An epidemiological overview on oral outbreaks of Chagas disease in South America

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Abstract

Introduction: Chagas disease is one of the world's neglected tropical diseases. The World Health Organization (WHO) estimates that presently 10 million people worldwide are infected. Recently the oral transmission of Chagas disease has been given more attention as a result of more outbreaks being detected in the Amazon region. There are still many uncertainties regarding oral outbreaks, one being the epidemiological picture, another whether oral transmission is an emerging transmission mode. Moreover, oral transmission is possibly more lethal as a form of transmission. Aim/objectives: Main objective: Perform an epidemiological overview of available literature on the oral outbreaks of Chagas disease in the countries of the Amazon Region. Specific objectives: Mapping oral outbreaks of Chagas disease according to available literature, Event Management System (EMS) and ProMED-mail data. To make a timeline of published cases and retrieve information on mortality, source and form of social gathering. Method: Literature review with a research synthesis of known cases of oral outbreaks and a meta-analysis of the data found. The search was conducted in PubMed/MEDLINE and LILACS. The limitation of the study was mainly access to South American journals. Results: Geographically there was a broad outbreak distribution and some clustering. Oral outbreaks were more extensively described in the Brazilian literature; however, Venezuela, Colombia and Bolivia had all reported oral outbreaks. Outbreaks occurred in rural and urban areas. Mortality of oral outbreaks ranged from 0-6 deaths; number of cases from 3-103. The source of the oral outbreaks was most often hypothesized to be palm fruit juice and undercooked meals. Social occasions were most often families sharing meals and drinks. The timeline showed that outbreaks were already mentioned in 1965. From then there was a large interval, and in the last decade the number of oral outbreaks has risen. Discussion: Oral outbreaks occur in several countries of the Amazon Region, and in both urban and rural areas. It was not possible to say if outbreaks are emerging; however, it was clear that there is a current risk of oral transmission for local people as well as tourists. Oral outbreaks can be large and severe, and rapid treatment needed. The conclusion from this thesis is that oral outbreaks are not sufficiently monitored. The strengthening of surveillance systems for oral outbreaks is a priority to establish further prevention measures.

Keywords: Oral, transmission, outbreak, Chagas disease, Amazon
1. Introduction

Chagas disease is one of the world's neglected tropical diseases. At present, the World Health Organization (WHO) estimates that 10 million people worldwide are infected (1). The largest part of infected cases occurs in the 21 Latin American countries. Chagas disease was restricted to Latin America for many years. This pattern has changed as cases in the last decades have occurred in the Region of the Americas, the Western Pacific Region and the European Region, as well (2, 3). This new pattern is mainly caused by population movement such as migration, but also through blood transfusion, congenital transmission and other less frequent routes of transmission (4).

Transmission of Chagas disease can occur in several different ways, including the contact of any skin break or mucosa with infected faeces of vectors, through transfusional, congenital transmission or organ transplantation and even laboratory incident. Oral transmission of Chagas disease has been considered to be a rare transmission form (3, 5). Recently, oral transmission has been given more attention as a result of more outbreaks being detected especially in the Amazon region (6-11). As of yet, there are still many uncertainties regarding oral transmission, one being the epidemiological picture, and also whether oral transmission is an emerging transmission mode, or if it has in fact been there all along. It has been estimated that there is an increase of 2.2 new cases per month of oral transmission in Brazil, and that this figure is underestimated mostly because of the access limitation of the Amazon region (12).

People in the countries of the Amazon Region have been struggling with Chagas disease for centuries. Oral transmission is possibly a more lethal form of transmission, which rise questions on both long term morbidity and mortality (13). One oral outbreak in Santa Catarina, Brazil in 2005 had a lethality rate of 12.5% (12). Family episodes with suggested oral transmission have been increasingly discovered, especially in Brazil (14). Oral transmission has implications not only for the people living in the countries of the Amazon Basin, but also for travelers to these regions. Cases of acute Chagas disease have been reported in European citizens returning to Europe from travels in South America (5, 15).

In view of the general lack of knowledge on oral transmission of Chagas disease, the importance of undertaking an epidemiological overview of this transmission form is evident from the public health point of view. Furthermore, there is a lack of surveillance of oral outbreaks in the countries of the Amazon Region, which may cause many cases to go undetected and untreated. Creating a surveillance system to detect acute cases efficiently and in a timely fashion may be an overlooked priority for those countries. This thesis will attempt to provide an overview of oral transmission in South America, looking at cases reported in the literature throughout history.
2. Background

2.1 Chagas disease at a glance

In the following, key aspects of Chagas disease will be presented to give a brief general overview of this neglected tropical disease and its many public health aspects.

The Brazilian scientist and medical doctor Carlos Chagas discovered the disease that now bears his name in 1909, whilst he was working in a poor rural area of the Brazilian State of Minais Gerais. Chagas noticed specific clinical symptoms in his patients and made the connection between the presence of the haematophagous triatomine bugs and these symptoms. During only a few years Carlos Chagas managed to map the aetiology of Chagas disease, the entomologic aspects of the disease-bearing vectors and to demonstrate the necessity to establish care for patients suffering from Chagas disease (1, 16).

Chagas is caused by the protozoan parasite Trypanosoma Cruzi (T.cruzi) and is transmitted primarily through insects of the triatomine subfamily. These vectors infect both humans and a very large number of other mammals and are present all over the Americas. There is no vaccine for Chagas disease, and the most effective ways of preventing it is through vector control, improvement of housing and hygiene conditions and blood screening to avoid infection through blood transfusion and organ transplantation. Chagas disease has an acute phase lasting about two months after infection and a chronic phase lasting for the lifetime of the patient without successful antiparasitic treatment. Chagas disease is curable if it is treated shortly after infection, in the acute or early chronic phase of the disease. Efficacy of the treatment decreases with the length of the infection. Specific treatment for cardiac, digestive, neurological or mixed alterations can also become necessary (4). Most patients are asymptomatic, and clinical manifestations of the disease and antiparasitic treatment response vary according to different geographical areas (1). Thus there are various public health aspects of Chagas disease to take into consideration for surveillance, control and prevention measures.

Since the time of Carlos Chagas there has been little development in underdiagnosis as well as treatment offer and a large number of people in South America are estimated to die of Chagas disease untreated and in silence. WHO estimates that over 25 million people are at risk of the disease, and that more than 10 000 people died from it in 2008 alone. Chagas disease has even spread outside Latin America. It has been detected in the United States of America, Canada, many European countries and some Western Pacific countries like Australia and Japan (17). The Amazon region had long been considered not to be endemic of Chagas disease, however, in recent years there has been more attention on the area due to an increased number of detected acute cases in the region (6-11, 14, 18).
2.1.1. The Amazon Region

The Amazon region is a diverse region in regards to environment, nature and population. The countries of this Region include Bolivia, Brazil, Colombia, Ecuador, French Guyana, Guyana, Suriname, Peru and Venezuela. The official languages are Portuguese in Brazil, French in French Guyana, English in Guyana, Dutch in Suriname and Spanish in the remaining Amazon countries. The region predominantly exists of tropical humid forest area, and over 30 million people live there, of which 6 million people alone are in the Brazilian Amazon. Around 260 000 Indigenous people live in the region, communicating in 170 different languages. Little is known yet, about the epidemiological status of endemic infectious diseases in this region, Chagas disease included (19). The Amazon region has not been considered endemic of Chagas disease until the last decade, however that has changed. Human encroachment of the natural habitats of the disease bearing vectors has forced them to adapt to human settings. Human migration, uncontrolled deforestation, road construction, mining and other commercial activities as well as keeping large animal pastures have changed the epidemiological pattern of Chagas disease (7, 19, 20).

The Amazon region consists largely of a rural and poor population. This has implications in the sense that Chagas disease and poverty have been closely linked throughout history. For centuries poor housing conditions in rural settings and more recently slum dwellings of larger cities have been a risk factor of transmission by domesticated and peri-domesticated insects (21, 22). Additionally to poor hygiene conditions, poor dwellings, like thatched straw huts, enable the domestication of vectors. Furthermore, living in close proximity with pets and animals facilitate peri-domestication of the vectors, and the risk of human infection increases. By encroaching on the natural life cycle of the vectors in the Amazon region, humans have become part of the feeding cycle of the vectors, as well as a part of the life cycle of the parasite T.cruzi (7).

