Towards sustainable management of arboviral diseases
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Introduction: Towards sustainable management of arboviral diseases

A multidisciplinary mixed-methods approach in Curaçao and Venezuela
General introduction

Emerging arboviral diseases

Over the past decades, arboviral diseases have emerged in the tropics and sub-tropics of Latin America, Asia, Africa and beyond [1-4]. The term arbovirus (arthropods-borne virus) refers to viruses being transmitted by arthropods, such as mosquitoes and ticks [5]. Over 400 arboviruses have been documented [6]. Amongst the most common and important arboviruses are dengue, chikungunya and Zika, which are transmitted by the day-biting mosquitoes of the Aedes spp., i.e. Ae. aegypti and Ae. albopictus [7,8]. The diseases are spread in areas where Ae. spp. reside, including areas where over 40-50% of the world’s population lives (Figure 1) [9,10]. The upcoming transmission of these arboviral diseases are driven by urbanisation, globalization and international mobility [11]. In the past years, devastating epidemics showed the major consequences of these diseases on community and individual health. Hence, it is important to prevent these diseases and improve medical care of affected populations.

In this thesis, the impact and prevention of dengue and chikungunya were investigated. Zika was not examined since major epidemics emerged after data-collection was performed at the study sites (Curaçao and Venezuela) (Figure 1).

Figure 1. Global predicted distribution of dengue, chikungunya and Zika.
Study sites
This thesis focused on two different study sites, i.e. Curaçao and Venezuela, which are neighbouring countries at the Caribbean Sea. Both countries confronted a devastating chikungunya outbreak in 2014, on an endemic background of all four serotypes of dengue [12]. The countries have a different political and socio-economic situation. This allowed us to obtain insights on the impact of arboviral transmission on Curaçao with a relatively compact, stable and affluent background, compared to Venezuela with a very unstable political background with poor socio-economic standards.

The disease presentation of dengue and chikungunya might be relatively similar in neighbouring countries. However, the impact and management of these disease can be considerably different due to behavioural and socio-economic strata, e.g. as education, access to care and preventive behaviour. In the following paragraphs we first describe dengue and chikungunya. Then, we introduce some of the principles of the behavioural and interdisciplinary research methodology, which was applied in this thesis.

Dengue and chikungunya
Dengue
Over the last decades, dengue has increasingly spread to formerly unaffected areas [4]. While only nine countries faced annual transmission of the virus before 1970, currently over 100 countries have established annual dengue transmission [13]. Four different, but closely related serotypes of the dengue flavivirus exist, i.e. DEN-1, DEN-2, DEN-3 and DEN-4. When infected, a person acquires lifelong immunity for the particular serotype. Dengue disease is characterized by an abrupt onset of fever normally lasting for 2-7 days. Skin erythema, myalgia, arthralgia, headache and generalized body pain are amongst the symptoms which can occur [8]. Dengue may evolve into severe dengue, characterized by (I) plasma leakage and shock, (II) bleeding manifestations and/or (III) severe organ impairment [8]. Clinical management of dengue is normally not complicated and relies mainly on cardiovascular resuscitation [8]. When early onset of treatment is secured, severe dengue morbidity can be reduced from 20% to 1% [14,15].

Chikungunya
Chikungunya virus is an alphavirus, first described in Tanzania in 1952. The name ‘chikungunya’ has its origin in the local Kimakonde language, meaning ‘to walk bent over’. This refers to the characteristic debilitating musculoskeletal pains caused by chikungunya disease, forcing people to walk contorted [16]. Chikungunya outbreaks were not frequently reported up until 2005 when the virus spread rapidly, causing major epidemics in islands in the Indian ocean, India and Southeast Asia. Currently, over 60 countries have reported chikungunya transmission [16]. Chikungunya typically has an abrupt acute disease onset, normally characterised by fever and debilitating joint pains. Often other symptoms can be present, such as myalgia, rash, headache, fatigue and nausea [17-22]. These symptoms can last 2-12 days, or may linger on as chronic chikungunya disease. A high proportion of infected individuals develop a chronic disease typically including musculoskeletal impairment [23]. This chronic disease could last for years and has major consequences for physical and mental quality of life [24-26]. Treatment is focused on pain-relieve, there is currently no anti-viral treatment available [16].
Impact of chikungunya
The long-lasting consequences of chikungunya have a major impact on the quality of life of affected persons [23]. Several studies showed, on top of the physical consequences, an impact on the emotional well-being of chikungunya patients [24-26]. It is not unlikely that long-lasting symptoms, e.g. musculoskeletal symptoms and fatigue, lead to lower emotional well-being or depression. However, to date, scientific literature provides little in-depth insights in this possible interplay of physical and emotional well-being. Furthermore, little is known on the influence of chikungunya on participation in normal daily life activities, such as work, household chores and social activities.

