CHIKUNGUNYA VIRUS: EVIDENCE FOR GLOBAL POLICY, PRACTICE AND RESEARCH IN DISEASE MANAGEMENT, SURVEILLANCE, AND MOSQUITO CONTROL

by

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DECLARATION

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Zhili Chen was responsible for the overall creation and writing of the manuscripts. As the primary author, I conceived and developed the manuscripts, conducted the comprehensive search for studies to be included in the systematic review and assessed each paper for eligibility. After that, critical appraisal, data extraction and data synthesis with meta-analysis were conducted. I was also responsible for the revisions by reviewers to the paper, its documentation and acted as corresponding author.

Assoc Prof Craig Lockwood Signature:_____ Date:_____

Assoc Prof Craig Lockwood contributed to the supervision of the research, assisted in data interpretation and the evaluation of manuscripts. I hereby give my permission for this submitted publication to be included in Zhili Chen's doctoral thesis for submission to the University of Adelaide.

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To God be the glory, great things you have done You have led the way in front of me and responded to my prayers when I learnt to put you first in everything I do. Thank you Lord Jesus Christ, for your unconditional love and joy forever in my heart.

DEDICATION

In loving memory of my twin sister, Chen Zhihui (3 May 1988–6 June 2011).

I dedicate this doctoral thesis in remembrance of my twin sister, Chen Zhihui, who suffered a *strange* disease for almost five years from 5 June 2006 – 6 June 2011. A series of high fever went on and off for a few weeks despite having medication prescribed by clinics and the hospital. She was not cured and her body became weak and she was unable to work. Medical records showed diagnoses from doctors during the first year of illness ranged from pyrexia of unknown origin (likely connective tissue disease), Epstein Barr virus infection to acute Rickettsia infection. On 27 September 2007, she was declared as being treated for severe rheumatoid arthritis and acute depression. A year later, visits to a hospital found that she had mix connecting tissue disease, pulmonary tuberculosis, lymphadenopathy and suspected dermatomyositis. One and a half years later on 10 February 2010, a memo by a doctor stated that she had juvenile rheumatoid arthritis and was on immunosuppressive drugs – prednisolone and methotrexate. Deformities of fingers and hands were observed, and she was in mid-pain but in a stable condition.

From February 2010 – December 2010, I did my honours year project on her illness, titled *East Meets West: A study of Traditional Chinese Medicine and Western Medical Practice for Juvenile Rheumatoid Arthritis*. The end of the project saw positive findings, together with Zhihui's first public testimony of God's grace and faithfulness during her illness on 19 December 2010 in Trinity Methodist Church, Singapore. She prepared for about six months for her first public speech and song in her life. Many who were present were touched with tears of joy from the testimony of this faithful and cheerful girl, who remembered every word to perfection and sang beautifully from her heart the mandarin worship song, *Paths of Grace*. At the end of her speech, she said, "I am now able to work and am looking forward to help others and to praise Lord Jesus. I sincerely thank Lord Jesus Christ for being my saviour. Then Jesus declared, 'I am the

bread of life. Whoever comes to me will never go hungry, and whoever believes in me will never be thirsty' (New International Version, John 6:35)."

Little did we know that her time was soon up, six months later. I remembered the huge red packet of SGD200 (a third of her pocket money) she gave me in February 2011 for the lunar new year and for me to buy office wear for the start of my career. I remembered that she still experienced bouts of excruciating joint pain, fever and fatigue even under medication. Although she was still young, 23 years, she looked like she had aged considerably, with a stooped back, thinned short hair, dark blood clots underneath the eyes, severely deformed fingers and would walk slowly with an intermittent need for rests. However, she always had a sweet joy in her heart and knew that the Lord Jesus was always with her, backed by her family, relatives and church friends. I remember celebrating our 23rd birthday two doors away from our shop house with Papa, Mummy, Nana and Yongsheng. I remember bringing her to the Universal Studios on 21 May 2011. She was looking forward to it two weeks before the trip. The morning rain could not hinder her eagerness to get there early and check everything out. She must have clocked her longest walk there ever since she had the illness, and that 'expedition' and exploration were so satisfying to her that she went home in the evening fully satisfied and happy.

Zhihui was feeling unwell two days before she passed on, and on the night before she passed away she had her last meal (home-cooked) at home. On the bed we shared, I remembered asking her whether she needed a cup of water in the middle of the night. I got up early on the next morning (6 June 2011) at about 6.45 am to read the newspapers and prepare myself for work. About 7.15 am, I heard her hurry towards the toilet and I followed her. She had soiled her pants and I went to get a clean change of clothes for her. When I came back, I saw her exert her last strength on the toilet bowl and lost her consciousness. I screamed and a sudden realisation hit hard, that I might have lost her forever. Everyone woke up, came to her rescue, and brought her to her bed. We screamed, we talked, we prayed. My mum shouted, 'I love you, Huihui.' I checked her

heartbeat and took her pulse but there was none and I performed resuscitation on her, learnt from a YouTube video a few days before. The ambulance finally came. We went to the hospital but we lost her to myocarditis.

'You have fought the good fight, you have finished the race, you have kept the faith' (2 Timothy 4:7). My sister, Zhihui, had lived a strong legacy; her kindness, gentleness and pure heart will always be remembered. We know she is in heaven with our Lord Jesus Christ, where God will 'wipe away every tear from your eyes. There will be no more death or mourning or crying or pain, for the old order of things has to pass away' (Revelations 21:4).

I am still investigating your illness. A year later, I chanced upon an email seminar announcement on Chikungunya disease, a disease that manifests in extreme fever and joint pain. Step-by-step, I begin to piece every puzzle together, and have no reason now not to believe that the *strange* disease you had all along was Chikungunya disease. I am determined to do all I can to bring this destructive illness to light for many patients and their families who have or are unwittingly suffering from this disease.

I love you, Huihui. You have asked me before on the bed whether it was better to be in heaven or on earth. I still say that it is better to be in heaven, because you will be with the Lord and there is no pain and suffering. May you rest in peace.

Your twin sister,
Lili

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ABBREVIATIONS

AAIs	Arthritogenic *Alphavirus* Infections
ADL	Activities of Daily Living
AGAUR	Agència de Gestió d'Ajuts Universitaris i de Recerca
AGREE	Appraisal of Guidelines for Research and Evaluation
ALT	Alanine transaminase
ArcGIS	Geographic Information System
BGS	BioGents Sentinel™
BFV	Barmah Forest virus
BI	Breteau Index
BPI	Barthel Pain Index
Bti	*Bacillus Thuringiensis Israelensis*
CCPPRB	Comit´e Consultatif de Protection des Personnes dans la Recherche Biom´edicale
CD4+	Cluster of differentiation antigen 4
CDC	Centers for Disease Control and Prevention, USA
CDC-EH	Centers for Communicable Diseases and Prevention— Environmental Health
CDNA	Communicable Disease Network Australia
CENTRAL	Cochrane Central Register of Controlled Trials
CHIK	Chikungunya
CHIKV	Chikungunya Virus
CLINHAQ	Clinical Health Assessment Questionnaire
CINAHL	Cumulative Index to Nursing and Allied Health
CReMS	Comprehensive Review Management System
CI	Container Index
CI	Confidence Interval
CRD DARE	Centre for Reviews and Dissemination Database of Abstracts of

	Reviews of Effects
DAS28	Disease Activity Score 28
Device TB2	Diflubenzuron
DDT	Dichlorodiphenyltrichloroethane
DMARDs	Disease-modifying Antirheumatic Drugs
DMSO	Dimethyl sulfoxide
DUET™	Dual-action Chemical Adulticide
ECDC	European Center for Disease Prevention and Control
ELISA	Enzyme-linked Immunosorbent Assay
ESR	Erythrocyte Sedimentation Rate
FUO	Fever of Unknown Origin
GBP	Great Britain Pound
GHSR	Groupe Hospitalier Sud Reunion
G-I-N	Guidelines International Network Library
GIS	Geographic Information System
GOARN	Global Alert and Response Network
GPs	General Practitioners
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAQ	Health Assessment Questionnaire
HBV	Hepatitis B virus
HCQ	Hydroxychloroquine
HCV	Hepatitis C virus
HRCS	Health Research Classification System
HRQoL	Health-related Quality of Life
HI	House Index
HIV	Human immunodeficiency virus
IADL	Instrumental Activities of Daily Living
ICRES	Integrated Chikungunya Research

IEDCR	Institute of Epidemiology, Disease Control and Research
IFN	Interferon
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IVM	Integrated Vector Management
JBI	Joanna Briggs Institute
JBI-MAStARI	Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument
JBI-SUMARI	Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information
KdT	Knockdown time
KEMRI	Kenya Medical Research Institute
LC	Lethal concentration
LILACS	Latin American and Caribbean Health Sciences Literature
LUTS	Lower Urinary Tract Symptoms
MAC-ELISA	Immunoglobulin M Antibody-capture Enzyme-linked Immunosorbent Assay
MAYV	Mayaro virus
MD	Mean Difference
MeSH	Medical Subject Headings
MOH	Ministry of Health
MOS SF-12	Medical Outcomes Study Short Form-12
MOS SF-36	Medical Outcomes Study Short Form-36
MTX	Methotrexate
NAMRU-2	Naval Medical Research Unit No. 2, Cairo
NAMRU-3	Naval Medical Research Unit No. 3, Cairo
NEA	National Environment Agency
NGC	National Guideline Clearinghouse
NHMRC	National Health and Medical Research Council

NHS	National Health Survey
NIH	National Institutes of Health
NIHRD	National Institute of Health Research and Development
NR	Not Reported
NRS	Numerical Rating Scale
NSAIDs	Non-steroidal Anti-inflammatory Drugs
nsP	Non-structural Protein
NVBDCP	National Vector-Borne Disease Control Programme
OR	Odds Ratio
ONNV	O'nyong-nyong virus
ORF	Open Reading Frames
PAHO	Pan American Health Organization
PI	Pupa Index
P value	Probability Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
ProQuest	Power of discovery through research
PubMed	Public/Publisher MEDLINE
PusKesMas	Pusat Kesehatan Masyarakat
QH	Queensland Health
RCTs	Randomised Controlled Trials
RevMan 5.2	Review Manager 5.2
RR	Resistance ratio
RRV	Ross River Virus
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RNA	Ribonucleic Acid
RV	Relative Variation
SD	Standard Deviation
SE	Standard Error

SF-MPQ	Short-form McGill Pain Questionnaire
SFV	Semliki Forest Virus
SIGN	Scottish Intercollegiate Guidelines Network
SINV	Sindbis Virus
SMD	Standard Mean Difference
SSZ	Sulfasalazine
TESSy	The European Surveillance System
ULV	Ultra-low Volume
USA	United States of America
USAID	United States Agency for International Development
USD	United States Dollars
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO	World Health Organization
WHOLIS	World Health Organization Library and Information Networks for Knowledge Database
WHO SEARO	World Health Organization Southeast Asia Regional Office

THESIS ABSTRACT

Background: Chikungunya virus is a member of the mosquito-borne *Alphaviruses* accountable for the unexpected rise in crippling febrile arthralgia in the past decade. The continued increase in mortality and morbidity attributed to Chikungunya in at least 55 affected countries highlights uncertainty on the effectiveness of Chikungunya management strategies. Given that these strategies are included in numerous public health systems worldwide, it is necessary that an inaugural critical review of international evidence be conducted, resulting in research findings that can facilitate decision-making in practice and policy.

Aims: This thesis specifically aims to conduct three comprehensive systematic reviews, to summarise evidence and to confirm the effectiveness of clinical manifestations management, early diagnosis of disease, disease education, public health surveillance systems and mosquito control strategies in Chikungunya. Thereafter, a content analysis involving the quality evaluation of existing Chikungunya management guidelines, and a cross-examination of guidelines and systematic reviews to formulate new graded evidence-based guideline recommendations is presented.

Methods: The *Joanna Briggs Institute model of evidence-based health care* and its accompanying systematic methodology provided the main conceptual framework and steps to conduct the systematic reviews. In addition, the statement on Preferred Reporting Items for Systematic Reviews and Meta-analysis was followed for reporting purpose. For the content analysis, quality of guidelines was assessed using the Appraisal of Guidelines for Research and Evaluation II instrument and the development of guideline recommendations was based on a comparative content-analytic approach.

Results: Several therapeutics, surveillance and mosquito control interventions werefound to be effective in the management of Chikungunya. The combination

therapy of prednisolone and acecylcofenac may be used to reduce inflammation, which in turn improves quality of life in Chikungunya patients with arthralgia. Chloroquine phosphate is recommended as an anti-viral agent option for Chikungunya-induced chronic arthritis, which was found to be effective in reducing joint pain and morning stiffness. Early diagnosis of Chikungunya can be beneficial to patients, suggesting the importance of Chikungunya early symptom control and disease management. Effective and rigorous surveillance systems are affirmed to play a vital role in reducing Chikungunya transmission, although high quality research findings are needed to support the finding. Single vector control interventions (such as fenitrothion, temephos, *Bacillus thuringiensis israelensis*, poecilia, pyriproxifen-treated bed nets and nighttime ultra-low volume adulticiding using DUET™) can be effective in short-term transitory control, to reduce the number of immature and adult mosquitoes *Aedes aegypti* and *Aedes albopictus*. Further, intensive mosquito control operations combining all chemical, biological and habitat control appeared to be effective in reducing *Aedes albopictus* eggs and adult populations. Existing Chikungunya guidelines were of low methodological quality and the *rigour of development* was the lowest-scoring domain. Twenty evidence-based guideline recommendations of grade B were carefully formulated. Research limitations included the paucity of high quality evidence from primary studies, small or inadequate samples sizes and poor reporting of interventions parameters.

Conclusion: The call to increase and improve research on Chikungunya management interventions is reiterated. Clinicians and public health providers should consider new research evidence that clarifies the desirable and undesirable effects and be open to potential effective management strategies for utilisation in differing contexts.

1 Introduction

1.1. Chikungunya

1.1.1. Mosquito-borne arthritogenic *Alphavirus*

Vector-borne disease is the main cause of human morbidity and mortality between 1700 and 2000, more than all other causes combined.[1] The incidence of people infected by mosquito vectors, in particular, is overwhelming. According to the 1996 World Health Organization (WHO) report, this small insect is accountable for a few million fatalities and many more morbidities each year.[2] Although Malaria and Dengue have taken the limelight as widely transmitted mosquito-borne diseases[2], the past decade has also seen epidemics attributed to the group of seven arthritogenic *Alphavirus*es belonging to the *Togaviridae* family.[3, 4]

The arthritogenic *Alphavirus*es are the Chikungunya virus (CHIKV), Ross River virus (RRV), O'nyong-nyong virus (ONNV), Barmah Forest virus (BFV), Mayaro virus (MAYV), Sindbis virus (SINV) and Semliki Forest virus (SFV).[3, 4] These viruses are enveloped positive-sense, single-stranded ribonucleic acid (RNA) viruses with a genome of approximately 10 - 12 kb in length. The *Alphavirus* genome is transcribed as two open reading frames (ORF), with the first ORF encoding three structural proteins (capsid, p62, E1) and the second ORF encoding the non-structural proteins (nsP1, nsP2, nsP3, and nsP4), which then undergo proteolytic processing that is necessary for the transcription and replication of the viral genome.[5, 6]

The emergence of athritogenic *Alphavirus*es infections (AAIs) epidemics worldwide poses a serious public health issue. It was estimated that 1.4 - 6.5 million people were infected with CHIKV in India during the 2005 - 2007 epidemics[3], about two million people were infected with ONNV in Uganda in the 1959 epidemic[7] and about 500,000 people acquired the RRV infection in Fiji during the 1979 epidemic.[8]

The principal focus of this thesis is chikugunya (CHIK). CHIK is a debilitating

mosquito-borne *Alphavirus* accountable for the unexpected rise in epidemics of febrile arthralgia in the past decade. A term developed to address the disease, infection or the virus, CHIK is a Makonde word from Tanzania and Mozambique that means *that which is bent up* and refers to the stooped posture of patients suffering from CHIK-induced joint pain.[9] To indicate clear reference to the CHIK virus and CHIK virus infection, this thesis will use the abbreviation, CHIKV and CHIKV infection respectively.

1.1.2. Epidemiology

CHIK may be traced as far back as 1779, in a *Knokkel-koorts* (a Dutch word meaning knuckle or joint) febrile epidemic, as recorded in the logbook of the Dutch physician, Dr David Bylon, in Batavia, Dutch East Indies (present day Jakarta, Indonesia).[10, 11] The first modern case of CHIK in humans was reported in 1952 - 1953 at Tanganyika, East Africa[12-14], while the first identified CHIK outbreak occurred in Bangkok, Thailand, in 1958[15] followed by a decade-long epidemic in India from 1963 - 1973.[16] While there were no further epidemics for 30 years, the CHIK epidemics re-emerged from 2004 onwards.[17] The people of Kenya, specifically in the area of Lamu province and the city of Mombasa, were hit by the CHIK epidemic.[18] This was soon followed by a series of epidemics that affected many areas around the Indian Ocean[19], including the La Reunion Island, where 266,000 (38.2%) of the population[14, 20] were infected and the Union of the Comoros, where more than 225,000 people were infected.[16] The epidemic reached India, affecting millions of people from 2005 - 2007.[14] As of 10 February 2014, autochthonous cases were found in 55 countries, including 25 countries in Africa, 19 countries in Asia, six countries in the Americas, two countries in Europe and three countries in the Oceania/Pacific islands.[21]

1.1.3. Strains and transmission cycles

Phylogenetic studies have recorded three genotypes of CHIKV strains, as characterised by their geographical localities – the Central/East/South African, West African and the Asian strains.[22-24] The Central/East/South African strain of CHIK has the largest

distribution of all, affecting Central/East/South Africa, India (for the 1963 - 1973 outbreaks) Indian Ocean islands, Europe, Australia and Japan. This is followed by the Asian strain found in India (2005 - 2007 outbreaks) and Southeast Asia and lastly, the Western African strain in Western Africa.[22]

The differing genotypes may explain the two distinct transmission cycles of CHIKV – the sylvatic cycle and the urban cycle. In Africa, CHIKV was first described circulating in a sylvatic cycle between forest-dwelling mosquito species *Aedes, Culex* and *Anopheles* and wild monkeys, galagos, squirrels, gossas and rodents. The sylvatic transmission cycle was characterised by quiescence duration of three to four years.[23] The virus then came to be transmitted in an urban transmission cycle in Asia between the main mosquitoes *Aedes (Stegomyia) aegypti* (Linnaeus) and *Aedes (Stegomyia) albopictus* (Skuse) and humans via a bite by an infected mosquito.[23, 25] The CHIKV is introduced to a susceptible human host when the CHIK-infected haematophagous female mosquito anaesthetises the human skin using its saliva and feeds on human blood plasma to obtain proteins needed for its eggs, inadvertently transferring the CHIKV carried in the salivary glands near the proboscis into the bloodstream of the human dermal tissue. The human then becomes infected with CHIKV and the virus replicates within the body, causing CHIK. The subsequent blood meal by another susceptible female mosquito will transfer the virus from one human to the next.[26] There is no direct human-to-human transmission of CHIK, except through vertical transmission, as documented in one study.[27]

1.1.4. Pathogenesis

After the mosquito bite, CHIKV replicates in the dermal fibroblasts, followed by virus dissemination in the bloodstream to the hepatic endothelial cells, muscle satellite cells, joint fibroblasts, lymphatic tissues and encephalitic tissue.[28] There is an incubation period of two to four days before clinical symptoms and signs appear.[28] During the third to fifth day of infection, viral load may rise to a high of 10^{10} copies of RNA per one millilitre serum[29] (median load is $10^{4.6}$ copies of RNA per one millilitre serum[30]),

with a corresponding increase in type I interferons as part of the innate immunity to restrict replication of CHIKV.[28] A successful attempt by the innate immune response will remove most CHIKV in about seven days and the complete eradication of CHIKV will be aided by the the adaptive part of the immune responses, particularly Cluster of Differentiation Antigen 4 ($CD4^+$) T cells and CHIKV-specific antibody responses.[31-33]

Although the acute stage of CHIKV infection is considerably better elucidated in scientific literature compared to the chronic stage[28, 34], knowledge on the pathogenesis of CHIKV infection is still progressing, likely due to late research interest from unexpected epidemics in the past decade. New susceptible host populations with almost no previous exposure to CHIKV were implicated during the outbreaks, causing notably high pathogenicity in India[35], La Reunion island[36], Union of the Comoros[36] and lately, the Caribbean islands.[37] With widespread transmission of CHIKV, the development of resistant CHIKV strains[38] could lower the effectiveness of current CHIK management interventions. Hence, precautionary measures should be taken, with a regular and conscientious assessment of the effectiveness of interventions.

1.1.5. Clinical presentation

Thiberville and colleagues described acute CHIKV infection with a viral stage from days one to four and a convalescent stage from days five to 14. The viral stage is characterised by a surge in viral load, associated with an increase in interferons and interleukins leading to clinical improvements. On the other hand, the convalescent stage shows minimal viral load, inflammatory response mediators and severity in clinical manifestations.[34] Only about 15% of serologically positive CHIKV patients are asymptomatic.[39]

During the acute stage of infection, a patient infected with CHIKV typically presents with a biphasic or saddle-back fever of at least 38.0°C, lasting several days to weeks.[40] This is often accompanied by arthritic-like symptoms of persistent pain, swelling and redness in major body joints in 80% - 90% of patients and the occasional appearance of

maculopapular rash. Recent studies have reported 70.6% specificity and 83.3% positive predictive value for the triad of fever, arthralgia and rash.[34, 41] Other symptoms that may be present are fatigue, headache, chills and myalgia. Although disease symptoms usually resolve after one to two weeks as a result of the body's innate and adaptive immunity, signs and symptoms such as arthralgia, myalgia, asthenia or fatigue may persist in 40% of infected patients, leading to chronicity of the disease.[34]

The chronic stage of CHIKV infection is commonly characterised by clinical manifestations lasting more than three months[42-44] or disabling arthralgia of at least four weeks from symptom onset.[45] Serious complications for both chronic and acute stages of CHIKV infection have been recorded, with deformed and painful joints[16], neurological disorders[46-49] (e.g. encephalitis and optic neuritis), cardiac disorders[46, 50] (e.g. myocarditis and myocardial infarction), ophthalmological disorders[48, 51] (e.g. macular choroiditis and uveitis), hepatic disorders[46] (e.g. hepatomegaly) or haemorrhage.[47, 52] These clinical manifestations have been found to decrease quality of life, negatively influencing work, family roles, performance and satisfaction.[44, 53, 54]

2.2. Management of CHIK

The successful control of a communicable disease is dependent on a robust public health infrastructure that comprises of health care and environmental officers, clinics and hospitals, research laboratories, health supra-organisations, surveillance and data systems.[55, 56] Apart from disparities in health care standards worldwide, the efficiency and effectiveness to which a public health agency carry out their prevention and control activities also differ, due to the scale and complexity in jurisdiction, collaboration, dedication and funding, and even due to the the socio-political stigma of epidemic diseases. Effective disease control and prevention rely on a strong comprehension of the complicated determinants involved in disease aetiology and pathogenesis. Given that interest and research funding in CHIKV infection are augmented only in the past decade as the virus infects populations of developed

countries, understanding of the infection and meeting demands through informed disease control still requires considerable work.

CHIK is currently managed through an array of interventions, the bulk of which comprise traditional modalities of disease management interventions, surveillance and mosquito control, known to effect clinical and public health outcomes. These domains encompass foundational public health protection strategies for vector-borne diseases, as used by the WHO and Centres for Prevention and Control (CDC) in their guidelines, which were hence also adopted in this thesis for the evaluation of CHIK management interventions.[57, 58]

1.2.1. Disease management interventions

1.2.1.1. Clinical manifestations management

There is currently neither a cure nor a licensed vaccine for CHIK, although some vaccine candidates tested on non-humans have proven to be effective and efficacious.[59-63] Only symptomatic treatments are available, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, chloroquine, paracetamol, anti-viral drugs, physical therapy and acupuncture. These measures may not be sufficient and their effectiveness has not been clearly established.[3, 64] A thorough evaluation of the effectiveness of pharmacological and non-pharmacological interventions is needed.

1.2.1.2. Early diagnosis of disease

When clinicians rarely consider CHIKV infection in their differential diagnosis of febrile diseases, patients with CHIKV infection will inevitably receive delayed or no treatment specific for CHIKV infection, and will hence be on the longer route to recovery. This can result in poor care and treatment-related outcomes for patients who may be misdiagnosed as having Dengue, Malaria or even fever of an unknown origin (FUO) during the disease onset.[11, 65] If patients with CHIKV infection only seek health care advice or treatment after a few months when chronic arthritis is more obvious, depending on how the patients present their clinical history, clinicians may then have a

good chance of diagnosing the patient as having a form of arthritis instead of the root cause, CHIKV infection. Therefore, without the early and accurate diagnosis of CHIKV infection by health care practitioners, the situation would be precarious and can severely delay the patient's quest for full recovery from CHIKV infection.[66]

For health authorities to track CHIKV infections, patients are encouraged to visit a licensed doctor at a clinic or hospital when they feel unwell. Patients expect to receive accurate diagnosis and relevant advice on their illness from health care professionals so that they have the correct medical guidance for treatment and recovery.

1.2.1.3. Disease education

Educating clinicians and other health care professionals to recognise signs and symptoms of the spectrum of CHIK is crucial for the functioning of CHIK surveillance and for CHIK patients' recovery.[67-70] One study found that CHIKV infection "is a diagnosis rarely considered by local clinicians, presumably due in part to a lack of information about disease prevalence."[71(p171)] The unpredictable nature of past CHIK outbreaks and the presence of CHIK cases during inter-epidemic periods mean that disease education of patients and health care professionals could play an integral role in the management of CHIK.

Functional re-education of professionals can assist CHIK patients to cope with the debilitating illness while continuing their commitments at home, in the workplace and within society. Sometimes, patient education may be less than ideal, resulting in misconceptions. Misconceptions could be aggravated when the state withholds crucial information on CHIKV infection from the public, as shown from the 2006 CHIK epidemic in La Reunion Island or when patients were not convinced by the given information. For example, some CHIK patients believed that CHIK was an air-borne disease instead of a mosquito-borne disease, despite having access to scientific knowledge. Consequently, some patients did not take precautions against mosquito bites, further increasing exposure to mosquito-borne diseases.[72]

1.2.2. Public health surveillance systems

Public health surveillance has always been a foundational public health strategy. It has existed since 3180 B.C. when there was a great pestilence during the rule of Pharaoh Mempses of the First Dynasty in Egypt.[73] Surveillance is defined as the collection, analysis and interpretation of surveillance data, leading to an appropriate public health response.[56, 74] It is a public health tool used by countries worldwide to perform numerous functions, including promptly detecting disease outbreaks, monitoring the spread of the disease and putting in place outbreak response measures.[56]

Surveillance systems may be generally classified as disease surveillance, vector surveillance or the combination of both. Data on CHIK cases that meet the possible, probable and confirmed case definitions are targeted for disease surveillance whereas vector surveillance addresses data on CHIK vectors, mainly *Aedes Aegypti* and *Aedes albopictus*. Another classification is based on the activeness of surveillance, passiveness or the combination of both. Active surveillance includes hired surveillance officers playing an active role in connecting with health care agencies for the consolidation of surveillance data, compared to passive surveillance that depends on the mandatory passive reporting of data submitted by health care institutions.[75] These surveillance systems may be administered geographically based on the hierarchical structure of the country, region, province, district, locality or enumeration.[76]

Many countries that experienced outbreaks and reported individual cases due to CHIK in the past have developed surveillance systems on national and sub-national levels with the overall objective of decreasing CHIK transmission and improving public health decision-making with up-to-date epidemiological surveillance reports. However, these surveillance systems can be implemented late, hence lowering their effectiveness in the early detection of outbreaks, as seen from studies during the 2006 epidemics in La Reunion Island and India. The French authorities from La Reunion Island took approximately a year to realise the severity of the CHIK epidemic before initiating response and control strategies. It was too late by then and the people in La Reunion

reportedly felt a sense of "neglect and abandonment."[72(p174)] In India, the WHO reportedly failed to trigger an alarm on the CHIK transmission and lacked active support to the country. In addition, there was a delay in the implementation of surveillance, with a surveillance system only put in place nine months after the first reported CHIKV infection. A complex interplay of factors, including surveillance, might explain the millions of infections and tens of thousands of deaths from the 2006 epidemic in India.[35]

As complete eradication of CHIKV is not possible, a spread of CHIKV during inter-epidemic periods is continued. Hence the role of surveillance to help detect CHIK cases that may often go unnoticed or are misdiagnosed is crucial. Vulnerable regions such as Kenya and Malaysia are continuously exposed to these diseases, with the detection of CHIKV seropositivity among humans in Kenya[77] and the CHIKV seropositivity among healthy Malaysian adults in localities that have no history of CHIK outbreaks.[78] A consistent surveillance of cases including the inter-epidemic periods is important so as to profile CHIK epidemiology, disease trends and more accurately estimate the national burden of CHIK.[68, 70, 79-83]

Although a WHO global strategy for Dengue prevention and control was formulated for 2012 - 2020, there is no similar document from WHO on CHIK prevention and control.[84] There is also uncertainty regarding the performance and usefulness of surveillance systems currently implemented to detect and monitor CHIK. This may be related to the fact that no systematic reviews have been published that address the effectiveness of surveillance systems in CHIK. Hence, there is an urgent need to evaluate the effectiveness of surveillance systems in alleviating the burden of the infections nationally and globally.[66, 85]

1.2.3. Mosquito control

Mosquitoes (Diptera: Culicidae) are the most important vectors responsible for deteriorating human health and debilitating diseases of epidemic proportions,

including Malaria and Dengue, affecting countries worldwide.[1] Consequently, governments of affected countries have invested large efforts and resources towards mosquito control, the mainstay of prevention and control of mosquito-borne diseases.[86]

Importantly, two types of mosquitoes *Aedes aegypti* and *Aedes albopictus* are known to transmit CHIKV.[87] Historically, *Aedes aegypti* was the main vector; however, recent outbreaks have been caused mainly by *Aedes albopictus*. A mutation in the envelope protein gene of a CHIK virus strain named E1-A226V gives the advantageous adaptation and specificity by increasing the viral infection and replication in *Aedes albopictus*.[88] Once thought to have a low capacity for mosquito-to-human transmission because of its zoophilic nature, the Asia tiger mosquito, *Aedes albopictus*, has become a highly intrusive species that originated from the tropical forests of SouthEast Asia and has now spread to 28 countries worldwide.[89, 90] This global transmission has been assisted by temperate climate, a conducive environment for breeding and resting, cross-border transport of goods, human travel and ineffective disease and entomological control strategies.[90, 91] Both mosquito species have a lifespan of about three weeks.[85, 87, 92] The gravid female *Aedes aegypti* has a preference for indoors with diurnal biting activity[93], a flight range of up to 100m and thrives in a more varied environment, compared to *Aedes albopictus*.[94] On the other hand, the *Aedes albopictus* has peak biting times of early morning and late afternoon with an inclination for outdoors and an active flight range of up to 525m.[49, 91, 95, 96] Nelder et al. 2010 highlighted the lack of specific strategies to control *Aedes albopictus* over its long flight range.[97] The differences in biting habits and flight ranges between the two mosquito species can have implications in achieving effective mosquito control.

The objective of mosquito control for CHIK prevention is to eradicate the mosquitoes that can transmit CHIKV. When entomological vectors of CHIKV are reduced, opportunities for human-mosquito-human contact are reduced, lowering the rates of viral acquisition that cause CHIKV infection and subsequent disease in humans.[98] Entomological indices including percentage mortality, Breteau Index (BI) and

Container Index (CI) have been used to assess the effectiveness of mosquito control interventions in CHIK. Mosquito control measures that have been used to reduce CHIKV transmission may be broadly categorised into three types: chemical control, biological control and habitat control.[85, 92, 99] Chemical control consists of the gamut of commercial synthetic chemical insecticides, including pyrethroids and organophosphates. Although they have also been used pervasively and successfully in the reduction of Dengue and Malaria mosquito vectors[100], the use of chemical larvicides (e.g. Temephos) and adulticides (e.g. Deltamethrin) in CHIK has encountered several issues such as *Aedes aegypti* and *Aedes albopictus* resistance, unintended adverse effects (e.g. contamination of vegetation) and insecticide registration requirements.[100, 101] Hence, considerations should be made when employing these entomological control measures. Biological control consists of measures that are derived biologically from plants (e.g. essential oils), animals (e.g. predatory fishes) or microorganisms (e.g. *Bacillus thuringiensis israelensis* [Bti]).[92, 102, 103] They are increasingly viewed as viable alternatives to chemical insecticides, due to their perceived effectiveness, biodegradability and environmental friendliness.[104] However, issues including ecological impact needs to be taken into account in the use of biological control. Habitat control consists of landfill cleaning and source reduction through the removal of water from receptacles, household containers and even large leaves.[85, 92]

With the increasing spread of CHIK vectors, public health officials and national agencies have implemented mosquito control strategies to control the growth of vectors *Aedes aegypti* and *Aedes albopictus*; however, some strategies may be ineffective or unnecessary.[1, 90] Experts in the field have called for effective, feasible and sustainable mosquito control measures for CHIK.[35, 97] Hence, an investigation on mosquito control strategies based on evidence is crucial to protect public health and halt transmission of CHIK.

1.3. Research objectives

The first objective of this research is to critically analyse currently available research studies and present the best available evidence related to the effectiveness of management interventions of CHIK. This is achieved through the conduct of a series of systematic reviews, specifically determining:

- The effectiveness of clinical manifestations management interventions on health-related quality of life (HRQoL) outcomes of patients with established AAIs
- The effectiveness of early diagnosis of the disease on HRQoL outcomes of patients with established AAIs
- The effectiveness of disease education on HRQoL outcomes of patients with established AAIs
- The effectiveness of public health surveillance systems in CHIK
- The effectiveness of mosquito control strategies in CHIK.

The second objective of this research is to determine the methodological quality of existing CHIK management guidelines. Subsequently, new graded evidence-based guideline recommendations pertaining to the management of CHIK are presented based on a careful cross-examination of systematic reviews and selected guidelines.

There is a pronounced need for valid and reliable evidence to guide practice and research, and to improve health outcomes of CHIK patients and populations living at risk of CHIK infection. Research findings on CHIK presented in this dissertation can serve as a comprehensive platform to improve CHIK patients' health outcomes and inform health care decisions, national policies and funding.

1.4. Significance of research

1.4.1. Public health importance

Studies have found that care for patients is not always at its best, with wide disparities between actual and expected care, large number of patients receiving unsuitable or damaging care, and that only about half of patients received care based on best

available evidence.[105, 106] CHIK is a mosquito-borne *Alphavirus* responsible for the unexpected rise in epidemics of debilitating febrile arthralgia in the past decade.[35, 82] Although numerous strategies have been employed to contain the virus, the transmission of CHIK continues to increase globally[21, 107-110], heightening its importance in the public health agenda[57, 111, 112] and signalling the growing uncertainty about the effectiveness of interventions.[35, 49, 113] Ineffective management of CHIK outbreaks can lead to impaired quality of life[42, 43], loss in productivity[53], stressed health care systems[114], loss of tourism revenues[115] and hindrance in economic growth.[115] The public health importance of CHIK can be elucidated through the high rates of morbidities and mortalities, the problem of underreporting, the impact of CHIK and their interventions on HRQoL.

1.4.1.1. Morbidities and mortalities

Although estimations of morbidity and mortality cases due to CHIK in the world were not obtainable, the prevalence and incidence of CHIK have been reported in some affected areas. The 2005 - 2006 outbreak in La Reunion Island showed 266,000 (38.2%) of the population[14, 20] infected with CHIK and about one fatality in every 1000 cases.[116] The similar period found 225,000 people from the Union of the Comoros infected with CHIK.[16] CHIK epidemics occurring in India from 2005 - 2007 infected millions of people.[35] The number of CHIK cases continues to rise, for example, in Singapore, with an unprecedented 1059 cases in 2013 compared to 22 in 2012, 12 in 2011 and 26 in 2010 cases.[107, 117] As of 10 February 2014, autochthonous cases of CHIK were found in 55 countries worldwide.[21]

1.4.1.2. Problem of underreporting

Post-epidemic studies have shown gross underestimation of CHIK morbidity and mortality cases.[10, 11, 35] For instance, describing CHIK as a "major public health disaster", Mavalankar et al. 2007 believed that there was a gross underestimate of CHIK cases for the 2006 epidemic in India.[35(p306)] The study authors estimated 6.5 million infected

patients instead of 1.39 million and between 1194 and 19,168 deaths instead of no fatality as reported by the Indian government.[35] Many reasons were attributed to severe underreporting, including: (1) the absence of a systematic surveillance system; (2) inactive aid from the WHO; (3) lack of virus testing facilities; (4) common practice of not reporting CHIK cases by private clinicians to health authorities; (5) no registration of deaths at home to the government; (6) poor health funding; and (7) the government's avoidance of full disclosure of deaths from epidemics.[35]

Misdiagnosis of CHIK clinical symptoms could further aggravate the under-reporting. Given the similarity between the triad (fever, arthralgia and rash) of clinical manifestations for CHIK and other types of *Alphavirus* infection, outbreaks historically ascribed to Dengue, dynga, mal de genoux, abu rokab and three-day fever were probably due to CHIK.[10, 11] In a scholarly article published in 1971, Dr Donald E Carey wrote, "It [1923 Dengue outbreak in Calcutta] was immediately apparent that the authors were describing not an epidemic of the disease presently called Dengue, but rather an epidemic similar in all respects to that associated with CHIKV in 1964 in South India."[11(p243)] Evidence collected from this study gave "a good basis for believing that the term *Dengue* was originally applied, in the early nineteenth century, to a clinical syndrome closely resembling that is now associated with CHIKV infection."[11(p243)]

1.4.1.3. HRQoL

CHIK patients with chronic symptoms often report debilitating arthritic pain and loss in productivity, resulting in a sharp decline in HRQoL.[42, 43, 118-120] According to Bowling (1995), HRQoL is defined as

> The optimal levels of mental, physical, role (e.g. work, parent, carer, etc.) and social functioning, including relationships and perceptions of health, fitness, life satisfaction and well-being. It should include some assessment of the patient's level of satisfaction with treatment, outcome and health status and with future

> prospects. HRQoL excludes factors such as sufficiency of housing, salary and the opinions of the immediate environment.[121(p3)]

The WHO Quality of Life group (1993b) has a similar yet broader definition of quality of life, defined as

> An individual's perception of their position in life in the context of culture and value systems in which they line and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships to salient features of their environment.[122(p3)]

From the definitions[121, 122], HRQoL encompasses more than the standard reporting of clinical case management. More importantly, it includes patient-centred perception and satisfaction with treatment, outcomes, health status, life and well-being, which are important to meet the ultimate goals of medical treatment – to increase survival rates and improve quality of life. Traditional clinical indicators of outcome are increasingly viewed as inadequate, especially when symptoms persist more than three months from disease onset (also termed the chronic stage of disease).[123]

Standardised survey assessment instruments are used to obtain patients' self-reported HRQoL. Health related quality of life can be analysed through specific domains, including overall HRQoL, disease-specific HRQoL, anxiety, depression, emotional functioning, fatigue, general health, pain, physical functioning, role functioning, sleep and social functioning.[121] To date, several of these surveys, such as the Medical Outcomes Study Short Form 36-item/12-item (MOS SF-36 / MOS SF-12) Heath Survey and the Clinical Health Assessment Questionnaire (CLINHAQ) were used to understand the impact of disease and its management on patients' HRQoL.[42, 119]

1.4.1.4. Economic and societal burden

CHIK can place a heavy burden on the economy. A cost-of-illness study on the 2005 - 2006 epidemic at La Reunion Island found a total economic burden of about USD60.2 million, with a direct financial loss of USD123 per outpatient and USD2742 per inpatient.[114] In India, the burden of disease during the 2006 epidemic was about 25,588 disability-adjusted life years (DALYs) and an economic loss of at least USD6.3 million.[53] Within an Indian village where the average wage for a male and female is about USD1 and USD0.26 per day respectively, the burden of disease is approximately 6.57 DALYs and an economic loss of USD37.50 per infected patient (with a breakdown of USD6.78 borne by government, USD25.20 borne by patient or family, and USD5.47 for loss of productivity).[124] Besides being an economic burden, CHIK burdens the society, with patients dealing with the crippling effects of painful chronic arthralgia, neurological disorders and other symptoms, affecting their physical, role, emotional and social functioning.[125]

1.4.2. Dearth of research on the effectivesness of interventions

A preliminary review of existing literature revealed no evaluation of primary research studies on the effectiveness of interventions for CHIK. Few would argue that effective management interventions play a positive role in patients' recovery and alleviating the burden of disease on the economy and society. Hence, this thesis serves to address this apparent deficiency by conducting research on the effectiveness of interventions for CHIK.

1.4.2.1. Significance of effectiveness research

Effectiveness is defined as "the extent to which an intervention, when used appropriately, achieves the intended effect. Clinical effectiveness is about the relationship between an intervention and clinical or health outcomes."[126(p87)] In the era of evidence-based practice, effectiveness research plays a significant role in generating scientific evidence to support the use of various health care interventions based on their positive effects to patients' health outcomes and populations living at risk of a particular disease.[127, 128] This is imperative to improving patient care, health care

standards and ensuring prudent use of health care resources. Effective interventions are encouraged for use in specific contexts and ineffective interventions are discouraged or improved based on recommendations from research findings.

1.4.2.2. Concerns raised by researchers

In light of the impact of CHIK epidemics, Padmakumar and colleagues exhorted the use of "effective preventive measures" to reduce patients' misery from the infection.[129(p94)] Several studies have expressed concern that the disease management interventions, including therapeutics[124, 129, 130], surveillance[35, 82, 124] and mosquito control[35, 101, 124] seemed inadequate and doubted their effectiveness. Without a licensed vaccine or a cure, it is vital that solid evidence for the effects of disease management on HRQoL to guide clinical practice and research is establised.[53, 125, 131]

1.5. Structure of thesis

This thesis comprises seven chapters. Chapter 1 provides an overall introduction to the thesis, in particular, the general and specific objectives of research, significance of research, structure of thesis and a background of CHIK and its disease control.

Chapter 2 elucidates the methodology and study designs used to conduct evidence-based effectiveness research. It gives a brief summary of the significance, development and deliverables of evidence-based health care. This chapter subsequently introduces the Joanna Briggs Institute (JBI) systematic methodology used to inform and guide the synthesis of three systematic reviews (Chapters 3, 4 and 6). Following the JBI systematic methodology, accounts of the quality assessment for guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and the content analysis methodology are elucidated in the content analysis.

Chapters 3 - 6 are related studies undertaken that have been (1) accepted in international peer-reviewed journals; or are (2) extracts of manuscripts for submission

to targeted peer-reviewed journals. Figure 1.1 below illustrates the phases of research undertaken for this thesis:

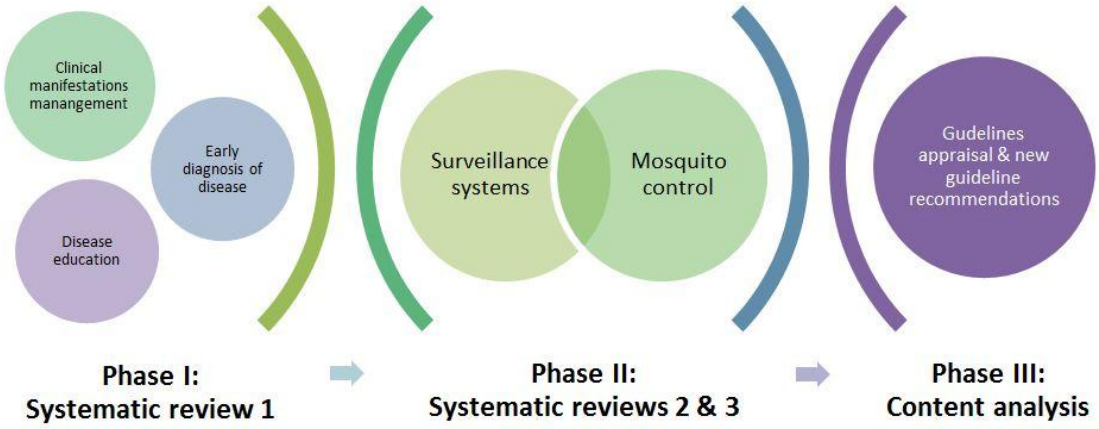

Figure 1.1. Phases of research

Chapter 3 is the first systematic review conducted for phase I research, as shown in Figure 1.1. It examines the effectiveness of disease management interventions on HRQoL of patients with established AAIs, a group of seven *Alphavirus*es including CHIK. As the systematic review found all primary studies on CHIK (with the exception of one on RRV), a decision was made to concentrate subsequent research efforts on CHIK for deeper evaluation into the most common AAI.

Phase I results led to phase II research, specifically investigating the effects of interventions for populations living at risk of CHIK. Hence, phase II research involved the conduct of the second and third systematic reviews, as shown in Figure 1.1. They focused on the exploration of the effectiveness of surveillance systems and mosquito control strategies in CHIK. These achieved objectives are discussed in Chapters 4 and 5 respectively.

The three systematic reviews (Chapters 3 - 5) evaluating the effectiveness of CHIK management interventions prompted the research in phase III. A content analysis (Chapter 6) was conducted to assess the methodological quality of CHIK management

guidelines and to thematically propose new guideline recommendations using a comparative content-analytic approach.

Chapter 7 discusses and concludes on the application of evidence-based decision-making in CHIK management and the addressment of translation gaps through the undertaking of a series of systematic reviews and a content analysis. After which, implications for evidence synthesis and evidence transfer, the focal conduits used in this research, are discussed.

2 Methodology

2.1. Evidence-based health care

2.1.1. Significance

Evidence-based health care has played a significant role in providing scientific proof to validate the use of specific clinical interventions used in health care systems. Sackett and colleagues defined evidence-based medicine as

> The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.[132(p71)]

Thus, evidence-based health care is not based on traditions, hunch or experience, but is rooted in reliable, appropriate and appraised scientific information by systematically generating, synthesizing and transferring research results to clinical and policy decision-making. This demand for appropriate analysis stems from the problems of prevalent unjustifiable variance of clinical activities, incorrect patient care and unnecessary increase in health costs.[133] Even in today's context, only 54.9% of American patients have the best quality health care to their medical problems.[134] Consequently, to account for patients' trust in health care and improve health care delivery, the utilisation of health care interventions by clinicians and healthcare professionals should ideally be backed up by empirical evidence of their effectiveness.

2.1.2. Development

Evidence-based health care had its origins between 1700 and 1800: beginning from Dr James Lind, who performed a randomised controlled trial (RCT) on sailors with scurvy using six different foods; Dr Pierre Charles Alexandre Louis, who investigated the effects of bloodletting on acute pneumonia patients; and Dr Ignaz Semmelweis, who examined the cause of differences in mother and infant mortality between two clinics in Vienna.[135] It was only in 1971 that evidence-based medicine was defined and

championed in a seminal book titled *Effectiveness and efficacy* by Archibald (Archie) Cochrane, who criticised the paucity of solid evidence for rarely disputed usual treatment modalities and rallied for the scrutiny of medical evidence through a unique repository of systematic reviews.[136] This foundation facilitated the growth in the evidence-based health care movement which saw the increase in dedicated research institutes and centres to evidence-based health care, including the establishment of the Joanna Briggs Institute in 1996, a fast-rising international leader in evidence-based health care.[137]

2.1.3. Systematic reviews

Systematic reviews are scholarly papers that attempt to answer a formulated research question based on the systematically identified selection of studies that meet a priori inclusion criteria of types of populations, interventions, comparisons, outcomes and study designs.[138] They can both be quantitative or qualitative in nature and tend to focus on the analysis of the effectiveness, diagnosis, prognosis, cost-effectiveness, meaningfulness, feasibility and appropriateness of specific health care interventions.[126, 139]

The production of systematic reviews is often laborious and daunting, owing to the transparent and reproducible process while minimising bias. Therefore, it is of little wonder that systematic reviews are regarded as having the strongest level of scientific evidence for each type of study design (e.g. RCT, quasi-experimental trial, cohort study, descriptive study and expert opinion).[126, 139] Systematic reviews play an important role to appraise, collate and transform existing and growing evidence from primary research studies into usable data to better inform health care policies and decision-making. They are condensed critical summaries made accessible for busy clinicians, health care professionals and managers who only have a maximum of an hour weekly for medical updates, very different from the ideal reading of 19 articles every day.[132, 140]

Although systematic reviews may inform clinical practice, it is recognised that they should never be substitutes for sound clinical judgement and expertise for modern medical treatments. Rather, they assist clinicians in making appropriate decisions based on best available evidence.[132, 141] They are also recognised as important sources to identify gaps in evidence and play an important role in the identification and prioritisation of research topics often not captured in individual primary studies.[142]

2.1.4. Practice guidelines

Published guidelines serve as important sources of condensed information to guide clinicians and health care professionals in practice and decision-making.[143] Guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific circumstances."[144(p35)] Used in tandem with clinical expertise and personalised patient care, guidelines advise clinicians to use effective interventions and give low priority to interventions that are outdated or discouraged.[145, 146] Hence, well-constructed guidelines play a critical role in increasing health care quality, improving patient outcomes, streamlining practices and maximizing resources.[146]

Guidelines synthesised from systematically derived and appraised scientific evidence (evidence-based guidelines) are only a recent endeavour spearheaded by the WHO in the past decade.[147] Prior to 2003, WHO guideline recommendations were largely based on expert opinion and not systematic reviews on the effectiveness of health care interventions. Even after the implementation of *guidelines for guidelines* within the WHO from 2003 and the set-up of the WHO guidelines review committee in 2007, several studies have observed the sluggish uptake of research evidence in guideline development and the questionable quality of guidelines within and external to WHO.[148, 149] Guidelines that do not ensure rigour in development risk delivering incomplete, inaccurate or misleading guidelines recommendations. This will affect patients' health outcomes and cause populations to be living at risk of the disease. Sub-standard guidelines can only provide limited benefits to their users.[150] To address the

inconsistencies in quality, several resources, such as the WHO Handbook for Guideline Development[147] or internationally validated appraisal instruments for guidelines (e.g. AGREE II instrument[151]) may be used.

2.2. The JBI approach to synthesis

To carry out the systematic reviews, the JBI approach was followed. The JBI approach involves the twin understanding of the JBI model of evidence-based health care and the JBI systematic methodology that have been used to guide the production of the systematic reviews.

The JBI model of evidence-based health care is a cyclical conceptual model of evidence-based practice, which attributes clinical decision-making to the best available evidence, clinician's judgment, patient's preferences and the health care context in order to reach the goal of improved global health. The model recognises that the clinician's practical experience plays a role in influencing evidence for practice and establishes a framework by which health care professionals may base their patient care on the latest evidence or information developed through rigorous and systematic clinical research. As shown in Figure 2.1, the four components of the JBI model of evidence-based health care are health care evidence generation, evidence synthesis, evidence (knowledge) transfer and evidence utilisation; systematic reviews play an important role in evidence synthesis.[126, 128]

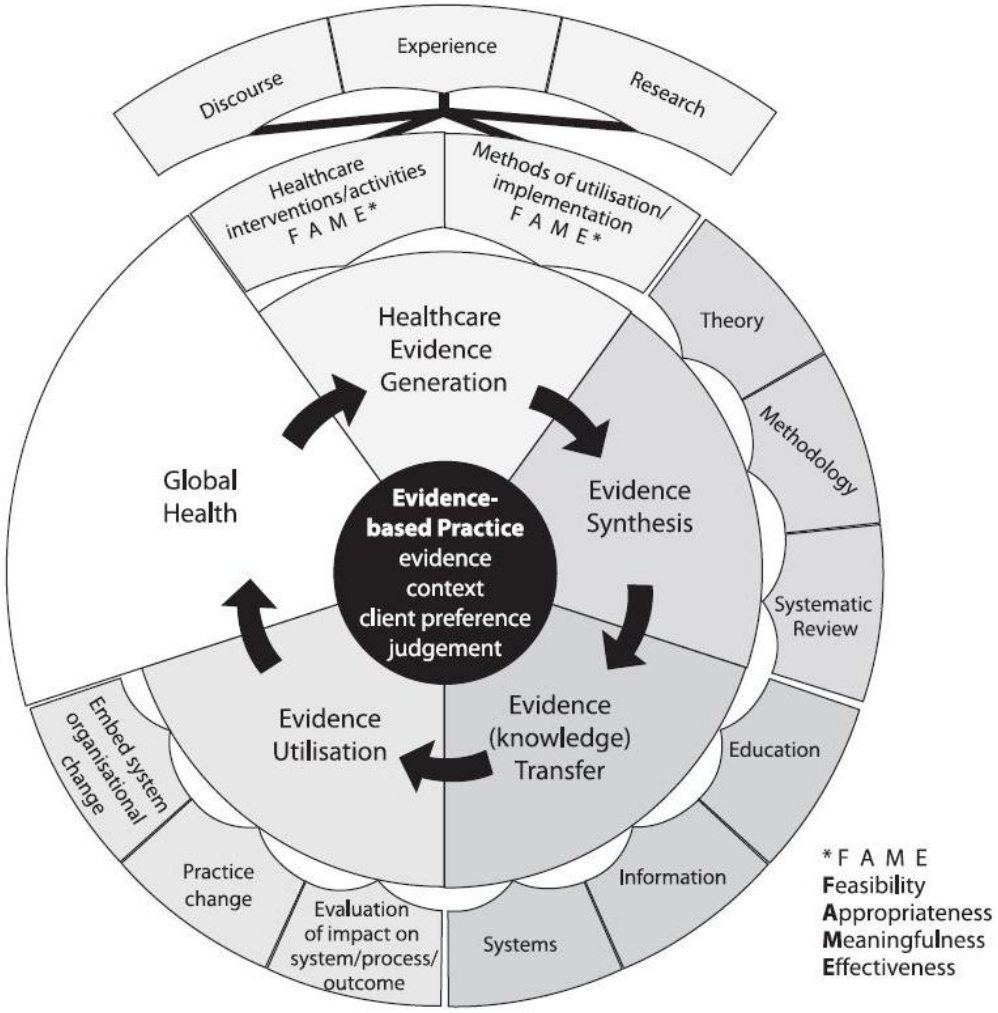

Figure 2.1. The JBI model of evidence-based healthcare[139(p209)]

The JBI methodology is documented in detail in the JBI Reviewers' Manual: 2014 edition[152] and in the user guides for the JBI System for the Unified Management, Assessment and Review of Information (JBI-SUMARI), the online software for the conduct of systematic reviews.[153] For quantitative evidence, the JBI-SUMARI software includes the Comprehensive Review Management System (CReMS) version 5.0.2 software to create systematic review protocols and complete systematic reviews with the aid of another JBI-SUMARI analytic module called the JBI Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). JBI-MAStARI enables systematic reviewers to appraise and synthesise quantitative evidence of intervention

effects and to conduct meta-analysis for the included primary studies. Review Manager 5.2 (RevMan 5.2) is used as alternative software for meta-analysis if required.

Appendices I and II show the JBI levels of evidence for effectiveness and grades of recommendation respectively. Levels of evidence estimate the credibility of review findings based on the study design of which the evidence is gained.[152] For example, research findings from systematic reviews of RCTs correspond to level I evidence. In this thesis, strong or weak grades are assigned to all recommendations of practice of every systematic review and to new guideline recommendations in the content analysis chapter.

The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement[154] (Appendix III) is a checklist of 27 reporting items published in 2009 and widely adopted for the reporting of systematic reviews and meta-analyses. This statement was followed in this thesis to increase the standard of reporting for systematic reviews and meta-analysis.

2.3. Systematic review methods

2.3.1. Research question and PICO inclusion criteria

The conduct of each systematic review begins with the preparation of a systematic review protocol that clearly documents the systematic review methods and analytical processes. The first step is the purposeful formulation of a research question to address an observed but unmet need for knowledge in the management of CHIK. Before the conduct of the systematic reviews, it is observed that there was a sizeable amount of literature on management interventions for CHIK; however, no systematic reviews have been conducted on their effectiveness. Hence, this thesis specifically addressed the translation gaps with three related systematic reviews, based on pre-specified inclusion criteria to answer specific questions on the effectiveness of: (1) disease management interventions on HRQoL of patients with established AAIs in Chapter 3;

(2) CHIK surveillance systems in Chapter 4; and (3) mosquito control strategies in CHIK in Chapter 5.

Each systematic review in this thesis had a priori inclusion criteria, based on the populations of interest, interventions of interest, comparators (if any) and outcomes of interest (referred to as PICO). A similarity amongst all three systematic reviews in this thesis was the inclusion of primary research studies of not only RCTs, but also quasi-experimental trials, cohort studies, cross-sectional studies, case-series and case reports. It has been recognised since the advent of evidence-based health care that "even he [Archie Cochrane] realized that RCTs did not always provide an unequivocal answer."[136(p5)] RCTs are minimal in certain specialised fields (e.g. surgery) and that there are varied streams of health care evidence that should not be neglected for completeness and to best reflect real life situations.[155] The JBI systematic methodology takes into account a broader scope of scientific evidence for the evaluation of effectiveness of healthcare interventions – that is, best available evidence from not only the *gold standard* RCTs, but also observational, descriptive studies and expert opinions.

2.3.2. Search strategy

Before developing the protocols for all three systematic reviews, the JBI Database of Systematic Reviews and Implementation Reports, Cochrane Database of Systematic Reviews, MEDLINE and the Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects (CRD DARE) were searched and no systematic reviews on the topics of interest were found.

A comprehensive and unique search algorithm was used for each systematic review. An initial limited search was conducted to identify keywords from Public/Publisher MEDLINE (PubMed) medical subject headings (MeSH) and Web of Science, followed by an analysis of the text words contained in the title and abstract and of the index terms used to describe the article. A second search using all the identified keywords and the index terms specific to each database was undertaken across all accessible

databases and websites. Published and unpublished primary research studies in English that fulfilled the inclusion criteria were targeted for inclusion in each systematic review, without employing any search filter and date limits. Modified block building was used to accommodate differences in search terms, indexes and Thesaurus across 14 - 16 electronic databases. Thirdly, the reference lists of all included reports and articles were searched for additional studies. The primary investigators were contacted for further details where necessary.

2.3.3. Study selection process

The PRISMA statement flow diagram on study selection process was also adopted for use in the systematic reviews.[154] Study selection comprises the four--step process: (1) identifying records from commercial electronic databases and grey literature sources; (2) screening records on the basis of title, abstract and full-text; (3) assessing full-text articles again for eligibility together with additional studies searched from reference lists of eligible studies; and (4) including studies that passed the critical appraisal in the systematic review. Studies may be excluded because of various reasons, including unmet inclusion criteria or poor methodological quality.

2.3.4. Primary studies appraisal

Critical appraisal is one of the main components that set systematic reviews apart from a conventional literature review or health technology assessment. The aim of critical appraisal in the systematic review is to establish the internal validity of studies to reduce the risk of bias or systematic error influencing the overall results of the review. Combining studies of low internal validity may result in misleading pooled estimates of interventions' effectiveness.[138, 152]

For the three systematic reviews, two trained JBI systematic reviewers independently assessed the methodological validity of quantitative papers selected for retrieval prior to inclusion in the review using the JBI critical appraisal checklists for randomised/ pseudo-randomised trial, comparable cohort/case-control and descriptive/case series

(Appendices IV, V and VI). Any disagreements that arose between the reviewers were resolved through discussion and with a third reviewer. However, arbitration by a third reviewer was not required.

2.3.5. Data extraction

Data was extracted from the included studies for each systematic review using an adapted JBI data extraction form for experimental/observational studies (Appendix VII). Extractions of data were completed in duplicate by the primary author. When required, two authors of each study were contacted via email to seek clarity on the information presented concerning population, interventions, comparators, outcomes of interest or study design and to obtain missing data and additional information.

2.3.6. Data synthesis

The three systematic reviews undertaken were conducted using the JBI-SUMARI. For the first systematic review (Chapter 3), findings from the included studies were both synthesised in narrative form and meta-analysis, as statistical pooling was possible for half of the included studies. Results from the other two systematic reviews (Chapters 4 and 5) were synthesised in narrative form, because meta-analysis was not possible or was inappropriate.

Meta-analysis for the first systematic review (Chapter 3) was initially conducted on the JBI-MAStARI. As most of the 7 studies did not have values for the control group sample size 'n' and/or the control mean and standard deviation (SD), the forest plots could not be generated using the JBI-MAStARI fixed or random effects model for continuous data. Hence, the alternative statistical software RevMan 5.2 was used.

Findings from the included studies were both synthesised in narrative form and meta-analysis, as statistical pooling was possible for seven out of 14 studies. A random effects generic inverse variance meta-analysis model was used. The generic inverse variance statistical method was employed in the studies, for meta-analysis that had

distinctive varied sample sizes, to allow greater weight for larger studies with smaller standard error (SE) and vice versa. Next, a random effects model was selected instead of a fixed effects model to account for intra- and inter-study variation. This was because the study samples were taken from different populations and the estimate of the treatment effect might be significantly different among studies.

Sub-group analyses based on study design (uncontrolled studies and controlled studies) and intervention follow-up duration (0-6, 7-12, 13-24 and 25-36 months) were conducted to reduce significant statistical heterogeneity.

Sensitivity analyses on health-related quality of life domains' follow-up scores and change scores were conducted, where available from study findings. Data were combined using standard mean difference (SMD) analysis across different tools measuring the same domain. Mean difference (MD) analysis was conducted within the same instrument. For the uncontrolled studies, the score difference between the baseline value and post-test value for the intervention group for the relevant HRQoL domains was calculated. Follow-up scores were not calculated due to the unavailability of control groups. For controlled studies, both follow-up scores and change scores were calculated for the relevant HRQoL domains.

The χ^2 test and I^2 test were used to investigate statistical evidence of heterogeneity of intervention effects.[138] If the χ^2 test probability (P) was less than 0.05, a statistically significant P value was noted and the results of the included studies were considered significantly different from each other. Hence, the meta-analysis was considered investigative rather than an end-point analysis. More investigations were done, such as sensitivity analyses by removing or adding results of various HRQoL domain sub-groups or studies, which were suspected of contributing to the heterogeneity. If the probability of the overall Z statistic was less than 0.0001, it meant that it was a highly significant overall effect size. Substantial heterogeneity was best detected by visually inspecting the forest plots of the included studies and the evaluation of statistical tests

results.

As varying HRQoL assessment tools were used across studies in meta-analysis, the signs of scores from scales that have higher scores indicating better outcomes were reversed by the multiplication of -1 to their follow-up and change scores, to ensure that all measurement data were analysed on the same direction of response.

A JBI grade of recommendation (Grade A or B) was assigned to each 'implications for practice' recommendation, based on criteria denoted in Appendix II.

2.4. Content analysis methods

2.4.1. Research questions and inclusion criteria

A content analysis in Chapter 6 was developed to assess the quality of existing published guidelines for CHIK and to critically formulate guidelines recommendations from the research findings of the completed systematic reviews from Chapters 3, 4 and 5. The inclusion criteria for guidelines selection were CHIK guidelines in English. Guidelines that were not specific to CHIK (e.g. mosquito control measures across general vector-borne diseases) were excluded. The search strategies for various databases are documented in Appendix XIX and the results of study selection process are recorded in Chapter 6, Section 4.1.