Mainly south of Amazon Basin there have been significant achievements with control programs, which have included vector control and blood screening approaches. At the same time, an improvement of housing conditions has occurred, especially for the rural population. Since the 1990s there have been considerable advances in parasite and vector control in South America, largely due to initiatives like the Southern Cone, Central American, Andean Pact and the Amazonian Intergovernmental Initiative in cooperation with the Pan American Health Organisation (PAHO) (4). Transmission by domiciliated vectors has been considerably reduced in many South American countries, and also transmission by blood transfusion has been reduced through these multinational initiatives (1). Brazil, Chile, Uruguay and Venezuela, for instance, have reduced the incidence of Chagas disease considerably through programs, but also due to a decrease in population and improved housing conditions in rural areas. Nevertheless, in Bolivia, Paraguay and southern parts of Peru, Chagas disease is still highly prevalent and control measures, including detection and treatment are insufficient. Despite advances in Colombia, Ecuador, Central America and Mexico the situation is quite similar, especially considering patient care (4, 22).
2.1.2. Triatomines and T.cruzi

To understand the epidemiology of Chagas disease one needs to look at the transmission vector and its particular habits. The *T.cruzi* parasite is transmitted to humans by vectors of the Reduviidae family and the subfamily of Triatomines. These insects feed on mammals by sucking blood, and *T.cruzi* is most often transferred via their faeces, deposited on the skin of the host after feeding. The parasites are able to penetrate through mucous membranes as well as skin injuries, when the host scratches the skin after being bitten (20). There are many popular names for the vector. In Brazil for instance a common name for the vector is *Barbeiro* - "the barber". In Argentina, Bolivia, Chile, Paraguay and Uruguay they are called *Vinchucas*. In Colombia, Peru and Venezuela they are called *Chipos* and in Central America, Mexico and Panama they are known as *Chinches*. The English name is the *kissing bug* (22). The quantity of local names suggests that humans have known the insects for a long time. Around 100 different triatomine species are susceptible to infection with the *T.cruzi* parasite. In Argentina, Bolivia, Brazil, Chile, Paraguay and Peru the principal vector species has been *Triatoma Infestans*. In Brazil, the species *Panstrongylus megistus* and *Triatoma sordida* are also prevalent. In Venezuela *Rhodnius prolirus* is present and in Central America *Triatoma dimidiatea*. Apart from the triatomine insects, *T.cruzi* is known to infect eight different mammalian orders. In the Amazon region *T.cruzi* is commonly found in animals (22). The geographical diversity of the parasite bearing vectors is evident. Since vectors are more or less prone to domestication, and because they carry different *T.cruzi* strains it is necessary to take vectors species into consideration for prevention as well as control strategies.

2.1.3. Pathological and clinical picture of Chagas disease

The parasite *T.cruzi* produces pathological processes in mammals that can occur in various organs and tissues. When *T.cruzi* is transmitted it invades the victim’s bloodstream and the lymphatic system. Hereafter it nestles in the muscle and cardiac tissue, which causes inflammation and immune system responses (23). Chagas disease has an acute as well as a chronic phase. Morbidity and mortality are higher in the acute phase for children under five, immune-suppressed people or people with high parasitemia as in patients from outbreaks of food-borne Chagas disease (5, 23).

The acute phase can occur at any age in disease endemic areas, however, the highest frequency is before the age of 15, typically starting in the age group 1-5 years. The acute phase of Chagas disease usually lasts 6-8 weeks, and most frequently is oligo- or asymptomatic. After the acute phase most patients appear to be healthy. The infection by *T.cruzi* can then only be detected serologically or through parasitological tests (3, 24). In the acute phase, if the transmission is vectorial, visible port of entry can be identified, such as the chagoma, a skin lesion in exposed areas of the body, or the Romaña’s sign, a purplish oedema on the lids of one eye. The sign occurs only in about 10% of infected persons, and can easily be misdiagnosed with conjunctivitis, for example, which is common in rural areas. Other clinical features of the acute phase, especially prevalent in
infected children, are fever, persistent fast heartbeat, swollen lymph nodes, oedema and liver and spleen enlargement. Generic and unspecific symptoms include; diarrhoea, vomiting, headache, muscle pain, loss of appetite and extreme fatigue (22, 25). These symptoms are not very specific, and can easily be confused with other disease aetiologies.

When the patient enters the chronic phase of Chagas disease it will last for the lifetime of the individual without successful antiparasitic treatment. The phase starts when parasitemia falls to a level where it is undetectable with direct parasitological tests, and when symptoms and clinical manifestations typically disappear. Depending on the geographical area, 10 - 40% of patients in the chronic phase will develop lesions in target organs according to the *T. cruzi* strain they are infected with and the host immune response, among others (3). The most common manifestations of chronic Chagas disease are mainly cardiomyopathy and also intestinal mega syndrome. Cardiomyopathy is found everywhere, from North to South America. Mega syndrome occur more often south of the Amazon Region (20). These differences are explained, among others by the presence of different strains of the parasite *T. cruzi* in different regions. Up to 30-50% of infected people, however, remain in an indeterminate form for their whole life, showing no symptoms (1, 22).

Chagas disease can be challenging to diagnose. There are several diagnostic tools including, direct parasitological tests, serological tests, molecular tests, hemaculture and xenodiagnosis (9, 26). Parasitemia is generally high in the acute phase (25). After this phase the parasitemea level most often stabilized because of the immune reaction of the patient. The parasite then nestles in specific target tissues of the body, preferably heart or muscle of the digestive system, thus making it difficult to isolate the parasite in the patient’s blood stream. Oral transmission in particular is often characterized by very high parasitemia in the bloodstream, probably due to higher inoculum of infection (13, 25).

### 2.1.4. *T. cruzi* transmission routes

The list of possible infection routes of Chagas disease includes vectorial, transfusional (through *T. cruzi* infected blood), congenital, through organ transplantation, oral transmission and accidental, through laboratory accidents (22). Vectorial transmission happens when the bug feeds on humans and defecates, and the human then smears faeces into the punctured skin, and become infected with *T. cruzi*. Vectorial transmission is considered the main transmission form in Latin America, whereas outside of Latin America the main transmission forms are transfusional, congenital and accidental due to the absence of the vector (5). In 2006 WHO certified Brazil as being free of transmission through *Triatoma infestans*, the main intradomiciliary vector of Chagas disease (12). However, with the new reports of oral transmission in the Amazon region, this victory was only partial (6-11). Brazil and other countries of the Amazon region now have to face the challenge of the sustainability of the vectorial achievements through entomological surveillance and the problem of an incipient knowledge of oral transmission and oral outbreaks.
2.2. Oral transmission and oral outbreaks in the scientific literature

Oral transmission is a transmission route that, like Chagas disease itself, has not received much attention in previous literature on Chagas disease. The following provides an overview of how oral transmission has appeared and reappeared in the scientific literature, since this mode of transmission was first hypothesized. The terminology and perception on the transmission mode’s technical features, its feasibility and the actual prevalence of it has changed throughout time.

2.2.1. Severity of oral outbreaks

Oral transmission of Chagas disease may or may not present more severe outcomes for the patient in the chronic phase. The inoculum or amount of *T. cruzi* at the initial infection is possibly important for how Chagas disease develops in the patient. A Brazilian study showed that patients with a known severe acute form had the most severe chronic forms (23). A very high quantity of parasites in the patient is the most plausible hypothesis of severe acute phase that often characterizes oral transmission of Chagas disease. This means that the chronic phase can have higher morbidity for victims that have been infected with Chagas disease orally. Moreover, the mortality of oral transmission is high and the risk is higher for younger children and immune-suppressed people more vulnerable to high parasitemia.

