q1–Q3)	38 (25–51)	35 (24–49)	35 (21–50)	42 (27–55)	35 (23–47)	36 (25–48)	47 (36–58)	37 (28–54)	23 (15–33)
Min-Max	0–96	1–92	3–74	0–92	2–92	0–79	18–96	8–69	1–90
Age category									
0–<5	26 (1.0%)	6 (1.2%)	1 (2.1%)	5 (0.4%)	8 (1.8%)	3 (1.3%)	0 (0.0%)	0 (0.0%)	3 (2.8%)
5–<18	294 (10.8%)	45 (9.2%)	6 (12.8%)	136 (10.6%)	53 (12.1%)	23 (10.0%)	0 (0.0%)	2 (3.6%)	29 (27.4%)
18–<40	1107 (40.8%)	228 (46.8%)	21 (44.7%)	453 (35.1%)	195 (44.4%)	105 (45.5%)	22 (36.1%)	27 (48.2%)	56 (52.8%)
40–<65	1047 (38.5%)	170 (34.9%)	14 (29.8%)	559 (43.4%)	148 (33.7%)	87 (37.7%)	31 (50.8%)	24 (42.9%)	14 (13.2%)
65 and above	239 (8.8%)	38 (7.8%)	5 (10.6%)	136 (10.6%)	35 (8.0%)	10 (4.3%)	8 (13.1%)	3 (5.4%)	4 (3.8%)
Unknown	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sex									
Female	1379 (50.8%)	232 (47.6%)	30 (63.8%)	618 (47.9%)	234 (53.3%)	131 (56.7%)	37 (60.7%)	25 (44.6%)	72 (67.9%)
Male	1334 (49.1%)	255 (52.4%)	17 (36.2%)	671 (52.1%)	205 (46.7%)	97 (42.0%)	24 (39.3%)	31 (55.4%)	34 (32.1%)
Not declared	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Self-reported race/ ethnicity[b]									
Parda	1347 (49.6%)	452 (92.8%)	0 (0.0%)	308 (23.9%)	406 (92.5%)	162 (70.1%)	19 (31.1%)	nc	nc
Blanco/Branca[c]	1005 (37.0%)	17 (3.5%)	9 (19.1%)	894 (69.4%)	33 (7.5%)	24 (10.4%)	28 (45.9%)	nc	nc
Asian	70 (2.6%)	0 (0.0%)	0 (0.0%)	55 (4.3%)	0 (0.0%)	15 (6.5%)	0 (0.0%)	nc	nc
Afrodescendiente/Preta[d]	65 (2.4%)	1 (0.2%)	7 (14.9%)	32 (2.5%)	0 (0.0%)	14 (6.1%)	11 (18.0%)	nc	nc
Mestizo	26 (1.0%)	0 (0.0%)	26 (55.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	nc	nc
Indigena	5 (0.2%)	0 (0.0%)	5 (10.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	nc	nc
Unknown	198 (7.3%)	17 (3.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (6.9%)	3 (4.9%)	nc	nc
Year									
2024	1666 (61.3%)	4 (0.8%)	9 (19.1%)	1250 (97.0%)	0 (0.0%)	231 (100.0%)	13 (21.3%)	56 (100.0%)	103 (97.2%)
2025	1050 (38.7%)	483 (99.2%)	38 (80.9%)	39 (3.0%)	439 (100.0%)	0 (0.0%)	48 (78.7%)	0 (0.0%)	3 (2.8%)
Type of case									
Autochthonous	2452 (90.3%)	486 (99.8%)	44 (93.6%)	1286 (99.8%)	439 (100.0%)	nc	35 (57.4%)	56 (100.0%)	106 (100.0%)
Travel-associated (internal)	33 (1.2%)	1 (0.2%)	3 (6.4%)	3 (0.2%)	0 (0.0%)	nc	26 (42.6%)	0 (0.0%)	0 (0.0%)
Unknown	231 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	nc	0 (0.0%)	0 (0.0%)	0 (0.0%)
Education									
No schooling	24 (0.9%)	0 (0.0%)	0 (0.0%)	17 (1.3%)	nc	nc	7 (11.5%)	nc	nc
Primary education	593 (21.8%)	106 (21.8%)	16 (34.0%)	464 (36.0%)	nc	nc	7 (11.5%)	nc	nc
Secondary education	920 (33.9%)	323 (66.3%)	16 (34.0%)	556 (43.1%)	nc	nc	25 (41.0%)	nc	nc
Postsecondary education	192 (7.1%)	0 (0.0%)	12 (25.5%)	159 (12.3%)	nc	nc	21 (34.4%)	nc	nc
Unknown	987 (36.3%)	58 (11.9%)	3 (6.4%)	93 (7.2%)	nc	nc	1 (1.6%)	nc	nc
Pregnant at time of OROV infection	108 (4.0%)	9 (1.8%)	2 (4.3%)	14 (1.1%)	9 (2.1%)	35 (15.2%)	5 (8.2%)	0 (0.0%)	34 (32.1%)
Gestational age (weeks)[e]	24 (16, 34)	22 (18, 30)	24 (24, 24)	34 (31, 35)	20 (16, 30)	25 (18, 33)	18 (14, 22)	–	27 (15, 35)
Pregnancy trimester[e]									
First trimester	13/108 (12.0%)	0 (0.0%)	0 (0.0%)	1/14 (7.1%)	1/9 (11.1%)	2/35 (5.7%)	1/5 (20.0%)	–	8/34 (23.5%)
Second trimester	26/108 (24.1%)	3/9 (33.3%)	1/2 (50.0%)	1/14 (7.1%)	4/9 (44.4%)	4/35 (11.4%)	4/5 (80.0%)	–	9/34 (26.5%)
Third trimester	37/108 (34.3%)	2/9 (22.2%)	0 (0.0%)	8/14 (57.1%)	4/9 (44.4%)	6/35 (17.1%)	0 (0.0%)	–	17/34 (50.0%)
Unknown	32/108 (29.6%)	4/9 (44.4%)	1/2 (50.0%)	4/14 (28.6%)	0 (0.0%)	23/35 (65.7%)	0 (0.0%)	–	0 (0.0%)

(Table 1 continues on next page)

Complications and outcomes

The overwhelming majority of participants (2542/2716; 94%) presented with uncomplicated OROV disease (Table 3). A total of 117/2716 (4%) reported suspected arthritis, while haemorrhagic manifestations were documented in 41/2716 (2%), including petechiae, vaginal bleeding, gingival bleeding, and epistaxis. Seven participants (0.3%) experienced severe disease temporally associated with OROV infection (case details in Table S4), including six with organ involvement; alternative causes could not be systematically excluded. Among these, two developed respiratory complications

