Health Concerns in Cambodia Compounded by Historical and Rural Setbacks

Ciera DeHart

A Senior Thesis submitted in partial fulfillment
of the requirements for graduation
in the Honors Program
Liberty University
Spring 2020

Acceptance of Senior Honors Thesis

This Senior Honors Thesis is accepted in partial
fulfillment of the requirements for graduation from the
Honors Program of Liberty University.

_____
Kimberly Mitchell, Ph.D.
Thesis Chair

_____
Abigail Solitro, Ph.D.
Committee Member

_____
Cindy Goodrich, EdD.
Assistant Honors Director

April 14, 2020
Date

Abstract

Cambodia is a country in the Greater Mekong Subregion of Southeast Asia. The Khmer Rouge genocide in the mid 1970s produced significant setbacks in the nation's healthcare system. While much progress has been made, rural areas still lack access to medical professionals, facilities, and equipment. Three of the most problematic diseases in Cambodia have been malaria, HIV, and tuberculosis. Due to the inadequacies of rural healthcare, treatment-resistant varieties of malaria and tuberculosis have become a serious concern for both the nation and Southeast Asia as a whole. The question of how to best provide aid to these isolated communities is characterized by complex and multifaceted discussions that seek to bring Cambodia to a place of greater health.

Health Concerns in Cambodia Compounded by Historical and Rural Inadequacies

Introduction

Encyclopedia Britannica describes the region of Southeast Asia as "a region of Asia situated east of the Indian subcontinent and south of China"; it can be divided into two mainland and insular portions, which are bridged by the Malay peninsula. Throughout much of history, this area was a crucial component of many trading networks and attracted many nations (Leinbach & Frederick, 2018). Eventually, Europe's arrival on the scene completely restructured the economy and increased the disparity between the rich and poor (Leinbach & Frederick, 2018). While some of the SE Asian nations have experienced notably increased development since the 1960s, particularly those who became members of the Association of Southeast Asian Nations (ASEAN) at the outset of its formation, others have struggled significantly (Leinbach & Frederick, 2018). Initially non-ASEAN countries, including Cambodia, Laos, Myanmar, and Vietnam, were, and still are, "among the poorest nations in the world" (Leinbach & Frederick, 2018).

Figure 1. Map of Southeast Asia. From "Which Countries Are Considered to Be Southeast Asia?", by V. Kiprop, 2018, https://www.worldatlas.com/articles/which-countries-are-considered-to-be-southeast-asia.html

Cambodia is bordered by Thailand, Laos, and Vietnam, and its landscape consists primarily of plains, low mountains, and the upper part of the Mekong River Delta (Chandler & Overton, 2019). The Khmer people comprise 90% of the population; although this does make for a fairly homogenous society, they struggle to integrate the Vietnamese, Chinese, Thai, Cham, and Lao minorities that make up the much smaller portion (Chandler & Overton, 2019). In its early days, Cambodia's civilization was primarily influenced by India and China (Chandler & Overton, 2019). In the 12th century, the Khmer (Cambodian) Empire reached its own golden age and constructed the stunningly beautiful Angkor temple complexes (Chandler & Overton, 2019).

From then on, the country experienced a steady decline as it was colonized by the French in 1863 and then occupied by the Japanese in the 20th century (Chandler & Overton, 2019). After regaining their independence in 1954, Cambodia began shifting from a monarchy to an authoritarian regime (Chandler & Overton, 2019). Following a brief civil war initiated by yet another regime change, the country was devastated by the Khmer Rouge, a "rural communist guerrilla movement" led by Pol Pot that lasted from 1975 to 1979 (Chandler & Overton, 2019). Prime minister Pol pot, also known as Saloth Sar, sought to follow Maoist China and convert the nation's people into a collectivized and unpaid labor force, but ultimately committed genocide in the process (Chandler & Overton, 2019). During this reign of terror, "at least 1.5 million Cambodians died or were killed" (Chandler & Overton, 2019). Primary causes of death were disease, starvation, overwork, and execution often brought on by the party's rampant paranoia (Chandler & Overton, 2019). Additionally, 'intellectual cleansing occurred' resulting in the mass

murder of educated individuals; “personal and political freedoms were outlawed” (Ozano et al., 2018).

Vietnamese intervention deposed the regime and started rebuilding Cambodia, but by then, many of the educated elite had fled and sought refuge in other countries (Chandler & Overton, 2019). Cambodia finally joined ASEAN in 1999 and the World Trade Organization in 2004; slowly, the country has been regaining the confidence of its foreign allies (Chandler & Overton, 2019). Steps have also been taken to control the AIDS epidemic and reduce the ‘runaway’ birth rate (Chandler & Overton, 2019). Despite this recent progress, there is still a long road of recovery ahead for Cambodia. While the capital of Phnom Penh has become a dense city, a 2018 survey reported that only 23.4% of Cambodians live in an urban setting and 76.6% of the population lives in rural areas (Chandler & Overton, 2019). These rural areas lack both healthcare facilities and healthcare professionals, as well as proper sanitation and clean water (McGrew, 1990). This only serves to exacerbate the current situation in which treatment-resistant strains of malaria and tuberculosis are sweeping across Southeast Asia (Giffels, 2019). Cambodia is not currently equipped to deal with these problems on its own. Foreign aid could prove instrumental in coming alongside this nation and its people that are fighting to get back on their feet. However, the manner in which the aid is rendered must be carefully evaluated.

