CLINICAL MANAGEMENT OF CHIKUNGUNYA FEVER

Guideline for Health Facilities in Maldives

2019
Health Protection Agency, Maldives

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Contents

Preface

Chikungunya was first described in Maldives in 2006. Ever since it has been present with periodical increase. In 2019 there is a significant rise in chikungunya cases effecting all age groups including newborns. This is the first time the country is facing an outbreak of this magnitude. Factors such as global warming creates a suitable environment in the temperate regions increasing the longevity of the mosquitos. Chikungunya is on the rise worldwide with wide spread of increased population of its vector Aedes mosquitoes[96].

The morbidity of chikungunya is very high. It has a high socioeconomic burden with lost working days and school days.

Chikungunya does not have a specific treatment. It could be quite new for many doctors especially those new expatriate medical professionals.

The major preventive method for chikungunya is removing mosquito breeding sites. There is no vaccine available for chikungunya.

The authors of this national guideline for chikungunya, were selected according to their clinical experience of chikungunya infection and/or expertise in the following fields: pediatrics, internal medicine, dermatology, physiotherapy and rehabilitation, tropical and travel medicine.

With this guideline I hope that health professionals will be able to manage chikungunya cases to decrease morbidity by providing the best evidence-based treatment available in their facilities.

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Introduction

The word chikungunya which means “that which bends up” comes from the Bantu language of the Makonde ethnic group where an outbreak occurred five decades ago in a province called Makonde, south of Tanzania bordering Mozambique. After this the virus was called chikungunya virus (CHIKV) which uses humans as an amplifying host and mosquitoes to transmit the virus during outbreaks causing an acute febrile undifferentiated illness in humans in the tropical region[1,95]. It is considered a neglected tropical disease and a zoonosis in Africa and Asia[98].

At present, there are no a commercially available approved vaccine or an approved therapeutic drug against the CHIKV. Prevention is by removing mosquito breeding sites and interrupting the spread of infection from human to mosquito by bite precautions.

Primary management of chikungunya involves symptomatic supportive management and can be managed at all health facilities. Individuals with atypical manifestations should be referred to the closest atoll or regional hospital. In severe cases where organ impairment is severe or worsening, the management must be at a tertiary care hospital with an intensive care unit that has facilities equipped for mechanical ventilation, dialysis, and access to blood products. Majority of patients require additional therapeutics such as anti-rheumatics, steroids, immune regulator and biologics to manage the persisting symptoms. Steroids and nonsteroidal anti-inflammatory drugs should not be used in the acute phase.

With the evolving nature of CHIKV, the recent observations during the 2019 outbreak in Maldives mirrors the protean nature of the virulence of the virus. Most of the individuals who are a higher risk of prolonged morbidity are individuals with underlying condition, such as diabetes or suffer from chronic kidney disease, chronic obstructive respiratory diseases and heart diseases. In these individuals CHIKV exacerbates the underlying condition[2].

The systemic manifestations of CHIKV infection can be similar to any other viral infections such as dengue, zika, japanese encephalitis, influenza, HIV, measles, rubella, enteroviruses and human herpes viral infections. Other microorganisms which should be considered in an individual with an acute febrile undifferentiated illness includes salmonellosis, rickettsiosis, scarlet fever and malaria. Emerging viral hemorrhagic pathogens such as Ebola virus or Lassa virus including meningococcemia, and respiratory pathogens such as Middle East Respiratory Syndrome Corona virus (MERS Co-V), the avian influenza

viruses and encephalitis causing viruses such as Nipah virus, Rabies virus and Polio virus should be considered when travel history is suggested from an individual returning from regions where these pathogens are endemic.

Clinicians are frequently challenged when they are faced with an individual with an acute febrile undifferentiated illness without having a focus of infection or a system involved. Facing this challenge is to aggregate careful history taking and good clinical examination. History should include recent travel history to disease endemic regions and the exposure history to caves, scrubs, forest, jungle, rivers, floods, animals (mammals: bats, rodents, camels, dogs, cats) dead poultry and pigs, unprotected sex, gay sex, getting tattoos, intravenous drug use, animal bites and the recent exposure to a sick individual. Obtaining a complete history and clinical examination with careful timely utilization of the available resources can guide to a clinical diagnosis.

Causative agent

Chikungunya virus (CHIKV) is an icosahedral shaped, enveloped, single stranded positive sense RNA virus that belong to alphavirus from *Togaviridae* family, a BSL3 pathogen. It is virulent in vitro with an early highly cytopathic effect known for its neuro-tropism, arthritogenicity[90] and protean to exacerbate comorbidities increasing morbidity.

The chikungunya virus measures 70nm in size and the structure is composed of structural proteins (E1, E2, E3, 6k), capsids (C) and non-structural proteins (NS1-4). Some of the identified functions of these structural proteins include virus attachment, membrane fusion as well as budding of new virions, whereas the non-structural proteins are involved in RNA replication. The CHIKV displays tropisms to numerous cells and organs including muscles, joints and the skin[4].

The virus enters muscles and skin by receptor mediated endocytosis[3] facilitated by the cell binding of the E2 glycoprotein, even though the cellular receptors involved in CHIKV entry have not yet been fully elucidated, some of receptors such as Prohibitin 1 (PBH1) a multifunctional membrane protein expressed by numerous cell types[5] and cell adhesion molecule Mxra8[6], in vitro reduced infection was associated by inhibiting these receptors. New data demonstrates viremia in CHIKV preceded the onset of fever by 6 days[7,97]. Peaking viremia is often at the onset of fever with the viral load ranging from $10x^7$ -$10x^9$ copies/mL[8]. The average duration of viremia is 6 days but detectable viremia 13 days after the onset of symptoms have been reported[8,91].

Data related to the persistence of CHIKV in other bodily fluids are currently scarce and all necessary preventive measures should be taken in preventing infection through inhalation of aerosolized CHIKV in a laboratory setting while handling clinical specimens. The virus is inactivated at temperatures > 58^0C, and to other inactivation and decontamination techniques (ultraviolet light, nano-filteration, 70% ethanol, hypochlorite).

Invertebrate vectors and vertebrate hosts

The CHIKV infection is a zoonosis and the virus is maintained in inter-epidemics by the sylvatic (jungle) cycle similarly as the yellow fever virus (YFV) and an urban transmission cycle (epidemic cycle). The sylvatic cycles occur in regions where population of non-human primates thrive in Africa, Asia and South America[86]. No data exists suggesting a presence of a zoonotic origin of CHIKV in Maldives. Bat species and rodents are mammals found in the Maldives that appear to be potential reservoir for the CHIKV and other encephalitic viruses. Epidemics of CHIKV in Maldives are speculated to be through an introduction of virulent travelers and mosquito potentiate the transmission domestically.

Female *Aedes Aegypti* and *Aedes Albopictus* are the principle mosquito species (spp.) functioning as competent vectors in transmitting the CHIKV while other mosquito species such as *Cluex* (spp.), *Anopheles* (spp.) and *Mansonia* (spp.) can be infected with CHIKV[4]. The introduction of CHIKV to *Aedes Albopictus* also known as the “Asian Tiger Mosquito” identified by the striped patterned body, is now considered the main vector for the urban cycle, which adapted through a mutation in one of the viral glycoproteins. These are very domesticated mosquitoes and usually bite indoors and are usually found to be present around people with movements and nesting limited with 100-400 meters of where they are found.

The other mosquito (spp.) and especially male mosquitoes are found in areas with plants and vegetation, these mosquitoes are usually most active during hours of dusk and during dawn. Human blood is used for development of its reproductive process of the female mosquito (spp.) During this period CHIKV is transmitted from a viremic individual to the mosquito. *Aedes Aegypti* is known to bite multiple humans while feeding, these mosquitoes rest in cool dark areas such as under tables, sink, shoes and lays eggs in water collected in reservoirs in and around the house.

The CHIKV can be vertically transmitted in mosquito and the eggs are robust and survives up to one year or longer in suitable dry conditions. After rainfall, even small volumes of water accumulated in discarded bottle caps, containers (cans, bottles) and even used coconuts shells are suitable reservoirs where mosquitos lay eggs. Domestic breeding sites include roof gutters, tanks and containers where water can be stagnant and is accessible to mosquitoes.