Health behaviour, a neglected topic in tropical research
Sociological and behavioural determinants of dengue and chikungunya can explain health outcomes, by addressing topics such as access to care, quality of life and preventive health behaviour. Currently, prominent research disciplines in the field of medical care are pathology and physiology. Based on pathological and physiological principles, research aims to develop medicines, vaccines or other treatment. Though health behaviour receives considerable less attention in research, it is a major determinant of health outcomes. It has been recognized that effective health promotion interventions should be based on health behaviour theories, in order to address local behaviours, to be applicable, and sustainable for the local beneficiaries [27,28]. Therefore, it is important to strengthen health behaviour research.

The definition of health is described by the WHO as ‘a state of complete physical, mental, and social well-being not merely the absence of disease’ [29]. Hence, health is a multidimensional concept [30-32], which may differ per individual, health condition and cultural context.

Health behaviours are driven by many complex determinants, which have been described in theory. These theories have successfully been applied in global health research. Regarding arboviral diseases (dengue and malaria), these theories served as theoretical framework to examine motivations for treatment seeking and preventive behaviours of various communities [33-37], and to develop efficient health education [38]. Two important health behaviour theories are the Health Belief Model (HBM) and the Theory of Planned Behaviour (TPB) [39-41]. These theories are based on similar concepts to understand the likelihood of (preventive) health behaviour. Though using similar concepts, the HBM and TPB have their unique concepts and value as well. The HBM includes the concept ‘perceived threat of a condition’, resulting from the perceived seriousness of and the perceived susceptibility (risk to acquire) to a disease [39,40]. On the other hand, the TPB recognizes the role that ‘subjective norms’ (the behaviour and influence of ‘significant’ other individuals) play in predicting health behaviours [41]. Later in this introduction we elaborate more on these health behaviour theories.

Interdisciplinary research and mixed methods
Different research disciplines (i.e. medicine, psychology and sociology) contribute substantially to achieving improved quality of life and preventive health behaviour. However, interdisciplinary research remains relatively scarce. This might be caused by low knowledge or undervaluation of other disciplines, but could also be a result of the challenge to combine different research methods in scientific valid ways.
Quantitative and qualitative research methods are two important research methods for global health research. In health research, quantitative research relies on statistics to e.g. observe patterns and estimate incidences of diseases in order to provide a generalizable outcome [42]. On the other hand, qualitative research is not designed to provide generalizable results, but to obtain in-depth understanding of motives and perceptions influencing e.g. patterns in health behaviour [43]. Therefore, a combination of these two research methods (mixed-methods) provides both in-depth and (to a certain degree) generalizable results leading to a valuable comprehensive view on a (global) health-problem (such as impact on QoL of chikungunya and promoting preventive behaviours).
Research questions of this thesis

This thesis examines the impact and health promoting behaviour of chikungunya and dengue in Curaçao and Venezuela. The first chapters focus on dengue in Venezuela and describe access to care, and health seeking behaviour for dengue and fever in a community in Venezuela. Then, communities’ mosquito control practices and ways to improve community participation in mosquito breeding site control are examined in Venezuela and Curaçao. The last chapters focus on the impact and sequelae of chikungunya disease, and examine the influence of co-infection with dengue on these sequelae. The chapters regarding Venezuela are based on common data sources. Likewise, this generally applies to the chapters regarding Curaçao.

Dengue and health behaviours in Venezuela

Dengue is endemic in Venezuela. Dengue-like diseases were already described in Venezuela in 1828 and 1946 [44]. However, the first epidemic of dengue in the country was reported in 1989-1990 [45]. Since then, dengue outbreaks occur on a regular base. The poor socio-economic circumstances and behavioural factors were facilitators for the increase of dengue cases in urban areas [14,15]. A major epidemic was established in 2010, when more than 120,000 cases were reported of which 8% were identified as severe dengue infections [46]. As for the Venezuelan population, people tend to seek medical treatment in a relatively late stage of disease (>3 days after onset symptoms [47]), when severe disease manifestations may already have emerged [48]. Insights in health seeking behaviour and access to care might therefore improve prompt medical treatment of dengue with an additional decrease of mortality due to dengue.