2.4.2. Quality assessment of guidelines

The methodological quality of the CHIK guidelines was assessed using the AGREE II instrument[151], a 23-item generic survey tool created in 2009 by the AGREE collaboration. The six domains assessed by the instrument are *scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability* and *editorial independence*. As defined by the collaboration, quality of guidelines is "the confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice."[156(p1)]

To ensure consistency in the quality assessment process[151], four reviewers trained in systematic methodology completed the AGREE II instrument online training and followed the user guide. Then, each reviewer independently conducted the quality assessment of the six provided guidelines within two weeks. The preliminary scores were tabulated by the primary reviewer, who sent the de-identified tabulated scores back to the secondary reviewers for the finalisation of scores. Secondary reviewers were given three days to correct errors, if needed. Following that, the scores from each reviewer were used to calculate the average score (in mean and SD) for each AGREE II item and the scaled domain percentage scores. Reviewers' recommendations for use of guidelines were also consolidated. For the second section of the content analysis, only guidelines that were recommended by at least one reviewer based on the AGREE II quality assessment (Table 6.3) would be used.

2.4.3. Background of content analysis

Content analysis is defined as

> A summarizing, quantitative analysis of messages that relies on the scientific method (including attention to objectivity-intersubjectivity, a priori design, reliability, validity, generalizability, replicability, and hypothesis testing) and is not limited as to the types of variables that may be measured or the context in which the messages are created or presented.[157(p10)]

Historically, content analysis started with the analysis of written text and has now evolved to include verbal messages, images and non-verbal gestures in the fields of arts and sciences.[157] The content analysis process is largely qualitative and is used widely in nursing research. Content analysis has the advantages of being sensitive to content, having a non-rigid range of research designs and can identify the significance, intent and characteristics of a particular content.[158]

2.4.4. Development of guideline recommendations

An evidence-based approach to the development of guideline recommendations necessitates that the evidence supporting an intervention be critically appraised and synthesised. Guideline recommendations are determined as actionable informative statements about what the target audience (e.g. policy decision-makers, health care professionals or patients) should do.[147, 159] As elucidated by Elo and Kyngas 2007[158], this content analysis involved the three phases of preparation (selecting unit of analysis and understanding data), organising (coding, grouping, categorising and abstracting content) and reporting results.

A comparative content-analytic approach was used to thematically organise, code and evaluate the data through a deductive iterative process. Two units were selected for comparative content analysis: (1) CHIK guidelines that were recommended for use based on the AGREE II appraisal; and (2) three systematic reviews in thesis Chapters 3, 4 and 5. To gain a systematic understanding and scope of data, a codebook (Appendix XX) and coding form (Appendix XXI) were first developed. The codebook directed the correct usage of the coding form and explained the terms used in the coding form. Then, the domains and subdomains were determined a priori based on the categorisation of interventions utilised in the systematic reviews of interest. Content was abstracted from both guidelines and systematic reviews through a rigorous computer searching method as detailed in Appendix XX. On the code form completed by a human coder, the extracted findings were critically evaluated for accordance or discordance across guidelines, followed by the cross-comparison between each extracted finding from the guideline and the corresponding systematic review finding, and finally to synthesise guideline recommendations.

A JBI grade of recommendation was assigned to each guideline recommendation, based on criteria denoted in Appendix II. Evidence from carefully conducted research and guideline recommendations should be connected with minimal content repetition by citing the systematic reviews from which the evidence is found. No guideline recommendation would be indicated if there was a dearth of evidence supporting its

use or if there was an unclear projection of balance between desirable effects and undesirable effects. Because the conduct of systematic reviews followed a set of inclusion criteria to answer particular research questions, a uni-directional analysis was employed, i.e. the coder sought to examine systematic review findings that could potentially add value and revise the current guideline recommendations. It was not in the interest of this content analysis for the coder to comment or revise a guideline recommendation if there was no finding evident from the systematic review specific to the particular guideline recommendation.

3 The effectiveness of disease management interventions on health-related quality of life of patients with established arthritogenic *Alphavirus* infections: A systematic review

3.1. Abstract

While epidemics of arthritogenic *Alphavirus* infections have emerged worldwide, posing public health threats, the establishment of effective disease management interventions on health-related quality of life of patients based on best available international evidence has never been achieved. Fourteen studies were included, with 3081 participants (1359 Chikungunya patients, 67 ross river patients, 27 Chikungunya controls and 1628 healthy controls). The included studies provided moderate evidence of clinical manifestations management on health-related quality of life. Clinical manifestations management for Chikungunya and ross river diseases had a positive impact on health-related quality of life domains including overall health-related quality of life, disease-specific concerns, depression, emotional functioning, fatigue, general health, pain, physical functioning, role functioning, sleep and social functioning at varying follow-up periods. There is insufficient evidence to enable any strong conclusions on the effects of early diagnosis of the disease on health-related quality of life. No conclusions are reached regarding the effects of disease education on health-related quality of life.

3.2. Concise introduction

This chapter examined the disease management interventions on HRQoL of patients with any of the seven AAIs – CHIKV, RRV, ONNV, BFV, MAYV, SINV and SFV. The following questions were addressed:

1. What is the effectiveness of clinical manifestations management interventions on HRQoL outcomes among patients with established AAIs?
2. What is the effectiveness of early diagnosis of disease on HRQoL outcomes among patients with established AAIs?

3. What is the effectiveness of disease education on HRQoL outcomes among patients with established AAIs?

The introduction of clinical manifestations management, early diagnosis of disease and disease education were reported in Chapter 1, Sections 2.1.1, 2.1.2 and 2.1.3 respectively. Mosquito-borne arthritogenic *Alphavirus*es and epidemiology of CHIKV infection were reported in Chapter 1, Sections 1.1 and 1.2.

Epidemiology of the remaining six AAIs:
The ONNV was first isolated from the *Anopheles* mosquitoes, primarily the *Anopheles funestus* and the *Anopheles gambiae* in 1959 in Northern Uganda during one of the worst Arbovirus epidemics recorded – with more than two million cases of ONNV. Fortunately, no deaths were reported.[160, 161]

The RRV is found mostly in Australia, New Guinea and the South Pacific islands and may be carried by more than 30 vectors, the main vector species being *Aedes vigilax*, *Aedes camptorhynchus* and *Culex annulirostris*. The first reported RRV outbreak occurred in 1928 in New South Wales.[162] Subsequently, more outbreaks of RRV occurred during World War II and in 1956. Currently, there are an estimated 5000 RRV infections reported per annum in Australia.[163]

The BFV is identified only in Australia, with about 400 cases reported in Queensland yearly. There were 15,592 BFV cases recorded during 1995 - 2008. The virus was first isolated in 1974 from the vectors *Culex annulirostris* mosquitoes collected from Northern Victoria and Southern Queensland, Australia.[164]

The MAYV is found mostly in the rainforest regions of South America, with sporadic outbreaks and small-scale epidemics affecting countries such as Brazil, Peru, Venezuela and Columbia. It was first isolated at Trinidad in 1954 and data point to *Haemagogus* mosquitoes as the main vectors of the MAYV transmission.[165, 166]

The SINV was originally isolated from the *Culex* mosquitoes at the Sindbis village, Nile Delta, Egypt in 1952. The vectors are ornithophilic, involving mosquito species of the genera *Culex, Culiseta, Coquillettidia, Ochlerotatus*, *Aedes* and *Anopheles*. Fortunately, no fatalities were reported; however, hundreds of SINV-infected cases were confirmed in South Africa, Uganda, Australia and Finland.[167, 168]

The SFV was first isolated from mosquitoes at the Semliki forest of Uganda in 1942. The virus can be transmitted via infected mosquitoes as well as the air-borne contaminated aerosols. The SFV is found mostly in Africa, Asia and Europe. Infections are generally asymptomatic and mild.[169, 170]

3.3. Methods unique to chapter

3.3.1. Types of participants

This systematic review included patients with established AAIs (CHIKV, RRV, BFV, ONNV, MAYV, SINV and SFV) of all ages and stages of infection. According to the WHO and the Commonwealth Department of Health and Aging, Australia, case definitions were provided only for CHIK, RRV, BFV and SINV but not for ONNV, MAYV and SFV.[171-174] The lack of case definitions for ONNV, MAYV and SFV was likely to be due to minimal active surveillance.[175-177]

An established case of CHIK in this systematic review was defined as a probable case or confirmed case. A probable CHIK case was defined as a patient who generally had clinical symptoms of sudden presentation of fever, arthralgia or arthritis with or without rash and was linked epidemiologically to a CHIK epidemic in a specific location and time.[174] A confirmed case was defined as a probable case with an additional positive laboratory result from:

- A serum sample of anti-CHIK Immunoglobulin M (IgM) antibody titre of at least 40 units via enzyme-linked immunosorbent assay (ELISA);

- A four-fold increase in paired sera of Immunoglobulin G (IgG) antibody titres between the acute and convalescent period obtained about three to four weeks apart via Ig M antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA);
- CHIK RNA by reverse transcriptase polymerase chain reaction (RT-PCR); or
- The isolation of the CHIK.[174]

An established case of RRV/BFV/SINV was similar but denoted a confirmed case only. A probable case of RRV/BFV/SINV was not defined in the literature. The confirmed RRV/BFV/SINV was dependent only on the laboratory evidence of:

- The isolated RRV/BFV/SINV virus;
- RRV/BFV/SINV nucleic acids;
- Anti-RRV/BFV/SINV IgG seroconversion; or
- A four-fold increase in RRV/BFV/SINV IgG antibody titre.

Additionally, for RRV, the detection of anti-RRV IgM and anti-RRV IgG together or the presence of anti-RRV IgM and absence of anti-BFV IgM together would constitute a confirmed case of RRV. Similarly, for BFV, the detection of anti-BFV IgM and anti-BFV IgG together or the presence of anti-BFV IgM and absence of anti-RRV IgM together would constitute a confirmed case of BFV.[172, 173, 178]

3.3.2. Types of interventions

The interventions of interest are:

- Clinical manifestations management
  The active management of clinical signs and symptoms by physicians and patients. This may be sub-categorised into pharmacological and non-pharmacological methods, such as drugs, herbs, physical therapy, occupational therapy, acupuncture, emergency hospitalisation and surgeries.
- Early diagnosis of disease

Early diagnosis of disease included the appropriate and timely clinical diagnosis by physician, which may be evident from patients' visits to the general practitioners (GPs) and specialists.

- Disease education
  Educating patients and physicians on disease management interventions, including psycho-education and functional re-education.

3.3.3. Types of outcomes

The outcomes of interest included: (1) overall and different domain scores from HRQoL assessment surveys, (2) disease- and treatment-specific clinical symptoms useful to understand HRQoL scores, and (3) any harm associated with management of AAIs, disease recurrence or the onset of secondary disease. The HRQoL domains included anxiety, depression, emotional functioning, fatigue, general health perspective, pain, physical functioning, role functioning, sleep and social functioning.

3.3.4. Search strategy

Two search algorithms were used as documented in Appendix VIII. The first search strategy structured the keywords using the operator *AND* into three concepts: names of arthritogenic *Alphavirus*es, disease management and quality of life. When no results were found from PubMed and Web of Science, two of the largest databases for biomedical literature and multidisciplinary databases respectively[179, 180], the second algorithm combining the keywords of the two concepts of disease management and quality of life into a category was also implemented to increase the sensitivity and specificity in capturing relevant studies.

A second search was undertaken in all seven scientific databases (PubMed, Web of Science, Scopus, ScienceDirect, Cumulative Index to Nursing & Allied Health (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL) and Scifinder) and seven grey literature sources (WHO Library (WHOLIS), CDC, European Center for Disease Prevention and Control (ECDC), Integrated CHIK Research (ICRES),

National Institutes of Health (NIH), Mednar and Google). The final search for studies was conducted from the reference lists of included studies.

The keywords identified were: arthritogenic *Alphavirus* infection; arthritogenic *Alphavirus*; *Alphavirus* arthritide; *Alphavirus* arthritis; *Alphavirus*; Chikungunya; O'nyong-nyong; Ross River; Barmah Forest; Mayaro; Sindbis; Semliki Forest; quality of life; health-related quality of life; disease management; symptom management. The secondary author reviewed the search strategies for face validity.

3.3.5. Critical appraisal

For this systematic review, both reviewers made decisions for the critical appraisal. The first decision made was that the characteristics of people who withdrew included patients who were withdrawn by the assessors of the study. The second decision made was that patients were considered entering at a similar point in their course of illness from disease onset (for example, after receiving the first IgM positive result on CHIKV). There was a buffer time that the patient recruited might be harbouring the virus for a while before the initial laboratory-confirmed detection; however, most studies did not measure that and it remained unknown. Thirdly, any efforts made to minimise bias in relation to the selection of cases and of controls would score a *yes*. Lastly, if there was no evidence or unclear evidence from a study on a critical appraisal question, a *not reported* was selected. A *no* was selected only when evidence was present for the decision.

3.3.6. Data synthesis

Full information on meta-analysis and narrative form were elucidated in Chapter 2, Section 3.6.

3.4. Results

3.4.1. Methodological results

3.4.1.1. Study selection

One thousand and two records were examined based on the title, abstract and full-text for a match with the a priori inclusion criteria. Figure 3.1 illustrates the search process for study selection.

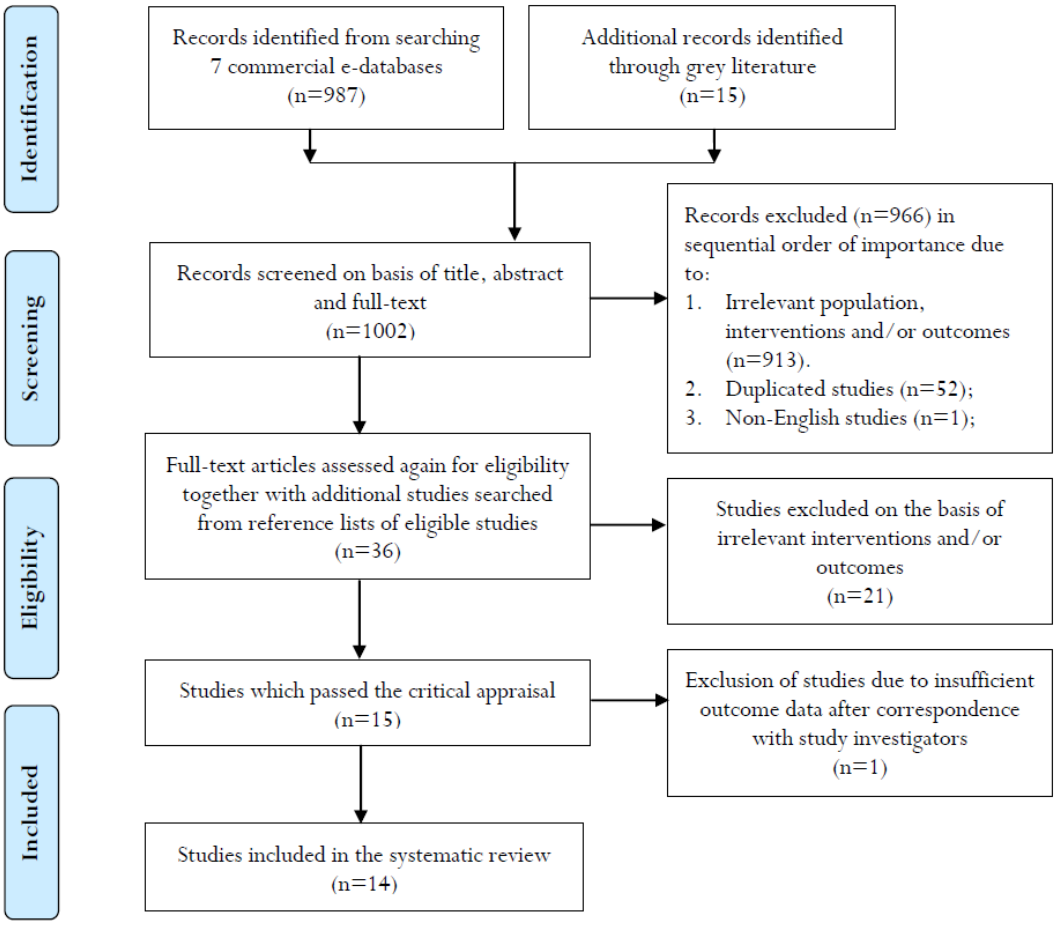

Figure 3.1. Search process for studies selection

3.4.1.2. Methodological quality

Overall, 15 studies passed critical appraisal and showed moderate methodological quality. Although one of the studies met the inclusion criteria and passed the critical appraisal, it was excluded from the systematic review based on insufficient outcome

data being available to verify results (more details are explained in the *Excluded studies* Section). Hence, critical appraisal results of 14 included studies are shown in Table 3.1.

Table 3.1. JBI-MAStARI critical appraisal of included studies

Randomised controlled trials/pseudo-randomised trials										
Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**
Brighton *et al.* 1984[181]	N	N	N	Y	N	N/A	N/A	Y	Y	Y
De Lamballerie *et al.* 2008[29]	Y	Y	U	N	Y	Y	Y	Y	Y	Y
Ganu *et al.* 2011[182]	N	U	U	N/A	U	N/A	N/A	Y	Y	Y
Padmakumar *et al.* 2009[129]	Y	N	Y	N	N	Y	Y	Y	Y	Y
%	50	25	25	33.33	25	100	100	100	100	100
Comparable cohort/case control studies										
Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	
Marimoutou *et al.* 2012[42]	N	Y	Y	Y	Y	Y	Y	Y	Y	
Mylonas *et al.* 2002[183]	N	Y	Y	Y	Y	Y	N	Y	Y	
Ravichandran *et al.* 2008[184]	N	Y	U	Y	Y	Y	U	Y	Y	
Sissoko *et al.* 2009[130]	N	Y	Y	Y	Y	Y	N	Y	Y	
Soumahoro *et al.* 2009[119]	Y	Y	Y	Y	Y	Y	Y	Y	Y	
%	20	100	80	100	100	100	40	100	100	
Descriptive/case series studies										
Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	
Baishya *et al.* 2010[185]	N	Y	Y	Y	N/A	Y	N	Y	Y	
Chang *et al.* 2010[186]	N/A	Y	N/A	Y	N/A	Y	N/A	Y	N/A	
De Andrade *et al.* 2010[44]	Y	Y	Y	Y	N/A	Y	N	Y	Y	
Menon *et al.* 2010[187]	N/A	Y	N/A	Y	N/A	Y	N/A	Y	Y	
Staikowsky *et al.*2008[45]	N	Y	Y	Y	Y	N/A	N	Y	Y	
%	33.33	100	100	100	100	100	0	100	100	

Refer to Appendices IV, V and VI for the critical appraisal checklist questions Q1-Q9/10.
Y: Yes; N: No; U: Unclear; N/A: Not applicable.

Based on Table 3.1, four out of 14 studies showed evidence of adequate randomisation

of samples. Participants from one study were randomly selected through a population-based cohort, where matched pairs of participants were obtained by balanced random sampling without replacement from 24 strata.[119] Another study used a form of random sequence generation to minimise selection bias, called the envelope method with stratification by sex.[129] One study was carried out in 12 general practices located throughout the Reunion Island[44] and another study reported but did not describe the method of randomization.[29] The appraisal question on randomization was not applicable to two studies as they were case reports.[186, 187] The remaining eight studies were at high risk of inadequate randomisation due to: no randomisation as reported[184]; recruitment of active healthy men not representative of the general population[42]; recruitment of study participants through requests to GPs[183]; selection of patients under the study investigator's care[181] or from following up 625 acute CHIK patients during a CHIK epidemic[182]; or, no evidence of randomisation from a sample obtained from a single centre.[185] A survey involving hospital staff only was carried out in the principal investigator's affiliated 1300-bed hospital. The survey also reported that the population sample was not representative of the Southern part of the La Reunion Island.[45]

One out of four experimental studies was at low risk of selection bias due to allocation concealment, as the envelope method was used.[129] One study had a high risk of bias due to inadequate allocation concealment; it was an open pilot study.[181] The remaining two studies had unclear evidence of allocation concealment.[29, 182]

There was no performance bias from the blinding of participants and outcome assessors as reported in one[29] out of four experimental studies. For two experimental studies, no blinding of participants and outcome assessors were reported.[129, 181] The remaining experimental study had unclear evidence of blinding of participants and outcome assessors.[182]

Five out of 11 studies had low risk of attrition bias as evidence of description and inclusion of people who withdrew from the studies were reported. For example, one

study reported that there was no withdrawal of participants[130] and another study reported a patient who withdrew and whose results were taken into account in the analysis.[181] One study reported that 65.6% of all eligible gendarmes (French military policemen) had completed the MOS SF-36 questionnaires. Missing data from the questionnaires were taken from the mean value of the MOS SF-36 domain in consideration, an approach recommended in the presence of missing data.[42] Three studies were considered to have a high risk of attrition bias because management of missing data was not described in the analysis, although patients had withdrawn from the study[183] or were lost to follow-up.[119, 129] Another study had a high risk of attrition bias because the percentage of participants who submitted incomplete surveys and how the incomplete surveys were dealt with were not reported.[45]

A *not applicable* answer was given for some critical appraisal questions as there was no systematic bias due to the inherent nature of the study design or disease management intervention.

In addition to the above critical appraisal questions, studies were examined for reporting bias (due to selective reporting). Ten studies appeared to have low risk of reporting bias, based on information provided by the study investigators.[29, 44, 45, 129, 130, 181, 182, 184, 186, 187] One study had unclear risk of selective reporting bias as missing or incomplete data was not reported.[185] Whether the retrospective extraction of medical records was done by an assessor who was blinded to the research question was also not described. Three studies had high risk of reporting bias due to selective reporting.[42, 119, 183] A study had high risk of reporting bias as the scores for the individual subscales for the HRQoL assessment instrument were not reported, although the summary scores for an additional two components were reported.[119] Another study had missing clinical data bias, as the determination of CHIKV infection was not based on laboratory-confirmed tests but self-declaration by participants.[42] The last study did not report the norm scores for age- and sex-matched general Australian population from the CLINHAQ, which might affect the gauging of treatment effect.[183]

In addition, three studies had high risk of other types of bias, such as recall bias on pain intensity for two studies[44, 45] and overmatching bias for one study.[119]

3.4.1.3. Included studies

Based on the JBI levels of evidence for the effectiveness of interventions[188], four studies were classified as level 1 evidence, five were level 3 evidence and the remaining five were level 4 evidence. The studies included were a double-blind RCT[29], a randomized uncontrolled parallel-group study[129], a non-randomized and uncontrolled experimental open pilot study[181], a non-randomized and uncontrolled experimental study[182], two prospective cohort studies[183,184], three retrospective cohort studies[42, 119, 130], two cross-sectional studies[44, 45], a case-series[185] and two case reports.[186, 187] The included studies were published from 1984 to 2012.[29, 42, 44, 45, 119, 129, 130, 181-187] More details of included studies are found in Appendix IX.

Twelve studies[29, 42, 44, 45, 119, 129, 130, 182, 184-187] on CHIK were conducted during or after a CHIK epidemic from 2005 to 2009, one study on CHIK was conducted during an endemic in 1984[181], and the only study on RRV[183] was conducted during an endemic period from November 1997 to April 1999. Six CHIK studies were conducted in La Reunion Island[29, 42, 44, 45, 119, 130], five CHIK studies were conducted in India[129, 182, 184, 185, 187], one CHIK study was conducted in Taiwan (imported case from Malaysia)[186], one CHIK study was conducted in an unknown area, most likely in South Africa, as deduced from another closely-related study by the same study investigator[181, 189] and the last RRV study was conducted in Australia.[183] In all, 3081 participants were included in the review, of whom 1359 were CHIK patients, 67 RRV patients, 27 CHIK controls and 1628 healthy controls. Two studies reported inclusion of children – a 5.5-year-old boy in one study[187] and an unspecified number of children aged two to 18 years for another study.[119]

All four experimental studies were on CHIK patients and had 201 participants, with 27

patients from only one study acting as controls receiving placebo treatment. The controls were given placebo, presumably because there was a lack of established efficacious treatment for CHIK. For uncontrolled studies, natural temporal trends or the use of undeclared concurrent interventions wass a risk and for controlled studies without randomization, there was the inability to account for imbalance factors between groups. It is also noteworthy that only three out of these 44 studies had measured direct outcomes on HRQoL domains of validated Visual Analog Scale (VAS) for pain, Activities of Daily Living (ADL) scale for physical functioning and Instrumental Activities of Daily Living (IADL) for role functioning in a study[129], Disease Activity Scores (DAS) and Health Assessment Questionnaire (HAQ) domains scores for the second study[182], as well as invalidated joint pain scores, morning stiffness scores, and global assessments scores by both patient and doctor in the third study.[181] The first two studies were conducted in 2009 and 2011 respectively, where more sensitive and specific validated HRQoL assessment tools have been developed and the third study was conducted in 1984, a time when HRQoL assessment tools were still in development with only crude variables measured such as returning to work and physical performance level.[121, 181] For the fourth study, which was the study highest in the hierarchy of study designs, the sole measurement outcome was a clinical outcome – the duration of arthralgia that was not measured by a HRQoL assessment tool.[29]

The dearth of large experimental studies on the effectiveness of disease management interventions on HRQoL of patients with AAIs led to the inevitable need toalso analyse available results from observational studies and descriptive studies. Measurement of intervention effects should ideally be based on well-performed experimental studies, the promulgated *gold standard* being RCTs, as there is assurance of unbiased and reliable estimates of intervention effects. However, this might be inappropriate and impossible for relatively under-researched and rare AAIs compared to other febrile viral diseases such as Dengue, a *Flavivirus* disease.

The observational cohort studies were good practical clinical studies for gauging the

effectiveness of disease management interventions. The study investigators of four out of five included cohort studies observed real-time outcomes with indirect estimates of the effectiveness of disease management interventions made through the patients' self-reported consumption of drug treatments, medicinal plants, alternative medicines, acupuncture, physiotherapy, visits to GPs and specialists and emergency departments in heterogeneous care settings and their self-reported scores for a broad spectrum of HRQoL domains over a period of time.[42, 119, 130, 183] The remaining cohort study measured directly the effects of ribavirin on disease-specific quality of life domains of CHIK arthritis, namely joint pain, joint swelling and mobility.[184]

The main concern in using observational studies to compare the effectiveness of disease management interventions is the high susceptibility to bias, mainly due to non-randomization during sample allocation; hence groups of participants might be dissimilar at the early stage of study. This form of bias was considerably reduced for all the five included observational studies, as shown in Table 3.1 where the critical appraisal results indicate that participants for the five studies were at a similar stage.

The five descriptive studies included had the least ability to show causative effects of disease management interventions on HRQoL of patients with AAI; however, the studies were important to show the relationship or association, if any, of the interventions with HRQoL.

Scientific literature has not reached an agreement on the exact definition of comorbidities. To assist in the understanding of the characteristics of the population included in the systematic review, comorbidity was defined as a medical condition which exists independently and concurrently of a condition in the patient.[190] Hence, any resultant syndrome or disease that emerged out of the primary disease or was dependent on a primary disease would not be named comorbidities; instead, for ease of comprehension, these were classified as complications arising out of the primary disease. In the population included in the systematic review, only two studies reported

57 patients with comorbidities of overweight (n=34), joint problems (n=22) and depression (n=1), making up a total of 0.19% of the participants.[42, 183] Five out of 14 included studies reported comorbidities in the exclusion criteria for selection of participants.[29, 44, 129, 184, 191]

3.4.1.4. Excluded studies

Only Ramachandran et al. 2012 was excluded from the review, as shown in Appendix X. Although the study met the inclusion criteria and passed the critical appraisal, it was excluded in the systematic review based on insufficient outcome data being available to verify the results after requests to the study investigators for clarification and missing data with was declined.

The study investigators were requested to provide any relevant primary data on patients' disease management interventions during infection. A concern was also raised on the evidence of declarations of any disease management interventions as, according to the study, under the data collection section, the study investigators had confirmed that the study participants had self-declared that they were not under any form of treatment at the point of the survey. However, it was noticed that for the follow-up duration of five months, there was a brief mention without substantiation that patients were referred to the nearest health care entity for treatment to provide continuity of care. Thirdly, the study investigators were requested to provide the numerical results on HRQoL scores of healed CHIK patients, which had only been presented graphically in the study. Fourthly, as the HRQoL scores were reported as median scores, the exact change and follow-up scores in mean (SD) for the 10 components of the MOS SF-36 questionnaire were also requested for potential meta-analysis. Lastly, any other primary data or advice that were thought to be helpful with the systematic review was requested for.

The lack of clarification and primary data to substantiate the validity of evidence caused great concern. Hence, a decision was made to exclude the study on the basis of

insufficient outcome data.[118]

3.4.1.5. Data management

Two study investigators from each of the 17 potential studies were contacted via email and phone to seek clarification of the information presented in their published papers concerning population, interventions, comparators, outcomes or study design, and to obtain missing data and additional information using a set of questions customised for each study. The email addresses were obtained from the primary contact information on the published papers, through online search engines or the study investigator's primary institution. Any other primary data including individual patient data or advice that may be helpful for the systematic review were also sought. If there was no response after the first email was sent two consecutive follow-up emails were sent to each study investigator. The study investigators had at least three weeks to provide the requested information. Then, a comprehensive data synthesis was undertaken by the primary reviewer based on the best available evidence in their published papers and if available, from supplementary papers, tables, graphs and email responses.

Investigators from 11 of 17 studies[42, 44, 118, 119, 129, 130, 183, 192-195] responded to the emails and the investigators from the six remaining studies were non-responders[43, 118, 182, 184, 185, 196]. Nine of 17 studies, for which the study investigators were contacted, were evaluated and were included in the systematic review.[42, 44, 119, 129, 130, 182-185] For an included study, the study investigators had provided the requested numerical data which was only graphically represented on the published paper. An Australian senior biostatistician had to be contacted separately, in his capacity as the author of the 1995 National Health Survey (NHS) MOS SF-36, to find the 1995 NHS MOS SF-36 population norm scores for RRV infection. These values were missing from the study as the study investigators reported that the population norms scores came from the publicly available Australian Bureau of Statistics database.[183]

Authors of another study provided the requested original standardised questionnaire

form, which was used during a phone interview and the primary data in the form of detailed de-identified raw individual patient data in French. The French data was initially translated with the assistance of an online statistical machine translator, Google Translate, after which it was hoped that the study investigators would confirm the results in English. The individual patient data was requested for in order to calculate the numerical rating scale pain intensity scores, lifestyle impact scores and impairment of ADL as continuous measurement variables instead of dichotomous categorical variables for potential meta-analysis. However, the values were not obtainable due to nil response from the study investigators. Hence, the results were reported in narrative form.[130]

Of 14 studies included in the systematic review, half were evaluated in narrative form and other half were synthesized in meta-analysis using RevMan 5.2. The generic inverse variance data type was used for the four uncontrolled studies instead of the conventional continuous data method as it required only one summary statistic and its standard error (SE) for the intervention group without the control group values.[129, 181-183] For two of the three controlled studies, the continuous data type was selected since the mean (SD) for both the intervention and control groups was available.[42, 119] For the remaining controlled study, the dichotomous data was transformed into continuous data in SMD (SE) using the inverse variance statistical method.[184] For two studies, no change scores were calculated because baseline scores for both the interventions and control groups were not reported for both MOS SF-12 and MOS SF-36 HRQoL domains.[42, 119]

Frequently, the SD instead of the SE was provided in the calculation of mean (SE) for the treatment and control groups (if any) for input into RevMan 5.2. The RevMan 5.2 calculator was used to calculate the SE from the given mean and the SD. To combine dichotomous data and continuous data or to find the adjusted SE difference from the SD baseline value and the SD follow-up value for either the treatment or control group with their known *n* values or from the SE values, statistical formulas were followed

from the Cochrane Handbook for Systematic Reviews of Interventions and the statistics course notes from the University of New Brunswick.[138, 197] The adjusted SE difference within individual correlation (r) between baseline and follow-up values was assigned an assumed value of 0.5 as the value of r was not obtainable from empirical data.[198]

Appendix XI summarizes the validated HRQoL assessment instruments used by the study investigators, together with their abbreviations, overall HRQoL domains or subscales, the direction of responses of the HRQoL instruments, as well as studies that utilised the particular HRQoL scales. The eight HRQoL assessment instruments used in the studies include the ADL score[129], CLINHAQ[183], DAS28[182], HAQ[182], IADL score[129], MOS SF-12[119], MOS SF-36[42, 183] and VAS[129]. The studies measured 12 domains of HRQoL altogether. The domains were HRQoL, disease-specific quality of life, anxiety, depression, emotional functioning, fatigue, general health perspective, pain, physical functioning, role functioning, sleep and social functioning.

3.4.2. Outcome results

This systematic review found 13 primary studies that showed evidence of effects of CHIK management on HRQoL and likewise one primary study of RRV disease. In contrast, no primary studies on the effects of disease management interventions on health-related quality of life for ONNV, BFV, MAYV, SINV and SFV were found. Outcome results are presented first in narrative form with available clinical data in percentiles, followed by statistical results to systematically address each of the three research questions.

Modes of disease management interventions differed across studies, with either single or a combination of interventions assessed. Studies that set forth with the objective of assessing a particular drug or a combination of treatments had well recorded dosage[29, 129, 181, 182, 184, 185], frequency[29, 129, 181, 182, 184, 185] and length of follow-up[29, 129, 181, 182, 184, 185] but not for route of administration.[29, 181, 184, 185] On the other hand, cross-sectional surveys, case

series and case reports that had indirect measurements of HRQoL had recorded percentage of CHIK or RRV patients who had health care intervention[44, 45, 119, 130, 183, 186, 187] or an average number of consultations per patient for a health care intervention[42] but almost no records of dosage, route of administration, application rate, frequency and length of follow-up.

The systematic review findings were analysed in the context of the limited number of studies, heterogeneity of disease management, direct and indirect measurements of effectiveness of disease management, various HRQoL domains measured using different assessment tools and risks of bias inherent in the included studies. Detailed information on the HRQoL instruments used is recorded in Appendix XI; detailed information on overall HRQoL and HRQoL domain outcomes, number of participants, effect estimates, statistical methods used in the analysis, meta-analysis data table and forest plots are found in Appendices XII, XIII and XIV. The forest plots showing only one HRQoL domain subscale score are not included in Appendix XIV due to incomparability of the single result.

3.4.2.1. Clinical manifestations management

All 14 included studies prescribed pharmacological and non-pharmacological treatments to manage clinical manifestations. Figure 3.2 shows the reporting frequency of types of drugs used in all included studies. The top five types of drugs used were anti-inflammatory drugs, analgesics, anti-pyretics, anti-virals and herbs. Effects of physical therapy[44, 130],occupational therapy[130], acupuncture[44], bladder training[185], urinary catheterization[185] and hospitalization for emergency or surgeries[42, 119, 130] on the management of clinical manifestations were not strongly evident and conclusive from the included studies.

A retrospective cohort study recorded that the treatment of CHIK-induced arthritic symptoms was generally insufficient. Almost half of CHIK patients with persistent

rheumatic pain had trouble in ADL for more than three months and 43% of CHIK patients had full remission after 15 months from disease onset.[130]

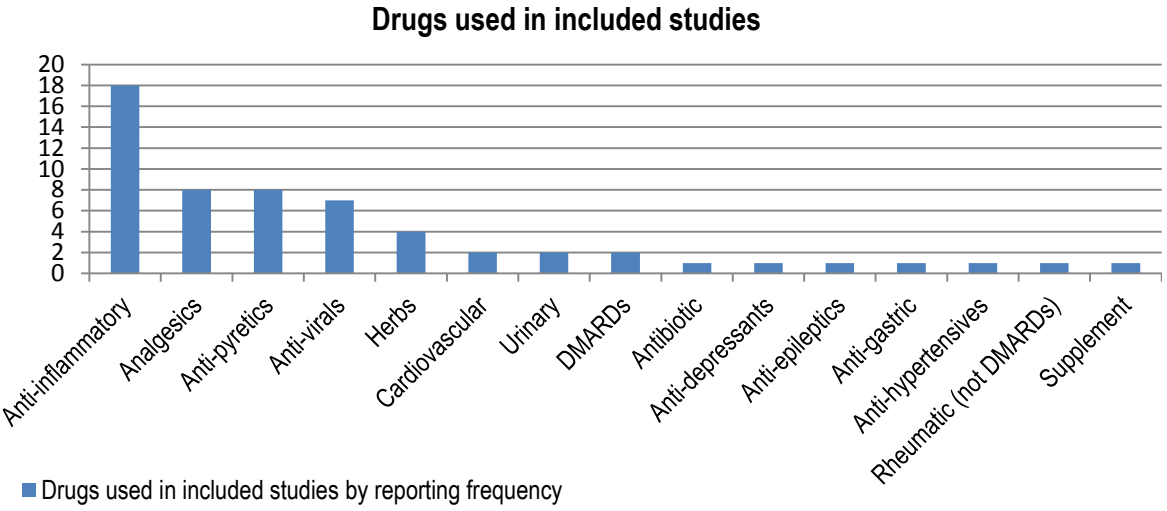

Figure 3.2. Drugs used in included studies by reporting frequency

Anti-inflammatory drugs with analgesic property

An included study reported that NSAIDs and corticosteroids have been widely used empirically to treat patients with CHIK-induced chronic arthritis, by acting to reduce inflammation and in turn, causes a decrease in pain. An included study found that the combination of acecyclofenac (NSAID) and prednisolone (corticosteroid) alleviated pain and improved quality of life in CHIK patients with arthralgia.[129] Another study observed that 76% of CHIK patients had higher perceived satisfaction with corticosteroids at any stage of the disease, compared to 36% with NSAIDs.[130] In another cross-sectional study that reported 40% of CHIK patients taking corticosteroids and 22% of CHIK patients taking NSAIDs, pain relief attributed to the clinical manifestations management was 52.79 ± 27.19%. The study found an association between CHIK and chronic pain. Patients who had a type of chronic pain with neuropathic characteristics were suggestive of more severe clinical presentations with an increased impact on quality of life and more complex drug treatments.[44]

NSAIDs were given credit in alleviating some but not all joint pain and stiffness, hence they played an analgesic role in CHIK treatment.[181] Satisfaction with NSAIDs treatment differed between CHIKV and RRV diseases, as shown in two included studies. A CHIK retrospective study reported 36% satisfaction with NSAIDs treatment in CHIK patients[130], compared to 70 - 100% satisfaction with NSAIDs treatment in 58% of RRV patients who took NSAIDs for a mean of 7.6 (2-22) weeks.[183] The same RRV study reported harm associated with RRV disease and its management, as expressed in percentage of RRV patients who had various medical conditions: pneumonia (1.67%); osteoarthritis (5%); rheumatoid arthritis (3.33%); psoriatic arthritis (1.67%); ankylosing spondylitis (1.67%); osteoarthritis plus psoriatic arthritis (1.67%); depression (10.45%); carpal tunnel syndrome (1.67%); back pain and obesity (1.67%); herniated disc (1.67%); melanoma (1.67%); hypercholesterolemia (1.67%); polycystic ovaries (1.67%); endometriosis (1.67%); urinary tract infection (1.67%); thrombocytopenia (1.67%); allergy (1.67%); and pregnancy (1.67%).[183]

With regards to harm from corticosteroid treatment, a retrospective cross-sectional study reported no statistically significant difference (P value was not reported) in the percentage of relapses, defined as the observation of arthralgia, oedema, fever and cutaneous presentation in CHIK patients compared to those who did not use corticosteroid treatment.[45]

Anti-pyretics with analgesic property

Anti-pyretic drugs are the mainstay of CHIK management, with an estimated 90% of CHIK patients found to have fever.[41, 45] They were the third in terms of frequency of reporting of drugs used in included studies, as shown in Figure 3.2.[44, 45, 129, 130, 183] Anti-pyretics used were mainly paracetamol, followed by aspirin and quinine. Although the effects of anti-pyretics have not been measured in silos in the treatment of CHIK fever, paracetamol was shown to be the chosen rescue medication in an included study, due to its dual anti-pyretic and analgesic functions.[129]

Paracetamol in CHIK treatment seemed to be associated with harm, as seen from two studies. In a retrospective cohort CHIK study that reported 93% of the patients taking paracetamol and 78% of patients taking NSAIDs, harm associated with the disease and its management was observed: chronic cardiac disease (10%); diabetes mellitus (22%); hypertension (33%); and osteoarthritis (26%). In addition, 21% of CHIK patients reported at least one relapse, and 36% of CHIK patients reported permanent symptoms of CHIK, in terms of joint pain, morning stiffness and joint swelling.[130]

Another CHIK study that reported 95.4% of patients taking paracetamol showed harm associated with the disease and its management, including relapses defined by the observation of arthralgia (96.7%), oedema (61%), fever (18.7%) and cutaneous presentation (5.7%). The mean number of relapses was 2.1±1.2 and the mean time interval between recovery and relapses was reported to be 4.2±3.9 weeks (range 1 - 32). A combination of fever, myalgia, asthenia and crippling arthralgia with walking difficulties (2.71%), cutaneous presentation and neurological disorders (2.26%), enlargement of the nodes and haemorrhage (1.81%) and CHIK chronic form (10%) was also present.[45]

Anti-virals

The use of chloroquine or hydroxychloroquine were assessed in five included studies[29, 45, 129, 181, 182] and the use of ribavirin was evaluated in an included study.[184] Ribavirin treatment was reported to have resulted in improvement in joint pain and a faster resolution of joint and soft tissue manifestations.[184] Chloroquine treatment was explored in a study because NSAIDs were reportedly not able to alleviate all of the joint pain and stiffness.[181] The effectiveness of the use of chloroquine or hydroxychloroquine in CHIK management has been contentious over many years, as it seemed to show varying efficacy depending on the stages of CHIKV infection.

During the acute stage of CHIKV infection, a double-blind RCT had demonstrated that there was no clear evidence to support the use of chloroquine to treat acute CHIKV

infection, after CHIK patients receiving the chloroquine treatment had arthralgia more frequently (4.7 days) compared to CHIK patients with placebo (3.9 days) after 200 days. 61% of the patients in the treatment group also declared that they suffered from arthralgia at day 200, compared to only 23% of patients from the placebo group. Although this study planned to have a larger sample size of 250 instead of 54 (in order to measure a day's difference between the chloroquine group and control group), the original trial with a larger sample size was terminated by the same study investigator in May 2007, citing reasons of CHIK abatement and the lack of patients.[29, 199]

Results from another included randomized uncontrolled study also supported the finding that in the acute CHIK phase, no benefits were observed from hydroxychloroquine treatment, particularly on decreasing VAS pain scores and improvement in ADL and IADL scores.[129]

Although chloroquine/hydroxychloroquine did not have clear evidence of positive improvements on acute CHIKV infection, an included open pilot study done in 1984 showed positive effects on chronic CHIK infection, particularly on improvements in chronic stage of CHIK arthritis on joint pain and morning stiffness.[181]

Harm associated with the use of chloroquine phosphate or chloroquine during the intervention period was reported in two included studies. Seven of 27 (12.96%) patients in the chloroquine treatment group suffered from nausea and pruritus ($P<0.01$), said to be the mild adverse effects of chloroquine treatment.[29] In another study, a female patient withdrew at the eighth week of intervention due to persistent headache; however, the patient was reported to have experienced less joint pain and stiffness up to her time of withdrawal.[181]

Results of HRQoL domains for clinical manifestations management

Overall health-related quality of life (Figures 3.3 - 3.5 in Appendix XIV)

A meta-analysis of the change in score from baseline value to post-test value in two

uncontrolled studies (one CHIK study and one RRV study) found statistically significant effects of drug treatments on HRQoL in all three follow-up periods of 0 - 6 months (SMD -0.63; 95% CI -0.97 to -0.29), 13 - 24 months (SMD -1.21; 95% CI -1.73 to -0.70) and 7 - 12 months (SMD -0.86; 95% CI -1.18 to -0.54). Significant effects were also found when HRQoL was evaluated using the HAQ and CLINHAQ, except when using HAQ at 0 - 6 months (MD -0.46; 95% CI -1.01 to 0.09). There was no significant heterogeneity using the χ^2 test for subgroup differences when results were analysed across (P=0.17) and within HAQ (P=0.14) and CLINHAQ (P=0.62); the results of the I^2 test (I^2=43.9%) for subgroup differences in Figure 3.3 might present moderate heterogeneity.

Disease-specific quality of life (Figures 3.6 - 3.11 in Appendix XIV)

A meta-analysis of the change in score from baseline value to post-test value in three (two CHIK and one RRV) uncontrolled studies showed statistically significant effects of drug treatments on disease-specific quality of life in all three follow-up periods of 0 - 6 months (SMD -6.22; 95% CI -10.05 to -2.40), 7 - 12 months (SMD -4.36; 95% CI -6.56 to -2.17) and 13 - 24 months (SMD -9.92; 95% CI -16.09 to -3.75). Significant effects were also found when disease-specific quality of life was evaluated within the various HRQoL instruments used, except the DAS overall change score at the 0 - 6 months follow-up (MD -1.33 95% CI -3.84 to 1.18) and CLINHAQ gastrointestinal symptoms subscale change score at 0 - 6 months (MD -0.18; 95% CI -0.57 to 0.21) and 7 - 12 months (MD -0.21; 95% CI -0.55 to 0.13). The χ^2 test for subgroup differences showed no significant heterogeneity (P=0.22) and the results of the I^2 test (I^2=34.9%) for subgroup differences in Figure 3.6 might present moderate heterogeneity.

Anxiety (Figure 3.12 in Appendix XIV)

A meta-analysis of the change in score from the baseline value to the post-test value in an uncontrolled RRV study showed significant effects on anxiety at 0 - 6 months (SMD -2.03; 95% CI -3.27 to -0.79) and 7 - 12 months (SMD -2.88;95% CI -4.06 to -1.70). The χ^2 test for subgroup differences showed no significant heterogeneity (P=0.33).

Depression (Figure 3.13 in Appendix XIV)

A meta-analysis of the change in score from baseline value to post-test value in an uncontrolled RRV study showed significant effects of drug treatments on anxiety at 0 - 6 months (SMD -1.99; 95% CI -3.27 to -0.71) and 7 - 12 months (SMD -2.54; 95% CI -3.75 to -1.33). The χ^2 test for subgroup differences showed no significant heterogeneity (P=0.54).

Emotional functioning (Figures 3.14 - 3.17 in Appendix XIV)

A meta-analysis of the change in score from baseline value to post-test value in an uncontrolled RRV study showed statistically significant effects of drug treatments on emotional functioning at 0 - 6 months (SMD -10.31; 95% CI -18.98 to -1.64) and 7 - 12 months (SMD -13.68; 95% CI -25.12 to -2.24). Significant effects were also found when emotional functioning was evaluated within the various HQoL instruments used, except from the MOS SF-36 mental component summary subscale change scores at 0 - 6 months ((MD -5.44; 95% CI -13.09 to 2.21) and 7 - 12 months (MD -6.41; 95% CI -14.04 to 1.22) and the MOS SF-36 role emotional subscale change scores at 0 - 6 months (MD -20.76; 95% CI -50.84 to 9.32) and 7 - 12 months (-26.47; 95% CI -56.45 to 3.51). The χ^2 test for sub-group differences showed no significant heterogeneity (P=0.64).

Fatigue (Figures 3.18 - 3.20 in Appendix XIV)

No strong evidence of significant effects was observed on overall fatigue scores across CLINHAQ and MOS SF-36 at 0 - 6 months (SMD -16.87; 95% CI -49.77 to 16.03) and 7 - 12 months (SMD -17.66; 95% CI -52.89 to 17.58). However, within each of the CLINHAQ and MOS SF-36, significant effects were observed in CLINHAQ fatigue change scores at 0 - 6 months (MD -0.97; 95% CI -1.53 to -0.41) and 7 - 12 months (MD -0.88; 95% CI -1.57 to -0.19), as well as significant effects in MOS SF-36 vitality change scores at 0 - 6 months (MD -34.59; 95% CI -49.91 to -19.27) and 7 - 12 months (MD -36.92; 95% CI -55.49 to -18.35). The χ^2 test for subgroup differences showed no significant heterogeneity (P=0.97).

General health perspective (Figures 3.21- 3.24 in Appendix XIV)

Two uncontrolled studies (one CHIK study and one RRV study) reported change in overall general health prospective scores between baseline value and post-test value in the drug treatments group. A statistically significant improvement in general health perspective was observed at 0 - 6 months follow-up period (SMD -0.89; 95% CI -1.29 to -0.48), but no strong evidence of an effect was observed at 7 - 12 months (SMD -0.08; 95% CI -1.88 to 1.73). Significant effects were also found when general health perspective was evaluated within the various HQoL instruments used, except from the MOS SF-36 general health perspective subscale change scores at 0 - 6 months (MD -11.07; 95% CI -24.25 to -2.11) and 7 - 12 months (MD -12.12; 95% CI -26.54 to 2.30). No significant heterogeneity was observed from the χ^2 test for subgroup differences (P=0.39) and the I^2 test (I^2=0%) from Figure 3.21 shows that heterogeneity might not be important.

Pain (Figures 3.25-3.26 in Appendix XIV)

Two uncontrolled studies (one CHIK study and one RRV study) and a CHIK controlled study reported change in overall pain scores between baseline value and post-test value in the drug treatments group and were analysed separately to reduce statistical heterogeneity.

For the uncontrolled studies, a statistically significant improvement in pain was observed at the 0 - 6 months follow-up period (SMD -7.52; 95% CI -11.56 to -3.48), but no strong evidence of effect was observed at 7 - 12 months (SMD -27.56; 95% CI -79.90 to 24.9). No significant heterogeneity was observed from the χ^2 test for subgroup differences (P=0.45) and the I^2 test (I^2=0%) from Figure 3.25 showed that heterogeneity might not be important. For the controlled study, there was a statistically significant improvement in CHIK patients given the synthetic nucleoside analogue anti-viral drug ribavirin compared to CHIK patients without ribavirin at 0 - 6 months follow-up (SMD

-0.93; 95% CI -1.54 to -0.33). No 7 - 12 months follow-up data was available for the controlled study.

Physical functioning (Figure 3.27 in Appendix XIV)

Two uncontrolled studies (one CHIK study and one RRV study) reported change in overall physical functioning scores between baseline value and post-test value in the drug treatments group. A statistically significant improvement in physical functioning was observed at 0 - 6 months (SMD -12.24; 95% CI -18.5 to -5.98) and at 7 - 12 months (SMD -21.68; 95% CI -42.19 to -1.17). No significant heterogeneity was observed from the χ^2 test for subgroup differences (P=0.39) and the I^2 test (I^2=0%) from Figure 3.27 showed that heterogeneity might not be important.

Role functioning (Figure 3.28 in Appendix XIV)

Two uncontrolled studies (one CHIK study and one RRV study) reported change in overall role functioning scores between baseline value and post-test value in the drug treatments group. A statistically significant improvement in role functioning was observed at 7 - 12 months (SMD -62.47; 95% CI -86.22 to -38.72), but no strong evidence of effect was observed at the 0 - 6 months follow-up period (SMD -31.48; 95% CI -87.24 to 24.27). No significant heterogeneity was observed from the χ^2 test for subgroup differences (P=0.32) and the I^2 test (I^2=0.4%) from Figure 3.28 showed that heterogeneity might not be important.

Sleep (Figure 3.29 in Appendix XIV)

The CLINHAQ sleep problem subscale change scores from an RRV study showed significant improvement in sleep problems at 0 - 6 months (MD -0.86; 95% CI -1.35 to -0.37) and at 7 - 12 months (MD -0.79; 95% CI -1.34 to -0.24). No significant heterogeneity was observed from the χ^2 test for subgroup differences (P=0.85).

Social functioning (Figure 3.30 in Appendix XIV)

The MOS SF-36 social functioning subscale change scores from an RRV study showed significant improvement at 0 - 6 months (MD -34.58; 95% CI -50.20 to –18.96) and at 7 - 12 months (MD -33.35; 95% CI -50.38 to -16.32). No significant heterogeneity was observed from the χ^2 test for subgroup differences (P=0.92).

3.4.2.2. Early diagnosis of disease

Clinically meaningful information on patients' visits to GPs and specialists was sparse in the included studies. Thus, the evidence was insufficient in terms of quality and reliability to enable any strong conclusion on the effects of early diagnosis of disease on HRQoL outcomes among patients with established AAIs.

Meta-analysis of the two retrospective cohort studies[42, 119] showed no strong evidence that early diagnosis of disease, in the form of mainly GP medical consultations, had any statistically significant effect on emotional and physical functioning HRQoL domains. From Figure 3.31, there is strong evidence that the intervention had a statistically significant effect on emotional functioning, when comparing mainly GP medical consultations in CHIK patients to standard care in CHIK negative controls during the 25 - 36 months follow-up period (SMD 0.68; 95% CI 0.54 to 0.82), but not during the 13 - 24 months follow-up period (SMD 0.01; 95% CI -0.21 to 0.23).From Figure 3.32, there was strong evidence that the intervention had a statistically significant effect on physical functioning at both follow-up periods of 13 - 24 months (SMD 0.27; 95% CI 0.05 to 0.49) and 25 - 36 months (SMD 0.91; 95% CI 0.57 to 1.24), when comparing mainly GP medical consultations in CHIK patients to standard care in CHIK negative controls.

There was significant statistical heterogeneity (P<0.00001 from Figure 3.31 and P=0.002 from Figure 3.32) from the χ^2 test for subgroup differences when results were analysed by including the two types of HRQoL instruments, MOS SF-12 and MOS SF-36. Correspondingly, the I^2 test showed considerable heterogeneity (I^2=96.1% from Figure 3.31 and I^2=89.7% from Figure 3.32) for the subgroup differences. The heterogeneity

was posited due to the clinical diversity between the study populations although they were from the same country, La Reunion Island, with the studies conducted around the same period, 2006 - 2008. In Marimoutou et al. 2012, the sample consisted of mostly healthy and fit men from the French Military (351 males and 31 females); however in Soumahoro et al. 2009, the sample consisted of citizens (196 males and 202 females). Although the mean age at 42.8 versus 42 respectively reported for both studies were similar, the age range varied at 39 - 48 versus 2 - 91 respectively.[42, 119]

Where data were available, follow-up scores for MOS SF-12 and MOS SF-36 in both studies was analysed separately and results (Appendix XIII) showed no strong evidence of statistically significant effect on emotional functioning and physical functioning.

Marimoutou et al. 2012 reported harm associated with CHIK and its management. For CHIK patients whose survey results revealed most frequent visits to the GPs (9.4 consultations per patient), followed by functional re-education (eight consultations per patient) and then less than one consultation per patient for acupuncture (0.7), specialist (0.32), emergency (0.3) and surgery (0.2), worsening of clinical conditions were reported. Results of the MOS SF-36 mental and physical component summaries scores were significantly impaired in CHIK patients, chronic fatigue was present in 20% and joint pain and their limitations could last for than two years after CHIK infection. The other three studies did not report harm associated with CHIK and its management.[119, 185, 186]

A case series and two case reports' results presented in narrative form also reported on the effects of early diagnosis of disease on HRQoL. In contrast to the lack of strong evidence from the cohort studies, evidence from descriptive studies suggested the importance of early diagnosis of CHIK in disease management.

A case series reported that the improvement of quality of life of CHIK patients with lower urinary tract symptoms (LUTS) was attributed to the accurate assessment of clinical manifestations and timely interventions. The improvement of quality of life in the study was defined as the complete voiding of urine and constant renal function in patients with LUTS after CHIK fever. Despite the favourable results, the study was underpowered to detect a true effect due to extremely small sample size of less than four CHIK patients for each of the six interventions described. [185]

A case report on the first Taiwanese importation of CHIK after travel to Malaysia recognised that early diagnosis of CHIK fever was difficult as the clinical symptoms were similar to other tropical diseases, particularly Dengue fever, thus CHIK might be underdiagnosed or misdiagnosed as Dengue.[186] Additionally, physicians had restricted knowledge and experience in CHIK, due to the absence of indigenous CHIK cases for about 40 years and imported CHIK cases before 2006. If physicians suspected CHIK in a patient, laboratory diagnostics such as RT-PCR and seroconversion were used to confirm CHIK infection. Hence, more education in the diagnosis and treatment of CHIK is recommended for Taiwanese clinicians.[186] In the other case report on chronic CHIK, physicians documented the extent of severe manifestations, such as myocarditis even in young children.[187]

3.4.2.3. Disease education

No conclusions could be drawn regarding the effectiveness of disease education on HRQoL outcomes among patients with established AAIs. In a retrospective cohort study, although functional re-education of eight consultations per patient was reported, its direct results on HRQoL were dwarfed by the influence of another intervention (early diagnosis of disease) that occurred at a higher rate (9.4 consultations per patient).[42] Despite the lack of evidence, a case report suggested the importance of education of clinicians in CHIK diagnosis and treatment.[186]

3.5. Discussion

To our knowledge, this study is the first to evaluate the effects of disease management interventions on HRQoL of patients with AAIs. Results of this systematic review suggest that at varying follow-up periods, clinical manifestations management for CHIKV and RRV diseases had a positive impact on some HRQoL domains including overall HRQoL, CHIK-specific concerns (e.g. rheumatic disease activity), anxiety, depression, emotional functioning, fatigue, general health, pain, physical functioning, role functioning, sleep and social functioning. There was no strong evidence that early diagnosis of disease had any significant effect on HRQoL domains of emotional functioning and physical functioning. Due to the dearth of evidence, no conclusions were drawn from included studies on the effects of disease education on any HRQoL domains.

Clinical guidelines and factsheets published for CHIK[57, 58, 200, 201], RRV, BFV and SINV made limited reference to evidence and none were based on comprehensive systematic reviews. Clinical guidelines and factsheets published for RRV, BFV and SINV were from mainly Australia, specifically the affected states of New South Wales (RRV and BFV)[202, 203], Queensland (RRV)[204] and Western Australia (RRV and BFV).[205, 206] These clinical guidelines for RRV, BFV and SINV recommended symptomatic treatment, although the guidance was not developed as evidence-based clinical practice. No evidence-based clinical practice guidelines were found for ONNV, MAYV and SFV.

3.5.1. Clinical manifestations management

Clinical guidelines have also shown that the use of NSAIDs continues to be recommended as the mainstay of treatment for CHIK.[58, 200, 201] This group of drugs falls under the class of anti-inflammatory drugs, and aids in reducing arthritic symptoms of CHIK through analgesic actions and by inhibiting synthesis of prostaglandins.[207] Besides the use of acecyclofenac from the systematic review, clinical guidelines also recommend various NSAIDs drugs such as ibuprofen and naproxen. Also, corticosteroids and analgesics (for example, morphine) are recommended for acute

CHIK. Anti-pyretics mainly paracetamol are also recommended to manage CHIK fever.[57, 200, 201]

The WHO clinical guidelines recommend the prescription of the anti-viral drug, hydroxychloroquine (200 mg/day oral), or chloroquine phosphate (300 mg/day oral) for four weeks at the tertiary care level, when other drugs are not effective to treat CHIK-induced arthralgia.[58] The evidence base for recommendation of the dosage, frequency and length of intervention is largely uncertain and may need re-evaluation. Based on the systematic review findings, there is no strong evidence for the use of chloroquine/hydroxychloroquine clinician on the use of chloroquine/hydroxychloroquine in CHIK treatment.

Clinical guidelines for CHIK have also recommended the consideration of methotrexate (MTX) to manage chronic pain. Anti-neuralgic drugs, calamine lotion, zinc oxide, saline compresses and antibiotics may help in the symptomatic treatment of neurological disorders and skin conditions. For severe CHIK complications, platelet transfusions, intravenous vitamin K, fluids, inotropics, dialysis, physiotherapy, surgery, systemic drugs, ventilation and intensive care are recommended, depending on diagnosis. Non-pharmacological methods, such as physiotherapy, cold compresses, mild exercise, rest, hydration, psychosocial community reassurance and support are also recommended.[57, 58, 200, 201]

The disease management guidelines recommended above are unfortunately symptomatic treatment and support which are not sufficient to restore a CHIK patient to full health. As seen from an included study, during the 15-month study period, 66% of CHIK patients over the age of 45 years from the study sample had persistent CHIK-induced arthritis compared to 34% of CHIK patients whose CHIK symptoms resolved and were in remission. This study also suggested insufficient treatment as a potential risk factor for the persistence of CHIK-induced arthritis.[130]

3.5.2. Early diagnosis of disease

Early and accurate identification of CHIK patients requires vigilant monitoring of clinical manifestations by clinicians, leading to prompt initiation of aggressive therapeutics management. The sooner an accurate diagnosis is made, the better it is for the patient because appropriate disease management can be initiated earlier to avert adverse outcomes and if need be, to trace contacts with exposure risk promptly. Strong and uniform detection and management protocols for the acute phase of AAIs are lacking, further complicating the resolution of symptoms. Concerns also arise that AAIs may be circulating undetected or may have been misdiagnosed and therefore mistreated as has occurred with other forms of disease, such as Dengue, even in endemics and high risk regions.[18, 186, 192, 196, 208] The failure to detect low level and continued transmission of AAIs in humans poses a risk of lowering HRQoL in patients. Hence, it behoves clinicians to have vigilant observation in order to assist patients receive speedy access to appropriate medical care.

3.5.3. Disease education

There is a dearth of evidence regarding the effectiveness of disease education on HRQoL. However, studies on diseases such as schizophrenia have found that multi-disciplinary and care groups established around promoting quality of life and education were successful in delivering better health outcomes in patients compared to patients in the control group receiving routine treatment.[209] The communication and trust involved in the relationship among the doctor, the patient and family are keys in helping the patient deal with the disease better, hence improving their quality of life.[209]

3.5.4. Limitations

Most of the included studies were of moderate quality with differing levels of risks of bias and had inadequate reporting of key variables (frequency, dosage, administration route, duration and adherence) for non-pharmacological interventions. Some of the included studies were of small sample sizes, not sufficient to detect a true effect. For included studies with sufficient effect size, a statistically significant finding of a disease

management intervention might not produce a clinically meaningful result that is helpful to the CHIK patient. The exclusion of non-English studies might also affect the effect estimates in meta-analyses.

Most of the included studies were conducted during or after an epidemic and might have neglected cases that occurred independently of the epidemic. Additionally, as an established case of AAI was based on the reporting of clinical symptoms with or without a link to epidemiology, no included study had examined the management strategies for infected patients during the latent period and the pre-patent period.[210] An inadequate follow-up duration is also a limitation on the assessment of effects of disease management interventions on HRQoL.

Subjective bias might arise from the self-reporting of HRQoL scores and the recall of severity of clinical symptoms. The acceptance of validated and invalidated HRQoL assessment tools with unclear sensitivity and specificity for the measurement of various HRQoL domains might pose a limitation to the accuracy of findings.

3.6. Conclusion

The systematic review results suggested that at varying follow-up periods, clinical manifestations management for CHIKV and RRV diseases had a positive impact on some HRQoL domains including overall HRQoL, CHIK-specific concerns (e.g. rheumatic disease activity), anxiety, depression, emotional functioning, fatigue, general health, pain, physical functioning, role functioning, sleep and social functioning. There was no strong evidence that early diagnosis of disease had any significant effect on HRQoL. No conclusions could be drawn from included studies on the effects of disease education on HRQoL.

3.6.1. Implications for practice

- The use of chloroquine/hydroxychloroquine and paracetamol in the management of CHIKV suggests association with harm, notably arthritic conditions (paracetamol),

oedema (paracetamol), hypertension (paracetamol), nausea (chloroquine/hydroxychloroquine) and pruritus (chloroquine/hydroxychloroquine). With such indications, the importance of pharmacological validation before being reconsidered for routine clinical application cannot be over-emphasised. Care should be rendered in treatment decisions with consideration of side effects. (Grade B)

- The use of NSAIDs in the management of RRV suggests association with harm, notably arthritic conditions. (Grade B)

- No benefits were observed with the duration and frequency of arthralgia, and VAS pains, ADL and IADL scores in acute CHIK infection from treatment with chloroquine/hydroxychloroquine. (Grade B)

- In patients with CHIK chronic arthritis, there is weak evidence showing alleviation of joint pain and morning stiffness using chloroquine phosphate (250 mg/day x 20 weeks). (Grade B)

- Clinicians are encouraged to build awareness on clinical manifestations of CHIK and RRV diseases, which have been commonly misdiagnosed as other diseases such as Dengue or arthritis. The ability to discern the triad of symptoms of fever, arthralgia and rash, and to consider specific AAIs as a possibility in the diagnoses of acute febrile diseases are important. (Grade B)

- The formulation of uniform detection and management protocols for both the acute and chronic phases for all AAIs is warranted. This is one of the ways to facilitate better diagnosis and treatment of AAIs, as well as accurate assessment of clinical manifestations and timely interventions for patients. (Grade B)

- A re-evaluation of past clinical records and logbooks of patients who have similar symptoms as those of AAIs is recommended to clinicians, who may be able to find misdiagnosed patients. (Grade B)

3.6.2. Implications for research

- The establishment of case definitions for ONNV, MAYV and SFV is required.