	Overall N = 2716[a]	Ceará N = 487[a]	Darién N = 47[a]	Espírito Santo N = 1,289[a]	Paraíba N = 439[a]	Pernambuco N = 231[a]	Rio de Janeiro N = 61[a]	Amazonas N = 56[a]	Loreto N = 106[a]
(Continued from previous page)									
Comorbidities									
Any comorbidity	305 (11.2%)	1 (0.2%)	0 (0.0%)	222 (17.2%)	3 (0.7%)	34 (14.7%)	25 (41.0%)	13 (23.2%)	7 (6.6%)
Hypertension	255 (9.4%)	0 (0.0%)	0 (0.0%)	199 (15.4%)	3 (0.7%)	26 (11.3%)	16 (26.2%)	10 (17.9%)	1 (0.9%)
Diabetes Mellitus	89 (3.3%)	1 (0.2%)	0 (0.0%)	58 (4.5%)	1 (0.2%)	16 (6.9%)	8 (13.1%)	0 (0.0%)	5 (4.7%)
Immunosuppression	20 (0.7%)	0 (0.0%)	0 (0.0%)	10 (0.8%)	0 (0.0%)	2 (0.9%)	5 (8.2%)	1 (1.8%)	2 (1.9%)
Unknown comorbidity status	1090 (40.1%)	484 (99.4%)	43 (91.5%)	0 (0.0%)	431 (98.2%)	28 (12.1%)	0 (0.0%)	0 (0.0%)	104 (98.1%)
Co-infections	35 (1.3%)	0 (0.0%)	1 (2.1%)	2 (0.2%)	0 (0.0%)	25 (10.8%)	2 (3.3%)	5 (8.9%)	0 (0.0%)
Dengue	23 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (6.9%)	2 (3.3%)	5 (8.9%)	0 (0.0%)
Chikungunya	18 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (7.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Zika	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mayaro	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other co-infection	3 (0.1%)	0 (0.0%)	1 (2.1%)[f]	2 (0.2%)[g]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a]Data are in median (IQR) or n/N (%), unless specified otherwise. nc indicates variables that were not collected at specific sites. [b]In sites where data on ethnicity were available, it was self-reported by participants based on the census definitions used in each country (more details in Supplementary Appendix). [c]9 Blanco and 996 Branca. [d]7 Afrodescendiente and 58 Preta. [e]Data shown for cohort of pregnant women only (n = 108). [f]Malaria. [g]Sepsis of urinary origin.

Table 1: **Demographic and epidemiological characteristics stratified by site.**

with pleural effusion, one of whom progressed to acute respiratory failure. One participant developed acute hepatitis with liver failure and coagulopathy. Cardiac complications occurred in two participants (decompensated heart failure and arrhythmia). Three participants developed shock and one hypotension, all requiring intravenous (IV) fluids. Acute kidney failure occurred in two participants in the context of presumed septic shock of urinary origin (blood culture were negative in both cases, and urine culture grew ESBL *Klebsiella pneumoniae* in one case). Central nervous system involvement was observed in two participants: one presented with bilateral lower limb weakness that progressed to gait instability with inability to walk (CSF: white blood cells <5/µl, protein >45 mg/dl; negative for RPR, DENV, ZIKV, CHIKV, MAYV, *S. pneumoniae*, *N. meningitidis*, *H. influenzae*; OROV RT-PCR not done); and another developed agitation, disorientation, and confusion in the context of multiorgan failure (lumbar puncture not performed). Another participant presented severe headache and prostration requiring admission for management (lumbar puncture not performed). All participants with arthritis, haemorrhagic manifestations, or severe disease tested negative by RT-PCR for DENV, ZIKV, and CHIKV; except for one participant with epistaxis who had confirmed DENV co-infection.

Among 108 pregnant women with symptomatic OROV disease during pregnancy, pregnancy outcomes were available for 59 women with completed pregnancies at the time of analysis. Of these, 40 resulted in live births with no complications, four in live births with incomplete neonatal outcome data, and 15/108 (14%) had documented adverse pregnancy outcomes (Table 3). Adverse outcomes comprised three abortions (3%), one threatened preterm labour (TPL) (1%), three preterm births (3%), six stillbirths (6%), and two neonatal outcomes (one newborn with febrile illness, and one infant with Down syndrome who died 14 days after birth) (Fig. 3). No congenital malformations were reported among newborns with available assessment during the follow-up period. Except for the four virologically confirmed stillbirths and the symptomatic newborn, foetal or neonatal samples were not available for virological confirmation in the remaining cases. The three spontaneous abortions occurred during the first trimester following maternal infection at gestational weeks 6–8, with pregnancy loss occurring 3–14 days after symptom onset. Two of the three preterm births and the single TPL occurred in women infected during the third trimester, within seven days of symptom onset. Among the six stillbirths, four occurred in women infected during the third trimester, with foetal death documented within 10 days after maternal symptom onset. In all four cases, OROV RNA was detected post-mortem in multiple foetal tissues, placenta, and umbilical cord. The remaining two stillbirths occurred 15 and 27 weeks after maternal symptom onset and were linked to placental abruption and foetal distress in the context of a hypertensive peak, respectively; no virological confirmation was obtained from foetal tissues in these two cases. Regarding neonatal outcomes, one infant born at 38 weeks of gestation to a mother with OROV disease-compatible symptoms developed fever on day 3 of life that lasted three days. Neonatal RT-PCR was negative, but OROV IgM was detected at day 40 of life. Another case involved a 43-year-old woman with gestational diabetes and hypertension who acquired OROV infection at 32 weeks of gestation and delivered at 36 weeks an infant with Down syndrome who died 14 days after birth; this case remains under investigation. All pregnant women with adverse outcomes tested negative by RT-PCR for