The mosquito life cycles is usually 7 days or less with suitable conditions and their life spans ranges from 4-8 weeks at optimum condition. *Aedes Albopictus* mosquitoes have the ability to deliver more than a single arbovirus in their saliva, raising the possibility of simultaneous transmission of the viruses[9,10]. Other mosquito (spp.) which exists in the Maldives are mosquitos of the *Culex* (spp.) and the *Mansonia* (spp.). *Anopheles* (spp.) are considered to be eradicated with no autochthonous transmission of malaria, however the risk still exist of the re-introduction of malaria (urban malaria) transmitted by the *Anopheles Stephensii.*

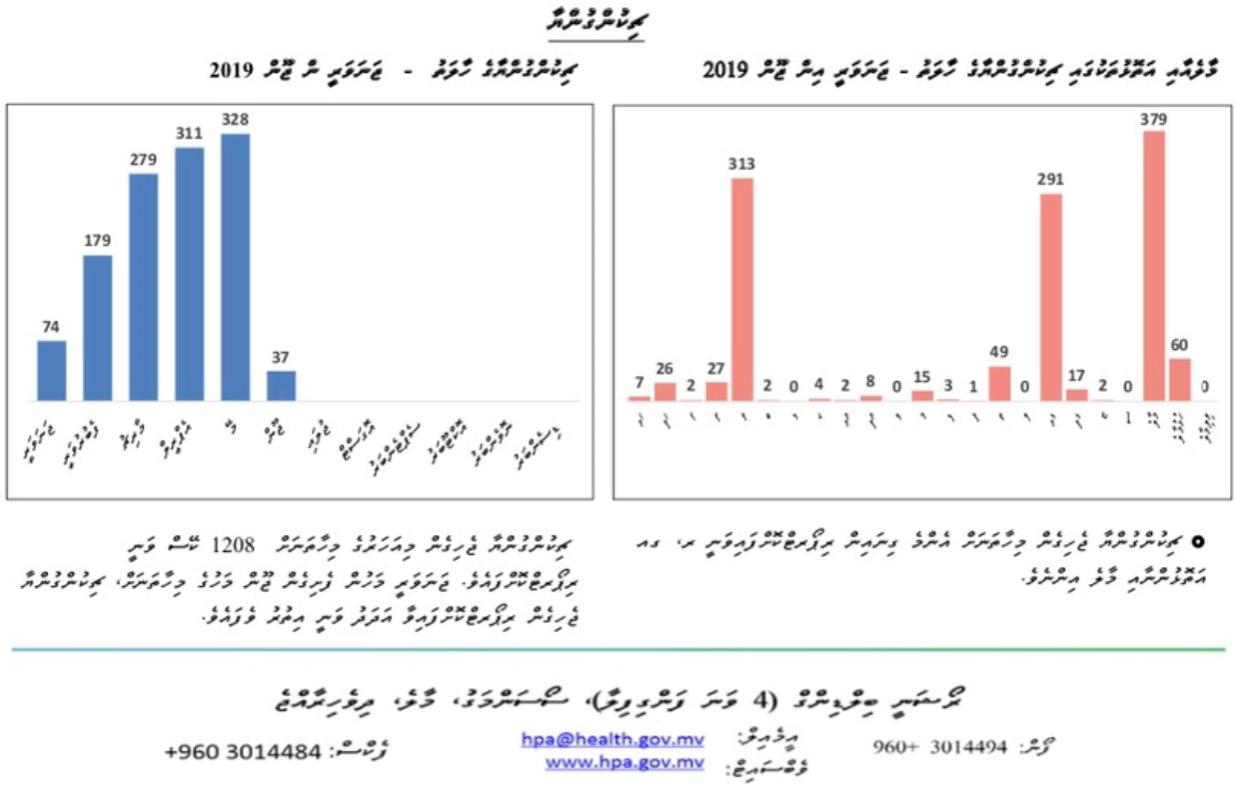
During urban outbreaks humans serve as an amplifying host and in the introduction to islands with CHIKV naïve populations. The CHIKV is also vertically transmitted from a pregnant mother to the fetus during viremia and cesarean sections does not help in preventing the transmission of infection. No clear data suggest transmission of CHIKV from breastfeeding[100] but there are reports of suspected transmission through sexual contact. However, evidence such as detectable viral loads preceding onset of any symptoms poses a possible risk of infection following transfusion of blood products collected from viremic asymptomatic donors. Infection with CHIKV provides life-long immunity[10] and may have some cross protection against other CHIKV lineages or alpha viruses, although there is no substantial evidence of waning the previous immunity or an ever growing CHIKV naïve population inflicting the outbreaks.

Epidemiology

There are no distinct links indicating of CHIKV outbreaks as mentioned by Hapuarachchi[11,12] prior to 1952 in Tanzania after which over seventy epidemics have occurred until 2018[13] with increase in the frequency and virulence of the viruses resulting with more severe clinical manifestations. In Asia it was first isolated in Bangkok in 1958, in 1964 in India and other countries experienced outbreaks (Sri Lanka in 1969, Vietnam in 1975, Myanmar in 1975 and Indonesia in 1982). Recent disease outbreaks include those that have been reported from Kenya in 2016 and 2018, France and Italy and India in 2017[14]. Four distinct lineages of the CHIKV have been identified (West African, East Central South African, Asian and Indian Ocean)[93].

In Maldives CHIKV causes epidemic as there are no existing sylvatic cycle identified for the virus to be maintained in nature to be endemic. The first documented CHIKV outbreak in Maldives occurred in 2006[15] where co-infections with DENV were also reported. The largest documented CHIKV outbreak in the Maldives likely began during November and December of 2018, and by early 2019, CHIKV has spread across Maldives to all atolls, only sparing a few islands. Affected population includes all age groups, including newborns. A large unaccounted number of refugees from the Indian subcontinent were affected during this outbreak in the Maldives.

The following weekly report is data from Health Protection Agency (HPA) of Maldives. Blue chart shows number of monthly cases of 2019, and the Orange one shows by atolls[52]. There are more than 1200 cases report in the first half of 2019. Most of the cases were reported from Male', G.A atoll and R atoll.



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Clinical Presentation and management

The CHIKV has a short incubation period, typically 2-4 days[16] or as long as twelve days[17]. Seroprevalence studies have demonstrated, 30-40% of CHIKV infected individuals can be asymptomatic[18], and the majority (60-80%) of infected individuals are symptomatic. The clinical course in CHIKV infections can be debilitating for some individuals, with persisting or relapsing symptoms often prolonged from many months to years. While the majority commonly experience a self-limited course of an acute febrile illness associated with polyarthralgia and rash. The acute phase in CHIKV infection is considered until the end of the third week following the onset of symptoms. Symptoms in a large portion of CHIKV infected individuals persists or reoccur beyond three weeks until several months (3-4 months) with a subset of them developing on to experiencing chronic symptoms which may last over the subsequent years[81].

At the end of the incubation period, an abrupt onset of a high grade (39^0C - 42^0C) fever associated with chills, headache, myalgia and fatigue develops. With a persistent character of fever with multiple peaks, it can last up to 4-5 days before the fever defervesce and poly-arthralgia or poly-arthritis ensues including rashes adenopathy and ataxia. The fever partially responds to antipyretic (acetaminophen) but recurs. Instructing patients with CHIKV infection with acetaminophen with increased frequency (round the clock), often causes aggravation of gastrointestinal symptoms including worsening transaminitis. Avoid prescribing maximum doses every fourth hourly and not exceeding four days. It is recommended as an analgesic not to exceed the recommended 4g per day in adults. However, in individuals who have fever and develop photophobia as well as hallucination during spiking temperatures, its use is often required. Antipyretics is also useful in children under 6 years with known case of febrile seizures, to decrease parental anxiety, though antipyretics have not shown to decrease incidence of febrile seizures. The use of aspirin and NSAIDs during acute period is not recommended as hemorrhagic diseases like dengue cannot be excluded and the use of it maybe consequential in leading to a poor prognosis when bleeding is present. Aspirin causes Reye's syndrome and must not be prescribed for children. Prescribing NSAIDs (Naproxen or Diclofenac or Ibuprofen) should only be after dengue infection is ruled out and in patients who do not have prior allergy reactions or any contra-indication (pregnancy, chronic kidney diseases) for NSAIDs. Care should be taken in thrombocytopenia. Ensure rationale clinical judgment when considering using NSAIDs, tools like the visual aid score[99] to help to scale the pain severity in combination with function limitation (see annex 4).

Symptoms of poly-arthralgia (joint pain) as well as poly-arthritis (inflammation, swelling and stiffness of the joints) are common and reported in 87-98% of CHIKV infected individuals[19,82], these symptoms may persist for several weeks[22]. Large joints (shoulders, elbows and knees) including peripheral small joints (wrists, ankles and phalanges) are equally affected either unilaterally or bilateral and involves inflammation of tendons, ligaments and muscles[19]. There could be migratory type of joint involvement[20, 21]. It exacerbates underlying rheumatologic conditions, resulting in flare ups. Joint involvement can be aggravated by over use and features of arthritis can be significant during morning and inactivity and relieved by mild exercise. These symptoms are more common in adults when compared to children. In individuals with prominent features of fever and poly-arthritis or poly-arthralgia with rash, CHIKV infection should be suspected, especially during the outbreaks.