2.2.2. Oral transmission and oral outbreaks

Oral transmission of Chagas disease has been hypothesized to derive from several different types of food contamination. The most commonly mentioned hypothesis is transmission through ingestion of food contaminated by infected insects or their faeces. Oral transmission has also been mentioned to happen through ingestion of food contaminated with the urine or anal gland secretion from the opossum (*Didelphis marsupialis*). Transmission to infants through mother’s milk is also technically oral transmission (22, 27). Even ingestion of infected undercooked or raw meat is a possible oral transmission route that is relevant particularly in relation to certain Indian initiation practices in Colombia (22, 28, 29).

It is important to make the distinction between oral outbreaks and oral transmission. Oral transmission is a term describing the way the *T. cruzi* parasite is transferred to the host. Oral outbreaks however, are related to food contamination and when two or more people are infected at the same time and place. Dias (28) describes outbreaks as occurring most often in secluded, defined geographical spaces in a specific moment with different types of food involved, such as sugar cane or açai juice, or other palm fruit juices, soup, under-cooked meat, milk and others. Outbreaks in the Amazon Region characteristically occur in small groups of people, like families, that share a
common meal (7, 30). This thesis will focus on oral outbreaks described in the scientific literature; however the technical features of oral transmission will also be described in some detail because of the rather complex nature of the transmission form.

2.2.3. Animal reservoirs of *T. cruzi*

In general, oral transmission has been mentioned sporadically in the scientific literature throughout history. The hypothesis of oral transmission was initially mentioned in connection with carnivorous transmission of Chagas disease, where carnivorous animals fed on other animals infected with *T. cruzi* and *T. cruzi* was transferred orally. As early as 1921, Nattan-Larrier experimented on oral infection of mice via blood infected with *T. cruzi* (31). Several people experimented on oral transmission of Chagas disease in animals in the early 30ies (32-35). In 1939 Mazza et al. experimented on *T. cruzi* infection by giving milk with infected insects to dogs (27). Diaz-Ungria (1968) macerated flies from a highly vector infested area in Venezuela and fed a dog with contaminated milk. The dog then presented symptoms of acute Chagas disease (36). Ribeiro, Garcia and Bonomo (1987) showed that omnivorous animals, especially the opossum, feeding on infected animals and triatomines gives high infection indices in same animals (37). This also highlights the importance of opossums as reservoirs due to the migratory habits of this animal. In the 2002 WHO report on Chagas disease, oral transmission is mentioned in connection with the sylvatic cycle in which mammals eat triatomines and other reservoir hosts and become infected, or when domestic pets eat infected rodents or bugs (3). In 2009 Roellig and his colleagues investigated scavenging behaviour of raccoons as a possible oral transmission route of *T. cruzi* in the sylvatic cycle (38).

These experiments on animals were performed both to investigate and demonstrate the sylvatic cycle of the *T. cruzi* parasite in nature, which is important in relation to vector control measures and to find possible hosts of the parasite that can come into contact with humans, such as the opossum, or domestic animals such as dogs or cats. However, the experiments also demonstrated the possibility of oral transmission. Oral transmission of *T. cruzi* to humans has not been experimented on directly; nevertheless the possible oral transmission routes to humans have been investigated, namely contaminated food.

2.2.4. Food contamination

Food contaminated with *T. cruzi* is often hypothesized to be the source of oral outbreaks of Chagas disease (25). There are several aspects of food contamination, among others the viability of the parasite surviving in the food, the way that the food has been contaminated and the actual infectivity of ingested contaminated food. Unfortunately it has never been possible to locate and test the source after an outbreak, because the symptoms appear some time after the infection occurred (39). This means that any contaminated food will have been thrown out by the time the outbreak is discovered.
Even if the food had been saved, the actual survival of the parasites in the food for longer periods is questionable.

Lainson, Shaw and Naiff (1980) looked at the survival rate of *T. cruzi* in different contaminated foods (40). Survival of the parasite was seen for up to three hours in as diverse foods as milk, beans, beef and rice. Cardoso et al. (2006) investigated the survival of *T. cruzi* in sugar cane used to prepare juice and found that *T. cruzi* was found in the juice up to four hours after contamination (41). Soarez, Dias, Marsden and Garcia-Zapata (1987) investigated the survival of trypomastigotes in sugar cane juice and found a 24-hour survival rate (42). Thus, juice, other beverages and food would be intermediary transmission vessels of *T. cruzi*, and therefore difficult to obtain samples from. In Brazil açaí juice has long been suspected as a possible source of outbreaks of acute Chagas disease (43).

Hervé Rogez from the Technical Institute of Amazônia investigated the possible ways that *T. cruzi* could enter into the production of açaí juice in Brazil. He found that the disease-bearing insect prefers palm trees, and in particular the açaí palm species. The açaí fruits are collected most often in the morning, and processed directly at a market with little hygienic procedures; thus, contaminated fruits could easily be processed into the açaí juice (44). Others have also hypothesized on juice production in the Amazon and oral transmission of Chagas disease, Brazil especially, where juice is often prepared outdoors during the evening under a strong light that attracts infected vectors, and then left to cool during night (7, 14). Household contamination of foods is also an issue for oral transmission. Lainson, Shaw and Naiff (40) speculated that kitchen foods can become contaminated with *T. cruzi* from vector faeces or if the entire insect falls into the food and disintegrate. Much food in the Amazon region is eaten cold, even if it is well cooked before. Leftovers from the day before will be kept at room temperature and contamination by the vectors can take place (40). In relation to household contamination there have also been speculations on transmission by the opossum, because this animal often enters human dwellings to scavenge for food. Opossums have been shown to secrete *T. cruzi* through the anal glands. If the animal secretes on food or kitchen utensils these would be contaminated with *T. cruzi* (29). Valente et al. (14) suggests that the presence of *T. cruzi* in the anal gland secretions of the opossum, which has both wild and peri-urban habits, is an important element of oral transmission that should not be overlooked. In short, research clearly shows the viability of *T. cruzi* in food and different possibilities for food contamination have been discussed.

Another issue in regards to food contamination is the infectivity of the parasite when it is actually ingested as opposed to entering through the skin. Some studies have suggested that the oral transmission route holds higher infectivity, because *T. cruzi* can penetrate the mucous membrane of the esophagus before reaching the gastric cavity (45, 46). Camandaroba, Lima and Andrade (45) experimented on the influence of the parasitic strain in relation to oral transmission, and found that some strains held higher infectivity through the oral route. Strains more adapted to the sylvatic cycle have been shown to be involved in family outbreaks in the Amazon Region (14). Also the higher infectivity may be connected to the high mortality detected in oral outbreaks (12). A further question is
whether or not the high parasitemia in the acute phase of an oral transmission case causes higher morbidity and mortality than other transmission forms in the chronic phase due to the degree of damage done to the tissue (12, 47).

### 2.2.5. Surveillance, control and prevention of oral outbreaks

On a global scale, oral outbreaks have only recently been recognized as a target area for prevention and attention. Current control and prevention recommendations from WHO include good hygiene practices in food preparation as well as for transportation, storage and consumption (4). In 2005 a scientific working group initiated by The Special Program for Research and Training in Tropical Diseases (TDR) coordinated by WHO and the Pan American Health Organization (PAHO), published a report on Chagas disease. This report looks at the objectives and recommendations for the future of Chagas disease. There is no mention of oral transmission, except in relation to mammals eating infected insects. In 2009, however, PAHO published the guide “Surveillance, prevention, control and clinical handling of Chagas disease transmitted through food.” This Spanish guide provides the most extensive information on oral transmission to date for health practitioners and health workers. There have been several Intergovernmental Initiative of Surveillance and Prevention of Chagas Disease (AMCHA) meetings in South America where oral outbreaks have been discussed (48). AMCHA is organized by the individual countries and WHO. Thus it can be said that there is growing attention on oral outbreaks globally as well as in the Amazon Basin countries. Prevention and surveillance of oral transmission, however, is still not present in all countries.