- Evidence-based clinical guidelines should be established for ONNV, MAYV and SFV as they are not currently available.

- Existing clinical guidelines for CHIK should be updated periodically and effectively, with clear evidence for the interventions used, to inform clinicians and patients on the management of CHIK for the improvement of HRQoL.

- More research is required to understand the natural disease progression of AAIs, so as to map out clearly defined acute and chronic phases of AAIs in adults and children and to consider possible pharmacological and non-pharmacological treatments.

- More research is required to establish the evidence base for the effectiveness of non-pharmacological interventions, including physiotherapy, occupational therapy, acupuncture and disease education on HRQoL of patients with AAIs.

- A broad approach to the management of CHIK is essential to alleviate the burden of CHIK on society. Systematic reviews on the effectiveness of current surveillance systems and mosquito control strategies are essential to understand if current preventive and control measures are effective in reducing the spread of CHIK.

4 The effectiveness of public health surveillance systems in Chikungunya: A systematic review

4.1. Abstract

Although surveillance is a basic public health tool to detect and monitor the transmission of diseases, its effectiveness in the management of Chikungunya has not been established. This systematic review included 12 studies that met the inclusion criteria. Based on the small number of mostly descriptive studies (except one case-control), eight of these studies affirmed that effective and rigorous public health surveillance systems play a vital role in reducing Chikungunya transmission. When assessed in the context of 28 surveillance system process and quality evaluation indicators within the World Health Organization framework for monitoring and evaluating surveillance and response systems, surveillance systems from the studies showed limited evidence in their effectiveness to meet the core functions, support functions, quality attributes and overall goals. As most surveillance systems were not rigorously evaluated, outcome data relevant to establishing effectiveness contained many gaps on evaluation indicators. Although case detection, confirmation and reporting evaluation indicators were positively met by 11 included studies, no included studies explicitly reported on indicators of registration, usefulness, specificity, simplicity, flexibility and acceptability of surveillance systems. Neither the frequency of surveillance analysis nor the frequency and distribution of surveillance reports was reported from at least nine studies. Some evidence of epidemic unpreparedness, delayed response and control, challenging coordination, untimely surveillance, poor positive predictive value and lack of representativeness was also found. More high quality rigorous primary studies are required to confirm the best available evidence on the effectiveness of surveillance systems specific to Chikungunya.

4.2. Concise introduction

CHIK is a debilitating mosquito-borne *Alphavirus* accountable for the unexpected rise in epidemics of febrile arthralgia in the past decade.[35, 82] Eradication of the virus has not

been possible, as shown by its continued circulation in existing and new territories.[37, 77, 78] Such challenges call for the need for establishing effective prevention and control measures, especially when neither a licensed vaccine nor specific treatment is available. Surveillance has always been a foundational public health strategy; however, its effectiveness specifically in CHIK has not been clearly evaluated based on evidence.[73] Therefore, the objective of this systematic review is to critically present the best available evidence related to the effectiveness of surveillance systems used in CHIK.

4.3. Methods unique to chapter

4.3.1. Types of participants

This systematic review included populations with exposure to or are at risk of CHIKV infection. There were no limits to the countries examined.

4.3.2. Types of interventions

The interventions of interest included:

- Disease surveillance systems: systems that detect or monitor trends of presence or absence of a disease, usually required for disease control.
- Vector surveillance systems: systems that detect or monitor the presence of existing or potential mosquitoes species (not limited to *Aedes aegypti* and *Aedes albopictus*) which are involved in the transmission of the CHIKV.[211, 212]

4.3.3. Types of outcomes

The effectiveness of surveillance systems was evaluated through an objective and transparent document audit, based on the compliance of the WHO framework for monitoring and evaluating surveillance and response systems for communicable diseases.[211] The audit examined the degree to which each surveillance study reported findings that adhered to the 28 process and quality evaluation indicators outlined in the WHO framework. The purpose of the evaluation indicators in the systematic review was to identify evidence on the effects of the surveillance system in relation to process functions and quality evaluation, enabling attention to aspects of CHIK surveillance that required refinement. The audit was conducted in consideration of

publication bias and the relevance of evaluation indicators to the study surveillance goals. It was also recognised that some evaluation indicators might be more important than others with respect to achieving the goals of a surveillance system; hence, a balance of its attributes is needed.

The following 28 process and quality evaluation indicators were considered[56, 74, 211] where relevant:

Degree of meeting core functions of surveillance systems:

1. Case detection
2. Registration
3. Confirmation
4. Reporting (Notification)
5. Data-analysis/interpretation
6. Epidemic preparedness
7. Response and control
8. Feedback.

Degree of meeting support functions of surveillance systems:

1. Standards and guidelines
2. Training
3. Supervision
4. Communication
5. Resources (including logistics)
6. Coordination.

Degree of meeting quality attributes of surveillance systems:

1. Timeliness
2. Completeness
3. Usefulness
4. Sensitivity
5. Specificity
6. Simplicity
7. Flexibility
8. Acceptability
9. Reliability
10. Positive predictive value
11. Representativeness.

Degree of meeting overall goals of surveillance systems, including:

1. Reduction in the case-fatality rate of epidemic-prone diseases.
2. Changes in the morbidity pattern of targeted communicable diseases.
3. Changes in behavior of health staff and of the general population.

The WHO framework was adapted from CDC updated guidelines for evaluating public health surveillance systems[74] as well as another study on the conceptual framework of public health surveillance and action.[56] Definitions of active surveillance, passive surveillance, integrated surveillance, syndromic surveillance, categorical surveillance and evaluation indicators were referenced from these studies, which also served as detailed guides to evaluate the effectiveness of surveillance systems in CHIK.

4.3.4. Search strategy

A literature search was performed from seven major scientific electronic databases: PubMed, Web of Science, Scopus, ScienceDirect, CINAHL, CENTRAL and ProQuest. In addition, nine sources of grey literature were searched: WHOLIS, CDC, ECDC, ICRES, NIH, Latin American and Caribbean Health Sciences Literature (LILACS), World Bank, Asia Development Bank and Google.

Appendix XV shows the comprehensive search strategy. The keywords used in the search strategy were:

1. Surveillance
2. Public health surveillance
3. Disease outbreak
4. Chikungunya
5. Alphavirus.

4.4. Results

4.4.1. Methodological results

4.4.1.1. Study selection

The titles and abstracts of the 2869 studies were examined for a match with the a priori inclusion criteria. When uncertain, the full-text of the study was retrieved for detailed examination. Of these, 2853 studies were excluded as they were not consistent with the review objectives and did not meet the inclusion criteria. Sixteen studies in English appeared to match the inclusion criteria and the full text was analysed in detail. Of the 16 studies, four were excluded based on irrelevant population, interventions or outcomes. As a result, 12 studies were finally included in this systematic review. Figure 4.1 illustrates the study selection process.

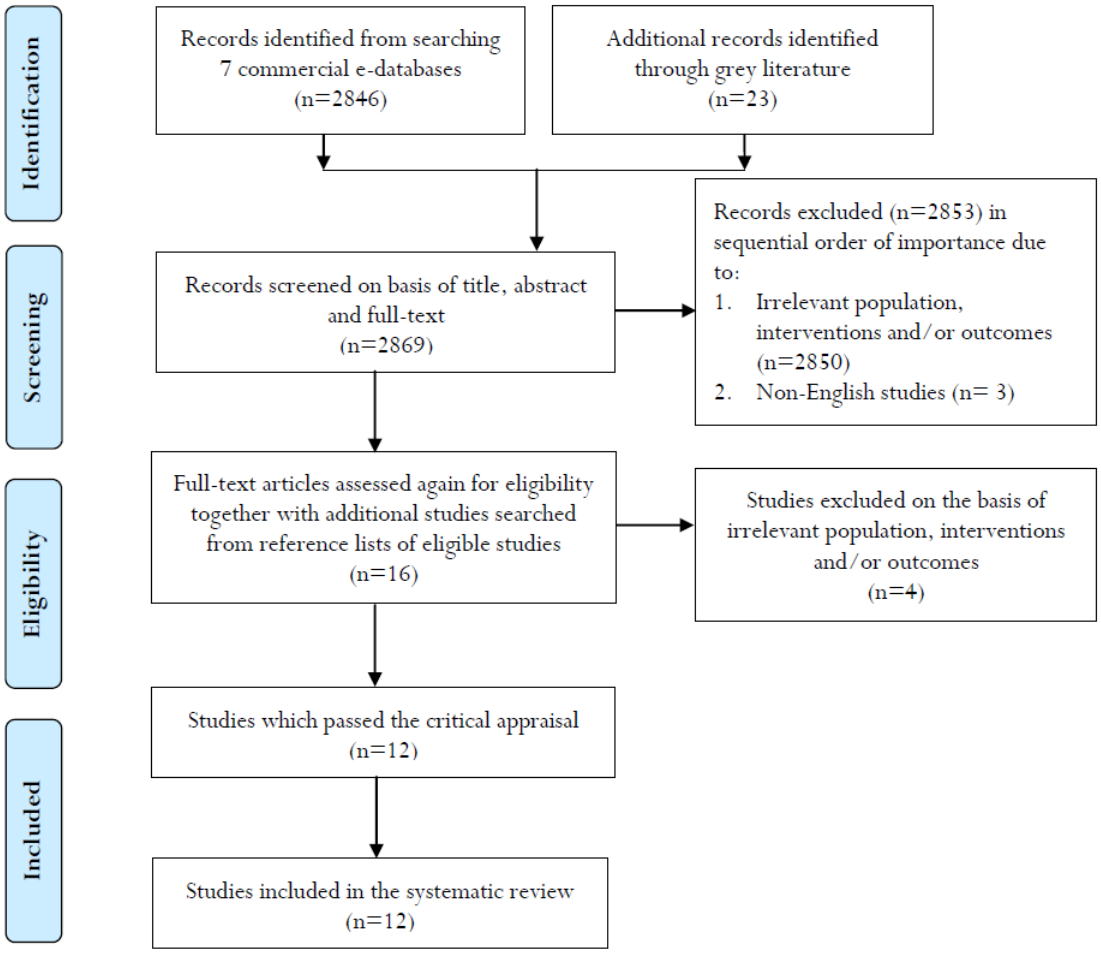

Figure 4.1. Study selection process

4.4.1.2. Methodological quality

Overall, 12 studies passed the critical appraisal and showed moderate methodological quality. Results of the critical appraisal are reported in Table 4.1.

Table 4.1. JBI-MAStARI critical appraisal of included studies

Comparable cohort / case control studies									
Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**
Disease surveillance systems									
Laras *et al.* 2005[80]	N	Y	Y	Y	Y	Y	N	Y	Y
%	0	100	100	100	100	100	0	100	100
Descriptive / case series studies									

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Disease and vector surveillance systems									
Gibney *et al.* 2011[79]	Y	Y	Y	Y	N/A	Y	N/A	Y	Y
Ho *et al.* 2011[69]	Y	Y	Y	Y	N/A	Y	N/A	Y	Y
Ng *et al.* 2009[213]	Y	Y	N	Y	Y	Y	N/A	Y	Y
Renault *et al.* 2007[82]	Y	Y	Y	Y	Y	Y	N/A	Y	Y
Disease surveillance systems									
Gobbi *et al.* 2012[68]	Y	Y	N	Y	Y	Y	N/A	Y	Y
Napoli *et al.* 2012[81]	Y	Y	Y	Y	Y	Y	N/A	Y	Y
Randrianasolo *et al.* 2010[70]	N	Y	Y	Y	N/A	Y	N/A	Y	Y
Sissoko *et al.* 2008[83]	Y	Y	Y	Y	Y	Y	N/A	Y	Y
Vector surveillance systems									
Carrieri *et al.* 2011[67]	Y	Y	Y	Y	Y	Y	N/A	Y	Y
Sang *et al.* 2008[214]	N	Y	Y	Y	N/A	Y	N/A	Y	Y
Zayed *et al.* 2012[215]	N	Y	Y	Y	N/A	Y	N/A	Y	Y
%	72.73	100	81.82	100	100	100	N/A	100	100

Refer to Appendices V and VI for the critical appraisal checklist questions Q1-Q9.
Y: Yes; N: No; U: Unclear; N/A: Not applicable.

Table 4.1 illustrates the combined critical appraisal undertaken by the two independent experienced JBI reviewers. Both reviewers agreed on the cut-off criteria for each critical appraisal question and sought clarity on study data.

An example of cut-off criteria:

If comparisons are made, were there sufficient descriptions of the groups?

Here, groups can refer to control groups or other groups such as other disease groups (e.g. CHIK and Dengue).

With respect to the research question, the critical appraisal question on sample representativeness was deemed the most important. Disease surveillance systems should have a design element enabling valid statistical inferences on the expected

degree of case detection. Hence, primary studies on surveillance systems, based on a representative, random or pseudo-random sample, would provide a foundation for valid statistical inference related to the population of interest.[216]

As reported in Table 4.1, eight of 12 studies showed that study samples were random/pseudo-random or were representative of the population. This was not surprising as surveillance systems from the included studies were implemented at the national, district or municipal levels to enhance case detection. However, for the remaining four studies, one was sampled from two of 24 suspected CHIK outbreak episode areas of Bogor and Bekasi, West Java province, Indonesia.[80] Another sampled collection of adult mosquitoes on one of three (Moroni, Mitsamiouli and Fumbouni) cities of Grande Comore, instead of all three affected cities[214], and the third selected sites for collection of adult resting mosquitoes.[215] The last study utilised voluntary sentinel GPs who were selected based on pre-specified criteria from 13 geographically-represented sentinel centers; hence, the surveillance was not representative of the entire country of Madagascar.[70]

Ten of 12 studies adequately identified confounding factors, such as epidemiological patterns of disease[82,67], changes in seasons or climates[67, 70, 79, 80, 215], changes in urbanization patterns[67, 69, 70, 80], changes in population dynamics (including density, dispersal, ecological and feeding patterns)[67, 70, 82, 83, 214] and the presence of disease control programs.[67] However, methods to deal with the confounding factors were minimally addressed, with the exception of one study that suggested additional research to be conducted to address mid-way switches in type of surveillance systems.[70, 82] A case-control study had controls to exclude the possibility of other viral infection outbreaks.[80] One study attributed the containment of CHIK outbreak to the rigorous mosquito control efforts. This, however, should not lead to an assumption that the surveillance systems were not effective in containing CHIK outbreak.[79] Two studies did not identify or deal with confounding factors.[68, 213] In addition, a case-control study did not describe

the outcomes of people who withdrew.[80] The rest of the critical appraisal questions were reviewed and were checked *yes*.

4.4.1.3. Excluded studies

No studies were excluded based on poor methodological quality.

4.4.1.4. Data extraction

The following data were extracted:

a) Study characteristics

Study design; study objective; duration of observation; study start and stop dates; approval by ethics committee; funding; and contacted authors.

b) Participants

Study sample; intervention group; control group; main sources of CHIK import; and high-risk people identified.

c) Surveillance interventions

Description; categories of surveillance; country/income; date when CHIK was made legally notifiable; mosquito species involved; cost-effectiveness; and limitations.

d) Outcomes

- Eight indicators for meeting the core functions of surveillance systems are case detection; registration; confirmation; reporting; data-analysis; epidemic preparedness; response and control; and feedback.
- Six indicators for meeting the support functions of surveillance systems are standards and guidelines; training; supervision; communication; resources; and coordination.
- Eleven indicators for meeting quality attributes of surveillance systems are timeliness; completeness; usefulness; sensitivity; specificity; simplicity; flexibility; acceptability; reliability; positive predictive value; and

representativeness.

- Four indicators for meeting overall goals of surveillance systems are the reduction in the case-fatality rate of epidemic-prone diseases; changes in the morbidity pattern of targeted communicable diseases; changes in behaviour of health staff and of the general population; and others.

e) Additional comments

Study conclusions as described by the authors of the included papers.

Note that data extraction for non-RCTs may not need to include intervention/control items.

4.4.2. Description of included studies

The JBI levels of evidence for effectiveness of interventions[188] were used to classify the evidence from the 12 included studies.[67-70, 79-83, 213-215] One study was a case-control study of level 3 evidence[80] and the rest were descriptive studies of level 4 evidence.[22-28, 36-40] Although RCTs are considered the *gold standard* in the evaluation of intervention effectiveness, no data on CHIK surveillance was available from an RCT.

Included studies were published recently, from 2005 - 2012. According to the World Bank's list of income classification of countries (valid from 1 July 2013 - 1 July 2014)[217], seven studies were conducted in high income countries of Singapore[69, 213], France[82], Italy[67, 68, 81] and the USA[79], two studies were conducted in lower middle income countries of Indonesia[80] and Yemen, and three studies were conducted in low income countries of Madagascar[70] and Union of the Comoros.[83, 214]

The comprehensive details of the included studies are presented in Appendix XVI. To gain better perspective and understanding, surveillance systems from the included studies were categorised according to human resource allocation (active/passive/active and passive surveillance)[75], surveillance on targeted populations of humans or

mosquitoes (disease/vector/disease and vector surveillance)[75] and the implementation of surveillance systems based on the country's administrative hierarchy (country/regional/province/district/locality/enumeration).[76]

Of the 12 included studies, five studies were on active surveillance[67, 70, 80, 214, 215] and seven studies were on a combination of active and passive systems.[68, 69, 79, 81-83, 213] Four studies concentrated on disease surveillance[23, 26, 28, 38], three studies concentrated on vector surveillance[36, 67, 215] and five studies concentrated on a combination of disease and vector surveillance systems.[69, 79, 81, 82, 213] Six included studies had surveillance systems with coverage at the national level[67, 69, 70, 79, 81, 213] while five included studies had surveillance systems with coverage at the regional level[67, 68, 82, 83, 214] and one included study had surveillance systems with coverage at the district level.[37]

Four main factors spurred the development of CHIK surveillance systems, namely the presence of CHIK cases as reported in eight studies[67, 70, 80-83, 214, 215], presence of CHIK susceptible vectors in one study[79], enhancement of CHIK detection in another study[68] and anticipation of imported CHIK cases from neighbouring countries in one study.[69] The final included study conducted in Singapore did not state the reason prompting development of surveillance on CHIK.[213]

The appearance of CHIK or *CHIK-like* cases was the impetus that prompted the development of CHIK surveillance systems in different countries. An example was the first CHIK outbreak in Europe, where 247 CHIK cases were identified in the Emilia-Romagna region of Northern Italy in 2007. This triggered the regional public health department to develop an improved version of an existing regional CHIK vector monitoring system.[67] In addition, in response to the same 2007 CHIK outbreak in Italy, a larger-scale study was conducted to examine the countrywide National Surveillance system. The large-scale study was dubbed the Italian Ministry of Health (MOH) special surveillance project and covered 72% of the 60-million Italian population.[81] Another study in Indonesia had a similar trigger for the CHIK surveillance, where

approximately 100 *CHIK-like* cases were reported in the local newspapers before a CHIK team was formed to investigate the unusual outbreak.[80] In Yemen, the report of 1542 cases of *Dengue-like* FUO in October 2010 from 19 districts of the Al Hodayda Governorate spurred eventual vector surveillance from the governorate in January 2011.[215] Similarly, more than 1100 CHIK cases in March 2005 prompted the active vector surveillance in the Union of the Comoros[214], and the detection of the first CHIK case in Mayotte led to the development of the CHIK surveillance in the island.[83] In the neighbouring country, Madagascar, the 2007 CHIK outbreak in the Indian Ocean prompted the MOH to develop an early CHIK outbreak detection system.[70] For the study conducted in La Reunion Island, besides the identification and report of the first CHIK cases in April 2005, the WHO international alert in March 2005 spurred the health authorities to establish an operational epidemiologic surveillance system.[82]

Another factor that prompted the development of CHIK surveillance systems was the presence of CHIK susceptible vectors. In one study in the USA, the presence of established CHIK susceptible vectors, *Aedes aegypti* and *Aedes albopictus*, raised the concern that the introduction of CHIKV from imported cases might lead to CHIK transmission and outbreaks locally. Hence, the option of reporting of CHIK cases to ArboNET, the national surveillance system that collates data on arthropod-borne virus infections in humans, was made available to state health departments from the year 2006.[79]

Another study reported a special integrated surveillance system developed to enhance the existing regular surveillance in the Veneto region of Northern Italy. The special surveillance had the twin goals of increasing detection rate of imported CHIK in travellers from endemic CHIK areas and rapidly detecting potential indigenous cases.[68]

As an anticipatory approach to potential imported CHIK cases from neighbouring countries, a study conducted in Singapore reported the implementation of CHIK surveillance by December 2006, after the first imported CHIK case was reported on 6

November 2006.[69] Only one of the 12 studies reported health legislation for CHIK required mandatory notification to the higher health authorities. Under Section 6 of the Infectious Disease Act by the Singapore government, from 19 December 2008, all medical practitioners and diagnosis laboratory staff have a legal responsibility to notify suspected CHIK cases and CHIK-related deaths to the director of the Communicable Diseases Division of MOH within two days from the time of diagnosis.[69]

Trends in rural-urban profiles using the CHIK surveillance systems were observed in seven studies.[67, 69, 70, 80, 83, 213, 215] The other five studies did not report separate rural-urban profiles.[68, 79, 81, 214, 215] It appeared that people who were living in highly populated or urban areas were at higher risk of contracting CHIK such as people living in the Northeast and North of Mayotte[28] and people living in urban areas of more than 600 ha in the Emilia-Romagna region of Northern Italy.[67] The sentinel centres in one study were located at places with a greater population, with the assumption that these places would experience a greater impact from CHIK outbreaks, as compared to places with a lesser population.[26] On the contrary, three studies observed that people living in rural areas of highly populated countries or provinces were at higher risk of contracting CHIK.[69, 80, 213] In the two studies conducted in Singapore, a highly urbanised tropical country, people living in the less urban areas of Singapore were observed to have a higher chance of being infected with CHIK, compared to those living in more urban areas such as shopping centres.[69, 213] Another study conducted in Indonesia found that suspected CHIK outbreaks occurred mostly (83%) on main Java island, with nearly 46% in highly populated central Java. These outbreaks were observed to occur mostly in rural areas (62%), followed by urban areas (21%) and then semi-urban areas (17%).[80] The above studies may indicate subtle differences in the definition of highly populated area across countries. However, there is a general agreement that high population density areas facilitate high CHIK transmission.[69, 80, 83, 215]

The included surveillance data also showed that international travel could also play a role in CHIK transmission. Three studies conducted in Veneto region of Italy and

Singapore observed that some CHIK cases were related to travellers returning from endemic areas or neighbouring countries.[68, 69, 82] In the Singapore study, excursions to Malaysian fruit plantations were cited as examples of high-risk activities associated with possible acquisition of CHIKV infections.[69]

Evidence from four included studies suggested that climate conditions may be an important factor as rainy and wet seasonal weather seemed to increase the spread of CHIK. [69, 80, 83, 215] It is possible that the increased hatching and development of *Aedes* mosquitoes during wet days would lead to a rise in entomological vectors carrying the CHIKV, hence favouring the onset of CHIK outbreaks.[37]

Cost-effectiveness and sustainability of surveillance systems were reported in two studies conducted in the Emilia-Romagna region of Italy and Madagascar. In 2008, costs amounted to GBP523,824 in the Emilia-Romagna region from the vector monitoring program activities, mainly on egg counting, ovitrap positioning and consultants and routine ovitrap management. This translated to GBP0.13 per capita. The low cost was found to be sustainable even in non-epidemic period.[67] The study conducted in Madagascar showed that a sentinel syndromic-based surveillance system is sustainable in developing countries as it is a low cost system. The cost of data transmission via mobile phone was less than USD1 per month, which was noted to be an efficient and cheaper way to report data daily. However, it was also noted that the cost and maintenance of the surveillance system needed to be calculated in terms of person-hours of sentinel GPs and person-hours in responding to surveillance system alerts.[70] The other 10 studies did not report cost-effectiveness and sustainability of surveillance systems.[68, 69, 79-83, 213-215]

4.4.3. Outcome results

Generally, the included studies described the specific CHIK surveillance systems. The lack of a large evidence base also did not mean that the surveillance systems were not of benefit. The best available evidence was synthesised from the properties reported

from each study, especially if there was no explicit evaluation on the effectiveness of surveillance in improving health outcomes of CHIK-exposed population.

4.4.3.1. Core functions of surveillance

4.4.3.1.1. Case detection

The detection of a CHIK case begins with the establishment of a standardised case definition. The case definition enables determination of a baseline of CHIK cases and increases the likelihood of producing interpretable trends within and across different human populations. Eleven of 12 included studies provided at least a CHIK case definition, as a suspected/possible[68, 80, 82, 83], probable[68] or confirmed case.[67-70, 79, 81-83, 213-215] Only one study investigating regional active vector surveillance did not report any CHIK case definition, as it might not be required to address the aim of the study.[67] In addition, definitions were also provided for CHIK cluster[68], CHIK imported case[68, 213], CHIK locally acquired case[68, 213], clinically recognised CHIK outbreaks[80], emerging severe forms of CHIK[82, 83], symptomatic severe CHIK case[82] and suspected materno-neonatal CHIK infection.[82, 83]

Primary sources of CHIK cases identified in the literature were from health facilities, including clinics, community health centers and hospitals by the GP, infectious disease consultant or other health care professionals, with or without the aid of laboratory tests.[54, 67-70, 79, 80, 82, 213-215] Primary sources of CHIK cases were not reported for one study[81] and only primary sources of CHIK clinical cases were not reported for another study.[215] For studies on vector surveillance, primary sources of CHIK cases also included field technicians on larval and adult mosquito collection.[67, 69, 82, 213-215] Medical professionals were usually alerted to potential CHIK epidemics or cases from international health organisations such as the WHO[83] or the country-level MOH[69, 70, 213] and were educated to diagnose CHIK to cope with the emerging cases.

4.4.3.1.2. Registration

None of the 12 included studies reported registration of case patients, regardless of confirmation status, into a public health record. Although this was the case, governmental bodies such as the Singapore MOH required legal notification (and hence registration) of suspected CHIK cases as imposed by the Infectious Disease Act. Without registration, there is a strong concern that public health authorities may not be notified of some suspected or confirmed CHIK patients, resulting in under-reporting at the international, national or regional surveillance level.

4.4.3.1.3. Confirmation

Confirmation of CHIK cases usually proceeded after registration. Eleven of 12 included studies had confirmed case definitions of CHIK, which varied, based on either single or a combination of syndromic, clinical, laboratory or epidemiological parameters.[67-70, 79, 81-83, 213-215] Only one study (on the Italian National Surveillance System) used the European Union definition of CHIK confirmed case.[81] Another study based on the Malagasy sentinel syndromic-based surveillance system was the only study where CHIK confirmed cases were based on clinical pre-diagnostic data, instead of laboratory or clinical diagnostic tests.[70]

4.4.3.1.4. Reporting

For 11 of the 12 studies, movements of CHIK patient data from lower primary health care levels to the upper district[80, 215], municipality[67], regional[68, 82, 83] and national[69, 70, 79, 81, 213] levels were reported. For the remaining study, flow of CHIK patient data to the higher levels was not reported.[214]

4.4.3.1.5. Data analysis

All 12 studies reported analysis of surveillance data. Disease and vector surveillance data were often analysed and reported as incidence[81-83, 213], prevalence[80, 81], demographic

data[79, 36], date of disease onset or diagnosis[69, 79], addresses of home/school/workplaces[36], patients' travel details[79], disease evolution and transmission[36], epidemic curves/distribution[69, 70, 80, 82, 83], weekly vector population density[67, 214], mosquito larval density[213, 215], vector egg density data (eggs/ovitrap/week)[67] and phylogenetic data[213]. Disease data analysis was done close to the primary reporting level.[68]

For all 12 studies included in this systematic review, the frequency of surveillance analysis, frequency of surveillance reports and distribution of surveillance reports were examined. It was found that the frequency of surveillance analysis was reported in three studies that conducted vector surveillance, which required the physical collection of larval and adult mosquitoes. The collection was done daily for three weeks in one study[214], once within seven days from the start of a CHIK outbreak (except for one location, which was carried out twice with a gap of one week) for the next study[213] and fortnightly to check ovitraps in another study.[67] The other nine studies did not report on the frequency of surveillance analysis.[22-28,69, 215] The frequency of surveillance reports was reported weekly in three studies[67, 80, 82] and not reported in nine studies.[68, 69, 79-81, 83, 213-215] One study reported distribution of surveillance reports electronically (www.zanzaratigreonline.it).[67] The other 11 studies did not report any form of distribution of surveillance reports to any targeted audience.[68-70, 79-83, 213-215]

4.4.3.1.6. Epidemic preparedness

Seven out of 12 included studies[67, 69, 81-83, 213, 215] reported on epidemic preparedness, whereas the other five studies[68, 70, 79, 80, 214] did not.

The study on La Reunion Island's largest CHIK epidemic showed that the original operational epidemiologic surveillance system was not ready for the explosion of CHIK cases. It exceeded its capacity and was not able to follow epidemic trends. Surveillance was then based entirely on sentinel network.[82] In another study, Yemen was unprepared for the CHIK outbreak in October 2010 as it seemed that little was done to tackle what was known as the *Dengue-like* fever/acute FUO.[215]

In another study on surveillance in Singapore, *all-out* approach was undertaken to contain CHIK clusters. Disease investigations were carried out rapidly and contacts were traced for every notified case to detect unreported cases.[69] The longitudinal tracking of E1 gene sequences in CHIKV is part of the coordinated efforts to monitor local transmission in Singapore, as Singapore is susceptible to CHIKV imports.[213] Another study reported that the monitoring surveillance system proved highly efficient and was prepared to face any potential viral infection pools, which could cause outbreaks if a high density of mosquitoes was present.[67] To better prepare the nation for impending CHIK epidemics and other vector-borne diseases, Italy developed a national plan on integrated human surveillance of vector-borne diseases, as reported in a study.[81] Another study reported that Mayotte's health care providers were alerted to CHIK fever after the Global Alert and Response Network (GOARN) reported a CHIK outbreak in La Grande Comore, a neighbouring island.[83]

4.4.3.1.7. Response and control

Five of the 12 included studies reported surveillance response and control, whereas the other seven studies did not.[68, 70, 80, 82, 83] Data from surveillance systems should be synthesised for public health action in the form of epidemic and management type responses and control.[56]

In Singapore, based on the CHIK surveillance data and analysis, a key response was the revision and expansion of the *Aedes* spp. control strategy, in order to concentrate on more rural areas with predominance of *Aedes albopictus* mosquitoes.[213] There was also a swift response to shift all available resources to high-risk areas and to focus vector surveillance and control efforts on workplaces and dormitories of foreign contract workers and on destruction of breeding sites. Residents and foreign workers were educated on common mosquito breeding sites and ways to destroy them. The Geographic Information System (ArcGIS), a nationwide mosquito control program database, was used to map out areas for rigorous vector surveillance and control.[69] In

an Italian study, a national plan on the integrated surveillance of vector-borne diseases was implemented in 2011 to replace a smaller and older version of CHIK surveillance established in 2007.[81] In another Italian study involving the Emilia-Romagna region, the geographical tracking of mosquito populations from the *Aedes albopictus* monitoring system allowed real-time data to be available for response and control.[67] In Grande Comore, after the initial outbreak in March 2005 which reported more than 1100 cases, an outbreak surveillance team, consisting of US CDC, Kenya Medical Research Institute (KEMRI), WHO and public health officials from Comoros, was formed to investigate the outbreak.[214] In Indonesia, an outbreak response team was formed rapidly after the first report of 100 *CHIK-like* cases in November 2001, with representatives from the local district health service, Indonesian MOH, National Institute of Health Research and Development (NIHRD), Centers for Communicable Diseases and Prevention—Environmental Health (CDC-EH) and USA Naval Medical Research Unit No. 3, Cairo (NAMRU-2).[80]

Response and control in Yemen were delayed as seen from a study on vector surveillance in Yemen. When WHO sent the USA Naval Medical Research Unit No. 3, Cairo (NAMRU-3) team to carry out laboratory investigations to the CHIK outbreak in Yemen, response was considered late as there were already 104 associated CHIK deaths in January 2011, three months after the reports on 1542 suspected CHIK cases in 19t of 26 districts of Al Hodayda in October 2010.[215]

4.4.3.1.8. Feedback

Five of 12 studies reported information flow from the higher level health authorities to the lower level, whereas seven remaining studies[70, 79, 81-83, 213, 214] did not. Downward flow of information was important to ensure prompt and regular follow-up on actions and updates needed to strengthen surveillance capability.

For CHIK surveillance in Indonesia, public announcements in local newspapers and anecdotes on CHIK outbreak information were relayed from the district or provincial

sources to the people.[80] Another study conducted in Singapore reported alerts from the MOH to GPs on the latest information on CHIK situation.[69] A study conducted in Veneto region of Italy reported the award of a ministry grant to develop a larger three-year integrated program of surveillance for arboviral diseases, animals and entomology, based on the study's successful small pilot surveillance program.[68] In another study, the Emilia-Romagna Public Health Department and collaborating institutions initiated the activation of mosquito control programs in response to the vector monitoring data to benefit the regional population of Italy.[67] In another study, ways of reducing *Aedes* larval breeding sites, such as cleaning water containers and removing stagnant water, were recommended to the people of Yemen. [215]

4.4.3.2. Support functions of surveillance systems

4.4.3.2.1. Standards and guidelines

Two of 12 studies[67, 70] reported surveillance standards and guidelines used, whereas the other 10 studies[68, 69, 79-83, 213-215] did not. However, it was also observed that none of the studies reported any adaptation of surveillance systems or evaluation of surveillance systems' effectiveness based on any standards or guidelines set by an international or national health organisation.

One study reported the homogenous technical coordination of *Aedes albopictus* surveillance and control through the set-up of a regional group in Emilia-Romagna, Italy. The regional group faced the issue of maximising the standardisation of environmental parameters and to avoid differences in the attractiveness among ovitraps.[67] Another study conducted in Madagascar reported that data derived from the sentinel syndromic-based surveillance system was analysed using standard epidemiological techniques.[70]

4.4.3.2.2. Training

Three of 12 studies[67-69] reported some sort of human resources training to boost the effectiveness of surveillance systems, whereas the other nine studies did not.[70, 79-83, 213-215]

In a study on the development of a large-scale, low cost and well-designed *Aedes albopictus* monitoring system in the Emilia-Romagna region of Italy, skilled technicians were used for the placement of ovitraps.[67] A study conducted in the neighbouring Veneto region of Italy showed the necessity to train physicians to detect CHIK cases.[68] Another study on surveillance in Singapore reported that environmental health officers were trained for vector surveillance, as well as their involvement in *search and destroy* operations.[69]

4.4.3.2.3. Supervision

Two of 12 studies[67, 70] reported supervision to aid in daily operations for disease and vector surveillance systems, whereas the other 10 studies[68-70, 79-81, 83, 213-215] did not report supervision.

In the Emilia-Romagna region of Italy, scientific group members provided expertise in entomology, epidemiology, meteorology and informatics for the development of a large-scale, low cost and well-designed *Aedes albopictus* monitoring system.[67] In Madagascar, the MOH supervised the surveillance. Further details on supervision were not specified.[70]

4.4.3.2.4. Communication

Four out of 12 studies[69, 70, 80, 82] reported communication between the public health authorities to the targeted population and vice versa, whereas the rest of the eight studies[67, 68, 79, 81, 83, 213-215] did not.

In a study, the Malagasy MOH recognised the necessity of strong communication systems for efficient and accurate sentinel surveillance system. Although the reporting of data was already done in a low cost and efficient manner via mobile phone, short text messages and paper forms, an improvement to this communication could be made by delivery of electronic records directly from sentinel GPs in future in the low income

country of Madagascar.[70] In another study on CHIK surveillance in Singapore, a high-income country, communication infrastructure appeared to be adequate, as gathered from the mandatory notification of cases and the immediate alert of all reported CHIK cases to the National Environment Agency (NEA).[69] The study conducted in La Reunion Island revealed that plans were underway for the introduction of an automated telecommunication system to increase speed of reporting from physicians.[82] For CHIK surveillance in Indonesia, public health information was relayed from the district or provincial sources to the people through public announcements in local newspapers and anecdotes.[80]

4.4.3.2.5. Resources

The availability of resources, in terms of finances, human resources and critical infrastructure for both disease and entomological surveillance is crucial to boost the effectiveness of CHIK surveillance systems. Nine of 12 studies[67-70, 79-82, 213] reported the provision of resources, whereas the three remaining studies[82, 83, 215] did not.

From the included studies, high-income countries seemed to be able to put in place more expansive and complex surveillance systems which tapped on better information technology and communication channels. For example, USA[79], Italy[68, 81] and Singapore[69, 213] had put in place a national integrated surveillance system for disease and vector surveillance for CHIK and other arthropod-borne viruses. In Singapore, an *all-out* approach was used to reduce the spread of CHIK by putting all available resources to high-risk areas from 2006 - 2009.[69]

La Reunion Island, an overseas department of France, also put in place an operational epidemiologic surveillance system for the entire island of estimated 244,000 people as of 2004. However, the overloaded disease and vector surveillance system was reduced to a sentinel network of 31 physicians due to a dramatic influx of CHIK cases during the 2005 - 2006 outbreak.[82]

A study conducted in the Emilia-Romagna region of Italy on *Aedes albopictus* monitoring surveillance supported its use, due to its low cost and efficiency.[67]

For low-income and lower middle income countries, certain surveillance systems have been adopted due to their use of fewer resources, as well as their low cost. The study conducted in Madagascar, a low-income country, showed that the implementation of a sentinel syndromic-based surveillance system might be a good option for boosting traditional disease surveillance due to its use of lesser resources compared to passive surveillance.[70]

In terms of establishing critical infrastructure for disease surveillance, the strategic involvement of basic units of the health care systems, including GPs, emergency department physicians, infectious disease unit and other health care professionals, was important, so that possible CHIK cases were referred within 24 hours. Reference laboratories and clinical and laboratory diagnosis test kits and blood sample apparatus (such as the OnSite CHIK IgM Combo Rapid Test or the Vacutainer® [Becton, Dickinson, Franklin Lakes, New Jersey, USA]) for CHIK made readily available were also crucial for the timely confirmation of CHIK cases.[68,80] Administrative infrastructure to facilitate formal requests for consent on research participation to collect CHIKV from infected patients was also required, for example, through the Indonesian NIHRD.[80]

In terms of establishing critical infrastructure for vector surveillance, ovitraps, BioGents Sentinel™ (BGS) traps, sweep nets, battery-operated backpack vacuum aspirators, hand-held chargeable insect vacuum (AC Insect Vac, BioQuip Products Inc.) and knockdown pyrethroid spray were commonly used in field surveys. In laboratories, the storage of sera and captured mosquitoes in liquid nitrogen for analysis were also described.[80, 213, 214]

4.4.3.2.6. Coordination

Three of 12 studies reported coordination of human resources and other resources to boost the effectiveness of surveillance systems, but not the remaining nine studies.[68, 79-83, 213-215]

In Singapore, there appeared to be adequate coordination in dealing with CHIK epidemics, as gathered from the surveillance coordination among GPs, medical community, hospitals, MOH, NEA, Defence and Environmental Institute and the public.[69] The organisational plan coordinated by the Emilia-Romagna Public Health Department worked well, with no major problems in system management.[67] In Madagascar, a challenge faced was the connection of GPs to the sentinel surveillance system and the coordination of their efforts to enhance the collaboration of health ministry services and GPs.[70]

4.4.3.3. Quality attributes of surveillance systems

4.4.3.3.1. Timeliness

Seven of 12 studies[67-70, 79, 213, 215] reported the attribute of timeliness in surveillance systems, but it was not reported in the remaining five studies.[80-83, 214]

In the study conducted in Yemen, three months (October 2010 – late January 2011) between the report of 1542 cases of *Dengue-like* unknown fever and the outbreak response by the Ministry of Public Health and Population (and WHO) was considered too long, leading to 104 associated CHIK deaths reported in January 2011. The *Aedes* mosquito control measures came too late, as revealed during the outbreak investigation. On hindsight, it was highlighted that instead delaying the timeliness of initial control efforts through waiting for cases to happen first before responding, routine vector surveillance could be strengthened for the early detection of a potential CHIK outbreak and adequate preparation of appropriate response and control measures.[215]

In the USA, there was delayed CHIK case reporting to the ArboNET. A median of 122 (44 - 273) days lapsed between the onset of CHIK and CHIK reporting on ArboNET.[79]

In the study conducted in Madagascar, the sentinel syndromic-based surveillance system acquired timely data for improving health care decision-making. Sentinel GPs sent completed patient data form to the disease management team every week, and reported data on various febrile diseases and diarrhoea at least once a day (by 8a.m.) via phone encrypted text message for daily data collection and analysis to detect abnormality by an epidemiologist. Eighty-nine percent of the CHIK case data was sent within 24 hours from the sentinel centres to the Access® database. An increase in cases was reported immediately via phone to the MOH. Even a rapid sentinel surveillance system could still be improved based on increased timeliness in the detection of unusual disease patterns instead of confirmed laboratory and clinical diagnoses.[70] On the other hand, extra time should be allocated for further case investigations on diagnostic and laboratory data.[70] It was also noted that timely detection of CHIK outbreak could lead to immediate implementation of disease control strategies that reduce and prevent future CHIK transmission.[70]

In Singapore, the CHIK surveillance implemented in December 2006 was considered timely as it detected the first indigenous CHIK outbreak in January 2008 that was successfully contained. Additionally, the public health agency, NEA, was immediately informed of all reported CHIK cases. Physicians were updated with the latest situation, particularly on the clinical symptoms, prevalence, incidence and localities of CHIK patients.[69] Another study reported that within one week of the CHIK outbreak being detected, adult mosquito surveillance was initiated for locations with the highest number of CHIK cases. Vector surveillance data on mosquito breeding site inspection was uploaded daily to the ArcGIS database of NEA.[213]

The on-going vector surveillance implemented in Emilia-Romagna, Northern Italy, appeared to be timely, with checks on ovitraps for regular positions and functioning

done weekly, and ovitraps monitoring data published on a website every week.[67] In Padua, Italy, possible CHIK cases were referred within 24 hours to the nearest infectious/tropical diseases unit.[68]

4.4.3.3.2. Completeness

One study accounted for completeness of surveillance system data. In the USA, there was incomplete CHIK case reporting to the ArboNET, making the system less helpful in detecting CHIK outbreaks. Some surveillance data fields were not recorded, such as demographics, travel data and *date of illness onset*. For missing data on *date of illness onset*, the *date of serum specimen sample collection* was used instead during data-analysis.[79] The remaining 11 studies did not report on completeness.[67-70, 80-83, 213-215]

4.4.3.3.3. Usefulness

None of the 12 studies explicitly reported on the usefulness of surveillance systems in effecting decision-making in policies and contributing directly to disease control measures.

4.4.3.3.4. Sensitivity

One of 12 studies reported on sensitivity of the surveillance, whereas the other 11 studies did not.[68-70, 79-83, 213-215] The study conducted in the Emilia-Romagna region reported that ovitraps had high sensitivity to detect low numbers of mosquitoes, but was not substantiated further.[67]

4.4.3.3.5. Specificity

None of the 12 studies reported on specificity of surveillance systems with respect to case definitions.

4.4.3.3.6. Simplicity

None of the 12 studies reported on simplicity with respect to design and ease in functioning.

4.4.3.3.7. Flexibility

None of the 12 studies reported on flexibility of surveillance systems, with respect to adapting and accommodating fluctuating needs.

4.4.3.3.8. Acceptability

None of the 12 studies reported on acceptability of surveillance systems with respect to compliance of people and organisations.

4.4.3.3.9. Reliability

One out of 12 studies reported on reliability of the surveillance whereas the other 11 studies did not.[79-27, 34, 36, 69, 213, 215]

In the study conducted in the Emilia-Romagna region, it was reported that ovitraps could be reliable in providing a good estimate of mosquito population density, depending on the number of ovitraps and their placement. The reliability of the monitoring surveillance system was calculated using the following formula:

> Relative Variation (RV) = (Standard error of the mean number of eggs / ovitrap / week)/ (Mean number of eggs / ovitrap / week)

Calculation results showed a mean RV of less than 0.25, hence the number of ovitraps placed in urban places of more than 600ha was calculated correctly for the monitoring precision level of D=0.2 for the best binomial sampling of *Aedes aegypti*.[67]

4.4.3.3.10. Positive predictive value

One of 12 studies[80] reported on positive predictive value of the surveillance, whereas the other 11 studies did not.[67-70, 79, 81-83, 213-215]

The study conducted in Indonesia on an active disease surveillance suggested poor positive predictive value of the system. Sixty-three percent of the 86 suspected serum

samples showed at least one positive laboratory test result for CHIK. However, there was no serum sample that tested positive across all three diagnostic tests of detecting anti-CHIK IgM and IgG antibodies, CHIK RNA via RT-PCR and virus isolation. Thirty-two serum samples were tested negative for CHIK across all three tests.[80]

4.4.3.3.11. Representativeness

Seven studies out of 12 studies[69, 70, 80-83, 215] reported representativeness of the surveillance whereas the other five studies did not.[67, 68, 79, 213, 214]

In the USA, CHIK cases identified through the three laboratories from 2006 - 2009 were compared with cases reported to ArboNET. Of 106 CHIK cases identified through the three laboratories, only 27 (25%) were reported to ArboNET. Geographical vector distribution was presented at the state level, which might be misrepresented because vector distribution was found only in specific areas within the state. Vector distribution mapping represented sustained vector populations as well as single observations in the upper mid-West, plains and arid West of USA. It was also noticed that there were no CHIK cases identified in children; all reported cases were adults. The lack of child representatives might reflect differences in diagnostic practices between adults and children, comparatively lesser chances of symptomatic clinical presentations of CHIK in infected children and the travellers' age.[79]

A study conducted in the Emilia-Romagna region investigated the minimum ovitrap numbers needed to accurately detect the mosquito eggs density in the provincial regions without risking an over- or under-estimation of ovitraps required for each region. Municipalities below 500m sea level (70% of total municipalities) in Emilia-Romagna region, which consist of nine provinces, were represented.[67]

In the Indonesian active disease surveillance, the denominator for calculating the CHIK attack rate was obtained from the Bekasi Regency census data 2001 to depict an accurate representation of CHIK in the Kali Jaya village. The demographic results

obtained were congruent with the CHIK characteristics shown in outbreaks occurring in other countries. The study investigators also suspected under-reporting of CHIK, due to a coincidental increase in FUOs and the exclusion of CHIK in the usual set of disease diagnosis algorithm used by physicians. It was postulated that there were many more CHIK outbreaks which were not reported in Indonesia.[80]

A study on the Italian National Surveillance System suggested under-reporting of imported CHIK cases as there was a of 48- to 276-fold increase in suspect CHIKV-exposed travellers who arrived in Italy, as compared to notified infection in Italy.[81]

In Madagascar, 13 sentinel centers were selected based on pre-specified criteria with coverage of only 3% of the population in Madagascar. Although sentinel GPs also participated voluntarily in the surveillance, the surveillance system is still not representative of Madagascar. For better representation, the number of participating GPs should be increased.[70]

In a La Reunion Island study, surveillance data is representative of the entire population, with every locality, both sexes and all age groups affected by the CHIK epidemic.[82] Women and all age groups except those who are less than 20 years old were found to be over-represented in the two epidemics in 2005 and 2006.[82] Comparison between global mortality rates and mortality rates attributed to the CHIK epidemic in La Reunion Island confirmed significant excess mortality.[82]

The disease surveillance system and the community-based survey were compared and there was a serious under-estimation of the outbreak severity by the surveillance system, possibly due to undisclosed CHIK cases from health care providers and public health officials, the tendency of patients to seek treatment from traditional medical practitioners and poor health insurance cover. In the seroprevalence survey, it was noted that asymptomatic or poorly symptomatic cases might be under-represented as the CHIK case definition was based on clinical manifestations. The study investigators

also reported an under-estimation of the scale of the CHIK outbreak by the surveillance system in the Mayotte officials' reports.[83]

4.4.3.4. Overall goals of surveillance systems

Studies on CHIK surveillance had three fundamentally important surveillance goals. The first surveillance goal was to detect and recognise potential CHIK cases.[68, 70, 79, 81, 82] The second surveillance goal was to collect CHIK surveillance data, including profiling CHIKV infection and epidemiology, disease trends and distribution.[79-83] The third surveillance goal was ultimately to reduce CHIKV infection, outbreaks and transmission through effective disease response, prevention and control.[69, 70, 79, 81, 82, 213] Other disease surveillance goals included monitoring incidence of CHIK[69, 80-83, 213], prevalence of CHIK[82, 83, 214, 215] and cost-effectiveness of surveillance systems.[67]

All six studies on vector surveillance had the central goal of identifying circulating entomological vectors carrying the CHIKV.[67, 70, 80, 213-215] Additionally, two studies had the vector surveillance goal of obtaining data on the density and geographical distribution of CHIK vectors.[67, 213]

4.5. Discussion

This systematic review incorporated the best available evidence to assess the effectiveness of surveillance systems based on the WHO framework for monitoring and evaluating surveillance and response systems[211], providing countries with the foundation that evidence-based rigorous and comprehensive surveillance programs for CHIK might be developed and efforts to detect potential CHIK cases might be enhanced. Based on the small number of mostly descriptive studies (except one case-control), eight of these studies affirmed that effective and rigorous surveillance systems play a vital role in reducing CHIK transmission.[67-69, 79, 81-83, 215] An important recurring research finding is the need to strengthen surveillance capability and capacity in CHIK.

When evaluated against the 28 evaluation indicators, surveillance systems from the studies showed limited evidence in its effectiveness to meet the core functions, support functions, quality attributes and overall goals. This was unfortunate, as much financial and human resources have been expended on public health surveillance, yet there was minimal scrutiny by health care and environmental authorities on the effectiveness, cost-effectiveness and sustainability of CHIK surveillance systems implemented. As most surveillance systems were not rigorously evaluated, outcome data relevant to establishing the effectiveness contained numerous gaps on evaluation indicators. Although case detection, confirmation and reporting evaluation indicators were positively met by 11 included studies, no included studies explicitly reported on indicators of registration, usefulness, specificity, simplicity, flexibility and acceptability of surveillance systems. Neither the frequency of surveillance analysis nor the frequency and distribution of surveillance reports was reported from at least nine studies. Some evidence of epidemic unpreparedness, delayed response and control, challenging coordination, untimely surveillance, poor positive predictive value and lack of representativeness were also found.

The first appearance of *CHIK-like* or CHIK outbreaks was the main impetus for the development of CHIK surveillance systems in more than half of the included studies. This reactive stance was not surprising, as considerable resources are required by countries, regions or districts.[67, 70] Hence, using the example of Indonesia, although sporadic CHIK cases and outbreaks have been reported since 1972, the scale of CHIK outbreak response action was considerably minimal, resulting in reportedly poor recognition of CHIK and under-reporting.[80]

Indeed, implementers understood the importance of CHIK surveillance systems. Investigators of two included studies observed that after the CHIK surveillance was established, intermittent CHIK cases began to appear in the *radar system*[69], and the first local CHIK case was detected by a physician who was part of the CHIK surveillance sentinel network.[213] This means that a crucial function of surveillance is to bring new

CHIK cases to light, particularly symptomatic CHIK infections, usually after an average of five days of asymptomatic phase.[13] The ability of the surveillance to detect and predict CHIK epidemics cannot be over-emphasised, because surveillance data triggers the early implementation of effective disease response, prevention and control.

Early detection of CHIK cases starts with the ability of family clinic doctors and hospital outpatient clinic medical officers to recognise and diagnose CHIK cases based on the triad of CHIK clinical manifestations of fever, arthralgia and rash. However, in reality, the recognition of CHIKV infection amidst all other possible diseases may be challenging and is made more complex by patient, doctor and environmental factors.

Often, the first few cases of CHIK patients in a potential outbreak may not seek medical treatment or may turn to traditional medicine physicians who do not have formal reporting rights to the disease surveillance network and are hence out of the surveillance radar from the start. The first few cases of CHIK patients from an outbreak who do present themselves to the doctor may report undifferentiated fever and several clinical manifestations that may not be recognised as CHIK. At this point, the onus lies with the doctor. A doctor who is part of a CHIK surveillance network, well trained in differential diagnosis of fevers or regularly keeps up with international medical news, would have a higher probability of suspecting CHIK fever and play the crucial role of making the right judgment to conduct more appropriate clinical or laboratory analysis.[163] If the wrong judgment is made, misdiagnosis can result and that can severely delay or remove entirely the patient's route to recovery from the CHIKV infection. This is an understandably long, continuous and arduous process involving responsible participation from the chain of people involved, including the suspected and confirmed CHIK patients, physicians, infectious disease units, laboratory personnel, field technicians, governing health care authorities and supra-national organisations such as the WHO.

The training and supervision of physicians and health care professionals in recognising CHIKV infection is the basis of the functioning of CHIK surveillance.[67-70] CHIKV infection has been misdiagnosed as other illnesses such as FUO, Dengue and forms of arthritis.[11, 218] In an included study, there was a coincidental rise in FUO cases, when CHIK outbreak was occurring during the same period from August – November 2001.[80] Indeed, several other studies on FUO also identified CHIKV as a causative agent.[65, 219, 220] Hence, an investigation on the rise in FUO cases can identify and increase the detection of prospective CHIK cases.

Although the main goal of many CHIK surveillance systems is to detect and recognise new CHIK cases, there are surprisingly no clinical management protocols or directives to detect a CHIK patient during the mid-course or the chronic stage of the disease. Due to the tendency of misdiagnosis, the ability of surveillance systems to detect CHIK infection mid-way or during the severe stage then gains comparatively greater importance. For example, a CHIK patient, who has been misdiagnosed with juvenile rheumatoid arthritis for more than two years, seeks a second opinion to alleviate arthritic pain and a recent bout of high fever. What is the chance of this patient meeting a physician who is able to suspect CHIKV infection based on the patient's recount of disease events over two years? Hence, this is an important gap to resolve to improve existing CHIK surveillance and to address the iceberg phenomenon, for CHIK cases that remain undiscovered.

Legislative requirement to notify health care authorities of suspected and confirmed CHIK cases may be a good strategy to enhance the effectiveness of CHIK surveillance systems. As of 10 February 2014, there were 55 countries with autochthonous cases.[21] However, of these, only France, Italy, Singapore and the Tamil Nadu state in India have established health care legislatures to make CHIK a legally notifiable disease. External to these 55 countries, the European Union 28-member countries and New Zealand have made CHIK a notifiable disease.[55] In Australia, CHIK has yet to attain nationally notifiable disease status despite endorsement by the Communicable Disease

Network Australia (CDNA).[171] The legislatures served to ensure mandatory reporting of suspected and confirmed CHIK cases within a period (usually 24 hours) to a central reporting system such as the Communicable Disease Division of MOH, Singapore.[69, 213] This means that information reported to the surveillance system is more likely to be timely, complete and representative of the actual CHIK situation to inform surveillance response and disease control strategies. The delay in detecting CHIK could seriously magnify the scale and duration of CHIK outbreak, the losses incurred and the country/region/district to recover, as observed from the example of the CHIK epidemic in La Reunion Island, which had an island-wide attack rate of 35%, with 244,000 CHIK cases reported during the 2005 - 2006 CHIK epidemics.[82]

To strengthen the effectiveness of CHIK surveillance, the availability of resources, in terms of finances, human resources and critical infrastructure, is required. Be it in a developed or developing country, the resources available to support the surveillance systems are finite. If CHIKV infections are of a public health concern and their notifications are mandatory, government agencies are more likely to receive allocated funding to carry out the CHIK surveillance to ensure better public health outcomes and reduce CHIK transmission. Critical infrastructure such as the strategic involvement of health care systems, diagnostic laboratories and research institutes for disease surveillance and field entomological survey equipment for vector surveillance would help to gather precise disease information to meet the second overall surveillance goal for profiling CHIK and epidemiology, disease trends and distribution.[55, 56] Communication infrastructure for relaying real-time surveillance information can be improved, together with the strategic utilisation oof automated telecommunication system devices, the internet, mobile phones and public announcement systems as permitted by available resources.

Increasingly, surveillance systems are not stand-alone for only a specific disease. Integrated surveillance systems that monitor several diseases at the same time may help in boosting the effectiveness of CHIK surveillance, by streamlining and allocating

expertise at key stages of the surveillance process.[75, 221] One example of such a surveillance system that is currently in use is The European Surveillance System (TESSy) that collects information on a standardised comparable template for all statutory communicable diseases in a database. It aims to detect potential public health threats early for a range of diseases. A vector surveillance strategy also employed is the creation of up-to-date maps on the currently known mosquito vector species involved in diseases transmission.[221]

Integrated surveillance systems also often involve strategic collaboration between public agencies, especially on a national level. An example of such collaboration can be seen from an included study. To deal with CHIK in Singapore, the MOH is responsible for case surveillance and epidemiological investigation and the NEA is responsible for vector surveillance and control.[222]

Future CHIK surveillance activities to be considered include the increased use of a CHIK case calculator[222, 223], an epidemic intelligence tool which may be used for CHIK mapping as it allows the extrapolation of results of serological studies from one sub-region to another sub-region and allows the identification of regions where populations do not have herd immunity.[222, 223]

4.5.1. Limitations

Most of the included studies were descriptive studies and hence were limited assessments of effectiveness of surveillance systems. Most of the study investigators who authored the included studies had institutional affiliations to the implementation of the surveillance; hence, there was a possibility of publication bias in favour of positive evaluation of the surveillance. Additionally, the acceptance of only studies published in English had excluded studies that otherwise met the inclusion criteria but were published in a non-English language, such as French.

4.6. Conclusion

Included studies in the systematic review showed limited evidence on effectiveness of surveillance systems specific to CHIK. More high quality rigorous primary studies are required to confirm the best available evidence.

4.6.1. Implications for practice

- There is evidence on how well CHIK surveillance performs in case detection, monitoring and the tendency to result in epidemic response actions. It is recognised that an effective and rigorous surveillance system plays an important role in the reduction of CHIK transmission. (Grade B)

- The establishment of a standardised CHIK case definition is the first important step in surveillance. (Grade B)

- Countries that have experienced indigenous CHIK outbreaks should consider making it a legislative requirement to notify health authorities on suspected and confirmed CHIK cases, to strengthen surveillance and control efforts in reducing CHIK transmission. (Grade B)

- Primary health care physicians usually are the first point of contact for a suspected CHIK patient. Hence, it is crucial for them to be discerning with clinical manifestations of CHIK during its early, middle and late stages, as well as to stay abreast of the latest CHIK situation, particular during an epidemic. (Grade B)

- Current CHIK surveillance systems should include periodical critical evaluation by public health authorities to strengthen surveillance capability and capacity. The evaluation should address the performance and usefulness of surveillance systems, as well as surveillance logistical, administrative and communicative gaps. (Grade B)

- Primary studies evaluating CHIK surveillance systems have not used any type of framework, such as the WHO framework of surveillance and response systems in communicable diseases, to conduct the evaluation. It is recommended that such a framework should be used to allow better comparability of outcomes across similar

primary studies. (Grade B)

- There is general agreement that high density areas encourage CHIK transmission. (Grade B)

- International travel plays an important role in the importation of CHIK cases from other countries. Hence, the monitoring of both imported and indigenous CHIK cases is important in surveillance. (Grade B)

- An investigation on the rise in FUO cases can identify and increase the detection of prospective CHIK cases. (Grade B)

4.6.2. Implications for research

- There is minimal evidence on the cost-effectiveness and sustainability of CHIK surveillance systems, hence, primary studies evaluating and describing surveillance are recommended to include components for cost and sustainability.

- Current primary studies do not have any evidence on the reporting of registration of CHIK patients, although standardised CHIK case definitions and confirmed CHIK case definitions are largely established. Clear reporting on the registration of CHIK patients into a public health record is recommended.

- Current primary studies on CHIK surveillance systems do not have any evidence for specificity, simplicity, flexibility, usefulness and acceptability of surveillance systems. There is also minimal evidence on completeness, sensitivity, positive predictive value and reliability of surveillance systems. These attributes of surveillance systems should be covered in future evaluations of CHIK surveillance systems.

- Numerous primary studies evaluated the diagnostic accuracy of laboratory confirmation tests for CHIK. However, no systematic review has been conducted to analyse the available data across studies. A systematic review exploring the best available evidence for diagnostic accuracy is recommended, with a focus on the sensitivity, specificity and positive predictive values of these laboratories tests to ensure uniform and accurate detection of true positives and to minimise false positives and

negatives.

- Primary studies should be conducted to evaluate the effectiveness of health alerts, notifications and similar advisories on CHIK outbreaks to update clinicians and to heighten awareness of impending CHIK cases.

- The lack of child representation in primary studies of CHIK surveillance may suggest differences in clinical manifestations of CHIK in children compared to adults. CHIK diagnosis parameters in children should be re-evaluated in future research.

5 The effectiveness of mosquito control strategies in Chikungunya: A systematic review

5.1. Abstract

Although mosquito control is the main intervention used in the prevention and control of mosquito-borne diseases, its effectiveness in the management of Chikungunya has not been established. This systematic review included ten studies of moderate methodological quality that met the eligibility criteria, all of which were either small field or experimental laboratory studies. Five studies on mosquito control interventions targeted *Aedes aegypti* and six studies on mosquito control interventions targeted *Aedes albopictus*. A range of single and combined mosquito control interventions were assessed, all broadly categorised as biological control, chemical control or habitat control. Results showed that current single and combined mosquito control interventions could be effective in short-term transitory mosquito control. In the context of Chikungunya, these interventions control both immature and adult mosquitoes *Aedes albopictus* and *Aedes aegypti*, with laboratory-conducted studies understandably having more pronounced positive results from measured chemical and biological larvicides and pupicides. Despite this, there is inconclusive evidence on mosquito control interventions that are long acting and there is limited evidence on the sustainability of mosquito control efforts.

5.2. Concise introduction

Mosquitoes are the most important vectors responsible for deteriorating human health and debilitating diseases of epidemic proportions.[1] CHIK is a crippling arthropod-borne viral disease that is transmitted by the mosquito species, mainly the *Aedes albopictus* and the *Aedes aegypti*.[87] Because there is no licensed vaccine or specific cure, mosquito control is the mainstay of CHIK prevention and epidemic control.[1, 35] However, the effectiveness of mosquito control in CHIK has not been clearly demonstrated and it is uncertain whether these mosquito control strategies are effective in decreasing the mosquito population, leading to decreased transmission of

CHIK. Therefore, the objective of this systematic review is to critically analyse currently available research studies and present the best available evidence related to the effectiveness of different mosquito control strategies used in the prevention and control of CHIK.

5.3. Methods unique to chapter

5.3.1. Inclusion criteria

The systematic review sought RCTs and in the absence of RCTs, other experimental, observational and descriptive study designs were included. Countries that had reported local or imported cases of CHIK and countries that are at risk of CHIK due to the presence of mosquito vectors of CHIK (including *Aedes aegypti* and *Aedes albopictus*) were included. Interventions of interest were mosquito control strategies broadly classified as chemical control, biological control or habitat control. These strategies were specifically used to target mosquitoes that transmit CHIK, including *Aedes aegypti* and *Aedes albopictus*. Studies that were not specific to CHIK (e.g. entomological control measures across generic mosquito-borne diseases) were excluded.