Cutaneous (skin) involvement during CHIKV infection are commonly reported with a spectrum of rashes. As described in the literature from previous CHIKV outbreaks some rashes described were morbilliform rash, hyperpigmentation, aphthous like ulceration in groin and axilla, vesicular and purpuric eruptions, toxic epidermal necrolysis like peeling, generalized pruritus, palmar and planter desquamation, urticaria, palmar erythema, and aggravation of pre-existing condition such as psoriasis[23,24,25]. Generalized erythema, macular or maculopapular, can present discretely during the febrile phase (2-5 days) and becomes more confluent towards defervescence. It is pruritic in nature having a centripetal distribution involving the extremities, face and trunk. Other cutaneous eruptions reported during the acute phase which includes angiomatous lesions, exfoliative dermatitis, epidermolysis bullosa, hyper melanosis, photosensitivity, exfoliative dermatitis, angiomatous lesions and epidermolysis bullosa. All the skin lesions are transient, but pigmentations may last for months, with mucocutaneous involvement include aphthous ulcers[23,24,25].

Neurological, cardiac, hepatic, renal, respiratory, pancreatic, thyroid, adrenal involvement and hemorrhagic syndrome or thrombotic complications has been labeled as atypical features of CHIKV infection[26]. These are also considered as severe infection when organ failure is present. Neurological complications are common in children when compared to adults, some complications reported are encephalitis, encephalopathy, Guillain-Barre syndrome, acute flaccid paralysis. Seizures were the most common reported neurological symptom[27]. Poor neurological prognosis is associated with intrauterine infections, with sequels such as encephalomalacia, epilepsy and global development delay[28]. Ophthalmic

manifestations are common in individuals with neurological involvement, these include photophobia, optic neuritis, and uveitis[29].

CHIKV exacerbates the underlying conditions, such as diabetes and hypertension, chronic kidney diseases, chronic obstructive respiratory diseases and heart diseases. These exacerbations of the comorbidities often lead to metabolic derangements and organ failure.

High risk patients

High risk patients include pregnant individuals (increased risk of fetal infection), elderly above 65 years, younger children, individuals who are diabetic, epileptic and those who suffer from chronic disease of the kidneys, lung, liver and of the heart.

In addition to this any individual with a known G6PD deficiency status or other hematological disorder such as thalassemia's, sickle cells anemia and immune mediated thrombocytopenia are all considered as high risk and require close monitoring during the acute course of infection.

Investigations

To avoid exhausting the available resources, investigations are advised to do after 72 hours after the onset of symptoms provided the patient is vitally stable. Blood investigations are done for total white blood cell count (TC), the differential counts (DC), hemoglobin (Hb), hematocrit (PCV) and platelets counts. The need for diagnostic CHIKV confirmation depends on the level of clinical evidence, of risk, and of the epidemic context.

The hematological profile during this period (1-3 days) of the acute phase of illness must be interpreted cautiously. The profile during this period cannot distinguish CHIKV infection from other viral infections such as dengue, influenza, EBV, HIV or bacterial infections like rickettsiosis and salmonellosis. A decreased white blood cell count (lymphopenia and leucopenia) with a neutrophilic predominance and moderate thrombocytopenia occurs. A platelet count below $50{,}000 \times 10^3$/uL during this period (1-3 days) could indicate a coinfection or due to an underlying condition (DENV, rickettsiosis, Leptospirosis, immune

mediated thrombocytopenia, cirrhosis). A history with information about any potential exposures to either of the likely pathogens can be crucial in providing timely the appropriate antimicrobials.

Hematocrit levels can be helpful to identify hemoconcentration in Dengue fever wit hdanger signs and severe dengue fever infection where there is extravasation of proteins to the extravascular spaces in addition to the bleeding which is commonly seen in dengue fever (DF), where hemoconcentration does not occur. A fall in the hematocrit including the hemoglobin levels with the MCV identifies blood loss. Blood film are helpful in screening for red blood cell disorders and provide valuable information such as bandemia, atypical lymphocytosis and hemolysis.

In CHIKV infection there is no data regarding hemoconcentration and atypical lymphocytosis. A bandemia is observed during this period (1-3) of early infection, with a background of decreased white blood cells and platelets. This is in response to the compensatory effect, and not a left shift indicating a bacterial infection, unless the history is suggestive of exposure to infective pathogens through coming in contact with rodents, and rodent excrement to cause murine typhus and leptospirosis. In addition, consuming contaminated food causes salmonellosis and exposure to forest causing scrub typhus and malaria. There are limited data showing lymphocytosis in CHIKV infection and neutrophils remain persistently elevated[80].

In the urban setting the most commonly found viruses to be transmitted through mosquitos to humans are the dengue viruses (DENV1-4). Manifesting as an acute febrile undifferentiated illness with bleeding as a prominent characterizing symptom. It is rationale to utilize the point of care (POC) test kit to confirm dengue infection in such individuals who presents within five days or earlier after developing symptoms. At present the rapid POC test kit available in Maldives includes a combination of detecting both the NS1 antigen and antibodies anti-DENV IgM and anti-DENV IgG against the DENV1-4. These test kits have demonstrated a fairly good sensitivity and specificity but do minimally cross react with other Flaviviruses and during outbreaks have false negative results. Avoid being heavily dependent on the POC, and resorting to competent clinical judgement, especially in the presence of bleeding such as petechiae, gingival bleeding, epistaxis and menorrhagia. The ready availability of these kits at all peripheral hospitals and health centers across Maldives helps with the diagnosis of individuals with DENV.

Having DENV excluded and if symptoms are pertaining to poly-arthralgia and arthritis, CHIKV is likely to be the causative pathogen. At this point all treatable causes as previously mentioned should be excluded and prophylaxis or treatment considered.

Further work up for ZIKV, is warranted in pregnant individuals with a negative DENV NS1 antigen and an anti-DENV IgM antibody results. This can be only be performed at a higher center (IGMH, Male'-Maldives) and other referral laboratories (TMDR, Bangkok – Thailand). Confirmation of ZIKV, blood should be collected in an ETDA vacutainer preferably within 5 days after developing symptoms, in volumes of 2-5mL. An uninterrupted cold chain logistics should be arranged for transportation of the clinical specimen. Should there be an expected delay in transporting the specimen for testing, the serum should be separated by centrifuge and made into aliquots (1mL- micro-tubes) containing 300uL of serum in each aliquot and frozen in a freezer at minus 80^0C until shipment maintaining the cold chain with dry ice only. Confirmation of ZIKV infection beyond 5 days can be performed by urine of infection individuals.

Do the following tests after 72 Hrs.

1. Total white blood cells count with Differential counts
2. Platelet count
3. Hemoglobin and Hematocrit (Packed Cell volume)
4. Electrolytes (Sodium, Potassium, Calcium) and Glucose
5. Liver profile
6. Renal function (Urea and Creatinine)
7. Routine Urine analysis

Additional investigations to consider when appropriate includes; pregnancy test, G6PD test, lactate, LDH and CPK levels, reticulocyte count, blood cultures, DENV NS1 antigen, Trio-plex assay (DENV/CHIKV/ZIKV), HIV ELISA, X-rays, electrocardiography and echocardiography.

Confirmatory diagnosis for CHIKV is isolation of the virus in cell culture. Other available methods to detect CHIKV include RT-PCR and serology. Some of the limitation with these techniques are the high costs, and

their unavailability. Existing commercially available antibody detection POC test kits which detects anti-CHIKV IgM, perform well when used during the second week after developing the symptoms and have no rationale of its use during the very first few days of illness. It should be noted that CHIKV is an alpha virus unlike DENV and ZIKV which are flaviviruses and immunoglobulin cross reactivity does not occur[30]. Some novel technologies that can detect the chikungunya antigens[31]have shown promising results and several commercial kits are expected to be available. The RT-PCR is performed using various clinical specimens and can provide results within four hours. The recommendation is to provide blood specimen collected within five days after developing symptoms. Data is limited about the duration of detection of the virus in other body fluids[83].

Differential Diagnosis

Fever with or without arthralgia or rash is very common in infective and non-infectious diseases. Co infection may also be present in chikungunya[32]. The absence of joint involvement, a hypotensive or bleeding trend, abdominal pain, and fever for more than 5 days are all symptoms justifying a diagnostic discussion.

