

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

by  
Zhili Chen

---

A dissertation presented to  
SCHOOL OF TRANSLATIONAL HEALTH SCIENCE  
in fulfilment of the requirements  
for the degree of  
DOCTOR OF PHILOSOPHY  
in the subject of  
MEDICINE

UNIVERSITY OF ADELAIDE  
Adelaide, South Australia

June 2014

## TABLE OF CONTENTS

---

<i>Declaration</i> .....	vii
<i>Publications</i> .....	viii
<i>Acknowledgements</i> .....	ix
<i>Dedication</i> .....	x
<i>List of figures</i> .....	xiii
<i>List of tables</i> .....	xvi
<i>Abbreviations</i> .....	xvii
<i>Thesis abstract</i> .....	xxii
1. Introduction .....	1
1.1. Chikungunya .....	1
1.1.1. Mosquito-borne arthritogenic <i>Alphavirus</i> .....	1
1.1.2. Epidemiology .....	2
1.1.3. Strains and transmission cycles .....	2
1.1.4. Pathogenesis .....	3
1.1.5. Clinical presentation .....	4
1.2. Management of Chikungunya .....	5
1.2.1. Disease management interventions .....	6
1.2.2. Public health surveillance systems .....	8
1.2.3. Mosquito control .....	9
1.3. Research objectives .....	12
1.4. Significance of research .....	12
1.4.1. Public health importance .....	12
1.4.2. Dearth of research on the effectiveness of interventions.....	16
1.5. Structure of thesis .....	17
2. Methodology .....	20
2.1. Evidence-based healthcare .....	20
2.1.1. Significance .....	20
2.1.2. Development .....	20

2.1.3. Systematic reviews .....	21
2.1.4. Practice guidelines .....	22
2.2. The JBI approach in synthesis .....	23
2.3. Systematic review methods .....	25
2.3.1. Research question and PICO inclusion criteria .....	25
2.3.2. Search strategy .....	26
2.3.3. Study selection process .....	27
2.3.4. Primary studies appraisal .....	27
2.3.5. Data extraction .....	28
2.3.6. Data synthesis .....	28
2.4. Content analysis methods .....	30
2.4.1. Research questions and inclusion criteria .....	30
2.4.2. Quality assessment of guidelines .....	30
2.4.3. Background of content analysis .....	31
2.4.4. Development of guideline recommendations .....	31
3. The effectiveness of disease management interventions on health-related quality of life of patients with established arthritogenic <i>Alphavirus</i> infections: A systematic review	
3.1. Abstract .....	34
3.2. Concise introduction .....	34
3.3. Methods unique to chapter .....	36
3.3.1. Types of participants .....	36
3.3.2. Types of interventions .....	37
3.3.3. Types of outcomes .....	38
3.3.4. Search strategy .....	38
3.3.5. Critical appraisal .....	39
3.3.6. Data synthesis .....	39
3.4. Results .....	40
3.4.1. Methodological results .....	40
3.4.2. Outcome results .....	50
3.5. Discussion .....	63
3.5.1. Clinical manifestations management .....	63

3.5.2. Early diagnosis of disease .....	65
3.5.3. Disease education .....	65
3.5.4. Limitations .....	65
3.6. Conclusion .....	66
3.6.1. Implications for practice .....	66
3.6.2. Implications for research .....	67
4. The effectiveness of public health surveillance systems in Chikungunya: A systematic review	
4.1. Abstract .....	69
4.2. Concise introduction .....	69
4.3. Methods unique to chapter .....	70
4.3.1. Types of participants .....	70
4.3.2. Types of interventions .....	70
4.3.3. Types of outcomes .....	70
4.3.4. Search strategy .....	73
4.4. Results .....	73
4.4.1. Methodological results .....	73
4.4.2. Description of included studies .....	78
4.4.3. Outcome results .....	82
4.5. Discussion .....	98
4.5.1. Limitations .....	103
4.6. Conclusion .....	104
4.6.1. Implications for practice .....	104
4.6.2. Implications for research .....	105
5. The effectiveness of mosquito control strategies in Chikungunya: A systematic review	
5.1. Abstract .....	107
5.2. Concise introduction .....	107
5.3. Methods unique to chapter .....	108
5.3.1. Inclusion criteria .....	108
5.3.2. Search strategy .....	109
5.4. Results .....	109

5.4.1. Methodological results .....	109
5.4.2. Description of included studies .....	114
5.4.3. Description of included study interventions .....	117
5.4.4. Outcome results .....	120
5.5. Discussion .....	128
5.5.1. Limitations .....	130
5.6. Conclusion .....	130
5.6.1. Implications for practice .....	130
5.6.2. Implications for research .....	132
6. Chikungunya guidelines and the synthesis of new guideline recommendations: A content analysis	
6.1. Abstract .....	133
6.2. Concise introduction .....	133
6.3. Methods unique to chapter .....	134
6.4. Results .....	134
6.4.1. Study selection .....	134
6.4.2. Guidelines appraisal .....	135
6.4.3. Proposed guideline recommendations .....	142
6.5. Discussion .....	149
6.6. Conclusion .....	150
7. Discussion and conclusion .....	152
7.1. Exposition .....	152
7.2. Evidence-based decision-making .....	152
7.3. Prioritising healthcare needs and addressing translation gaps .....	153
7.4. Implications for evidence synthesis .....	157
7.4.1. Improvements in effectiveness primary research .....	157
7.4.2. Improvements in methodology for systematic review of effectiveness .....	158
7.5. Implications for evidence transfer .....	159
7.6. Conclusion .....	161