	Overall N = 2716[a]	Ceará N = 487[a]	Darién N = 47[a]	Espírito Santo N = 1,289[a]	Paraíba N = 439[a]	Pernambuco N = 231[a]	Rio de Janeiro N = 61[a]	Amazonas N = 56[a]	Loreto N = 106[a]
Clinical presentation									
Fever	2413 (88.8%)	434 (89.1%)	37 (78.7%)	1142 (88.6%)	400 (91.1%)	195 (84.4%)	49 (80.3%)	56 (100.0%)	100 (94.3%)
Unknown	24 (0.9%)	1 (0.2%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	22 (9.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Headache	2389 (88.0%)	399 (81.9%)	37 (78.7%)	1177 (91.3%)	410 (93.4%)	187 (81.0%)	54 (88.5%)	54 (96.4%)	71 (67.0%)
Unknown	25 (0.9%)	1 (0.2%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	23 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Myalgia	1597 (58.8%)	19 (3.9%)	28 (59.6%)	1026 (79.6%)	400 (91.1%)	3 (1.3%)	48 (78.7%)	4 (7.1%)	69 (65.1%)
Unknown	231 (8.5%)	1 (0.2%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	228 (98.7%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Retro-orbital pain	1287 (47.4%)	368 (75.6%)	21 (44.7%)	679 (52.7%)	56 (12.8%)	52 (22.5%)	35 (57.4%)	35 (62.5%)	41 (38.7%)
Unknown	31 (1.1%)	1 (0.2%)	2 (4.3%)	0 (0.0%)	0 (0.0%)	27 (11.7%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Nausea	888 (32.7%)	68 (14.0%)	23 (48.9%)	598 (46.4%)	29 (6.6%)	86 (37.2%)	29 (47.5%)	7 (12.5%)	48 (45.3%)
Unknown	31 (1.1%)	1 (0.2%)	2 (4.3%)	0 (0.0%)	0 (0.0%)	27 (11.7%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Back pain	869 (32.0%)	3 (0.6%)	0 (0.0%)	674 (52.3%)	30 (6.8%)	93 (40.3%)	29 (47.5%)	nc	40 (37.7%)
Unknown	565 (20.8%)	479 (98.4%)	3 (6.4%)	0 (0.0%)	1 (0.2%)	26 (11.3%)	0 (0.0%)	nc	0 (0.0%)
Arthralgia	528 (19.4%)	83 (17.0%)	25 (53.2%)	244 (18.9%)	10 (2.3%)	69 (29.9%)	26 (42.6%)	2 (3.6%)	69 (65.1%)
Unknown	29 (1.1%)	1 (0.2%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	26 (11.3%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Vomiting	369 (13.6%)	95 (19.5%)	7 (14.9%)	151 (11.7%)	9 (2.1%)	31 (13.4%)	8 (13.1%)	15 (26.8%)	53 (50.0%)
Unknown	32 (1.2%)	1 (0.2%)	2 (4.3%)	0 (0.0%)	0 (0.0%)	28 (12.1%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Skin rash	151 (5.6%)	3 (0.6%)	6 (12.8%)	57 (4.4%)	0 (0.0%)	39 (16.9%)	28 (45.9%)	13 (23.2%)	5 (4.7%)
Unknown	506 (18.6%)	479 (98.4%)	2 (4.3%)	0 (0.0%)	0 (0.0%)	25 (10.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abdominal pain	65 (2.4%)	3 (0.6%)	8 (17.0%)	1 (0.1%)	0 (0.0%)	1 (0.4%)	12 (19.7%)	18 (32.1%)	22 (20.8%)
Unknown	1519 (55.9%)	1 (0.2%)	2 (4.3%)	1285 (99.7%)	0 (0.0%)	230 (99.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Diarrhoea	62 (2.3%)	7 (1.4%)	10 (21.3%)	1 (0.1%)	2 (0.5%)	nc	20 (32.8%)	19 (33.9%)	3 (2.8%)
Unknown	1519 (55.9%)	1 (0.2%)	1 (2.1%)	1285 (99.7%)	0 (0.0%)	nc	1 (1.6%)	0 (0.0%)	0 (0.0%)
Dizziness	50 (1.8%)	18 (3.7%)	3 (6.4%)	2 (0.2%)	2 (0.5%)	2 (0.9%)	nc	23 (41.1%)	0 (0.0%)
Unknown	1579 (58.1%)	1 (0.2%)	1 (2.1%)	1287 (99.8%)	0 (0.0%)	229 (99.1%)	nc	0 (0.0%)	0 (0.0%)
Number of symptoms[b]	4.00 (3.00, 5.00)	3.00 (2.00, 4.00)	5.00 (3.00, 8.00)	4.00 (3.00, 6.00)	4.00 (4.00, 4.00)	3.00 (2.00, 4.00)	8.00 (5.00, 10.00)	4.00 (3.00, 7.00)	5.00 (4.00, 6.00)
Overall duration of symptoms in days									
Median (Q1–Q3)	3 (2, 7)	2 (1, 3)	21 (15, 59)	9 (9, 9)	5 (5, 6)	nc	11 (7, 23)	12 (6, 28)	6 (5, 12)
Min-Max	0, 65	0, 14	7, 62	9, 9	5, 6	nc	0, 65	3, 48	5, 12
Unknown	2346	215	41	1288	436	231	3	29	103
OROV diagnosis									
Confirmed case	2687 (98.9%)	487 (100.0%)	41 (87.2%)	1289 (100.0%)	439 (100.0%)	228 (98.7%)	56 (91.8%)	56 (100.0%)	91 (85.8%)
Probable case	29 (1.1%)	0 (0.0%)	6 (12.8%)	0 (0.0%)	0 (0.0%)	3 (1.3%)	5 (8.2%)	0 (0.0%)	15 (14.2%)
Positive RT-PCR test	2660 (97.9%)	487 (100.0%)	41 (87.2%)	1289 (100.0%)	439 (100.0%)	228 (98.7%)	56 (91.8%)	29 (51.8%)	91 (85.8%)
Positive OROV-specific IgG serum		nc	14/47 (29.8%)	nc	nc	nc	0/61 (<0.1%)	nc	nc
Positive OROV-specific IgM serum		nc	29/47 (61.7%)	nc	nc	4/231 (1.7%)	18/61 (29.5%)	nc	18/106 (17.0%)
OROV-specific neutralising antibodies		nc	nc	nc	nc	nc	nc	41/56 (73.2%)	nc
Days from symptom onset to positive RT-PCR test									
Median (Q1–Q3)	2 (1, 3)	2 (1, 3)	1 (0, 2)	2 (1, 3)	2 (1, 3)	3 (2, 5)	4 (1, 6)	3 (2, 4)	1 (1, 3)
Min-Max	0, 42	0, 21	0, 31	0, 42	0, 29	2, 5	0, 11	0, 10	0, 10
Unknown	923	424	6	177	–	228	42	27	19
Laboratory results									
Elevated ALT	50/89 (56.2%)	nc	nc	3/3 (100.0%)	nc	nc	12/27 (44.4%)	32/55 (58.2%)	3/4 (75.0%)
Elevated haematocrit	8/98 (8.2%)	nc	nc	1/4 (25.0%)	nc	nc	0/27 (0.0%)	7/56 (12.5%)	0/11 (<0.1%)
Thrombocytopaenia	12/113 (10.6%)	nc	nc	1/1 (100.0%)	nc	nc	0/27 (0.0%)	8/56 (14.3%)	3/29 (10.3%)
Elevated creatinine	11/56 (19.6%)	nc	nc	0 (0.0%)	nc	nc	5/27 (18.5%)	6/29 (20.7%)	0 (0.0%)
Lymphopenia	16/64 (25.0%)	nc	nc	0/1 (<0.1%)	nc	nc	0 (0.0%)	11/56 (19.6%)	5/7 (71.4%)

[a]Data are in median (IQR) or n/N (%), unless specified otherwise. nc indicates variables that were not collected at specific sites. [b]Other symptoms only counted once.