Outcomes of interest were the changes in mosquito (egg, larvae, pupae and adult stages) populations, which were described using entomological indices including:

- Percentage mortality or survival rates of mosquitoes.
- Lethal concentrations (LC_{50} or LC_{90}): toxicity measure of an insecticide that will kill 50% or 90% of the mosquito sample population in a specific period of time.[224]
- Knockdown time (Kdt_{50} or Kdt_{95}): time required to kill 50% or 95% of the mosquito sample population.[225]
- Breteau index (BI): number of positive containers for every 100 inspected houses.[226]
- Container index (CI): percentage of water-containing receptacles filled with larvae or pupae.[226]
- House index (HI): percentage of houses filled with larvae or pupae.[226]
- Pupa index (PI): number of pupae for every 100 inspected houses.[226]

- Number of adult mosquitoes is measured using traps, such as ovitraps and BG-Sentinel traps.

Mosquito control strategies to decrease mosquito populations can lead to a decrease in CHIK cases. Hence, an epidemiological disease link to the entomological results shall be discussed, but will not be listed as a required outcome for this systematic review.

5.3.2. Search strategy

Seven major scientific databases (PubMed, Web of Science, Scopus, ScienceDirect, CINAHL, CENTRAL and ProQuest) and nine grey literature sources (WHOLIS, CDC, ECDC, ICRES, NIH, LILACS, World Bank, Asia Development Bank and Google) were searched. Appendix XVII shows the comprehensive search strategy.

5.4. Results

5.4.1. Methodological results

5.4.1.1. Study selection

The titles and abstracts of the 1512 studies were examined for a match with the a priori inclusion criteria. When uncertain, the full-text of the study was retrieved for detailed examination. Of these, 1488 studies were excluded, as they did not meet the inclusion criteria. Although another three studies met the inclusion criteria, two were non-English language[227, 228] and the other study was not available as a full-text paper.[229] Hence, these three studies were also excluded. When the full text of 21 studies was assessed again for eligibility, a further 11 studies were excluded, as they did not meet the inclusion criteria. Ten studies in English appeared to match the inclusion criteria and the full-text was analysed in detail. Figure 5.1 reports in full the search process for study selection.

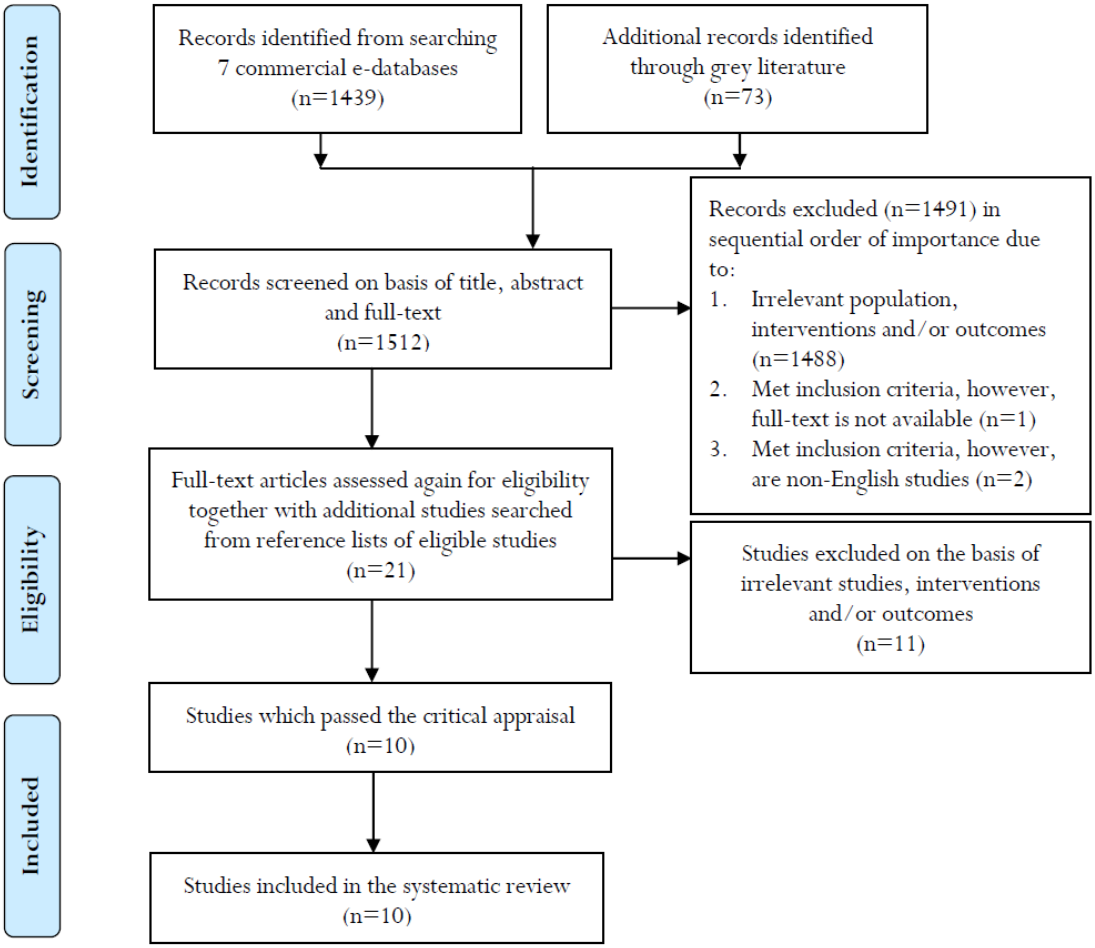

Figure 5.1. Study selection process

5.4.1.2. Methodological quality

Overall, 10 studies passed the JBI-MAStARI critical appraisal test and showed moderate methodological quality. No study was excluded based on poor methodological quality. Results of critical appraisal are shown in Table 5.1.

Table 5.1. JBI-MAStARI critical appraisal of included studies

Randomised control trials / pseudo-randomised trials										
Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**
Abramides *et al.* 2011[92]	N	N/A	N/A	N/A	N/A	N	N	Y	Y	Y
Farajollahi *et al.* 2012[99]	N	N/A	N/A	N/A	N/A	Y	Y	Y	Y	Y
Ghosh *et al.* 2011[102]	U	N/A	N/A	N/A	N/A	U	N	Y	Y	Y
Kamgang *et al.* 2011[101]	Y	N/A	N/A	N/A	N/A	Y	Y	Y	Y	Y

Nelder *et al.* 2010[97]	Y	N/A	N/A	N/A	N/A	Y	Y	Y	Y	Y
Ohba *et al.* 2013[103]	N	N/A	N/A	N/A	N/A	Y	Y	Y	Y	Y
Preet *et al.* 2011[100]	N	N/A	N/A	N/A	N/A	Y	Y	Y	Y	Y
Rajkumar *et al.* 2010[104]	Y	N/A	N/A	N/A	N/A	Y	Y	Y	Y	Y
Tan *et al.* 2011[85]	N	N/A	N/A	N/A	N/A	N/A	Y	Y	Y	Y
Tikar *et al.* 2008[230]	N	N/A	N/A	N/A	N/A	Y	Y	Y	Y	Y
%	30	N/A	N/A	N/A	N/A	77.78	80	100	100	100

Refer to Appendix IV for the critical appraisal checklist questions Q1-Q9/10.
Y: Yes; N: No; U: Unclear; N/A: Not applicable.

Three out of 10 studies[97, 101, 104] showed some evidence of random assignment of mosquitoes to intervention and control areas. For this review, samples of immature *Aedes aegypti* or *Aedes albopictus* mosquitoes were considered randomised when reared from a lab colony to an F1 generation[101], F4 generation[97] or an unspecified generation[104], which then had equal chances of being allocated to an intervention or control group. Two studies[92, 102] showed unclear evidence of random assignment of houses/villages for *Aedes* larval house-to-house survey. In a study, villages were randomly selected from two highly CHIK-infected districts, which were purposefully selected in Karnataka, South India. Additionally, *Aedes* larval surveys were undertaken on every fourth line-listed house, hence the study had overall unclear risk of selection bias from inadequate randomisation.[102] Another study had unclear reporting of randomisation of study samples, as data was reportedly consolidated from randomly selected houses from control areas, but the selection method was not reported from experimental areas.[92] The remaining eight studies did not report random assignment to treatment groups.[85, 97, 99-101, 103, 104, 230]

Seven of 10 studies[97, 99-101, 103, 104, 230] had control and intervention groups that were comparable at entry, whereas the remaining three studies[85, 92, 102] showed signs of incomparability. In a study with incomparable groups at entry, spatial and ecological differences between neighbourhoods within the intervention areas were reported. These differences were likely to increase, when comparing intervention and control

areas in neighbouring municipals. This was despite the study investigators' planned approach to selecting intervention and control areas which were similar in housing, surrounding environment and climate.[92] Another study was unclear in the comparability at entry due to insufficient details – no details on the locality and matched characteristics of controls were provided, even though baseline *Aedes* indices and matched control villages were reported.[102] The last study was a non-randomised non-controlled trial, hence comparable group demographics was not a requirement.[85]

Nine of 10 studies[85, 92, 97, 99-101, 103, 104, 230] showed evidence groups were treated similarly other than for named interventions. For one study, the matched control group was found to have adopted the mosquito control intervention of releasing predatory fishes into water storage tanks after they found out that that was the test intervention. The study investigators tried to assess the impact of the action on pre- and post-intervention in consultation with a statistician; however, no further ratification or correction of results were reported.[102]

In one study, the effectiveness of an adulticide was potentially confounded by other mosquito control interventions (such as larvicide use, source reduction and educational strategies) which were conducted in the treatment area as part of a concurrent integrated pest management strategy. It was argued that the additional interventions would not have immediately affected the adult mosquito population, which was the target of the study.[99]

Publication bias in favour of positive findings from mosquito control interventions was of concern. Company-sponsored funding was reported for one study, in which study investigators were employees from the company and all patent rights resulting from a novel mosquito control product developed from the study were to be assigned to the company.[103] Another study was led by the NEA of Singapore, a national level mosquito control authority.[85] The other eight studies were investigators-led research projects, which were found to represent a low risk for conflict of interests.[13, 14, 19, 97, 21, 22, 26, 27]

The four critical appraisal questions on blinding of participants to treatment allocation, allocation concealment, withdrawal of people and blinding of assessors to treatment allocation were found not applicable to the context of the 10 included studies, as there was no systematic bias due to the nature of the interventions on mosquitoes, not humans. These four excluded criteria were deemed to be not making a true difference in increasing the measurement of the methodological validity. For the question on blinding of participants to treatment allocation, it was found that in most of the included field trials and laboratory studies evaluating chemical and biological control strategies, these mosquito control strategies target mosquitoes. Hence, it did not make sense to blind the mosquitoes to treatments.

For the question on allocation concealment, experiments involving specific mosquito species were not reportedly tagged and labelled individually, likely because mosquitoes used in such studies were reared from a specific lab colony to F1, F4 generations or an unspecified generation. This question is only logically appropriate for allocation of humans (not mosquitos) to treatment groups.

For the question on description and inclusion of outcomes of people who had withdrawn from the analysis, this was not applicable, since mortality outcomes of mosquitoes (not humans) are of interest in the context of included studies. Lastly, the rationale behind the question on blinding of assessors to treatment allocation was to reduce the risk of bias affecting the assessors' outcome assessments on human-directed interventions. Because the measurement of outcomes (e.g. wooden paddles from ovitraps to collect mosquito eggs) was distinct from the conduct of the mosquito control (e.g. chemical, biological and habitat control), this question was found irrelevant to the needs and context of the included studies.

5.4.2. Description of included studies

All 10 studies included in the systematic review were classified as level 2 evidence, according to the JBI levels of evidence for the effectiveness of interventions.[188] Specific details of all included studies are found in Appendix XVIII.

The studies were published from 2008 – 2013. One was an RCT[104], two were cluster-RCTs[97, 101], one was a pseudo-randomised controlled study[102], five were controlled non-randomised studies[92, 99, 100, 103, 230] and one was a non-randomised non-controlled study.[85] One was conducted in Spain[92], two were conducted in the USA[97, 99], four were conducted in India[100, 102, 104, 230], one was conducted in South Africa[101], one was conducted in Japan[103] and one was conducted in Singapore[85]. Five were conducted in laboratory conditions[97, 100, 101, 104, 230], four were small field trials[85, 97, 102, 103] and two were large field trials.[92, 99] Five studies on mosquito control interventions targeted *Aedes aegypti*[100-102, 104, 230] and six studies on mosquito control interventions targeted *Aedes albopictus*.[85, 92, 97, 99, 101, 103]

Two from Spain and Singapore investigated the use of a combination of mosquito control strategies across all three types – biological control, chemical control and habitat control.[85, 92] One examined the use of combined biological and chemical control methods together[97], one examined the use of one biological and five chemical control methods separately[101], six examined the use of biological control[100, 102-104] and two examined the use of chemical controls.[99, 230] Table 5.2 summarises the characteristics of the mosquito control interventions in the included studies.

Table 5.2. Characteristics of mosquito control interventions

S/N	Condition	Type	Name	Application dosage	Length of intervention	References
Single mosquito control interventions						
1.1	Lab	Larvicide/ Chemical	Temephos	5 conc (unidentified) at 1ml:99ml of mineral H_20	24h	Kamgang *et al.* 2011
	Lab	Larvicide/ Chemical	Temephos 90.63%	6-7 conc (unidentified) at 1ml;99ml of dechlorinated tap H_20	24h	Tikar *et al.* 2008
	Lab	Larvicide/ Chemical	Fenthion 98%	6-7 conc (unidentified) at 1ml;99ml of dechlorinated tap H_20	24h	Tikar *et al.* 2008
	Lab	Larvicide/ Chemical	Malathion 96%	6-7 conc (unidentified) at 1ml;99ml of dechlorinated tap H_20	24h	Tikar *et al.* 2008
	Lab	Larvicide/ Chemical	DDT 70%	6-7 conc (unidentified) at 1ml;99ml of dechlor tap H_20	24h	Tikar *et al.* 2008
1.2	Lab	Larvicide/ Biological	Essential oil	100, 200, 300 and 400 mg/l	24h	Rajkumar *et al.* 2010
	Lab	Larvicide/ Biological	Sabinene	20, 40, 60 and 80 mg/l	24h	Rajkumar *et al.* 2010
	Lab	Larvicide/ Biological	Biofloratriene	20, 40, 60 and 80 mg/l	24h	Rajkumar *et al.* 2010
	Lab	Larvicide/ Biological	Borneol	20, 40, 60 and 80 mg/l	24h	Rajkumar *et al.* 2010
	Lab	Larvicide/ Biological	Beta-bisabolol	20, 40, 60 and 80 mg/l	24h	Rajkumar *et al.* 2010
	Lab	Larvicide/ Biological	Potash alum	10,20,30,50,70 – 100mg/L	24h	Preet *et al.* 2011
	Lab	Larvicide/ Biological	Bti	5 conc (unidentified) at 1ml:99ml of mineral H_20	24h	Kamgang *et al.* 2011
2.1	Field	Larvicide/ Chemical	DUET™	A total of 4015 drops of DUET™ were applied at 136.04ml/min 2009: 86.2g/ha (0.81 g/ha a.i. of prallethrin, 4.04 g/ha a.i. of sumithrin, and 4.04 g/ha a.i. of piperonyl butoxide) 2010 and 2011: 42.7g/ha (0.40 g/ha a.i. of prallethrin, 2.02 g/ha a.i. of sumithrin, and 2.02 g/ha a.i. of piperonyl butoxide)	2h/time 2009: Single nighttime 2010 and 2011: Dual nighttime, spaced 1-2 days	Farajollahi *et al.* 2012
2.2	Field	Larvicide/	Pyriproxife	Exp 1: 350mg/m2	0-44 days	Ohba *et*

		Biological	n 1% (juvenile hormone analogue) treated mosquito nets	Exp 2: 35mg/m2		*al.* 2013
	Field	Larvicide/ Biological	Poecilia	10-15 fishes/indoor cement tank	1 week and 1 month	Ghosh *et al.* 2011
	Field	Larvicide/ Biological	Gambusia	10-15 fishes/indoor cement tank	1 week and 1 month	Ghosh *et al.* 2011
3.1	Lab	Adulticide/ Chemical	Deltamethrin 0.06%	Not reported	1h	Kamgang *et al.* 2011
	Lab	Adulticide/ Chemical	DDT 4%	Not reported	1h	Kamgang *et al.* 2011
	Lab	Adulticide/ Chemical	Fenirothion 0.5%	Not reported	1h	Kamgang *et al.* 2011
	Lab	Adulticide/ Chemical	Propoxur 0.3%	Not reported	1h	Kamgang *et al.* 2011
Combined mosquito control interventions						
4.1	Lab	Larvicide/ Chemical	Agnique®	0.13±0.009g/pellet/cup	10 days	Nelder *et al.* 2010
4.2		Larvicide/Biological	Altosid®	0.13±0.009g/pellet/cup		
5.1	Field	Larvicide/ Chemical	Agnique®	0.13±0.009g/pellet/bucket	24/7/08-31/10/08 (3mths)	Nelder *et al.* 2010
5.2		Larvicide/Biological	Altosid®	0.13±0.009g/pellet/bucket		
6.1	Field	Larvicide/ Chemical	DEVICE TB2/Diflubenzuron 2%	1g/hl	Periodic treatment (unclear)	Abramides *et al.* 2011
	Field	Larvicide/ Chemical	Temephos 1% SG	1g/10L H_20	5 days (Day 0,1,3,4,5)	Tan *et al.* 2011
6.2	Field	Larvicide+Adulticide/ Chemical	Acetellic 50EC (Primiphos-methyl)	Indoor ultraviolet misting 200g a.i./ha and thermal fogging 100g a.i./ha	2 days (Day 0,3) 3 days (Day 1(6am),4,5)	Tan *et al.* 2011
6.3	Field	Larvicide/Biological	Bti (Vectobac WG)	500g/ha	5 days (Day 0,1,3,4,5)	Tan *et al.* 2011
	Field	Larvicide/Biological	Bti 1.2%	1g/m^2	Periodic treatment (unclear)	Abramides *et al.* 2011

7.1	Field	Adulticide/ Chemical	Fastac/Alfa cipermetrin 10%	50cc/hl	2008: 1x 2009: 4x	Abramides *et al.* 2011
8.1	Field	Habitat control	Source reduction	924 houses visited	2008-2009	Abramides *et al.* 2011
	Field	Habitat control	Source reduction	A factory and surrounding factories	Day 0: 4hrs(70 officers) Daily for next 1 mth: 24 officers	Tan *et al.* 2011
8.2	Field	Habitat control	Remove uncontrolled rubbish dumps	2.6ha intervention area	2008-2009	Abramides *et al.* 2011

* A.I.: Active ingredient
† Ha: Hectare
§ HL: hectolitre

5.4.3. Description of included study interventions

Of the five studies conducted in the laboratory[97, 100, 101, 104, 230], four reported following the WHO guidelines for the conduct of larval and adult mosquito susceptibility bioassays. Of the four studies using WHO guidelines, two studies used the same WHO guidelines published in 2005 for larval mosquito bioassays[100, 104], one used the WHO guidelines published in 1981 for larval mosquito bioassays[230] and the last used the WHO guidelines published in 2006 for adult mosquito bioassays.[101] Only one study did not report following the WHO guidelines for the larval bioassay, although it reported the use of established protocols for mosquito colony maintenance and rearing.[97] In contrast, there were no established guidelines or protocols reported for the testing of mosquito control strategies in small and large fields included in the systematic review.

Six field trials reported breeding sites for *Aedes albopictus* and *Aedes aegypti*, such as household water storage containers[85, 92], outdoor water tanks,[92, 102] houses and back yards[99] and plants in public gardens.[92] Field habitats, such as microcosms in a

greenhouse[103] and black plastic buckets containing water and crushed oak leaves placed in shaded areas of field plots[97], were simulated for two studies.

Some studies confirmed the species of mosquitoes collected during the pre- or post-interventions or both in field trials and one study sought to confirm the presence of CHIKV in the collected mosquitoes. In the pre-intervention phase of a study conducted in Singapore, 120 of 173 (69.4%) of mosquitoes caught were *Aedes albopictus* and the rest were *Culex spp.* The study then identified six of 120 *Aedes albopictus* that were positive carriers of CHIKV. Three of these six CHIKV positive *Aedes albopictus* were found to have carried CHIKV, as evident by the presence of CHIKV RNA in the head and thorax and the range of CHIK viral load of 50 pfu – $5x10^4$ pfu/mosquito.[85] In another study, the pre-intervention phase found that 45% and 70% of mosquitoes, collected in Mercer County and Monmouth County respectively, were *Aedes albopictus*.[97]

In the field study conducted in Spain, post-intervention mosquito population abundance was based on eggs per positive ovitrap. The mosquito species were confirmed as *Aedes albopictus*, by rearing the eggs to the larvae stage.[92] Similarly, in another field trial, post-intervention identification of *Aedes albopictus* adult mosquitoes were calculated and other species of mosquitoes were not taken into account.[99] In India, a small field trial[102] and three laboratory studies[100, 104, 230] only experimented with the *Aedes aegypti* larvae because it was reportedly the primary vector of CHIK in India.

Only one study took into consideration differing urban-rural profiles affecting effectiveness of mosquito control operations. In field trials, urban areas were selected for two studies[92, 99], suburban and urban areas were selected for one study[97] and rural areas were selected for two studies.[85, 102] One field study did not report on the urban-rural profile.[103] In the five laboratory studies, *Aedes aegypti*/*Aedes albopictus* were sampled from urban areas[101, 230], laboratory-maintained strains[100, 104] and an auto-salvage yard.[97]

Similar to other mosquito-borne diseases, climate changes and seasonal variations may have an impact on distribution of CHIK vectors.[231, 232] Seasonal and climatic conditions were recorded for all field trials[92, 97, 99, 102, 103] except one field study.[85] Although not assessed in this systematic review, these factors were important to consider because some insecticides, such as Altosid® ((S)-methoprene), break down and decrease residual activity in the presence of ultraviolet light. For a study, precipitation and rainfall information were obtained for the study sites and there was the intentional use of black plastic buckets to reduce ultraviolet and wind exposure.[97] Another small simulated field trial maintained average temperatures of 25.9°C and 20.2°C for two experiments in a greenhouse.[103] Active seasons of *Aedes albopictus* over three years (2009 - 2011) were reported in the conduct of one study.[99] Only one of 5 laboratory studies reported season and climate conditions for the location of mosquito sampling[230]. Temperature[19, 97, 21, 26], humidity[19, 21, 26] and photoperiods[97, 100, 104, 230] for maintenance of laboratory *Aedes* mosquito colonies were reported for all five laboratory studies.

Two of 10 studies reported the epidemiological disease link to the entomological mortality results collected from the evaluation of mosquito control interventions. A study tested for the presence of CHIKV in mosquito samples and proceeded to isolate CHIKV.[85] Another study surveyed for pre- and post-intervention fever cases presenting with *CHIK-like* symptoms.[102] The other eight studies did not show collection of epidemiological data from both intervention and control sites.[92, 97, 99-101, 230 103, 104]

The successful implementation of mosquito control strategies in the short and long-term was attributed to the cooperation and support from the community in one study. The study reported that the key for success of mosquito control was community acceptance and uptake of the control interventions, for example, by opening their houses for house inspection to eliminate mosquitoes and its breeding sites and to take ownership on the implementation of mosquito control efforts at home.[92] In another study, although community involvement was not reported, the study attributed the

success of interrupted CHIK transmission to positive coordination between field and laboratory staff.[85] The other eight studies did not report on community involvement and support.[85, 97, 100-104, 230]

One of 10 studies reported the efficiency of mosquito control interventions. In a study, the cost-effectiveness of the predatory fishes used to control *Aedes* larval levels in water tanks was reported, with a sustainable and cost-effective operational cost of USD0.011 per capita per application of Poecilia fishes. The study recommended proper educational guidance and the monthly monitoring and release of Poecilia in water tanks.[102]

5.4.4. Outcome results

5.4.4.1. Single mosquito control interventions in laboratory

5.4.4.1.1. Chemical larvicides

Two controlled laboratory studies assessed the susceptibility of Aedes *aegypti* and *Aedes albopictus* third to forth instars larvae to the following chemical larvicides: temephos[101, 230], fenthion[230], malathion[230] and DDT[230]. Table 5.3 shows the decreasing potency of chemical larvicides, with its larvae mortality rates adjusted using the Abbott's formula:

Table 5.3. Decreasing potency of chemical larvicides following 24 hours exposure

S/N	Intervention	LC50* (mg/l)	95% CI	LC90* (mg/l)	95% CI	$\chi 2$	References
Against *Aedes aegypti*							
1	Temephos	0.0021-0.0441	0.0012-0.0531	0.0139-0.1169	0.0109-0.167	0.992-1.57†	Tikar *et al.* 2008
2	Fenthion	0.0025-0.0207	0.0018-0.0254	0.0077-0.0659	0.0058-0.0933	0.113-2.247†	Tikar *et al.* 2008
3	Temephos	0.004-0.009	0.003-0.017	-	-	-	Kamgang *et al.* 2011

4	Malathion	0.0633-0.276	0.0543-0.334	0.136-0.818	0.108-1.163	2.417-4.829†	Tikar *et al.* 2008
5	DDT§	0.188-0.5883	0.1504-0.938	0.535-8.024	0.417-21.788	0.05-1.165†	Tikar *et al.* 2008
Against *Aedes albopictus*							
6	Temephos	0.0049-0.0076	0.0013-0.024	-	-	-	Kamgang *et al.* 2011

* Readings against late third to early fourth instars were recorded for both studies.
† χ^2 probability was not reported.
§ DDT can work as a chemical larvicide or a chemical adulticide.

In Tikar et al. 2008, the LC_{50} values and its 95% CI showed susceptibility of all mosquito samples to temephos, fenthion, malathion and DDT at the six to seven unidentified concentrations with 10 – 90% mortality. Compared to the lab reference strain of *Aedes aegypti*, there was 0.33 - 7.11, 0.36 – 3.00, 0.65 – 2.84 and 2.16 – 20.8 fold more LC_{50} of temephos, fenthion, malathion and DDT respectively, in *Aedes aegypti*. Low levels of DDT resistance were noticed in *Aedes aegypti*.[230]

The LC_{50}, LC_{95}, RR_{50} and RR_{95} values and the 95% CI from Kamgang et al. 2011 showed susceptibility of all *Aedes aegypti* and *Aedes albopictus* mosquito samples to temephos at the five unidentified concentration levels. Kamgang et al. 2011 did not report percentage mortality rates against temephos.

Both studies found the chemical larvicides effective in the CHIK mosquito control program, with the second study concluding that temephos was found to be relatively more effective in controlling *Aedes aegypti*, followed by fenthion, malathion and DDT.

5.4.4.1.2. Biological larvicides

Three controlled laboratory studies assessed the susceptibility of *Aedes aegypti*[100, 101, 104] and *Aedes albopictus*[101] larvae to the following biological larvicides: the essential oil of the Clausena dentate leaves and its four major compounds (Sabinene, Beta-bisabolol,

Borneol and Biofloratriene)[104], crude and standard potash alum[100] and Bti.[101] Across the three studies, potency of the biological larvicides was evaluated, as shown in Table 5.4:

Table 5.4. Decreasing potency of biological larvicides following 24 hours exposure

S/N	Intervention	LC_{50}* (mg/l)	95% CI	LC_{90}* (mg/l)	95% CI	$\chi 2$	References
Against Aedes aegypti							
1	Bti	0.18-0.27	0.03-0.39	-	-	Not reported	Kamgang *et al.* 2011
2	Sabinene	27.3	24.1-30.2	62.2	56.1-68.3	4.2†	Rajkumar *et al.* 2010
3	Beta-bisabolol	33.2	30.1-36.3	70.3	64.2-76.8	3.9†	Rajkumar *et al.* 2010
4	Borneol	43.5	39.4-47.6	73.4	66.2-79.3	3.2†	Rajkumar *et al.* 2010
5	Biofloratriene	47.4	43.2-51.2	78.3	71.4-85.2	2.8†	Rajkumar *et al.* 2010
6	Crude potash alum	48.53	36.74-68.48	204.8	122.29-624.74	0.893§	Preet *et al.* 2011
7	Standard potash alum	65.1	50.57-94.7	224.41	137.07-654.55	1.628§	Preet *et al.* 2011
8	Clausena dentate essential oil	140.2	121.4-160.1	341.6	322.3-360.2	5.5†	Rajkumar *et al.* 2010
Against Aedes albopictus							
9	Bti	0.19-0.27	0.17-0.28	-	-	Not reported	Kamgang *et al.* 2011

* Readings against fourth instar, except in Kamgang *et al.* 2011, which recorded readings against late third to early fourth instars.

† χ^2 probability is significant at P<0.5.

§ χ^2 probability was not reported.

Table 5.5. Percentage mortality of forth instar larvae *Aedes aegypti* following 24 hours exposure

S/N		% mortality							
	Concentrations (mg/l)	Sabinene	Beta-bisabolol	Borneol	Biofloratriene	Crude potash alum	Standard potash alum	Clausena dentate essential oil	
1	10	-	-	-	-	10	0	-	

2	20	42.8	32.5	27.5	22.5	20	10	-
3	30	-	-	-	-	35	30	-
4	40	67.8	56.8	46.5	40.5	-	-	-
5	50	-	-	-	-	45	40	-
6	60	89.3	81.8	75.3	69.8	-	-	-
7	70	-	-	-	-	60	50	-
8	80	100	100	98.5	91.8	-	-	-
9	100	-	-	-	-	80	65	39.3
10	200	-	-	-	-	-	-	58.8
11	300	-	-	-	-	-	-	82.3
12	400	-	-	-	-	-	-	100

As shown from Table 5.5, the larvicidal activity was dose dependent, with maximum mortality attained using 80 mg/l of Sabinene, beta-bisabolol, bomeol and biofloratriene, 100mg/l of crude and standard potash alum and 400mg/l attained for Clausena dentate essential oil. There was positive correlation between larvicide concentrations and percentage mortality rates. Kamgang et al. 2011 did not report percentage mortality rates against Bti.

Rajkumar et al. 2010 concluded that the four individual compounds of Clausena dentate leaves were more potent larvicides than the essential oil. The essential oil of Clausena dentate leaves and its four major compounds may be a potent source of natural larvicides against *Aedes aegypti* larvae.[104] Preet *et al.* 2011 found that the first instar larvae were the most susceptible to potash alum and the fourth instar was the least susceptible to potash alum. Potash alum, a fairly cheaper and readily available eco-friendly compound might be recommended as a potential potent chemical larvicide against *Aedes aegypti* breeding sites in homes.[100] In Kamgang et al. 2011, the LC_{50} values and the 95% CI showed susceptibility of both *Aedes aegypti* and *Aedes albopictus* mosquito samples to Bti. Although the results of these studies are inconclusive, it can still be used to guide future research into insecticide-based vector control strategies as there remains a need for a more extensive monitoring of insecticide resistance in *Aedes* mosquitoes.[101]

5.4.4.1.3. Chemical versus biological larvicides

None of the included laboratory studies attempted to compare the effectiveness of chemical larvicides to biological larvicides.

5.4.4.1.4. Chemical adulticides

Kamgang et al. 2011 was the only study that evaluated the susceptibility of four chemical adulticides: deltamethrin, DDT, fenitrothion and propoxur.[101] Study results show that most field mosquito samples were susceptible to deltamethrin, DDT, fenitrothion and propoxur, with the following exceptions suggesting resistance to DDT and deltamethrin. One *Aedes aegypti* sample from Libreville and two *Aedes albopictus* samples from Buea and Yaoundé were resistant to DDT (mortality 36% to 71%). Resistance to deltamethrin was also suspected in *Aedes albopictus* from Yaoundé (83% mortality). There was no increase in the knockdown times (KdT_{50} and KdT_{95}) in the Yaoundé resistant sample compared to other *Aedes albopictus* samples, suggesting the possible involvement of metabolic resistance to deltamethrin and DDT.[101]

5.4.4.1.5. Chemical larvicides versus chemical adulticides

None of the included laboratory studies attempted to compare the effectiveness of chemical larvicides to chemical adulticides.

5.4.4.2. Single mosquito control interventions in field trials

5.4.4.2.1. Biological larvicides

Two studies assessed a total of three biological larvicides: Pyriproxyfen[103], a juvenile hormone analogue in a greenhouse and two predatory fishes, Poecilia and Gambusia[102] in indoor cement tanks.

Ohba et al. 2013 showed that the number of eggs laid by the released adult mosquitoes in the pyriproxyfen-treated microcosms was significantly lowered (day 6, $F_{1,4}$ =17.69,

P<0.05), and that the hatching of *Aedes albopictus* eggs was significantly suppressed (treatment, $F_{1,4}$ =3657.6, P<0.05), as compared to untreated control. In addition, the pupae mortality was significantly increased (day 6, $F_{1,4}$ =120.17, P<0.05) compared to controls. The study confirmed pyriproxyfen's effectiveness against *Aedes albopictus* in semi-field conditions. Adult *Aedes albopictus* mosquitoes in contact with pyriproxyfen-treated bed nets has been shown to decrease egg hatching in adult females and increase pupae mortality. It could be an important tool to control *Aedes albopictus* transmitted diseases.[103]

In the study assessing the effectiveness of Poecilia and Gambusia predatory fishes release against *Aedes aegypti*, the supporting education intervention on the use of larvivorous fishes and water storage were distinct in analysis. Both Poecilia and Gambusia (with education) proved effective in controlling larvae levels up to one week (OR: 1.96 and 2.18 respectively, p<0.001); however, only Poecilia proved effective up to one month (OR: 1.58, P<0.001). The study found that the use of Poecilia (with supporting community education) was an effective and sustainable mosquito control strategy. Proper water storage practices, focused on information, education and communication about Poecilia introductions and vector sanitation involving the local administration and community, was recommended as a strategy for *Aedes* control.[102]

5.4.4.2.2. Chemical adulticides

Farajollahi et al. 2012 was the only study that evaluated the efficacy of a dual-action chemical adulticide, DUET™ during night against *Aedes albopictus*. DUET™ adulticide, consisting of sumithrin (5%, 44.94g/L Active Ingredient) and prallethrin (1%, 8.99g/L AI) with the synergist piperonyl butoxide (5%, 44.94g/L AI), was applied using a vehicle-mounted ultra-low volume (ULV) cold aerosol sprayer and a SmartFlow system in the houses and yards of Mercer County, New Jersey, USA. Each application took two hours and the application dosage varied throughout the three years from 2009 (86.2 g/ha single application) to 2010 and 2011 (42.7g/ha dual applications). The

volume median diameter of adulticide was 15.2um and a total of 4015 drops were applied at 136.04ml/min. Adult *Aedes albopictus* were monitored using BGS traps and sampled weekly for 24 hours from 2009 - 2011.

Study results showed an overnight percentage reduction of mosquito adult population. Single adulticide treatment at full label rate of 86.2gm/ha resulted in 72.7±5.4(SE) percentage reduction, which was significantly higher (p=0.04) than 54.0±4.7 percentage reduction from adulticide treatment at mid-label rate of 42.7gm/ha. Dual adulticide treatments at mid-label rate was significantly more effective (p=0.003) than single adulticide treatment at full rate and resulted in an average percentage reduction of 85.0±5.4. Nighttime ULV adulticiding was effective in reducing *Aedes albopictus* adult mosquitoes and might be considered for use in integrated pest management programs and during disease epidemics.[99]

5.4.4.3. Combined mosquito control interventions in laboratory

5.4.4.3.1. Combined chemical and biological larvicides and pupicides

Nelder et al. 2010 was the only study that evaluated the combined effectiveness of a chemical and a biological larvicide, Agnique® and Altosid® ((S)-methoprene) against *Aedes albopictus* in the laboratory.

Although laboratory results showed that the combined use of Agnique® and Altosid® suppressed *Aedes albopictus* for a minimum of 120 days, the combined use of Agnique® and Altosid® was not recommended by the study as unclear costs and limited efficacy were taken into account. The study proposed Agnique® and Altosid® to be considered as important interventions in the management and prevention of *Aedes albopictus*, and could provide long-term control of *Aedes albopictus* larvae and pupae.[97]

5.4.4.4. Combined mosquito control interventions in field trials

5.4.4.4.1. Combined chemical and biological larvicides and pupicides

Same conclusions were drawn from Nelder et al. 2010, except that in the field study, the combined use of Agnique® and Altosid® suppressed *Aedes albopictus* for a minimum of 32 days.[97]

5.4.4.4.2. Combined chemical, biological and habitat control

Two studies from Spain and Singapore evaluated the effectiveness of five combined chemical, biological and habitat control strategies.[92]

In Abramides et al. 2011, Device TB2 (Diflubenzuron), Fastac® (Alfacipermetrin), Bti, source reduction and removal of uncontrolled rubbish dumps were used in Sant Cugat del Valles in Spain. Study results showed that the combined mosquito control strategies were effective in reducing *Aedes albopictus* eggs, as a statistically significant ($P<0.05$) reduction in the number of eggs in treated against untreated areas was observed in 2008 and 2009.

In Tan et al. 2011, Bti, temephos, Actellic 50EC and source reduction were carried out at a concrete slabs factory in an industrial area NorthWest of Singapore. The study found that the extensive combination of mosquito control strategies was effective in reducing risk of CHIK in Kranji. Although mosquito control measures resulted in a 90% reduction of adult *Aedes albopictus* caught by BGS traps, post-intervention measures still showed one CHIKV positive female *Aedes albopictus* (compared to six of them during the pre-intervention phase). With the incomplete eradication of CHIKV-positive mosquitoes, the intensive mosquito control operations persisted in affected localities, which eventually led to decrease in mosquito numbers and interrupted spread of disease.

5.5. Discussion

Overall, single and combined mosquito control interventions can be effective in transitory mosquito control. These interventions control both immature and adult *Aedes albopictus* and *Aedes aegypti* mosquitoes, with laboratory-conducted studies understandably having more pronounced positive results from measured chemical and biological larvicides and pupicides. Despite this, there is inconclusive evidence on long-acting mosquito control interventions, in addition to limited evidence on the sustainability of mosquito control efforts.

With respect to CHIK, no high quality studies of the same intervention type was included, nor were direct comparisons of mosquito control interventions. The heterogeneity across the 10 included studies also precluded meaningful meta-analysis for the desired outcome measurements. Despite this, numerous guidelines by the WHO pesticide evaluation scheme on mosquito control strategies against other long-standing vector-borne diseases, namely Dengue and Malaria, have been published and could serve as useful material to guide the development of evidence-informed guidelines for CHIK-specific mosquito control strategies.[84, 233]

Current CHIK mosquito control strategies intrinsically target all four stages (eggs, larvae, pupae and adults) of the *Aedes* mosquitos' life cycle, with larvicides most commonly used. Various reasons were adduced for that, including its vast effects over a short period.[85] However, it remains contentious whether larvicides were favoured over source reduction, as another included study raised that source reduction is positively advocated by some researchers as the only sustainable mosquito control strategy.[92]

The translation of research findings from investigator-led laboratory and small field projects to larger community-based mosquito control operations approaching or during CHIK epidemics has been documented in few studies. Mosquito control strategies currently aim to limit the contact between mosquito vectors carrying CHIKV

and the susceptible human population. The long-term sustainability and success of mosquito control interventions have been attributed to active community participation as they take ownership of mosquito control activities to reduce mosquito breeding in homes.[85, 92] With limited financial and human resources, the cognizant use of mosquito control at the right localities and timing, optimum application doses and frequency are important in entomological indices and eventually, the interrupted transmission of CHIK.

The effectiveness of mosquito control interventions in real epidemics can be indicated with vector and disease surveillance, as a good mosquito control intervention decreases the vector population carrying CHIKV and results in a decrease in CHIK cases. However, the assessment can be very complex given the potential confounders, such as the epidemiological patterns of disease, changes in seasons or climate, correct placement of mosquito traps and presence of subtle and competing concurrent mosquito control operations (such as vector surveillance itself) for CHIK and other mosquito-borne diseases such as Dengue and Malaria.

Included studies showed that *Aedes albopictus* and *Aedes aegypti* are amenable to short periods of control. Although an included study showed that mosquito control interventions that could last long-term were found favourable due to reduced application frequencies of short residual insecticides, saving time, labour and finances,[97] more studies are needed to provide clear evidence of the benefits of long-term mosquito control measures.

To prevent future CHIK outbreaks during summer, some studies have estimated a reduction of less than 83% or around 90% of adult mosquitoes as discussed in an included study.[99] To control and prevent future CHIK outbreaks, included studies had in view the potential for integrated vector management (IVM), as applied in other diseases such as Malaria and Dengue. Although not CHIK-specific, the WHO position statement on IVM and the WHO global strategic framework for mosquito control

management are two umbrella documents which could be the springboard for the development of CHIK-specific mosquito control measures, with consideration of the feasibility and appropriateness of mosquito control measures in the long run.[234, 235]

5.5.1. Limitations

The safety assessment of mosquito control strategies is beyond the scope of this systematic review and hence is a limitation. Mosquito control strategies, particularly chemical insecticides, should be chosen in view of their effectiveness, cost-effectiveness and safety. For example, there is a global ban on DDT for agriculture under the 2011 Stockholm Convention, citing harm to human health, but indoor residual spraying with DDT in Malaria control is still allowed in Africa and Asia due to its effectiveness.[236] Studies that were not specific to CHIK were excluded from the systematic review, hence mosquito control strategies that might be effective in other mosquito-borne diseases were not evaluated. In addition, studies that were not in English were excluded, hence there was the possibility of excluding studies from La Reunion Island or India, where the largest CHIK epidemics have occurred.

5.6. Conclusion

The systematic review results found that current single and combined mosquito control interventions can be effective in short-term transitory mosquito control. In CHIK, these interventions control both immature and adult *Aedes albopictus* and *Aedes aegypti* mosquitoes, with laboratory-conducted studies understandably having more pronounced positive results from chemical and biological larvicides and pupicides. However, there is inconclusive evidence on mosquito control interventions that are long-acting and there is limited evidence on the sustainability of mosquito control efforts. More research is required to address these concerns.

5.6.1. Implications for practice

- Although the combined use of chemical larvicide Agnique® and biological larvicide Altosid® was shown to decrease 95% of *Aedes albopictus* in the field for a minimum effect

benefit time of 32 days, it is not recommended due to costs and limited efficacy. (Grade B)

- *Aedes aegypti* and *Aedes albopictus* mosquitoes generally show susceptibility to deltamethrin, DDT, fenitrothion and propoxur, although there is some evidence of metabolic resistance to deltamethrin and DDT. Hence, strict monitoring of resistance to larvicides and adulticides is required in the field. (Grade B)

- Poecilia (with supporting education) is found to be effective and sustainable in mosquito control. Proper water storage practices, focused information, education and communication with Poecilia introductions and vector sanitation involving the local administration and community, may be good strategies for *Aedes aegypti* control. (Grade B)

- The use of the three chemical larvicides, temephos, fenthion and malathion, are effective and are recommended for use in CHIK mosquito control. (Grade B)

- Biological larvicides may be used in CHIK mosquito control, according to the decreasing order of potency against *Aedes aegypti* fourth instar larvae: Bti, Sabinene, Beta-bisabolol, Borneol, Biofloratriene, crude potash alum, standard potash alum and Clausena dentate essential oil. (Grade B)

- In semi-field conditions, adult *Aedes albopictus* mosquitoes in contact with pyriproxyfen-treated bed nets have been shown to decrease egg hatching in adult females and increase pupae mortality. (Grade B)

- In field conditions, nighttime ULV adulticiding using a chemical adulticide, DUET™ is effective in reducing *Aedes albopictus* adult mosquitoes and may be considered for use in integrated pest management programs and during disease epidemics. (Grade B)

- In field conditions, intensive mosquito control operations combining all chemical, biological and habitat control appeared to be effective in reducing *Aedes albopictus* eggs and adult populations. (Grade B)

5.6.2. Implications for research

- There is a general lack of high quality field studies on mosquito control strategies. High quality mosquito control intervention field studies on CHIK should be designed and conducted with close evaluation of long-term follow-up, sustainability and cost-effectiveness of operations. In field trials, pre-intervention measurement of mosquito abundance in intervention and control areas should be done for better comparability. Concentrations of insecticides, treatment dosage, application rates and length and frequency of mosquito control interventions should be adequately documented for better replication of result findings.

- IVM has been raised as a possible way to improve mosquito control interventions specific to CHIK; however, there is a lack of primary studies investigating IVM for CHIK control. This highlights the need for more primary studies investigating and documenting IVM for CHIK control, especially in countries where numerous mosquito-borne diseases are prevalent.

6 Chikungunya guidelines and the synthesis of new guideline recommendations: A content analysis

6.1. Abstract

Chikungunya guidelines have been developed to guide clinicians and other public health professionals on disease management. However, the evaluation of these guidelines based on methodological rigorous grounds and the formulation of guideline recommendations based on systematic reviews have not been conducted. Utilising the AGREE II instrument, the reviewers found six identified guidelines to be of low methodological quality. The main methodological weaknesses identified were *rigour of development* and *editorial independence*. Three guidelines that were recommended for use by at least one reviewer were utilised for coding and abstraction in the content analysis, together with three systematic reviews. Twenty guideline recommendations pertaining to six domains were carefully formulated in this content analysis. The guideline recommendations should be peer-reviewed and pilot-tested before gaining approval for use in international guidelines.

6.2. Concise introduction

CHIK, an *Alphavirus* mosquito-transmitted disease, continues to pose a serious threat to public health, with autochthonous cases found in as many as 55 countries worldwide.[21] Given the growing variation of therapeutics, prevention and control measures available to manage CHIK[57, 58], published guidelines can be an important source of data to guide practice in clinical and public health settings. This content analysis assessed the methodological quality of the published guidelines in CHIK and thematically proposed new or updated guideline recommendations based on findings from the three systematic reviews (Chapters 3, 4 and 5) in relation to existing guideline recommendations, relevant to the six thematic domains of treatment, early diagnosis of disease, disease education, surveillance and mosquito control.

6.3. Methods unique to chapter

The full methods for the content analysis are reported in Chapter 2, Section 2.4. This chapter focuses on reporting the content analysis findings.

6.4. Results

6.4.1. Study selection

An extensive systematic search on six online scientific databases (PubMed, Web of Science, Scopus, ScienceDirect, CINAHL, ProQuest) and 11 grey literature sources (Guidelines International Network (G-I-N) Library and the National Guideline Clearinghouse (NGC), WHOLIS, CDC, ECDC, NIH, LILACS, CHIK Virus Net, World Bank, Asia Development Bank and Google) were conducted, using the keywords *Chikungunya* and *guideline*. Neither filters nor date limits were applied during the search process. The search strategies for the databases and grey literature sources are in Appendix XIX. Figure 6.1 shows the study selection process.

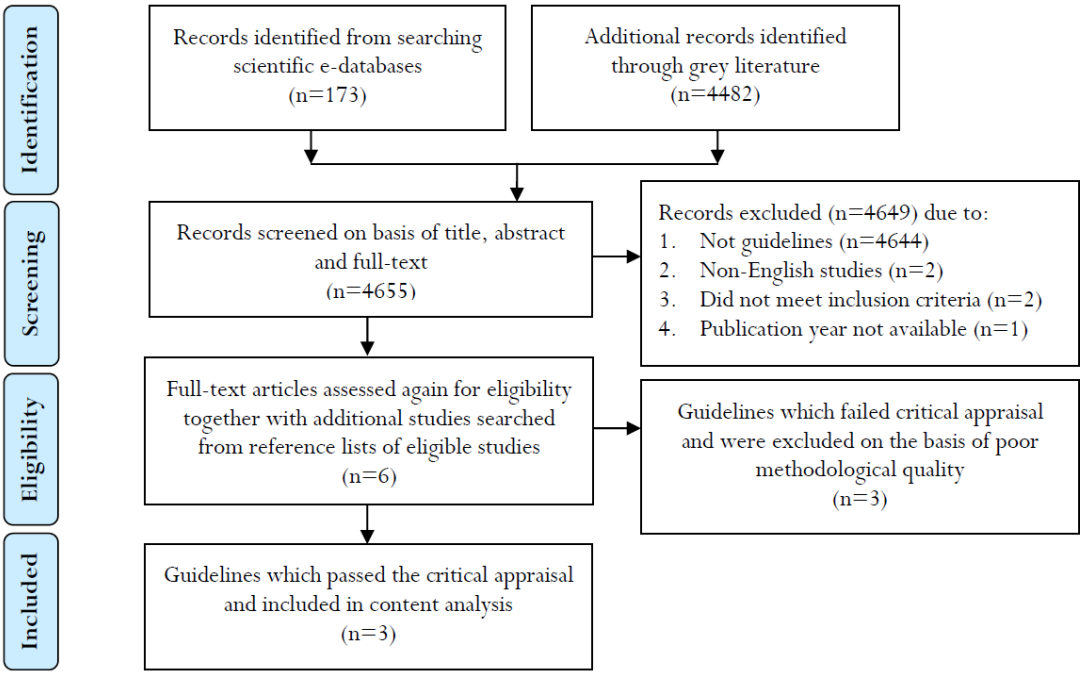

Figure 6.1. Study selection process

The primary author screened 4655 records based on title, abstract and full-text. Six guidelines for the management of CHIK were finally included for quality appraisal:

- World Health Organization, Regional Office for South-East Asia, India, 2008[201] (WHO SEARO 2008)
- World Health Organization, Regional Office for South-East Asia, India, 2009[58] (WHO SEARO 2009)
- Queensland Health Communicable Diseases Branch, Australia, 2010[237] (QH 2010)
- Institute of Epidemiology, Disease Control and Research, Bangladesh, 2011[238] (IEDCR 2011)
- Directorate of National Vector-Borne Disease Control Programme, India, 2011[200] (NVBDCP 2011)
- Pan American Health Organization, USA, 2011[57] (PAHO 2011)

6.4.2. Guidelines appraisal

Six original guidelines that were also of the latest published version were independently appraised by four reviewers for methodological quality. The quality assessment results are reported in Tables 6.1 - 6.3.

Table 6.1. AGREE II item scores (mean ± SD) of guidelines

AGREE II items	WHO SEARO 2008	WHO SEARO 2009	QH 2010	IEDCR 2011	NVBDCP 2011	PAHO 2011
Scope and purpose						
1. The overall objective(s) of the guideline is (are) specifically described.	3.25 ±1.26	6.25 ±0.96	2 ±0.82	1.5 ±1	6.25 ±0.96	7±0
2. The health question(s) covered	2.75	4.75	1.5	1±0	5±1.15	4.75

by the guideline is (are) specifically described.	±0.96	±1.89	±0.56			±1.5
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	2.75 ±0.5	5.75 ±1.89	3±1.83	1.5±1	4±1.15	6±2
Stakeholder involvement						
4. The guideline development group includes individuals from all relevant professional groups.	3.75 ±0.5	2±1.41	1±0	1±0	1±0	5.25 ±1.71
5. The views and preferences of the target population (patients, public, etc.) have been sought.	2.25 ±1.5	2±1.41	1±0	1±0	1±0	1±0
6. The target users of the guideline are clearly defined.	3 ±0.82	6±1.41	1.75 ±0.96	1±0	3.25 ±0.5	6.75 ±0.5
Rigour of development						
7. Systematic methods are used to search for evidence.	1.25 ±0.5	1±0	1±0	1±0	1±0	1±0
8. The criteria for selecting the evidence are clearly described.	1±0	1±0	1±0	1±0	1±0	1±0
9. The strengths and limitations of the body of evidence are clearly described.	1±0	1±0	1±0	1±0	1±0	1±0
10. The methods for formulating the recommendations are clearly described.	1±0	1±0	1±0	1±0	1±0	1.75 ±0.96
11. The health benefits, side effects and risks have been considered in formulating the	2.25 ±0.96	2.25 ±0.96	1.5±1	2.25 ±0.96	2.5 ±1.29	4±0.82

recommendations.						
12. There is an explicit link between the recommendations and supporting evidence.	1±0	1.25 ±0.5	1±0	1±0	1±0	2±1.41
13. The guideline has been externally reviewed by experts prior to its publication.	4.25 ±2.36	2±1.41	1±0	1±0	1±0	4.75 ±0.5
14. A procedure for updating the guideline is provided.	1.25 ±0.5	2.25 ±1.5	1±0	1±0	1±0	1±0
Clarity of presentation						
15. The recommendations are specific and unambiguous.	4±0.82	5.25 ±0.96	2.5 ±1.73	3±1.15	4.75 ±0.5	5.75 ±1.26
16. The different options for management of the condition or health issue are clearly presented.	4±1.63	4.75 ±1.5	2.5 ±1.73	2.75 ±1.71	3.75 ±1.5	4.75 ±1.5
17. Key recommendations are easily identifiable.	4.75 ±1.26	4.5 ±1.91	3.25 ±1.5	3 ±1.15	4.75 ±1.26	5.5 ±1.73
Applicability						
18. The guideline describes facilitators and barriers to its application.	1.25 ±0.5	2.5±1	1±0	1.5 ±0.58	3. 5 ±0.58	1±0
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	1.25 ±0.5	2±0.82	1±0	1.5 ±0.58	5.25 ±0.5	3.25 ±0.5
20. The potential resource implications of applying the recommendations have been considered.	1.25 ±0.5	2.25 ±1.5	1±0	1.5 ±0.58	3.75 ±1.26	2.25 ±1.26

21. The guideline presents monitoring and/or auditing criteria.	1±0	3.5 ±1.73	1±0	1.25 ±0.5	4.25 ±2.22	4.75 ±2.63
Editorial independence						
22. The views of the funding body have not influenced the content of the guideline.	2.25 ±1.5	1.25 ±0.5	1.75 ±1.5	1±0	1.75 ±1.5	4.75 ±0.96
23. Competing interests of guideline development group members have been recorded and addressed.	1.5±1	1.25 ±0.5	1±0	1±0	1±0	2.75 ±2.06
Calculated average score	2.26 ±0.49	2.86 ±0.73	1.47 ±0.26	1.42 ±0.20	2.73 ±0.26	3.57 ±0.52
Overall guideline assessment score	2.5 ±0.58	3±0.82	1.5 ±0.58	1.5 ±0.58	2.75 ±0.5	4 ±0.82

*AGREE II items are rated on a 7-point scale: 1, strongly disagree; 7, strongly agree.

Table 6.2. Scaled domain percentage scores for each guideline

Domains	**WHO SEARO 2008**	**WHO SEARO 2009**	**QH 2010**	**IEDCR 2011**	**NVBDCP 2011**	**PAHO 2011**
***Scope and purpose* (%)**	32	76	19	6	68	82
***Stakeholder involvement* (%)**	33	39	4	0	13	56
***Rigour of development* (%)**	10	8	1	3	3	18
***Clarity of presentation* (%)**	54	64	29	32	57	72
***Applicability* (%)**	3	26	0	7	53	30
***Editorial independence* (%)**	15	4	6	0	6	46

*Each scaled domain percentage score is calculated using the following formula:

[(Obtained score – Minimum possible score) /(Maximum possible score – Minimum possible score)] x 100.

Table 6.3. Reviewers' recommendations for use of guidelines

Guidelines	Reviewer 1	Reviewer 2	Reviewer 3	Reviewer 4
WHO SEARO 2008	Recommended with modifications	Not recommended	Not recommended	Not recommended
WHO SEARO 2009	Recommended with modifications	Not recommended	Not recommended	Recommended with modifications
QH 2010	Not recommended	Not recommended	Not recommended	Not recommended
IEDCR 2011	Not recommended	Not recommended	Not recommended	Not recommended
NVBDCP 2011	Not recommended	Not recommended	Not recommended	Not recommended
PAHO 2011	Recommended with modifications	Recommended with modifications	Not recommended	Recommended with modifications

Quality assessment results of guidelines showed low methodological quality, with a calculated average score range of 1.42 - 3.57 out of 7 (Table 6.1). It was also observed that the average overall guideline assessment scores were consistently slightly above the calculated average scores, indicating congruent judgement amongst the independent reviewers.

The average numeric scores of the AGREE II instrument revealed the inherent strengths and weaknesses of methodological quality in existing CHIK guidelines. From Table 6.2, the highest scoring domain was *clarity of presentation*, followed by *scope and purpose*. Similar to appraisal of guidelines of other diseases[239, 240], *clarity of presentation* and *scope and purpose* were the top scorers in AGREE II assessment, suggesting that guideline development groups were cognisant of the overall aims, scope and target audience of the produced guideline. To further increase *clarity of presentation*, guideline

recommendations could be more specific and encompassing of the context of implementation, target population and caveats; however, that would be subjected to the availability of evidence.

On the other hand, the lowest scoring domain was *rigour of development*, followed by *editorial independence*, then *applicability* and lastly, *stakeholder involvement*. The greatest methodological weakness of the CHIK guidelines was *rigour of development*. The *rigour in development* was unexpectedly low across guidelines, indicating a critical lack of evidence-based guidelines. All six assessed guidelines showed limited reference to evidence, with only two systematic reviews referenced in PAHO 2011. The WHO SEARO 2008 guideline was reportedly developed based on the restricted clinical experience from managing patients suffering from CHIK, an emerging infectious disease. Only two CHIK guidelines had explicit linkage of recommendations to citations and no guidelines had grading of recommendations.

The next weakness in the guidelines was *editorial independence*. Declaration of conflicts of interest was not detailed in any assessed guideline. Funding support was acknowledged only in PAHO 2011. In the AGREE evaluation of knee osteoarthritis[240], acute low back pain[241] and maternal health guidelines[239], e*ditorial independence* and *stakeholder involvement* were observed with similar low scores; therefore, guideline developers seemed to struggle with these components. Transparency is of benefit to the target audience to ensure credibility of guideline recommendations and to reduce the risk of bias due to competing interests.

Applicability of guideline recommendations was of concern, as considerations of facilitators, barriers, practice implementation, costs and auditing criteria were minimally covered in the guidelines. The difficulty in application was attributed to the low rigor of guideline development and the unclear and limited pool of evidence in which the guidelines recommendation were based. Actionable steps to guide the usage

of CHIK guideline recommendations in practice should be evaluated, bearing in mind the context and the optimisation of expertise and resources.

Stakeholder involvement could be further improved through public engagement, by allowing CHIK patients to voice their views in the guideline development process. Evidence seeking the opinions of target audience in the guidelines was lacking in all the assessed guidelines. In addition, none of the guidelines referred to any published or unpublished literature regarding the experiences of CHIK patients in their healing process. All three guidelines that were produced by government departments (QH 2010, IEDCR 2011 and NVBDCP 2011) lacked reporting of guideline development participants. Description of the intended target audience was missing in two guidelines (IEDCR 2011 and NVBDCP 2011) and it was observed that the description could be improved for WHO SEARO 2008. To increase transparency, a guideline development committee that includes professionals from relevant areas of expertise should be formed and named in the guidelines, similar to the process adopted by health supra-organizations.

Three of seven guidelines (WHO SEARO 2008, WHO SEARO 2009 and PAHO 2011) showed similarity in drug treatment recommendations, despite scoring very low (1 - 18%) in *rigour of development*. It was highly uncertain whether the recommendations made were based on best available evidence due to difficulty in locating evidence for the recommendations. Although the three guidelines showed an increase in average quality over time (2.26 [2008]; 2.86 [2009]; 3.57 [2011]), recommended pharmacological and non-pharmacological treatments bore similarities in guidelines, suggesting a slow progress in finding the most effective treatment for the disease. On the other hand, case management seemed to have improved over the years, with the PAHO 2011 guidelines giving detailed information on effective triage systems at each health care level to reduce CHIK burden.

The six guidelines varied considerably in length, with four to 149 pages. Number of references also differed from 0 - 88. Three out of six guidelines were formulated by supra-organizations, namely the WHO[58, 201] and PAHO[57]; one guideline was nation-based[200]; and the remaining three guidelines were state-based. [200, 237, 238] Guidelines WHO SEARO 2008, WHO SEARO 2009, PAHO 2011 were recommended with modifications by at least one reviewer, as shown in Table 6.3; therefore, these guidelines were included in the units of analysis for this content analysis.

6.4.3. Proposed guideline recommendations

The guideline recommendations were formulated based on the evaluation of selected guidelines and the conduct of systematic reviews in Chapters 3, 4 and 5 of this thesis. These systematic reviews shall herein be referred to as HRQoL 2014, Surveillance 2014 and EControl 2014 respectively. The synthesis of guideline recommendations is based on the entirety of evidence body; however, an asterisk (*) is marked at the end of the recommendation if only one primary study is used as a basis for evidence.

DOMAIN A: TREATMENT

Chloroquine/hydroxychloroquine

Guideline recommendation 1a: *Chloroquine/hydroxychloroquine should not be used routinely in the management of acute CHIKV infection. However, chloroquine/hydroxychloroquine may be an anti-viral agent option for CHIK-induced chronic arthritis. (Grade B)*

Guideline recommendation 1b: *Clinicians must exercise caution in the administration of chloroquine/hydroxychloroquine because presence of nausea and pruritus adverse effects have been established, although the association is unclear. In chronic CHIKV infection, chloroquine/hydroxychloroquine may be continued only if there is a recorded positive clinical response. (Grade B)*

Two reviewed studies (a double-blind RCT[29] and a randomised uncontrolled study[129])

from a systematic review (HRQoL 2014) found no evidence for the use of chloroquine/hydroxychloroquine in the acute phase of CHIK. No benefits were observed with the duration and frequency of arthralgia, VAS pain scores, ADL and IADL scores in acute CHIK infection from treatment with chloroquine/hydroxychloroquine.[129] On the other hand, clinical benefits of reduction of joint pain and morning stiffness were found from a small open pilot study of 11 patients with CHIK-induced chronic arthritis. [181]

Corticosteroids

Guideline recommendation 2a: *The combination of prednisolone* (corticosteroid) *and acecyclofenac* (NSAID) *may be used to reduce inflammation, that in turn can alleviate pain and improve quality of life in CHIK patients with arthralgia.* (Grade B)*

A single prospective randomised parallel-group study found that the combination of prednisolone and acecyclofenac alleviated pain and improved HRQoL in CHIK patients with arthralgia.[129]

Guideline recommendation 2b: *Corticosteroids should not be used routinely in the management of CHIK. Rather, corticosteroids should only be an option and used with caution if there is a recorded favourable clinical response. Usual care practices should be continued in place of corticosteroids. (Grade B)*

A systematic review (HRQoL 2014) has shown insufficient reliable evidence to show that corticosteroids are effective in improving HRQoL outcomes of CHIK patients. An included retrospective cross-sectional study found no statistically significant difference (P value was not reported) on the percentage of relapses (defined as the observation of arthralgia, oedema, fever and cutaneous presentation) in CHIK patients compared to those who did not use corticosteroid treatment.[45]

Unless there is an obvious likelihood of benefit, monotherapy with corticosteroids

should be used with caution. Several studies included in the systematic review (HRQoL 2014) showed inconclusive signs of their potential, particularly for their anti-inflammatory and resulting analgesic properties in the symptomatic treatment of CHIK-induced chronic arthritis. Clinical experiences suggested that 76% of CHIK patients had higher perceived satisfaction with corticosteroids at any stage of the disease, compared to 36% with NSAIDs.[130] In addition, some CHIK patients with corticosteroids treatment reported pain relief; however, the degree of statistical and clinical significance was unclear.[44]

NSAIDs

Guideline recommendation 2a is the only guideline recommendation for the use of NSAIDs in CHIK management.

Although a retrospective cohort study reported 36% of CHIK patients having satisfaction with NSAIDs[130], there is insufficient evidence to make a recommendation on the sole use of NSAIDs in CHIK, based on the findings of a systematic review (HRQoL 2014).

Paracetamol

No guideline recommendation: Although paracetamol is commonly used for its anti-pyretic and analgesic functions to treat CHIK fever, the effectiveness of paracetamol on HRQoL of patients with CHIK fever has not been investigated in experimental studies, as shown from a systematic review (HRQoL 2014). A retrospective cohort study[130] and a retrospective cross-sectional study[45] from the systematic review suggested adverse effects of arthritic conditions, oedema and hypertension from the use of paracetamol, although the association is not clear. Until additional experimental and observational studies are completed, no conclusive recommendation can be drawn. Therefore, usual care practices should be continued.