Overview of the Health Care Situation

By the end of the Khmer Rouge, Cambodia’s health care system had been severely crippled (McGrew, 1990). Major infrastructure was destroyed along with supplies, equipment, and personnel (McGrew, 1990). Many of the people killed during the regime were educated professionals, and reports say that only 45 doctors survived; of those 45, 20 fled Cambodia (McGrew, 1990). By the end of 1979, only 728 medical students remained in the country

(McGrew, 1990). The majority of hospitals and medical facilities were also destroyed ("Health First…", 2016).

Current Health Care System

Cambodia's Ministry of Health "worked with several international development agencies to reform the country's healthcare system" during the 1990s ("Healthcare in Cambodia", 2017). This department has invested in numerous strategies including private insurance, voluntary community-based health insurance, and Health Equity Funds ("Healthcare in Cambodia", 2017). The government is investing in both the public and private health sectors, with emphasis on the establishment of provincial health departments ("Healthcare in Cambodia", 2017). Despite these efforts, medical professionals are still severely lacking, and as of 2017, there were only 0.7 hospital beds per 1000 people ("Healthcare in Cambodia", 2017). Although a concerted effort has been made to educate greater numbers of medical professionals, there is still a drastic shortage ("Healthcare in Cambodia", 2017). Currently, the majority of the public health workers are hardworking midwives and nurses, but they are unable to meet the extensive needs of the nation ("Healthcare in Cambodia", 2017). Private healthcare has grown significantly and dominates the curative care field ("Healthcare in Cambodia", 2017). Additionally, private spending has increased notably as a direct reaction to the inadequacy of public services ("Healthcare in Cambodia", 2017). Over half of Cambodians went to private providers in 2015 ("Healthcare in Cambodia", 2017). In light of this rapid growth, the Ministry of Health has now turned to the development of more effectual regulations concerning licensing requirements and enforcements in the private sector ("Healthcare in Cambodia", 2017).

The Rural Disparity

As previously mentioned, the majority of the Cambodian people live in provincial areas far away from structured medical care (McGrew, 1990). This has resulted in significant "inequities in health outcomes based on socio-economic status and between rural and urban populations" ("Health First…", 2016). Phnom Penh has the most advanced healthcare facilities in the country, along with the greatest concentration of medical professionals; the vast majority of rural areas however, lack clean water, sanitation, trained personnel, facilities, and medicine (McGrew, 1990). Cambodia's poor, disabled, and indigenous minorities face overwhelming obstacles to obtaining health services ("Health services and centers", 2016). Various programs have been initiated to help provide health care at minimal costs, but access to quality care is still limited ("Health services and centers", 2016).

Primary Health Concerns for Cambodia and Southeast Asia

As a region, Southeast Asia is not only plagued by numerous natural disasters, it is also home to a number of emerging and remerging infections (Acuin et al., 2011). There are a number of factors that have facilitated this increased risk of emergent diseases (Coker, Hunter, Rudge, Liverani, & Hanvoravongchai, 2011). First, this region is home to a large diversity of vector-borne and zoonotic pathogens; compounding this is the existence of ecological factors that promote rapid mutation of the pathogens, along with host adaptation (Coker et al., 2011). Additionally, "the high density, proximity, and mobility of human beings and animal reservoirs provide fertile conditions for transmission between species, within human populations, and across geographic areas" (Coker et al., 2011). Urbanization and the growth of livestock and agriculture have ultimately reshaped Southeast Asia (Coker et al., 2011). The varying quality of healthcare throughout the nations often exacerbates issues and presents unique challenges to controlling the spread of diseases across country borders (Acuin et al., 2011). This problem

requires the increased and effective cooperation of global and regional communities (Acuin et al., 2011). Oftentimes, irregular migration of peoples in the region can lead to microcosms plagued by inadequate medical care and living conditions; such migrants are also particularly vulnerable to exploitation (Acuin et al., 2011).

Cambodia's health 'landscape' has been shaped and characterized by a number of concerns. One of the primary issues has revolved around the maternal mortality rate; thankfully, the ratio has fallen from 1,020 in 100,000 births in 1990, to 161 in 2015 ("Priority health concerns", 2017). This was largely due to an increasing number of mothers whose babies were delivered by health professionals and in medical facilities ("Priority health concerns", 2017). Moreover, the vast majority attended antenatal care and most HIV+ mothers received antiretroviral treatments to prevent viral transmission to their infants ("Priority health concerns", 2017). Although progress has been made in this area and mortality rates have dropped, the prevalence of child death and the birth of underweight newborns is still high compared to many other countries ("Priority health concerns", 2017). Other notable concerns include Dengue fever, along with diarrhea diseases, acute respiratory infections, and malnutrition, all of which particularly contribute to the child mortality rate ("Priority health concerns", 2017). The *Asia Pacific Journal of Clinical Nutrition* reported in 2014 that "malnutrition costs Cambodia more than $400 million annually and contributes to the deaths of 6,000 children each year"; additionally, UNICEF says that "2,000 Cambodian children die from preventable diarrhea diseases annually" ("Priority health concerns", 2017).

There are three notable diseases that Cambodia as a whole has especially struggled with, namely, malaria, tuberculosis, and HIV (Tomb, 2016). Despite recent advances made in the

treatment of these infections, the rural disparity slows progress and acts as a stumbling block to the quick responses needed to keep on top of and ultimately eliminate the issues (Tomb, 2016).

Malaria

Malaria is caused by the intracellular parasites of the genus *Plasmodium,* but *Plasmodium falciparum* is the most lethal variety transmitted (Gardner et al., 2002). The most common vector that transmits this parasite is the *Anopheles (An.)* mosquito and 40% of humans live in a region where this disease is transmitted (Gardner et al., 2002). In Cambodia the dominant vectors are *An. dirus and An. minimus* (see Figure 2) (Sinka et al., 2012).