Appendix I: JBI levels of evidence for effectiveness .....	163
Appendix II: JBI grades of recommendation .....	165
Appendix III: PRISMA statement checklist .....	166
Appendix IV: JBI critical appraisal checklist for randomised control / pseudo- randomised trial .....	168
Appendix V: JBI critical appraisal checklist for comparable cohort / case-control	169
Appendix VI: JBI critical appraisal checklist for descriptive / case series .....	170
Appendix VII: JBI data extraction form for experimental / observational studies .	171
Appendix VIII: Search strategy for systematic review (as of 2 May 2013) .....	173
Appendix IX: Included studies .....	179
Appendix X: Excluded studies .....	204
Appendix XI: HRQoL instruments used in meta-analysis of included studies ....	205
Appendix XII: Data and analyses for uncontrolled studies .....	208
Appendix XIII: Data and analyses for controlled studies .....	213
Appendix XIV: Forest plots for uncontrolled studies .....	215
Appendix XV: Search strategy (as of 25 July 2013) .....	228
Appendix XVI: Included studies .....	229
Appendix XVII: Search strategy (as of 26 July 2013) .....	270
Appendix XVIII: Included studies .....	271
Appendix XIX: Search strategy (as of 30 December 2013) .....	295
Appendix XX: Codebook .....	296
Appendix XXI: Code form .....	298
Thesis references .....	301

## 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.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

## PUBLICATIONS

---

Chen, Z and Lockwood, C. The effectiveness of disease management interventions on health-related quality of life of patients with established arthritogenic Alphavirus infections: A systematic review protocol. The JBI Database of Systematic Reviews and Implementation Reports. 2013;11(9):56-72.

Chen, Z and Lockwood, C. The effectiveness of disease management interventions on health-related quality of life of patients with established arthritogenic Alphavirus infections: A systematic review. The JBI Database of Systematic Reviews and Implementation Reports. [Accepted]

Chen, Z. The effectiveness of public health surveillance systems in Chikungunya: A systematic review protocol. The JBI Database of Systematic Reviews and Implementation Reports. 2014. [Accepted]

Chen, Z. The effectiveness of mosquito control strategies in Chikungunya: A systematic review protocol. The JBI Database of Systematic Reviews and Implementation Reports. 2014. [Accepted]

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.



## ACKNOWLEDGEMENTS

---

*Assoc Prof Craig Lockwood* My PhD supervisor who saw the potential and believed in me. Thank you very much for the pearls of wisdom, knowledge, understanding and patience. More than an academic supervisor who generously shared expertise on evidence-based research with me, you also reminded me through your actions that it is possible to follow and serve God first wholeheartedly even with a busy schedule. I am so blessed to be under your mentorship.

*Dr Mohammed Alsharifi* My PhD supervisor who inspired me to give my best for my research and to tune my thoughts and attitude to think like a scientist.

*Dr Dora Lang, Dr Zachary Munn, Dr Xue Yifan and Dr Yee Mei Lee* My secondary reviewers for the quality assessments of primary studies and guidelines in the thesis. Thank you for your dedicated work. A toast to our friendship and more collaborations to come.

*Siew Siang Tay, Stirling Ha, Ivan Teo, Joseph Yue and David Lee* My proofreaders who generously give their time and effort to proofread my work, to whom I am very grateful.

*Papa, Mummy, Ahma, Nana, Yongsheng and Stirling* My family for your love and more love and always being supportive of everything I do. Thank you for always reminding me to enjoy my studies, to not worry about finances and to always think of safety. I know you care so much about me and always want me to be happy.

*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 23<sup>rd</sup> 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

## LIST OF FIGURES

---

Figure 1.1.	Phases of research .....	18
Figure 2.1.	The JBI model of evidence-based healthcare .....	24
Figure 3.1.	Search process for studies selection .....	40
Figure 3.2.	Drugs used in included studies by reporting frequency .....	52
Figure 3.3.	Forest plot of comparison: 1 HRQoL, outcome: 1.1 Overall quality of life change scores .....	215
Figure 3.4.	Forest plot of comparison: 1 HRQoL, outcome: 1.3 HAQ change scores .....	215
Figure 3.5.	Forest plot of comparison: 1 HRQoL, outcome: 1.2 CLINHAQ global severity subscale change scores .....	216
Figure 3.6.	Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.1 Overall disease-specific quality of life change scores .....	216
Figure 3.7.	Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.5 DAS overall change scores .....	217
Figure 3.8.	Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.6 DAS ESR change scores .....	217
Figure 3.9.	Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.7 DAS swollen joint count change scores .....	218
Figure 3.10.	Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.8 DAS tender joint count change scores .....	218
Figure 3.11.	Forest plot of comparison: 2 Disease-specific Quality of Life, outcome: 2.2 CLINHAQ gastrointestinal symptoms subscale change scores .....	219
Figure 3.12.	Forest plot of comparison: 3 Anxiety, outcome: 3.1 CLINHAQ anxiety subscale change scores .....	219
Figure 3.13.	Forest plot of comparison: 4 Depression, outcome: 4.1	219