Non-pharmacological interventions

No guideline recommendation: There is a dearth of evidence to enable the development of a recommendation regarding the use of non-pharmacological interventions, based on the analysis of coding content from systematic review (HRQoL 2014). Therefore, usual care practices should be continued.

DOMAIN B: EARLY DIAGNOSIS OF DISEASE

Early diagnosis of disease

Guideline recommendation 3a: *Clinicians should inquire about symptoms and build awareness on clinical manifestations of CHIK. They should differentiate it from Dengue, Malaria and other febrile arthralgia.*

Guideline recommendation 3b: *Clinicians are to be trained in recognising all stages of CHIKV infection and delivering the recommended care. (Grade B)*

Guideline recommendation 3c: *The formulation of uniform detection and management protocols for both the acute and chronic phases of CHIK is recommended to facilitate early diagnosis and treatment of CHIK. (Grade B)*

Guideline recommendation 3c: *A re-evaluation of past clinical records of patients with similar clinical manifestations as those of CHIK is recommended to find misdiagnosed patients. (Grade B)*

These recommendations were made due to the anticipated likelihood of desirable effects outweighing the undesirable effects, despite a systematic review (HRQoL 2014) finding a lack of high quality evidence in the effectiveness of early diagnosis of disease on HRQoL in CHIK patients. Early diagnosis of CHIK can be beneficial to patients[185-187], highlighting the importance of CHIK early symptom control and disease management.

The training and supervision of clinicians in recognizing CHIKV infection at all stages are the basis of CHIK surveillance[67-70], as shown from another systematic review (Surveillance 2014). This may also address the iceberg phenomenon for CHIK cases that remain undiscovered.

DOMAIN C: DISEASE EDUCATION

No guideline recommendation: There is no evidence to make a recommendation regarding effective disease education of clinicians and patients, based on the analysis of coding content from a systematic review (HRQoL 2014).

DOMAIN D: SURVEILLANCE

Guideline recommendation 4a: *Effective and rigorous surveillance systems can play a vital role in reducing CHIK transmission. The establishment of a standardised CHIK case definition is the first important step in surveillance. Possible and probable case definitions for CHIK should also be formulated to better manage surveillance data. (Grade B)*

A systematic review (Surveillance 2014) affirmed that effective and rigorous surveillance systems play a vital role in reducing CHIK transmission, although high quality research findings are needed to support the finding. Surveillance systems from the systematic review showed limited evidence in their effectiveness to meet the core functions, support functions, quality attributes and overall goals of surveillance systems, when evaluated against the WHO framework for monitoring and evaluating surveillance and response systems.

Guideline recommendation 4b: *Implementation of surveillance can detect and predict CHIK epidemics and may lead to triggering early implementation of effective disease response, prevention and control. Legislative requirement to notify health care authorities of suspected and confirmed CHIK cases within 24 hours may be a good strategy to enhance the effectiveness of CHIK surveillance systems in countries that have experienced indigenous CHIK outbreaks.*

(Grade B)

Information reported to the surveillance system is more likely to be timely, complete and representative of the actual CHIK situation to inform surveillance response and disease control strategies.

Guideline recommendation 4c: *To better manage surveillance data, clear reporting on the registration of CHIK patients into a public health record is recommended. (Grade B)*

Guideline recommendation 4d: *Routine vector surveillance before CHIK cases happen should be strengthened to avoid delay in timeliness of first response and control efforts. (Grade B)*

Guideline recommendation 4e: *Current CHIK surveillance systems should include periodical critical evaluation by public health authorities to strengthen surveillance capability and capacity. The evaluation will need to address the performance and usefulness of surveillance systems, as well as the logistical, administrative, and communicative gaps. (Grade B)*

Guideline recommendation 4f: *Monitoring both imported and indigenous CHIK cases is important as international travel plays an important role in the importation of CHIK cases from other countries to local territories. (Grade B)*

DOMAIN E: MOSQUITO CONTROL

Guideline recommendation 5a: *Some single and combined mosquito control interventions can be effective in short-term transitory control to reduce immature and adult Aedes albopictus and Aedes aegypti mosquitoes, as reported in a systematic review (EControl 2014). (Grade B)*

Guideline recommendation 5b: *The chemical adulticides fenitrothion, propoxur deltamethrin and DDT may be recommended for use against Aedes aegypti and Aedes*

albopictus mosquitoes. However, metabolic resistance to deltamethrin and DDT makes them less effective as chemical larvicides. (Grade B)*

Guideline recommendation 5c: *Three chemical larvicides, temephos, fenthion and malathion, are effective and are recommended for use in CHIK mosquito control. (Grade B)*

Guideline recommendation 5d: *Biological larvicides may be used in CHIK mosquito control, according to the decreasing order of potency against Aedes aegypti fourth instar larvae: Bti, Sabinene, Beta-bisabolol, Borneol, Biofloratriene, crude potash alum, standard potash alum and Clausena dentate essential oil. (Grade B)*

Guideline recommendation 5e: *Poecilia (with supporting education) is effective and sustainable in mosquito control. Proper water storage practices, focused information, education and communication with Poecilia introductions and vector sanitation involving the local administration and community may be good strategies for Aedes aegypti control.* (Grade B)*

Guideline recommendation 5f: *Pyriproxyfen-treated bed nets may be recommended for use to decrease egg hatching in adult Aedes albopictus females and increase pupae mortality.* (Grade B)*

Guideline recommendation 5g: *Nighttime ULV adulticiding using a chemical adulticide, DUET™ may be effective in reducing Aedes albopictus adult mosquitoes and may be considered for use in integrated pest management programs and during disease epidemics.* (Grade B)*

Guideline recommendation 5h: *Intensive mosquito control operations combining all chemical, biological and habitat control appear to be effective in reducing Aedes albopictus eggs and adult populations. (Grade B)*

6.5. Discussion

Practice guidelines are intended to provide reliable and authoritative guidance to clinicians and public health professionals for use in decision-making.[242, 243] Unfortunately, quality assessment of CHIK guidelines showed low methodological quality that was below expected standards.

Woolf et al. 1999 highlighted that "the greatest danger of flawed clinical guidelines is to patients. Recommendations that do not take due account of the evidence can result in suboptimal, ineffective, or harmful practices."[145(p529)] Low r*igour of development* is an emphasised problem in CHIK guidelines that can be resolved if the acceptance and publication of guidelines required the fulfilment of reporting criteria for guideline development. One reporting criterion that should be fulfilled is the use of best available evidence from studies, including systematic reviews, as the foundation for the formulation of guideline recommendations. The need for a systematic and rigorous guideline development process involving the commissioning of systematic reviews and synthesis of evidence summaries was emphasised in the recently published *WHO handbook for guideline development*[147] in 2012. An intentional effort to ensure that guideline recommendations are informed by evidence is essential to ensure that CHIK patients will receive point-of-care supported by research evidence. To ensure *rigour of development*, two approaches to critically evaluate evidence quality and formulate guideline recommendations would be the use of AGREE II instrument and following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[147] There is a persistent need to develop evidence-based clinical guidelines, for example, by using systematic methods to search for evidence, report criteria for evidence selection, describe the strengths and limitations of evidence, describe formulation methods for recommendations, show derivation of recommendations based on supporting evidence and provide a procedure for updating the guideline.[151]

In the second section of content analysis for the development of evidence-based guideline recommendations for CHIK, several concerns emerged. It was difficult to be detailed in the guideline recommendations due to varied evidence quality and inadequate reporting from the primary studies in systematic reviews. Where evidence existed for the indication of clinical or public health circumstance in which an intervention should be applied in a certain population, the evidence was incorporated into the guideline recommendation. Cost evaluations on specific interventions, particularly on pharmacological and surveillance interventions, were sought but were minimally covered in the included primary studies of systematic reviews; hence the formulated guideline recommendations could not take into account cost-effectiveness. Assessed CHIK guidelines also revealed no costing information tied to the recommended interventions that would benefit developing or underdeveloped countries. Guideline recommendations should be peer-reviewed and pilot-tested before they are approved for use in international guidelines.

Evidence-based guidelines can be effective in improving healthcare quality.[106, 143, 145] However, application of guideline recommendations may be challenging and may involve a host of factors, from clinicians' behaviour to guidelines, to organisational and economic considerations.[244] A study evaluating guidelines for family medicine showed that 67% of decisions made were in accordance with guideline recommendations.[106] With inordinate efforts put into synthesising the evidence for accurate guideline recommendations, it is crucial to ensure that every CHIK patient receives the best treatment informed by best available evidence and that people at risk of CHIK can be assured that the best preventive and control strategies are in place to reduce CHIK transmission.

6.6. Conclusion

Methodological quality and reporting of CHIK guidelines require improvement, particularly in areas of *rigour of development*, *editorial independence*, *applicability* and *stakeholder involvement.* Twenty guideline recommendations have been formulated on

the basis of this content analysis. Some recommendations from guidelines may become outdated as new, conflicting or controversial research findings emerge. Hence, a regular update and improvement of guidelines is important to keep abrEast with the recent evidence from new or updated systematic reviews.

7 Discussion and conclusion

7.1. Exposition

This chapter presents a general overview for the thesis. Applying research evidence into CHIK management decision-making is advocated, followed by a review of the unmet needs for knowledge investigated through the series of JBI-informed systematic reviews and content analysis. Consequently, strategies to improve the transfer of research evidence into practice and the implications for practice are discussed. Lastly, recommendations for future research in CHIK management are proposed.

7.2. Evidence-based decision-making

Health care systems worldwide have failed to optimally utilise research evidence in decision-making.[245] As pressure to improve health care continues to rise, greater efforts by clinicians, nurses and other health care professionals to incorporate appraised information in their routine clinical and public health decisions is increasingly necessary.[246] Knowledge translation is a complex process that promotes evidence-based decision-making and involves the use of the best available evidence in individualised patient care.[247] Research evidence that is timely, relevant and within reach is increasingly crucial to guide health care decisions.[248] Conventional but unsupported practices that are not beneficial or even harmful to patients have been uncovered through research. For example, evidence-based studies had found no credible evidence to support the use of statins in treatment of cardiovascular diseases[249] and the use of homeopathy in the treatment of diseases.[250]

While CHIK research has gained increased attention due to epidemics in the past decade, the establishment of effective interventions based on the best available international evidence to guide practice and research has never been achieved (Chapter 1). To augment evidence-based decision-making for CHIK management (Chapter 1, Section 1.2), this thesis highlights the findings of a series of systematic reviews in establishing the effectiveness of various management interventions, particularly in the

prime domains of clinical manifestation management, early diagnosis of disease, disease education, surveillance and mosquito control.

7.3. Prioritising health care needs and addressing translation gaps[251]

The JBI model of evidence-based health care and its close association with three translation gaps, as shown in Figure 7.1, provided the conceptual framework to achieve the thesis objectives:

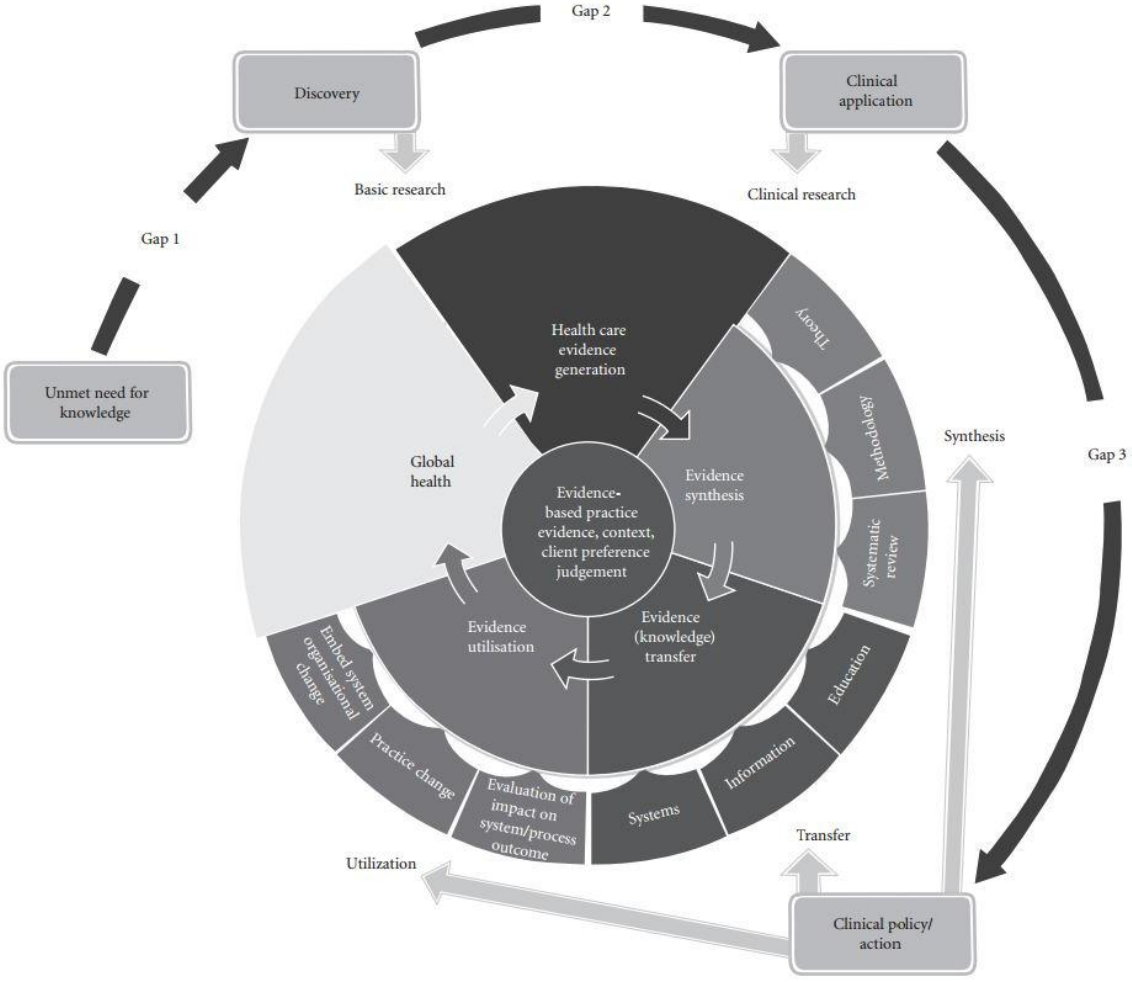

Figure 7.1. Relationship between translational science and evidence-based health care[251(p5)]

Gap 1: Unmet need for knowledge to discovery

Much of this research interest grew out of a national public health perspective against a background of CHIK outbreaks worldwide and the questionable effects of CHIK management interventions. This project identified the unmet need for knowledge in effective CHIK management interventions. Unmet health care needs are "the differences between the services judged necessary and the services actually received, and stemmed from barriers related to accessibility, availability and acceptability."[252(p2017)] Recognising the need for scientific knowledge is the first initiative to drive the translational science and evidence-based health care cycles.

Gap 2: Discovery to clinical application

A sizeable number of existing primary studies generated empirical evidence for the effectiveness of various CHIK interventions; however, many had small sample sizes, were associated with lower levels of evidence or had questionable methodological quality. As systematic reviews can address the deficiencies of primary studies while avoiding investing unnecessary capital and resources on primary research, the conduct of systematic reviews was found to be ideal in answering research questions on the effectiveness ofinterventions. The findings of the systematic reviews and content analysis are summarized in Gap 3 below.

Gap 3: Clinical application to clinical policy/action

Evidence synthesis

Evidence synthesis (evidence evaluation and analysis) is the main procedure of the research presented in the thesis. Evidence synthesis follows the three core elements: (i) theories corroborating evidence synthesis (Chapter 2); (ii) methodology in analysing evidence from heterogeneous sources (Chapter 2); and (iii) the development of systematic reviews (Chapters 3, 4 and 5).

A series of three systematic reviews examining the effects of therapeutics, prevention and control measures for CHIK was undertaken. The first systematic review

investigated the best available evidence for effectiveness of the therapeutics, early diagnosis of disease and disease education on HRQoL of patients with any of the seven AAIs, including CHIK. The findings of this systematic review as presented in Chapter 3 demonstrate that although clinical manifestations management had positive effects on 12 HRQoL domains at varying follow-up periods, the included studies also suggested harm associated with several routine symptomatic drugs and, specifically, that no benefits were observed from chloroquine treatment in acute CHIKV infection. No affirmative conclusions could be determined for the effects of early diagnosis of disease and disease education, due to the dearth of evidence.

Besides disease management interventions, surveillance and mosquito control are the two other public health protection strategies known to effect clinical and public health outcomes. Hence, phase II research focused on the systematic reviews on the effects of public health surveillance systems (Chapters 4) and mosquito control strategies (Chapter 5) specific to CHIK.

To evaluate the effects of surveillance systems in CHIK, epidemiological data from the surveillance systems systematic review were evaluated against the evaluation indicators within the WHO framework for monitoring and evaluating surveillance and response systems. From the included studies, evidence of epidemic unpreparedness, delayed response and control, challenging coordination, untimely surveillance, poor positive predictive value and lack of representativeness of surveillance systems was found. These results were consistent with published research[19, 35, 124], especially in India and La Reunion Islands, the localities of large CHIK epidemics. Limited evidence was found on the effectiveness of surveillance systems to meet the core functions, support functions, quality attributes and overall goals. The next step of research was to critically review the effects of mosquito control measures adopted against CHIK.

Mosquito control measures to reduce mosquito populations implicated in the human-mosquito-human transmission of CHIKV were evaluated for their effectiveness,

because effective mosquito control measures can be indicated in vector and disease surveillance data. A diverse range of chemical, biological and habitat mosquito control measures were evaluated and stratified according to these named types and analysed according to their effects on particular growth stages of *Aedes aegypti* and *Aedes albopictus*. The systematic review demonstrates that current single and combined mosquito control strategies might be effective in short-term transitory control; however, evidence that is more concrete is required on long-acting mosquito control interventions and the sustainability of mosquito control efforts.

Evidence transfer

Clinical and public health decisions should be based on scientific evidence as much as possible, but research knowledge stays generally underutilised. Evidence transfer is a possible solution to common barriers to using evidence in practice. Besides circulating information, the evidence transfer process outlines the best conduits of data delivery, such as guidelines, to identified receivers of the evidence to fulfil two needs: education, and information via team management systems (Figure 7.1).

Since guidelines are an important source of evidence transfer for health care decision-making to improve patient care, ensuring that guidelines meet expected quality standards remains paramount.[244, 253] For the phase III research, content analysis (Chapter 6) was undertaken to assess the quality of existing guidelines for CHIK management and propose new guideline recommendations. A striking finding was the limited reference to research evidence by guidelines and their low methodological quality. The inadequacy of basing guideline recommendations on poor quality evidence has been identified in numerous papers.[146, 148, 149, 253, 254]

Then, a comparative content-analytic approach was utilised to formulate 20 new CHIK guideline recommendations. They stressed using interventions that have been shown to be effective in improving HRQoL outcomes, meeting process measures from the

WHO framework for monitoring and evaluating surveillance, and response systems for decreasing mosquito populations.

7.4. Implications for evidence synthesis

7.4.1. Improvements in effectiveness primary research

The systematic reviews presented in Chapters 3, 4 and 5 reveal methodological limitations linked to the available empirical data from primary studies. A recurrent finding across the systematic reviews was the absence of high quality RCTs, and the prevalence of observational and descriptive studies in the effectiveness of interventions for CHIK. Small or inadequate sample sizes were also observed, resulting in under-powered studies insufficient to detect a true effect. Poor reporting of the delivery of interventions (e.g. drug administration route, dosage and frequency, as well as application dosage of mosquito control measures) was found, which can lead to compromised systematic review findings and hinder the usefulness of translated guideline recommendations. During quantitative analysis, non-uniform summary statistics, absence of control groups and lack of baseline scores (for intervention and control groups) and inadequate pre-intervention measurements also characterised studies and complicated the interpretation of data.

Although not an emphasised outcome from the systematic reviews, it was found that most included studies failed to include economic considerations. Meaningful evaluation of the cost-effectiveness of interventions can only be conducted with plausible estimates of clinical effectiveness, hence allowing systematic reviews to provide an unequivocal edge in informing CHIK practice and guidelines.

Given the limited pool of effective CHIK interventions based on evidence, additional research will be required to validate potential and existing therapeutics. Continuous work in conducting effective research with the aim of providing effective and beneficial CHIK interventions during periods of epidemics and low seasons should be done with international collaboration amongst funding agencies, national

communicable disease programs, health care entities, research institutes, the academia and patients with CHIK. Intentional teamwork efforts can lead to transformation in clinical and public health practice patterns to reduce CHIK transmission and ultimately eradicate the disease.

7.4.2. Improvements in methodology for systematic review of effectiveness

Like other risk of bias assessments for systematic reviews, the JBI-MAStARI critical appraisal checklists are primarily suited for human clinical research and can also be used in epidemiological public health topics. However, systematic review questions spanning various health care fields and differing study designs will benefit from more specific critical appraisal assessment tools with customised checklist criteria as observed from the systematic review on mosquito control in Chapter 5.

Analysis of prevailing literature showed that systematic reviews on mosquito control for Dengue[255] and Malaria[256] failed to assess quality of included studies, possibly due to the unavailability of congruent methods to appraise the quality of epidemiological studies. While critical appraisal checklists and criteria continue to evolve to suit various public health needs, systematic reviewers should be encouraged to utilise the critical appraisal tools best suited for the research question to increase the credibility and impact of findings from epidemiological systematic reviews.

Well-conducted systematic reviews provide accurate and critical findings to defined focal questions and hence have real influence on clinical policy and action. Similar to other research study designs, systematic reviews may be subjected to risk of bias in either conduct or reporting and therefore provide misleading recommendations. Strategies to reduce the risk of bias include setting explicit a priori inclusion criteria, having two instead of one independent selector of eligible studies, interpreting well the generalisability of evidence and providing comprehensive quality reporting. It is also important to differentiate between a criterion that is not reported and a criterion that is

not met; the former does not imply the latter. Strict adherence to reporting guidelines such as the PRISMA statement help to overcome some limitations of a systematic review.

Looking methodologically at the literature in its entirety through a systematic process is a robust and reliable way to make informed decisions on CHIK management. The importance of systematic reviews in scientific research cannot be underestimated; the utilisation of evidence from systematic reviews in primary research proposals has become a mandatory requirement for seeking grants from well-known funding agencies, including the NIH (e.g. Research for Patient Benefit Programme) and the United Kingdom Medical Research Council (e.g. Global Health Trials Programme). Additionally, these systematic reviews can guide the development of guideline recommendations and crucial primary research questions that can improve patient outcomes.

7.5. Implications for evidence transfer

The knowledge transfer process as described by the JBI model of evidence-based healthcare (Figure 7.1) encompasses three features.[128] Firstly, the development of comprehensible and actionable informative statements can be encapsulated in full guidelines in the management of CHIK. Therefore, one potentially effective method to improve evidence transfer is the tailoring of clear and concise research findings that include explicit, functional and actionable steps or recommendations to specific beneficiaries.[248]

To increase reliability and reduce research bias, the formulation of guideline recommendations in the content analysis followed a systematic three-phase iterative approach of preparation, organisation and reporting of synthesised content, as described in Chapter 2, Section 2.4. The formulation of guideline recommendations requires *considered judgement*, a conceptual term coined by the Scottish Intercollegiate Guidelines Network (SIGN) to assist understanding on how guideline developers

actually derive their final recommendations, through evidence tables that incorporate their summarised opinions.[257] Surprisingly, many disease guidelines have avoided the explicit reporting of this gap in evidence transfer, possibly because: (1) No standardised reporting requirement has been mandated for guideline developers to follow; and (2) It is a tedious and time-consuming task. Derivation of recommendations should be documented in a transparent manner, including the use of coding forms and evidence tables.

The second feature of evidence transfer is tailoring guidelines to suit the target population's information needs. CHIK patients and the public are important stakeholders, being at the receiving end of interventions recommended in guidelines. One main criticism of existing CHIK guidelines is the lack of stakeholder involvement, particularly the evidence informing experiences and preferences of patients and public. This is also an issue faced by guideline developers of other diseases that can be solved one way by ensuring patient and public participation in the guideline development group. Additionally, guideline information delivered to target users (GPs, infectious disease specialists, epidemiologists and public health officials) needs to be of quality, through *rigour of development*. Guideline developers would benefit in producing quality guidelines by following internationally recognised guidelines for guidelines (e.g. the 23-item AGREE II tool[147]). Adherence to these guidelines would also reduce content variability across guidelines and increase uniformity in intervention standards.

None of the evaluated CHIK guidelines has been subjected to revision or updates since their first publication between the years 2008 - 2011. Recognising that the full guideline development process typically takes two to three years[147], authors of existing CHIK guidelines should be encouraged to update the guidelines with the monitoring of newly appraised evidence produced in published and unpublished sources and remove out-of-date information. According to the Infectious Diseases Society of America[258], the optimal frequency for reviewing and updating a guideline is every two years. Other guideline publishers such as WHO and SIGN have a longer time frame of

two to five years.[147, 257] As appropriate to the amount of new evidence generated for CHIK interventions, an update of CHIK guidelines every three years is recommended.

The third feature of evidence transfer is disseminating the information in economical ways. Information technology can speed up the updating process and make available electronically CHIK guidelines to developed and developing countries. In underdeveloped countries, dissemination alternatives such as paper-based information sheets, seminars and workshops can be explored to deliver the most up-to-date guideline recommendations to health care professionals and patients.

7.6. Conclusion

While CHIK research has gained increased attention due to epidemics in the past decade, the establishment of effective interventions based on best available international evidence has not been achieved. This dissertation comprehensively brings together the evidence synthesis and validation of effective CHIK-specific management interventions to inform decision-making in CHIK practice and research. Based on the JBI model for evidence-based health care, the JBI systematic methodology for conducting comprehensive systematic reviews of effectiveness was adopted to address primary concerns related to disease management interventions on HRQoL, surveillance and mosquito control strategies.

This thesis also contends there is a need for high quality effectiveness research with strong reporting requirements to translate the results into usable credible compendium for decision-making in clinical and public health practice and research. In addition, the use of appraised research evidence is advocated in clinical and public health practice. However, recommendations made in this thesis are limitated by time; hence, a regular update of systematic reviews to incorporate new findings of research and to cull outdated recommendations based on best available evidence is necessary to advance clinical practice. Raising the methodological quality through transparent, inclusive

reporting is a key strategy for objective extraction, synthesis and interpretation of primary result findings in the evidence synthesis process.

The degree to which CHIK treatments, prevention and control are based on evidence will determine short- and long-term benefits and outcomes for the patient and society. While there are gaps in research evidence identified in CHIK management interventions employed at the point-of-care, the methodologically rigorous systematic reviews and content analysis reported in this dissertation have revealed key implications for practice and research to strengthen clinical practice and health care decision-making in an era of evidence-based practice. Newly synthesised knowledge generated from this thesis is intended to serve as a comprehensive platform to inform health care decisions and national and international policies on the management of CHIK for the improvement of health outcomes of patients with CHIK.

Appendix I: JBI levels of evidence for effectiveness

New JBI Levels of Evidence

Developed by the Joanna Briggs Institute Levels of Evidence and Grades of Recommendation Working Party October 2013

PLEASE NOTE: These levels are intended to be used alongside the supporting document outlining their use. Using Levels of Evidence does not preclude the need for careful reading, critical appraisal and clinical reasoning when applying evidence.

LEVELS OF EVIDENCE FOR EFFECTIVENESS

Level 1 – Experimental Designs

Level 1.a – Systematic review of Randomized Controlled Trials (RCTs)

Level 1.b – Systematic review of RCTs and other study designs

Level 1.c – RCT

Level 1.d – Pseudo-RCTs

Level 2 – Quasi-experimental Designs

Level 2.a – Systematic review of quasi-experimental studies

Level 2.b – Systematic review of quasi-experimental and other lower study designs

Level 2.c – Quasi-experimental prospectively controlled study

Level 2.d – Pre-test – post-test or historic/retrospective control group study

Level 3 – Observational – Analytic Designs

Level 3.a – Systematic review of comparable cohort studies

Level 3.b – Systematic review of comparable cohort and other lower study designs

Level 3.c – Cohort study with control group

Level 3.d – Case – controlled study

Level 3.e – Observational study without a control group

Level 4 – Observational –Descriptive Studies

Level 4.a – Systematic review of descriptive studies

Level 4.b – Cross-sectional study

Level 4.c – Case series

Level 4.d – Case study

Level 5 – Expert Opinion and Bench Research

Level 5.a – Systematic review of expert opinion

Level 5.b – Expert consensus

Level 5.c – Bench research/ single expert opinion

Appendix II: JBI grades of recommendation

New JBI Grades of Recommendation

Developed by the Joanna Briggs Institute Levels of Evidence and Grades of Recommendation Working Party October 2013

JBI Grades of Recommendation	
Grade A	A 'strong' recommendation for a certain health management strategy where (1) it is clear that desirable effects outweigh undesirable effects of the strategy; (2) where there is evidence of adequate quality supporting its use; (3) there is a benefit or no impact on resource use, and (4) values, preferences and the patient experience have been taken into account.
Grade B	A 'weak' recommendation for a certain health management strategy where (1) desirable effects appear to outweigh undesirable effects of the strategy, although this is not as clear; (2) where there is evidence supporting its use, although this may not be of high quality; (3) there is a benefit, no impact or minimal impact on resource use, and (4) values, preferences and the patient experience may or may not have been taken into account.

The FAME (Feasibility, Appropriateness, Meaningfulness and Effectiveness) scale may help inform the wording and strength of a recommendation.

F – Feasibility; specifically:

- What is the cost effectiveness of the practice?
- Is the resource/practice available?
- Is there sufficient experience/levels of competency available?

A – Appropriateness; specifically:

- Is it culturally acceptable?
- Is it transferable/applicable to the majority of the population?
- Is it easily adaptable to a variety of circumstances?

M – Meaningfulness; specifically:

- Is it associated with positive experiences?
- Is it not associated with negative experiences?

E – Effectiveness; specifically:

- Was there a beneficial effect?

Appendix III: PRISMA statement checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix IV: JBI critical appraisal checklist for randomised controlled/pseudo-randomised trial

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix V: JBI critical appraisal checklist for comparable cohort/case-control

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix VI: JBI critical appraisal checklist for descriptive/case series

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix VII: JBI data extraction form for experimental/observational studies

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Appendix VIII: Search strategy for systematic review (as of 2 May 2013)

S/N	Databases	Block Building
1	PubMed	**1st search strategy:** (health-related quality of life[tw] OR HRQOL[tw] OR quality of life[mh] OR quality of life[tw] OR life quality[tw] OR life qualit*[tw]OR QoL[tw]) AND (disease management[mh] OR disease management[tw] OR symptom management[tw]) AND (*Alphavirus*[mh] OR *Alphavirus*[tw] OR *Alphavirus* infections[mh] OR *Alphavirus* infections[tw] OR arthritogenic *Alphavirus* infection[tw] OR arthritogenic *Alphavirus*[tw] OR *Alphavirus* arthritide[tw] OR *Alphavirus* arthritis[tw] OR Chikungunya OR o'nyong-nyong OR ross river OR barmah forest OR mayaro OR sindbis OR semliki forest) **1st search strategy results: 0 result** 2nd search strategy was used, essentially to combine the first 2 entities "quality of life" and "disease management" separated using the Boolean term "or" instead of "and": --- **2nd search strategy:** (health-related quality of life[tw] OR HRQOL[tw] OR quality of life[mh] OR quality of life[tw] OR life quality[tw] OR life qualit*[tw]OR QoL[tw] OR disease management[mh] OR disease management[tw] OR symptom management[tw]) AND (*Alphavirus*[mh] OR *Alphavirus*[tw] OR *Alphavirus* infections[mh] OR *Alphavirus* infections[tw] OR arthritogenic *Alphavirus* infection[tw] OR arthritogenic *Alphavirus*[tw] OR *Alphavirus* arthritide[tw] OR *Alphavirus* arthritis[tw] OR Chikungunya OR o'nyong-nyong OR ross river OR barmah forest OR mayaro OR sindbis OR semliki forest) **2nd search strategy results: 16 results**
2	Web of Science	**1st search strategy:** TS=(("health-related quality of life" OR HRQOL OR "quality of life" OR "life qualit*" OR QoL)

		AND ("disease management" OR "symptom management") AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest")) **1st search strategy results: 0 result** 2nd search strategy was used, essentially to combine the first 2 entities "quality of life" and "disease management" separated using the Boolean term "or" instead of "and": --- **2nd search strategy:** TS=(("health-related quality of life" OR HRQOL OR "quality of life" OR "life qualit*" OR QoL OR "disease management" OR "symptom management") AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest")) **2nd search strategy results: 14 results**
3	Scopus	TITLE-ABS-KEY (("health-related quality of life" OR HRQOL OR "quality of life" OR "life qualit*" OR QoL) AND ("disease management" OR "symptom management") AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest")) **1st search strategy results: 11 results** 2nd search strategy was used, essentially to combine the first 2 entities "quality of life" and "disease management" separated using the Boolean term "or" instead of "and": --- **2nd search strategy:** TITLE-ABS-KEY (("health-related quality of life" OR HRQOL OR "quality

		of life" OR "life qualit*" OR QoL OR "disease management" OR "symptom management") AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest")) **2nd search strategy results: 6 results**
4	ScienceDirect	("health-related quality of life" OR HRQOL OR "quality of life" OR "life qualit*" OR QoL) AND ("disease management" OR "symptom management") AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest") **1st search strategy results: 30 results** 2nd search strategy was used, essentially to combine the first 2 entities "quality of life" and "disease management" separated using the Boolean term "or" instead of "and": --- **2nd search strategy:** ("health-related quality of life" OR HRQOL OR "quality of life" OR "life qualit*" OR QoL OR "disease management" OR "symptom management") AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest") **2nd search strategy results: 31 results**
5	CINAHL	(TX "health-related quality of life" OR TX HRQOL OR TX "quality of life" OR TX "life qualit*" OR TX QoL) AND (TX "disease management" OR TX "symptom management") AND (TX "*Alphavirus*" OR TX "*Alphavirus* infections" OR TX "arthritogenic *Alphavirus* infection" OR TX "arthritogenic *Alphavirus*" OR TX "*Alphavirus*

		arthritide" OR TX "*Alphavirus* arthritis" OR TX Chikungunya OR TX o'nyong-nyong OR TX ross river OR TX "barmah forest" OR TX mayaro OR TX sindbis OR TX "semliki forest") **1st search strategy results: 345 results** 2nd search strategy was used, essentially to combine the first 2 entities "quality of life" and "disease management" separated using the Boolean term "or" instead of "and": --- **2nd search strategy:** (TX "health-related quality of life" OR TX HRQOL OR TX "quality of life" OR TX "life qualit*" OR TX QoL OR TX "disease management" OR TX "symptom management") AND (TX "*Alphavirus*" OR TX "*Alphavirus* infections" OR TX "arthritogenic *Alphavirus* infection" OR TX "arthritogenic *Alphavirus*" OR TX "*Alphavirus* arthritide" OR TX "*Alphavirus* arthritis" OR TX Chikungunya OR TX o'nyong-nyong OR TX ross river OR TX "barmah forest" OR TX mayaro OR TX sindbis OR TX "semliki forest") **2nd search strategy results: 529 results**
6	Cochrane Central Register of Controlled Trials	TITLE-ABS-KEY (("health-related quality of life" OR HRQOL OR "quality of life" OR "life qualit*" OR QoL) AND ("disease management" OR "symptom management") AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest")) **1st search strategy results: 1 result** 2nd search strategy was used, essentially to combine the first 2 entities "quality of life" and "disease management" separated using the Boolean term "or" instead of "and": --- **2nd search strategy:** TITLE-ABS-KEY (("health-related quality of life" OR HRQOL OR "quality of life" OR "life qualit*" OR QoL OR "disease management" OR "symptom management")

		AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest")) **2nd search strategy results: 1 result** (same result as 1st search strategy)
7	SciFinder	("health-related quality of life" OR HRQOL OR "quality of life" OR "life qualit*" OR QoL) AND ("disease management" OR "symptom management") AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest") **1st search strategy results: 0 result** 2nd search strategy was used, essentially to combine the first 2 entities "quality of life" and "disease management" separated using the Boolean term "or" instead of "and": --- **2nd search strategy:** ("health-related quality of life" OR HRQOL OR "quality of life" OR "life qualit*" OR QoL OR "disease management" OR "symptom management") AND (*Alphavirus* OR "*Alphavirus* infections" OR "arthritogenic *Alphavirus* infection" OR "arthritogenic *Alphavirus*" OR "*Alphavirus* arthritide" OR "*Alphavirus* arthritis" OR Chikungunya OR o'nyong-nyong OR ross river OR "barmah forest" OR mayaro OR sindbis OR "semliki forest") **2nd search strategy results: 0 result** Due to the limited number of words imposed in the search engine for "Research Topic" in SciFinder, we simplify the search strategy to the following: --- **3rd search strategy:** "health-related quality of life" AND "disease management"

	AND *Alphavirus* **3rd search strategy results: 0 result** No references were found containing all of the concepts of "health related quality", "life", "disease management" and "*Alphavirus*". However, there were **3 results** for references containing all of the concepts "life", "disease management" and "*Alphavirus*". The 3 results were examined and found not eligible for inclusion in the systematic review.
Total records	**0+16+0+14+11+6+30+31+345+529+1+1+0+0+0+3=987**

Appendix IX: Included studies

Baishya *et al.* 2010

Study method	Study design: Descriptive (Case series) Study start and stop dates: Not reported Approval by ethics committee: Not reported Epidemic/endemic, country: 2006-2007 epidemic, India Funding: Nil Study investigators were contacted for additional data.
Participants	Infection type: CHIK Number of participants: 13 Time since CHIK diagnosis: 163 (range 30-360) days after CHIK fever with lower urinary tract symptoms presentation Inclusion criteria: • Serologically confirmed cases of CHIK fever, without prior history of lower urinary tract symptoms and with lower urinary tract symptoms. Eligibility criteria related to intervention: Not reported Exclusion criteria: Not reported Gender: 9 male, 4 female Age reported during study, mean (range) years: 39.2 (30-70) Ethnicity/race: Not reported Education level: Not reported Employment status: Not reported Comorbidities: Not reported
Interventions	<u>Clinical manifestations management interventions</u> 13 CHIK patients with lower urinary tract symptoms (LUTS) were given various management interventions: • Urethral catheterization and anticholinergic Oxybutynin hydrochloride (0.1mg/kg/day) (n=1). • Supra pubic diversion, bladder training and chronic suprapubic catheter (n=2). • Suprapubic diversion, bladder training and voiding (n=3). • Timed frequent double voiding (n=2). • Alpha-blocker Tamsulosin (0.4mg) (n=3). • Clean intermittent catheterization (n=2).

	Length of intervention (mean): n=1 (Tamsulosin for 3.25 months); n=5 (Suprapubic catheterization and bladder training for 3 months); n=2 (Clean intermittent catheterization for 3.5 months); n=2 (Tamsulosin for 5 months); n=2 (Timed frequent double voiding); n=1 (Oxybutynin hydrochloride daily for 3 months) Length of follow-up: A mean of 11 months (1-24 months) Adherence: Not reported.
Outcomes	<u>Clinical outcomes</u> • Improvement in CHIK patients by the rate of successful urine void. • Voided volume (Mean): 197 ml. • Volume of post-void residue (Mean): 76 ml. • Presence of voiding symptoms. • Deterioration of renal function: 0 patients. • Mean serum creatinine level: 2.1mg/dl during follow-up compared to initial high levels at 2.8mg/dl. Overall, 11/13 CHIK patients had successful outcome as determined by complete voiding of urine without extra assistance while having good renal function. The remaining 2 CHIK patients who did not show significant improvement continued on regular monthly suprapubic catheterization. <u>Adverse outcomes</u> No adverse outcomes were reported.

Brighton *et al.* 1984

Study method	Study design: Non-randomized & non-controlled open experimental pilot study Study start and stop dates: Not reported Approval by ethics committee: Not reported Epidemic/endemic, country: Endemic, most likely South Africa Funding: Not reported Study investigators were not contacted for additional data.
Participants	Infection type: CHIK Number of participants: 11 Time since CHIK diagnosis: Estimated at least 5-8 years, since the patients had CHIK arthritis from 5-8 years Inclusion criteria:

	• Present with chronic CHIK arthritis with a typical history of an acute attack with severe joint pains. • Anti-CHIK IgM/IgG antibody titre. • Minimum of 5 painful joints, scored as at least moderately painful by the patient. • Morning stiffness of at least 15 minutes' duration. Eligibility criteria related to intervention: Not reported Exclusion criteria: Not reported Gender: 6 male, 5 female Age reported during study, mean (range) years: 44.3 (20-70) Ethnicity/race: White patients Education level: Not reported Employment status: Not reported Comorbidities: Not reported
Interventions	<u>Clinical manifestations management interventions</u> Chloroquine phosphate (250mg/day x 20 weeks) Patients were allowed to continue on their own NSAIDs treatment with the condition that the NSAID drug was in continuous use for the preceding 12 weeks before the study and the dosage remains unaltered. Length of intervention (mean): 20 weeks Length of follow-up: 4-weekly intervals for 20 weeks from baseline Adherence: Not reported.
Outcomes	<u>HRQoL domain scores and clinical outcomes</u> • Joint pain scored on a modified Ritchie articular index scale of 0-4. • Morning stiffness measured in minutes. • Global assessment by both doctor and patient. <u>Adverse outcomes</u> Side effects not reported. One patient withdrew at the 8th week and did not complete the study due to persistent headache. Noted that this patient had improved joint pain and stiffness up to her time of withdrawal.

Chang *et al.* 2010

Study method	Study design: Descriptive (Case report) Study start and stop dates: Not reported Approval by ethics committee: Not applicable

	Epidemic/endemic, country: Taiwanese imported case after travel to Malaysia Funding: Nil Study investigators were not contacted for additional data.
Participants	Infection type: CHIK Number of participants: 1 Time since CHIK diagnosis: 30 days Inclusion criteria: • CHIK nucleic acids in serum by RT-PCR. • Anti-CHIK IgM/IgG antibody titre by ELISA. Eligibility criteria related to intervention: Not reported Exclusion criteria: Not applicable Gender: Female Age reported during study, mean (range) years: 40 Ethnicity/race: Not reported Education level: Not reported Employment status: Not reported Comorbidities: Not reported
Interventions	Early diagnosis of disease: Early clinical and lab diagnosis Disease education: Education of clinicians in diagnosis and treatment Clinical manifestations management: Doxycycline (antibiotic) A 40 year old female patient at the hospital emergency room who returned from travel in Malaysia was presented with fever, rash on torso and bilateral arthralgia over her wrists, knees and ankles, the main clinical symptoms for CHIK. She also had headache, neck soreness, bilateral conjunctivitis, chills, cough with whitish sputum, dyspnoea, sore throat, and difficulty in walking. Bronchitis, influenza, Dengue fever, and CHIK fever were the initial suspects. Her high fever lasted for 3 days. Physical tests for blood pressure, heart rate, respiratory rate, temperature, were conducted and laboratory tests were carried out for haemoglobin level, platelet count, white blood cell count, prothrombin time, activated prothrombin time, aspartate amino transferase, alanine aminotransferase, electrolytes, and blood bacteria culture results. The only abnormalities were mild thrombocytopenia and mild anaemia. Hence, the probable diagnosis was CHIK fever, while suspecting other diseases such as bronchitis, influenza and Dengue fever. Doxycycline was used as an empirical antibiotic. A serological test for anti-CHIKV IgM or IgG using ELISA showed negative results during the initial fever, however, a positive test result was obtained from RT-PCR. 2 weeks later, a serological test for anti-CHIKV IgM or IgG using ELISA was carried out again, which proved positive for both CHIK IgM and IgG.

	Length of intervention (mean): 34 days under observation Length of follow-up: 30 days Adherence: Not applicable.
Outcomes	<u>Clinical outcomes</u> Bilateral ankle pain persisted for 30 days after discharge from the hospital Discharged without fever after a 4-day hospitalization 4 days of hospitalization <u>Adverse outcomes</u> No adverse reactions were reported.

De Andrade *et al.* 2010

Study method	Study design: Descriptive study (Cross-sectional) Study start and stop dates: June – July 2006 Approval by ethics committee: Yes, approval was given by the institutions ethics review board Epidemic/endemic: CHIK epidemic in 2005-2006, La Reunion Island (Overseas region of France) Funding: Not reported. Study investigators were contacted for additional data.
Participants	Infection type: CHIK Number of participants: 106 Time since CHIK diagnosis: Not reported Inclusion criteria: • Presented with any type of pain. • Anti-CHIK IgM/IgG antibody titre by ELISA. Eligibility criteria related to intervention: Not reported Exclusion criteria: • Signs of severe disease such as meningismus, intense headaches or hemodynamic instability. • Pain unrelated to CHIK such as rheumatic pain, muscular pain and migraines. • Diabetes. • Psychiatric illness. • Drug.

	• Alcohol abuse history. Gender: 27 male, 79 female Age reported during study, mean(SD) years: 47.3(11.9), range 19-73 Ethnicity/race: Not reported Education level: Not reported Employment status: Not reported Comorbidities: Not reported, mainly due to the exclusion criteria
Interventions	<u>Clinical manifestations management intervention</u> Participants reported taking the following pharmacological treatments for pain (80%): Antalgic drugs • Paracetamol (8%). • Dextropropoxiphen (6%). • Paracetamol + opioid (1%). • Tramadol (1%). Anti-inflammatory drugs • NSAIDS (22%). • Corticosteroids (40%). Anti-depressants • Tricyclic antidepressants (1%). • Antiepileptic drugs (1%). Participants reported taking the following non-pharmacological treatments for pain (3%): • Physical therapy (2%) • Acupuncture (1%) 17% of participants reported taking no pain treatment. Length of intervention: Not applicable Length of follow-up: Not applicable Adherence: Not applicable
Outcomes	<u>HRQoL domain scores</u> • Pain relief from disease management interventions, percentage: 52.79±27.19.

	• BPI mean duration of pain, days: 89±55.5 days. • BPI pain intensity subscale score, mean (SD): 5.8±2.1. • BPI pain interference subscale score, mean (SD): 6.31±1.88. • Short-form McGill Pain Questionnaire (SF-MPQ) pain total score, mean (SD): 12.34±5.40. • SF-MPQ sensory subscale score, mean (SD): 26.75±10.65. • SF-MPQ affective subscale score, mean (SD): 14.42±6.91. <u>Adverse outcomes</u> No adverse outcomes were reported.

De Lamballerie *et al.* 2008

Study method	Study design: Double-blind placebo-controlled randomized study Study start and stop dates: 20 May 2006; stop date was not reported. Approval by ethics committee: Approved by the French Health Products Safety Agency and Ethics/Protection of Patients Committee Epidemic/endemic, country: CHIK epidemic in 2005-2006, La Reunion Island (Overseas region of France) Funding: Funded by the French government, the University of Marseille, the Pole de Competitive Morpheme and Sanofi-Aventis France. Study investigators were not contacted for additional data.
Participants	Infection type: CHIK Number of participants: 54 (27 on chloroquine: 27 on placebo; it was reported that a sample size of 250 patients was needed to detect a difference of 1 day between the treatment and control groups.) Time since CHIK diagnosis: Not reported Inclusion criteria: • Adult patients between 18–65 years old. • Reside in La Reunion Island. • Have a body weight ≥60 kg. • Presented with acute CHIK febrile arthralgia. • Diagnosed with CHIK ≤48 hours. • Anti-CHIK IgM/IgG antibody titre by ELISA between day 1 and day 16 of the protocol.

	• CHIK nucleic acids in serum by RT-PCR between day 1 and day 16 of the protocol. Eligibility criteria related to intervention: No adverse reactions to chloroquine Exclusion criteria: Pregnant patients, patients with renal disorders, retinopathy or celiac disease Gender: Not reported Age reported during study, mean (range) years: Not reported Ethnicity/race: Not reported Education level: Not reported Employment status: Not reported Comorbidities: Not reported, mainly due to the exclusion criteria
Interventions	<u>Clinical manifestations management intervention</u> 27 CHIK patients received chloroquine treatment of 600 mg (one dose) at day 1, 600 mg (300 mg twice daily) at days 2 and 3, and 300 mg at days 4 and 5 (total dose: 2,400 mg). Length of intervention: 5 days Length of follow-up: 25-day follow-up with a day 200 telephone interview; Biologic investigations at days 1, 3, 6, and 16; clinical examination by a GP at days 1, 7, and 25; and clinical self-evaluation at days 1 to 5 (twice a day) and 6 to 14 (once a day). Adherence: Not reported
Outcomes	<u>Clinical outcomes</u> To evaluate efficacy of chloroquine treatment, duration of febrile arthralgia was determined. It was reported that the mean duration of febrile arthralgia was 4.3 days. There was no significant difference between the chloroquine treatment and placebo treatment, as mean duration of febrile arthralgia was 4.7 days for the treatment group and 3.9 days for the control group. Although 61% of patients in the treatment group declared that they still suffer from arthralgia at day 200, only 23% of the placebo group declared the same. However, it was still not statistically significant ($P<0.01$). It was also noted that the sample size of 54 was too small to conclude the efficacy of the chloroquine treatment. <u>Adverse outcomes</u> 7 patients in the treatment group suffered from moderate adverse reactions, mainly nausea and pruritus, the classical side effects of chloroquine treatment. Study concluded that there was no clear evidence to support chloroquine

	therapy for acute CHIK infections.

Ganu *et al.* 2011

Study method	Study design: Uncontrolled experimental study Study start and stop dates: December 2006 - December 2008 Approval by ethics committee: Yes Epidemic/endemic, country: 2006 epidemic, India Funding: Not reported Study investigators were contacted for additional data.
Participants	Infection type: CHIK Number of participants: 16 Time since CHIK diagnosis: Estimated at least 3 months from initial acute attack of CHIK arthritis Inclusion criteria: • Anti-CHIK IgM antibody titre. • CHIK arthritis for more than 3 months despite on NSAIDs and hydroxychloroquine treatment. • With CHIK arthritis-induced synovitis. Eligibility criteria related to intervention: Not reported Exclusion criteria: Patients with arthritis before CHIK infection or clinically diagnosed with similar illnesses like CHIK Gender: Not reported Age reported during study, mean (range) years: 50.93 (23-75) Ethnicity/race: Not reported Education level: Not reported Employment status: Not reported Comorbidities: Not reported
Interventions	<u>Clinical manifestations management interventions</u> Effectiveness of DMARDs (Sulfasalazine + Methotrexate) in treatment of post-CHIK chronic arthritis: • For the first 2 weeks, all 16 patients were given NSAIDs (Etoricoxib 90mg/day or Aceclopfenac 100mg 2x/day; oral tablet) and when needed for symptomatic relief after that. • For the first 2-4 weeks, steroids (Prednisolone oral tablet 5-10mg/day) were given to all patients and stopped thereafter for synovitis control. • Initially, all patients were given a combination treatment of Sulfasalazine (1-2gm/day in gradually increasing and divided doses) +

	Hydroxychloroquine (200mg/day). Patients with good response were continued on the combination treatment till 24 months. • Methotrexate (15-20 mg/weekly pulse therapy; oral/injection) was added after 3 months to patients with poor to moderate response to Sulfasalazine + Hydroxychloroquine treatment. Length of intervention (mean): 24 months Length of follow-up: First reviewed at 6th week after enrolment, followed by a bi-monthly follow-up for a mean of 18 months. Evaluation of disease and treatment was done at the baseline, 3rd, 6th, 12th and 24th month. Adherence: Not reported.
Outcomes	<u>HRQoL domain scores and clinical outcomes</u> • HAQ assessed tenderness joint count, swollen joint count, and erythrocyte sedimentation rate (ESR) and HAQ scores. • DAS scores of 4.8-7.4 showed moderate to severe disease from treatment. • Positive response of 71.4% to Sulfasalazine treatment and 12.5% to Sulfasalazine and Methotrexate combination treatment. For the combination treatment, 56.2% showed moderate response and 31.25% showed poor response. • 87.45% (14/16) of patients needed additional Methotrexate (15-20 mg weekly pulse therapy orally or via injection) after 3 months. Responses were good (10/14), moderate (3/14) and poor (1/14). <u>Adverse outcomes</u> No patients had worsening of symptoms or major drug adverse reactions after starting DMARDs or steroids.

Marimoutou *et al.* 2012

Study method	Study design: Retrospective cohort study Study start and stop dates: June 2006 – December 2008 Approval by ethics committee: Not recorded, however, study was approved by the French military health headquarters department of research. Epidemic/endemic, country: 2006 epidemic, La Reunion Island (Overseas region of France) Funding: French Health Military Headquarters (2008-RC-15). Study investigators were contacted for additional data.
Participants	Infection type: CHIK Number of participants: 382

	Time since CHIK diagnosis: 30 months Inclusion criteria: • All gendarmes included in the 2006 study with valid available mailing addresses. • CHIK patients were self-declared and their reliability of declaration was cross-checked with their serological tests. It was reported that 99% of 2008 CHIKV negative subjects were serologically negative in June 2006, and 73% of 2008 CHIKV positive subjects were serologically positive in June 2006. Eligibility criteria related to intervention: Not reported Exclusion criteria: Non-responders of the HRQoL questionnaire were excluded from analyses. Gender: 351 male, 31 female Age reported during study, median(interquartile) years: 42.8 (39-48) Ethnicity/race: Not reported Education level: Not reported Employment status: Gendarmes who were part or out of service as of 2006 Comorbidities: Out of all CHIK and CHIK negative Gendarmes who participated, 56 (8.8%) were overweight and 22 (5.8%) reported joint problems. 1% of the participants had a medical history of heart/respiratory diseases and 6.3% had bone fractures in the past.
Interventions	Early diagnosis of disease • GP (9.4 consultations/patient). Disease education • Functional re-education (8 consultations/patient). Clinical manifestations management intervention • Specialist (0.32 consultations/patient). • Acupuncture (0.7 consultations/patient). • Surgery (0.2 consultations/patient). • Emergency (0.3 consultations/patient). Length of intervention: Not applicable Length of follow-up: Not applicable Adherence: Not applicable
Outcomes	HRQoL domain scores • MOS-SF36 10-component subscale scores for physical function, role physical, body pain, general health, vitality, social function, role emotional,

	mental health, physical component summary and mental component summary. Outcomes were measured at 30 months for non-healed CHIK, healed CHIK and CHIK negative participants. <u>Adverse outcomes</u> • Joint pain and their limitations could last ≥2 years after CHIK infection. • Results of MOS-SF36 mental and physical component summaries scores were significantly impaired in CHIK patients. • 1/5 of CHIKV patients had chronic fatigue besides rheumatism. • The chronic symptoms of CHIK had increased healthcare consumption.

Menon *et al.* 2010

Study method	Study design: Descriptive (Case report) Study start and stop dates: Not reported Approval by ethics committee: Not applicable Epidemic/endemic, country: Epidemic, India Funding: Nil Study investigators were not contacted for additional data.
Participants	Infection type: CHIK Number of participants: 1 Time since CHIK diagnosis: 2 months 3 days Time beyond active treatment: 2 months Inclusion criteria: • Anti-CHIK IgM antibody titre in serum by MAC ELISA 5 days after disease onset. Eligibility criteria related to intervention: Not reported Exclusion criteria: Not applicable Gender: Male Age reported during study, mean (range) years: 5.5 Ethnicity/race: Not reported Education level: Not reported Employment status: Not reported Comorbidities: Not reported
Interventions	<u>Clinical manifestations management interventions</u> A 5.5-year-old boy, presenting with serious CHIK infection and evidence of probable CHIK-induced myocarditis and congestive heart failure, was given

	the inotropic drug infusion of dopamine (cardiac) and dobutamine (cardiac). Losartan (anti-hypertensive) and levocarnitine (supplement) medication were also given. Length of intervention (mean): 3 days under observation Length of follow-up: 2 months Adherence: Not reported
Outcomes	<u>Clinical outcomes</u> After 3 days of drug therapy, he improved symptomatically. At discharge from hospital, the child has no signs of cardiomegaly. A week later, he returned for follow-up and the repeat echocardiogram showed normal left ventricle function and mild mitral regurgitation. The child continued to be asymptomatic after 2 months. The study did not conclude on the effectiveness of drugs used to treat probable CHIK-induced myocarditis. Instead, the study concluded that CHIK might show severe clinical presentation such as cardiotropism even in young children with ordinary medical histories. <u>Adverse outcomes</u> No adverse outcomes were reported.

Mylonas *et al.* 2002

Study method	Study design: Prospective cohort study Study start and stop dates: November 1997 – April 2000[Approval by ethics committee: Yes, approval was given by the ethics committees of the Royal Australian College of GPs, the Queensland Institute of Medical Research, and the Princess Alexandra Hospital, Brisbane Epidemic/endemic, country: Nov 1997 – Apr 1999 endemic, Australia (Brisbane) Funding: Queensland Health, the Australian Rotary Health Research Fund (Arbovirus Prevention Research Grants), the Australian National Centre for International and Tropical Health and Nutrition, and the Queensland Institute of Medical Research Trust. Study investigators were contacted for additional data.
Participants	Infection type: RRV Number of participants: 67 Time since RRV diagnosis: 12 months Inclusion criteria: • Diagnosed with RRV disease by a GP in the greater Brisbane area based on clinical symptoms.

	• Positive results of paired anti-RRV IgM antibody titre in serum by ELISA. Eligibility criteria related to intervention: Not reported Exclusion criteria: Not reported Gender: 29 male, 38 female Age reported during study, mean (range) years: 41.6 (20-89) Ethnicity/race: Not reported Education level: Not reported Employment status: Full time (66%); Part-time (18%); Unemployed/retired (16%) Comorbidities: Premorbid medical conditions were documented in the first visit but were not clearly reported, saved for the proportion of patients with pain in the first visit interview and that 1 patient had a depression history or serious illness before RRV diagnosis. The study results showed similar pain profiles between patients with RRV alone and patients with RRV and its complications. For this systematic review, based on the definition of comorbidities explained in the systematic review, the systematic review primary author interpreted the misnomer comorbidity used in Mylonas *et al.* 2002 as complications arising from the dependent RRV disease itself. Hence, the MOS SF-36 and CLINHAQ scores for the 2 groups of patients (1 group with RRV disease alone and 1 group with RRV disease plus other conditions) were evaluated in the systematic review.
Interventions	<u>Clinical manifestations management interventions</u> Participants reported taking the following drug treatments: • NSAIDs (58%) 7.6 (7-22) weeks; the percentage of patients taking NSAIDs decreased over the 12 months after diagnosis, from 55% (initial interview), to 31% (1 month), 21% (2 months), 15% (3 months), 5% (6 months), and 2% (12 months). At each visit, from 70% to 100% of patients taking NSAIDs reported being satisfied with this treatment. • Paracetamol or aspirin (15%). • Corticosteroids (4%). • NSAIDs + aspirin/paracetamol (3%). • No conventional medication (21%). Length of intervention: Not applicable Length of follow-up: Not applicable Adherence: Not applicable

Outcomes	HRQoL domain scores • MOS-SF36 10-component subscale scores for physical function, role physical, body pain, general health, vitality, social function, role emotional, mental health, physical component summary and mental component summary. • CLINHAQ 10-component subscale scores for functional disability index, depression, anxiety, satisfaction with health, patient estimated health status, global severity, pain, fatigue, gastrointestinal symptoms and sleep problems. Outcomes were measured at 0 month, 1 month, 2 months, 3 months, 6 months and 12 months. Adverse outcomes One patient was hospitalized for pneumonia 6 months after RRV diagnosis. Complications of disease: Six months after diagnosis, 28/60 patients had mainly more chronic rheumatic conditions of osteoarthritis (n=3), rheumatoid arthritis (n=2), psoriatic arthritis (n=1), ankylosing spondylitis (n=1) and osteoarthritis plus psoriatic arthritis (n=1). Seven developed depression after RRV diagnosis. The following complications had a patient each: carpal tunnel syndrome, back pain and obesity, herniated disc, melanoma, pneumonia, hypercholesterolemia, polycystic ovaries, endometriosis, urinary tract infection, thrombocytopenia, allergy and pregnancy.

Padmakumar *et al.* 2009

Study method	Study design: Randomized uncontrolled clinical trial (Prospective randomized parallel-group study) Study start and stop dates: November 2007 – June 2008 Approval by ethics committee: Yes, approved by Institutional Ethics Committee of T.D. Medical College, Alappuzha Epidemic/endemic, country: CHIK epidemic in 2007, India Funding: Joint funding by the Ministry of Health and Family Welfare, Government of Kerala and National Rural Health Mission, Kerala. Study investigators were contacted for additional data.
Participants	Infection type: CHIK Number of participants: 120 Time since CHIK diagnosis: Not reported Inclusion criteria: • CHIKV fever within 6 weeks and CHIK joint pains, presenting with

	inflammatory polyarthritis affecting joints of upper or lower limbs or both. • 20-80 years old. • Haemoglobin ≥ 13 g/dL for women and ≥ 12 g/dL for men. • White blood cell (WBC) count > 4000 cells/mm. • Platelet count > 1.5 lakhs/mm^3. • Normal Alanine transaminase (ALT) and serum creatinine. • Negative urine pregnancy (females). • Negative Hepatitis B virus (HBV) and Hepatitis C virus (HCV) and Human immunodeficiency virus (HIV) blood tests. Eligibility criteria related to intervention: No paracetamol allergy, no influenza vaccination within prior 12 months, no treatment with antiarrhythmics, no cytotoxic medications Exclusion criteria: Significant renal (creatinine clearance < 30 ml/min) and hepatic disorders, class III/IV angina pectoris, uncontrolled hypertension, diabetes mellitus , congestive cardiac failure, stroke, transient ischemic attack within the last 6 months, pregnancy, lactation, rheumatoid arthritis, gout, gastric or duodenal ulcers, gall stones or hepatic disorders. Gender: 25 male, 95 female Age reported during study, mean (SD) years: 49.4 (10.55) Ethnicity/race: Not reported Education level: Most patients were from a lower socioeconomic stratum Employment status: 70.83% patients were either unemployed or manual labourers Comorbidities: Not reported, mainly due to exclusion criteria
Interventions	<u>Clinical manifestations management intervention</u> 4 groups of treatment: Group A: Aceclofenac (200mg/day; 2 doses) Group B: Aceclofenac (200mg/day) + Hydroxychloroquine (400 mg/day) Group C: Aceclofenac (200mg/day) + Prednisolone (10 mg/day) Group D: Aceclofenac (200mg/day) + Hydroxychloroquine (400 mg/day) + Prednisolone (10 mg/day) *Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID); hydroxychloroquine is an anti-viral drug; prednisolone is a corticosteroid Additionally,

	• Pantoprazole (40 mg/day; optional) was used to counteract gastric side effects of Aceclofenac. • Paracetamol (500 mg; maximum 3 tablets/day) was used to alleviate pain, to be consumed when needed. It was chosen as a rescue medication as it is a good analgesic lacking anti-inflammatory properties, which would not affect treatment efficacy assessment directly. During study duration, no other drug treatments such as nephrotoxic drugs, other NSAIDs, DMARDs, corticosteroids and immunosuppressant drugs were allowed. However, other drug treatments such as antacids, H_2 blockers, antihypertensive medications, insulin and oral hypoglycaemic agents were permitted. Length of intervention: 6 weeks Length of follow-up: 12 weeks; weekly follow-ups for the first 6 weeks, followed by a 6-week drug-free follow-up at week 8 and 12. Adherence: Patients were told to bring the empty strips to account for drugs use and to evaluate compliance.
Outcomes	<u>HRQoL domain scores</u> included: • VAS. • ADL. • IADL. <u>Clinical outcomes</u> included: • Paracetamol consumption. Outcomes were measured at baseline; weekly for the first 6 weeks; and the 8th week and 12th week • Group A: n=30 at baseline; n=28 week 3-6. • Group B: n=30 at baseline; n=28 week 3-6. • Group C: n=30 at baseline; n=29 week 2-6. • Group D: n=30 at baseline; n=29 week 3-6. <u>Adverse outcomes</u> No adverse outcomes were reported.