Figure 2. Geographical distribution of malaria Anopheles vectors in Asia. From “A global map of dominant malaria vectors", by M. Sinka et al., 2012, https://parasitesandvectors.biomedcentral.com/articles/10.1186/1756-3305-5-69

Plasmodium invades host erythrocytes while in its infective sporozite stage (Mota et al., 2001). The sporozite breaches the plasma membrane of one cell, traverses the cytosol, and then exits

and invades the next cell (Mota et al., 2001). This occurs several times before the final invasion in which a parasitophorous vacuole is formed that facilitates the development of the parasite into the next stage (Mota et al., 2001). As the parasite matures, it causes waste and toxic factors to accumulate in the red blood cell ("Disease", 2019). The genome of the *Plasmodium* parasite primarily directs the production of genes dedicated to host-parasite interactions and the evasion of the immune system (Gardner et al., 2002). *Plasmodium falciparum* causes infected erythrocytes to attach to the vascular endothelium of the smaller blood vessels in a process called cytoadherence (Ho & White, 1999). This prevents detection of the parasite by the spleen and also obstructs normal fluid flow through the circulatory system, ultimately compromising the flow of oxygen between tissues (Ho & White, 1999). This leads to hypoxia, metabolic disturbances, and the failure of multiple organs (Ho & White, 1999). Common symptoms include headaches, fever, muscular pain, nausea, and vomiting ("Treatment of Malaria…", 2019). More serious cases can also produce disorientation, coma, and anemia ("Diagnosis and Treatment…", 2018).

Malaria is divided into two main varieties described as being either uncomplicated or severe ("Diagnosis and Treatment…", 2018). Severe malaria is most often caused by *Plasmodium falciparum* and requires immediate assessment and treatment ("Diagnosis and Treatment…", 2018). In the developed world, microscopy and laboratory diagnostic tests are used to make a definitive diagnosis; blood smears from the patient are viewed under the microscope (see Figure 3) and the parasite's density is estimated if present ("Treatment of Malaria…", 2019). After confirmation of the malaria, appropriate treatment is determined based on the "infecting *Plasmodium* species, the clinical status of the patient, expected drug susceptibility of the infecting parasite as determined by the geographic area where the infection was acquired, and previous use of antimalarials" ("Treatment of Malaria…", 2019).

Figure 3. Plasmodium falciparum (dark rings) in blood smear. From “Plasmodium falciparum”, by H. Fadel, 2014, http://www.pathologyoutlines.com/topic/parasitologymalariapfalciparum.html Copyright 2003-2020 by PathologyOutlines.com, Inc.

The most common antimalarials drugs include artemisinin-based combination therapies (ACTs), which are a combination of two or more drugs, and chloroquine phosphate; chloroquine, however, is now no longer effective in all parts of the world due to resistance developed by some malarial parasites (“Malaria”, 2018).

The United States Agency for International Development reports that “despite many public health advancements in the region, 65 million people in Southeast Asia are at risk of malaria infection” (“Malaria: Asia Regional”, 2019). It also stated that, in the Greater Mekong Subregion, an estimated 260,000 people are infected with malaria each year; this number is most likely higher due to the lack of proper reporting and detection in rural areas that commonly suffer from the disease (“Malaria: Asia Regional”, 2019). Symptoms of malaria are generally non-specific, making it somewhat difficult to diagnose (“Diagnosis and Treatment…”, 2018).

Various problems can arise in developing countries when attempting to run diagnostic tests ("Diagnosis and Treatment…", 2018). First, many clinics lack the equipment necessary, especially microscopes, to make laboratory diagnoses ("Diagnosis and Treatment…", 2018). Microscopic test results can be affected by the quality of the microscope itself, the quality of the reagents used, and the experience of the lab technician ("Diagnosis and Treatment…", 2018). They also often do not possess rapid diagnostic tests (RDTs); RDTs are immunochromatographic tests that can detect malarial antigens in the patient's blood, oftentimes in as little as 20 minutes ("Diagnosis and Treatment…", 2018). Additionally, many of the health personnel in these areas are undertrained ("Diagnosis and Treatment…", 2018). Nonetheless, many countries' community health workers (CHWs) can be and have been trained to use RDTs if they have them and are educated on "integrated community case management of common childhood illnesses, including malaria" ("Diagnosis and Treatment…", 2018).

HIV

The human immunodeficiency virus (HIV) takes over host cell systems in order to carry out self-replication (Monette, Panté, & Mouland, 2011). One mechanism by which HIV-1, the most common type of HIV, exerts viral control over the host cell is by interfering with the proteins and components embedded in the membrane surrounding the cell's nucleus (Monette et al., 2011). With the alteration of the nucleoporins, the virus blocks nuclear transport and interferes with normal homeostatic processes (Short, 2011). This includes enacting extreme changes in the host cell nuclear envelope, resulting in the disruption of transport between the cytoplasm and nucleus and contributes to the production of viral proteins (Short, 2011). Ultimately, HIV attacks the immune system and leaves the individual susceptible to life-threatening cancers and infections ("HIV Treatment Overview", 2019). Opportunistic infections

are those that would not typically threaten a healthy person, but can occur when an immunocompromised individual's CD4 count falls below a certain level; patients with HIV must therefore take appropriate precautions to avoid such infections ("HIV Treatment Overview", 2019).

While no cure currently exists for HIV, certain drugs can be taken in order to slow disease progression and lessen its severity ("HIV Treatment: The Basics", 2019). The primary treatment, antiretroviral treatment (ART), combats the virus attacking the immune system and reduces the risk of transmittance ("HIV Treatment: The Basics", 2019). Some side effects do exist but differ from person to person; effects include nausea and vomiting, headache, diarrhea, rash, fatigue, dry mouth, pain, and insomnia ("HIV Treatment Overview", 2019). If the patient stops treatment, resistance may develop and hinder future treatment attempts ("HIV Treatment Overview", 2019). The virus can mutate on its own as it reproduces and generate variations that are no longer responsive to ART ("HIV Treatment Overview", 2019).