Table 2: **Clinical presentation and laboratory findings stratified by site.**

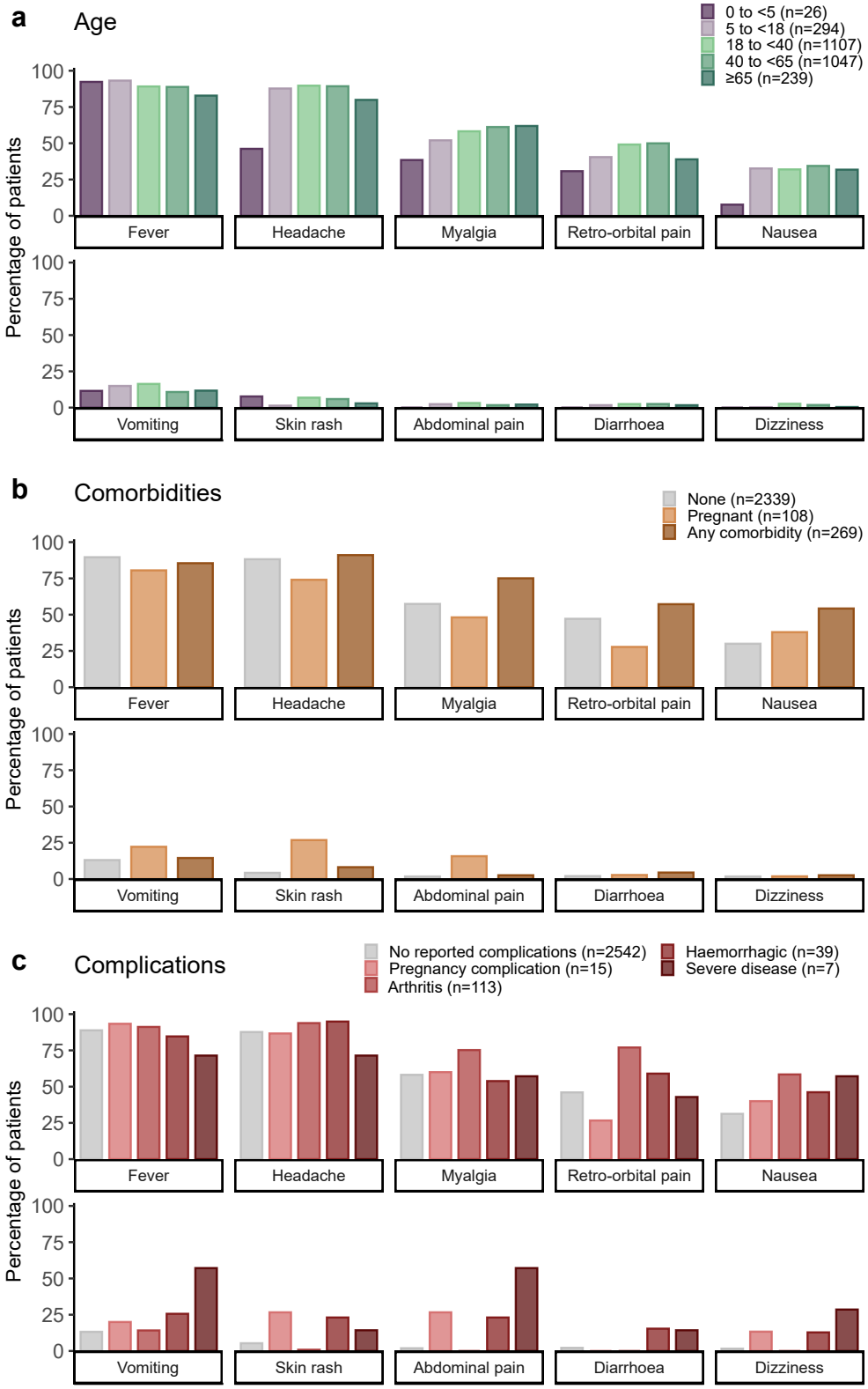


Fig. 2: **Symptoms stratified by age, comorbidities, and complications**. Symptoms of OROV cases stratified by age (a), presence of comorbidities (b), and complications (c). We categorised patients with more than one complication into the most severe form of complication (pregnancy complication, haemorrhagic, arthritis). Six patients with more than one complication were categorised as follows: 3 participants with arthritis and haemorrhagic complications as Haemorrhagic, 1 patient with arthritis and pregnancy complication as Pregnancy complication, 2 patients with haemorrhagic complications and pregnancy complications as Pregnancy complications.