1. Dengue fever (DF) is very common arthropod borne febrile illness in Maldives and needs to be ruled out in any acute undifferentiated febrile illness. DF is characterized with an abrupt onset of high-grade persistent fever, associated with a profound headache, retro-orbital pain, body aches comprising of arthralgia's and myalgia's. There is loss of appetite and anorexia, with other gastrointestinal symptoms including vomiting and diarrhea. Bleeding can manifest as petechiae, ecchymosis, gingival bleeding, epistaxis, hemoptysis, hematemesis, melena, hematochezia, hemoperitoneum and as intracranial bleeding.

   Typical blood investigations show low white blood cell count followed by subsequently decreasing trend in thrombocytes. Platelets show decreasing trend even during the initial 48-72 hours in the afebrile phase and later returns to normal ranges.

   Symptoms of dengue infection does not last for more than ten days (usually 5 to 7 days).

   The hematocrit can be utilized to screen for hemoconcentration observed in DF with warning signs or severe dengue. The hemoglobin levels together with mean corpuscular volume and blood picture can provide valuable information identifying bandemia, atypical lymphocytosis and

hemolysis. Intravascular volume might rapidly deplete, and tissue hypoxemia and organ failure ensure. Impairment of the coagulation and worsening of liver functions contribute and impact on the bleeding manifestations. The DENV is also known to cause encephalitis, myocarditis, and renal failure.

Majority of individuals recover with adequate hydration. Paracetamol (Acetaminophen) is the only drug to be used as an antipyretic. Tramadol may be added for analgesia if acetaminophen does not relieve pain adequately. Non-steroidal anti-inflammatory drugs and steroids are contraindicated because it might cause bleeding and death. Patients who are on prolonged medication, acetylsalicylic acid and other anti-platelets and anti-coagulants must be halted until thrombocytes are normalized.

Interpretation of NS1 antigen and antibodies IgM and IgG against DENV should be carefully done not to miss diagnosis and mismanagement of a falsely negative DENV infection.

2. Zika virus (ZIKV) infection is another viral infection similar like chikungunya and dengue. Usually causes a mild self-limiting course of illness and is comparatively milder when compared to infections with DENV or CHIKV. The illness is characterized by fever, rash and non-purulent conjunctivitis but can present with encephalitis, GBS and with congenital infections. Infection during pregnancies should be confirmed and close monitoring with the antenatal team must be established. All newborns with microcephaly and brain anomalies should be investigated for ZIKV infection.
3. Scrub typhus is endemic to Maldives. It is a rickettsiosis, caused by *Orientia tsutsugamushi*, a gram-negative intracellular bacterium, transmitted by the bite of an infected chigger mite. It presents with high grade persistent fever with or without an eschar (a centrally necrotized painless ulcer), regional lymphadenopathy, hepatomegaly and a maculopapular rash. The total white blood count is normal or elevated with mildly depleted platelets and impaired liver enzymes. These findings are commonly observed when infected individual presents towards the end of the first week or second week of illness which does not respond to cephalosporins and penicillins. The fever persists and other organ involvement like pneumonitis, transaminitis, meningoencephalitis or sepsis with disseminated intravascular coagulation can develop and if left undetected and untreated individuals succumbs to infection. Macrolides (Azithromycin) and tetracyclines (Doxycycline) are the drugs of choice.
4. Murine typhus is another rickettsiosis to consider especially when there is no history of exposure to scrub vegetation or forested area. This is caused by Murine *Typhi* a gram-negative intracellular

bacterium. Transmitted by the rat flea, there is no eschar in murine typhus, but the clinical manifestations are as any other undifferentiated febrile illness with a maculopapular rash predominant on the trunk and prominent complaint of headache or difficulty to concentrate. Both these rickettsiosis responds dramatically to tetracycline (Doxycycline), in pregnant individual's alternatives such as macrolides (Azithromycin) must be considered.

5. Leptospirosis is a zoonosis which occurs in the tropics, especially when there is exposure to flooding or rodent excrements. The illness presents with fever, jaundice, myalgia predominantly involving the lower extremities, especially the calf muscles are tender to touch. They also present with conjunctival suffusion, conjunctival hemorrhage, uveitis and conjunctivitis. Hemoptysis or a dry cough with blood stain sputum are earlier signs of pulmonary hemorrhage with additional kidney failure in severe forms of this disease, known as Weil's disease. Leptospirosis is characterized to have a spiremic phase initially and an immunological phase week subsequently. The treatment of choice for mild disease is doxycycline and in hospitalized patients or severe manifestations, parenteral penicillin (Penicillin G) or a third generation of cephalosporin (Ceftriaxone). Treatment with parenteral penicillin should be administered with caution during the spiremic phase as it can initiate a Jarisch-Herxheimer reaction. The gold standard for diagnosis of leptospirosis is using the microscopic agglutination test (MAT) available only at reference laboratories, convalescent serum should be collected for the confirmation of leptospirosis.
6. Influenza during the peaks of the annual seasonal outbreaks is the most contagious viral infection in humans. Apart from involvement of the upper and lower respiratory tract infection, influenza viruses cause systemic involvement in individuals suffering from diabetes, chronic kidney diseases or on regular hemodialysis or with ischemic heart disease. Influenza viruses can cause worsening of organ function leading to acute kidney injury, rhabdomyolysis, arrhythmias, myocarditis and GBS. A neuraminidase inhibitor (Oseltamivir) is available for treatment and for prophylaxis. Dosage adjustments based on the creatinine clearance in needed. During outbreaks along with influenza circulates the Respiratory Syncytial Virus (RSV), which commonly is self-limiting but in severe cases the prodrug (Ribavirin) can be used to salvage from infection. Laboratory confirmation of influenza is not required to initiate treatment, during major influenza outbreaks.
7. Salmonella and malaria should be considered if there is a history of recent travel from endemic regions and consideration of the regional resistance patterns should be a focused before treatment. Acute retroviral syndrome to be considered in the high-risk groups such as men who

have sex with men (MSM) or in individuals who engage in unprotected sex with female sex workers and post exposure prophylaxis should be offered timely when appropriate.

8. Rheumatic fever (RF)is not common in Maldives. Jones criteria is used to diagnose RF.
9. Malaria is not present in Maldives as Anopheles mosquito is eradicated in Maldives. However, it can present in travelers coming from endemic areas.

Management of Chikungunya virus infection

All patients who present to health facilities in Maldives as a case of an acute febrile undifferentiated illness must be suspected of having dengue infection and it need to be ruled out.

All patients must be properly evaluated by obtaining the history of the presenting illness followed by a complete physical examination to assess and determine if the patient can allow to be sent back home and to follow back or requires hospitalization, especially high-risk groups. There are no approved treatment for chikungunya and during the initial days of illness, only supportive management with acetaminophen and rehydration are recommended. Patients can be allowed to return home if there are no signs of dehydration (see the annex for signs of dehydration) and able to take adequately oral fluids without any bleeding manifestations.

Advice to patients regarding management at home

If the patient can be sent to home, clear written advice must be given.

Rest is important. Refrain from heavy exertion. It is very important to emphasis this to employers who has expatriate workers as they might be subjected to work without medical leave. Mild exercise can be started during recovery phase.

Keep hydrated. ORS and coconut water are ideal for rehydration. For adults minimum 2 liters of fluid is required per day. For children fluids are given frequently in small amounts. Urine should be passed adequately in every 6 hours. The darker the urine the more fluid patient requires for rehydration.

Paracetamol and tramadol are given as an antipyretic and analgesic. Since signs and symptoms of CHIKV infection can mimic dengue fever, it is important to avoid steroids and NSAIDs until dengue fever is ruled

out and platelet count is normalized. Dose of paracetamol is less than 4g per day for adults and for children it should be 10-15mg/kg/dose with maximum 50-60mg/kg/day. Use paracetamol with caution if there is liver impairment.

Patients also should be advised not to share drugs among others without consulting doctor. Herbal medicines must be avoided.

Cold compressions of joints are helpful during acute stage.

Patients should be advised to come back to health facility if;

1. Fever persists for more than 3 days to do investigations and re-evaluation or even if less than 3 days with any of the following symptoms;
2. Urine is not passed for more than 6 hours
3. Patient feel dizzy, peripheries are cold or there is severe abdominal pain
4. Unable to take orally due to persistent vomiting or abdominal pain
5. If there are any bleeding manifestations such as in the skin, oral cavity, in the vomitus or stool.

Any patient with above symptoms should be carefully evaluated to decide whether admission in health facility is required.

Admission criteria

The following patients need to be admitted and re-evaluated before discharge.

1. Any patient presented with unstable vitals (immediate danger)
2. Atypical or severe complication
3. High risk patients
4. Uncertain diagnosis
5. Pregnancy
6. Social isolation

A short admission can be made in the emergency room for rehydration, if it is the only complication. Patient can be discharged after rehydration with advice and follow up plan.