Oral outbreaks are a form of transmission of Chagas disease that needs surveillance and rapid control and treatment measures. Rapid detection and action is a necessity to ensure recovery of patients. Oral outbreaks have a different social aspect than vectorial transmission, as it has been happening in different social settings such as schools, health facilities and parties (30, 43, 49). Because oral outbreaks are connected with food handling hygiene and food safety measures, it is necessary to take these aspects into consideration for prevention and surveillance measures (25).

### 2.2.6. Travel medicine

As previously mentioned, the production of acai juice in Brazil is an issue for oral outbreaks as described by Hervé Rogez (44). The juice is sold at markets, and if it is contaminated there is the possibility of infection of a large number of otherwise socially unconnected people. The fact that juice and other food products are sold to tourists as well could have implications for travel medicine, because tourists could become infected by drinking contaminated juice when visiting such markets in Brazil, or drinking unpasteurized juice from similar places. This raises the question on whether oral transmission should be included in differential diagnosis for travellers and tourists to these regions.
In Europe there is some focus on the immigration aspect of Chagas disease, which implicates blood transfusions and organ donation, however oral transmission has not received enough attention (5). Brazil has one reported case of an Italian tourist infected orally with Chagas disease. This case was discovered in Italy, after the tourist had returned from Brazil, and later discovered to be connected with an oral outbreak in Santa Catarina (50). Tourist statistics for Brazil shows that the largest number of travellers and tourists are from Italy and the United States of America (51). However, Italy currently has no travel recommendations concerning the risk of Chagas disease (5).

Surveillance could be necessary to establish in the Amazon region to discover the real number of oral outbreaks, as well as enable treatment. If, the number of oral outbreaks are indeed higher than estimated this would mean that a lot of people in the Amazon Region are suffering as well as dying silently from oral outbreaks. This thesis will attempt to look at the epidemiological distribution of oral outbreaks and try to determine the need for surveillance in the countries of the Amazon Region.

3. Aim

Main objective:

To perform an epidemiological overview of available literature on the oral outbreaks of Chagas disease in the countries of the Amazon basin: Brazil, Venezuela, Colombia, Bolivia, Ecuador, Peru, Guyana, Suriname, and French Guyana.

Specific objectives:

- To map oral outbreaks of Chagas disease in the Amazon Basin according to available literature and the surveillance systems; Event Management System of WHO and ProMED- mail from the International Society for Infectious Diseases.

- To make a timeline of published cases and retrieve information on mortality of outbreaks, source of outbreaks and the form of social gatherings of outbreaks.
4. Methods

4.1. Study design

This thesis is a literature review study. It includes a research synthesis on known cases of oral outbreaks as well as a meta-analysis of the data found.

4.2. Data collection methods

The search was conducted in the databases: PubMed/MEDLINE and LILACS. LILACS is a Latin American and Caribbean health science database. It is a unique source of information because it contains articles published in local languages such as Portuguese, Spanish, French as well as English. With regards to time specification there was none, because the aim included a chronological overview of all oral outbreaks.

4.2.1. Definitions

It was important to define oral transmission and oral outbreaks for the process of data collection and to define inclusion and exclusion criteria. The following definitions were formulated and used:

**Oral transmission** can occur when infected vector faeces come into contact with the mouth, either through food or simply by touching a contaminated surface and then putting the fingers in the mouth.

**Oral outbreaks** happen when a number of people ingest food contaminated with infected faeces from the vector or the vector itself. An oral outbreak is when two or more autochthonous cases appear at the same time.

4.2.2. Search words

The search words were chosen to concentrate the search on oral outbreaks of Chagas disease. Articles on acute cases were initially included because of the possibility of acute cases not being recognized as oral outbreaks in early literature. English key words were translated into four different languages for the LILACS search, so as to broaden the search, and include non-English articles. Seeing that the languages most spoken in the Amazon Region are Spanish and Portuguese, the translation of search words in these languages was included. A French translation and search for key words was included because of French Guyana. Dutch, which is spoken in Suriname and Guyana, was excluded, as it is not an indexed language in LILACS. The key words and combinations...
used for the search were very broad so as to include as many articles as possible. The fact that Chagas disease is a neglected tropical disease necessitated as well as enabled this search approach. Using Mesh terms was neither feasible nor practical because of the specificity of the search words themselves (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>English</th>
<th>Spanish</th>
<th>Portuguese</th>
<th>French</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chagas</td>
<td>Chagas</td>
<td>Chagas</td>
<td>Chagas</td>
<td>Chagas</td>
</tr>
<tr>
<td>trypanosomiasis</td>
<td>tripanosomiasis</td>
<td>tripanossomíase</td>
<td>trypanosomiase</td>
<td></td>
</tr>
<tr>
<td>Acute cases</td>
<td>casos agudos</td>
<td>casos agudos</td>
<td>Aiguë, cas aigus</td>
<td></td>
</tr>
<tr>
<td>oral</td>
<td>oral</td>
<td>oral</td>
<td>orale</td>
<td></td>
</tr>
<tr>
<td>outbreaks</td>
<td>brotes</td>
<td>surtos</td>
<td>épidémie</td>
<td></td>
</tr>
<tr>
<td>transmission</td>
<td>transmisión</td>
<td>transmissão</td>
<td>transmission</td>
<td></td>
</tr>
</tbody>
</table>

The search was made in PubMed for English results and LILACS for Spanish, Portuguese and French. LILACS also included translation of the search word to the indexed languages in each search, which broadened the search. The search words were combined in the following way:

Chagas/trypanosomiasis + (AND/OR) acute cases/oral/outbreaks/transmission

This gave eight combinations that were used for the English search in PubMed and the combinations were repeated for Spanish, Portuguese and French in LILACS. All in all that gave 36 combinations of search words in the four different languages. The search resulted in 66 articles. After this first search, a second search was conducted manually. Reference lists of the 66 articles were read and experts at WHO were consulted to discover any articles that might be missing from the resulting list of articles. These procedures resulted in 95 articles. All articles were then sorted in EndNote Web ®.

4.3. Selection method

For the overview on oral outbreaks studies with a quantitative disposition was included with empirical character. After the 95 articles had been entered into EndNote Web®, full text and/or abstracts of articles were reviewed and the articles were classified according to inclusion and exclusion criteria. If inclusion criteria were fulfilled the article was included. This selection process resulted in a total number of 43 articles. After this a second selection took place, where the articles were read thoroughly according to a set of pre-defined information retrieval categories for the analysis. The articles had to contain information on country, area of case origin and number of cases. This more thorough selection resulted in 25 articles for the meta-analysis.

Figure 1 displays the search and selection process in the form of a flowchart.
4.3.1. Inclusion criteria

Studies where the definition of an oral outbreak was compatible with the description of the cases in the studies were included. Thus, studies with only one acute case were not included, or several cases reported in different points of time or different geographical locations. The study cases had to constitute an outbreak according to the definition of oral outbreaks provided for this thesis. Geographical restrictions were the countries of the Amazon Basin: Brazil, Venezuela, Colombia, Bolivia, Ecuador, Peru, Guyana, Suriname, and French Guyana. Only studies pertaining to these countries were included. This was done because of the aim to provide an overview of this particular region.

4.3.2. Exclusion criteria

If the case description did not fit the definition of an oral outbreak they were excluded. Assessment of the quality of the study took place in the sense that the case information validity or credibility was assessed for all sources. Only published cases were included, thus government reports and other reports were excluded. In some cases, where older publications of acute Chagas disease where hypothesized to derive from oral transmission, the study cases had to constitute an outbreak according to the definition of oral outbreaks of this thesis. The fact that oral outbreaks have been reported to such a limited degree, made it necessary to include as much information as possible.

4.3.3. ProMED-mail and EMS

To supplement the scarce material on oral outbreaks, outbreak information was included from ProMED-mail and the Event Management System of WHO (EMS) according to the same inclusion criteria as the literature search. EMS and ProMED-mail are international surveillance systems of infectious diseases. EMS is an internal information system of WHO and a disease surveillance tool. Chagas disease was included in this surveillance system from 2005, however it has not been updated regularly and the reports are sporadic. WHO representatives in the Amazon region as well as other parts of South America can use the EMS as a tool, however not all have chosen to do so. This means that the information from the EMS is not complete, however the reports might show a trend, and were therefore included in this thesis. The same accounts for ProMED-mail that is an open and online information system where newspaper reports, government reports and physicians reports outbreak information from affected countries are registered.