Ravichandran *et al.* 2008

Study method	Study design: Prospective cohort study Number of participants: 20 Study start and stop dates: Not reported. Approval by ethics committee: Approved by the ethics committee of Vijaya Hospital Epidemic/endemic, country: CHIK epidemic of 2006, India Funding: Not reported Study investigators were not contacted for additional data.
Participants	Infection type: CHIK Time since CHIK diagnosis: 2 weeks - 2 months from CHIK fever Inclusion criteria: • Patients who continued to have crippling lower limb pains and arthritis for at least two weeks after a fever. • Anti-CHIK IgM antibody titre by ELISA. Eligibility criteria related to intervention: No adverse reactions to chloroquine Exclusion criteria: • Patients who recovered spontaneously within two weeks after fever. • Critically ill patients. • Patients with systemic disease. • Pregnant patients. Gender: 11 male; 9 female Age reported during study, range (years): 27-72 (treatment); 25-65 (control) Ethnicity/race: Not reported Education level: Not reported Employment status: Not reported Comorbidities: Not reported
Interventions	<u>Clinical manifestations management interventions</u> In the treatment group, 10 CHIK patients were given the synthetic nucleoside analogue drug, ribavirin (200 mg 2x/day x 7days) All analgesics were stopped for the treatment group. The control group consisting of 10 similar CHIK patients during the same period continued to receive analgesics when required. Length of intervention: 4 weeks Length of follow-up: For the first 4 weeks, patients were evaluated weekly basis

	and were called again after 8 weeks Adherence: Not reported
Outcomes	HRQoL domain scores • Assessment of joint involved, joint pain, joint tenderness and swelling using an arthritis score of 0-5. Adverse outcomes No adverse outcomes were reported.

Sissoko *et al.* 2009

Study method	Study design: Retrospective cohort study Study start and stop dates: June – September 2006 Approval by ethics committee: No approval by an ethics committee was reported, however, the survey design used was approved by the French Data Protection Authority (Commission Nationale Informatique et Liberte) and the National Council for Statistical Information. Epidemic/endemic: CHIK epidemic in 2005, La Reunion Island (Overseas region of France) Funding: Supported by the Institut de Veille Saniataire. Study investigators were contacted for additional data.
Participants	Infection type: CHIK Number of participants: 147 Time since CHIK diagnosis: 15 months Inclusion criteria: • Patients ≥16 years old. • Anti-CHIK IgM/IgG ELISA antibody titre in serum. • CHIK nucleic acids in serum by RT-PCR . • Disease commencing between 1 March and 30 June 2005. • Telephone number provided in the database. • Oral informed consent for all participants and parents/guardians for participants <18 years old. Eligibility criteria related to intervention: Not reported Exclusion criteria: • Patients <16 years old. Gender: 45 male, 102 female

	Age reported during study, mean (SD) years: 52(15) Ethnicity/race: Not reported Education level (years): 0-6 (34%); 7-9 (42%); ≥10 (24%) Employment status: Student (3%); salaried employment (42%); unemployed (12%); retired (29%); homemaker (14%) Comorbidities: Not reported.
	Clinical manifestations management intervention Participants reported taking the following pharmacological and non-pharmacological treatments: • NSAIDs (78%). • Corticosteroids (23%). • Paracetamol (93%). • Medicinal plants (46%). • Hospitalization (15%). • Physical/occupational therapy (20%). Length of intervention: Not applicable Length of follow-up: Not applicable Adherence: Not applicable
Outcomes	HRQoL domains • Joint pain intensity using the NRS scale: i. Mild (83.3%). ii. Moderate (15.5%). iii. Severe (1.2%). • Instrumental activities of daily living (Lifestyle impact): i. Missed school/work (66.6%). ii. Household/daily activities (75%). • General health perspective At 15 months after disease onset, CHIK patients reported perceived satisfaction with the following treatments:

i. NSAIDs (36%).

ii. Corticosteroids (76%).

iii. Paracetamol (34%).

iv. Medicinal plants (31%).

v. Physical/occupational therapy (14%).

Clinical outcomes

43% experienced full recovery during interview.

Adverse outcomes

Adverse outcomes, in terms of complications of disease, were reported:

- Diabetes mellitus (22%).
- Hypertension (33%).
- Osteoarthritis (26%).
- Chronic cardiac disease (10%).

Additionally, 21% of CHIK patients reported at least 1 relapse and 36% reported permanent symptoms of CHIK, in terms of joint pain, morning stiffness and joint swelling.

The study did not conclude on the effectiveness of clinical manifestations management interventions used to treat CHIK. However, the study showed that treatment of rheumatic clinical manifestations was generally insufficient. 43% of CHIK patients had full remission after 15 months from disease onset and almost half of CHIK patients with persistent rheumatic pain had trouble in activities of daily living for more than 3 months. Concerning clinical manifestations management, perceived satisfaction with corticosteroids was much higher at any stage of CHIK. Only 1/3 of patients were satisfied with NSAIDs.

Soumahoro *et al.* 2009

Study method	Study design: Retrospective cohort study Study start and stop dates: March – June 2007 Approval by ethics committee: Ethics approval was hinged on another study, the SEROCHIK survey[259] Epidemic/endemic: CHIK epidemic in 2005-2006, La Reunion Island (Overseas region of France)

	Funding: Student grant from Pierre et Marie Curie University Study investigators were contacted for additional data.
Participants	Infection type: CHIK Number of participants: 398 (199 pairs) Time since CHIK diagnosis: 17 months (range 5-28 months) from acute phase of disease Inclusion criteria: • History of CHIK infection. • Serologically confirmed CHIKV infection by ELISA. • Matched CHIK negative subjects. Eligibility criteria related to intervention: Not reported Exclusion criteria: Not reported Gender: 196 male, 202 female Age reported during study, mean (range) years: 42 (2-91) Ethnicity/race: Not reported Education level: Not reported Employment status: Not reported Comorbidities: Not reported
Interventions	<u>Clinical manifestations management interventions</u> Participants were interviewed of their medical consumption for the past 12 months using a standardized questionnaire on 3 areas, reported in RR[95% CI]: • Taking analgesic (26%) 1.2 [1.0-1.4], P=0.42. • Medical consultations (80%) 0.9 [0.9-1.0], P=0.25. • Hospitalization (7%) 0.8 [0.5-1.2], P=0.57. Length of intervention: Not applicable Length of follow-up: Not applicable Adherence: Not applicable
Outcomes	<u>HRQoL domain scores</u> • MOS-SF12 physical component summary subscale scores. • MOS-SF12 mental component summary subscale scores. Outcomes were measured at the end of follow-up, of an average of 17 months (range 5-28). <u>Adverse outcomes</u>

	No adverse outcomes were reported.

Staikowsky *et al.* 2008

Study method	Study design: Descriptive study (Retrospective survey) Number of participants: 1745 participants; 567 Groupe Hospitalier Sud Reunion (GHSR) hospital staff had responded to the survey on behalf of their household members and themselves. Study start and stop dates: 1 April 2006 – stop date not reported Approval by ethics committee: Yes, approval was given by the scientific and ethics committee of GHSR. Epidemic/endemic: CHIK epidemic in 2005-2006, La Reunion Island (Overseas region of France) Funding: Little funding was reported. Study investigators were not contacted for additional data.
Participants	Infection type: CHIK Time since CHIK diagnosis: Not reported, however, it would be an estimation of less than 6 months as it was reported that 161 CHIK participants were infected between January – March 2006 and the survey was made available from 1 April 2006 onwards. Inclusion criteria: • GHSR staff and their household members. • CHIK patients (613/1745) self-declared based on their own observation of CHIK clinical signs or a medical diagnosis with or without serological confirmation during the epidemic. If a household member had contracted CHIK, the date of onset of first HIK symptoms, duration of arthralgia and CHIK relapses were recorded. Eligibility criteria related to intervention: Not reported Exclusion criteria: Not reported Gender: 48.6% male, 51.4% female Age reported during study, mean (SD) years: 30 (39.6) Ethnicity/race: Not reported Education level: Not reported Employment status: Not reported Comorbidities: Not reported
Interventions	<u>Clinical manifestations management interventions</u> 217/221 CHIK participants reported having medical prescription. 221 CHIK participants reported taking the following main pharmacological treatments: • Antalgic drugs i. Paracetamol (95.4%). ii. Morphine derivatives (3.7%).

	iii. Tramadol (1.4%). • Anti-inflammatory drugs. i. NSAIDs (55.3%). ii. Corticosteroids (27.7%) - to treat arthralgia. • Quinine i. Quinine + Thiamine (3.2%). • Synthetic anti-Malaria drugs i. Chloroquine (1.4%). ii. Hydroxychloroquine (0.5%). iii. Colchicines (0.9%). • Plants (Natural herbs) i. Morinda citrifolia (neem) (12.6%). ii. Cannabis sativa (marijuana) (10.4%). iii. Eugenia uniflora (pitanga) (6.3%). iv. Other plants such as aloe vera, benjoin, buis, cinnamon, lemon grass, eucalyptus, galabert, geranium, panax ginseng, quinquina, reine des pre´ s, lemon verbena. Five people (2.2%) also took propolis. In addition, some CHIK patients were prescribed both NSAIDs and corticosteroids (18.3%). Some CHIK patients took both paracetamol and morphine derivatives (3.6%). CHIK participants also reported taking the following non-pharmacological treatments: • Physiotherapy (13.1%). More CHIK patients with relapse or difficulty walking used physiotherapy. <u>Early diagnosis of disease</u> CHIK participants also consulted GPs (85.5%) and took duration of 9.9±8.7 days' sick leave. Length of intervention: Not reported Length of follow-up: Not applicable Adherence: Not applicable
Outcomes	<u>Clinical outcomes</u> Full recovery for 71/221 CHIK patients without any relapse or clinical manifestations for more than a month. <u>Adverse reactions</u> Relapse in 123/221 CHIK patients were defined by the observation of clinical manifestations of arthralgia (96.7% of cases), oedema (61%), fever (18.7%); and cutaneous presentation (5.7%). Mean number of relapses was 2.1±1.2 and mean

	time interval between recovery and relapses was reported to be 4.2±3.9 weeks (range 1-32). There was no statistically significant difference in the percentage of relapses in CHIK patient using corticosteroid therapy versus those who did not. 6 CHIK patients were hospitalised, with all developed fever, myalgia, asthenia and crippling arthralgia with walking difficulties; 5/6 had cutaneous presentation and neurological disorders; 4/6 had enlargement of the nodes and haemorrhage. Chronic form of CHIK was reported in 10% cases. The study did not conclude on the effectiveness of drugs used to treat CHIK. Instead, the study identified clues for the management of future CHIK cases by investigating the pharmacological prescriptions and herbal medicines from the surveyed CHIK patients. It was noted also in the study that the efficacy or association of the natural herbs to treat CHIK had not been studied.

Appendix X: Excluded studies

S/N	Excluded study
1	Ramachandran V, Malaisamy M, Ponnaiah M, Kaliaperuaml K, Vadivoo S, Gupte MD. Impact of Chikungunya on health related quality of life Chennai, South India. PloS one. 2012;7(12):e51519.

Reason for exclusion: Study investigators had declined giving the requested clarification, missing data and other assistance after a critical analysis on their published paper. The lack of addressing the gaps and the inadequate providence of strong primary data to substantiate the validity of evidence caused great concern. Hence, it was decided that the study was excluded based on insufficient outcome data.

Appendix XI: HRQoL instruments used in meta-analysis of included studies

No	Name of Instrument	Abbreviation	Domain/ Sub-scale	Direction of Response	Studies
1	**HRQoL**				
	Clinical Health Assessment Questionnaire	CLINHAQ	Rheumatic diseases - global severity	Lower scores indicate better status	Mylonas *et al.* 2002
	Health Assessment Questionnaire	HAQ	Overall HRQoL score	Lower scores indicate better status	Ganu *et al.* 2011
2	**Disease-specific quality of life**				
	Brighton *et al.* Joint Pain Assessment	-	Joint pain	Lower scores indicate better status	Brighton *et al.* 1984
	Brighton *et al.* Joint Morning Stiffness	-	Joint morning stiffness	Lower scores indicate better status	Brighton *et al.* 1984
	Clinical Health Assessment Questionnaire	CLINHAQ	Rheumatic diseases - gastrointestinal symptoms	Lower scores indicate better status	Mylonas *et al.* 2002
	Disease Activity Score	DAS28	Rheumatoid arthritis disease activity, tender joint count, swollen joint count and ESR	Lower scores indicate better status	Ganu *et al.* 2011
3	**Anxiety**				
	Clinical Health Assessment Questionnaire	CLINHAQ	Rheumatic diseases - anxiety	Lower scores indicate better status	Mylonas *et al.* 2002
4	**Depression**				
	Clinical Health Assessment Questionnaire	CLINHAQ	Rheumatic diseases - depression	Lower scores indicate better status	Mylonas *et al.* 2002
5	**Emotional functioning**				
	Medical Outcomes Study Short Form-12	MOS SF-12	Mental component summary	Higher scores indicate better status*	Soumaho ro *et al.* 2009

	Medical Outcomes Study Short Form-36	MOS SF-36	Mental component summary, mental health and role emotional	Higher scores indicate better status*	Marimou tou *et al.* 2012; Mylonas *et al.* 2002
6	**Fatigue**				
	Clinical Health Assessment Questionnaire	CLINHAQ	Rheumatic diseases - fatigue	Lower scores indicate better status	Mylonas *et al.* 2002
	Medical Outcomes Study Short Form-36	MOS SF-36	Vitality	Higher scores indicate better status*	Marimou tou *et al.* 2012; Mylonas *et al.* 2002
7	**General Health Perspective**				
	Brighton *et al.* Doctors' Assessment of Therapy	-	Doctors' Assessment of Therapy	Higher scores indicate better status*	Brighton *et al.* 1984
	Brighton *et al.* Patients' Assessment of Therapy	-	Patients' Assessment of Therapy	Higher scores indicate better status*	Brighton *et al.* 1984
	Clinical Health Assessment Questionnaire	CLINHAQ	Rheumatic diseases – patient estimated health status & satisfaction with health	Lower scores indicate better status	Mylonas *et al.* 2002
	Medical Outcomes Study Short Form-36	MOS SF-36	General health	Higher scores indicate better status*	Marimou tou *et al.* 2012; Mylonas *et al.* 2002
8	**Pain**				
	Clinical Health Assessment Questionnaire	CLINHAQ	Rheumatic diseases - Pain	Lower scores indicate better status	Mylonas *et al.* 2002
	Medical Outcomes Study Short Form-36	MOS SF-36	Body pain	Higher scores indicate better status*	Marimou tou *et al.* 2012; Mylonas

					et al. 2002
	Visual Analog Scale	VAS	Pain	Lower scores indicate better status	Padmakumar *et al.* 2009
9	**Physical functioning**				
	Activities of Daily Living	ADL	Physical functioning	Higher scores indicate better status*	Padmakumar *et al.* 2009
	Clinical Health Assessment Questionnaire	CLINHAQ	Rheumatic diseases – functional disability index	Lower scores indicate better status	Mylonas *et al.* 2002
	Medical Outcomes Study Short Form-12	MOS SF-12	Physical component summary	Higher scores indicate better status*	Soumahoro *et al.* 2009
	Medical Outcomes Study Short Form-36	MOS SF-36	Physical functioning & physical component summary	Higher scores indicate better status*	Marimoutou *et al.* 2012; Mylonas *et al.* 2002
10	**Role functioning**				
	Instrumental Activities of Daily Living Scale	IADL	Role functioning	Higher scores indicate better status*	Padmakumar *et al.* 2009
	Medical Outcomes Study Short Form-36	MOS SF-36	Role physical	Higher scores indicate better status*	Marimoutou *et al.* 2012; Mylonas *et al.* 2002
11	**Sleep**				
	Clinical Health Assessment Questionnaire	CLINHAQ	Rheumatic diseases-sleep problem	Lower scores indicate better status	Mylonas *et al.* 2002
12	**Social functioning**				
	Medical Outcomes Study Short Form-36	MOS SF-36	Social functioning	Higher scores indicate better status*	Marimoutou *et al.* 2012; Mylonas *et al.* 2002

*The mean values for these scores were multiplied by -1 to ensure that all the HRQoL instruments measure the same direction of response.

Appendix XII: Data and analyses for uncontrolled studies

1 Health-related Quality of Life

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Overall quality of life change scores	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 0-6 months follow-up	2	46	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.97, -0.29]
1.1.2 7-12 months follow-up	2	47	Std. Mean Difference (IV, Random, 95% CI)	-0.86 [-1.18, -0.54]
1.1.3 13-24 months follow-up	1	17	Std. Mean Difference (IV, Random, 95% CI)	-1.21 [-1.73, -0.70]
1.2 CLINHAQ global severity subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.16, -0.30]
1.2.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-0.88 [-1.28, -0.48]
1.3 HAQ change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 0-6 months follow-up	1	17	Mean Difference (IV, Random, 95% CI)	-0.46 [-1.01, 0.09]
1.3.2 7-12 months follow-up	1	17	Mean Difference (IV, Random, 95% CI)	-0.83 [-1.36, -0.30]
1.3.3 13-24 months follow-up	1	17	Mean Difference (IV, Random, 95% CI)	-1.21 [-1.73, -0.70]

2 Disease-specific Quality of Life

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Overall disease-specific quality of life change scores	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 0-6 months follow-up	7	113	Std. Mean Difference (IV, Random, 95% CI)	-6.22 [-10.05, -2.40]
2.1.2 7-12 months follow-up	5	94	Std. Mean Difference (IV, Random, 95% CI)	-4.36 [-6.56, -2.17]
2.1.3 13-24 months follow-up	4	64	Std. Mean Difference (IV, Random, 95% CI)	-9.92 [-16.09, -3.75]
2.2 CLINHAQ gastrointestinal symptoms subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.57, 0.21]
2.2.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.55, 0.13]
2.3 Brighton et al. joint pain change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 0-6 months change scores	1	10	Mean Difference (IV, Random, 95% CI)	-9.40 [-17.18, -1.62]
2.4 Brighton et al. joint morning stiffness change duration (min)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.4.1 0-6 months follow-up	1	10	Mean Difference (IV, Random, 95% CI)	-15.30 [-30.82, 0.22]
2.5 DAS overall change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.5.1 0-6 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-1.33 [-3.84, 1.18]
2.5.2 7-12 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-1.63 [-2.27, -0.99]
2.5.3 13-24 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-2.17 [-2.75, -1.59]

2.6 DAS ESR change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.6.1 0-6 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-23.31 [-30.79, -15.83]
2.6.2 7-12 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-21.56 [-29.13, -13.99]
2.6.3 13-24 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-25.00 [-32.43, -17.57]
2.7 DAS swollen joint count change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.7.1 0-6 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-3.57 [-6.74, -0.40]
2.7.2 7-12 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-6.32 [-9.01, -3.63]
2.7.3 13-24 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-8.44 [-11.20, -5.68]
2.8 DAS tender joint count change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.8.1 0-6 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-5.48 [-9.38, -1.58]
2.8.2 7-12 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-6.87 [-10.20, -3.54]
2.8.3 13-24 months follow-up	1	16	Mean Difference (IV, Random, 95% CI)	-8.18 [-11.51, -4.85]

3 Anxiety

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 CLINHAQ anxiety subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-2.03 [-3.27, -0.79]
3.1.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-2.88 [-4.06, -1.70]

4 Depression

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 CLINHAQ depression subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-1.99 [-3.27, -0.71]
4.1.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-2.54 [-3.75, -1.33]

5 Emotional functioning

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Overall emotional functioning change scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1.1 0-6 months follow-up	3	87	Std. Mean Difference (IV, Random, 95% CI)	-10.31 [-18.98, -1.64]
5.1.2 7-12 months follow-up	3	90	Std. Mean Difference (IV, Random, 95% CI)	-13.68 [-25.12, -2.24]
5.2 MOS SF-36 mental component summary subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.2.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-5.44 [-13.09, 2.21]
5.2.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-6.41 [-14.04, 1.22]
5.3 MOS SF-36 mental health subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.3.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-16.35 [-28.69, -4.01]
5.3.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-19.50 [-31.81, -7.19]

5.4 MOS SF-36 role emotional subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.4.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-20.76 [-50.84, 9.32]
5.4.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-26.47 [-56.45, 3.51]

6 Fatigue

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 Overall fatigue change scores	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1.1 0-6 months follow-up	2	58	Std. Mean Difference (IV, Random, 95% CI)	-16.87 [-49.77, 16.03]
6.1.2 7-12 months follow-up	2	60	Std. Mean Difference (IV, Random, 95% CI)	-17.66 [-52.89, 17.58]
6.2 CLINHAQ fatigue subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.2.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-0.97 [-1.53, -0.41]
6.2.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-0.88 [-1.57, -0.19]
6.3 MOS SF-36 vitality subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.3.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-34.59 [-49.91, -19.27]
6.3.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-36.92 [-55.49, -18.35]

7 General Health Perspective

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Overall general health perspective change scores	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1.1 0-6 months follow-up	5	107	Std. Mean Difference (IV, Random, 95% CI)	-0.89 [-1.29, -0.48]
7.1.2 7-12 months follow-up	3	90	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-1.88, 1.73]
7.2 CLINHAQ patient estimated health status subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.2.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.16, -0.22]
7.2.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.27, -0.21]
7.3 CLINHAQ satisfaction with health subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.3.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-1.32 [-2.07, -0.57]
7.3.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-1.01 [-1.83, -0.19]
7.4 MOS SF-36 general health perspective subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.4.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-11.07 [-24.25, 2.11]
7.4.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-12.12 [-26.54, 2.30]
7.5 Brighton et al. patients' assessment of therapy change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.5.1 0-6 months follow-up	1	10	Mean Difference (IV, Random, 95% CI)	-1.00 [-4.01, 2.01]
7.6 Brighton et al. doctor's assessment of therapy change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.6.1 0-6 months follow-up	1	10	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.80, 0.20]

8 Pain

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Overall pain change scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1.1 0-6 months follow-up	3	172	Std. Mean Difference (IV, Random, 95% CI)	-7.52 [-11.56, -3.48]
8.1.2 7-12 months follow-up	2	60	Std. Mean Difference (IV, Random, 95% CI)	-27.56 [-79.90, 24.79]
8.2 CLINHAQ pain subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.2.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-1.20 [-1.27, -1.13]
8.2.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-1.23 [-1.32, -1.14]
8.3 MOS SF-36 body pain subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.3.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-49.54 [-60.81, -38.27]
8.3.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-54.65 [-67.17, -42.13]
8.4 VAS pain change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.4.1 0-6 months follow-up	1	114	Mean Difference (IV, Random, 95% CI)	-4.50 [-5.16, -3.84]

9 Physical functioning

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
9.1 Overall physical functioning change scores	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1.1 0-6 months follow-up	4	201	Std. Mean Difference (IV, Random, 95% CI)	-12.24 [-18.50, -5.98]
9.1.2 7-12 months follow-up	3	90	Std. Mean Difference (IV, Random, 95% CI)	-21.68 [-42.19, -1.17]
9.2 CLINHAQ functional disability index subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.2.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-0.69 [-0.98, -0.40]
9.2.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-0.72 [-1.04, -0.40]
9.3 ADL change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.3.1 0-6 months follow-up	1	114	Mean Difference (IV, Random, 95% CI)	-8.31 [-8.81, -7.80]
9.4 MOS SF-36 physical component summary subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.4.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-20.45 [-26.55, -14.35]
9.4.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-21.46 [-27.35, -15.57]
9.5 MOS SF-36 physical functioning subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.5.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-44.29 [-61.49, -27.09]
9.5.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-48.22 [-65.39, -31.05]

10 Role Functioning

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
10.1 Overall role functioning change scores	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1.1 0-6 months follow-up	2	143	Std. Mean Difference (IV, Random, 95% CI)	-31.48 [-87.24, 24.27]
10.1.2 7-12 months follow-up	1	30	Std. Mean Difference (IV, Random, 95% CI)	-62.47 [-86.22, -38.72]
10.2 IADL change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.2.1 0-6 months follow-up	1	114	Mean Difference (IV, Random, 95% CI)	-4.21 [-4.40, -4.03]

10.3 MOS SF-36 role physical subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.3.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-61.16 [-84.09, -38.23]
10.3.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-62.47 [-86.22, -38.72]

11 Sleep

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
11.1 CLINHAQ sleep problem subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.35, -0.37]
11.1.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-0.79 [-1.34, -0.24]

12 Social Functioning

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
12.1 MOS SF-36 social functioning subscale change scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1.1 0-6 months follow-up	1	29	Mean Difference (IV, Random, 95% CI)	-34.58 [-50.20, -18.96]
12.1.2 7-12 months follow-up	1	30	Mean Difference (IV, Random, 95% CI)	-33.35 [-50.38, -16.32]

Appendix XIII: Data and analyses for controlled studies

1 Emotional functioning

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Overall emotional functioning follow-up scores	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 13-24 months follow-up	1	324	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.21, 0.23]
1.1.2 25-36 months follow-up	3	1146	Std. Mean Difference (IV, Random, 95% CI)	0.68 [0.54, 0.82]
1.2 MOS SF-12 mental component summary subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 13-24 months follow-up	1	324	Mean Difference (IV, Random, 95% CI)	0.10 [-2.21, 2.41]
1.3 MOS SF-36 mental component summary subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	5.87 [3.65, 8.09]
1.4 MOS SF-36 mental health subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	11.06 [7.20, 14.92]
1.5 MOS SF-36 role emotional subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	13.86 [6.39, 21.32]

2 Fatigue

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 MOS SF-36 vitality subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	16.07 [11.33, 20.80]

3 General Health Perspective

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 MOS SF-36 general health perspective subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1.1 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	10.46 [6.10, 14.81]

4 Pain

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Overall pain change scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1.1 0-6 months follow-up	3	60	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.54, -0.33]
4.2 Arthritis joint pain relapse change scores	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.2.1 0-6 months follow-up	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.54, -0.33]

4.3 Arthritis joint swelling change scores	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.3.1 0-6 month follow-up	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-10.22, 9.14]
4.4 Patients free of analgesics change scores	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.4.1 0-6 months follow-up	1	20	Std. Mean Difference (IV, Random, 95% CI)	-3.00 [-21.03, 15.03]
4.5 MOS SF-36 body pain subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.5.3 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	28.40 [22.36, 34.44]

5 Physical functioning

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Overall physical functioning follow-up scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1.1 13-24 months follow-up	1	324	Std. Mean Difference (IV, Random, 95% CI)	0.27 [0.05, 0.49]
5.1.2 25-36 months follow-up	2	764	Std. Mean Difference (IV, Random, 95% CI)	0.91 [0.57, 1.24]
5.2 Arthritis mobility change scores	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.2.1 0-6 months follow-up	1	20	Std. Mean Difference (IV, Random, 95% CI)	-3.00 [-21.03, 15.03]
5.3 MOS SF-12 physical component summary subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.3.1 13-24 months follow-up	1	324	Mean Difference (IV, Random, 95% CI)	2.70 [0.51, 4.89]
5.4 MOS SF-36 physical component summary subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.4.3 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	6.46 [4.67, 8.24]
5.5 MOS SF-36 physical functioning subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.5.3 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	6.86 [3.77, 9.94]

6 Role Functioning

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 MOS SF-36 role physical subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1.1 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	22.70 [14.62, 30.77]

7 Social Functioning

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 MOS SF-36 social functioning subscale follow-up scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1.1 25-36 months follow-up	1	382	Mean Difference (IV, Random, 95% CI)	15.03 [9.61, 20.45]

Appendix XIV: Forest plots for uncontrolled studies

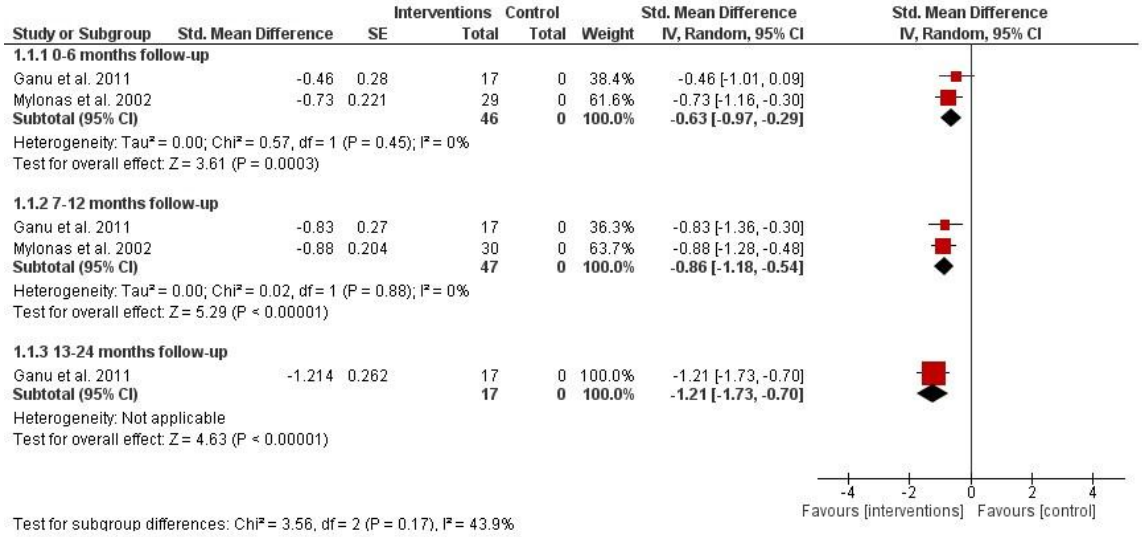

Figure 3.3. Forest plot of comparison: 1 Health-related Quality of Life, outcome: 1.1 Overall quality of life change scores

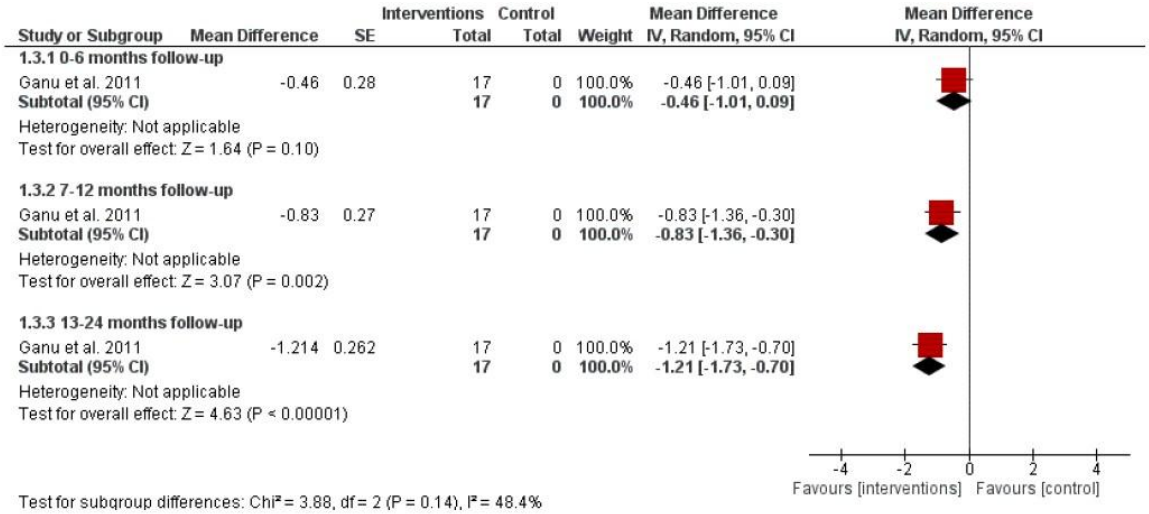

Figure 3.4. Forest plot of comparison: 1 Health-related Quality of Life, outcome: 1.3 HAQ change scores

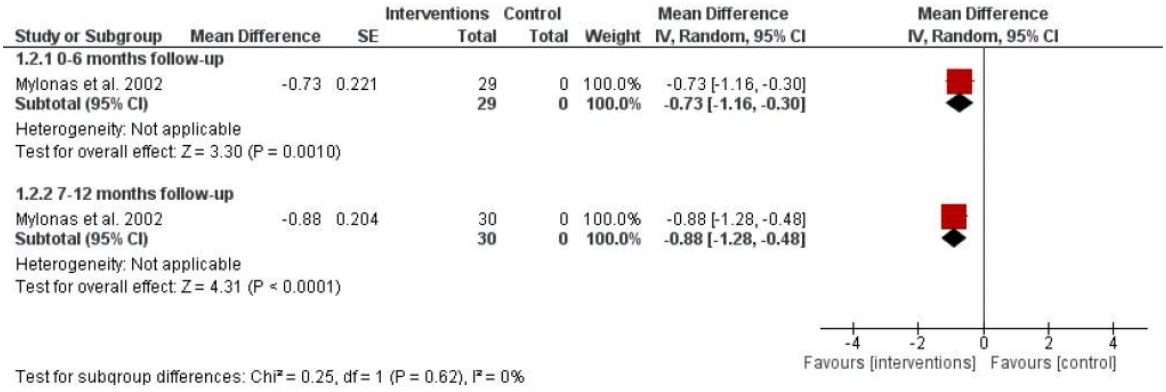

Figure 3.5. Forest plot of comparison: 1 Health-related Quality of Life, outcome: 1.2 CLINHAQ global severity subscale change scores

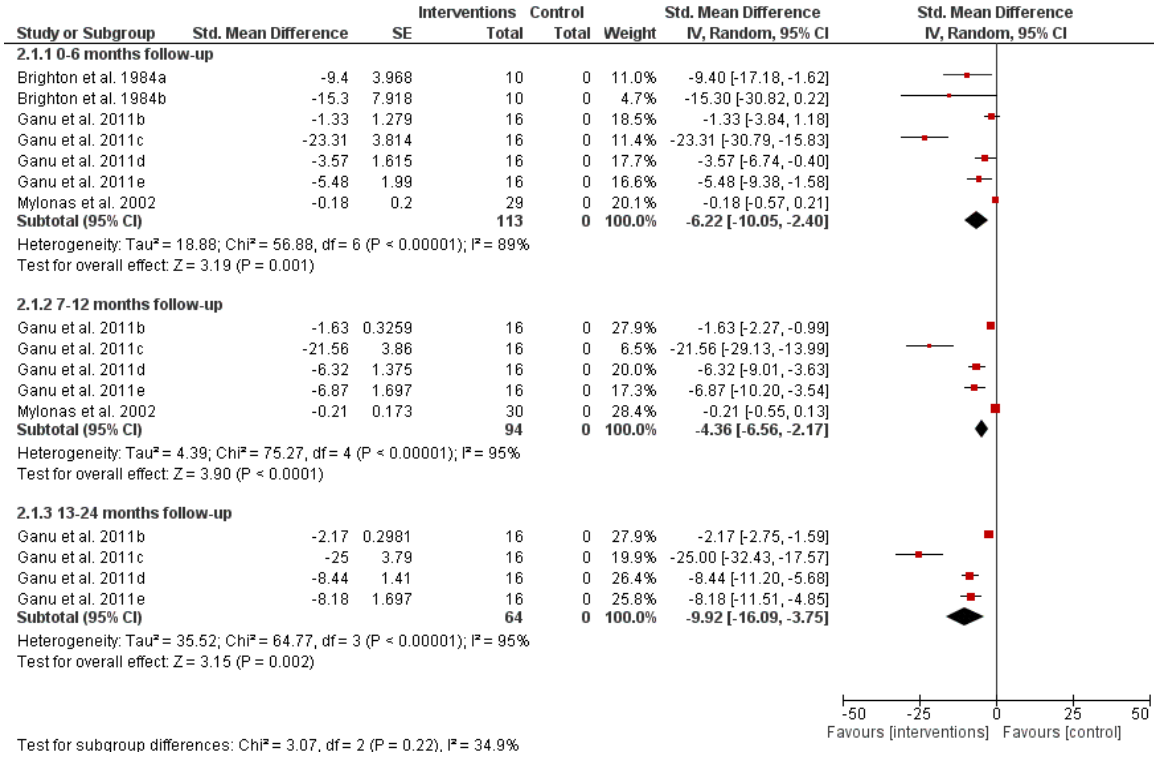

Figure 3.6. Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.1 Overall disease-specific quality of life change scores

Brighton *et al.* 1984a: Brighton *et al.* joint pain change scores

Brighton *et al.* 1984b: Brighton *et al.* joint morning stiffness change duration (min)

Ganu *et al.* 2011b: DAS overall change scores

Ganu *et al.* 2011c: DAS ESR change scores

Ganu *et al.* 2011d: DAS swollen joint count change scores

Ganu *et al.* 2011e: DAS tender joint count change scores

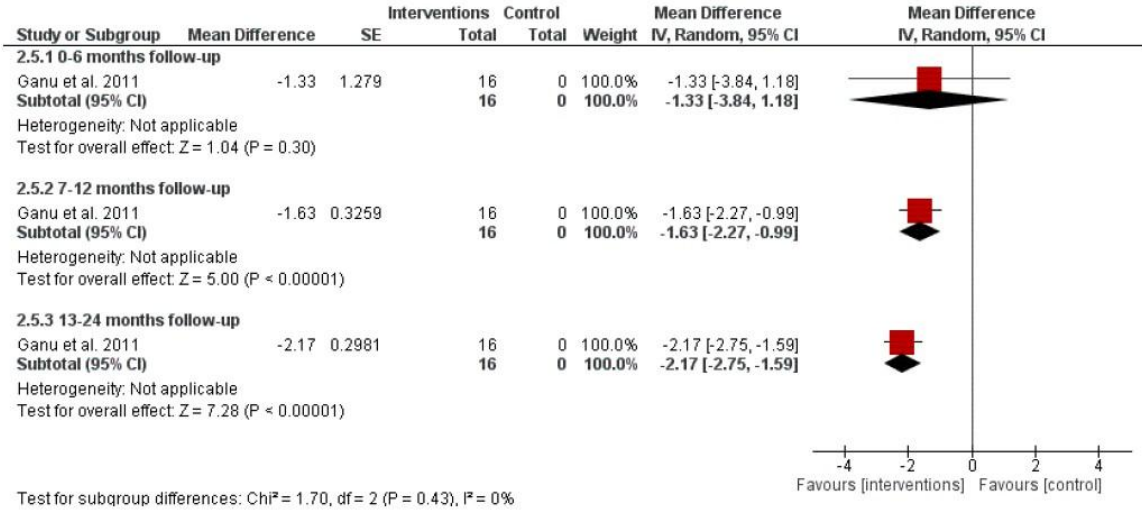

Figure 3.7. Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.5 DAS overall change scores

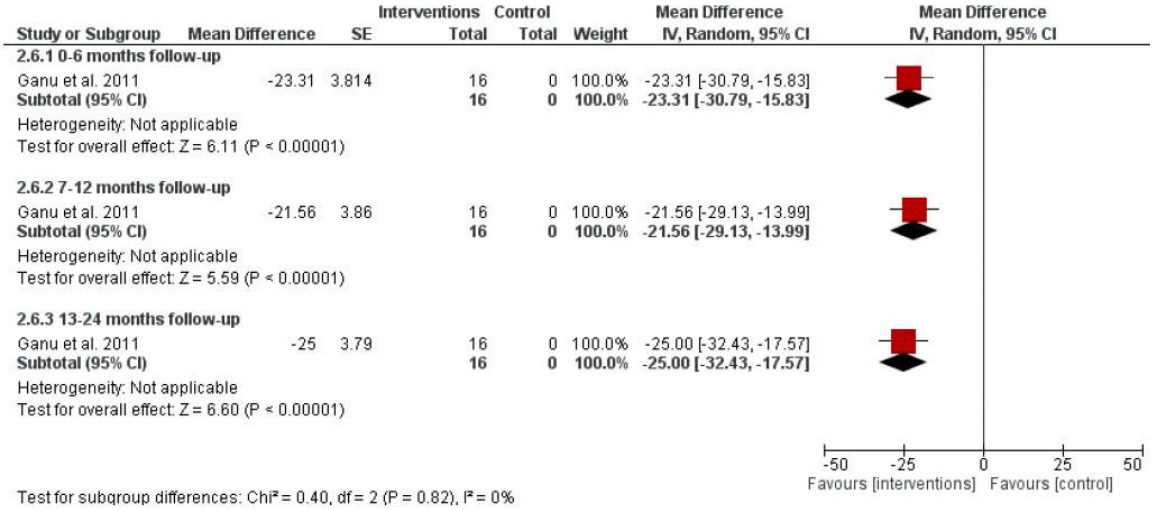

Figure 3.8. Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.6 DAS ESR change scores

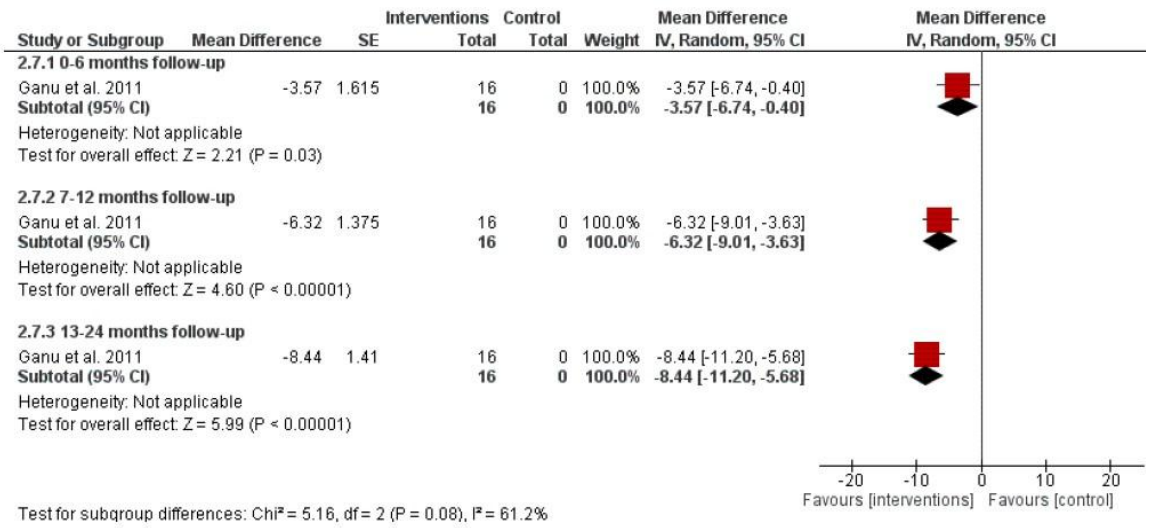

Figure 3.9. Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.7 DAS swollen joint count change scores

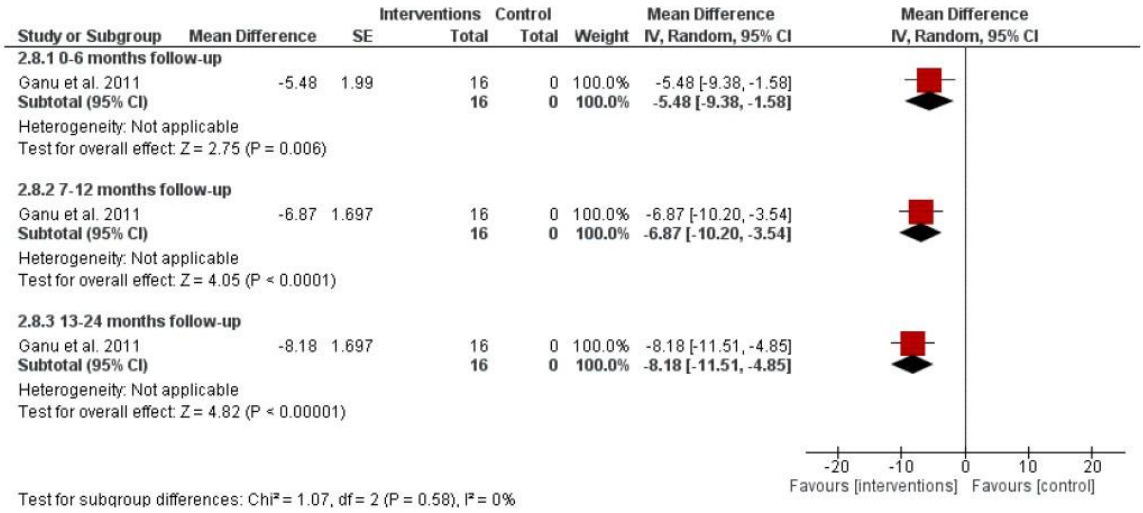

Figure 3.10. Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.8 DAS tender joint count change scores

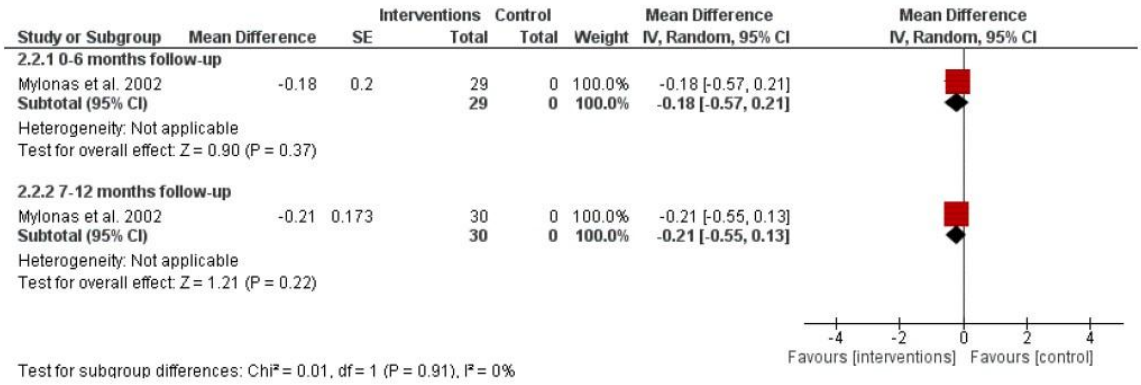

Figure 3.11. Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.2 CLINHAQ gastrointestinal symptoms subscale change scores

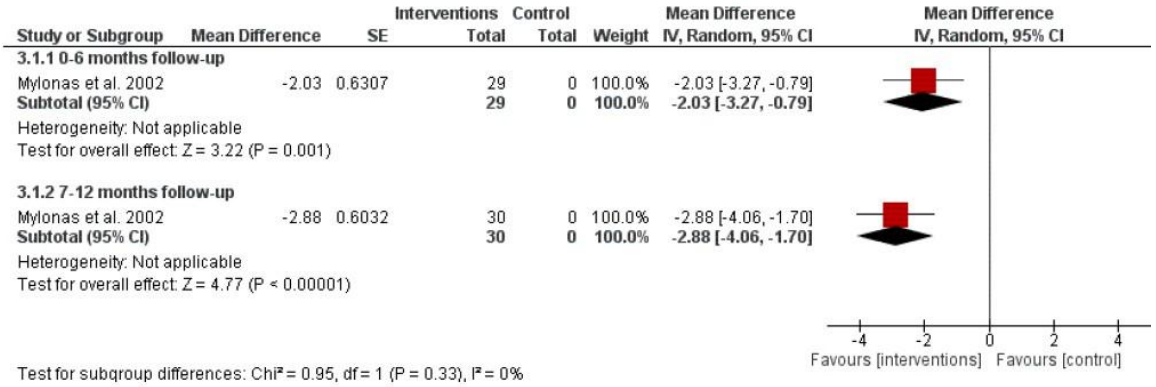

Figure 3.12. Forest plot of comparison: 3 Anxiety, outcome: 3.1 CLINHAQ anxiety subscale change scores

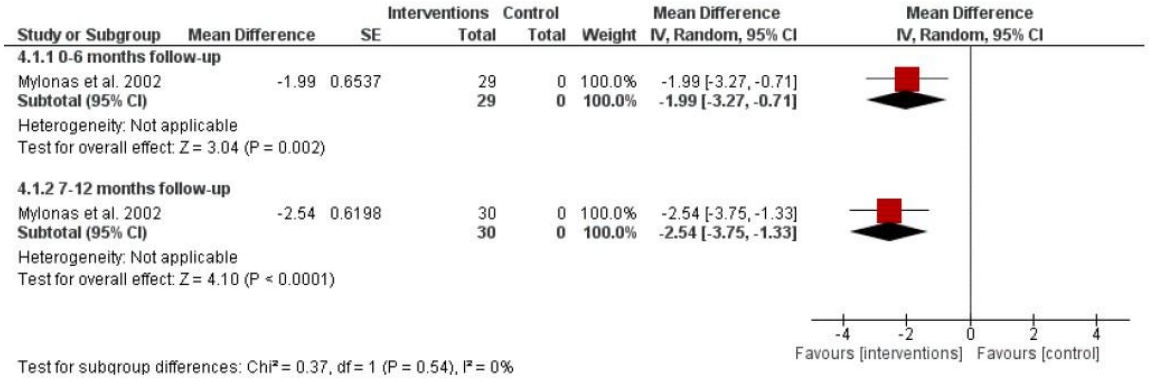

Figure 3.13. Forest plot of comparison: 4 Depression, outcome: 4.1 CLINHAQ depression subscale change scores

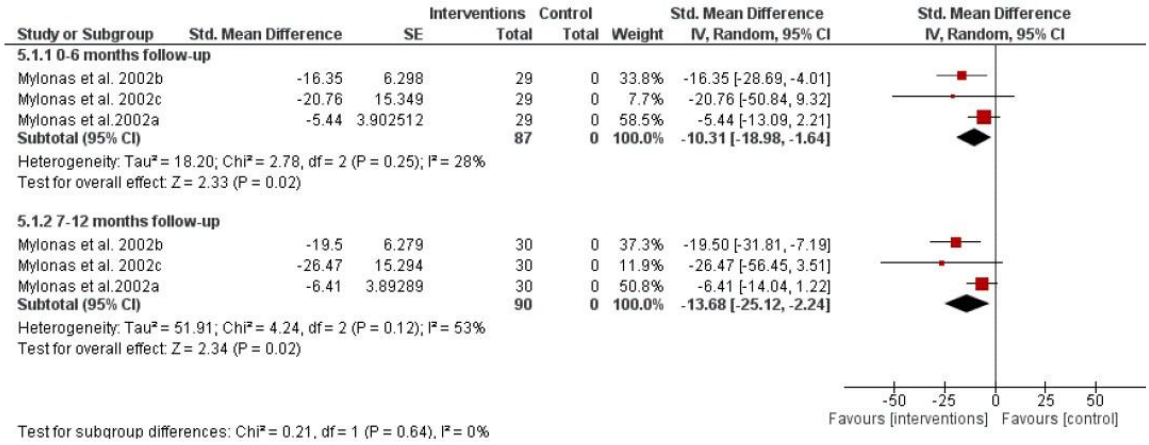

Figure 3.14. Forest plot of comparison: 5 Emotional functioning, outcome: 5.1 Overall emotional functioning change scores

Mylonas *et al.* 2002a: MOS SF-36 mental component summary subscale change scores

Mylonas *et al.* 2002b: MOS SF-36 mental health subscale change scores

Mylonas *et al.* 2002c: MOS SF-36 role emotional subscale change scores

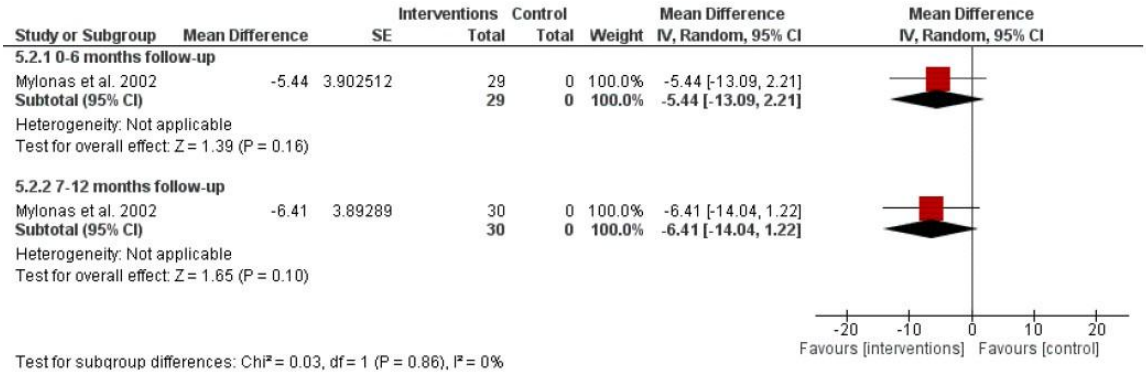

Figure 3.15. Forest plot of comparison: 5 Emotional functioning, outcome: 5.2 MOS SF-36 mental component summary subscale change scores

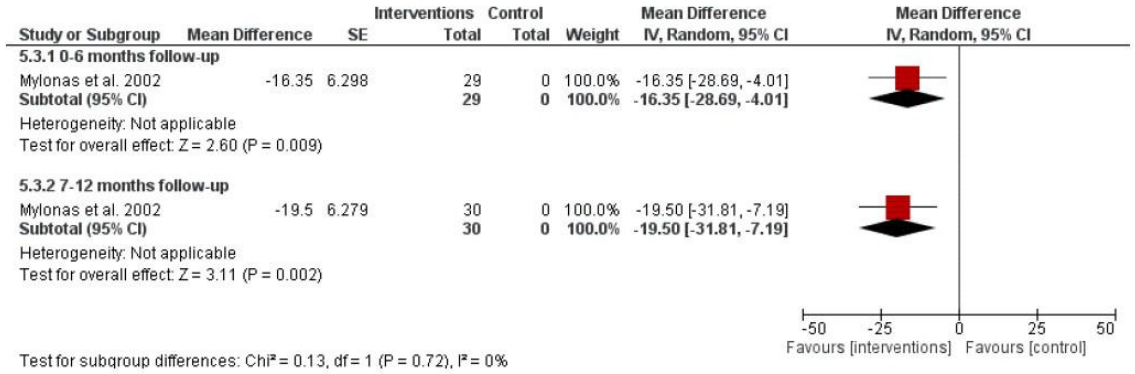

Figure 3.16. Forest plot of comparison: 5 Emotional functioning, outcome: 5.3 MOS SF-36 mental health subscale change scores

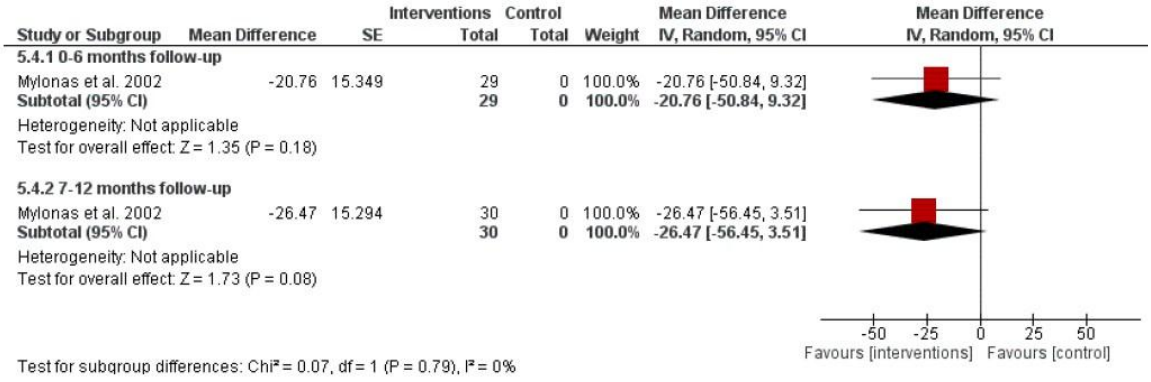

Figure 3.17. Forest plot of comparison: 5 Emotional functioning, outcome: 5.4 MOS SF-36 role emotional subscale change scores

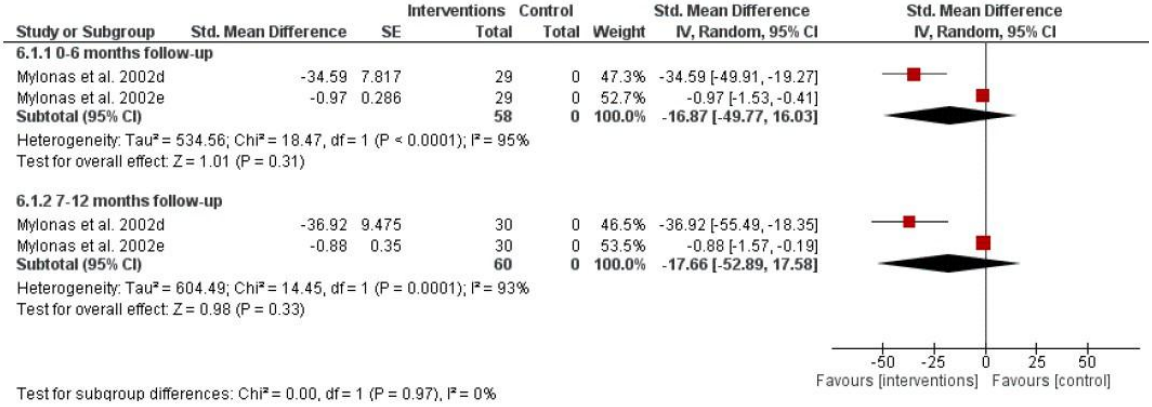

Figure 3.18. Forest plot of comparison: 6 Fatigue, outcome: 6.1 Overall fatigue change scores.