Preferred rehydration route is oral. However, if unable to take orally intravenous rehydration therapy with an isotonic solution is given. Preferred solutions for rehydration include normal saline (NS) and ringers' lactate (RL) for adults and Dextrose normal saline (DNS) for children.

Referral criteria to tertiary centers

Health facilities in Maldives are divided into 4 tiers; island health centers, atoll hospitals, regional hospital and tertiary hospitals. Government tertiary referral center is Indira Gandhi Memorial Hospital (IGMH). It is in Male', which is the capital city of Maldives. In IGMH on-call pediatricians and physicians are available 24 hours. Any doubts and queries regarding management of any patients can be enquired from them at any time via phone.

Patients with the following complications need to be referred to tertiary level hospital where intensive care can be given.

1. Bleeding manifestation
2. Refractory hypotension
3. Meningoencephalitis or altered sensorium
4. Infants below 1 year
5. Pregnant mothers
6. Worsening liver or renal impairment

Patient can be referred to higher center after discussion with consultants in the receiving end. Referrals can be from island health center to atoll hospital or from atoll hospital to regional hospital or to tertiary level. Patients can also be referred to private tertiary hospitals ADK Hospital and Treetop Hospital. As it is a private hospital, additional cost may be applied to patient.

If a medical evacuation needs to be done to tertiary hospital, Government Health Insurance covers for transport from peripheries to IGMH using sea ambulance of MNDF or by helicopter as well.

The patient should receive adequate initial resuscitation, stabilization and continuous care before and during transport to ensure that patient arrives to referral center in a stable condition. Safe and timely transport needs good communication between referral team, transport team and receiving centers.

Special consideration should be given to continue care such as maintaining intravenous hydration and medication and oxygen. Dislodging of IV cannula is common and should be prevented. Patient should be monitored clinically as well as with pulse-oximeter. Monitors must be charged enough to continue throughout the travel. An experienced nurse or a doctor should accompany all patients during transport. All documentations including X-rays should be sent. The notes must include detailed treatment that is provided including input and output charts and drugs administered.

When patients are transferred to higher centers the following should be followed.

1. Discussion with referral hospital to inform doctors and nurses who will be receiving the patient.
2. Discuss with family members and explain the risk and probable outcomes.
3. Stabilize the patient before and during transfer.
4. Detailed referral letter. This should include current conditions, monitoring parameters (vital signs, input output chart, HCT, laboratory findings).
5. At least an experienced nurse should accompany the patient.
6. Intravenous fluid must be continued at correct rate.
7. Review of the patient by specialist at receiving end.

Management of complications

Although mortality of chikungunya is rare[75], chronic debilitating morbidity is high. It has been seen that severe complications of chikungunya infection typically arise in those with co-morbidities or at extreme of age[96]. All cases with complications should be managed or consulted to respective team. In tertiary hospitals multidisciplinary approach is advised.

1. Joint Involvement;

People with chikungunya may present with bilateral and symmetrical arthralgia with or without fever[62, 63,102]. The characteristic pattern of arthralgia tends to be more intense in the morning, relieved by gentle movements and aggravated by vigorous activities[33]. Pain in the joints can be intense and disabling,

primarily affecting the ankles, wrists, and small joints of the hand[34]. Larger joints such as knee, shoulder and joints of the spine are also involved. Costochondral, hip and temporomandibular joint involvement are also reported. Following an initial infection, the symptoms of polyarthralgia may decrease over time[35]. However, the duration of full recovery is not predictable as some people continue to have symptoms six to eight years after the initial infection which significantly compromises the functional capacity and quality of life[36]. About 10% patients suffer from chronic arthritis (more than 3 months). Some of them will have relapse with febrile illness.

Cold compression has been shown to decrease inflammatory damage to joints in the acute period. NSAIDs are avoided in the first 10 days of infection. After the first 10 days, NSAIDs can be used and complete rest should be avoided. Ensure about allergies to NSAIDs and status of G6PD deficiency. Care should be taken not to overuse NSAIDS as its adverse effects are common. If NSAIDS are used, patient should be informed of its overdose and toxicity. Patient should be monitored for gastritis, renal impairment, cardiac involvement and bone marrow toxicity. NSAID classes do not show effectiveness over the other. However, if one class NSAID is not producing enough response even with increased dose and frequency for 10 days, another class should be used. NSAIDs are used for several days and then weaned off[85]. During the outbreak in Reunion hydroxychloroquine was used to treat complaints of arthritis, however present data suggest there is no benefit from using chloroquine and its derivatives. Neuropathic medications such as nefopam, pregabalin and gabapentin can be used in addition to NSAIDs. A short course of steroid may be used if NSAIDs are contraindicated. Steroids are beneficial in chronic cases and where there is suspected damage to metatarsal heads[37,38]. Prednisolone 10mg per day for adults can be used for a period of 5 days to 4 weeks. It is recommended to give an NSAID for few weeks if steroid has to be stopped to avoid recurrence of arthropathy. A specialized consultation in rheumatology is required in case of inflammatory disease with painful and debilitating arthritis persisting beyond 6 weeks or if bone erosion is observed[39].

Topical or infiltration of anti-inflammatory therapy should be prescribed in case of tenosynovitis, bursitis, tunnel syndrome, capsulitis, or synovitis inadequately controlled by oral treatment. Surgical decompression of a tunnel syndrome is not advised in an inflammatory setting as it might be complicated with risk for poor healing and reflex sympathetic dystrophy syndrome. There is no indication to initiate disease-modifying antirheumatic drug (DMARD) therapy such as methotrexate before 8 weeks in the post-acute stage.

Physiotherapy in chikungunya arthritis

Physiotherapy intervention specifically focuses on decreasing pain, improving range of motion and muscle strength and more broadly assists in regaining functional capacity and enhancing the quality of life of people. As such physiotherapists can play a pivotal role in improving analgesic picture and the quality of life of people affected by chikungunya.

Research suggests that physiotherapy should be considered at the acute phase of polyarthralgia in Chikungunya. Cold therapy is recommended at this stage to reduce inflammation and pain around the joints and muscles[39,40]. In addition, active and active assisted exercises and use of hands for activities of daily living such as bathing, dressing, eating etc. are recommended[41]. Furthermore, maintaining correct posture and prevention of contractures and deformities by targeted stretching and the use of orthoses is advised. Initial non-weight bearing exercises followed by weight bearing as tolerated can be commenced. Light intensity walking, gentle ankle and foot exercises and pulley assisted exercises can be practiced. Heat therapy is recommended at the chronic stage and exercises can be progressed as tolerated. Anti-inflammatory patches are used around painful joints. If joints are infiltrated, drainage of joint fluid might be required. Avoid lying on the affected side. A resting orthosis at night for a short duration can be applied. Isometric muscular contraction followed by isotonic and isokinetic contraction are used ensuring good posture. Management by physiotherapists is often required and may be followed by self-rehabilitation.

Table: Treatment of CHIKV arthritis according to clinical stages

Drugs/Interventions	**Acute stage (first 3 weeks)**	**Post-acute stage (week 4 to week 12)**	**Chronic Stage (after 3 months)**
Acetaminophen (< 4 g/day for adults)	+	+	+
Level 2 pain killers (Codeine is contraindicated in children less than 12 years)	+	+	+
Antineuropathic drugs (nefopam, pregabalin, gabapentin)	-	±	+

NSAIDS	Not indicated in the first 2 weeks	+	+
Corticosteroids	-	±	+
DMARDS	-	±	+
Physiotherapy	+	+	+

2. Neurological manifestations;

Neurological complications are very common atypical features in chikungunya[76]. This could be the primary presentation in some patients. Neurological manifestations are more common in children than adults. Children under six are prone to febrile seizures following CHIKV infection and seizures are frequently reported in epileptics as break-through seizures. During outbreaks, if neurological symptoms are associated with fever and arthralgia patients should be suspected for chikungunya.

Neurological manifestations are either due to direct infection of brain tissue or hypoperfusion of brain as a complication of systemic infection[89]. Neurological syndromes could be encephalopathy, encephalitis, myelitis, myelopathy, encephalomyeloneuropathy, Guillain-Barre Syndrome, neonatal hypotonia and Neuro-ocular disease. Symptoms including photophobia, seizures, impaired consciousness level and behavioral changes. Stroke, sensorineural hearing loss, third nerve palsy, bilateral ophthalmoplegia, carpel tunnel syndrome, Bickerstaff brainstem encephalitis–Miller Fisher syndrome–Guillain-Barré syndrome overlap, ascending polyneuritis have been reported[28,78]. Less than only 10% patients will have permanent neurological sequalae[28,78]. Peripheral neuropathy is the most common among the neurological permanent manifestations. Involvement of motor nerves are rare. Paresthesia, pins and needle sensations, crawling warm sensations and other disturbing sensations are mentioned. Anti-neuralgic drugs such as amitriptyline, gabapentin, carbamazepine may be used.