4.4. Limitations

The objective was not to give a perfect image of the oral outbreak history. The scarcity of information reduced the possibility of obtaining such an image. What was feasible to do was to give an overview of the information available, however imperfect. The main
limitations of this study were the access to journals pertaining from South America. The literature search took place at WHO library in Geneva, which can be considered to have one of the most well assorted European collections of journals and articles from development countries, South America included. Nevertheless, there were some articles that were inaccessible, and that would only be accessible in the individual South American countries. This was especially the case for supplement editions of certain South American Journals. Efforts were made to procure the articles through contacts in the countries concerned, however not all were retrievable.

4.5. Method of analysis

The following information was extracted from the 25 articles found in the literature search; country, area of case origin, number of cases and mortality of outbreak. Moreover, suspected transmission source and form of social gathering were included as categories to look at geographical variation or homogeneity of the cases described. The age and sex of the patients were not included as predefined information retrieval categories because oral outbreaks have not been shown to differentiate for age and sex. The following data analysis was performed on the collected data:

- A map of the reported outbreaks was produced to graphically show the dispersion of outbreaks in the Amazon Region.

- A timeline of the reported outbreaks was produced to look at whether outbreak reports have increased and to which degree.

- Number of cases and mortality was compared to see the range as well as the size of the outbreaks.

- Suspected transmission and form of social gathering was compared country wise to see geographical variation or homogeneity.
Figure 1. Flowchart for article search and selection

1st. search
- English key word search in PubMed
- Spanish, Portuguese, French search in LILACS

2nd search
- Manual search: reading reference lists and consultation of experts

1st. selection
- Reviewed the full text of articles and classified according to:
  • Inclusion criteria
  • Exclusion criteria

2nd selection
- Thorough reading of articles following a set of pre-defined information retrieval categories for the meta-analysis

Total no. of articles, n = 66
Total no. of articles, n = 95
Total no. of articles, n = 43
Articles for result, n = 25
5. Results
The 25 articles that the literature search resulted in were written mainly in English and Portuguese. One article was written in Spanish and no articles were found in French. The main part of the literature found came from Brazil. Moreover, ten reports were found in EMS and ten reports from ProMED-mail. The articles were sorted in table 2 and 3 according to what year the outbreaks had occurred. The reports from EMS and ProMED-mail were sorted in table 4 and 5 according to the time of the reports.

5.1. Published cases
Table 2 presents the data of published cases in Brazil that was found in the literature search. In table 3 the published cases of Venezuela and Colombia are presented. Brazil, Venezuela and Colombia were the only countries beside Brazil that had published cases that lived up to the inclusion criteria.

Table 2. Published cases in Brazil

<table>
<thead>
<tr>
<th>Article</th>
<th>Year</th>
<th>Area</th>
<th>Cases</th>
<th>Deaths</th>
<th>Source of transmission</th>
<th>Social occasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>da Silva et al., 1968 (53); Nery-Guimarães et al., 1968 (54)</td>
<td>1965</td>
<td>Teutônia, Estrela, Rio Grande do Sul State</td>
<td>17</td>
<td>6</td>
<td>Infected opossum found, contaminated food from this animal reservoir was suspected</td>
<td>Attended local agricultural college, all ate there</td>
</tr>
<tr>
<td>Shaw et al., 1969 (55)</td>
<td>1969</td>
<td>Belém. Pará State</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>Family</td>
</tr>
<tr>
<td>Shikanai-Yasuda et al., 1991 (39); Pereira et al., 2009 (25); Umezawa et al., 1996 (56)</td>
<td>1986</td>
<td>Paraíba, Catolé do Rocha State</td>
<td>26</td>
<td>2</td>
<td>Sugar can juice, infected opossum found, infected utensils by faeces suspected</td>
<td>Meeting on farm</td>
</tr>
<tr>
<td>Valente et al., 2009 (30) &amp; Valente, 1999 (14)</td>
<td>1996</td>
<td>Rio Bispo, Mazagão, Amapá State</td>
<td>17</td>
<td>0</td>
<td>Consumption of açai juice</td>
<td>Geographical isolation, involved families</td>
</tr>
<tr>
<td>Pinto et al., 2001 (57)</td>
<td>1998</td>
<td>Abaetetuba, Pará State</td>
<td>13</td>
<td>-</td>
<td>Shared meal</td>
<td>Family outbreak</td>
</tr>
<tr>
<td>Pinto, Valente &amp; Valente, 2004 (58); Pinto et al., 2009 (59)</td>
<td>2000</td>
<td>Cametá, Pará State</td>
<td>3</td>
<td>2</td>
<td>No hypothesis of source</td>
<td>-</td>
</tr>
<tr>
<td>Pinto et al., 2009 (59)</td>
<td>2000</td>
<td>Belém, Pedreira district, Pará State</td>
<td>11</td>
<td>0</td>
<td>Unprocessed beverage suspected</td>
<td>No common gatherings</td>
</tr>
<tr>
<td>Pinto et al., 2003 (60)</td>
<td>2002</td>
<td>Igarapé-Mirí, Pará State</td>
<td>12</td>
<td>2</td>
<td>Food contamination- poor hygiene</td>
<td>Family outbreak</td>
</tr>
<tr>
<td>Barbosa-ferreira et al., 2010 (61); Medeiros, Guerra &amp; Lacerda 2008 (62), Monteiro et al., 2010 (63)</td>
<td>2004</td>
<td>Tefé, Amazônia State</td>
<td>9</td>
<td>-</td>
<td>açai wine</td>
<td>-</td>
</tr>
<tr>
<td>Article</td>
<td>Country</td>
<td>Year</td>
<td>Area</td>
<td>Cases</td>
<td>Deaths</td>
<td>Source</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Ianni &amp; Mady, 2005</td>
<td>Navegantes, Santa Catarina State</td>
<td>2005</td>
<td>Sugar cane juice</td>
<td>Road side food court</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ianni &amp; Mady, 2005</td>
<td>Bacia do Igarapê da Fortaleza – Macapá, Amapá State</td>
<td>2005</td>
<td>açai juice</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dias et al., 2008 (65); Bastos, 2010 (66)</td>
<td>Macaúbas, Chapada Diamantina, Bahia State</td>
<td>2006</td>
<td>Improperly stored water possibly infected by faeces from T. Sordida</td>
<td>Single household, two parties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nóbrega et al., 2009 (43)</td>
<td>Barcarena, Pará State</td>
<td>2006</td>
<td>açai juice</td>
<td>Staff members og health post attending meeting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bastos et al., 2010 (66)</td>
<td>Ipipitanga, Bahia State</td>
<td>2006</td>
<td>sugar cane juice</td>
<td>Family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavalcanti, 2009</td>
<td>Aratuba municipality, Ceará State</td>
<td>2006</td>
<td>stew with liquid coriander and scallion from orchard</td>
<td>Family together on vacation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbosa-ferreira et al., 2010 (61)</td>
<td>Coari, Amazônia State</td>
<td>2007</td>
<td>açai juice</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barros et al., 2009 (30)</td>
<td>Breves, Pará State</td>
<td>2007</td>
<td>meal</td>
<td>Members of an extended family who had shared a common meal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barros et al., 2009 (30)</td>
<td>Bagre, Pará State</td>
<td>2007</td>
<td>meal</td>
<td>Members of an extended family who had shared a common meal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Published cases in Venezuela and Colombia

