3. CLINICAL

3A. Clinical Presentation of Acute Disease

Following the bite of a mosquito infected with CHIKV, most individuals will present with symptomatic disease after an incubation period of 3-7 days (range: 1-12 days). However, not all individuals infected with the virus develop symptoms. Serosurveys indicate that 3 to 28% of persons with antibodies to CHIKV have asymptomatic infections[6, 7]. Individuals acutely infected with CHIKV, whether clinically apparent or asymptomatic, can contribute to the spread of the disease if the vectors that transmit the virus are present and active in the same location.

CHIKV can cause acute, subacute, and chronic disease. Acute disease is most often characterized by sudden onset of high fever (typically greater than 102°F [39°C]) and severe joint pain[8-10]. Other signs and symptoms may include headache, diffuse back pain, myalgias, nausea, vomiting, polyarthritis, rash, and conjunctivitis (Table 1)[11]. The acute phase of CHIK lasts for 3-10 days.

Table 1. Frequency of Acute Symptoms of CHIKV Infection[a]

Symptom or Sign	*Frequency Range (% of symptomatic patients)*
Fever	76-100
Polyarthralgias	71-100
Headache	17-74
Myalgias	46-72
Back Pain	34-50
Nausea	50-69
Vomiting	4-59
Rash	28-77
Polyarthritis	12-32
Conjunctivitis	3-56

[a] Table compiled from a number of different studies[8, 9, 11-17]

- Fever typically last from several days up to a week. The fever can be continuous or intermittent; however a drop in temperature is not associated with worsening of symptoms. Occasionally, the fever may be associated with relative bradycardia.
- Joint symptoms are usually symmetric and occur most commonly in hands and feet, but they can affect more proximal joints. Swelling can also be seen and is often associated with tenosynovitis. Patients are often severely incapacitated due to pain, tenderness, swelling, and stiffness. Many patients are unable to perform normal tasks or go to work and many will be confined to bed due to these symptoms.
- Rash usually occurs 2 to 5 days after onset of fever in approximately half of all patients. It is typically maculopapular, involving the trunk and extremities, but can also include palms, soles, and face. The rash can also present as a diffuse erythema that blanches with pressure. In infants, vesiculobullous lesions are often the most common skin manifestation.

There are no significant pathognomonic hematologic findings seen with CHIKV infections. Abnormal laboratory findings can include mild thrombocytopenia (>100,000/mm^3), leukopenia, and elevated liver function tests. Erythrocyte sedimentation rate and C-Reactive Protein are usually elevated.

Rarely, severe forms of the disease can occur with atypical manifestations (see below). Fatalities related to CHIKV infection are thought to be uncommon.

However, an increase in crude death rates has been reported during the 2004-2008 epidemics in India and Mauritius[18, 19].

3B. Atypical Manifestations

Although most CHIKV infections result in fever and arthralgias, atypical manifestations can occur (Table 2). These manifestations can be due to the direct effects of the virus, immunologic response to the virus, or drug toxicity.

Table 2: Atypical Manifestations of CHIKV Infection

System	*Clinical Manifestations*
Neurological	Meningoencephalitis, encephalopathy, seizures, Guillain-Barré syndrome, cerebellar syndrome, paresis, palsies, neuropathy.
Ocular	Optic neuritis, iridocyclitis, episcleritis, retinitis, uveitis
Cardiovascular	Myocarditis, pericarditis, heart failure, arrhythmias, hemodynamic instability
Dermatological	Photosensitive hyperpigmentation, intertriginous aphthous-like ulcers, vesiculobullous dermatosis
Renal	Nephritis, acute renal failure
Other	Bleeding dyscrasias, pneumonia, respiratory failure, hepatitis, pancreatitis, SIADH, hypoadrenalism

Adapted from Rajapakse et al. [20]

Certain atypical manifestations are more in common in certain groups. For instances meningoencephalitis and vesiculobullous dermatosis are observed more frequently in children and infants, respectively[21, 22].

3C. High Risk Groups

CHIKV can affect individuals of all ages and sexes. However, clinical presentation is thought to vary by age with very young (neonatal) and older age noted as a risk factor for more severe disease[23-26]. In addition to age, comorbidities (underlying diseases) have also been identified as risk factor for poor disease outcome[8, 23, 24, 27].

Most CHIKV infections that occur during pregnancy will not result in the virus being transmitted to the fetus[25, 28]. There are, however, rare reports of spontaneous abortions following maternal CHIKV infection[26]. The highest transmission risk appears to be when women are infected during the intrapartum period[29]. The vertical transmission rate is as high as 49% during this period. Infants are typically asymptomatic at birth and then develop fever, pain, rash, and peripheral edema. Those infected during the intrapartum period may also develop neurologic disease (e.g., meningoencephalitis, white matter lesions, brain swelling, and intracranial hemorrhage), hemorrhagic symptoms, and myocardial disease[30]. Laboratory abnormalities included raised liver function tests, reduced platelet and lymphocyte counts, and decreased prothrombin levels. Neonates who suffer from neurologic disease often develop long-term disabilities[31]. There is no evidence that the virus is transmitted through breast milk[25].

Older adults are more likely to suffer from severe atypical disease and death. Individuals >65 years had a 50-fold higher mortality rate when compared to younger adults (<45 year old)[23]. Although it is unclear why older adults are at

increased risk for more severe disease, it may be due to the frequency of concomitant underlying diseases or decreased immunlogic response[23].