Research objective 1:
To investigate the health seeking behaviour (Chapter 2) and access to care (Chapter 3) of dengue and fever amongst a community in Maracay, Venezuela.

Mosquito control in Curaçao and Venezuela

Currently, there are no widely available treatments or vaccines for dengue, chikungunya and Zika. Therefore, the only effective way to prevent these diseases is vector control [49,50]. Mosquitoes breed in stagnant water, which is usually available around people’s houses, especially in rainy seasons. Typical breeding places are e.g. car tires, water containers, pet drinking bowls or garbage cans. Hence, mosquitoes can be prevented from multiplication by covering these potential sources, or eliminate stagnant water [51,52]. This type of vector control is called ‘source reduction’ and has shown its potency by reducing dengue incidences. Source reduction has also shown to be more effective than application of insecticides, which is limited by insecticides resistance and inadequate vector control infrastructure [36,53].

Efforts in the past illustrate the challenge to achieve sustainable vector control. In the 1950s and 1960s, an intensive mosquito elimination program had reduced the vector drastically in Latin America. However, after cessation of this program, the vector of these arboviral diseases returned causing major epidemics of arboviral diseases [54]. From the latter we learn that mosquito breeding site control will only be sustainable
when based on mutual efforts from both governmental bodies and communities, as was also recognized by several studies [53,55-57]. The challenge though, is that mobilizing communities in mosquito control is often hard to achieve.

Research objective 2:
To investigate (behavioural) determinants and possible interventions related with improved communities’ mosquito control in Venezuela (Chapter 4) and Curaçao (Chapter 5).

Theoretical background
To strengthen scientific value of the study, this aim was performed using mixed-method research based on a theoretical framework. We examined the behavioural determinants of mosquito breeding site control performed by the community, based on an integrated theoretical model (Figure A in S2 Additional file Chapter 5). This framework was built on the HBM and the TPB.

The concepts of the HBM are the perceived susceptibility (the risk perception to the threat) and the perceived severity to a treat. The evaluation of the latter concepts result in a perceived threat of a disease, which predicts if a person is willing to engage in preventive behaviour. However, this preventive behaviour should be perceived as effective (perceived benefits) and performable without significant obstacles (perceived barriers). Further, the person must believe that he/she has the ability to perform the behaviour, which is the self-efficacy (Figure 1 in S2 Additional file Chapter 5).

The TPB predicts the likelihood that a person engages in preventive behaviour through the attitudes towards behaviour, subjective norms and the perceived behavioural control. The attitudes towards behaviour results from a valuation of accessible beliefs (positive and negative) about the behaviour, the concept subjective norms covers the influence (actions and pressure) of significant others, and the perceived behavioural control refers to the individual’s evaluation of easiness or hardship of carrying out the behaviour (Figure 1 in S2 Additional file Chapter 5).

Using the aforementioned theories (HBM and TPB), we focused on assessing the likelihood (intention) of the health behaviour (performing mosquito breeding site control). This concept is the most significant predictor of the actual performed behaviour. Another important concept is the self-efficacy for the behaviour. If self-efficacy is low, this will lower (the intention to perform) the behaviour. As depicted in Figure 1 in S2 Additional file Chapter 5, several other concepts influence the likelihood of behaviour. The likelihood of performing preventive behaviour will rise if the perceived threat of a condition is high (i.e. a higher perceived susceptibility and increased perceived severity of the condition, more cues to action), when the attitudes towards the behaviour are positive, and when subjective norms are supportive [39-41].

The impact of chikungunya on quality of life
Over the past years, chikungunya was introduced in the Americas. In December 2013, chikungunya transmission was reported in the Caribbean island of Saint Martin [58]. Soon other countries followed [59] resulting in over one million confirmed or suspected cases throughout the Americas [2]. At the start of
2014, chikungunya transmission became evident in Curaçao, resulting in high attack rates within a formerly naïve population [2]. The epidemic ceased in the first months of 2015, when an estimated 50,000-75,000 individuals had been infected with chikungunya.

As was described before, the acute disease of chikungunya is characterized by a sudden onset of fever and devastating arthralgia [17-22]. Accompanied by other symptoms, chikungunya may linger on as sub-chronic and chronic disease which may last up to years [23] with consequent impact on physical and emotional QoL [24-26]. To date, only few studies were dedicated to assess QoL of chikungunya patients with quantitative research methods, and none have investigated this topic using mixed-method research.

Research objective 3:  
To obtain an in-depth understanding of the impact of chikungunya on quality of life of infected individuals (Chapter 6, 7), and examine its link with coping strategies (Chapter 7).