<table>
<thead>
<tr>
<th>Article</th>
<th>Country</th>
<th>Year</th>
<th>Area</th>
<th>Cases</th>
<th>Deaths</th>
<th>Source</th>
<th>Social gathering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alarcón de Noya et al., (2010) (67)</td>
<td>Venezuela</td>
<td>2007</td>
<td>Caracas</td>
<td>103</td>
<td>1</td>
<td>Fresh guava juice</td>
<td>School</td>
</tr>
<tr>
<td>Hernández L.M.L. et al. (2009) (68)</td>
<td>Colombia</td>
<td>1999</td>
<td>Guamal, Magdalena</td>
<td>13</td>
<td>5</td>
<td>Palm wine</td>
<td>-</td>
</tr>
<tr>
<td>Hernández L.M.L. et al. (2009) (68)</td>
<td>Colombia</td>
<td>2003</td>
<td>Bucamaranga, Santander</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hernández L.M.L. et al. (2009) (68)</td>
<td>Colombia</td>
<td>2008</td>
<td>Lebrija, Santander</td>
<td>10</td>
<td>2</td>
<td>Orange juice</td>
<td>Party, everyone drank orange juice</td>
</tr>
<tr>
<td>Ríos J.F. et al. (2011) (69)</td>
<td>Colombia</td>
<td>2009</td>
<td>Turbo, Antioquia</td>
<td>3</td>
<td>1</td>
<td>Meal</td>
<td>Common source of food/ate at the same occasion in the same house</td>
</tr>
</tbody>
</table>
Comparing table 2 and 3 it shows that oral outbreaks were most extensively described and investigated in the Brazilian literature. The areas were the outbreaks occurred were most often in the Amazon Region in rural and poor localities, however, outbreaks like Santa Catarina was in an urban setting. In the Santa Catarina case the source was traced to a juice producer in the nearby slum area (49). It is remarkable that only Venezuela and Colombia had published oral outbreak cases.

5.2. Synthesis of outbreaks extracted from ProMED-mail

In table 4 the oral outbreaks of ProMED-mail are presented. Data was extracted from the system in the same manner as for the published cases, so as to make them more compatible. Shortly, there were three outbreaks in Brazil; three in Venezuela; two in Colombia; one in Bolivia. In total ten oral outbreaks were reported from 2005 to 2011.

Table 4. Oral outbreak reports extracted from ProMED-mail (70)

<table>
<thead>
<tr>
<th>No of reports</th>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
<th>Time of report</th>
<th>Transmission mode</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brazil</td>
<td>19</td>
<td>4</td>
<td>23-mar-05</td>
<td>Sugar cane juice</td>
<td>Santa Catarina</td>
</tr>
<tr>
<td>1</td>
<td>Brazil</td>
<td>20</td>
<td>-</td>
<td>28-jul-06</td>
<td>Bacaba wine</td>
<td>Santarem, Para State</td>
</tr>
<tr>
<td>2</td>
<td>Venezuela</td>
<td>128</td>
<td>1</td>
<td>19-dec-07</td>
<td>Juice</td>
<td>Caracas, (School)</td>
</tr>
<tr>
<td>3</td>
<td>Colombia</td>
<td>9</td>
<td>2</td>
<td>10-dec-08</td>
<td>Food Contamination</td>
<td>Bucaramanga, (Santander)</td>
</tr>
<tr>
<td>4</td>
<td>Venezuela</td>
<td>80</td>
<td>4</td>
<td>03-apr-09</td>
<td>Guyaba juice, (chipo)</td>
<td>Vargas, (school)-(Chichiviri de la costa)</td>
</tr>
<tr>
<td>5</td>
<td>Brazil</td>
<td>13</td>
<td>-</td>
<td>12-jan-10</td>
<td>Acai Juice</td>
<td>Santa Isabel do Rio Negro (Amazonas)</td>
</tr>
<tr>
<td>6</td>
<td>Venezuela</td>
<td>58</td>
<td>-</td>
<td>08-may-10</td>
<td>Food Contamination, (chipo)</td>
<td>Caracas</td>
</tr>
<tr>
<td>7</td>
<td>Colombia</td>
<td>7</td>
<td>-</td>
<td>03-jun-10</td>
<td>Food contamination</td>
<td>Cesar</td>
</tr>
<tr>
<td>8</td>
<td>Venezuela</td>
<td>6</td>
<td>1</td>
<td>08-nov-10</td>
<td>Food contamination</td>
<td>Táchira</td>
</tr>
<tr>
<td>9</td>
<td>Bolivia</td>
<td>14</td>
<td>-</td>
<td>25-nov-10</td>
<td>Food contamination</td>
<td>Beni</td>
</tr>
</tbody>
</table>

5.3. Synthesis of outbreaks extracted from EMS

The EMS system revealed some reports of oral outbreaks. In table 5 the oral outbreaks that have been reported to the system by WHO employees is presented. There were six outbreaks reported in Colombia, two outbreaks in Venezuela, one outbreak in Bolivia and one outbreak in Brazil. A total of ten outbreaks were reported from 2005 to 2011.
### Table 5. Oral outbreak reports extracted from EMS (WHO)

<table>
<thead>
<tr>
<th>No of reports</th>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
<th>Time of report</th>
<th>Transmission mode</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Brazil</td>
<td>-</td>
<td>-</td>
<td>06-Apr-05</td>
<td>Infectious label in EMS</td>
<td>Santa Catarina</td>
</tr>
<tr>
<td>2</td>
<td>Venezuela</td>
<td>-</td>
<td>-</td>
<td>14-Dec-07</td>
<td>Infectious label in EMS</td>
<td>Caracas</td>
</tr>
<tr>
<td>3</td>
<td>Colombia</td>
<td>-</td>
<td>-</td>
<td>10-Dec-08</td>
<td>Infectious label in EMS</td>
<td>Santander</td>
</tr>
<tr>
<td>4</td>
<td>Colombia</td>
<td>5</td>
<td>1</td>
<td>18-Jan-09</td>
<td>Food Safety label in EMS</td>
<td>Santander</td>
</tr>
<tr>
<td>5</td>
<td>Colombia</td>
<td>-</td>
<td>-</td>
<td>24-May-09</td>
<td>Food Safety label in EMS</td>
<td>Santander</td>
</tr>
<tr>
<td>6</td>
<td>Colombia</td>
<td>8</td>
<td>-</td>
<td>05-Feb-10</td>
<td>Eating at the same restaurant</td>
<td>Antioquia</td>
</tr>
<tr>
<td>7</td>
<td>Venezuela</td>
<td>16</td>
<td>-</td>
<td>06-May-10</td>
<td>Suspected consumption of contaminated products</td>
<td>Caracas</td>
</tr>
<tr>
<td>8</td>
<td>Colombia</td>
<td>5</td>
<td>-</td>
<td>28-May-10</td>
<td>Not mentioned</td>
<td>Santander</td>
</tr>
<tr>
<td>9</td>
<td>Colombia</td>
<td>10</td>
<td>-</td>
<td>13-Jun-10</td>
<td>Oral transmission suspected (Family party)</td>
<td>Cesar</td>
</tr>
<tr>
<td>10</td>
<td>Bolivia</td>
<td>14</td>
<td>0</td>
<td>26-Oct-10</td>
<td>Consumption of Mayo fruit juice</td>
<td>Guayaramerin</td>
</tr>
</tbody>
</table>

Comparing the outbreak information from EMS and ProMED there are overlaps where the surveillance systems describe the same outbreaks such as the outbreaks in Santa Catarina, Brazil; Caracas, Venezuela; Santander, Colombia; Cesar, Colombia and Beni, Bolivia. Moreover, some outbreaks have already been described in the published literature; Santa Catarina, Brazil; Caracas, Venezuela; Bucaramanga, Colombia. The systems do not just describe the same outbreaks however. The outbreak information from these surveillance systems appears sporadic and the cases reported are those that have been given attention in the Medias mainly. Nevertheless, the information from the systems clearly shows an upward trend in number of reports as well as a geographical diversity of outbreaks.

Moreover both systems register outbreaks from 2005 where the Santa Catarina outbreak in Brazil took place, and thereafter reports sporadically occurred until 2010 where both systems have a large increase in number of reports (see tables 4 And 5). This development mirrors the development for the publication of outbreaks in the scientific literature.