Symptoms of encephalitis is seen between 0-13 days of infection. Encephalitis has a worse prognosis than encephalopathy alone. Common CSF analysis shows a lymphocytic predominance, however pleocytosis is not seen in all the cases[42], consecutive analyses can provide more information suggestive of viral etiology. Radiological and electroencephalographic findings do not have a typical characteristic finding[43]. Reported findings vary from normal findings to edema and hemorrhage[42,44].

Chikungunya myelopathy is a pathology of spinal cord disease, characterized by limb weakness, sensory changes, hyperreflexia, and bowel and bladder disturbances, depending on the level of the lesion and extent to which the cord is involved. MRI finding may suggest demyelination[45].

Chikungunya acute disseminated encephalopathy is like other viral diseases that involves brain parenchyma and spinal cord. Patients present with headache, drowsiness, facial nerve palsy, vertigo, bulbar palsy and nystagmus. MRI shows poorly demarcated demyelinating white matter lesions. Treatment is intravenous methyl prednisolone. Outcome varies from good prognosis to persistent neurological sequel such as wheel chair bound disability and incontinence[46].

Guillain Barre Syndrome (GBS) has been described in few patients who present with acute flaccid paralysis. Weakness and areflexia is found symmetrically in limbs and sometimes associated with cranial nerve involvement[47]. GBS symptoms are similar to those found in other etiologies. Neuroelectric studies show motor and sensory involvement. Treatment includes intravenous immunoglobulin, methyl prednisolone and plasmapheresis. Prognosis is good[28]. Most patients recover after immunomodulatory therapies.

Eye involvement is common in neurologically affected patients and it should be excluded.

Other isolated manifestations include behavioral changes, memory loss, irritability, chronic fatigue syndrome and attention disorders.

Persistent neurological sequel has been reported in the form of epilepsy, cognitive disorders, dementia and developmental delays[48] in 18-43% of patients who presented with neurological involvement. There are mortalities reported up to 13% -31% in some series[28,42]. There was a case of intrauterine infections of fetus complicated with encephalomalacia in IGMH, Maldives.

There is no specific treatment for neurological complications of chikungunya. Treatment is given as in other etiologies. Initial treatment of encephalitis should be covered empirically until chikungunya is confirmed. Literature shows cases been treated with either antiviral (acyclovir) or antibiotics, intravenous immunoglobulin, methyl prednisolone and other steroids depending with varies response.

3. Ophthalmological complications

Acute manifestations include photophobia, retro-orbital pain, conjunctivitis, color vison defects and visual impairment. Chronic symptoms may present till 12 weeks. Uveitis[84], keratitis, episcleritis and retinitis have been reported up to 4-6 weeks after the onset of initial symptoms. Optic neuritis has been described in the acute and chronic phase[50].

Uveitis is the most common finding[87], of which anterior uveitis is the most common type[51]. Anterior, intermediate, posterior and pan-uveitis have been described. Other findings include Fuchs' heterochronic iridocyclitis with iris nodules, cataract, increased intraocular pressure, retinal detachment, intraretinal hemorrhage, and branch retinal artery occlusion. Increased number of cases of retinitis after epidemics of chikungunya has been referred as “epidemic retinitis”.

Uveitis may be treated with topical prednisolone acetate, diclofenac sodium, as well as a topical cycloplegic and topical anti-glaucoma drops Progression of these symptoms need to be treated with oral steroids. Cataract surgery has been done for Fuchs heterochromic iridocyclitis.

Prognosis varies from good to persistent symptoms such as visual impairment. Follow up is mandatory to review the progress.

4. Psychiatric manifestations

Chikungunya fever can result in significant psychiatric morbidity, mainly in the form of acute and chronic depressive episodes, mood disorders[53,54], anxiety disorder, long persisting illnesses like somatoform disorders, phobic anxiety disorder (Claustrophobia), neurasthenia (Fatigue syndrome), sleep disorder (Hypersomnia) and manic disorders[55]. Quality of life is low during the acute and chronic symptoms due to loss of work days and impaired ability to work effectively[36]. These are more common among patients with a history of previous psychiatric illness[59].

Timely recognition and treatment can help these individuals to recover quickly and effectively.

5. Myopericarditis

Cardiac involvement may progress in phases; pre-congestive or prodromal phase, arrhythmic phase, and decompensated phase[56].

Diffuse chest myalgia and arthralgia are common in acute stage of chikungunya fever. These symptoms may be due to CHIKV-induced myo-pericarditis without heart failure. Cardiomyopathy may be observed during and after months of chikungunya infection and may be unexpectedly increased after months of an epidemic[57]. ECG, echocardiography and MRI are choice of investigation.

Patients have presented with hypotension, shock and circulatory collapse, Raynaud phenomenon, arrhythmias, murmurs, myocarditis, dilated cardiomyopathy, congestive insufficiency, heart failure and altered troponins and CPK[58]. The most documented electrocardiographic changes were T wave inversion in DII, III, aVF and V5–V6, and ST elevation.

Involvement of the cardiovascular system can be fatal. Patients with existing cardiovascular disease can deteriorate quickly, worsening the short-term prognosis.

6. Dermatological manifestations

Multiple mucocutaneous manifestations are observed with chikungunya fever. A generalized erythematous maculopapular eruption is the most common cutaneous manifestation of chikungunya. Rash which develops after the first 2-3 days of fever, is mostly seen over the face, ear lobes, trunk and limbs, including palms and soles[23,60,61,62]. Patients complain of itching and burning sensation all over the body which is usually mild but can be severe in some patients. Rash subsides in about a week.

Hemorrhagic rashes are less frequently seen in chikungunya than in dengue fever. Oral aphthae, and aphthous like ulcers have been reported, mostly in intertriginous areas like axilla, genitals and groin. Vesiculobullous lesions have also been reported[60].

Pigmentary changes mainly involving the face are seen in patients with Chikungunya. Pigmentation is brownish black and diffuse, or freckle like, mainly involving the nose and central face. Pigmentation usually occurred after the fever subsides and is exacerbated on exposure to sunlight[88].

Desquamation of the skin over palms, soles and face is commonly seen. Nail changes including subungual hemorrhages and red lunular have been reported. Exacerbation of existing dermatoses like psoriasis and lichen planus has been documented.

Treatment is usually symptomatic. Most symptoms are self-limited. Topical calamine lotion and antihistamines can be given. Sunscreens over the face to prevent facial pigmentation. Desquamation is treated with topical emollients. Topical antibiotics maybe required in treating the ulcerations.

7. Hemorrhagic manifestations

Bleeding manifestations are rare in CHIKV infection and are considered as atypical. There are reports of mucocutaneous bleeding. Some are coinfections with dengue which can be complicated with severe thrombocytopenia, bleeding and thrombotic thrombocytopenic purpura[63].

8. Perinatal management in Vertically infections

A congenital chickungunya case can be defined as a baby born to mother with high grade fever within seven days before delivery with IgM seropositivity or CSF positivity at time of neonatal diagnosis, or a symptomatic baby in first seven days of life having a positive IgM ELISA/RT-PCR in serum/CSF and negative bacteriological cultures[92]. Any seropositivity or CSF-positivity found in a symptomatic baby not associated with maternal infection can be defined as acquired Chikungunya. However, symptoms may be missed in mothers due to mild symptoms or poor recall of mother. Coinfection has also been reported in mothers, the significance of which to neonate is not known[64, 94].

Mother to child transmission rate was observed to be between 27.7% and 48.29%[65,66,67]. Early fetal infection has resulted in fetal loss without birth defects. Cesarean section does not decrease the transmission rate, therefor there is no recommendation to deliver by Cesarean section[66,68]. Careful monitoring of affected parturients should be done in a tertiary facility where intensive care is available.

Maternal chikungunya infection near the time of delivery require admission of neonate for observation for signs of vertical transmission for at least 7 days postpartum, as they may be asymptomatic for the first

few days of life. The only drug recommended for pain and fever for pregnant mother is paracetamol. Maximum daily dose is 4g per day. All oral and topical NSAIDs are contra-indicated after 24 weeks of amenorrhea. NSAIDS are known to cause renal failure and closure of the ductus arteriosus, eventually leading to fetal death in utero. Mother and relatives should be informed about the risks of self-medication and aromatherapy which might induce hepatic enzymes.