Cambodia has made significant strides in addressing the HIV/AIDS crisis within its borders (Heidt & Emond, 2016). By leaning on the advice of its international partners, the nation has been able to greatly reduce the number of new infections and implement antiretroviral treatment almost immediately after diagnosis (Heidt & Emond, 2016). Better education has reduced the risk of contracting this disease, and it is now not as widespread in the commercial sex trade, although this practice contributed greatly to the disease's initial spread ("Spread of HIV Is Slowing…", 2003). However, many people that are currently infected are still unreached and untreated (Heidt & Emond, 2016).

Tuberculosis

Tuberculosis (TB) results from an infection by *Mycobacterium tuberculosis* (Flynn & Chan, 2001). This organism is a slow-growing, acid-fast rod bacterium that is primarily transmitted by the respiratory route (Flynn & Chan, 2001). Individuals with laryngeal or pulmonary TB transmit the disease via talking, coughing, or sneezing, when airborne droplets are expelled into the air and subsequently inhaled by another person (Dye & Floyd, 2006). The inhaled bacteria are deposited in the alveoli of the lung, where they are then engulfed by macrophages (Dye & Floyd, 2006). Tuberculosis can either actively manifest or remain latent; in its latent stage, the bacteria remain dormant for some amount of time before possible reactivation (Flynn & Chan, 2001). The infecting bacteria survive within a granuloma composed of fibroblasts, macrophages, B cells, and T cells (Flynn & Chan, 2001). While the most common manifestation is pulmonary tuberculosis, a number of organs can be targeted (Flynn & Chan, 2001). Pulmonary varieties typically occur in the parenchyma of the middle and lower lung (Dye & Floyd, 2006). Symptoms of active TB in the lung include night sweat, cough with sputum and occasional blood, weakness, chest pains, weight loss, and fever (“Tuberculosis”, 2019). The disease is especially deadly when contracted in conjunction with HIV (“Tuberculosis”, 2019).

Figure 4. Mycobacterium tuberculosis bacilli (pink) in sputum. From "Interrupting Transmission of Tuberculosis Key to Containing Global Epidemic", by J. Oriol, 2017, https://www.infectiousdiseaseadvisor.com/home/topics/respiratory/interrupting-transmission-of-tuberculosis-key-to-containing-global-epidemic/

Tuberculosis is typically diagnosed through either a sputum, skin, or blood test ("Diagnosing and Treating Tuberculosis", 2018). Sputum samples are viewed by a laboratory technician under a microscope (see Figure 4) in order to identify the bacteria ("Tuberculosis", 2019). The World Health Organization (WHO) also recommends the rapid test Xpert MTB/RIF®, as it "simultaneously detects TB and resistance to rifampicin, the most important TB medicine" ("Tuberculosis", 2019). Treatment differs depending on whether the TB is latent or active ("Diagnosing and Treating Tuberculosis", 2018). If the infection is latent, then the measures taken are preventative in nature, and isoniazid (INH) is prescribed ("Diagnosing and Treating Tuberculosis", 2018). In active cases, treatment entails a combination drug therapy; the most common drugs used are INH, rifampin, pyrazinamide, and ethambutol ("Diagnosing and Treating Tuberculosis", 2018). Additional strategies are used when TB is detected in an individual with HIV. According to the WHO, "people living with HIV are 19 (15-22) times more likely to develop active TB disease than people without HIV"; both diseases serve to amplify and quicken each other ("Diagnosing and Treating Tuberculosis", 2018). This phenomenon is of particular concern, due to the great prevalence of HIV in Cambodia (Zaman, 2010).

While tuberculosis is curable, areas with restricted access to healthcare, such as those in Cambodia, have greatly struggled in implementing treatment (Zaman, 2010). Poorer areas are more at risk for TB, possibly stemming from immune systems weakened by malnourishment and increased risk of transmission resulting from a lack of effective ventilation and hygiene (Zaman, 2010). Southeast Asia is estimated to be carrying one-third of the world's TB burden, with

approximately 4.9 million cases (Nair, Wares, & Sahu, 2010). Also reported by the WHO is that "at least one-third of TB patients go undetected or get treated outside national programmes"; once again, inadequate facilities, detection equipment, and staffing contribute to the challenges hindering proper treatment (Nair et al., 2010). The WHO believes focusing on the implementation of DOTS (directly observed treatment, short-course) strategies can help overcome some of the constraints (Nair et al., 2010).

Antimicrobial Resistance as it affects this Region

Southeast Asia as a region, and specifically Cambodia, has experienced a frightening increase in antimicrobial resistance (AMR) over the last decade, and it is recognized as one of the most severe threats to global public health (Giffels, 2019). AMR refers to a phenomenon in which first-line treatments for a particular disease, in this case malaria and tuberculosis, are becoming ineffective on a much larger scale than previously witnessed (Giffels, 2019). While the issue partly stems from unavoidable natural occurrences, it has been amplified by human activities ("Antibiotic resistance", 2018). The unregulated sale of antibiotics and the use of antibiotics for livestock in addition to human prescription are common problems in Southeast Asia (Giffels, 2019). Once again, poverty has exacerbated health concerns due to a lack of effective structured health care (Giffels, 2019). Resistant strains are currently spreading, and the majority of public health systems across the region are ill-equipped to handle such an issue (Giffels, 2019). Growing AMR in malaria and tuberculosis is of particular concern.