Theoretical background
We investigated the Health-Related Quality of Life (HRQoL) using quantitative and qualitative methods. HRQoL is a multidimensional concept which refers to physical, emotional and social well-being [60-62]. This was assessed with quantitative methods by using a widely accepted, relatively short but comprehensive HRQoL questionnaire; the RAND-36/SF-36 [63,64]. Furthermore, these same concepts (physical, emotional and social well-being) were examined with qualitative methods and linked to Lazarus’ theory on coping strategies. This theory categorized coping strategies in ‘problem-focused’ (aimed at targeting the cause of stress) or ‘emotional’ (aimed at e.g. acceptance of the stressor) strategies [65,66].

Clinical manifestations of chikungunya and concomitant dengue

Research objective 4:  
a. To design a tool which can be used to easily and rapidly assess severity of chronic chikungunya sequelae (Chapter 6).  
b. To assess the influence of concomitant chikungunya and dengue on disease manifestations (Chapter 8).

To date, there is still no consensus on how to define and characterize chronic chikungunya disease. Furthermore, the similar acute disease manifestations of chikungunya and dengue make it difficult to distinguish these diseases at acute presentation. Both diseases are transmitted by the same vector (Aedes spp.) in the same areas, which means that the diseases can be transmitted concurrently. Concomitant transmission of chikungunya and dengue have been reported in many countries [67], and this might also be the case in Curaçao, where dengue has been endemic since years [68]. There is limited knowledge on the clinical consequences in the case that individuals are co-infected with these viruses, due to the scarcity of studies regarding this topic [69-71].
Outline of this thesis per chapter

This thesis investigates arboviral diseases in two countries and is ordered chronologically, based on time of data-collection. In the first chapters, we present the data on dengue collected in Venezuela in 2013-2014. The studies on mosquito breeding site control which were performed in both study sites, are subsequently presented. Lastly, we present the studies on chikungunya, which were performed in Curaçao in 2015.

In the case of dengue, people in Venezuela tend to seek care when they might already have developed severe disease manifestations. Therefore, we investigated the health seeking behaviour of dengue and fever in Chapter 2, in order to find ways to promote prompt medical treatment of dengue. Another barrier to obtain timely healthcare for dengue might be the complex healthcare situation of Venezuela. Hence, the access to care may be limited for Venezuelan people. To assess this problem, Chapter 3 examines access to care, and perceived motivations and barriers to obtain healthcare at the different health centres of Venezuela.

Venezuela has established ideal circumstances for mosquitoes, with a consequent rise of arboviral diseases [14,15]. A key to improve mosquito control will be source reduction in and around people their homes. Therefore, we assessed communities’ knowledge, attitudes and practices towards dengue and mosquito breeding site control in Chapter 4. Arboviral diseases are a constant threat for Curaçao as well. Community participation in mosquito breeding site control is crucial to achieve sustainable mosquito control and lower the burden of arboviral diseases [27, 30-32]. In Chapter 5 we examined the perceptions on and performance of personal protection against mosquitoes and mosquito breeding site control of the communities in Curaçao. Mixed-methods were used based on two behavioural theories, i.e. the Health Believe Model [39,40] and the Theory of Planned Behaviour [41], in order to examine ways to improve community participation in mosquito breeding site control.

Chikungunya has caused major burden on community level in Curaçao. While the acute disease of chikungunya is known to be debilitating, a considerable proportion of infected people remain with chronic complaints [24]. To date, there is no consensus on how to define chikungunya chronic disease. We investigated chronic disease sequelae and its impact on Quality of Life (QoL), and provided a new tool to classify chikungunya chronic disease severity in Chapter 6. Quantitative research methods were used to describe chronic sequelae and impact on QoL in Chapter 6. Chapter 7 examines the impact on Health-Related QoL with qualitative research methods, in order to obtain in-depth understanding of how chikungunya disease affects people’s QoL. Furthermore, Chapter 7 investigates how coping strategies are linked to the Health-Related QoL impairment of chikungunya.

The arboviral diseases chikungunya and dengue circulate in the same areas, making it possible to acquire both infections on the same time [54]. A concomitant chikungunya and dengue infection might have implications for disease development. However, knowledge on this topic is very limited. Therefore, we compared acute and chronic disease manifestations of chikungunya mono-infected vs. (recent) chikungunya and dengue co-infected patients in Chapter 8. In Chapter 9 the results of this thesis are summarized.
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