Congenital chikungunya can have severe neonatal complications. These include fever, lethargy, poor feeding, hyperalgesia syndrome, hypotonia, diffuse limb edema, hyperpigmentation, erythematous skin rash, bullous dermatitis, perioral rash, irritability, apnea, hemodynamic instability, respiratory failure, seizures, intracranial bleeding, encephalomalacia and myocarditis [65,69,70]. Neurological manifestations may not be obvious at birth. Mortality has also been reported[65,89]. Conjunctivitis was not observed in neonates. Encephalopathy was the main feature in some studies while others classified only 7% neonates with encephalopathy though even in those studies almost all presented with irritability and poor feeding[65]. A higher incidence of encephalitis in neonates could be attributed to greater viral replication and delayed clearance in this age group[71]. Proportion of patients with persistent neurological disabilities varies from 30-45% to almost 100% in different studies[66,69].

Developmental delays have been seen as motor coordination, speech and socialization[72,74]. A standard neurological examination such as Hammersmith infant neurological examination should be done at the time of discharge and used in the follow up for at least 2 years, regardless of symptoms in the first week of life. Neurodevelopment of those without clinical encephalopathy at birth can still be affected. Visual and hearing impairment is unlikely to persist.

Blood Investigations may show increased, normal or decreased lymphocyte count and thrombocytopenia. C-reactive protein may be mildly positive. CSF shows hypoglycorrachia, increased or normal protein, lymphocytic pleocytosis and produce a sterile culture[65,69].

Ultrasound scan of brain is indicated in the acute phase. A follow up MRI at 3 months is indicated even if USG Brain is normal. Follow up MRI brain might show hyperintensities on T2 and FLAIR images involving frontal and parietal lobes in bilateral peri-ventricular and subcortical region with evidence of diffusion restriction in rostrum and splenium of corpus callosum, cystic encephalomalacia and ventricular dilatation with or without diffuse cerebral atrophy. All patients with abnormal MRI showed developmental delays[69]. Fixed flexion deformity in bilateral thumbs is also reported[73].

Management of congenital chikungunya is supportive. All patients in delivery unit should be questioned about symptoms to identify any risk for CHIKV transmission for the unborn child. Breast feeding is not contraindicated in mothers suffering or who has recovered from chikungunya.

Notification to Health Protection Agency

Chikungunya is a notifiable disease in Maldives. The revised International Health Regulations (IHR 2005) adopted by the 58th World Health Assembly of WHO provide the legal framework for mandating countries to have a disease surveillance system. It is Mandatory under the International Health Regulations (IHR 2005) and the Public Health Protection Act 7/2012 of Maldives to notify communicable diseases.

Chikungunya can be classified into the following 3 categories for notification to Health Protection agency. Definitions[101] are as follows.

Suspected case of chikungunya

Acute onset of fever which is more than 38^{o}C with severe arthralgia which is not explained by any other medical condition without been residing or travelled to a place with chikungunya epidemic.

Probable case of chikungunya

Acute onset of fever more than 38^{o}C and severe arthralgia which is not explained by any other medical condition in a patient who is residing or having visited an epidemic area having reported transmission within 15 days prior to the onset of symptoms.

Confirmed case of chikungunya

Any patient who has a positive confirmatory test for chikungunya. These tests include IgM or increasing IgG titer for chikungunya, positive PCR or viral isolation.

Fever and Rash Investigation

Maldives has eliminated Measles and is working on eliminating Rubella and Congenital Rubella Syndrome. To sustain the status of measles elimination and achieve Rubella and CRS elimination, a vigilant surveillance system is required to screen for any possible occurrence of these diseases.

All cases of fever and maculopapular rash need to be evaluated for measles and Rubella irrespective of age, gender and existing co-infection. Notification and sample taking must be done even if another diagnosis is suspected or confirmed to ruled out coexisting measles or rubella. Notification using fever rash (measles, rubella) investigation form (see annex 3) must be done. Samples required are serum and throat sample that has to be sent to IGMH laboratory. Public health units must facilitate sample delivery.

Prevention of chikungunya

1. Vector control is the only available effective method to decrease the incidence of chikungunya. There is no available vaccine for chikungunya[77].

Mosquitoes can be controlled with removal of mosquito breeding sites, using larvicides and larva feeding fishes and insecticide sprays. Use of mosquito repellants and covering the body can reduce mosquito bites. It is important to note that fogging does not control mosquitoes effectively. Chlorine is not a mosquito larvicide. Chemicals such as Temephos has to be used as larvicide.

2. It is important that individuals who are showing symptoms of chikungunya to take all the available necessary precautions in preventing themselves being bitten by mosquitoes to interrupt further spread to prevent escalation during an outbreak.

Frequently Asked Questions in Chikungunya Fever.

1. What is chikungunya fever?

Chikungunya is a viral fever transmitted through the bite of an infected Aedes mosquito. The word chikungunya is derived from an African language and means "that which bends up" or "stooped walk" because of the incapacitating arthralgia caused by the disease.

2. What are the symptoms of chikungunya fever?

The symptoms of chikungunya include a sudden onset of fever, severe headache, chills, nausea, vomiting, fatigue, muscle pain, joint swelling and joint pain.
The disease is characterized by severe – sometimes persistent – joint pains. The areas around the joints become swollen and painful to touch.
Skin rashes occur in 40–50% of patients, usually appearing between 2 and 5 days after the onset of fever.

3. How to differentiate between chikungunya and dengue?

In chikungunya, there is a severe joint/bone pain and lasts for a longer duration. There is more frequent maculopapular rash, but shock and haemorrhage are rare compared to Dengue. Dengue, on the other hand, has a less severe and shorter duration of joint pain, infrequent maculopapular rash. Dengue fever can have severe manifestations like bleeding from the nose, gums or skin, and/or gastrointestinal bleeding and may also lead to develop dengue shock.

4. Is there any laboratory tests that can be used to confirm chikungunya?

Yes, there are laboratory tests that can be used to diagnose chikungunya.
It is done by detection of chikungunya viral RNA via real-time reverse-trancriptase (RT-PCR) or using serology. RT-PCR can be done during first week of illness.

Anti-chikungunya Ig-M antibodies can be detected from 5 days of onset of symptoms (range from 1 to 12 days) and persists for several weeks to three months. IgG antibodies begin to appear about two weeks following onset of illness.

5. What is the incubation period of the disease?

Incubation period for Chikungunya is usually 3 to 7 days (range 1 to 14 days).

6. What is the treatment of chikungunya?

   There is no specific drug against chikungunya. Proper rest and fluid intake is recommended. Paracetamol is commonly used to relieve symptoms of fever and joint pains.

7. How to prevent chikungunya?

   Since there is no specific treatment or vaccination against chikungunya, prevention is aimed at controlling the vector, Aedes mosquito and to taking measures to prevent mosquito bite.

Annex

1. Signs of Dehydration

Following table is adopted from Module 4 of Integrated Management of child Hood illness (W.H.O)

Clinical sign of dehydration	**No Dehydration**	**Mild dehydration (any of the 2 criteria)**	**Severe Dehydration (any of the 2 criteria)**
Alertness	Alert	Restless and irritable	Abnormal sensorium Excessive lethargy
Eyes	Not sunken	Sunken	Deeply Sunken
Thirst	Slight	Moderate	Intense or Unable to take
Tongue	Moist	Dry	Coated
Skin turgor	Normal	Decreased	Decreased
Capillary refill time	Less than 3 seconds	More than 3 seconds	More than 3 seconds
Heart rate	Normal	Increased	Increased
Blood Pressure	Normal	Normal	Low
Urine Output	Normal	Markedly decreased	Anuria

2. Communicable disease notification form

Following Communicable notification form can be downloaded from HPA website[79].

Communicable Disease Notifying Form

FORM 001
HPA/2015

Health Protection Agency
Male', Republic of Maldives

Reporting Facility	☐ ***Re-notification** (required for changes in diagnosis (e.g. Dengue Fever to DHF), case confirmation or outcome (e.g. death).

Notifiable Diseases (place ✔appropriately)

Immediately notifiable via form and Telephone (✆+960 3014496)	**Notifiable within 24 hrs to HPA**
☐ Acute Flaccid Paralysis (use Polio investigation form) ☐ Cholera ☐ Diphtheria ☐ Encephalitis (specify organism if known)_____ ☐ Food Poisoning (use investigation form) ☐ Measles (complete measles investigation form) ☐ Meningitis (specify organism if known)_____ ☐ Mumps ☐ Rabies ☐ Rubella / ☐ Congenital rubella syndrome ☐ Tetanus / ☐ Neonatal tetanus ☐ Tuberculosis (use TB investigation form) ☐ Whooping Cough ☐ Yellow Fever	☐ Chikungunya ☐ DF/☐DHF/☐DSS ☐ Filariasis ☐ Hepatitis A / B/ C/ D/E (circle appropriately) ☐ Leprosy ☐ Leptospirosis ☐ Malaria ☐ Plague ☐ Scrub Typhus ☐ SARI (Severe Acute Respiratory Infection = ARI requiring hospital admission) ☐ Typhoid/ ☐Paratyphoid (complete case investigation form) ☐ Toxoplasmosis/ ☐ Congenital toxoplasmosis ☐ Other emerging disease (specify)_____

Case Details (Mandatory fields are marked with (*) and underlined. Please make sure to complete them.