Malaria

Resistant malaria is characterized by an unresponsiveness to first-line ACT treatment (Dondorp et al., 2009). Failure of the ACT combination drugs, dihydroartemisinin and piperaquine, was first clinically reported in western Cambodia in 2013, five years after the drugs

were first introduced (Dall, 2018). Treatment resistance in Cambodia has increased in frequency since then, and now its neighbors, Thailand, Laos, Vietnam, and Mynamar in the Greater Mekong Subregion, are experiencing the same phenomenon (Dall, 2018). Research has pointed to a particular strain of mutant *Plasmodium falciparum* as the primary cause behind this dihydroartemisinin-piperaquine resistance (Dall, 2018). From 2007 to 2013, the Wellcome Sanger Institute conducted a study in which they collected and analyzed the genome sequence data of 1,492 *P. falciparum* samples from 11 locations across Southeast Asia, including 464 samples retrieved from western Cambodia (Dall, 2018). They found that the majority of the samples carried mutations of the *kelch13* gene, which resulted in artemisinin resistance; resistance to piperaquine was connected to another genetic marker that showed the amplification of the *plasmepsin* 2 and 3 genes (Dall, 2018). The combination of these markers is found in the parasites with increased biological fitness that are primarily responsible for the spread of this crisis (Dall, 2018).

This emergent strain threatens to hinder recent progress made in global malaria control efforts; according to the WHO, “malaria deaths in the [southeast Asian] region have declined by 44%” since 2010 (Dall, 2018). Much of this success was dependent on ACT; as a result, increasing ACT resistance does not bode well (Dall, 2018). Of particular concern is the possibility of the artemisinin-resistant strain spreading to Africa, “which accounts for 90% of malaria cases” (Dall, 2018). Resolution of this issue may prove complicated; some believe ACT can continue to be effective under strict management of dihydroartemisinin-piperaquine and introduction of artesunate-mefloquine, which is another variation of ACT (Dall, 2018). However, the concern is that history will repeat itself, with the parasite becoming resistant to new therapies

and rendering them ineffectual as well (Dall, 2018). Many scientists advocate for greater genetic surveillance in order to better monitor malarial mutation and improve response time (Dall, 2018).

Tuberculosis

Since TB is caused by bacteria, treatment failure in this case falls into the category of antibiotic resistance ("Antibiotic-Resistant Mycobacterium…", 2012). There are two types of resistant TB that are creating challenges ("Antibiotic-Resistant Mycobacterium…", 2012). The most common variety is multidrug-resistant tuberculosis (MDR TB); the TB bacteria in this form are unresponsive to treatment by at least one first-line anti-TB drug and cannot be killed by either isoniazid (INH) or rifampin (RIF), which are the two antibiotics most commonly used in therapy ("Antibiotic-Resistant Mycobacterium…", 2012). Treatment of MDR TB is therefore more complicated and involves up to two years of multidrug administration, involving second-line drugs ("Antibiotic-Resistant Mycobacterium…", 2012). Another, much more rare type of TB is extensively drug-resistant TB (XDR TB), which is "is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)" ("Treatment for TB Disease", 2016). This is therefore, the most challenging to treat ("Antibiotic-Resistant Mycobacterium…", 2012).

Antibiotic resistance occurs when bacteria change in their response to antibiotic medications. Even when resistant bacteria could be killed or inhibited by a sufficiently high concentration of medication, that large of a dose would ultimately prove harmful to the patient (Hawkey, 1998). Clinical resistance is characterized by the interaction of "the type of infecting bacterium, its location in the body, the distribution of the antibiotic in the body and its concentration at the site of infection, and the immune status of the patient" (Hawkey, 1998). There are also four main mechanisms by which resistance can arise (Hawkey, 1998). First, the

most well-known mechanism is that of antibiotic modification; this occurs when the antibiotic is prevented from reaching its target, although the target remains as sensitive as it would in a normal strain (Hawkey, 1998). Second, the resistant bacteria can protect the target by blocking the antibiotic's entrance to the cell or "pumping it out faster than it can flow in" (Hawkey, 1998). Another mechanism involves the alteration of the primary site of action (Hawkey, 1998). This means that, although the antibiotic is able to enter the cell and reach the target site, it cannot generate any action due to structural changes in the molecule (Hawkey, 1998). The final way by which bacteria can resist treatment is via the creation "of an alternative target (usually an enzyme) that is resistant to inhibition by the antibiotic while continuing to produce the original sensitive target" (Hawkey, 1998).

In 2017, the European Respiratory Journal reported that there are "an estimated 480,000 new cases [of MDR-TB] emerging globally each year" (Chee et al., 2017). Drug-resistant tuberculosis primarily occurs as a result of drug misuse or mismanagement ("What is multidrug…", 2018). This can include circumstances where healthcare providers make mistakes concerning the treatment, duration of treatment, or dosage, patients do not finish the entire course of treatment, or when the proper quality or supply of medication is lacking ("What is multidrug…", 2018). MDR-TB is therefore more common in areas, such as developing countries, where regulation of TB treatment is insufficient (Zaman, 2010). As discussed above, the rural nature of much of Cambodia's healthcare hinders surveillance endeavors and the rapid identification of cases (Zaman, 2010).