### 5.4. Mortality, outbreak source and social occasion

Looking at the data from both published outbreaks and outbreaks from the surveillance systems, the mortality of oral outbreaks in Brazil and other countries together ranged from 0-6 deaths. Number of infected cases ranged from 3-103. The ProMED-mail report citing 128 cases (see table 4.) in Caracas, Venezuela was not included in this range because the scientific publication on the same outbreak citing 103 cases has more validity and credibility.
In figure 2 the mortality is plotted according to number of cases, year and deaths. From the graph displayed in figure 2 the number of deaths from oral outbreaks does not seem to follow any particular pattern. The mortality differs in size as is shown in Figure 4. It is high in some cases like the Santa Catarina outbreak, the Guamal outbreak and the Teutônia outbreak, and low in others. The Caracas outbreak for example had a very low mortality. This particular outbreak happened at a school and the deceased was a child with very high parasitemia (67).

Figure 2. Mortality of oral outbreaks from the scientific literature

<table>
<thead>
<tr>
<th>Year</th>
<th>Deaths</th>
<th>Chagas disease cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1960</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>1970</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td>103</td>
<td></td>
</tr>
</tbody>
</table>

Note: For figure 2 only outbreaks with information on deaths were included.

The source of the oral outbreaks was hypothesized to be açai juice, sugar cane juice, water, palm wine and meals that were undercooked or contaminated in some way. The most commonly suspected source was açai juice and it was the most common source suspected in Brazil. Otherwise there was little geographic variation and the scarcity of data on the source made it difficult to say if there was any geographical variation or indeed homogeneity. Poor hygiene in handling food or drinks was hypothesized, as well as the contamination of food via the opossum. Nevertheless, no sources had been directly investigated in any published cases or surveillance system case reports.

The social occasions related to the outbreaks were most often families sharing meals and drinks. Other social occasions included eating at the same roadside food court, eating a common meal at a school or workplace and attending parties. It was difficult to see if there was any geographical variation, again due to the scarcity of the data.
5.5. Map of oral outbreaks

Figure 3. Map showing the distribution of oral outbreaks in the Amazon basin

To display the spread of oral outbreaks, a map was produced from the information retrieved from the scientific articles, ProMED-mail reports and EMS reports. Figure 3 displays the distribution of oral outbreaks in the Amazon region. That is, in the countries of Brazil, Colombia, Venezuela and Bolivia. Red dots marked on the map means that the outbreaks were described in the literature, and orange dots are the outbreaks that were found in the surveillance systems EMS and ProMED-mail. The map shows a broad distribution and some clustering of oral outbreaks, especially in Brazil in the state of Pará. The size of the dots in Venezuela indicates very large outbreaks in that particular region and country. Furthermore, it seems the largest outbreaks were in Venezuela, and the largest quantity reported from Brazil.
Figure 4. Timeline of published oral outbreaks and EMS and ProMED-mail reports on oral outbreaks

Note: The size of the dots of the Figure 4 denotes the outbreak size

Figure 4 shows a large gap in outbreak reports from the first outbreaks in 1965 and 1969 to the next in 1986. Then there is another gap lasting around ten years till the next case in 1996 and two years after in 1998. The number of outbreaks rises rapidly from then on till now. The size of the dots shows the size of the outbreak and it seems like the size of outbreaks varies significantly. However large outbreaks seems to have been registered from the beginning.
6. Discussion

The severity of oral outbreaks was clearly shown in the previous results (see Figure 2). It is certain that oral outbreaks can have a very high mortality rate. Mortality risk will depend on the condition and age of the patient. Oral transmission of Chagas disease could possibly be more severe to young children, older people and immune-suppressed people. The range of cases for oral outbreaks was shown to vary from 3 to 103. This is a large case range and an indication of the diverse nature of oral transmission and oral outbreaks. An oral outbreak of 100 cases at the same point in time will require a coordinated and rapid effort from health authorities. The social aspect of oral outbreaks is important also for prevention measures as it is to be a common factor for oral outbreaks.

6.1. Emerging transmission form?

The trend for reports of oral outbreaks in the Amazon region is that the number of reports has been rising rapidly in the latest couple of years. The timeline in Figure 4 displays the fact that the scientific community has been aware of oral outbreaks since 1965. Furthermore, scientists have been aware of the possibility of oral outbreaks since the 30ies when scientists began experimenting on oral transmission of Chagas disease (32). It is clear that oral transmission is not a new event; however it is possible that oral outbreaks are increasing as well. The results of this thesis did not reveal whether or not Chagas disease is emerging or if the problem has been there all along. Looking at the timeline though it seems very evident that oral outbreaks have been happening for a very long time and also that outbreaks can have passed by unnoticed. Silent suffering and death of thousands of people have been the rule rather than the exception for Chagas disease in general. The silence surrounding oral outbreaks is not an exception. The fact that encroachment on the vectors natural habitat, the rain forest, is increasing could also be an explanatory factor to the increase in cases that has been detected recently.

However one looks at it, oral outbreaks are a real risk for all inhabitants of the countries of the Amazon region. The distribution of cases was very wide geographically speaking, and not only limited to the Amazon forest region.

6.2. Geographical distribution

The mapping of cases showed clearly that oral outbreaks are occurring all over the Amazon Region countries and there are several implications to this (see Figure 3). Increasing surveillance in the Amazon region could possibly reveal a significantly larger number of outbreaks than described in this thesis. In any case the results show that oral outbreaks are a common occurrence in Brazil, however the occurrence of oral outbreaks in Venezuela, Bolivia and Colombia show that oral outbreaks are not limited to Brazil. Moreover, the outbreaks were not only restricted to regions with Amazon forest, but
appeared also in urban areas and areas far from the Amazon, like the outbreak in Caracas, Venezuela, and the outbreak in Santa Catarina, Brazil which is near Argentina. Although not included in the results because of the inclusion criteria, French Guyana has suspected outbreaks as well due to several acute cases (71). They have even started informing the public about the risk of oral transmission (72).

Brazil is one of the countries that have been very active in elimination and control of Chagas disease, and one of the first countries of the Southern Cone initiative to be declared free of transmission by the main domiciliated vector (*Triatoma infestans*). Brazil is in this light well equipped for the discovery of Chagas disease cases, as the country has experts as well as knowledge on Chagas disease in general. Also the encroachment of humans on the Amazon forest in Brazil has increased in recent years, which increases the risk of infection (7). The country has perhaps been more vigilant in discovering cases, which can explain that most oral outbreaks have been reported from Brazil. The sheer size of the country Brazil compared to the other countries may also be a factor. Yet looking at the geographical distribution of oral outbreaks clearly shows that there is a real risk of oral outbreaks in all countries of the Amazon Region.

### 6.3. Surveillance system in the Amazon Region

The scientific literature that was included in this literature review serves to show the need for increased surveillance of oral outbreaks. EMS and ProMED-mail have similar timelines of outbreak registration, however the reports appear to be random and should not be taken as to reflect the real number of outbreaks. It should be mentioned also that EMS is a complimentary working tool and as such not a highly vigilant surveillance system unit in the WHO. ProMED-mail also cannot be taken to be highly accurate and all encompassing as a surveillance system, since it is based on voluntary reports. Thus, none of these systems are really meant to monitor oral outbreaks on a systematic basis. The question is then what is being done otherwise to monitor outbreaks in the Amazon Region.

Local surveillance efforts pertain to governments of the Amazon countries, most notably Brazil where the focus on oral transmission transpires as the strongest in the Amazon basin. This is evident from the number of publications from Brazil. However, the AMCHA meetings has recently had increased focus on oral outbreaks as an emerging problem in the Amazon basin (48). Thus, the need for prevention and surveillance are being acknowledged to some extent.

### 6.4. The social aspect of transmission

The conclusion from the case information listed in tables 2 to 5 is that oral outbreaks occur at social occasions including different sources of food and drinks. The social occasion varied from schools to eating at the same roadside food court or family dinners and parties. Sources listed ranged from hypotheses on juice, wine, water and other
beverages or undercooked meat. For prevention measures there are several implications of this. In Brazil for example the most commonly suspected source açai juice is a very common beverage often sold under unhygienic conditions in market places. This means that food hygiene and safety measures are of importance for Brazil and that particular attention should be given to the production, sale distribution and ingestion of açai juice. Possibly export of açai juice can be an issue of prevention for Brazil, as the parasite has been shown to be able to survive up to 24 hours in unpasteurized juice (42).