1-*Case classification: Suspect ☐ Probable ☐ Confirmed ☐ (as per surveillance case definition)

2-*Patient Nation ID No: A_____ For foreigners include passport number	**3-*Patient Name:**	**4-*Age:** YY / MM	**5-*Sex:** ☐M ☐F If pregnant ☐
6- *Patient's residential Address (pls confirm with patient.)	**7-*Atoll/Island**	**8-Contact number(✆)**	**9-Foreigners** country of origin

10-*Date of onset of illness: DD / MM / YYYY	**11-Date of consultation:** DD/ MM /YYYY
12-*Patient category ☐**Out-patient** ☐**In-patient:** ☐ Ward _____ Bed _____ ☐ICU _____ Bed _____	**13-*Case outcome:** ☐ Death ☐ On treatment ☐ Referred to higher center ☐ Recovered with disability ☐ Recovered fully

14- Recent travel history if relevant (include countries visited)

15- Date of arrival in Maldives: DD/ MM/ YYYY

16-Clinical details (include risk factors, mode of transmission, etc.) **17- Condition of patient:** ☐ Stable ☐ Sick ☐ Critically ill	**18-Laboratory Confirmation:** ☐ Confirmed: Test specifics_____ ☐ If Requested, Date: DD/ MM /YYYY ☐ Not Requested
Notifier details (eg:Dr, Nurse ,HW or other designated person) Name:_____ Designation: _____ Signature: _____ Date: DD/ MM/ YYYY	**Data entry use** (use by PHUs and entry users) Date received: DD/ MM/ YYYY Date of entry: DD/ MM/ YYYY Checked and entered by: _____

For further information or inquiries, please contact:
Health Protection Agency, Ministry of Health,
Roshanee Building, Sosun Magu, Male'.
Telephone: +960-3014 496, Hotline: +960-3014 333, Fax: +960-3014 484 email: hpa@health.gov.mv
Forms and case definition booklet are available on http://www.hpa.gov.mv , http://www.health.gov.mv

Revised 21st Jan2015

3. Measles Rubella Investigation form

Measles and Rubella Case Investigation Form
Health Protection Agency
Male', Maldives

Form 004
HPA/2015

Reporting Institution:

Instructions:
1. This form should be completed for **each suspected or confirmed measles** case.
2. All cases must have samples collected and send to IGMH lab for testing.
3. Attach copies of documents showing evidence of measles vaccination.

Outbreak number and ID
Only in outbreaks(HPA use only)

Minimum clinical criteria for each suspected Measles case
1. Fever over 101 degrees F(38.3 °C) or Hot and
2. Rash-like illness for over 3 days; and
3. One of the following, cough, runny nose, red eyes.

☐**Measles**

☐**Rubella**

Case identification	**Date of investigation:** ___/___/_____		
1-Patient ID card Number Foreigners Passport number	**2-Date of Birth:** ___/___/_____	**4- Age :** (yy/mm)	**5-Sex:** ☐ Male or ☐ Female
3- Name of the patient:		**Contact Number:**	
Address:	**Atoll:**	**Island:**	

Travel History

Clinical Information **LABORATORY SAMPLE MUST BE TAKE 72 hours AFTER ONSET OF FEVER.**

Date onset of Rash: ___/___/_____ (dd/mm/yyyy)

1. Fever(>101F or 38 °C)	☐Yes	☐No	**Date of onset of fever:** ___/___/_____
2. Runny nose (coryza)	☐Yes	☐No	
3. Conjunctivitis or red eyes	☐Yes	☐No	
4. Cough	☐Yes	☐No	

Vaccination History

MMR vaccination status	**Measles vaccination status**
No of doses _____ ☐ Yes: Date of last dose:_____ ☐No: reason:_____	No of doses _____ ☐ Yes: Date of last dose:_____ ☐No: reason:_____

Serum Sample collection	**IGMH Lab ID:** ___/___/___	**Virology Sample collection**	**IGMH Lab ID:** ___/___/___
Data of collection		Data of collection	
Date of send to IGMH lab		Date of send to IGMH lab	
Date of Received by IGMH lab		Date of Received by IGMH lab	
Adequate sample	☐Yes ☐No	Adequate sample	☐Yes ☐No
Date of result		**Date of result**	
Result (IgM)	☐+ve, ,	**Results virus detection**	☐-ve ☐+ve
	☐-ve	**Genotype**	
	☐ equivocal	**Date of result to HPA**	

Contact tracing

	Name	Age	Immunization status (immune=vaccinated for Measles or MMR)		Vaccination Date	Phone number
1			☐Immune	☐Non immune		
2			☐Immune	☐Non immune		
3			☐Immune	☐Non immune		
4			☐Immune	☐Non immune		
5			☐Immune	☐Non immune		

Case investigated by

Name of the investigator	**Position**
Date :_____	**Sign :**_____

Final Classification (to be completed by Health Protection Agency)

1-☐ Clinically Confirmed Measles;
2-☐ Laboratory Confirmed Measles;
3-☐ Epidemiologically Confirmed Measles;
4-☐ Laboratory Confirmed Rubella;
5-☐ Epidemiologically Confirmed Rubella;
6-☐ Discarded;
7-☐ Pending)_____

HPA SURVEILLANCE USE

Date of Notification to HPA ___/___/_____

For further information or inquiries, please contact:
Health Protection Agency, Ministry of Health, Roshanee Building, Sosun Magu, Male'.
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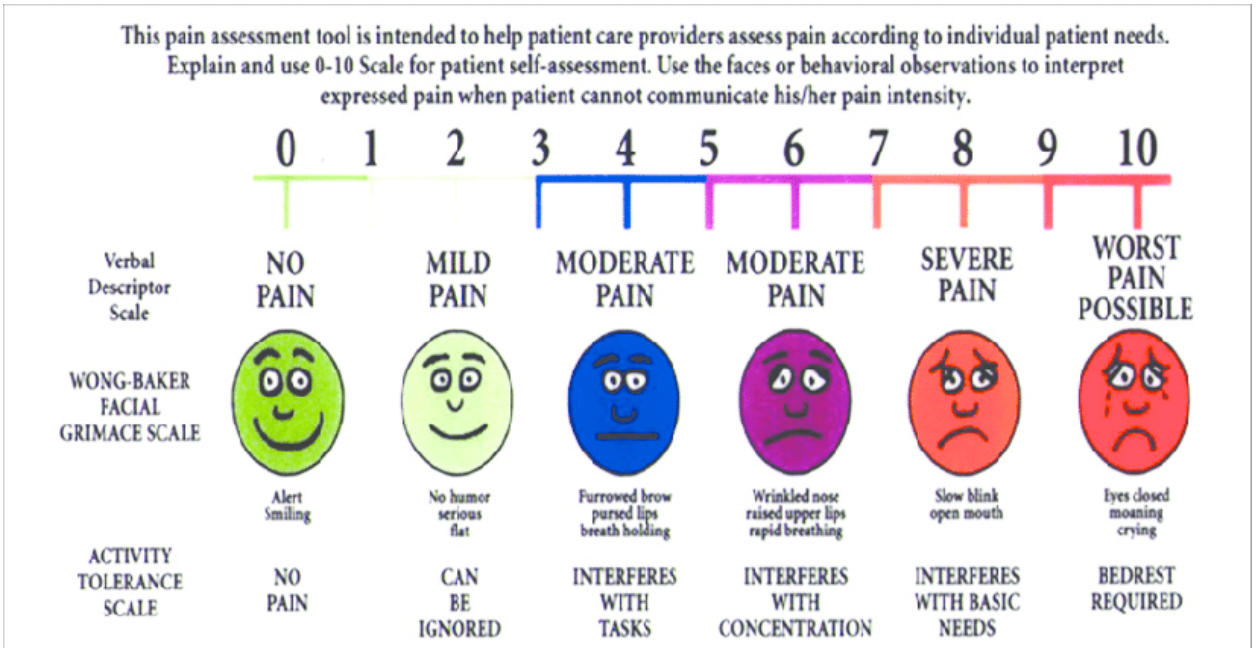
Revised 21st Jan2015

4. Visual analogue scale pain assessment



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