Rural Healthcare Challenges

As compared to metropolitan and urban environments, 'rurality' "reflects smaller populations, and distance and isolation from major centres with a corresponding lack of access to

the full range of services and infrastructure"; healthcare in these areas is different in demographic, geographic, and sociological settings (Paliadelis, Parmenter, Parker, Giles, & Higgins, 2017). Even in developed countries, rural healthcare presents challenges both for physicians and patients (Paliadelis et al., 2017). Any existing healthcare professionals in remote regions must possess a wider variety of skills, due to the lack of available specialists (Paliadelis et al., 2017). Oftentimes physicians in isolation have minimal access to professional development, peer support, and supervision (Paliadelis et al., 2017). These circumstances place enormous pressure on professionals and can limit the amount knowledge they are able to acquire (Paliadelis et al., 2017). Other challenges, some of which have already been highlighted in brief, include limited access to specialized treatments and diagnostic equipment, as well as inadequate facilities, if they even exist at all (Ryan, 2004). Another point of concern is the economic burden caused when patients are required to travel great distances for treatment (Ryan, 2004).

Ultimately, rural areas in Cambodia are lacking in the detection and reporting of several diseases, including malaria and tuberculosis; this inability to quickly and accurately diagnose patients is a major factor contributing to the AMR phenomenon (Zaman, 2010). Increased access to diagnostic tools, including rapid test kits, can help affected individuals receive treatment more promptly ("Malaria: Asia Regional", 2019). Even so, ineffectual or nonexistent equipment is only one part of the problem; even if communities are supplied with the proper tools, there must be individuals trained to use them and provide comprehensive care.

When attempting to develop solutions for the difficulties faced by rural communities, there are a number of challenges that must be considered (Ryan, 2004). First of all, not everyone agrees on what 'adequate' healthcare access entails and which services are most important (Ryan, 2004). Additionally, urban models do not always translate well to rural communities;

there can exist a “tendency to direct strategies towards alleviation of symptoms as opposed to elimination of etiologies” and ultimately miss the fundamental causes of the health deficit (Ryan, 2004). The sustainability of healthcare in remote areas is of particular concern. (Ryan, 2004).

Avenues of Aid

As seen in the above section, multiple factors have to be considered when possible solutions are being discussed. The manner in which aid is provided can almost be as important as the aid itself. Several organizations and governments are currently offering assistance to Cambodia through a variety of avenues. Both national and foreign efforts have been made to strengthen rural healthcare.

Empowering Local Volunteers

One way that rural communities can be better supported and integrated into the ‘fold’ of Cambodian healthcare is by better equipping national volunteers (Ozano, Simkhada, Thann, & Khatri, 2018). In recent years, Cambodia created the ‘Community Participation Policy for Health’, which led to the creation of community health workers; the policy dictated that “CHWs should be literate, live in the communities they serve and be elected by community members” (Ozano et al., 2018). CHWs are responsible for about 10 to 50 households, depending on the community and are trained at and supervised by a national health center (Ozano et al., 2018). These national volunteers are integral components of connecting rural communities to public health systems (Ozano et al., 2018). Many national and international non-government organizations (NGOs) contribute to the financing of this initiative (Ozano et al., 2018).

CHWs serve as front-line caregivers in under-served regions, but they have experienced numerous challenges that limit the care they could be providing (Ozano et al., 2018). Many of the CHMs are close to the poverty line and risk reduction of income as a result of their volunteer

work (Ozano et al., 2018). The main issues include a lack of support and leadership from the local government, inadequate resources, and inconsistent training programs; additionally, the CHWs are pulled in many directions due to a mixture of external foreign influences (Ozano et al., 2018). Increased dependency on international support raises a concern as to the sustainability of this program in the future, due to the partners' geographic and resource limitations (Ozano et al., 2018). CHWs need "a more structured delivery system that allows them to be part of the planning and development process", as well as more tools and comprehensive training (Ozano et al., 2018).

The Complexity of Short-Term Missions

In addition to the niche filled by national support, foreign aid has a big role to play (Chiu, Weng, Chen, Yang, & Lee, 2012). Short-term medical missions (STMMs) primarily target rural and underprivileged areas and offer health care to those without access to any developed system (Chiu et al., 2012). The primary goal of most of these trips is to lift the burden of disease associated with physician shortages and meet unmet needs (Sykes, 2014). They are typically organized from high-income countries (HICs) to low- and middle-income countries (LMICs) and have risen in frequency with increased globalization (Sykes, 2014). STMMs can be defined as "trips in which volunteer medical providers from HICs travel to LMICs to provide health care over periods ranging from 1 day to 8 weeks" and can be associated with either faith-based or non-faith-based organizations (Sykes, 2014).

STMMs face a variety of challenges including "a lack of follow-up care, short duration, too many patients, language and cultural barriers, limited medications and supplies, and a lack of support services from local authorities" (Chiu et al., 2012). These mission trips are not part of any standardized system, which is a cause of concern (Sykes, 2014). Very little empirical data

exists concerning the results of these projects and some fear unintended consequences, including lax drug accountability (Johnson, 2017). Despite the best intentions of the outreach, "service trips can often become self-serving for the institution and ineffective, inappropriate, or burdensome to the existing health care infrastructure and to the local population" (Johnson, 2017). Respectful and effective communication with the local community is a key component to successful STMMs is (Johnson, 2017). A good relationship with the national community will ensure the team understands the community's priorities and is working within any preexisting infrastructure, so as to not undermine local care (Johnson, 2017).

Conclusion

Cambodia is a beautiful nation, characterized by a warm and vibrant people grounded in a proud and long-enduring culture. Its position in the Greater Mekong Subregion places it in the beating heart of Southeast Asia. Once a prospering and thriving market for trade, modern history has seen a large part of this region rocked by a series of devastating events. The horrific genocide committed by the Khmer Rouge under the leadership of Pol Pot set Cambodia back in a significant number of areas. Of particular concern is how it affected the country's healthcare system; Cambodia experienced a crippling loss of facilities and trained personnel. Although the nation's capital of Phnom Penh and its more metropolitan areas have made remarkable progress on the road to recovery, the majority of Cambodian people live in rural communities that lack sufficient healthcare.