	Overall N = 2716[a]	Ceará N = 487[a]	Darién N = 47[a]	Espírito Santo N = 1,289[a]	Paraíba N = 439[a]	Pernambuco N = 231[a]	Rio de Janeiro N = 61[a]	Amazonas N = 56[a]	Loreto N = 106[a]
Complications[b]									
Arthritis	117 (4.3%)	0 (0.0%)	0 (0.0%)	117 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haemorrhagic	41 (1.5%)	2 (0.4%)	1 (2.1%)	21 (1.6%)	0 (0.0%)	0 (0.0%)	4 (6.6%)	10 (17.9%)	3 (2.8%)
Epistaxis	1 (<0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)
Gingival bleeding	4 (0.1%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	2 (3.6%)	0 (0.0%)
Petechia	31 (1.1%)	1 (0.2%)	0 (0.0%)	21 (1.6%)	0 (0.0%)	0 (0.0%)	3 (4.9%)	6 (10.7%)	0 (0.0%)
Vaginal bleeding	5 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	3 (2.8%)
Severe disease temporally associated with OROV infection	7 (0.3%)	0 (0.0%)	0 (0.0%)	4 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	2 (2.8%)
CNS involvement[c]	2 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory complications	2 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Renal complications	2 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatic complications	1 (<0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac complications	2 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other complications[d]	4 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.9%)
No reported arthritis, haemorrhagic manifestations or severe disease	2554 (94.0%)	485 (99.6%)	46 (97.9%)	1149 (89.1%)	439 (100.0%)	231 (100.0%)	56 (91.8%)	46 (82.1%)	102 (96.2%)
Pregnancy outcomes									
Adverse pregnancy outcomes	15/108 (13.9%)	1/9 (11.1%)	0/2 (0.0%)	2/14 (14.3%)	2/9 (22.2%)	5/35 (14.3%)	0/5 (0.0%)	–	5/34 (14.7%)
Abortion	3/108 (2.8%)	0/9 (0.0%)	0/2 (0.0%)	1/14 (7.1%)	0/9 (0.0%)	1/35 (2.9%)	0/5 (0.0%)	–	1/34 (2.9%)
Stillbirth	6/108 (5.6%)	1/9 (11.1%)	0/2 (0.0%)	0/14 (0.0%)	1/9 (11.1%)	3/35 (8.6%)	0/5 (0.0%)	–	1/34 (2.9%)
Preterm	3/108 (2.8%)	0/9 (0.0%)	0/2 (0.0%)	1/14 (7.1%)	0/9 (0.0%)	0/35 (0.0%)	0/5 (0.0%)	–	2/34 (5.9%)
Symptomatic newborn	1/108 (0.9%)	0/9 (0.0%)	0/2 (0.0%)	0/14 (0.0%)	0/9 (0.0%)	1/35 (2.9%)	0/5 (0.0%)	–	0/34 (0.0%)
Newborn with microcephaly	0/108 (0.0%)	0/9 (0.0%)	0/2 (0.0%)	0/14 (0.0%)	0/9 (0.0%)	0/35 (0.0%)	0/5 (0.0%)	–	0/34 (0.0%)
Other[e]	2/108 (1.9%)	0/9 (0.0%)	0/2 (0.0%)	0/14 (0.0%)	1/9 (11.1%)	0/35 (0.0%)	0/5 (0.0%)	–	1/34 (2.9%)
Completed pregnancies with no complications	40/108 (37%)	5/9 (55.6%)	0/2 (0.0%)	8/14 (57.1%)	1/9 (11.1%)	1/35 (2.9%)	0/5 (0.0%)	–	25/34 (73.5%)
Completed pregnancies with live birth with incomplete neonatal data	4/108 (3.7%)	0/9 (0.0%)	0/2 (0.0%)	1/14 (7.1%)	0/9 (0.0%)	0/35 (0.0%)	0/5 (0.0%)	–	3/34 (8.8%)
Pregnancy with unknown outcome	49/108 (45.3%)	3/9 (33.3%)	2/2 (100.0%)	3/14 (21.4%)	6/9 (66.7%)	29/35 (82.9%)	5/5 (100.0%)	–	1/34 (2.9%)
Outcomes									
Highest care level									
Outpatient	2691 (99.1%)	486 (99.8%)	47 (100.0%)	1284 (99.6%)	439 (100.0%)	231 (100.0%)	59 (96.7%)	56 (100.0%)	89 (84.0%)
Hospitalisation in general ward	22 (0.8%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	0 (0.0%)	0 (0.0%)	2 (3.3%)	0 (0.0%)	17 (16.0%)
Intensive unit	2 (0.1%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	1 (<0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Organ support[f]									
Kidney replacement therapy	1 (<0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ventilated	1 (<0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Inotropic support	1 (<0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IV fluid	3 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
No reported organ support	2712 (99.9%)	487 (100.0%)	47 (100.0%)	1286 (99.8%)	439 (100.0%)	231 (100.0%)	61 (100.0%)	56 (100.0%)	105 (99.1%)

[a]Data are in median (IQR) or n/N (%), unless specified otherwise. nc indicates variables that were not collected at specific sites. [b]Complication categories are not mutually exclusive; individual participants may have more than one complication. [c]One agitation and one limb weakness. [d]Three shock and one severe headache. [e]One newborn with Down syndrome and death, and one threatened preterm labour (TPL) (33w) during OROV infection. [f]Organ support categories are not mutually exclusive; individual participants may have required more than one organ support.

Table 3: **Complications and outcomes stratified by site.**

DENV, ZIKV, and CHIKV and had confirmed OROV infection by serum RT-PCR, except one who was classified based on positive IgM. Negative investigations for TORCH infections (toxoplasma, syphilis, rubella, cytomegalovirus, herpes simplex virus), as well as HIV, HBV and HCV, were available for two of three women with abortion, five of six stillbirths, and the newborn with febrile illness; results for the remaining cases were