Furthermore, there is the problem of hygiene during cooking, and undercooked meals, as well as food storage practices. These are also issues for prevention measures and related to family practices and poverty issues. Hygienic practices in poor rural and urban settings are important when people live in close proximity with either palm trees were infected vectors reside or with animals such as the opossum (14, 29). Both vectors and mammals have easy access to kitchen spaces in thatched huts with poor possibilities of adequate food storage. Nevertheless, the diversity of the social occasions shows that oral outbreaks happen indiscriminately of social layers. The Caracas school outbreak in Brazil showed a high number of cases and low number of deaths, which could be related to the fact that the outbreak happened in a urban area with easy access to health care and prevention measures (67). Outbreaks happening in rural settings do not have the same opportunities for rapid detection and care. The obstacles for reporting and detecting outbreaks in regions that are very hard to access are thus issues needing to be addressed.
7. Recommendations

7.1. Food safety prevention measures

Knowledge on oral transmission and the necessity of food hygiene practices should be promoted in all countries. There are two levels of society that should be taken into consideration for food safety practice guidelines. First of all, governments should provide regulation and recommendations for food production for producers and manufacturers, and second of all, recommendations and awareness should be spread at population level. The contamination of high risk foods that have been presented here in this thesis, such as açai juice, sugar cane juice and undercooked meals are target areas of food protection measures. However, all sources of food or drinks can be contaminated in an area where T. cruzi is present in wild animals, vectors or domestic animals. If unsafe food handling practices take place at some point in the food production chain there is a risk of contamination.

WHO recommendations for effective control of food borne diseases are that it should always be based on updated disease information and incidence of the disease in question (73). The conclusion from this thesis is that oral outbreaks are not sufficiently monitored in the Amazon region, and thus the basis for an effective control of food contamination is not present. The strengthening of surveillance systems for oral outbreaks in the countries of the Amazon region is therefore a priority to establish food safety measures.

7.2. Travel medicine implications of oral outbreaks

The oral transmission case of the Italian tourist in Brazil is important because it shows that oral transmission is a risk for anyone at present (15, 50). Tourists as well as other travelers could be in danger of contracting Chagas disease orally. Common food safety precautions when traveling to the Amazon region should be sufficient. Nevertheless, travel clinics and physicians have to be aware of the risk, as well as raise awareness of the risk of contracting Chagas disease orally in the countries of the Amazon Region. Some European countries like Belgium, Spain and the Netherlands have included counseling about Chagas disease for travelers to South America, as well as included Chagas disease as a differential diagnosis after such trips in travels clinics (5). Oral outbreaks of Chagas disease can also have implications for travel medicine in the sense that the level of parasitemia may produce more severe symptoms and outcomes. Travelers to the Amazon Region should be forewarned of the risk of ingesting food that has not been properly handled and in places where hygiene is lacking.
7.3. Prevention target areas

Preventing oral outbreaks is a definite public health recommendation from the results above. The severity and risk for the people if the countries of the Amazon Region are clear from the epidemiological overview given in this thesis. Public health scientists usually refer to three types of prevention. Primary prevention is about creating awareness of a particular public health problem. Secondary prevention is to create a system for detection and rapid response to a disease and tertiary prevention is treatment of the disease. For oral outbreaks of Chagas disease the prevention recommendations would thus be:

- Primary prevention: Information campaigns on oral transmission and oral outbreaks.
- Secondary prevention: Information systems, surveillance systems, outbreak alert info.

7.3.1. Primary, secondary and tertiary prevention

Primary prevention would be information campaigns. French Guyana has already made efforts to warn people of oral transmission. Information posters on food hygiene, vectors and protection exist already. In their information poster campaign the government of French Guyana urges people to cover food, to sleep under a bed net, to cover all openings of the house and to avoid sources of light directly over the food. They also provide pictures of the vectors that can transmit *T. cruzi* to people (72). This is an example of an information campaign that focuses on oral transmission and to prevent oral outbreaks. In Brazil, the Health Ministry and the Ministry of Agriculture have jointly set down regulations for the manufacturing and processing of açai. In addition they published Technical Regulation on health and hygiene procedures for food handling and drinks made with açai product (74). Primary prevention efforts should also include the establishment of travel recommendations and advice for tourists travelling to the Amazon Region.

Secondary prevention efforts include creating or improving surveillance systems. There are several difficulties in developing a surveillance system in the Amazon region. As mentioned earlier, large areas of the Amazon Region are very hard to access, because there is no developed infrastructure and some villages are only accessible by the Amazon River. This means that even if local physicians and health professionals are vigilant, they may not be able to discover all oral outbreaks. Moreover, the sheer size of the area presents a major challenge for developing a surveillance system, as well as a rapid response system for outbreaks. From a public health and health economic perspective, investing in prevention efforts, however, will save both Disability Adjusted Life Years (DALY’s) and treatment costs in the long run. There are thus great advantages for the countries of the Amazon Region to invest or reallocate money to prevention efforts.
To implement the other prevention levels, a sound surveillance system is the basis to be able to evaluate the prevention needs. Health policy making relies on the ability to evaluate need and efforts (73). Secondary prevention also includes the direct work of preventing the actual contamination of foods—food safety measures. Existing procedures to implement contamination control are for example Standard Operational Procedures, Pest Control, Good Manufacturing Practices and Hazard Analysis and Critical Control Points, as suggested by Pereira et al. (2009) (25). Standard Operational Procedures and Good Manufacturing Practices refers to a set of standards for among other things; manufacturing, storage and distribution of foods. Hazard analysis and critical control points refer to a systematic preventive approach to ensuring food safety and includes physical as well as chemical and biological contamination hazards. These methods are implementation tools for food safety policy programs and for prevention of oral outbreaks they may be useful (25).

Rapid treatment is the third aspect of prevention and includes treatment of acute Chagas disease. It is necessary to discover and treat patients of an oral outbreak quickly. This is linked with surveillance efforts. Even though diagnosis is made more difficult due to unspecific symptoms, Chagas disease should be suspected in endemic areas or areas where the vector has been detected to be prevalent. Including Chagas disease as a differential diagnosis for tourists returning from the Amazon Region is necessary at the tertiary prevention level. Another issue is the availability of medicine to treat acute patients. The two medications produced to treat Chagas disease are Benznidazole® and Nifurtimox®. These drugs are effective, but with many side-effects (1). Optimally they should be made available to all countries of the Amazon Region to treat acute patients rapidly.

Conclusively, prevention of oral outbreaks includes intervention on several levels of society and presents a future challenge to the countries of the Amazon Region; a challenge that possibly could save the lives of a great deal of people.
8. Conclusion

The conclusions that can be made from this thesis are that oral outbreaks of Chagas disease are happening all over the Amazon Region. Oral outbreaks can be severe and affect a great deal of people. It is clear that there is a distinct need of increasing both awareness and surveillance of this problem on several levels of society in the countries of the Amazon region. Detection and rapid treatment are priorities for oral outbreaks and oral transmission. Surveillance data is required for health policy making, implementation and evaluation.

It is not possible to say whether or not oral outbreaks are an emerging disease or if it has been prevalent in the Amazon region all along. However, an epidemiological overview of oral outbreaks in the Amazon was given. Even though the information may be incomplete due to the lack of surveillance systems and published cases, the indication is that oral outbreaks are a real threat in the countries of the Amazon Region as well as to tourists traveling to these countries. Europe and other countries with large tourist flux to the Amazon Region should develop guidelines for oral transmission of Chagas disease as a differential diagnosis to physicians and travel clinics.

If oral outbreaks are actually happening on a much larger scale than is known, people are dying and suffering in silence. It is clear from this thesis that oral outbreaks deserve more attention than it is getting. In general the silence surrounding Chagas disease needs to be broken to stop the suffering of millions.
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