3D. Differential Diagnosis

Fever with or without arthralgia is a very common manifestation of several other diseases. CHIK may not have the typical manifestations or it may co-exist with other infectious diseases like dengue fever or malaria. Diseases that can be considered in the differential diagnoses may vary based on pertinent epidemiologic features such as place of residence, travel history, and exposures (Table 3).

Table 3: Diseases or Agents in the Differential Diagnosis of CHIK

Disease or agent	***Presentation***
Malaria	Periodicity of fever and alteration of consciousness
Dengue Fever	Fever and two or more of the following, retro-orbital or ocular pain, headache, rash, myalgia, arthralgia, leucopenia, or hemorrhagic manifestations. See section and table below for more information on dengue.
Leptospirosis	Severe myalgia localized to calf muscles with conjunctival congestion/ or subconjunctival hemorrhage with or without jaundice or oliguria. Consider history of contact with contaminated water.
Alphaviral infections (Mayaro, Ross River, Barmah Forest, O'nyong nyong, and Sindbis viruses)	Similar clinical presentation as CHIK; utilize travel history and known areas of Mayaro in the Americas

Post-infectious arthritis (including rheumatic fever)	Arthritis of one or more, typically larger joints due to an infectious disease such as Chlamydia, shigella, gonorrhea, among others. Rheumatic fever (RF) is seen more commonly in children as migratory polyarthritis predominantly affecting large joints. Consider ASO titer and history of sore throat with Jones criteria for RF.
Juvenile rheumatoid arthritis	Abrupt onset of fever and subsequent joint involvement in children.

Overlap and confusion with dengue fever:

CHIK has to be distinguished from dengue fever which has the potential for much worse outcomes, including death. The two diseases can occur together in the same patient. Observations from previous outbreaks in Thailand and India have characterized the principal features distinguishing CHIK from dengue fever. In CHIK, shock or severe hemorrhage is very rarely observed; the onset is more acute and the duration of fever is much shorter. Also in CHIK, maculopapular rash is more frequent than in dengue fever (Table 4). Although people may complain of diffuse body pain, the pain is much more pronounced and localized to the joints and tendons in CHIK in comparison of dengue fever.

Table 4. Comparison of the Clinical and Laboratory Features of Chikungunya and Dengue Virus Infections[1]

Clinical and Laboratory Features	***Chikungunya virus infection***	***Dengue virus infection***
Fever (>102°F or 39°C)	+++	++
Myalgias	+	++
Arthalgias	+++	+/-
Headache	++	++[2]
Rash	++	+

Bleeding dyscrasias	+/-	++
Shock	-	+
Leukopenia	++	+++
Neutropenia	+	+++
Lymphopenia	+++	++
Elevated HCT	-	++
Thrombocytopenia	+	+++

[1] Mean frequency of symptoms from studies where the two diseases were directly compared among patient seeking care; +++ = 70-100% of patients; ++ = 40-69%; + = 10-39%; +/- = <10%; - = 0% [32, 33]
[2] Often retroorbital
Table modified from Staples et al.[34]

3E. Subacute and Chronic Disease

After the first 10 days, most patients will feel an improvement in their general health and joint pain. However following this period, a relapse of symptoms can occur with some patients complaining of various rheumatic symptoms, including distal polyarthritis, exacerbation of pain in previously injured joints and bones, and subacute hypertrophic tenosynovitis in wrists and ankles. This is most common two to three months after their illness onset. Some patients can also develop transient peripheral vascular disorders, such as Raynaud's syndrome. In addition to physical symptoms, majority of patients will complain of depressive symptoms, general fatigue, and weakness[13].

Chronic disease is defined by symptoms persisting more than three months. The frequency of persons reporting persistent symptoms varies substantially by study and the amount of time that had elapsed between symptom onset and follow-up. Studies from South Africa note that 12-18% of patients will have persistent symptoms at 18 months up to two to three years later[35, 36]. From more recent studies in India, the proportion of patients with

persistent symptoms at 10 months was 49%[37]. Data from La Réunion have found as many as 80-93% of patients will complain of persistent symptoms three months after disease onset; this decreases to 57% at 15 months and 47% at 2 years[38, 39] (F. Simone, Dept of Infectious Diseases and Tropical Medicine, Laveran Military Hospital, Pais, France, *personal communication*).

The most common persistent symptom is inflammatory arthralgias in the same joints that were affected during the acute stages. Usually, there is no significant change in laboratory tests and x-rays of the affected areas. However, some individuals will go onto develop destructive arthropathy/arthritis resembling rheumatoid or psoriatic arthritis[40]. Other symptoms or complaints of the chronic phase of the disease can include fatigue and depression[6]. Risk factors for non-recovery are older age (> 45 years), pre-existing joint disorders, and more severe acute disease[38, 41].

Summary of Clinical ***Section***

- Acute stage is symptomatic in most people and causes acute fever, distal polyarthralgias, and occasional rash
- Severe and lethal forms are more frequent among patients older than 65 years and/or with underlying chronic diseases
- Maternal-fetal transmission is possible among pregnant women with the highest risk for severe infection in the neonates during the antepartum period.
- Most patients initially will have severe and incapacitating joint symptoms; many will go on to develop long-lasting rheumatism, fatigue, and depression resulting in an impaired quality of life for months to years