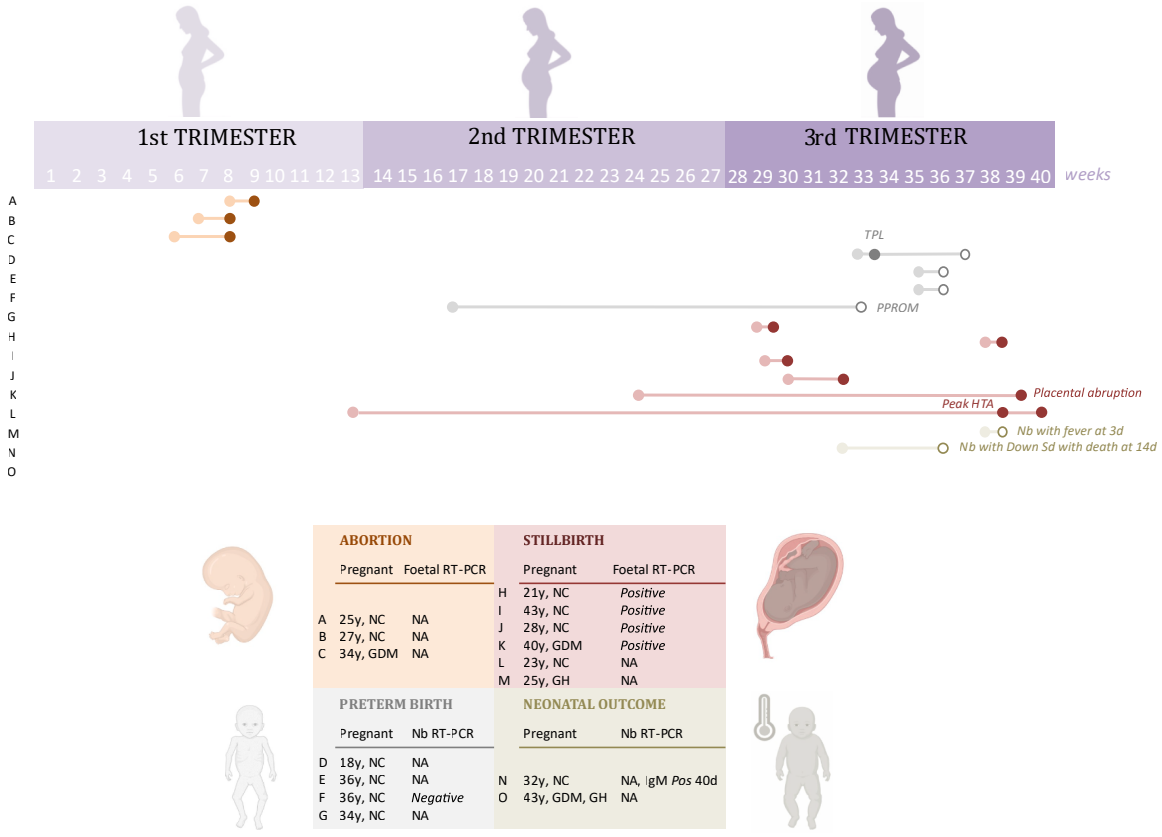


***Fig. 3:* Adverse pregnancy outcomes among pregnant women with symptomatic OROV disease during pregnancy**. Adverse pregnancy outcomes among pregnant women with symptomatic OROV disease during pregnancy, including abortions (orange), preterm births (grey), stillbirths (red), and neonatal outcomes (brown). Each case is represented by a unique letter. For each case, two points connected by a horizontal line indicate the gestational age at OROV disease presentation and at the time of the adverse outcome. A light-shaded closed point represents OROV disease, a dark-shaded closed point represents an adverse outcome, and an open point represents live birth. All pregnant women with adverse pregnancy complications were diagnosed by positive serum RT-PCR, except for I, who was diagnosed by IgM positive. Pregnant, Pregnant participant age and comorbidities; NA, Not available; NC, No comorbidities; GH, Gestational hypertension; GDM, Gestational Diabetes Mellitus; HTA, Hypertension; PPROM, Preterm Premature Rupture of Membranes; Sd, Syndrome; TPL, Threatened Preterm Labour; Nb, newborn.

unavailable or not performed. Details on all pregnant participants and their outcomes are provided in Table S5; site-specific and country-specific risks, including comparisons with DENV, ZIKV, and CHIKV, are presented in Table S6.

In a sub-cohort of participants with available haematology and biochemistry laboratory results, 8/98 (8%) had increased haematocrit levels, 12/113 (11%) had thrombocytopaenia, 16/64 (25%) presented with lymphopenia, 11/56 (20%) had elevated creatinine levels, and 50/89 (56%) had elevated alanine aminotransferase (ALT) (Table 2, Table S7).

Severe disease and adverse pregnancy outcomes were identified across most included sites, with no clear geographic clustering observed (Fig. 1, Table S1). Severe disease was more frequently observed among participants with comorbidities; adverse pregnancy outcomes were more common among women with diabetes (Fig. 4a, Table S8). The frequency of severe disease increased with age, particularly among participants aged 65 years or older (Fig. 4b). Participants with severe disease less often reported fever, headache, and retro-orbital pain, and more often presented with abdominal pain, vomiting, nausea, diarrhoea, dizziness, and rash; these symptoms were also more frequent among those with haemorrhagic manifestations. Pregnant women with adverse pregnancy outcomes more frequently reported abdominal pain, vomiting, nausea, and rash (Fig. 2c). When abdominal pain and vomiting were considered as warning signs (as in dengue), the presence of two warning signs was more frequent in participants with severe disease and, to a lesser extent, in those with haemorrhagic manifestations or adverse pregnancy outcomes (Fig. 4c). Participants with complications reported a higher overall number of symptoms, particularly those with