Mylonas *et al.* 2002d: MOS SF-36 vitality subscale change scores

Mylonas *et al.* 2002e: CLINHAQ fatigue subscale change scores

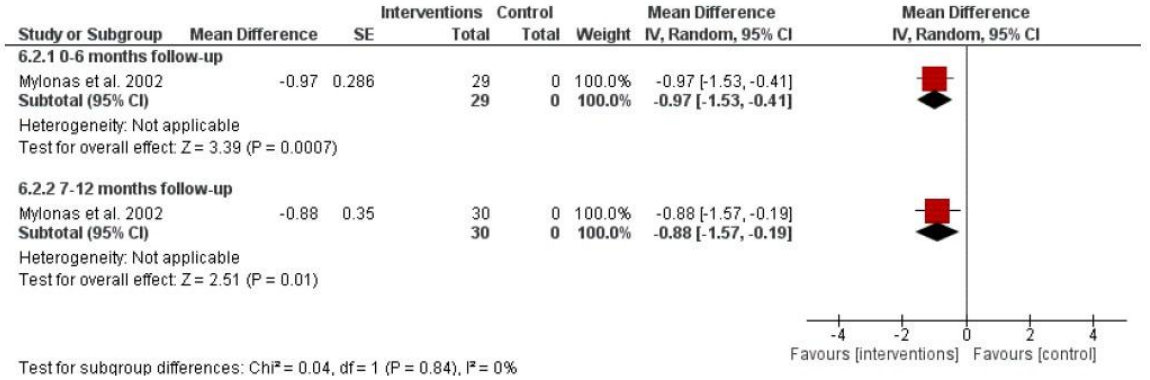

Figure 3.19. Forest plot of comparison: 6 Fatigue, outcome: 6.2 CLINHAQ fatigue subscale change scores

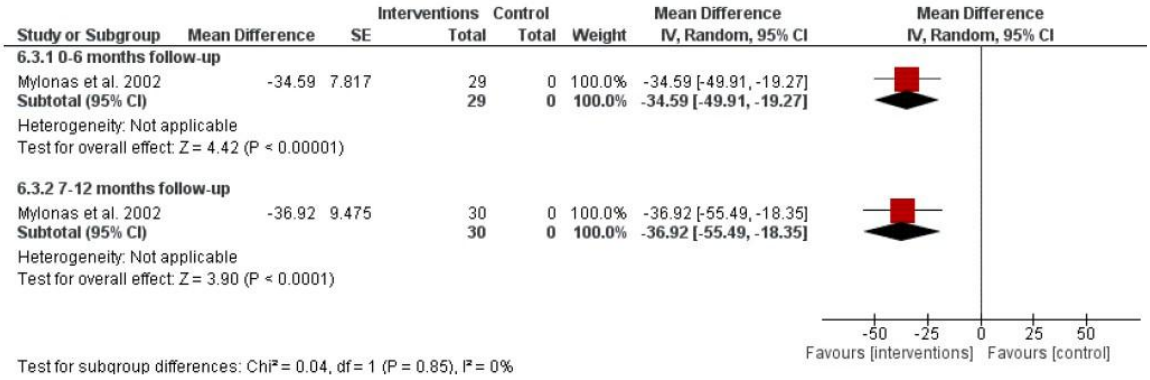

Figure 3.20. Forest plot of comparison: 6 Fatigue, outcome: 6.3 MOS SF-36 vitality subscale change scores

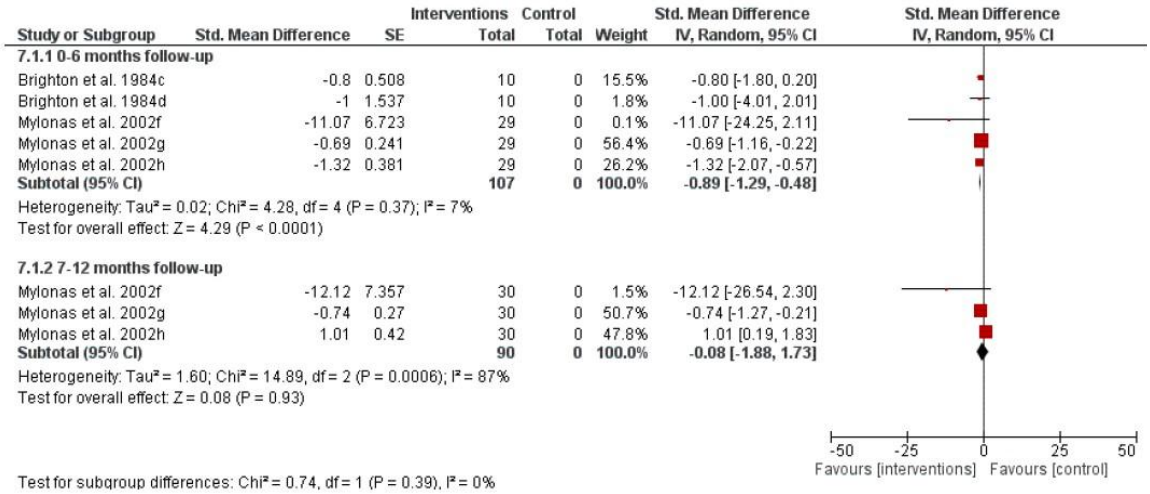

Figure 3.21. Forest plot of comparison: 7 General Health Perspective, outcome: 7.1 Overall general health perspective change scores

Brighton *et al.* 1984c: Brighton *et al.* patients' assessment of therapy change scores

Brighton *et al.* 1984d: Brighton *et al.* doctors' assessment of therapy change scores

Mylonas *et al.* 2002f: MOS SF-36 general health perspective subscale change scores

Mylonas *et al.* 2002g: CLINHAQ patient estimated health status subscale change scores

Mylonas *et al.* 2002h: CLINHAQ satisfaction with health subscale change scores

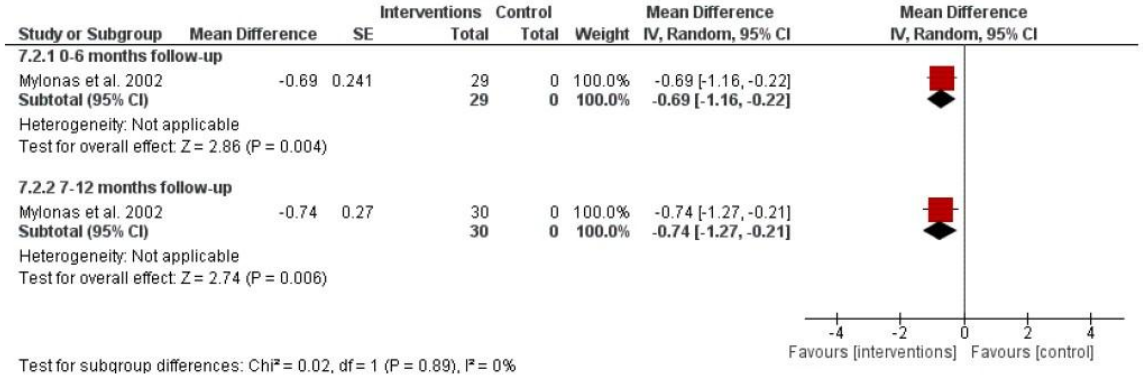

Figure 3.22. Forest plot of comparison: 7 General Health Perspective, outcome: 7.2 CLINHAQ patient estimated health status subscale change scores

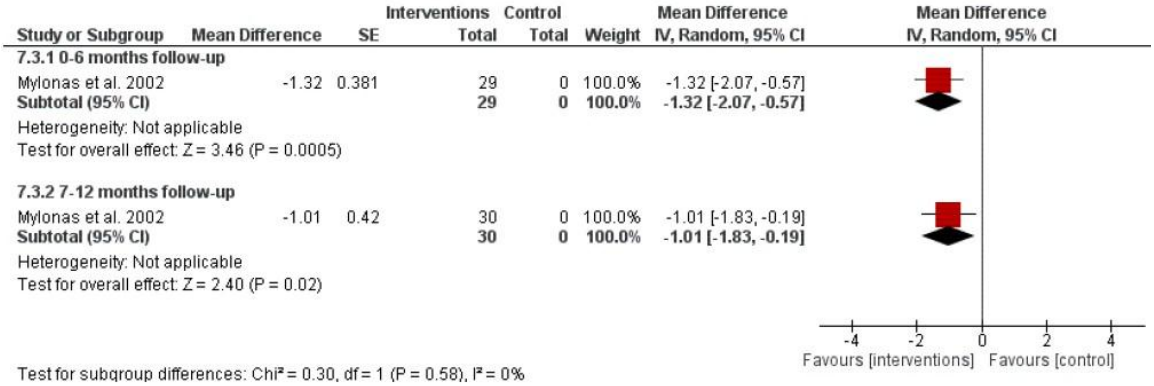

Figure 3.23. Forest plot of comparison: 7 General Health Perspective, outcome: 7.3 CLINHAQ satisfaction with health subscale change scores

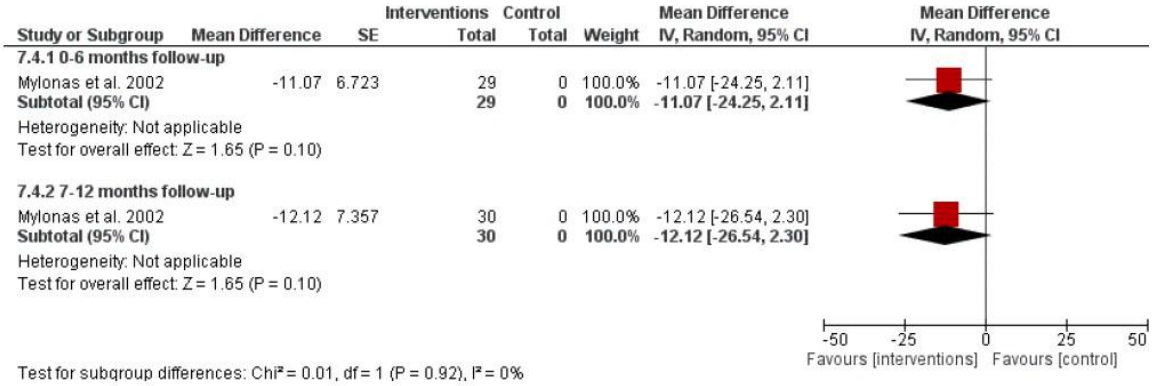

Figure 3.24. Forest plot of comparison: 7 General Health Perspective, outcome: 7.4 MOS SF-36 general health perspective subscale change scores

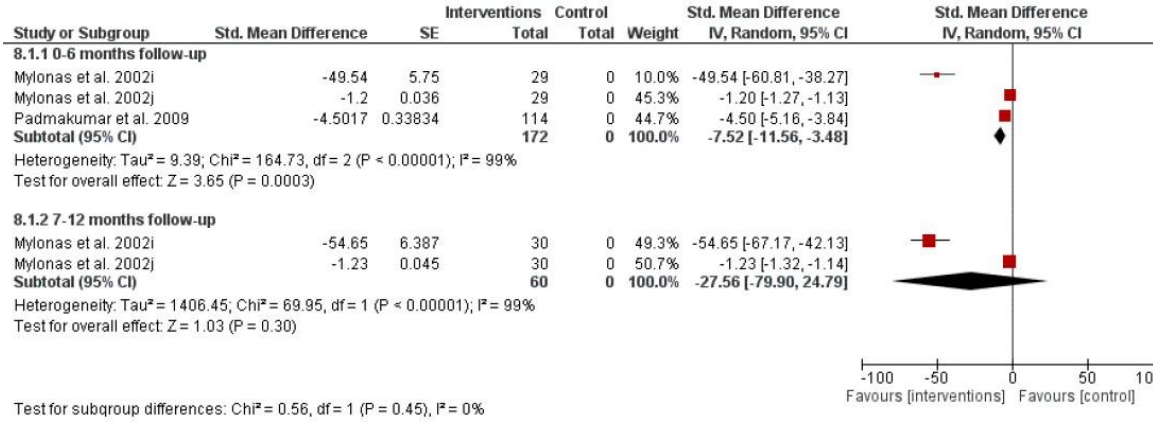

Figure 3.25. Forest plot of comparison: 8 Pain, outcome: 8.1 Overall pain change scores (uncontrolled study)

Mylonas *et al.* 2002i: MOS SF-36 body pain subscale change scores

Mylonas *et al.* 2002j: CLINHAQ pain subscale change scores

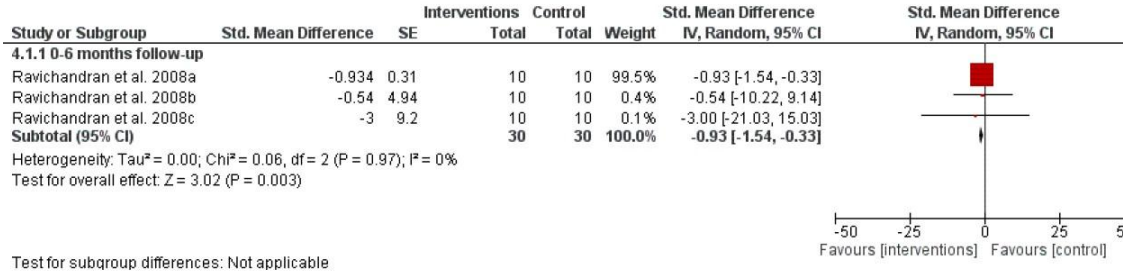

Figure 3.26. Forest plot of comparison: 4 Pain, outcome: 4.1 Overall pain change scores (controlled study):

Ravichandran *et al.* 2008a: Arthritis joint pain relapse change scores

Ravichandran *et al.* 2008b: Arthritis joint swelling change scores

Ravichandran *et al.* 2008c: Patients free of analgesics change scores

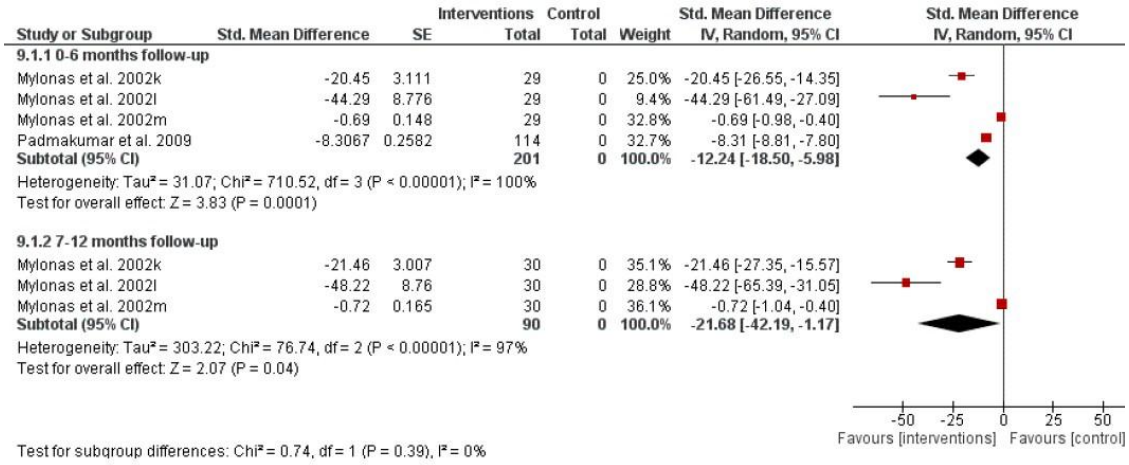

Figure 3.27. Forest plot of comparison: 9 Physical functioning, outcome: 9.1 Overall physical functioning change scores

Mylonas *et al.* 2002k: MOS SF-36 physical component summary subscale change scores

Mylonas *et al.* 2002l: MOS SF-36 physical functioning subscale change scores

Mylonas *et al.* 2002m: CLINHAQ functional disability index subscale change scores

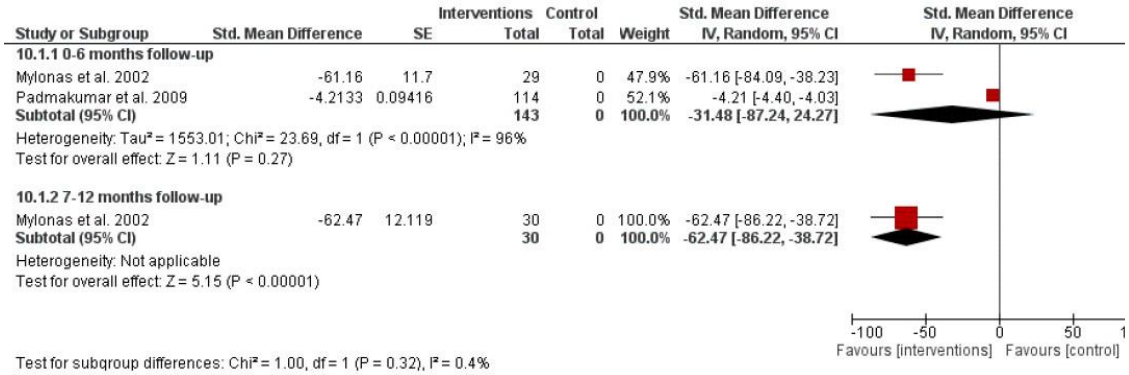

Figure 3.28. Forest plot of comparison: 10 Role Functioning, outcome: 10.1 Overall role functioning change scores

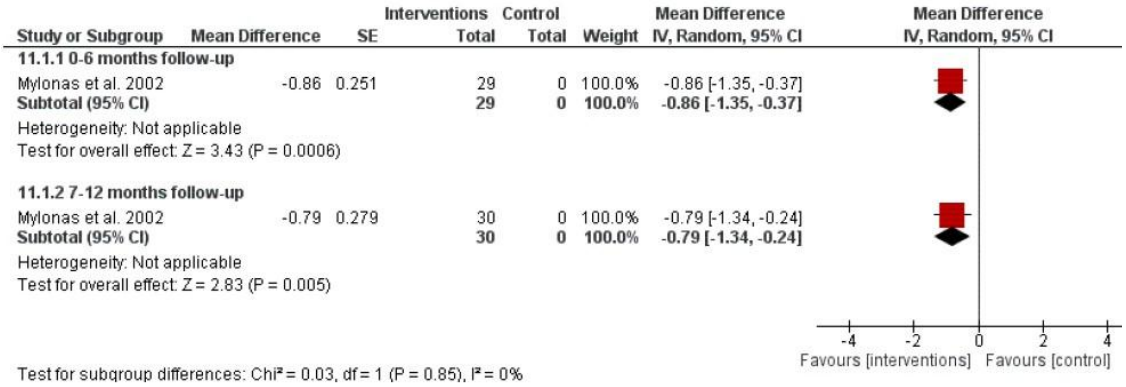

Figure 3.29. Forest plot of comparison: 11 Sleep, outcome: 11.1 CLINHAQ sleep problem subscale change scores

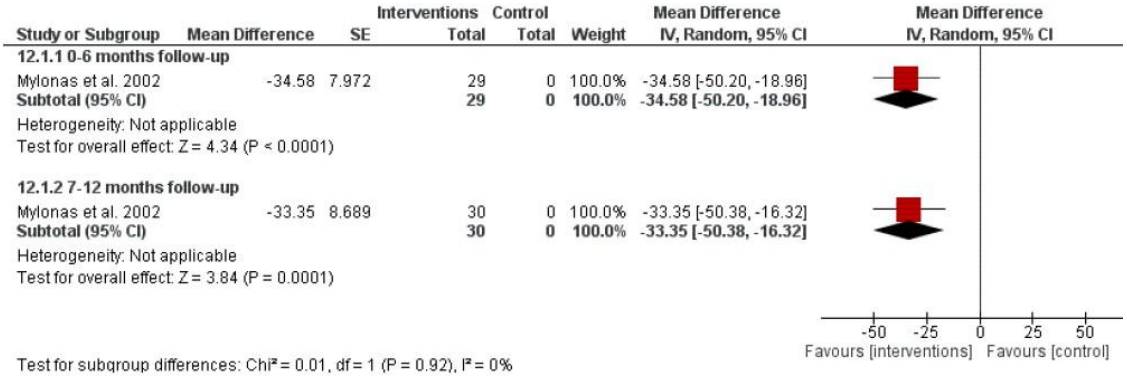

Figure 3.30. Forest plot of comparison: 12 Social Functioning, outcome: 12.1 MOS SF-36 social functioning subscale change scores

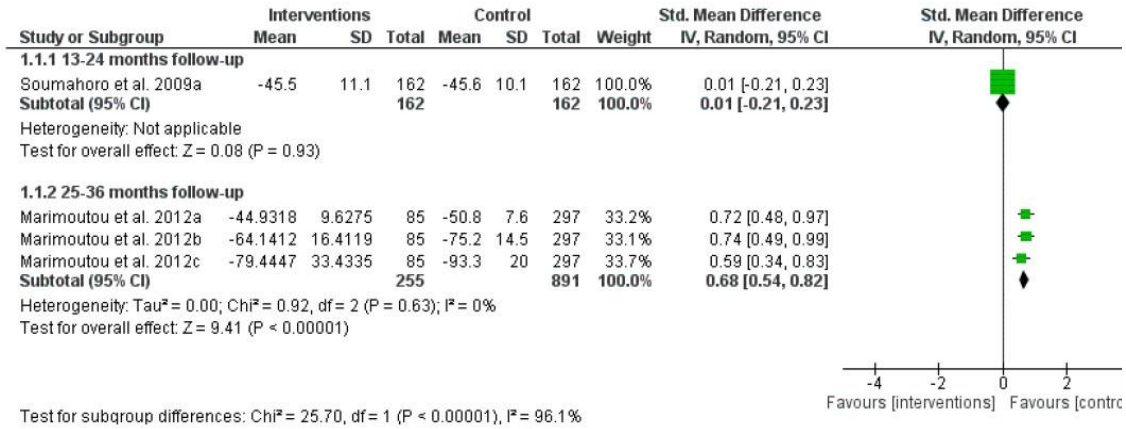

Figure 3.31. Forest plot of comparison: 1 Emotional functioning, outcome: 1.1 Overall emotional functioning follow-up scores

Soumahoro *et al.* 2009a: MOS SF-12 mental component summary subscale follow-up scores

Marimoutou *et al.* 2012a: MOS SF-36 mental component summary subscale follow-up scores

Marimoutou *et al.* 2012b: MOS SF-36 mental health subscale follow-up scores

Marimoutou *et al.* 2012c: MOS SF-36 role emotional subscale follow-up scores

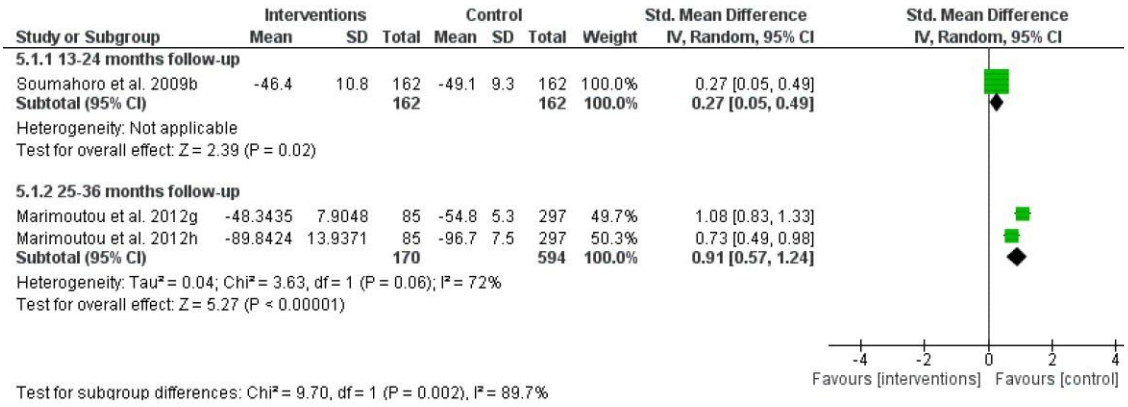

Figure 3.32. Forest plot of comparison: 5 Physical functioning, outcome: 5.1 Overall physical functioning follow-up scores

Soumahoro *et al.* 2009b: MOS SF-12 physical component summary subscale change scores

Marimoutou *et al.* 2012g: MOS SF-36 physical component summary subscale change scores

Marimoutou *et al.* 2012h: MOS SF-36 physical functioning subscale change scores

Appendix XV: Search strategy (as of 25 July 2013)

S/N	Databases	Block Building
1	PubMed	(surveillance[tw] OR public health surveillance[mh] OR public health surveillance[tw] OR disease outbreaks[mh] OR disease outbreak[tw]) AND (*Alphavirus*[mh] OR *Alphavirus*[tw] OR Chikungunya) **Results: 767**
2	Web of Science	TS=((surveillance OR "public health surveillance" OR "disease outbreak") AND (*Alphavirus* OR Chikungunya)) **Results: 161**
3	Scopus	TITLE-ABS-KEY ((surveillance OR "public health surveillance" OR "disease outbreak") AND (*Alphavirus* OR Chikungunya)) **Results: 778**
4	ScienceDirect	(surveillance OR public health surveillance OR disease outbreak) AND (*Alphavirus* OR Chikungunya) **Results: 1037**
5	CINAHL	(TX surveillance OR TX "public health surveillance" OR TX "disease outbreak") AND (TX *Alphavirus* OR TX Chikungunya) **Results: 53**
6	CENTRAL	TITLE-ABS-KEY ((surveillance OR "public health surveillance" OR "disease outbreak") AND (*Alphavirus* OR Chikungunya)) **Results: 0**
7	ProQuest	AB,TI(surveillance OR public health surveillance OR disease outbreak) AND (*Alphavirus* OR Chikungunya) **Results: 50**
Total records		**2846**

Appendix XVI: Included studies

Carrieri *et al.* 2011

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	Develop a large-scale, low cost, and well-designed *Aedes albopictus* vector monitoring surveillance system.
Duration of observation:	May – October 2008
Study start and stop dates:	Not reported
Approval by ethics committee:	Not reported
Funding:	Not reported
PARTICIPANTS	
Study sample:	Municipalities below 500 m sea level (70% of total municipalities) in Emilia-Romagna region, which consist of 9 provinces.
Intervention group:	242/341 municipalities, monitored over total surface area of 104,973 ha and a human population of 1,202,223.
Control group:	Nil
Main sources of CHIK import:	Not reported
High-risk people identified:	People who lived in large urban areas of more than 600 ha had higher risk of arthropod-borne diseases.
SURVEILLANCE INTERVENTIONS	
Description:	A large-scale monitoring system developed in 2007, following the 2007 CHIK outbreak. This system replaced an older monitoring system, which had the objective of gathering temporal evolution data.
Categories of surveillance:	• Active/passive/active+passive surveillance. • Disease/vector/disease+vector surveillance. • Administrative hierarchy: Country/regional/province/district/locality/enumeration.
Country/Income:	Northern Italy/high income
Date when CHIK was made legally notifiable:	Not reported
Mosquito species involved:	*Aedes albopictus*
Cost-effectiveness:	Costs on 2008 monitoring program activities, mainly on egg counting, ovitrap positioning and consultants and routine ovitrap management, amounted to GBP523,824. This translated to GBP0.13/person. The low cost is sustainable even in non-epidemic period.

OUTCOMES

Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases.

✓ positive fulfillment of the evaluation indicator
× negative fulfillment of the evaluation indicator
? uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)

INDICATORS	SUPPORTING EVIDENCE	✓/×/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	No CHIK case definitions were used in the study. Primary sources of cases were from physicians, laboratories, field technicians and local health units. They belonged to the overall monitoring surveillance network of Emilia-Romagna public health department, regional group for technical coordination, scientific centers, analysis laboratories and municipalities monitoring management.	✓
Registration	Not reported	?
Confirmation	No confirmed CHIK case definitions were used in the study.	×
Reporting	A monitoring system organization was reported, involving movement of patient data from the Emilia-Romagna region public health department to the municipalities monitoring management. Details of monitoring network, monitoring results and monitoring design validation were also reported.	✓
Data-analysis	• Weekly *Aedes albopictus* population density mean. • Trend of mosquito infestation in provinces. • Data on egg density data (eggs/ovitrap/week). • Frequency of analysis: Fortnightly (check ovitraps). • Frequency of surveillance reports: Weekly. • Surveillance report distribution: Electronic distribution (www.zanzaratigreonline.it).	✓
Epidemic preparedness	The monitoring system proved highly efficient and prepared to face any potential viral infection pools, which could cause outbreaks if a high density of mosquitoes is present.	✓
Response and control	The tracking of mosquito populations geographically allowed real-time data to be available for response and control.	✓
Feedback	Monitoring data was promptly passed from field to the Institutions for activation of mosquito control programs and to the citizens.	✓

SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	One study reported the homogenous technical coordination of *Aedes albopictus* surveillance and control through the set-up of a regional group in Emilia-Romagna, Italy.One area of concern was to maximise the standardization of the environmental parameters and to avoid differences in the attractiveness among ovitraps.	✓
Training	Skilled technicians were used for the placement of ovitraps.	✓
Supervision	Scientific Group members provided expertise in entomology, epidemiology, meteorology and informatics.	✓
Communication	Not reported	?
Resources	Low cost and efficiency	✓
Coordination	The organizational plan coordinated by Emilia-Romagna public health Department worked well, with no major problems in system management.	✓
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	The on-going vector surveillance system implemented in Emilia-Romagna, Northern Italy, appeared to be timely, with checks on ovitraps for regular positions and functioning done weekly and ovitraps monitoring data published on a website every week.	✓
Completeness	Not reported	?
Usefulness		
Sensitivity	Ovitraps have high sensitivity to detect low numbers of mosquitoes.	✓
Specificity	Not reported	?
Simplicity	Unskilled field technicians can easily handle the use of ovitraps.	✓
Flexibility	Not reported	?
Acceptability	Not reported	?
Reliability	Depending on the number of ovitraps and their placement, ovitraps can be reliable to provide a good estimate of mosquito population density. The reliability of the monitoring system was calculated by: RV= (Standard error of the mean number of eggs/ovitrap/week)/ (Mean number of eggs/ovitrap/week). It was also noted that the CHIK control strategies adopted by different municipalities might influence the reliability	✓

	of ovitrap monitoring.	
Positive predictive value	Not reported	?
Representativeness	The study investigated the minimum ovitrap numbers needed to detect accurately the mosquito eggs density in the provincial regions without risking an over- or under-estimation of ovitraps required for each region. Municipalities below 500m sea level (70% of total municipalities) in Emilia-Romagna region, which consist of 9 provinces, were represented.	✓
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDED:		
Reduction in the case-fatality rate of epidemic-prone diseases	Not reported	?
Changes in the morbidity pattern of targeted communicable diseases	Not reported	?
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	[Surveillance goal] Obtain geographically comparable data on vector species density in provinces, municipals and urban areas of Northern Italy. [Surveillance goal] Estimate the level of infestation of Aedes albopictus in urban areas of more than 600 ha. Cost-effectiveness of monitoring program.	✓
ADDITIONAL COMMENTS		
Study conclusions	An efficient vector monitoring system is important to validate the effectiveness of control strategies. The monitoring system proved highly efficient and prepared to face any potential viral infection pools, which could cause outbreaks if a high density of mosquitoes is present. There is positive support for a monitoring system based on ovitraps placement once every 2 weeks. The reduction of arthropod-borne virus transmission is dependent on disease and vector surveillance.	

Gibney *et al.* 2011

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	Describe epidemiology of CHIK cases in USA, examine risks of indigenous CHIK transmission and evaluate CHIK cases reporting to ArboNET.

Duration of observation:	1995 - 2009 (2006-2009 ArboNET)
Study start and stop dates:	Not reported
Approval by ethics committee:	Not reported
Funding:	Not reported
PARTICIPANTS	
Study sample:	USA
Intervention group:	109 CHIK cases identified, of which 106 cases were confirmed from 2006-2009.
Control group:	Nil
Main sources of CHIK import:	India (57%), other Asian country (8%), Africa (6%) and Indian Ocean (2%).
High-risk people identified:	Nil
SURVEILLANCE INTERVENTIONS	
Description:	ArboNET, a national integrated surveillance system on arthropod-borne virus infections in humans, animal hosts and vectors.
Categories of surveillance:	• Active/passive/active+passive surveillance. • Disease/vector/disease+vector surveillance. • Administrative hierarchy: Country/regional/province/district/locality/enumeration.
Country/Income:	USA/high income
Date when CHIK was made legally notifiable:	Not a nationally notifiable disease
Mosquito species involved:	*Aedes aegypti* and *Aedes albopictus*
Cost-effectiveness:	Not reported

OUTCOMES

Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases.

✓ positive fulfillment of the evaluation indicator
× negative fulfillment of the evaluation indicator
? uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)

INDICATORS	SUPPORTING EVIDENCE	✓/×/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	The only case definition provided was that of a confirmed CHIK case and of a CHIK viremic patient. Primary sources of cases were from 3 laboratories named CDC Arbovirus	✓

	Diagnostic Laboratory (Fort Collins, CO), Wadsworth Center of New York State Department of Health and Focus Diagnostics.	
Registration	Not reported	?
Confirmation	Confirmed CHIK case was via laboratory testing in serum sample. CHIKV confirmation testing was available only at CDC, a public laboratory and a commercial laboratory.	✓
Reporting	State health departments report CHIK cases to ArboNET.	✓
Data-analysis	Data was collected on sex, age, state from which specimen was submitted, start date of disease, date of specimen collection, travel destination and travel dates. All 78 cases with travel details declared travelling out of USA immediately before or during onset of disease, of which 92% has travelled to a place with CHIK outbreak.	✓
Epidemic preparedness	Not reported	?
Response and control	Not reported	?
Feedback	Not reported	?
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training		
Supervision		
Communication		
Resources		
Coordination		
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	There was delayed CHIK case reporting to the ArboNET. A median of 122 (44-273) days was taken between the onset of CHIK and CHIK reporting on ArboNET	×
Completeness	There was incomplete CHIK case reporting to the ArboNET, making the system less helpful in detecting CHIK outbreaks. Some surveillance data fields were not recorded, such as demographics, travel data and *date of illness onset*. For missing data on *date of illness onset*, the *date of serum specimen sample collection* was used as the result for *date of illness onset* during data-analysis.	×
Usefulness	Not reported	?
Sensitivity	It was reported that no data was available for comparison of sensitivity or specificity of CHIKV diagnostic tests used.	×
Specificity		
Simplicity	Not reported	?
Flexibility		
Acceptability		
Reliability	Noted unreliable reporting of vectors to ArboNET prior to	×

	2002, hence, vector surveillance duration was shorter than duration of CHIK cases detected.	
Positive predictive value		
Representativeness	CHIK cases might have been under-reported. CHIK cases identified through the 3 laboratories from 2006-2009 were compared with cases reported to ArboNET. Out of 106 CHIK cases identified through the 3 laboratories, only 27 (25%) were reported to ArboNET. Geographical vector distribution was presented at state level, which might be misrepresented because vector distribution was found only in specific areas within the state. Vector distribution mapping represented sustained vector populations as well as single observations in upper mid-West, the plains and arid West of USA. There were no CHIK cases identified in children; all reported cases were adults. The lack of children representatives might reflect differences in diagnostic practices between adults and children patients, comparatively lesser chances of symptomatic clinical presentations of CHIK in infected children and the travellers' age.	×
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDED:		
Reduction in the case-fatality rate of epidemic-prone diseases	Not reported	?
Changes in the morbidity pattern of targeted communicable diseases	Not reported	?
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	Collate data on arthropod-borne infections among humans, animal hosts and vectors. Information may be used to recognize potential CHIK cases and reduce spread of CHIK.	✓
ADDITIONAL COMMENTS:		
Study conclusions	To reduce the risks of importation and transmission of CHIK, timely recognition, appropriate diagnosis and laboratory testing and case reporting to public health officials are needed. With incomplete and delayed CHIK case reporting to ArboNET, it is less	

	helpful in detecting CHIK outbreaks. Ways to improve the timeliness and completeness of the ArboNET surveillance system have been suggested, including improvements in education of healthcare professionals on diagnosis and reporting of CHIK cases, improvements in communication between laboratories and public health departments and having CHIK as a nation-wide notifiable disease.

Gobbi *et al.* 2012

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	Analyse special integrated surveillance system of CHIK, West Nile and Dengue viral infections in Veneto, Italy.
Duration of observation:	15 June 2008 – 31 October 2010
Study start and stop dates:	Not reported
Approval by ethics committee:	Not applicable
Funding:	Not reported
PARTICIPANTS	
Study sample:	Veneto region, Italy
Intervention group:	Out of 79 possible cases among febrile travellers, 1 CHIK case was detected.
Control group:	Nil
High-risk people identified:	Travellers from endemic areas, including new and settled immigrants.
SURVEILLANCE INTERVENTIONS	
Description:	Special integrated surveillance system established in Veneto, Northeastern Italy.
Categories of surveillance:	Active/passive/active+passive surveillance Disease/vector/disease+vector surveillance Administrative hierarchy: Country/regional/province/district/locality/enumeration
Country/Income:	Veneto, Northeastern Italy/high income
Date when CHIK was made legally notifiable:	Not reported
Mosquito species involved:	Not reported
Cost-effectiveness:	Not reported
OUTCOMES	
Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases.	

✓ positive fulfillment of the evaluation indicator
✖ negative fulfillment of the evaluation indicator
? uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)

INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	CHIK case definitions were provided for possible case, probable case and confirmed case. Study protocol for surveillance was developed. Primary sources of cases were from GPs, emergency departments and the infectious/tropical diseases unit in Padua, Italy.	✓
Registration	Not reported	?
Confirmation	Confirmed CHIK case definition was provided. Blood serum samples from potential cases were delivered to the regional reference laboratory in Padua, Italy for confirmation.	✓
Reporting	Clear movement of patient data from GPs and emergency departments to Infectious/Tropical Diseases unit, and then to the regional reference laboratory.	✓
Data-analysis	Analysis of patient cases were done close to the primary reporting level.	✓
Epidemic preparedness	Not reported	✓
Response and control	Not reported	✓
Feedback	The successful pilot special surveillance system grew to a bigger 3-year ministry-funded integrated surveillance of arboviral diseases, animal and entomology.	✓
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training	Surveillance showed the necessity to train physicians.	✖
Supervision	Not reported	?
Communication		
Resources	Reference laboratories and clinical and laboratory diagnosis test kits and blood sample apparatus (such as the OnSite CHIK IgM Combo Rapid Test or the Vacutainer® (Becton, Dickinson, Franklin Lakes, NJ, USA)) for CHIK made readily available were also crucial for the timely confirmation of CHIK cases.	
Coordination	Not reported	?
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	Possible CHIK cases were referred within 24 hours to the nearest infectious/tropical diseases unit in Padua, Italy.	✓
Completeness	Not reported	?

Usefulness		
Sensitivity		
Specificity		
Simplicity		
Flexibility		
Acceptability		
Reliability		
Positive predictive value		
Representativeness		
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDED:		
Reduction in the case-fatality rate of epidemic-prone diseases	Not reported	?
Changes in the morbidity pattern of targeted communicable diseases	One imported CHIK case was detected during the surveillance period.	✓
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	[Surveillance goal] To increase detection rate of imported CHIK in travellers from endemic CHIK areas and promptly detect potential indigenous cases.	✓
ADDITIONAL COMMENTS:		
Authors' conclusions	The special surveillance system allowed detection of more CHIK cases. The study emphasised the need for modified case definitions, trained clinicians and response actions through implementation of mosquito control strategies.	

Ho *et al.* 2011

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	To analyses CHIK epidemiology and outbreak progression and describe measures to prevent CHIK.
Duration of observation:	3 years; 2006-2009
Study start and stop dates:	Not reported
Approval by ethics committee:	Not applicable
Funding:	Not reported
PARTICIPANTS	
Study sample:	Whole Singapore
Intervention group:	From 2006 - 2009, there were CHIK cases and sporadic outbreaks of

	CHIK, making up 260 imported cases and 812 locally acquired cases.
Control group:	Nil
Main sources of CHIK import:	India and Malaysia
High-risk people identified:	Foreign contract workers working in areas with a high density of *Aedes albopictus* and dwelling in temporary housing quarters
SURVEILLANCE INTERVENTIONS	
Description:	(a) Active laboratory-based (RT-PCR and serology) sentinel surveillance system involving a sentinel network of GPs and 2 restructured hospitals established by December 2006; (b) Extensive case surveillance where local transmission was reported, which included mass blood screening of the household, neighbourhood and close contacts; (c) Passive surveillance network, based on required reporting of infectious diseases, was established in 19 December 2008 and was enhanced by alerting and updating GPs of the latest information, especially GPs working close to cluster areas; (d) Vector surveillance by mapping out localities with high vector population using Geographical Information System (GIS).
Categories of surveillance:	• Active/passive/<u>active+passive</u> surveillance • Disease/vector/<u>disease+vector</u> surveillance • Administrative hierarchy: <u>Country</u>/regional/province/district/locality/enumeration
Country/Income:	Singapore/high income
Date when CHIK was made legally notifiable:	19 December 2008
Mosquito species involved:	*Aedes aegypti* and *Aedes albopictus*
Cost-effectiveness:	Not reported

OUTCOMES

Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases.

✓ positive fulfillment of the evaluation indicator
✖ negative fulfillment of the evaluation indicator
? uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)

INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	Case definitions were provided for CHIK case, CHIK	✓

	cluster, CHIK imported case and CHIK locally acquired case. Clinicians were on the alert for CHIK cases and were advised to consider CHIK as a differential diagnosis to Dengue. Primary sources of CHIK cases were from physicians, hospitals, field technicians and the government agencies, MOH (case surveillance and epidemiological surveillance) and NEA (vector surveillance and control).	
Registration	Not reported	?
Confirmation	CHIK cases were confirmed by 2 ways: (1) clinical manifestations and positive laboratory tests via RT-PCR or serology; (2) clinical manifestations and positive anti-CHIK IgM serum sample and linked epidemiologically.	✓
Reporting	Patient data were reported from clinics and hospitals to MOH and NEA.	✓
Data-analysis	• Strong evidence of data-analysis and interpretation, leading to public health actions. • Information gathered included demographics, addresses of homes/schools/workplaces, dates for diagnosis and onset of disease. • Evolution of CHIK transmission from a period of sporadic importation to sporadic local transmission to sustained local transmission to sporadic local transmission from 2006-2009. • The CHIK surveillance systems have enabled the identification of the reason for the rapid transmission of CHIK in Singapore. It was due to the mutation of the CHIKV with an amino acid substitution A226V of the E1 gene. With this mutated virus carried by *Aedes albopictus,* mosquito control strategies were altered by targeting *Aedes albopictus* instead of *Aedes aegypti.*	✓
Epidemic preparedness	• Investigation was done rapidly. • Contacts were traced for every notified case to detect unreported cases. • "All-out approach" was undertaken to contain CHIK clusters.	✓
Response and control	• Residents and foreign workers were educated on common mosquito breeding sites and ways to destroy them. • It was found that more vector surveillance and control efforts might be focused workplaces and dormitories of foreign contract workers to destroy breeding sites.	✓

	• All available resources were shifted to areas at high risk of CHIK. • Used GIS to map out areas for rigorous vector surveillance and control.	
Feedback	Alerted and provided GPs with the latest information on CHIK situation.	✓
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training	Trained environment health officers were tasked for vector surveillance and were involved in *search and destroy* operations.	✓
Supervision	Not reported	?
Communication	Appeared adequate, as gathered from the mandatory notifications of cases and the immediate alert of all reported CHIK cases to NEA. Singapore is a high-income country, according to World Bank classification of countries by gross national income.	✓
Resources	All-out approach was used to reduce spread of CHIK by putting all available resources to high-risk areas.	✓
Coordination	Appeared to be adequate, as gathered from the surveillance coordination among GPs, medical community, hospitals, MOH, NEA and Defence Medical and Environmental Institute and the public.	✓
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	Not reported	?
Completeness		
Usefulness		
Sensitivity		
Specificity		
Simplicity		
Flexibility		
Acceptability		
Reliability		
Positive predictive value		
Representativeness		
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDED:		
Reduction in the case-fatality rate of epidemic-prone diseases	Deaths were not reported in the study.	?
Changes in the morbidity pattern of	The study suggested successful control of CHIK outbreaks, which saw a drastic decline from January 2009. The	✓

targeted communicable diseases	incidence rate of locally acquired CHIK cases decreased from 11.1 per 100,000 in 2008 to 5.5 per 100,000 in 2009, and then down to 28 reported CHIK cases, as of November 2 010.	
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	[Surveillance goal] Prevent CHIK from becoming an endemic disease.	✓
ADDITIONAL COMMENTS:		
Study conclusions	A strong surveillance system is needed for early detection and response to prepare for the next CHIK outbreak, with an importance in examining systemic and demographic vulnerabilities.	

Laras *et al.* 2004

STUDY CHARACTERISTICS	
Study design:	Case-control
Study objective:	(a) To confirm CHIK epidemic occurrence with fever and arthralgia. (b) To find cause of CHIK cases. (c) To calculate attack rate. (d) To find demographic or environmental risk factors or both. (e) To describe epidemic movement.
Duration of observation:	September 2001- March 2003
Study start and stop dates:	Not reported
Approval by ethics committee:	Not reported
Funding:	US Department of Defense and the Global Emerging Infections System.
PARTICIPANTS	
Study sample:	Sample was taken from 2/24 suspected CHIK outbreak episodes areas of Bogor and Bekasi, West Java province, Indonesia.
Intervention group:	119 clinically recognised CHIK cases were identified from Bogor and Bekasi.
Control group:	Randomly selected healthy controls matched by age and gender formed the control group. They served to exclude causes of other viral outbreaks. In addition, a village with no recent CHIK case was chosen as a control village.
Main sources of CHIK import:	Not reported
High-risk people	Not reported

identified:

SURVEILLANCE INTERVENTIONS		
Description:	Routine surveillance, involving house-to-house visits to detect CHIK cases by community health centre staff.	
Categories of surveillance:	• Active/passive/active+passive surveillance. • Disease/vector/disease+vector surveillance. • Administrative hierarchy: Country/regional/province/district/locality/enumeration.	
Country/Income:	Indonesia/Lower middle income	
Date when CHIK was made legally notifiable:	Not reported	
Mosquito species involved:	*Aedes aegypti* and *Aedes albopictus*	
Cost-effectiveness:	Not reported	
Limitations:	Not reported	

OUTCOMES

Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases.

✓ positive fulfillment of the evaluation indicator
✖ negative fulfillment of the evaluation indicator
? uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)

INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	Definitions were given for suspected CHIK case and clinically recognised outbreaks. Primary sources of CHIK cases were from Pusat Kesehatan Masyarakat (PusKesMas) (community health centers).	✓
Registration	Not reported	?
Confirmation	Outbreaks were confirmed based on positive CHIKV serology or RT-PCR or both at the US NAMRU-2 laboratory.	✓
Reporting	General disease weekly reporting from community health centers (PusKesMas) to district and provincial health authorities and finally to the national level CDC-EH.	✓
Data-analysis	The age-specific attack rates were 4.6 cases/1000 pax (≥40 years old), 3.7/1000 (30-39 years old), 2.7/1000 (20-29 years old), 1.6/1000 (10-19 years old) and 0.5/1000 (< 10 years old). Epidemic curve was recorded, with a 23-week outbreak period and 3 sharp rises in cases.	✓

Epidemic preparedness	Not reported	?
Response and control	An outbreak response team was formed rapidly after the first report of 100 *CHIK-like* cases in November 2001, with representatives from the local district health service, Indonesian MOH, NIHRD, CDC-EH and US NAMRU-2.	✓
Feedback	Anecdotal reporting from district or provincial sources and public announcements in local newspapers were used to communicate CHIK outbreak information. For Bekasi CHIK outbreak, a review of reported clinical manifestations before the outbreak period was conducted and showed no evidence of CHIK cases over a 4-year period (January 1998 to July 2002) from Kali Jaya community health center data. However, possible CHIK was detected 4 months before the CHIK outbreak (September 2001), when clinical records were limited to FUO cases.	✓
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training		
Supervision		
Communication	Public announcements in local newspapers and anecdotes on CHIK outbreak information was relayed from the district or provincial sources to the people.	✓
Resources	Reference laboratories and clinical and laboratory diagnosis test kits and blood sample apparatus for CHIK made readily available were also crucial for the timely confirmation of CHIK cases. Administrative infrastructure to facilitate formal requests for consent on research participation to collect CHIKV from infected patients was also required, for example through the Indonesian NIHRD. Sweep nets were commonly used in field surveys. In laboratories, the storage of sera and captured mosquitoes in liquid nitrogen for analysis were also described.	✓
Coordination	Not reported	?
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	Not reported	?
Completeness		
Usefulness		
Sensitivity	Refer to Section 3.10 on positive predictive value.	×

Specificity		
Simplicity	Not reported	?
Flexibility		
Acceptability		
Reliability		
Positive Predictive Value	63% of the 86 suspected serum samples showed at least 1 positive laboratory test result for CHIK. However, there was no serum sample tested positive across all 3 diagnostic tests of detecting anti-CHIK IgM and IgG antibodies, CHIK RNA via RT-PCR and virus isolation. Thirty-two serum samples were tested negative for CHIK across all 3 tests.	✗
Representativeness	To depict accurate representation of CHIK in Kali Jaya village, Bekasi Regency, the denominator to calculate the CHIK attack rate was obtained from the Bekasi Regency census data 2001. The demographic results obtained were congruent with the CHIK characteristics shown in outbreaks occurring in other countries. The study investigators also suspected under-reporting of CHIK, due to a coincidental increase in FUOs and the exclusion of CHIK in the usual set of disease diagnosis used by physicians. It was postulated that there were many more CHIK outbreaks, which were not reported in Indonesia.	✓
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDED:		
Reduction in the case-fatality rate of epidemic-prone diseases	No deaths were reported.	✓
Changes in the morbidity pattern of targeted communicable diseases	Not reported	?
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	• Attack rates in various areas, including Bogor at 2.8/1000 and Bekasi at 6.7/1000. • Detail epidemiological profiles of CHIK outbreaks. • Identify adult mosquito species from daytime indoor resting collections.	✓
ADDITIONAL COMMENTS		
Study conclusions	There are general under-reporting and poor detection of CHIK during occasional episodes and long inter-epidemic duration.	

	Given a notable absence of reported CHIK for nearly 20 years, the extensive outbreaks from Sumatra to Lombok and Sulawesi were remarkable. The health authorities were caught unprepared when the intensity of the CHIK epidemic re-emerged.

Napoli *et al.* 2012

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	Analyse and estimate imported CHIK and Dengue cases within the National Surveillance System, a national integrated disease and vector surveillance system in Italy.
Duration of observation:	January 2008 – October 2011
Study start and stop dates:	Not reported
Approval by ethics committee:	Not reported
Funding:	Italian MOH Special Surveillance project (Grant no. 1M61)
PARTICIPANTS	
Study sample:	Reporting regions represent 72% of 60-million Italian population.
Intervention group:	130 people notified from 10 regions of Italy, of which 21 were CHIK cases. 12/21 CHIK cases were Italians and the others were of other nationalities.
Control group:	Nil
Main sources of CHIK import:	Mauritius, Maldives, Sri Lanka, Bali, Asia and Africa.
High-risk people identified:	Travellers returning to Italy
SURVEILLANCE INTERVENTIONS	
Description:	Disease surveillance for CHIK was implemented after CHIK outbreak in 2007, followed by a national plan on integrated human surveillance of vector-borne diseases in 2011.
Categories of surveillance:	Active/passive/<u>active+passive</u> surveillance Disease/vector/<u>disease+vector</u> surveillance Administrative hierarchy: <u>Country</u>/regional/province/district/locality/enumeration
Country/Income:	Italy/high income
Date when CHIK was made legally notifiable:	Not reported
Mosquito species involved:	*Aedes albopictus*
Cost-effectiveness:	Not reported
OUTCOMES	

Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases.

✓ positive fulfillment of the evaluation indicator
✖ negative fulfillment of the evaluation indicator
? uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)

INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	No other case definitions were provided, except that of a CHIK confirmed case. Primary sources of CHIK cases were not reported.	✓
Registration	Not reported	?
Confirmation	CHIK confirmed case definition was provided and followed that of EU case definition (clinical + lab). Confirmation of CHIK case was via laboratory test using RT-PCR, isolated CHIKV or anti-CHIK IgM antibodies in serum sample.	✓
Reporting	A case report form for each patient was completed, detailing information on age, sex, countries visited, travel dates and start date of clinical symptoms. The case report forms were reported to the National Institute of Health and MOH.	✓
Data-analysis	Number of imported CHIK infections were estimated based on airport arrival travellers' data and data from surveillance system to measure degree of under-reporting. Distribution of CHIK imported cases was calculated per month from 2008 – 2011. The introduction of CHIK imported cases and indigenous spread of CHIK was dependent on the presence and the activity level of *Aedes albopictus* (Italy is free of *Aedes aegypti*).	✓
Epidemic preparedness Response and control	A nation-wide plan on integrated surveillance of vector-borne diseases, including CHIK, was implemented in 2011.	✓
Feedback	Not reported	?
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training		
Supervision		
Communication		
Resources		
Coordination		

QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	Not reported	?
Completeness	Two out of 21 CHIK cases did not indicate travel history on the case report form.	✓
Usefulness	Not reported	?
Sensitivity		
Specificity		
Simplicity		
Flexibility		
Acceptability		
Reliability		
Positive predictive value		
Representativeness	There was a suggested under-reporting of imported CHIK cases, as there was an increase of 48- to 276-fold in CHIKV estimated exposed travellers who arrived in Italy, as compared to notified infection in Italy.	×
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDED:		
Reduction in the case-fatality rate of epidemic-prone diseases	Not reported	?
Changes in the morbidity pattern of targeted communicable diseases	Allowed for the distribution mapping of CHIK imported cases per month from 2008-2011.	✓
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	Detect imported CHIK cases to put in place rapidly mosquito control strategies to reduce mosquito population.	✓
ADDITIONAL COMMENTS:		
Study conclusions	Twin efforts on human and vector surveillance are important to monitor CHIK transmission and to put in place public health interventions to reduce spread of disease. An integrated surveillance may quickly identify risks associated with introduction of CHIK in Europe.	

Ng *et al.* 2009

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	To highlight the usage of mosquito and virological data to aid CHIK control in Singapore.
Duration of observation:	December 2006 - September 2008

Study start and stop dates:	Not reported
Approval by ethics committee:	Not applicable
Funding:	Ministry of Finance Reinvestment Fund
PARTICIPANTS	
Study sample:	Whole Singapore
Intervention group:	Initially, 1375 samples were tested for CHIK, of which 10 were lab-tested positive for CHIK. In 2008, 13 CHIK cases were confirmed by PCR, out of more than 7000 samples tested.
Control group:	Nil
Main sources of CHIK import:	Maldives, India, Indonesia, Malaysia and Sri Lanka.
High-risk people identified:	People living in more rural areas of Singapore.
SURVEILLANCE INTERVENTIONS	
Description:	CHIK surveillance system was established in late 2006; the MOH alerted the medical personnel to look for *CHIK-like* symptoms. Active laboratory-based sentinel surveillance system involving a network of GPs was set up. Active case detection was conducted during two episodes of CHIK transmission in May and June 2008. After July 2008, active case surveillance using PCR found two CHIK viremic cases a day before clinical symptoms onset. Vector surveillance was done with the selection of seven CHIK clusters, representing local CHIK outbreaks. In each cluster area, adult vector surveillance was done within a week of the outbreak onset, starting at the location with the highest number of reported cases. The data of *Aedes* mosquito larvae collected from various CHIK clusters were mapped on the Geographic Information System (ArcGIS), a nation-wide mosquito control program database that was updated daily, with fieldwork done by about 500 mosquito control officers. The objectives of the vector surveillance were to identify all active breeding sites, determine the make-up of *Aedes spp.* and find CHIKV in the mosquitoes.
Categories of surveillance:	• Active/passive/<u>active+passive</u> surveillance. • Disease/vector/<u>disease+vector</u> surveillance. • Administrative hierarchy: <u>Country</u>/regional/province/district/locality/enumeration.
Country/Income:	Singapore/high income

Date when CHIK was made legally notifiable:	Not reported	
Mosquito species involved:	*Aedes aegypti* and *Aedes albopictus*	
Cost-effectiveness:	Not reported	
OUTCOMES Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases. ✓ positive fulfillment of the evaluation indicator ✖ negative fulfillment of the evaluation indicator **?** uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)		
INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	No other case definitions were provided, except that of a CHIK confirmed case. Clinicians were on the alert for CHIK cases and were advised to consider CHIK as a differential diagnosis to Dengue. Primary sources of CHIK cases were from physicians, hospitals and field technicians.	✓
Registration	Not reported	?
Confirmation	CHIK cases were confirmed in the laboratory via RT-PCR or anti-CHIK IgM test and were further classified as an imported case or an indigenous case based on travel history.	✓
Reporting	Reporting of case-patient data and vector surveillance was evident, based on the active laboratory surveillance at Environmental Health Institute and the ArcGIS database.	✓
Data-analysis	*Aedes* larvae surveillance data showed that *Aedes albopictus* was the main species in all CHIK cluster areas except Little India, where only *Aedes aegypti* was caught. Aedes aegypti carried CHIK strains with A226 of E1 gene; however, *Aedes albopictus* carried CHIK strains with A226V mu tation of the East, Central and South African genotype. Larval surveillance data was quantified in larval abundance index. The index was calculated using the larval data collected 3 months before and after the first case from cluster. Phylogenetic data showed 3 different CHIK strains closely associated to those from India, Malaysia and Sri Lanka for CHIK transmissions from 4 January 2008 – 9 June 2008.	✓

	The data was used to trace origins of CHIK viral strains causing the CHIK outbreaks.	
Epidemic preparedness	The longitudinal tracking of E1 gene sequences in CHIKV is part of the coordinated efforts to monitor local transmission. Singapore is susceptible to CHIKV imports.	✓
Response and control	The nation's *Aedes* spp. control strategy was revised and expanded, particularly in areas that are more rural with predominance of *Aedes albopictus* mosquitoes.	✓
Feedback	Not reported	?
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training		
Supervision		
Communication		
Resources	BG Sentinel traps and sweep nets, were commonly used in field surveys.	✓
Coordination	Not reported	?
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	Within 1 week of CHIK outbreak onset, adult mosquito surveillance was done once and carried out starting from locations with the highest number of CHIK cases. Vector surveillance data on mosquito breeding site inspection was input daily into the ArcGIS database of NEA.	✓
Completeness	Not reported	?
Usefulness		
Sensitivity		
Specificity		
Simplicity		
Flexibility		
Acceptability		
Reliability		
Positive predictive value		
Representativeness		
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDING:		
Reduction in the case-fatality rate of epidemic-prone diseases	Not reported	?
Changes in the morbidity pattern of targeted communicable diseases	Briefly reported. Allowed for the geographical distribution mapping of locally acquired CHIK cases.	✓
Changes in behaviour of health staff and of the	Not reported	?

general population.	
Others	[Surveillance goal] Minimise CHIK outbreaks. ✓ Identified circulating vectors carrying the virus. Identified phylogenicity of CHIK E1 gene.
ADDITIONAL COMMENTS	
Study conclusions	Singapore is susceptible to imports of CHIKV. The A266V CHIKV variant is a challenge to face.

Randrianasolo *et al.* 2010

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	Describe the challenges and process of developing a sentinel surveillance system and the resulting information it brings for public health decision-making.
Duration of observation:	1 April 2007 – 31 December 2008
Study start and stop dates:	Not reported
Approval by ethics committee:	Approved by MOH and the National Ethics Committee of Madagascar.
Funding:	World Bank, Institut Pasteur de Madagascar and United States Agency for International Development (USAID)
PARTICIPANTS	
Study sample:	13 sentinel centers in Madagascar
Intervention group:	Dengue-like syndromes (Including CHIK) formed 3,280 (12.3%) of 26,669 febrile syndromes.
Control group:	Nil
Main sources of CHIK import:	Not reported
High-risk people identified:	Not reported
SURVEILLANCE INTERVENTIONS	
Description:	After the Indian Ocean CHIK outbreak, there was a need for a rapid surveillance system that was able to detect abnormal patterns instead of surveillance based on confirmed diagnoses for febrile syndromes and diarrheal. Hence, a sentinel syndromic-based real-time surveillance system was established in March 2007. It sends patient data daily from voluntary GPs of the 6 provinces to the Institut Pasteur de Madagascar.
Categories of surveillance:	• Active/passive/active+passive surveillance. • Disease/vector/disease+vector surveillance.

	• Administrative hierarchy: Country/regional/province/district/locality/enumeration.	
Country/Income:	Madagascar/low income	
Date when CHIK was made legally notifiable:	Not reported	
Mosquito species involved:	Not reported	
Cost-effectiveness:	The cost of data transmission via mobile phone was less than USD1/month, which was noted to be an efficient and less-costly way to report data daily. However, it was also noted that the cost and maintenance of the surveillance system needed to be calculated, in terms of person-hours of sentinel GPs and person-hours in responding to surveillance system alerts.	
OUTCOMES Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases. ✓ positive fulfillment of the evaluation indicator ✖ negative fulfillment of the evaluation indicator **?** uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)		
INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	The surveillance system was based on syndromic clinical pre-diagnostic information, specifically for febrile diseases, Malaria-confirmed cases, influenza-like cases, arbovirus and diarrheal. 10 cases of fever clusters were detected by the sentinel surveillance system, but not the traditional one. From this, 5 outbreaks were confirmed, of which 2 outbreaks had an increase in Dengue-like syndrome ratio in ¼ sentinel centers that have reported CHIKV circulation. Primary sources of CHIK cases were from sentinel physicians and laboratories.	✓
Registration	Not reported	?
Confirmation	Confirmation of CHIK cases was based on syndromic clinical pre-diagnostic information, specifically for febrile diseases, Malaria-confirmed cases, influenza-like cases, arbovirus and diarrheal.	✓
Reporting	A paper form detailing sex, age, date and time of visit and main symptoms was recorded for each case by the sentinel GPs and these completed forms were sent to the disease management team every week. Correspondence between	✓

	sentinel GPs and Institut Pasteur de Madagascar staff was anonymous and identified using an identification number. Additionally, sentinel GPs reported data on various febrile diseases and diarrheal at least once a day via encrypted mobile phone text message. Eventually, aggregate data are reported to the Malagasy MOH, regional health department and district managers.	
Data-analysis	Data from 13 sentinel centers were evaluated for variation daily and separate analysis was done according to each syndrome category to look for temporal distribution increases at each center. Analysis of data was descriptive and direct, using standard epidemiological methods. Peak detection in graphical plots was used to identify abnormal trends. Increase in peaks was notified immediately to regional health officers and public health officers at MOH. If a change was detected, signals were verified and affected patients were identified.	✓
Epidemic preparedness	The sentinel surveillance system prepared the people for potential outbreaks and had confirmed 5 outbreaks.	✓
Response and control	Not reported	?
Feedback		
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Data derived from the sentinel syndromic-based surveillance system was analysed using standard epidemiological techniques. Other standards and guidelines related to surveillance were not reported.	✓
Training	Not reported	?
Supervision	Supervision of the surveillance system was done by MOH.	✓
Communication	Strong communication systems are required for efficient and accurate surveillance system. Electronic records delivered directly from sentinel GPs in future may replace the current use of paper forms and mobile phone text message.	✗
Resources	Implementation of a sentinel syndromic-based surveillance system might be a good option to consider boosting traditional disease surveillance due to its use of lesser resources compared to passive surveillance.	✓
Coordination	Sentinel surveillance system may enhance collaboration of health ministry services and GPs. One challenge faced is	✓

	connecting the GPs to the sentinel surveillance system and the coordination of their efforts.	
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	The sentinel syndromic-based surveillance system acquired timely data for improving healthcare decision-making. Sentinel GPs sent completed patient data form to the disease management team every week, and reported data on various febrile diseases and diarrheal at least once a day (by 8 am) via phone encrypted text message for daily data collection and analysis to detect abnormality by an epidemiologist. 89% of the CHIK cases data were sent within 24 hours from the sentinel centers to the Access® database. Increases in cases were reported immediately via phone to the MOH. With an excellently rapid sentinel surveillance system, it could still be improved based on detection of unusual disease patterns instead of confirmed laboratory and clinical diagnoses. On the other hand, extra time should be allocated for further case investigations on diagnostic and laboratory data. It was also noted that timely detection of CHIK outbreak would lead to disease control strategies that reduce and prevent future CHIK transmission.	✓
Completeness	Not reported	?
Usefulness		
Sensitivity		
Specificity		
Simplicity		
Flexibility		
Acceptability		
Reliability		
Positive predictive value		
Representativeness	13 sentinel centers were selected based on pre-specified criteria and were represented geographically but only covered 3% of the population in Madagascar. However, the sentinel GPs were voluntary, hence, surveillance system is not representative of Madagascar. Participating GPs should increase for better representation.	×
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDING:		
Reduction in the case-fatality rate of epidemic-prone diseases	Not reported	?
Changes in the morbidity	Not reported	?

pattern of targeted communicable diseases		
Changes in behaviour of health staff and of the general population	Not reported	?
Others	[Surveillance goal] Early detection of epidemics/disease clusters, before diagnoses are confirmed and reported to public health authorities. [Surveillance goal] Rapid response measures to reduce deaths and diseases. [Surveillance goal] Identify circulating arthropod-borne viruses.	✓
ADDITIONAL COMMENTS		
Study conclusions	A sentinel syndromic-based surveillance system might be the key to detect and react quickly to a disease outbreak. It is feasible to implement a sentinel syndromic-based surveillance system in a developing country at a low cost way, with good cooperation efforts by sentinel GPs (daily data transfer rate estimated to 89%) and low staff effort. The sentinel surveillance system is a critical step to address the gap in Madagascar disease surveillance, although it cannot replace traditional disease surveillance and should not be a substitute for the direct reporting of unusual or suspect disease cases by clinicians.	

Renault *et al.* 2007

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	Describe the largest CHIK epidemic course in La Reunion Island
Duration of observation:	28 March 2005 – 16 April 2006
Study start and stop dates:	Not reported
Approval by ethics committee:	Not reported
Funding:	Not reported
PARTICIPANTS	
Study sample:	Whole La Reunion Island of estimated 766,000 people (as of 2004)
Intervention group:	Estimated 244,000 CHIK cases were reported, with attack rate of 35%.
Control group:	Nil.
Main sources of CHIK import:	Grande-Comore
High-risk people	Not reported

identified:

SURVEILLANCE INTERVENTIONS		
Description:	Operational epidemiologic surveillance system for the island was established in April 2005 after the first CHIK cases were reported. It involved mosquito control teams who were involved in active case finding around cases reported by sentinel physician network, laboratories, GPs and CHIK patients. However, by December 2005, the capacity of the surveillance system was overloaded, when cases increased exponentially from the weekly peak of the first epidemic wave of 450 cases during 9-15 May 2005 to more than 47,000 cases during 30 January to 5 February 2006 in the second epidemic wave. Surveillance was then based only on sentinel network with 31 clinicians. Deaths due to CHIK were recorded from death certificates and hospitals surveillance in the form of finding severe CHIK cases and materno-neonatal transmission were carried out.	
Categories of surveillance:	• Active/passive/<u>active+passive</u> surveillance. • Disease/vector/<u>disease+vector</u> surveillance. • Administrative hierarchy: Country/<u>regional</u>/province/district/locality/enumeration.	
Country/Income:	La Reunion Island, France/high income	
Date when CHIK was made legally notifiable:	Not reported	
Mosquito species involved:	*Aedes albopictus* was the main vector	
Cost-effectiveness:	Not reported	

OUTCOMES

Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases.

✓ positive fulfillment of the evaluation indicator
✖ negative fulfillment of the evaluation indicator
? uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)

INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	Case definitions were provided for suspected case, confirmed case, emerging severe forms of CHIK and suspected case of materno-neonatal CHIK infection. When active case finding by mosquito control teams were deployed, CHIK transmission localities could be identified	✓

	even with low incidence of CHIK and the heterogeneous locations. However, when the epidemic turned severe, symptomatic severe cases definitions were used to track infected CHIK cases, hence the actual number of CHIK cases might be under-reported by leaving out asymptomatic CHIK cases. Primary sources of CHIK cases were from physicians, hospitals, laboratories and field technicians.	
Registration	Not reported	?
Confirmation	A confirmed CHIK case had anti-CHIK IgM antibodies or CHIK RNA or both detected by RT-PCR in the laboratory.	✓
Reporting	Reporting of patient data included reports from physicians outside sentinel network, hospital activity, health insurance fund data and self-reports from infected population to a toll-free hotline. Patient case-data were saved in a EpiData database managed by Cellule Interrégionale d'Epidémiologie.	✓
Data-analysis	Weekly incidence of CHIK cases was recorded from 28 March 2005 to 16 April 2006. Comparative distribution of CHIK cases was tabled by 10-year age group and sex, as reported by active case finding system and sentinel physician network.	✓
Epidemic preparedness	With the explosion of CHIK cases, the surveillance system put in place exceeded its capacity and was not able to follow epidemic trends. Surveillance was then based entirely on sentinel network.	×
Response and control	Not reported	?
Feedback	Not reported	?
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training		
Supervision		
Communication	The study conducted in La Reunion Island revealed that plans were underway for an automated telecommunication system to increase speed of reporting from physicians.	✓
Resources	An operational epidemiologic surveillance system was put in place for the entire island of estimated 244,000 people as of 2004; however, due to a dramatic influx of CHIK cases during the 2005-2006 outbreak, the overloaded capacity of the disease and vector surveillance system was reduced to	×

	a sentinel network of 31 physicians.	
Coordination	Not reported	?
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	Not reported	?
Completeness		
Usefulness		
Sensitivity		
Specificity		
Simplicity		
Flexibility		
Acceptability		
Reliability		
Positive predictive value		
Representativeness	Surveillance data is representative of the entire population, with every locality, both sexes and all age groups affected by the CHIK epidemic. Women and all age groups except those who are less than 20 years old were found to be over-represented in the 2 epidemics in 2005 and 2006. Comparison between global mortality rates and mortality rates attributed to the CHIK epidemic in La Reunion Island confirmed significant excess mortality.	✓
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDING:		
Reduction in the case-fatality rate of epidemic-prone diseases	121/203 death certificates mentioned CHIK as the leading cause of death and the rest stated CHIK as a morbid condition which might have contributed to death. Overall mortality rate was 0.3/1000 persons and median age at death was 79 years old.	✓
Changes in the morbidity pattern of targeted communicable diseases	123 CHIK cases which were deemed more severe had frequent complications of CHIK, including respiratory failure (n=19), cardiovascular decompensation (n =18), meningoencephalitis (n =16) or another neurological disorder (n=7), severe acute hepatitis (n = 11), severe cutaneous effects (n =10), and kidney failure (n=7).	✓
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	[Surveillance goal] Monitor CHIK epidemic trends. [Surveillance goal] Characterise CHIK cases. [Surveillance goal] Detect new clusters of CHIK for location basis for prevention and mosquito control.	✓
ADDITIONAL COMMENTS		
Study conclusions	A more rigorous vector surveillance and control are crucial to	

	reduce health risks linked to CHIK. When incidence of CHIK has been reduced to a low level, early case detection system is needed. To aid that, automated data transmission system is underway to facilitate communication of reports by local clinicians.