	CLINHAQ depression subscale change scores .....	
Figure 3.14.	Forest plot of comparison: 5 Emotional functioning, outcome: 5.1 Overall emotional functioning change scores .....	220
Figure 3.15.	Forest plot of comparison: 5 Emotional functioning, outcome: 5.2 MOS SF-36 mental component summary subscale change scores .....	220
Figure 3.16.	Forest plot of comparison: 5 Emotional functioning, outcome: 5.3 MOS SF-36 mental health subscale change scores .....	220
Figure 3.17.	Forest plot of comparison: 5 Emotional functioning, outcome: 5.4 MOS SF-36 role emotional subscale change scores .....	221
Figure 3.18.	Forest plot of comparison: 6 Fatigue, outcome: 6.1 Overall fatigue change scores .....	221
Figure 3.19.	Forest plot of comparison: 6 Fatigue, outcome: 6.2 CLINHAQ fatigue subscale change scores .....	221
Figure 3.20.	Forest plot of comparison: 6 Fatigue, outcome: 6.3 MOS SF-36 vitality subscale change scores .....	222
Figure 3.21.	Forest plot of comparison: 7 General Health Perspective, outcome: 7.1 Overall general health perspective change scores ...	222
Figure 3.22.	Forest plot of comparison: 7 General Health Perspective, outcome: 7.2 CLINHAQ patient estimated health status subscale change scores .....	223
Figure 3.23.	Forest plot of comparison: 7 General Health Perspective, outcome: 7.3 CLINHAQ satisfaction with health subscale change scores .....	223
Figure 3.24.	Forest plot of comparison: 7 General Health Perspective, outcome: 7.4 MOS SF-36 general health perspective subscale change scores .....	223
Figure 3.25.	Forest plot of comparison: 8 Pain, outcome: 8.1 Overall pain change scores .....	224

Figure 3.26.	Forest plot of comparison: 4 Pain, outcome: 4.1 Overall pain change scores .....	224
Figure 3.27.	Forest plot of comparison: 9 Physical functioning, outcome: 9.1 Overall physical functioning change scores .....	225
Figure 3.28.	Forest plot of comparison: 10 Role Functioning, outcome: 10.1 Overall role functioning change scores .....	225
Figure 3.29.	Forest plot of comparison: 11 Sleep, outcome: 11.1 CLINHAQ sleep problem subscale change scores .....	226
Figure 3.30.	Forest plot of comparison: 12 Social Functioning, outcome: 12.1 MOS SF-36 social functioning subscale change scores .....	226
Figure 3.31.	Forest plot of comparison: 1 Emotional functioning, outcome: 1.1 Overall emotional functioning follow-up scores .....	226
Figure 3.32.	Forest plot of comparison: 5 Physical functioning, outcome: 5.1 Overall physical functioning follow-up scores .....	227
Figure 4.1.	Study selection process .....	74
Figure 5.1.	Study selection process .....	110
Figure 6.1.	Study selection process .....	134
Figure 7.1.	Relationship between translational science and evidence-based healthcare .....	153

## LIST OF TABLES

---

Table 3.1.	JBI-MAStARI critical appraisal of included studies .....	41
Table 4.1.	JBI-MAStARI critical appraisal of included studies .....	74
Table 5.1.	JBI-MAStARI critical appraisal of included studies .....	110
Table 5.2.	Characteristics of mosquito control interventions .....	115
Table 5.3.	Decreasing potency of chemical larvicides following 24 hours exposure .....	120
Table 5.4.	Decreasing potency of biological larvicides following 24 hours exposure .....	122
Table 5.5.	Percentage mortality of fourth instar larvae <i>Aedes aegypti</i> following 24 hours exposure .....	122
Table 6.1.	Average AGREE II item scores of guidelines .....	135
Table 6.2.	Scaled domain percentage scores for each guideline .....	138
Table 6.3.	Reviewers' recommendations for use of guidelines .....	139



## ABBREVIATIONS

---

AAIs	Arthritogenic <i>Alphavirus</i> 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	<i>Bacillus Thuringiensis Israelensis</i>
CCPPRB	Comit'ée Consultatif de Protection des Personnes dans la Recherche Biomédicale
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 were found to be effective in the management of Chikungunya. The combination

therapy of prednisolone and acecylofenac 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.