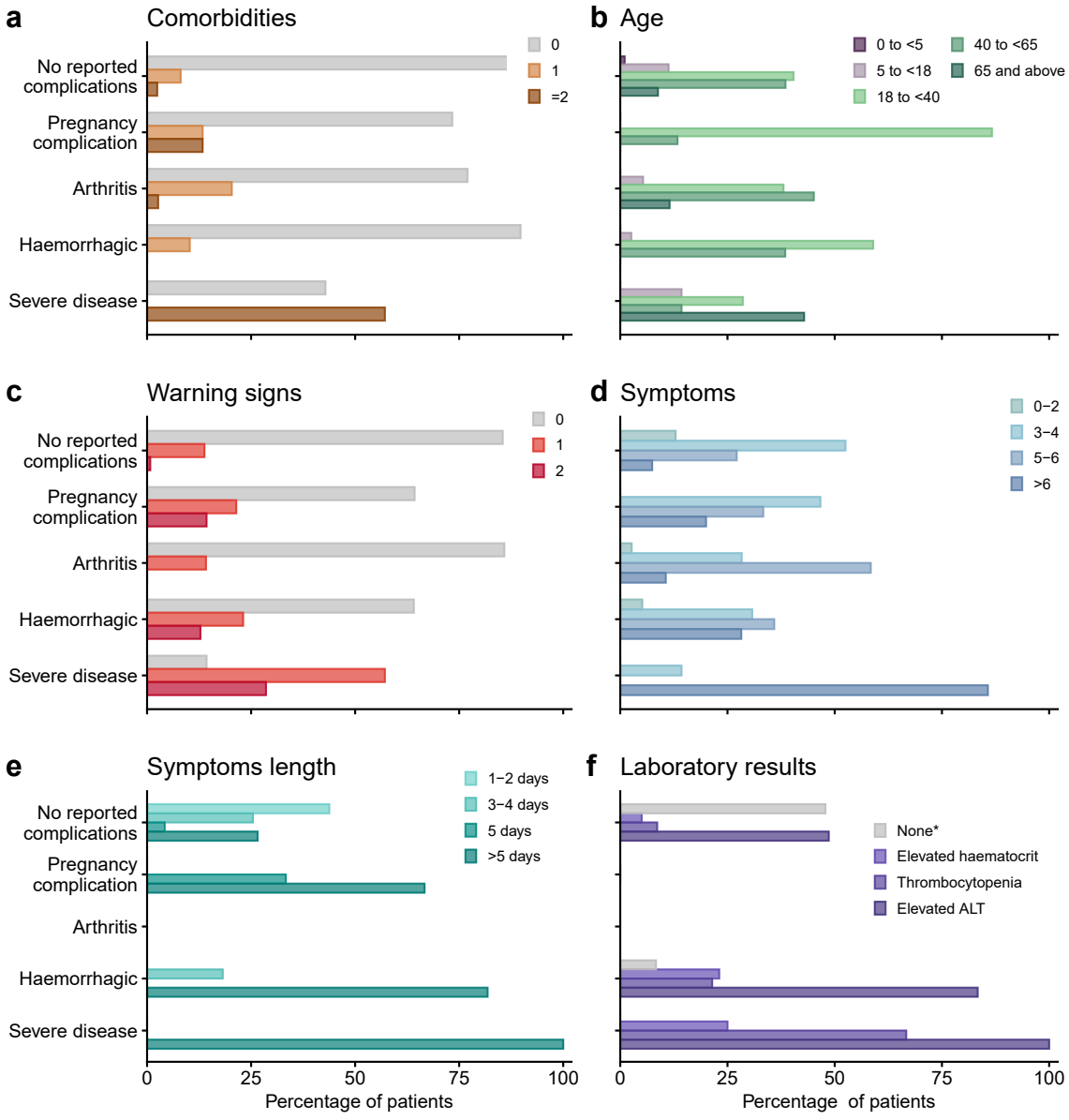


***Fig. 4:* Complications stratified by comorbidities, age, symptoms, and laboratory results**. Complications stratified by comorbidities (n = 2716) (a), age (n = 2713) (b), number of warning signs (i.e., abdominal pain, vomiting) (n = 2684) (c), number of symptoms (n = 2716) (d), length of symptoms (n = 270) (e), and laboratory results (f). In A-E, a complete-case subset of each variable of interest was used. The proportions in F are calculated as the number of participants having one of three laboratory abnormalities over those that had available test data for each abnormality in each complication stratum. The abnormalities are non-exclusive, as a patient could have had more than one laboratory abnormality. *Participants without elevated ALT, haematocrit or thrombocytopaenia, but who could have had another abnormal test result over the total number of participants with available data for all three tests. We categorised patients with more than one complication into the most severe form of complication (pregnancy complication, haemorrhagic, arthritis). Six patients with more than one complication were categorised as follows: 3 participants with arthritis and haemorrhagic complications as Haemorrhagic, 1 patient with arthritis and pregnancy complication as Pregnancy complication, 2 patients with haemorrhagic complications and pregnancy complications as Pregnancy complications.

severe disease, who frequently presented six or more concurrent symptoms (Fig. 4d). Overall symptom duration was longer among complicated cases (Fig. 4e); and laboratory abnormalities, including elevated haematocrit, thrombocytopaenia, and increased ALT, were more commonly observed among participants with severe disease and haemorrhagic complications (Fig. 4f).

Regarding outcomes, 99% of participants were managed in the outpatient setting, whereas 25 (1%) required hospital admission, including two admitted to the intensive care unit (ICU), and one who died (Table 3). Three participants required IV fluids, one required noradrenaline, one inotropic support with dobutamine, one kidney replacement therapy, and one required ventilatory support. The median length of hospital admission (including ICU) was 3 days (IQR 2–6; range 2–18), increasing to 8 days (IQR 6–16) among the 7 participants with severe disease, which falls within the range of administrative estimates reported for dengue and other arboviral disease admissions in Brazil during the same period (Table S9).

Virological features

Almost all participants (99%) were classified as confirmed cases, the majority based on a positive RT-PCR result; while the remaining 1% as probable cases based on a single positive IgM (Table 2). Among 1793 participants with available data, the median duration of symptoms at the time of positive diagnostic RT-PCR in serum was two days (IQR 1–3); 39 (2%) were positive beyond seven days, with a maximum of 42 days (Figure S5). Among 53 participants with urine RT-PCR, the median time to positivity was 14 days (IQR 8–25), with 42 (74%) being positive beyond seven days, and detection extending up to 49 days (Figure S6). The distribution of Ct values, used as a proxy for viral load and available for a subset of 1158 participants, did not show clear differences according to age (Figure S7), symptom duration (Figure S8), or complication status (Figure S9), when interpreted within the relevant assay and site. An exception was observed among stillbirths with virological confirmation, all of which had very low Ct values (<25), particularly in the brain. Median Ct values within the first 24 h after symptom onset ranged from 20.8 to 22.8 and progressively increased from day 2 to a median of 35.8 by day 6 (Figure S10, Table S10). Among a small number of RT-PCR-positive cases beyond day 7, low Ct values within the relevant assay and site were observed (Ct < 30) (Figure S11). Genomic data were available for six sites (except Paraiba and Loreto), with sequences clustering closely within the novel reassortant OROV lineage driving the 2023–2025 outbreak in the Americas (Table S11).

Discussion

This large multi-country case series describes 2716 Oropouche virus disease cases, including 108 pregnant women, identified during the 2023–2025 epidemic across ten states in Brazil, Panama, and Peru. These findings arise in the context of an unprecedented regional expansion of OROV into previously unaffected areas, raising concerns about an evolving clinical and epidemiological profile, potentially driven by viral evolution, as well as environmental, social, and ecological factors.[3,27] By including diverse populations across several countries substantially affected by the recent epidemic, our study provides the most comprehensive characterisation to date of the clinical spectrum, virological features, and characteristics more frequently observed among participants with complications during this recent epidemic.

The clinical presentation observed is consistent with previous descriptions,[8,9] with fever, headache, and myalgia as the most frequent symptoms, followed by retro-orbital pain and nausea. Importantly, our large and diverse cohort allowed identification of age-related differences that may inform clinical recognition: adults older than 65 years reported lower frequencies of fever, headache, and retro-orbital pain, whereas children more often presented with fever and rash. Although OROV disease is typically considered an acute illness resolving within a week, we observed prolonged symptom duration in a substantial proportion of participants, with one-fourth reporting symptoms beyond seven days and some persisting for up to 65 days. Further research into the average duration of each symptom, as well as the real frequency of biphasic disease with symptom recurrence,[28] and potential longer-term *sequelae* are warranted. Co-infections with other co-circulating arboviruses were identified, although likely underestimated, as OROV testing in many regions was restricted to dengue-negative cases. Together, these observations support the integration of OROV into multiplex diagnostic strategies in arbovirus-endemic settings and provide a more robust framework for differential diagnosis during outbreaks.

A relevant concern raised during the 2023–2025 epidemic was the increased clinical severity. Our findings are overall reassuring, as most cases were mild and self-limiting, with nearly all participants managed as outpatients. Nevertheless, severe manifestations and one death were documented. Haemorrhagic manifestations were non-severe and occurred in 2% of participants, a lower frequency than reported in previous outbreaks.[9,14] Severe disease temporally associated with OROV infection was rare (<1%), and included pleural effusion, respiratory failure, hepatic failure with coagulopathy, shock, and central nervous system involvement. Although causality cannot be definitely established, the clinical patterns observed resemble complications described in other reports of severe OROV disease and share similarities with features of severe dengue.[16,29,30] Neurological manifestations were uncommon, with only two cases identified, including one compatible with Guillain-Barré syndrome (GBS), and none of encephalitis. This contrasts with observations from Cuba, where markedly higher frequencies of OROV disease-associated GBS have been described,[31] as well as earlier reports of encephalitis.[10–12] Whether these differences reflect true spatiotemporal variation or

disparities in detection and reporting remains unclear. No consistent geographic clustering of severe manifestations was observed; however, interpretation is limited by the low frequency of severe outcomes and heterogeneity in study design, surveillance systems, diagnostic algorithms, and healthcare-seeking behaviour across sites. Overall, these findings indicate that although OROV disease is typically mild, severe and potentially life-threatening complications can occur, warranting continued clinical vigilance and strengthened surveillance, particularly in the absence of licenced vaccines, antivirals, or routine surveillance systems for OROV.