Sang *et al.* 2008

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	Identify primary vectors involved in CHIK transmission for implementation of appropriate health measures.
Duration of observation:	11 March 2005 – 31 March 2005
Study start and stop dates:	11 March 2005 – 31 March 2005
Approval by ethics committee:	Ethics approval was not required, as determined by Comoros MOH.
Funding:	Not reported
PARTICIPANTS	
Study sample:	Grande Comore
Intervention group:	2326 adult mosquitoes and 530 mosquito larvae were collected.
Control group:	Nil
Main sources of CHIK import:	Not reported
High-risk people identified:	Not reported
SURVEILLANCE INTERVENTIONS	
Description:	Vector surveillance after a CHIK outbreak of more than 1100 reported cases was carried out. An additional estimated 2500 cases were recorded during the investigation period. Larval and adult mosquito surveys were conducted. CHIKV was isolated from the captured mosquitoes or CHIK RNA was detected by RT-PCR.
Categories of surveillance:	• Active/passive/active+passive surveillance • Disease/vector/disease+vector surveillance • Administrative hierarchy: Country/regional/province/district/locality/enumeration
Country/Income:	Grande Comore, Union of the Comoros/low income
Date when CHIK was made legally notifiable:	Not reported
Mosquito species involved:	Predominantly *Aedes aegypti* and *Culex spp*.
Cost-effectiveness:	Not reported

OUTCOMES:

Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases.

✓ positive fulfillment of the evaluation indicator
✖ negative fulfillment of the evaluation indicator
? uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)

INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	No other case definitions were provided, except that of a CHIK confirmed case. Primary sources of CHIK cases were from public health officers, field technicians and laboratories.	✓
Registration	Not reported	?
Confirmation	The presence of CHIKV was confirmed through virus isolation and CHIK RNA via RT-PCR in the laboratory.	✓
Reporting	Not reported	?
Data-analysis	The estimation of *Aedes aegypti* population density was calculated via the house index, container index and the Breteau index. Adult mosquitoes collection was done by backpack vacuum aspirators and landing collections.	✓
Epidemic preparedness	Not reported	?
Response and control	After the initial outbreak in March 2005 which reported more than 1100 cases, an outbreak surveillance team, consisting of US Centers for Disease Control and Prevention, Kenya Medical Research Institute (KEMRI), WHO and public health officials from Comoros, was formed to investigate the outbreak.	✓
Feedback	Not reported	?
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training		
Supervision		
Communication		
Resources	Backpack vacuum aspirators were commonly used in field surveys. In laboratories, the storage of sera and captured mosquitoes in liquid nitrogen for analysis were also described.	✓
Coordination	Not reported	?
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		

Timeliness	Not reported	?
Completeness		
Usefulness		
Sensitivity		
Specificity		
Simplicity		
Flexibility		
Acceptability		
Reliability		
Positive predictive value		
Representativeness		
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDING:		
Reduction in the case-fatality rate of epidemic-prone diseases	Not reported	?
Changes in the morbidity pattern of targeted communicable diseases	Not reported	?
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	Identify primary vectors involved in CHIK transmission for implementation of appropriate health measures.	✓
ADDITIONAL COMMENTS		
Study conclusions	The study found prominent *Aedes aegypti* breeding sites and there was an abundance of larvae in *disposable* breeding sites. The information allowed planning of control strategies for the short and long-term.	

Sissoko *et al.* 2008

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	Describe Mayotte's first CHIK outbreak.
Duration of observation:	April 2005 - July 2006
Study start and stop dates:	Not reported
Approval by ethics committee:	Comit´e Consultatif de Protection des Personnes dans la Recherche Biom´edicale (CCPPRB) Cr´eteil Henri Mondor (n◦ 06-013), Paris, France.
Funding:	Nil
PARTICIPANTS	
Study sample:	Whole Mayotte

Intervention group:	From 1 January – 7 May 2006, there were 5849 patients notified of CHIK, based on clinical only or lab-confirmed methods. A random sample of 2235 people participated in the cross-sectional survey, using a multi-stage cluster sampling process proposed by WHO.
Control group:	Nil
Main sources of CHIK import:	Possibly La Grande Comore
High-risk people identified:	At high population density areas, like the North-East and North of Mayotte.
SURVEILLANCE INTERVENTIONS	
Description:	• Enhanced passive case notification system. • Active hospital-based surveillance. • Seroprevalence survey. • Cross-sectional clinical community survey to calculate cumulative incidence of presumptive CHIK cases.
Categories of surveillance:	• Active/passive/active+passive surveillance. • Disease/vector/disease+vector surveillance . • Administrative hierarchy: Country/regional/province/district/locality/enumeration.
Country/Income:	Mayotte, Union of the Comoros/low income
Involvement:	Direction des affaires sanitaires et sociales (Dass Mayotte), healthcare providers, hospitals
Date when CHIK was made legally notifiable:	Not reported
Mosquito species involved:	*Aedes albopictus*
Cost-effectiveness:	Not reported

OUTCOMES

Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases.

✓ positive fulfillment of the evaluation indicator
✖ negative fulfillment of the evaluation indicator
? uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)

INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		

Case detection	Case definitions were provided for suspected case, confirmed case, materno-neonatal CHIK fever case and case of severe form. For the seroprevalence survey, CHIK case definition was based on clinical manifestations. Community-based survey respondents had presumptive CHIK fever if there were acute febrile illness and arthralgia from 1 January 2006 – date of interview. Primary sources of CHIK cases were from healthcare providers and hospitals.	✓
Registration	Not reported	?
Confirmation	CHIK case was confirmed in the laboratory via RT-PCR for CHIK RNA or anti-CHIK IgM in serum sample, together with CHIK clinical manifestations and no signs or symptoms of Malaria.	✓
Reporting	Health care professionals and hospitals were encouraged to report suspected and confirmed CHIK cases.	✓
Data-analysis	Index CHIK case was identified in week 15 of 2005. Epidemic curve was plotted from April 2005 - July 2006. Incidence of CHIK cases according to localities were recorded, together with demographics.	✓
Epidemic preparedness	The healthcare providers were alerted and aware of CHIK fever after the GOARN reported a CHIK outbreak in La Grande Comore, a neighbouring island.	✓
Response and control	Not reported	?
Feedback		
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training		
Supervision		
Communication		
Resources		
Coordination		
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	Not reported	?
Completeness	Not reported	×
UsEfulness	Not reported	?
Sensitivity		
Specificity		
Simplicity		
Flexibility		
Acceptability		
Reliability		

Positive Predictive Value	The twin clinical manifestations of fever and joint pain were considered having a highly positive predictive value of CHIK, as both were reported in 90% of CHIK cases in Mayotte and 80-100% of CHIK cases in Asia.	✓
Representativeness	The disease surveillance system and the community-based survey were compared and there was a serious under-estimation of the outbreak severity by the surveillance system, possibly due to undisclosed CHIK cases from the healthcare providers to public health officials, seeking treatment from traditional medical practitioners and poor health insurance cover. For the seroprevalence survey, it was noted that asymptomatic or poorly symptomatic cases might be under-represented, as the CHIK case definition was based on clinical manifestations. The study investigators also found the under-estimation of the scale of CHIK outbreak by the surveillance system and suggested an under-reporting of CHIK cases in the Mayotte's officials' reports.	✗
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDING:		
Reduction in the case-fatality rate of epidemic-prone diseases	One death was reported in a newborn infected with CHIK after birth, and subsequently had septicemia.	✓
Changes in the morbidity pattern of targeted communicable diseases	Morbidity pattern was observed in 316 patients hospitalised with CHIK as of 7 May 2006. Several clinical presentations were reported in 9/316 patients who were in the maternal fetal form, as well as severe complications in 6/316 CHIK patients.	✓
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	[Surveillance goal] Monitor CHIKV infection on a long-term basis. Documented a few unusual CHIK clinical presentations, such as maternal fetal forms and neurological disorders.	✓
ADDITIONAL COMMENTS		
Study conclusions:	The enhanced disease surveillance system detected 6346 CHIK cases between 1 January and 7 May 2006, relating to an overall attack rate of 39.6/1000 population. The study recommended proactive case finding system, complemented with laboratory test and enhanced passive surveillance system for fast detection and prompt response against CHIK. With the first and large CHIK	

	outbreak, efforts are needed to strengthen surveillance and prevent CHIK infections regionally and nationally.

Zayed *et al.* 2012

STUDY CHARACTERISTICS	
Study design:	Descriptive
Study objective:	Describe the vector surveillance in Khokha district and Al Muneera district of the Al Hodayda governorate, Yemen.
Duration of observation:	October 2010 - April 2011
Study start and stop dates:	January 2011 - end date not reported
Approval by ethics committee:	Not reported
Funding:	Department of Defense Global Emerging Infections System (GIS)
PARTICIPANTS	
Study sample:	Khokha district and Al Muneera district of the Al Hodayda governorate.
Intervention group:	From October 2010 – January 2011, 1542 *Dengue-like* (likely CHIK) cases were recorded from 19/26 districts in Al Hodayda governorate, including Khokha district and Al Muneera district. In April 2011, more than 5352 *Dengue-like* (likely CHIK) cases were reported in Al Hodayda, based on clinical diagnosis only.
Control group:	Not reported
Main sources of CHIK import:	Not reported
High-risk people identified:	Not reported
SURVEILLANCE INTERVENTIONS	
Description:	No formal vector surveillance system was in place in Yemen, although it was recognised that CHIK was a major public health issue. The study performed vector surveillance in 2 specific districts to detect CHIKV in captured mosquitoes during the 2011 CHIK outbreak.
Categories of surveillance:	• Active/passive/active+passive surveillance. • Disease/vector/disease+vector surveillance . • Administrative hierarchy: Country/regional/province/district/locality/enumeration.
Country/Income:	Yemen/lower middle income
Involvement:	Ministry of Public Health and Population, WHO, US NAMRU-3, EpiSouth.

Date when CHIK was made legally notifiable:	Not reported	
Mosquito species involved:	*Aedes aegypti*, dominant mosquito	
Cost-effectiveness:	Not reported	
OUTCOMES Based on the 2004 WHO Framework for Monitoring and Evaluating Surveillance and Response Systems for Communicable Diseases. ✓ positive fulfillment of the evaluation indicator ✖ negative fulfillment of the evaluation indicator **?** uncertainty in the fulfillment of the evaluation indicator (including unavailable evidence)		
INDICATORS	SUPPORTING EVIDENCE	✓/✖/?
CORE FUNCTIONS OF SURVEILLANCE SYSTEMS		
Case detection	CHIK case was defined as one that showed CHIK clinical manifestations only. Primary sources of CHIK clinical cases were not reported, although field technicians were the sources for field cases.	✓
Registration	Not reported	?
Confirmation	From October 2010 – January 2011, confirmation of CHIK case was based on clinical manifestations only, without positive laboratory tests. However, in February and March 2011, with the help of NAMRU-3, serology and molecular laboratory tests on human samples were performed to detect CHIKV. It was noted that 15% of 15 hospitalised cases were CHIK, based on the laboratory tests. Subsequently, for the vector surveillance specifically in Khokha and Al Muneera districts, presence of CHIK in the mosquitoes collected was confirmed via molecular tests and isolation of virus.	✓
Reporting	CHIK cases were recorded from the districts in the governorate, but reporting process was not reported.	?
Data-analysis	First reported CHIK isolation from *Aedes aegypti* in Yemen. Four mosquito collection methods were used for field surveillance, including indoor aspirations, indoor and outdoor trapping, knockdown spray of adult and larval collection. Analyses were done on the mosquito larvae, generating mean *Aedes aegypti* larval density and container and Breteau indices. Analyses were also performed on adult mosquitoes (*Aedes aegypti* and *Culex spp*.) and the detected CHIKV.	✓

Epidemic preparedness	When CHIK outbreak happened in October 2010, it was known as a *Dengue-like* unknown fever/ acute FUO. It seemed that little was done until January 2011, when NAMRU-3 team responded to the outbreak, which then had 104 associated CHIK deaths. CHIK cases occurred in the first instance, before response measures were taken, which was too late.	×
Response and control		
Feedback	Mosquito control strategies, such as cleaning water containers and removing stagnant water, were recommended to the people to reduce *Aedes* larval breeding sites. However, these seemed to be futile attempts as water is scarce. Local community cooperation was critical to successful mosquito control.	×
SUPPORT FUNCTIONS OF SURVEILLANCE SYSTEMS		
Standards and guidelines	Not reported	?
Training		
Supervision		
Communication		
Resources		
Coordination		
QUALITY ATTRIBUTES OF SURVEILLANCE SYSTEMS		
Timeliness	The time interval of 3 months (October 2010 – late January 2011) between the Ministry of Public Health and Population report of 1542 cases of *Dengue-like* unknown fever and outbreak response by the Ministry (and WHO) was too long, leading to 104 associated CHIK deaths reported in January 2011. The *Aedes* mosquito control measures came too late, as revealed during the outbreak investigation. Indoor residual spraying was needed for *Aedes* mosquito control, instead of using the methods targeted to eliminate different mosquito species to prevent Malaria transmission. On hindsight, it was highlighted that instead of waiting for cases to happen first then respond, which would delay the timeliness of immediate control efforts, strengthening of routine vector surveillance is crucial for early detection of a potential CHIK outbreak and adequate preparation of appropriate response and control measures.	×
Completeness	Not reported	?
Usefulness		
Sensitivity		

Specificity		
Simplicity		
Flexibility		
Acceptability		
Reliability		
Positive Predictive Value		
Representativeness		
OVERALL GOALS OF SURVEILLANCE SYSTEMS, INCLUDING:		
Reduction in the case-fatality rate of epidemic-prone diseases	104 CHIK associated deaths were reported.	✓
Changes in the morbidity pattern of targeted communicable diseases	Not reported	?
Changes in behaviour of health staff and of the general population.	Not reported	?
Others	[Surveillance goal] Identify primary vector and associated epidemic causative agent.	✓
ADDITIONAL COMMENTS		
Study conclusions:	The CHIK outbreak investigation and vector surveillance showed clearly that suitable mosquito control measures were not present to control CHIK. Strengthening of routine vector surveillance is crucial for early detection of a potential CHIK outbreak and adequate preparation appropriate response and control measures. Current measures underway are the monitoring of abundance of Aedes mosquitoes in Al Hodayda sentinel sites, CHIK/Dengue RNA and degree of insecticide resistance of adult mosquitoes.	

Appendix XVII: Search strategy (as of 26 July 2013)

S/N	Databases	Block Building
1	PubMed	(disease vectors[mh] OR vector[tw] OR mosquito control[mh] OR mosquito control[tw] OR entomology[mh] OR entomolog*[tw] OR surveillance[tw] OR public health surveillance[mh] OR public health surveillance[tw] OR disease outbreaks[mh] OR disease outbreak[tw]) AND (*Aedes aegypti* OR *Aedes albopictus*) AND (*Alphavirus*[mh] OR *Alphavirus*[tw] OR Chikungunya) **Results: 362**
2	Web of Science	TS=((vector OR "mosquito control" OR entomolog* OR surveillance OR "public health surveillance" OR "disease outbreak") AND (*Aedes aegypti* OR *Aedes albopictus*) AND (*Alphavirus* OR Chikungunya)) **Results: 379**
3	Scopus	TITLE-ABS-KEY ((vector OR "mosquito control" OR entomolog* OR surveillance OR "public health surveillance" OR "disease outbreak") AND (*Aedes aegypti* OR *Aedes albopictus*) AND (*Alphavirus* OR Chikungunya)) **Results: 41**
4	ScienceDirect	(vector OR mosquito control OR entomolog* OR surveillance OR public health surveillance OR disease outbreak) AND (*Aedes aegypti* OR *Aedes albopictus*) AND (*Alphavirus* OR Chikungunya) **Results: 438**
5	CINAHL	(TX vector OR TX "mosquito control" OR TX entomolog* OR TX surveillance OR TX "public health surveillance" OR TX "disease outbreak") AND (TX "*Aedes aegypti*" OR TX "*Aedes albopictus*") AND (TX *Alphavirus* OR TX Chikungunya) **Results: 36**
6	CENTRAL	TITLE-ABS-KEY ((vector OR "mosquito control" OR entomolog* OR surveillance OR "public health surveillance" OR "disease outbreak") AND ("*Aedes aegypti*" OR "*Aedes albopictus*") AND (*Alphavirus* OR Chikungunya)) **Results: 0**
7	ProQuest	AB,TI(vector OR "mosquito control" OR entomolog* OR surveillance OR public health surveillance OR disease outbreak) AND ("*Aedes aegypti*" OR "*Aedes albopictus*") AND (*Alphavirus* OR Chikungunya) **Results: 183**
Total records		**1439**

Appendix XVIII: Included studies

Abramides *et al.* 2011

STUDY CHARACTERISTICS		
Study design:		Non-randomised controlled study; large field trial
Study objective:		Examine effectiveness of 5 combined mosquito control interventions to reduce *Aedes albopictus*.
Duration of observation:		Feb - Oct 2008 and May - Dec 2009
Approval by ethics committee:		Study was done according to Research Ethics Committee of Mutua Terrassa Hospital. Inhabitants gave verbal informed consent.
Funding:		Two grants from the Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) and Comissionat per Universitats i Recerca.
Study setting and sample:		Sant Cugat del Valles and Rubi, the towns of Catalonia, Spain. Sample: 6 neighbourhoods of Sant Cugat del Valles, which formed the intervention and control areas. Additionally, the standard area, which consists of other areas (unclear exact locations) of Sant Cugat del Valles, was studied.
Mosquito species:		*Aedes albopictus*
Seasonality of transmission:		Mediterranean climate, with average minimum temperature of 10.2°C. Months of highest activity for *Aedes albopictus* were studied.
Rainfall pattern:		Average annual rainfall of 605 mm
MOSQUITO CONTROL INTERVENTIONS A combination of 5 mosquito control strategies Control: 2 control zones (Mas Gener and Can Barata in 2008; Can Ximelis and Can Mir in 2009) were selected, as no *Aedes* mosquito control programmes was conducted.		
S/N	Description	
1.1	Type:	Habitat control
	Description:	Source reduction via Educational house-to-house visits Remove water from household water storage containers Overturn containers
	Type of habitat:	Houses
	Treatment dosage/ Application rate:	924 houses were visited for source reduction in the intervention areas.
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	2008-2009
1.2	Type:	Habitat control
	Description:	Remove uncontrolled rubbish dumps

	Type of habitat:	Municipal sites and wooden areas
	Treatment dosage/ Application rate:	2.6 ha in the intervention areas.
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	2008 - 2009
1.3	Type:	Chemical control; Larvicide
	Description:	Device TB2/Diflubenzuron (2%; 1 g/hl)
	Type of habitat:	Scuppers, water tanks and road drains with stagnant water.
	Larval instar:	Not reported
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	Not reported
	Droplet size:	Not reported
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	Only mentioned periodic treatment
1.4	Type:	Chemical control; Adulticide
	Description:	Fastac®/Alfacipermetrin (10%; 50 cc/hl)
	Type of habitat:	Plants of public gardens
	Larval instar:	Not reported
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	Not reported
	Droplet size:	Not reported
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	Once in 2008 and 4 times in 2009
1.5	Type:	Biological control; Larvicide
	Description:	Granular Bti (1.2%; 1 g/m^2)
	Type of habitat:	Seasonal streams
	Larval instar:	Not reported
	Residual efficacy:	Not reported

	Treatment dosage/ Application rate:	Not reported
	Droplet size:	Not reported
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	Only mentioned periodic treatment
OUTCOMES		
S/N	Description	
2.1	Type:	Monitoring of intervention outcomes using ovitraps
	Description:	Fifteen ovitraps were used to measure the outcomes of interventions at each of the 6 study areas, by monitoring the amount of mosquito eggs, larvae and pupae. Bti was added to water to prevent formation of adult mosquitoes in trap. Mosquito eggs collected were examined via stereomicrope and water in ovitrap was always checked (frequency unclear) for larvae and pupae. Mosquito eggs were grown to larval stage to confirm species identity in the lab.
	Type of habitat:	Ovitraps were positioned about 200 m away from each other in shaded vegetation at intervention and control areas.
	Length and frequency of intervention:	Fortnight collection of ovitrap wooden paddles to collect mosquito eggs from Aug - Oct 2008 and May - Dec 2009.
	Outcomes on mosquito survival rates or mortality or both:	Mosquito population abundance=mean and median no. of eggs per positive ovitrap; No. of eggs=abundance of sexually active females All mosquito eggs were confirmed *Aedes albopictus*. Statistically significant reduction in no. of eggs in treated areas compared to untreated areas in 2008 and 2009. Median no. of eggs was higher in 2009. Accumulated median of eggs (2008): 175 (intervention); 272 (control) Accumulated median of eggs (2009): 884 (intervention); 1668 (control) *Optimum field application dosage (larvicides): Not reported*
STUDY CONCLUSION		
The 5 combined mosquito control strategies were effective in reducing *Aedes albopictus* eggs in the intervention areas compared to control areas, showing the inaugural evidence in Europe the		

effectiveness of IVM on controlling *Aedes albopictus*.

Farajollahi *et al.* 2012

STUDY CHARACTERISTICS		
Study design:		Non-randomised controlled study; large field trial
Study objective:		Assess the efficacy of dual-action adulticide (DUET™) during night (1 am - 6 am) against *Aedes albopictus*
Duration of observation:		2009 - 2011
Approval by ethics committee:		Not reported
Funding:		By an agreement between US Department of Agriculture and Rutgers University.
Study setting and sample:		Urban residential area; 2315 parcels in Mercer, USA County, New Jersey, USA. The 2315 parcels were distributed into intervention area in Trenton city of 48.4 ha with 1251 parcels and control area of 62.4 ha with 1064 parcels.
Mosquito species:		*Aedes albopictus*
Seasonality of transmission:		Active seasons of *Aedes albopictus*
Rainfall pattern:		Not reported
MOSQUITO CONTROL INTERVENTIONS		
Control: The untreated (no active mosquito control interventions were conducted) control area is similar to the intervention area in terms of socioeconomic conditions and level of *Aedes albopictus*.		
S/N	Description	
1.1	Type:	Chemical control
	Description:	DUET™ adulticide, consisting of sumithrin (5%, 44.94 g/L Active Ingredient) and prallethrin (1%, 8.99 g/L AI) with the synergist piperonyl butoxide (5%, 44.94 g/L AI), was applied using a vehicle-mounted ULV cold aerosol sprayer and a SmartFlow system.
	Type of habitat:	Houses and yards
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	2009: 86.2g/ha (0.81 g/ha AI of prallethrin, 4.04 g/ha AI of sumithrin, and 4.04 g/ha AI of piperonyl butoxide) 2010 and 2011: 42.7 g/ha (0.40 g/ha AI of prallethrin, 2.02 g/ha AI of sumithrin, and 2.02 g/ha AI of piperonyl butoxide) A total of 4015 drops of adulticide were applied at 136.04ml/min.
	Droplet size:	Volume median diameter(VMD)=$DV_{0.5}$=15.2um
	Pre-intervention mosquito	Reported for both intervention area and control area

	measurement:	
	Length and frequency of intervention:	2009: Single nighttime application 2010: Dual nighttime application, spaced 1-2 days 2011: Dual nighttime application, spaced 1-2 days Each application took about hrs.
OUTCOMES		
S/N	Description	
2.1	Type:	Monitoring of intervention outcomes using BGS traps
	Description:	BGS traps were used with BG-lure, a combination of fatty acids, ammonia and lactic acid. 2009 and 2010: 12 BGS traps (intervention) and 15 BGS traps (control) in 200 m sampling 2011: 16 BGS traps (intervention) and 24 BGS traps (control) in 175 m sampling
	Type of habitat:	BGS traps were positioned about 175 - 200 m away from each other in the backyards of homes. Adult mosquitoes collected from traps were brought back to lab for identification and measurement of abundance.
	Length and frequency of intervention:	Sampled weekly for 24 hrs from 2009 - 2011
	Outcomes on mosquito survival rates or mortality or both:	Overnight percentage reduction of mosquito adult population. Single adulticide treatment at full label rate of 86.2 gm/ha resulted in 72.7±5.4% (SE) reduction, which is significantly higher (p= 0.04) than 54.0±4.7% reduction from adulticide treatment at mid-label rate of 42.7 gm/ha. Dual adulticide treatment at mid-label rate were significantly more effective (p= 0.003) than single adulticide treatment at full rate and resulted in an average percent reduction of 85.0±5.4%.
STUDY CONCLUSION		
Nighttime ULV adulticiding is effective in reducing *Aedes albopictus* adult mosquitoes and may be considered for use in integrated pest management programs and during disease epidemics.		

Ghosh *et al.* 2011

STUDY CHARACTERISTICS	
Study design:	Pseudo-randomised controlled study; small field trial
Study objective:	Examine the efficacy of 2 potential fish guppy and mosquito fish (*Poecilia reticulata* and *Gambusia affinis*) on *Aedes aegypti* larvae
Duration of observation:	Mar – May 2006 and Jul – Oct 2006
Approval by ethics committee:	Ethics approval was obtained by the Institutional Ethics Committee of National Institute of Malaria Research for the knowledge, attitude and practice survey and community consent

		was given for whole study.
Funding:		Indian Council of Medical Research, New Delhi
Study setting and sample:		Domatmari village (2040 people) and Srinivaspura village (568 people) from the Tumkur district and Balmanda village (1342) from the Kolar district.
Mosquito species:		*Aedes aegypti*
Seasonality of transmission:		Dry and prone to drought, with temperatures from 13 - 39°C
Rainfall pattern:		Low, irregular rainfall of 600 – 800 mm
MOSQUITO CONTROL INTERVENTIONS		
Control: Although matched control villages were reported, insufficient details were reported, except that during the study, villagers from the control areas also adopted the mosquito control intervention of releasing predatory fishes into the tanks. Study investigators reported consulting a statistician regarding the consequential effect on the results, and the impact of pre- and post-treatment was purportedly assessed, however no further elaboration was made.		
S/N	Description	
1.1	Type:	Biological control with strong concentration on information, education and communication.
	Description:	• Fish guppies Poecilia were used in Domatmari and Srinivaspura (482 tanks for both villages) and mosquito fishes Gambusia were used in Balmanda (337 tanks). • A knowledge, attitude and practice survey on CHIK was conducted in the 2 villages of Tumkur district. • Information, education and communication campaigns were done in Domatmari and Balmanda, before and after predatory fish interventions. • Aedes larval surveys on impact of interventions were conducted in all 3 villages.
	Treatment dosage/ Application rate:	Ten to fifteen fishes were released into each indoor cement tank.
	Type of habitat:	Indoor cement tanks in homes
	Pre-intervention mosquito measurement:	Yes; Pre-intervention *Aedes* larval surveys were conducted in Mar and Jul 2006 to determine types of breeding sites and % breeding contribution. Pre-intervention CHIK fever cases were also surveyed to compare with post-intervention CHIK fever cases.
	Length and frequency of intervention:	Tanks that had predatory fishes were checked after a week and after a month.
OUTCOMES		
S/N	Description	

2.1	Outcomes on mosquito survival rates or mortality or both:	The impact of predatory fishes (*Poecilia*) on *Aedes* larval was estimated: • HI 83.9 baseline to 7.1 1-wk post-fish to 35.7 1-mth post-fish. • CI 32.5 baseline to 7 1-wk post-fish to 13.9 1-mth post-fish. • BI 90.3 baseline to 10.7 1-wk post-fish to 39.2 1-mth post-fish. The impact of predatory fishes (*Gambusia* + information, education and communication) on *Aedes* larval was estimated: • HI 38.4 baseline to 1.2 1-wk post-fish to 18.9 1-mth post-fish. • CI 26.1 baseline to 1.9 1-wk post-fish to 15.2 1-mth post-fish. • BI 43.5 baseline to 2.5 1-wk post-fish to 21.5 1-mth post-fish. Mean *Aedes* larval density (per dip): At baseline: Domatmari 9.2 (95% CI: 7.4-12.2); Srinivaspura 10.6 (95% CI: 7.8-14.4); Balmanda 14.3 (95% CI: 11.2-16.4) After 1 wk: No larvae After 1 mth: Domatmari 0.2(95% CI: 0.08-0.4, $p > 0.001$); Srinivaspura 7.8 (95% CI:4.8-9.7, $p < 0.05$); Balmanda (95% CI: 8.5-14.1, $p < 0.05$)

STUDY CONCLUSION

Poecilia with information, education and communication is an effective and sustainable mosquito control strategy. After information, education and communication, monthly monitoring and release of *Poecilia* into indoor water tanks may be recommended. *Gambusia* does not work well due to their unsustainable population in domestic receptacles. Proper water storage practices focused information, education and communication with *Poecilia* introductions and vector sanitation involving the local administration and community, is suggested as the best strategy for *Aedes* control.

Kamgang *et al.* 2011

STUDY CHARACTERISTICS

Study design: Cluster-randomised controlled study; lab study

Study objective:	Examine the resistance level of larval and adult *Aedes albopictus* and *Aedes Aegypti* to the 4 insecticides deltamethrin, DDT, fenitrothion and propoxur.
Duration of observation:	April 2007 (Cameroon) and June 2007 (Gabon)
Approval by ethics committee:	Not reported
Funding:	Agence Nationale pour la Recherche that funded the EpiDengue project (ANR 05 SEST 010-01).
Study setting and sample:	5 urban areas (Garoua, Bertoua, Yaoundé, Bafia, Buea) of Cameroon and an urban area (Libreville) of Gabon, Central Africa
Mosquito species:	*Aedes albopictus* and *Aedes Aegypti*
Seasonality of transmission:	Not reported
Rainfall pattern:	Not reported

MOSQUITO CONTROL INTERVENTIONS

WHOPES guidelines were used to guide the conduct of the larval and adult bioassays in the lab.

Control: For each larval bioassay, a control was set up, consisting of 1ml of ethanol (for temephos) or 1ml of mineral water (for Bti), 99ml of mineral water and 25 late-third/fourth instars. For each adult bioassay, 1 batch of 25 mosquitoes was used as control.

S/N	Description	
1.1	Type:	Chemical control; Larvicide
	Description:	Temephos, an organophosphate larvicide
	Type of habitat:	Lab study; larvae were placed in water-filled plastic cups
	Larval instar:	25 late 3rd or early 4th larval instars for each bioassay
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	5 concentrations (specifics unclear) of temephos at 1ml were used with 99 ml of mineral water; done with 2 - 4 replicates
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	24 hrs
1.2	Type:	Biological control; Larvicide
	Description:	Bti
	Type of habitat:	Lab study; larvae were placed in water-filled plastic cups
	Larval instar:	25 late 3rd or early 4th larval instars for each bioassay
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate::	5 concentrations (specifics unclear) of Bti at 1 ml were used with 99 ml of mineral water; done with 2 - 4 replicates
	Pre-intervention	Not reported

	mosquito measurement:	
	Length and frequency of intervention:	24 hrs
1.3	Type:	Chemical control; Adulticide
	Description:	0.06% Deltamethrin (pyrethroid)
	Type of habitat:	Deltamethrin-impregnated filter papers
	Larval instar:	2 - 4 batches of 25 females mosquitoes (2 - 4 days old)
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	Not reported
	Droplet size:	Not applicable
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	1 hour
1.4	Type:	Chemical control; Adulticide
	Description:	4% DDT (organochlorine)
	Type of habitat:	DDT-impregnated filter papers
	Larval instar:	2 - 4 batches of 25 females mosquitoes (2 - 4 days old)
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	Not reported
	Droplet size:	Not applicable
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	1 hour
1.5	Type:	Chemical control; Adulticide
	Description:	0.5% fenitrothion (organophosphate)
	Type of habitat:	Fenitrothion-impregnated filter papers
	Larval instar:	2 - 4 batches of 25 females mosquitoes (2 - 4 days old)
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	Not reported

	Droplet size:	Not applicable
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	1 hour
1.6	Type:	Chemical control; Adulticide
	Description:	0.3% propoxur (carbamate)
	Type of habitat:	Propoxur-impregnated filter papers
	Larval instar:	2 - 4 batches of 25 females mosquitoes (2 - 4 days old)
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate::	Not reported
	Droplet size:	Not applicable
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	1 hour
OUTCOMES		
S/N	Description	
2.1	Outcomes on mosquito survival rates or mortality or both:	• The larval and adult mosquitoes mortality rates were corrected with Abbott's formula, as recommended by WHOPES guidelines. • The LC_{50}, LC_{95}, RR_{50} and RR_{95} values and the 95% CI showed susceptibility of all mosquito samples to temephos and Bti. • One Aedes aegypti sample from Libreville and 2 Aedes albopictus samples from Buea and Yaoundé were resistant to DDT (mortality 36% to 71%). • Resistance to deltamethrin was also suspected in Aedes albopictus from Yaoundé (83% mortality). • All other field mosquito samples were susceptible to deltamethrin, DDT, fenitrothion and propoxur. • There was no increase in the knockdown times (Kdt_{50} and Kdt_{95}) in the Yaoundé resistant sample compared to other

	Aedes albopictus samples, suggesting the possible involvement of metabolic resistance to deltamethrin and DDT. • Optimum field application dosage (larvicides/adulticides): Not reported
STUDY CONCLUSION The study results may guide insecticide-based mosquito control strategies. There is a need for a bigger monitoring of insecticide resistance in *Aedes* mosquitoes.	

Nelder *et al.* 2010

STUDY CHARACTERISTICS	
Study design:	Cluster-randomised controlled study; lab study and small simulated field trial
Study objective:	Examine the combined effectiveness of Agnique® and Altosid® in lab and field conditions
Duration of observation:	Aug 2007- Aug 2008
Approval by ethics committee:	Not reported
Funding:	New Jersey Agricultural Experiment Station and federal funds from an agreement between the USDA and Rutgers University
Study setting and sample:	Field trials were conducted in 100m^2 field plots in Mercer County and Monmouth County, New Jersey. *Aedes albopictus* larvae were collected from an auto-salvage yard in Trenton, New Jersey, USA.
Mosquito species:	*Aedes albopictus*
Seasonality of transmission:	Field site temperatures of 6- 28°C
Rainfall pattern:	20 - 75 mm precipitation
MOSQUITO CONTROL INTERVENTIONS A combination of two mosquito control strategies. Mosquito colony maintenance and rearing were guided by established protocols. Control: Lab: Controls were without insecticides, consisting of 10 of 400 ml Tri-Pour VWR lidded containers with 250 ml of tap water and 10 4th instars and 0.04 g of lactalbumin/Brewer's yeast. Field: 10 paired control buckets without insecticides, randomly placed in shaded areas, with 8l of tap water and 5 g of crushed oak leaves.	

S/N	Description	
1.1	Type:	Biological control; Insect growth regulator
	Description:	Altosid® ((S)-methoprene) is tested against *Aedes albopictus* in lab and field conditions.
	Type of habitat:	Lab: 250 ml of tap water in 400 ml Tri-Pour lidded containers at 25 - 27°C.

		Field: Simulated field habitats were created using 11 L black plastic buckets filled with 8 8 L water and 5g of crushed oak leaves for nutrients. Ten treatment and 10 control buckets were paired and randomly placed in shaded areas.
	Larval instar:	Lab: Ten 4th instars/container x 5 replicates x 11 treatment conc
	Residual efficacy:	Reported long residual
	Treatment dosage/ Application rate:	Lab: Mean pellet mass=0.13 ± 0.009 g Field: A pellet each of Agnique® and Altosid® were added to each intervention bucket.
	Droplet size:	Not applicable
	Pre-intervention mosquito measurement:	Lab: Not reported Field: Pre-intervention collection on 8 Aug 2008 was done. Buckets were placed 15 days before insecticide treatment to collect the mosquito eggs, then using aquarium fish net (25 x 55 cm) attached to each bucket to collect the larvae and pupae for identification.
	Length and frequency of intervention:	Lab: 10 days x [11(treatment conc)+1(control)]= 120 days. Each day = 12 hr light: 12 hr dark Field: 24 Jul 2008 – 31 Oct 2008 (Field trials ended on 24 Oct 2008 in Mercer County)
1.2	Type:	Chemical control; Larvicide and pupicide
	Description:	Agnique® MMF acts by producing a monomolecular film on water surface.
	Type of habitat:	Lab: 250 ml of tap water in 400ml Tri-Pour lidded containers at 25 - 27°C. Field: Simulated field habitats were created using 11 L black plastic buckets filled with 8 8L water and 5 g of crushed oak leaves for nutrients. Ten treatment and 10 control buckets were paired and randomly placed in shaded areas. Buckets were placed 15 days before insecticide treatment to collect the mosquito eggs, then using aquarium fish net attached to each bucket to collect the larvae and pupae for identification.
	Larval instar:	Lab: Ten 4th instars/container x 5 replicates x 11 treatment conc
	Residual efficacy:	Reported long residual
	Treatment dosage/ Application rate:	Lab: Mean pellet mass=0.06 ± 0.006 g Field: A pellet each of Agnique and Altosid were added to each intervention bucket.
	Droplet size:	Not applicable
	Pre-intervention mosquito measurement:	Lab: Not reported Field: Pre-intervention collection on 8 Aug 2008 was done. Buckets were placed 15 days before insecticide treatment to collect the

		mosquito eggs, then using aquarium fish net (25 x 55 cm) attached to each bucket to collect the larvae and pupae for identification.
	Length and frequency of intervention:	Lab: 10 days x [11(treatment conc)+1(control)]= 120 days. Each day = 12 hr light:12 hr dark Field: 24 Jul 2008 – 31 Oct 2008 (Field trials ended on 24 Oct 2008 in Mercer County)
OUTCOMES		
S/N	Description	
2.1	Type:	In lab
	Description:	Both insecticides Agnique® and Altosid® were added to containers 2 hours before experiment and the number of adult mosquitoes evolved and survived was counted after 10 days. This number was converted to the proportion of *Aedes albopictus* surviving.
	Outcomes on mosquito survival rates or mortality or both:	Combined efficacy of Agnique® and Altosid® • Survival was highest in the control and lowest in the Altosid® groups (T2–T11), and the Agnique® alone (T1) group was in between the other groups. Efficacy of Agnique® and Altosid® after drying in lab • No differences were found between the 120-day pre-drying survival and post-drying with flooding survival. Removing moisture from simulated habitats in the lab does not neutralize the effects of Altosid® against fourth instar Aedes albopictus. Effect of stage-specific mortality using Agnique® only • had reduced the fourth instar the most among all first to fourth instars.
2.2	Type:	In field
	Description:	Collection of 15 pupae was done every 7 days for 70 days at Mercer County and 77 days for Monmouth County. The number of pupae surviving was calculated and number of adult mosquitoes was converted to the proportion of *Aedes albopictus* surviving.
	Outcomes on mosquito survival rates or mortality or both:	Combined efficacy of Agnique® and Altosid® Although survival was different between intervention and control groups from 7 – 70 days post-intervention, there was no difference in survival after 70 days.
STUDY CONCLUSION		
The combined use of Agnique® and Altosid® suppressed *Aedes albopictus* for a minimum of 120 days in lab conditions and 32 days in field. Taking into account costs and limited efficacy, the combined use of Agnique® and Altosid® is not recommended. However, Agnique® and		

Altosid® should be considered as important interventions in the management and prevention of establishment of *Aedes albopictus*, and can provide long-term control of *Aedes albopictus* larvae and pupae.

Ohba *et al.* 2013

STUDY CHARACTERISTICS		
Study design:		Non-randomised controlled study; small simulated field trial
Study objective:		Examine the effectiveness of pyriproxyfen against *Aedes albopictus* in semi-field conditions
Duration of observation:		Not reported
Approval by ethics committee:		Not reported
Funding:		Innovative Mosquito control Consortium, Bill & Melinda Gates Foundation and joint research fund between Nagasaki University and Sumitomo Chemical Co. Ltd
Study setting and sample:		6 microcosms in a greenhouse of Nomozaki Experimental Station, Nagasaki University, Japan
Mosquito species:		*Aedes albopictus* collected as eggs and larvae, to allow for growth to fourth instars larvae.
Seasonality of transmission:		Not reported
Rainfall pattern:		Not reported
MOSQUITO CONTROL INTERVENTIONS		
A combination of 2 mosquito control strategies. Mosquito colony maintenance and rearing were guided by established protocols.		
Control:		
For experiment 1: Untreated 195-denier 75 holes/inch^2 50 x 50 x 50 cm square polyethylene net		
For experiment 2: Similar to experiment 1 control		
S/N	Description	
1.1	Type:	Biological control; Insect growth regulator (Juvenile hormone analogue)
	Description:	Pyriproxyfen-treated mosquito nets It works by limiting egg hatching in adult female mosquitoes in contact with pyriproxyfen and limiting growth of larvae *of Aedes albopictus* to the pupae and adult stages by the dissemination of pyriproxyfen into larvae breeding areas by adult mosquitoes contact with the pyriproxyfen impregnated bed nets. <u>Experiment 1</u> *Intervention:* 350 mg/m^2 of 1% pyriproxyfen (Sumilarv®) impregnated on a 195-denier 75 holes/inch^2 50 x 50 x 50 cm square polyethylene net.

		<u>Experiment 2</u> *Intervention:* Similar to experiment 1 intervention, except using 35 mg/m^2 of 0.1% pyriproxyfen
	Type of habitat:	Six microcosms in a greenhouse were prepared. Five artificially torn holes of 5 cm in diameter were created on each net to mimic damage and let mosquitoes fly through to reach the mouse within the net for blood feeding. A mouse was placed in each microcosm for blood feeding by mosquitoes at about 1-week intervals for the 2 experiments.
	Larval instar:	None. One humdred pairs of lab-reared *Aedes albopictus* released into each microcosm.
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	350 mg/m^2 (experiment 1)/ 35 mg/m^2 (experiment 2) of 1% pyriproxyfen (Sumilarv®) impregnated on the polyethylene net. The net was immersed in pyriproxyfen solution for 1 hour and dried overnight.
	Droplet size:	Not applicable
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	*Aedes albopictus* abundance was monitored on each day of mouse blood feeding: Experiment 1: 0, 4, 11, 20 days after release of mosquitoes Experiment 2: 0, 6, 13, 21, 27, 34, 44 days after release of mosquitoes
OUTCOMES		
S/N	Description	
2.1	Outcomes on mosquito survival rates or mortality or both:	The number of eggs laid by the released adult mosquitoes in the pyriproxyfen-treated microcosms was significantly lowered compared to untreated control in experiments 1 and 2. Hatching of *Aedes albopictus* eggs was significantly suppressed compared to untreated control in both experiments 1 and 2. Pupal mortality was significantly increased compared to control in both experiments 1 and 2. The effect of pyriproxyfen-treated bed nets covers a maximum distance of 500 m, taking into account the flight distance of *Aedes albopictus*.
STUDY CONCLUSION		
The study confirmed pyriproxyfen's effectiveness against *Aedes albopictus* in semi-field conditions. Adult *Aedes albopictus* mosquitoes in contact with pyriproxyfen-treated bed nets has been shown to decrease egg hatching in adult females and increase pupae mortality. It could be an important tool to control *Aedes albopictus* transmitted diseases.		

Preet *et al.* 2011

STUDY CHARACTERISTICS		
Study design:		Non-randomised controlled study; lab study
Study objective:		Examine the efficacy of potash alum against the larvae of *Aedes aegypti* in laboratory conditions.
Duration of observation:		Not reported
Approval by ethics committee:		Not reported
Funding:		University Grants Commission and the Department of Science and Technology, New Delhi, India
Study setting and sample:		Dayalbagh in Agra, India
Mosquito species:		*Aedes aegypti* larvae
Seasonality of transmission:		Not reported
Rainfall pattern:		Not reported
MOSQUITO CONTROL INTERVENTIONS		
WHO guidelines were used to guide the conduct of the larval bioassays in the lab. Control: Four control beakers were prepared for each of the 4 types of instars, each control containing 250 ml of water and 20 of the particular instars.		
S/N	Description	
1.1	Type:	Biological control; Botanical compound: Potash alum
	Description:	Potash alum is the potassium double sulphate of aluminium, commonly known as Ming Fan in traditional Chinese medicine and Phitkari in Ayurveda.
	Type of habitat:	250 ml deionised water/beaker
	Larval instar:	All 4 instars were used: [20 1st instars/beaker x 5 replicates x 6 treatment conc] x 4 instars= 2400 larvae
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	Potash alum at 6 concentrations of 10, 20, 30, 50, 70 to 100 mg/l was used
	Droplet size:	Not applicable
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	24 hrs
OUTCOMES		
S/N	Description	
2.1	Outcomes on	% mortality for all instars after 24-hour exposure to potash alum:

mosquito survival rates or mortality or both:	• 10 ppm: 0-35%. • 20 ppm: 10-55%. • 30 ppm: 30-80%. • 50 ppm: 40-95%. • 70 ppm: 50-100%. • 100 ppm:65-100% . LC_{50} of crude potash alum:15.29-48.53 ppm LC_{50} of standard potash alum:20.50-65.10 ppm LC_{90} of crude potash alum:39.29-204.8 ppm LC_{90} of standard potash alum:54.22-224.41 ppm LC_{99} of crude potash alum:84.81-662.25 ppm LC_{99} of standard potash alum:119.78-615.41 ppm No mortality in control groups over the experiment. First instar larvae was the most susceptible; fourth instar was the least susceptible to potash alum.

STUDY CONCLUSION

Potash alum, a fairly cheaper and readily available eco-friendly compound might be recommended as a potential potent chemical parricide against *Aedes aegypti* breeding sites in homes.

Rajkumar *et al.* 2010

STUDY CHARACTERISTICS	
Study design:	Randomised controlled study; lab study
Study objective:	Examine the larvicidal activities of essential oil of Clausena dentate leaves and its 4 major compounds.
Duration of observation:	Not reported
Approval by ethics committee:	Not reported
Funding:	Not reported
Study setting and sample:	India
Mosquito species:	*Aedes aegypti* larvae obtained from a lab colony
Seasonality of transmission:	Not reported
Rainfall pattern:	Not reported

MOSQUITO CONTROL INTERVENTIONS

WHO guidelines were used to guide the conduct of the larval bioassays in the lab.

Control: The control beaker contained 1ml of Dimethyl Sulfoxide (DMSO) in 249 ml of filtered

tap water and 25 early 4th instars.		
S/N	Description	
1.1	Type:	Biological control; Botanical compound: Essential oil and its components from the *Clausena dentata* leaves
	Description:	*Clausena dentata* leaves were collected from the Sirumalai hills, Dinugal District, India and its essential oil and 4 different compounds were tested at different mass concentrations: Essential oil (100, 200, 300 and 400 mg/l) Sabinene (20, 40, 60 and 80 mg/l) Biofloratriene (20, 40, 60 and 80 mg/l) Borneol (20, 40, 60 and 80 mg/l) Beta-bisabolol (20, 40, 60 and 80 mg/l)
	Type of habitat:	*Aedes aegypti* larvae were reared from a lab colony at 27±2 °C, 70 – 80% relative humidity and 14:10 light and dark photoperiod.
	Larval instar:	25 early 4th instars/beaker x 4 replicates x 4 treatment conc= 400 mosquito larvae
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	Potash alum at 6 concentrations of 10, 20, 30, 50, 70 to 100 mg/l was used
	Droplet size:	Not applicable
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	24 hrs
OUTCOMES		
S/N	Description	
2.1	Outcomes on mosquito survival rates or mortality or both:	24-hr % mortality using essential oil • 100 mg/l: 39.3%. • 200 mg/l: 58.8%. • 300 mg/l: 82.3%. • 400 mg/l: 100%. Control (no essential oil): 1.5% LC_{50} of essential oil: 140.2 mg/l LC_{50} of Sabinene: 27.3mg/l (most potent compound) LC_{50} of Biofloratriene: 47.4mg/l LC_{50} of Borneol: 43.5mg/l LC_{50} of Beta-bisabolol: 33.2mg/l

	LC_{90} of essential oil: 341.6 mg/l LC_{90} of Sabinene: 62.2 mg/l LC_{90} of Biofloratriene: 78.3mg/l LC_{90} of Borneol: 73.4mg/l LC_{90} of Beta-bisabolol: 70.3mg/l Overall significant larvicidal activity.

STUDY CONCLUSION

The 4 individual compounds of Clausena dentate leaves were more potent larvicides than the essential oil. The essential oil of Clausena dentate leaves and its 4 major compounds may be a potent source of natural larvicides against *Aedes aegypti* larvae.

Tan *et al.* 2011

STUDY CHARACTERISTICS	
Study design:	Non-randomised non-controlled study; small field trial
Study objective:	Assess mosquito control operation against CHIK
Duration of observation:	July – September 2008
Approval by ethics committee:	Not reported
Funding:	Ministry of Finance for the Reinvestment Fund
Study setting and sample:	A concrete slabs factory in an industrial estate of Kranji, Northwest of Singapore
Mosquito species:	*Aedes albopictus*
Seasonality of transmission:	Not reported
Rainfall pattern:	Not reported

MOSQUITO CONTROL INTERVENTIONS

Day 0: A cluster of 22 CHIK cases was notified on 1 Aug 2010; pre-intervention phase

A combination of 5 mosquito control strategies was employed over a period of 1 month.

Control: No control

S/N	Description	
1.1	Type:	Habitat control; Source reduction
	Description:	Operations were carried out to search and destroy mosquito breeding sites. Overgrown vegetation were shortened and removed.
	Type of habitat:	Factory and surrounding factories
	Treatment dosage/ Application rate:	Not reported
	Pre-intervention mosquito measurement:	Before the start of mosquito control activities (day 0), sweep net method was employed by 12 officers and BGS traps were placed to survey mosquitoes. 140 mosquitoes (64.3% *Aedes albopictus* and 35.7% *Culex spp*.) were caught.

	Length and frequency of intervention:	Day 0 (1 - 5 p.m.): 70 officers deployed Daily for next 1 month: 24 officers deployed
1.2	Type:	Biological control; Larvicide
	Description:	Bti (Vectobac WG) misting with water-dispersable granules formulation
	Type of habitat:	Observable but inaccessible potential breeding sites
	Treatment dosage/ Application rate:	500 g/ha
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	Days 0,1,3,4,5
1.3	Type:	Chemical control; Larvicide
	Description:	1% SG temephos (Abate)
	Type of habitat:	Mosquitoes in about 180-ha, including a 20-ha concrete slabs factory with a worker's dormitory and 8 other industrial areas
	Larval instar:	Not reported
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	1g/10L water
	Droplet size:	Not reported
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	Days 0,1,3,4,5
1.4	Type:	Chemical control; Larvicide and adulticide
	Description:	Actellic 50EC (Pirimiphos-methyl) is an organophosphate released via indoor ULV misting
	Type of habitat:	The factory's workers' dormitories
	Larval instar:	Not reported
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	200g a.i./ha
	Droplet size:	Not reported
	Pre-intervention mosquito measurement:	Not reported

	Length and frequency of intervention:	Days 0 and 3
1.5	Type:	Chemical control; Larvicide and adulticide
	Description:	Actellic 50EC (Pirimiphos-methyl) released via mass outdoor thermal fogging using 48 portable and 1 vehicle-mounted fogging machines
	Type of habitat:	About 180 ha of factory area and other 8 industrial areas
	Larval instar:	Not reported
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	100 g a.i./ha
	Droplet size:	Not reported
	Residential block configuration:	Not reported
	Route of spray vehicle:	Not reported
	Meteorological conditions:	Not reported
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	Days 1 (6 a.m.), 4, 5
OUTCOMES		
S/N	Description	
2.1	Type:	Monitoring of intervention outcomes using BGS traps
	Description:	Effectiveness of mosquito control strategies was determined by placing 4 BGS traps for adult mosquitoes at the same location from 4pm-10am the following day and monitored weekly for 7 weeks) Identification and analyses of mosquitoes were done in the national mosquito reference lab (Environmental Health Institute) by RT-PCR.
	Type of habitat:	Outdoor, surrounding the factory workers' quarters and in the open shed
	Length and frequency of intervention:	Days 0, 1, 8, 15, 22, 29, 36, 43, 50
	Outcomes on mosquito survival	173 adult mosquitoes were captured, out of which 120 (69.4%) were *Aedes albopictus*. None was *Aedes aegypti*.

rates or mortality or both:	2700 *Aedes albopictus* larvae were collected from 33 breeding sites found. Female *Aedes albopictus* caught were tested for CHIKV via real-time RT-PCR assay. Pre-intervention: 6/71 female *Aedes albopictus* were CHIK positive. Three out of these 6 CHIKV positive *Aedes albopictus* were found to have spread CHIK, as evident by the presence of CHIKV RNA in the head and thorax. Viral load was 50pfu – $5x10^4$pfu/mosquito. • Post-intervention: 1/71 female Aedes albopictus were CHIK positive. There was still CHIK-infected mosquito after intervention. Mosquito control measures resulted in a 90% reduction of adult *Aedes albopictus* caught by BG Sentinel Traps. Findings above brought about continued intensive mosquito control operation in affected localities, leading to decrease in mosquito numbers and interrupted spread of disease.

STUDY CONCLUSION

The extensive combination of mosquito control strategies was effective in reducing risk of CHIK in Kranji.

Tikar *et al.* 2008

STUDY CHARACTERISTICS	
Study design:	Non-randomised controlled study; lab study
Study objective:	Monitor *Aedes aegypti* susceptibility to the insecticides so as to develop suitable and effective mosquito control strategy for CHIK/Dengue
Duration of observation:	July 2005 – January 2006
Approval by ethics committee:	Not reported
Funding:	Not reported
Study setting and sample:	Urban areas of Delhi, Jodhpur, Chennai, Mumbai and Coimbatore, India
Mosquito species:	*Aedes aegypti* larvae were collected mainly from air coolers, water storage tank, earthen pots and plastic containers of selected areas.
Seasonality of transmission:	Tropical wet and dry
Rainfall pattern:	Tropical wet and dry

MOSQUITO CONTROL INTERVENTIONS

WHO guidelines were used to guide the conduct of the larval bioassays in the lab.

Control: A laboratory-reared GS1 strain of *Aedes aegypti* larvae without selection pressure to any insecticide was used. Two replicates were done for the control.

S/N	Description	
1.1	Type:	Chemical control; Larvicide
	Description:	90.63% pure Temephos
	Type of habitat:	Lab: 99 ml of dechlorinated tap water in a 200 ml disposable cup
	Larval instar:	Field *Aedes aegypti* larvae collected were reared to adult stage and the females produced eggs, which were reared to late third and early fourth instars before use. Lab: Twenty 4th instars/container x 3 replicates x 6-7 treatment conc
	Treatment dosage/ Application rate:	Unidentified 6-7 concentrations of temephos, giving 10-90% mortality
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	24 hrs; Each day = 12 hr light: 12 hr dark
1.2	Type:	Chemical control; Larvicide
	Description:	98% pure Fenthion
	Type of habitat:	Lab: 99 ml of dechlorinated tap water in a 200 ml disposable cup
	Larval instar:	Field *Aedes aegypti* larvae collected were reared to adult stage and the females produced eggs, which were reared to late third and early fourth instars before use. Lab: Twenty 4th instars/container x 3 replicates x 6-7 treatment conc
	Treatment dosage/ Application rate:	Unidentified 6-7 concentrations of fenthion, giving 10-90% mortality
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	24 hrs; Each day = 12 hr light: 12 hr dark
1.3	Type:	Chemical control; Larvicide
	Description:	96% pure Malathion
	Type of habitat:	Lab: 99 ml of dechlorinated tap water in a 200 ml disposable cup
	Larval instar:	Field *Aedes aegypti* larvae collected were reared to adult stage and the females produced eggs, which were reared to late third and early fourth instars before use. Lab: Twenty 4th instars/container x 3 replicates x 6-7 treatment conc
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	Unidentified 6-7 concentrations of malathion, giving 10-90% mortality

	Droplet size:	Not reported
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	24 hrs; Each day = 12 hr light: 12 hr dark
1.4	Type:	Chemical control; Larvicide
	Description:	70% pure DDT
	Type of habitat:	Lab: 99 ml of dechlorinated tap water in a 200 ml disposable cup
	Larval instar:	Field *Aedes aegypti* larvae collected were reared to adult stage and the females produced eggs, which were reared to late third and early fourth instars before use. Lab: Twenty 4th instars/container x 3 replicates x 6-7 treatment conc
	Residual efficacy:	Not reported
	Treatment dosage/ Application rate:	Unidentified 6 - 7 concentrations of DDT, giving 10 - 90% mortality
	Droplet size:	Not reported
	Pre-intervention mosquito measurement:	Not reported
	Length and frequency of intervention:	24 hrs; Each day = 12 hr light:12 hr dark
OUTCOMES		
S/N	Description	
2.1	Type:	24-hr % mortality of larvae was calculated.
	Outcomes on mosquito survival rates or mortality or both:	Compared to lab reference strain of *Aedes aegypti*, • 0.33-7.11 fold more LC_{50} of temephos in field-reared Aedes aegypti. • 0.36–3.00 fold more LC_{50} of fenthion in field-reared Aedes aegypti. • 0.65–2.84 fold more LC_{50} of malathion in field-reared Aedes aegypti. • 2.16–20.8 fold more LC_{50} of DDT in field-reared Aedes aegypti.
STUDY CONCLUSION		
All 4 larvicides tested were still effective in the CHIK/Dengue control program. *Aedes aegypti* from various locations studied are still susceptible to temephos, fenthion and malathion, whereas low level of DDT resistance was noticed in field-collected *Aedes aegypti*. Temephos was found to be relatively more effective in controlling *Aedes aegypti*, followed by fenthion, malathion and DDT.		

Appendix XIX: Search strategy (as of 30 December 2013)

S/N	Databases	Block Building
1	PubMed	Chikungunya AND guideline **Results: 2**
2	Web of Science	TS=(Chikungunya AND guideline) **Results: 9**
3	Scopus	TITLE-ABS-KEY (Chikungunya AND guideline) **Results: 23**
4	ScienceDirect	Chikungunya AND guideline **Results: 3**
5	CINAHL	Chikungunya AND guideline **Results: 5**
6	ProQuest	AB,TI (Chikungunya AND guideline) **Results: 131**
7	G-I-N Library	Chikungunya AND guideline **Results: 0**
8	NGC	Chikungunya AND guideline **Results: 0**
9	WHOLIS	Chikungunya AND guideline **Results: 14**
10	CDC	Chikungunya AND guideline **Results: 354**
11	ECDC	Chikungunya AND guideline **Results: 9**
12	NIH	Chikungunya AND guideline **Results: 4100**
13	LILACS	Chikungunya AND guideline **Results: 0**
14	CHIK Virus Net	Chikungunya AND guideline **Results: 3**
15	World Bank	Chikungunya AND guideline **Results: 0**
16	Asia Development Bank	Chikungunya AND guideline **Results: 0**
17	Google	Chikungunya AND guideline **Results: 2**
Total records		**4655**

Appendix XX: Codebook

Coder: Index number assigned to human coder.

Date: DD/MM/YYYY–DD/MM/YYYY. Period for the conduct of content analysis.

DOMAIN [A/B/C/D/E]: Treatment / Early diagnosis of disease / Disease education / Surveillance / Mosquito control

Subdomain: Chloroquine / Hydroxychloroquine / Corticosteroids / NSAIDs / Paracetamol / Non-pharmcological interventions / Early diagnosis of disease / Disease education / Surveillance / Mosquito control**.** Subdomains were determined primarily from interventions which were covered in the systematic reviews of interest.

Guideline ID: Abbreviated name of guideline (Publisher name of the guideline, Publication year of guideline). Guidelines are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific circumstances."[144(p35)] The systematic selection of guidelines was limited to two areas:

(1) Made guideline recommendations specifically on CHIK; and

(2) Presented recommendations on the domains of

(a) Treatment;

(b) Early diagnosis of disease;

(c) Disease education;

(d) Surveillance; or

(e) Mosquito control

Systematically selected guidelines that passed the methodological quality assessment and included in the content analysis were described in Chapter 6 of thesis.

Systematic review ID: Abbreviated name of systematic review (select either one: HRQoL 2014; Surveillance 2014; EControl 2014) Since the targeted three systematic

reviews are by the same primary author (Z Chen) and were completed in the same year (2013), in this content analysis, the following abbreviations were used:

(1) HRQoL 2014: The effectiveness of disease management interventions on health-related quality of life of patients with established arthritogenic *Alphavirus* infections: A systematic review (Thesis Chapter 3)

(2) Surveillance 2014: The effectiveness of public health surveillance systems in Chikungunya: A systematic review (Thesis Chapter 4)

(3) EControl 2014: The effectiveness of mosquito control strategies in Chikungunya: A systematic review (Thesis Chapter 5)

Extracted findings: Extracted findings are relevant informative statements (in words / phrases / sentences / paragraphs) that contain the keywords from the guidelines. The informative statements were found by standardised computer searching using the Cntl+F function on the computer keyboard to search for keywords (the subdomain word and word(s) relevant to subdomain) in the PDF guideline. The page number where the extracted finding was found in the guideline was also recorded for ease of reference. A dash (-) indicated that there was no finding from the particular guideline on the subdomain of interest.

Remarks: Allocated space for notes and comments made by the coder during the comparative analysis research process.

Appendix XXI: Code form

Coder: _____ **Date:** _____

DOMAIN A: TREATMENT

Chloroquine/hydroxychloroquine

In guidelines	Extracted findings from keyword(s):	Remarks:
Guideline ID		
Guideline ID		
Guideline ID		
In systematic review		
Systematic review ID		

Corticosteroids

In guidelines	Extracted findings from keyword(s):	Remarks:
Guideline ID		
Guideline ID		
Guideline ID		
In systematic review		
Systematic review ID		

NSAIDs

In guidelines	Extracted findings from keyword(s):	Remarks:
Guideline ID		
Guideline ID		
Guideline ID		
In systematic review		
Systematic		

review ID		

Paracetamol

In guidelines	**Extracted findings from keyword(s):**	**Remarks:**
Guideline ID		
Guideline ID		
Guideline ID		
In systematic review		
Systematic review ID		

Non-pharmacological interventions

In guidelines	**Extracted findings from keyword(s):**	**Remarks:**
Guideline ID		
Guideline ID		
Guideline ID		
In systematic review		
Systematic review ID		

DOMAIN B: EARLY DIAGNOSIS OF DISEASE

In guidelines	**Extracted findings from keyword(s):**	**Remarks:**
Guideline ID		
Guideline ID		
Guideline ID		
In systematic review		
Systematic review ID		

DOMAIN C: DISEASE EDUCATION

In guidelines	Extracted findings from keyword(s):	Remarks:
Guideline ID		
Guideline ID		
Guideline ID		
In systematic review		
Systematic review ID		

DOMAIN D: SURVEILLANCE

In guidelines	Extracted findings from keyword(s):	Remarks:
Guideline ID		
Guideline ID		
Guideline ID		
In systematic review		
Systematic review ID		

DOMAIN E: MOSQUITO CONTROL

In guidelines	Extracted findings from keyword(s):	Remarks:
Guideline ID		
Guideline ID		
Guideline ID		
In systematic review		
Systematic review ID		

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