This rural disparity has amplified many of the issues the region is already dealing with. Malaria, tuberculosis, and HIV have been three of the worst and most lethal diseases, both in Cambodia and throughout the Greater Mekong area. There has been significant success achieved in combatting these issues, but antimicrobial resistant varieties threaten to halt and undermine the

work that has already been done. Without the proper tools, diagnoses are often not made soon enough and resistant strains spread quickly; the lack of effective equipment and adequate medical supplies and professionals have made treatment extremely difficult.

In attempting to rectify and alleviate many of the unique challenges faced by rural regions, much concern has arisen as to how ‘solutions’ are being enacted. Many avenues exist by which aid can be offered, but each one possesses its own complexities and complications. National efforts must be supported in their endeavors to provide healthcare. CHW are a promising step forward in decreasing the rural disparity, but the current system is far from perfect. Foreign medical aid is a powerful tool that brings quality care to places that would never have access to comprehensive modern medicine otherwise. However, there are ethical components that require careful analysis. A healthy Cambodia could help its fellow Southeast Asian nations in their own endeavors to combat disease and institute widespread quality medical care.

References

Acuin, J., Firestone, R., Htay, T. T., Khor, G. L., Thabrany, H., Saphonn, V., & Wibulpolprasert, S. (2011). Southeast Asia: an emerging focus for global health. *The Lancet*, *377*(9765), 534–535. doi: 10.1016/s0140-6736(10)61426-2

Antibiotic resistance. (2018, February 5). Retrieved from https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance

Antibiotic-Resistant Mycobacterium tuberculosis (TB). (2012, April 3). Retrieved from https://www.niaid.nih.gov/research/tuberculosis-definitions

Chandler, D. P., & Overton L. C. (2019). Cambodia. In *Encyclopædia Britannica Online.* Retrieved from britannica.com/place/Cambodia

Chee, C. B., Khinmar, K.-W., Sng, L.-H., Jureen, R., Cutter, J., Lee, V. J., & Wang, Y.-T. (2017). The shorter multidrug-resistant tuberculosis treatment regimen in Singapore: are patients from South-East Asia eligible? *European Respiratory Journal*, *50*(2), 1700753. doi: 10.1183/13993003.00753-2017

Chiu, Y.-W., Weng, Y.-H., Chen, C.-F., Yang, C.-Y., & Lee, M.-L. (2012). Perceptions and Efficiency of Short-Term Medical Aid Missions Among Key Groups of Health Professionals. *Evaluation & the Health Professions*, *37*(3), 379–393. doi: 10.1177/0163278712461503

Coker, R. J., Hunter, B. M., Rudge, J. W., Liverani, M., & Hanvoravongchai, P. (2011). Emerging infectious diseases in southeast Asia: regional challenges to control. *The Lancet*, *377*(9765), 599–609. doi: 10.1016/s0140-6736(10)62004-1

Dall, C. (2018, February 2). Drug-resistant malaria spreading fast in Southeast Asia. *Center for Infectious Disease Research and Policy*. Retrieved from http://www.cidrap.umn.edu/news-perspective/2018/02/drug-resistant-malaria-spreading-fast-southeast-asia

Diagnosing and Treating Tuberculosis. (2018, December 13). Retrieved from https://www.lung.org/lung-health-and-diseases/lung-disease-lookup/tuberculosis/diagnosing-and-treating-tuberculosis.html

Diagnosis and Treatment of Malaria in the Malaria-Endemic World. (2018, July 23). Retrieved from https://www.cdc.gov/malaria/malaria_worldwide/reduction/dx_tx.html

Disease. (2019, January 4). Retrieved from https://www.cdc.gov/malaria/about/disease.html

Dondorp, A. M., Nosten, F., Yi, P., Das, D., Phyo, A. P., Tarning, J., . . . Silamut, K. (2009). Artemisinin resistance in Plasmodium falciparum malaria. *The New England Journal of Medicine,361*, 455-467. doi:10.1056/NEJMoa0808859

Dye, C., & Floyd, K. (2006). Tuberculosis. In *Disease Control Priorities in Developing Countries*(2nd ed.). New York: Oxford University Press.

Fadel, H. (2014, December 1). Plasmodium falciparum. Retrieved March 3, 2020, from http://www.pathologyoutlines.com/topic/parasitologymalariapfalciparum.html

Flynn, J. L., & Chan, J. (2001). Immunology of tuberculosis. *Annual Review of Immunology, 19*, 93-129.

Frederick, W. H., & Leinbach, T. R. (1999). Encyclopædia Britannica. In *Encyclopædia Britannica*. Encyclopædia Britannica. Retrieved from https://www.britannica.com/place/Southeast-Asia

Gardner, M. J., Hall, N., Fung, E., White, O., Berriman, M., Hyman, R. W., . . . Barrell, B. (2002). Genome sequence of the human malaria parasite Plasmodium falciparum. *Nature 419*, 498-511.