The OROV 2023–2025 epidemic has also raised important concerns regarding infection during pregnancy.[17,18] In this largest reported series of pregnant women with symptomatic OROV disease, adverse pregnancy outcomes were documented in 15 of 108 cases, including spontaneous abortions (3%), preterm births (3%), stillbirths (6%), and symptomatic newborns (2%). Four stillbirths and one symptomatic newborn had virological confirmation, whereas the remaining adverse outcomes lacked foetal or neonatal virological confirmation. We did not observe congenital malformations among newborns with available assessment during the follow-up period, in contrast to other reports suggesting congenital syndromes potentially linked to OROV vertical transmission.[17,19] Outcomes appeared to vary by gestational age at infection, with first-trimester infections associated with abortions, and third-trimester infections linked to preterm births, stillbirths, and possible intrapartum transmission with neonatal clinical manifestations. Increased risk of foetal loss, premature birth, neonatal disease, and congenital malformations has been associated with other arboviral diseases during pregnancy, with highly variable prevalence across specific viruses and studies.[32–36] The highest risks have been reported for preterm birth in DENV, CHIKV, and ZIKV infections (10–27%); followed by foetal loss in DENV and CHIKV (2–20%); and congenital malformations, particularly microcephaly, in ZIKV infection (1.5–3%).[32–36] Our findings extend the available evidence and highlight a clinically relevant spectrum of maternal–foetal complications observed among individuals with OROV infection during pregnancy; however, interpretation should be cautious given the potential overrepresentation of adverse outcomes, the inclusion of symptomatic OROV infections only, the absence of systematic foetal or neonatal virological confirmation and testing for other pathogens, the variability in the completeness and duration of foetal and neonatal follow-up, and the lack of a comparison group. Further controlled and prospective studies are needed to determine the true frequency of these events, assess whether they exceed expected background rates, and better characterise the potential causal role of OROV infection during pregnancy. Nevertheless, the frequency and diversity of adverse outcomes observed in this series highlight a clinically relevant signal that warrants further investigation.

We also identified characteristics more frequently observed among participants with complications not previously assessed. Older age and pre-existing comorbidities were markedly more common among participants with severe disease, while diabetes was more frequent among women with adverse pregnancy outcomes. Clinically, higher symptom burden, and longer duration were more frequently observed in participants with haemorrhagic and severe complications, as were features commonly considered warning signs in other arboviral diseases, particularly dengue, including abdominal pain, vomiting, and other symptoms such as nausea, diarrhoea, dizziness, and rash. Laboratory abnormalities, including thrombocytopaenia, elevated haematocrit, and increased ALT, were also more frequent in these patients. By contrast, Ct values, used as a proxy for viral load, did not show relevant differences according to complications, symptom duration, or age, when interpreted within the relevant assay and site. An exception was observed among four stillbirths with virological confirmation, in which very low Ct values were detected in foetal tissues, particularly in the brain, suggesting high viral burden in these cases. However, interpretation of Ct values is inherently limited by variability in timing of sample collection, specimen type, and RT-PCR platforms across sites, which may limit comparisons between groups. Our findings have implications for current diagnostic approaches, which recommend RNA detection in serum during the first week of illness. Although RT-PCR positivity in serum peaked early (median two days from symptom onset), we detected OROV RNA in serum beyond seven days in 39 participants, all but one being immunocompetent, with some samples showing significant viral loads (Ct values below 30). Prolonged RNA detection was observed for up to 42 days in serum and 49 days in urine. As testing in several sites was restricted to the first 5–7 days of illness, prolonged RNA detection may be more common than captured in our data. These findings extend previous reports of prolonged RT-PCR positivity,[37,38] albeit with higher Ct values. Although replication competence could not be assessed, our results raise important questions regarding the duration of viral shedding and infectiousness. Extending the diagnostic window beyond the first week, particularly by incorporating urine, as implemented for other arboviruses such as Zika, could improve diagnostic yield in later stages of disease. Further longitudinal studies are needed to characterise viral shedding across biological compartments and define its implications for transmission and public health policy.

Several limitations of our study must be highlighted. First, our dataset is subject to selection and information

biases due to heterogeneous data sources, data availability and reporting, variable diagnostic practices across sites, and inclusion of symptomatic and care-seeking individuals only, which may have affected the ascertainment and comparability of findings. The geographic distribution of cases overlapped with areas reporting the highest OROV burden according to surveillance data; however, reported incidence is likely influenced by heterogeneous surveillance and access to testing, as suggested by discrepancies between reported and modelled risk estimates.[39] Second, variability in follow-up limited our ability to comprehensively assess symptom duration (including individual symptoms), symptom recurrence and long-term outcomes across all participants. Third, the absence of data from other affected countries, including Cuba, Colombia, and Bolivia, may have restricted our ability to fully capture the spectrum of severe disease, including neurological involvement. Fourth, the combination of incomplete genomic coverage and limited lineage diversity precluded lineage-stratified analyses of clinical presentation and disease severity. Finally, the inclusion of only OROV cases precluded direct comparison with co-circulating arboviruses, such as dengue, to support differential diagnosis.[40]

In this large multi-country case series across Latin America, Oropouche virus disease during the 2023–2025 epidemic was predominantly mild and self-limiting, but severe disease with organ involvement and adverse pregnancy outcomes were observed. We identified older age, comorbidities, clinical warning signs, and laboratory abnormalities (thrombocytopaenia and elevated haematocrit and liver enzymes) as characteristics more frequently observed among participants with complications. We also documented prolonged symptom duration and viral RNA detection in serum and urine. Clinicians in regions with arbovirus circulation should consider the diagnosis of OROV disease in patients with prolonged febrile illness, particularly in the presence of warning signs such as abdominal pain or vomiting, and in high-risk groups, including older adults with comorbidities and pregnant women. In addition to clinical assessment, basic haematology and biochemistry testing may support early risk stratification and guide hospital admission decisions. Testing algorithms incorporating both serum and urine should be considered to extend the diagnostic window beyond the first week of illness and improve case detection. Additional research into viral kinetics and determinants of severity is necessary to inform diagnostic and management strategies for this re-emerging arboviral disease.

Contributors

AA, QB, MPM, and OR conceived and designed the study. AA, MPM, OR, and QB coordinated the global collaboration. AA and FV managed the global data collection. AA, MPM, FV developed the case report form. FV and AA analysed, interpreted, and vouch for the data. All authors except AA, FV, BB, QB, and OR, submitted cases. AA, FV, MPM, OR, and QB wrote the first draft of the manuscript. All authors reviewed the manuscript and vouched for the accuracy and completeness of the data. All authors were responsible for the final decision to submit for publication and have seen and approved the manuscript. AA and FV had full access to all data.

Data sharing statement

De-identified participant data collected, including individual participant data, will be made available on reasonable request to the corresponding author. All scripts that were generated for data wrangling, analysis, and plotting are publicly available on an online repository (https://github.com/fiovialard/orov_out).

Declaration of interests

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2026.101678.

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