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

by 
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A dissertation presented to 
SCHOOL OF TRANSLATIONAL HEALTH SCIENCE 
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DOCTOR OF PHILOSOPHY 
in the subject of 
MEDICINE 

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DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary education and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I clarify that no part of this work will, in future, be used in a submission for any degree or diploma in any university or other tertiary institution without prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Date: ____________________
PUBLICATIONS

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Zhili Chen (candidate) Signature:____________ Date:____________
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


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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<tr>
<td>AAIs</td>
<td>Arthritogenic <em>Alphavirus</em> Infections</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>AGAUR</td>
<td>Agència de Gestió d’Ajuts Universitaris i de Recerca</td>
</tr>
<tr>
<td>AGREE</td>
<td>Appraisal of Guidelines for Research and Evaluation</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
</tr>
<tr>
<td>ArcGIS</td>
<td>Geographic Information System</td>
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<tr>
<td>BGS</td>
<td>BioGents Sentinel™</td>
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<tr>
<td>BFV</td>
<td>Barmah Forest virus</td>
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<tr>
<td>BI</td>
<td>Breteau Index</td>
</tr>
<tr>
<td>BPI</td>
<td>Barthel Pain Index</td>
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<tr>
<td>Bti</td>
<td><em>Bacillus Thuringiensis Israelensis</em></td>
</tr>
<tr>
<td>CCPPRB</td>
<td>Comit’è Consultatif de Protection des Personnes dans la Recherche Biom’édicale</td>
</tr>
<tr>
<td>CD4+</td>
<td>Cluster of differentiation antigen 4</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention, USA</td>
</tr>
<tr>
<td>CDC-EH</td>
<td>Centers for Communicable Diseases and Prevention—Environmental Health</td>
</tr>
<tr>
<td>CDNA</td>
<td>Communicable Disease Network Australia</td>
</tr>
<tr>
<td>CENTRAL</td>
<td>Cochrane Central Register of Controlled Trials</td>
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<tr>
<td>CHIK</td>
<td>Chikungunya</td>
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<td>CHIKV</td>
<td>Chikungunya Virus</td>
</tr>
<tr>
<td>CLINHAQ</td>
<td>Clinical Health Assessment Questionnaire</td>
</tr>
<tr>
<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health</td>
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<tr>
<td>CReMS</td>
<td>Comprehensive Review Management System</td>
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<td>CI</td>
<td>Container Index</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CRD DARE</td>
<td>Centre for Reviews and Dissemination Database of Abstracts of</td>
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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
<table>
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<th>Acronym</th>
<th>Full Form</th>
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<tr>
<td>IEDCR</td>
<td>Institute of Epidemiology, Disease Control and Research</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
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<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>IVM</td>
<td>Integrated Vector Management</td>
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<tr>
<td>JBI</td>
<td>Joanna Briggs Institute</td>
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<tr>
<td>JBI-MASr</td>
<td>Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument</td>
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<tr>
<td>JBI-SUMr</td>
<td>Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information</td>
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<tr>
<td>KdT</td>
<td>Knockdown time</td>
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<td>KEMRI</td>
<td>Kenya Medical Research Institute</td>
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<tr>
<td>LC</td>
<td>Lethal concentration</td>
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<tr>
<td>LILACS</td>
<td>Latin American and Caribbean Health Sciences Literature</td>
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<tr>
<td>LUTS</td>
<td>Lower Urinary Tract Symptoms</td>
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<tr>
<td>MAC-ELISA</td>
<td>Immunoglobulin M Antibody-capture Enzyme-linked Immunosorbent Assay</td>
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<tr>
<td>MAYV</td>
<td>Mayaro virus</td>
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<tr>
<td>MD</td>
<td>Mean Difference</td>
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<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
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<tr>
<td>MOH</td>
<td>Ministry of Health</td>
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<tr>
<td>MOS SF-12</td>
<td>Medical Outcomes Study Short Form-12</td>
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<td>MTX</td>
<td>Methotrexate</td>
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<tr>
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<td>Naval Medical Research Unit No. 2, Cairo</td>
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<td>NEA</td>
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<td>National Guideline Clearinghouse</td>
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<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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</table>
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 were found to be effective in the management of Chikungunya. The combination
therapy of prednisolone and aceclofenac 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.