Giffels, A. (2019, September 17). Poverty and Antibiotic Resistance in Southeast Asia. Retrieved from https://borgenproject.org/poverty-and-antibiotic-resistance-in-southeast-asia/

Hawkey, P. M. (1998). The origins and molecular basis of antibiotic resistance. *British Medical Journal*, *317*(7159), 657–660. doi: 10.1136/bmj.317.7159.657

Health First: Boosting health care services helps millions in Cambodia. (2016, April 15). http://www.worldbank.org/en/results/2016/04/15/health-first-boosting-health-care-services-helps-millions-in-cambodia

Health services and centers. (2016, December 23). https://opendevelopmentcambodia.net/profiles/access-to-public-service/health-services-and-centers/

Healthcare in Cambodia. (2017, July 11). https://www.pacificbridgemedical.com/publication/healthcare-in-cambodia/

Heidt, W., & Emond, M.-O. (2016, December 1). Ending AIDS in Cambodia. Retrieved from https://kh.usembassy.gov/ending-aids-cambodia/

HIV Treatment Overview. (2019, March 29). Retrieved from https://www.hiv.gov/hiv-basics/staying-in-hiv-care/hiv-treatment/hiv-treatment-overview

HIV Treatment: The Basics. (2019, January 15). Retrieved from https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/51/hiv-treatment--the-basics

Ho, M., & White, N. J. (1999). Molecular mechanisms of cytoadherence in malaria. *American Journal of Physiology-Cell Physiology*, *276*(6), 1231–1242. doi: 10.1152/ajpcell.1999.276.6.c1231

Johnson, K. L., Alsharif, N. Z., Rovers, J., Connor, S., White, N. D., & Hogue, M. D. (2017). Recommendations for Planning and Managing International Short-term Pharmacy Service Trips. *American Journal of Pharmaceutical Education, 81*(2). doi: 10.5688/ajpe81223

Kiprop, V. (2018, August 9). Which Countries Are Considered to Be Southeast Asia? Retrieved from https://www.worldatlas.com/articles/which-countries-are-considered-to-be-southeast-asia.html

Leinbach, T. R., & Frederick, W. H. (1999). Encyclopædia Britannica. In *Encyclopædia Britannica*. Encyclopædia Britannica. Retrieved from https://www.britannica.com/place/Southeast-Asia

Malaria. (2018, December 13). Retrieved from https://www.mayoclinic.org/diseases-conditions/malaria/diagnosis-treatment/drc-20351190

Malaria: Asia Regional. (2019, July). Retrieved from https://www.usaid.gov/asia-regional/malaria

McGrew, L. (1990, September). Health care in Cambodia. *Cultural Survival Quarterly Magazine, 14*(3).

Monette, A., Panté, N., & Mouland, A. J. (2011). HIV-1 remodels the nuclear pore complex. *The Journal of Experimental Medicine, 193* (4). doi:10.1084/jem2086oia16*

Mota, M. M., Pradel, G., Vanderberg, J. P., Hafalla, J. C. R., Frevert, U., Nussenzweig, R. S., … Rodríguez Ana. (2001). Migration of Plasmodium Sporozoites Through Cells Before Infection. *Science, 291*(5501), 141–144. doi: 10.1126/science.291.5501.141

Nair, N., Wares, F., & Sahu, S. (2010). Tuberculosis in the WHO South-East Asia Region. *Bulletin of the World Health Organization, 88*(3), 164–164. doi: 10.2471/BLT.09.073874

Oriol, J. M. (2017, March 21). Interrupting Transmission of Tuberculosis Key to Containing Global Epidemic. Retrieved from

https://www.infectiousdiseaseadvisor.com/home/topics/respiratory/interrupting-transmission-of-tuberculosis-key-to-containing-global-epidemic/

Ozano, K., Simkhada, P., Thann, K., & Khatri, R. (2018). Improving local health through community health workers in Cambodia: challenges and solutions. *Human Resources for Health, 16*(2). doi: 10.1186/s12960-017-0262-8

Paliadelis, P., Parmenter, G., Parker, V., Giles, M., & Higgins, I. (2017). The challenges confronting clinicians in rural acute care settings: a participatory research project. *Rural and Remote Health, 12*(2). Retrieved from https://www.rrh.org.au/journal/article/2017

Priority health concerns. (2017, February 10). https://opendevelopmentcambodia.net/topics/priority-health-concerns/

Ryan, K.D. (2004). Health and sustainability of rural communities. *Rural and Remote Health*, *4*(1). Retrieved from https://www.rrh.org.au/journal/article/242

Short, B. (2011). HIV-1 makes a pore adjustment. *The Journal of Cell Biology, 193*(4). doi:10.1083/jcb.1934iti1

Sinka, M. E., Bangs, M. J., Manguin, S., Rubio-Palis, Y., Chareonviriyaphap, T., Coetzee, M., … Hay, S. I. (2012). A global map of dominant malaria vectors. *Parasites & Vectors*, *5*(1). doi: 10.1186/1756-3305-5-69

Spread of HIV Is Slowing in Cambodia. (2003, March 1). Retrieved from https://www.prb.org/spreadofhivisslowingincambodia/

Sykes, K. J. (2014). Short-Term Medical Service Trips: A Systematic Review of the Evidence. *American Journal of Public Health, 104*(7), e38–e48. doi: 10.2105/ajph.2014.301983

Tomb, C. (2016, October 12). Top Diseases in Cambodia. Retrieved from https://borgenproject.org/top-diseases-in-cambodia/

Treatment of Malaria: Guidelines For Clinicians (United States). (2019, December 11). Retrieved from https://www.cdc.gov/malaria/diagnosis_treatment/clinicians1.html

Treatment for TB Disease. (2016, April 5). Retrieved from https://www.cdc.gov/tb/topic/treatment/tbdisease.htm

Tuberculosis. (2019, October 17). Retrieved from https://www.who.int/news-room/fact-sheets/detail/tuberculosis

What Is Multidrug and Extensively Drug Resistant TB? (2018, December 13). Retrieved from https://www.lung.org/lung-health-and-diseases/lung-disease-lookup/tuberculosis/drug-resistant-tb.html

Zaman, K. (2010). Tuberculosis: A Global Health Problem. *Journal of Health, Population and Nutrition*, *28*(2), 111–113. doi: 10.3329/jhpn.v28i2.4879