Current Situation of Chagas Disease in Non-Endemic Countries

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Chagas disease, or American trypanosomiasis, is caused by the parasitic protist *Trypanosoma cruzi*. 10 million people are estimated to live with this disease. Chagas disease is endemic to the Americas, which corresponds to the distribution of the insect vectors, blood-sucking triatomine bugs. The presence of many mammalian species as reservoir hosts and the occurrence of a long asymptomatic phase of infection that may last more than 10 years make control difficult. In the United States, domestic transmissions from triatomines to humans are rarely reported, but it is estimated that there are 300,000 people living with Chagas disease among Latin American immigrants. Patients with Chagas disease are also found outside the Americas, as well as in Japan, via international migration. Thus, there is a growing need to understand the current situation in non-endemic countries in terms of establishing better preparedness against the incursion of Chagas disease.

Key words: Chagas disease, *Trypanosoma cruzi*, Latin America, insect vector, transfusion

Introduction

Chagas disease, which was discovered by the Brazilian physician Carlos Chagas in 1909, is endemic in 21 countries of Latin America and affects 10 million people with some 12,000 annual deaths. Chagas disease is typical zoonosis, where more than 100 mammalian species including marsupials, rodents, bats, armadillos, and carnivores, can be infected with *T. cruzi* and become reservoir hosts. The transmission of *T. cruzi* from infected bugs occurs via their feces, a unique feature among the vector-borne parasites, and is called stercorarian transmission (Figure-1). Although more than half of 141 triatomine species are potentially able to transmit *T. cruzi*, only several species are epidemiologically important for human transmission. Other routes of transmission include blood transfusion, organ transplantation, and congenital transmission. To minimize risks of the transfusional transmission, screening of blood donors by detecting anti-*T. cruzi* antibody has become necessary.
been implemented in all Latin American countries, with the relatively lower coverage in Mexico and Panama (Figure-2)\(^3\). Oral infection also occurs via foods and fresh fruit juice, which are presumably contaminated with *T. cruzi*-infected bugs.

Manifestation and progress of Chagas disease are complex but generally divided into acute and chronic phases\(^4\). After invasion of an infective form of *T. cruzi* via wound skin or mucosa, the parasite parasitizes and multiplies inside any type of host cell, followed by successive multiplication and subsequent destruction of the tissues such as heart. The acute phase lasts about 2 months with detectable parasitemia in the blood and accompanies malaise, fever, and anorexia as the systemic expansion occurs. The acute phase is often obscure and confused with common infectious diseases. Myocarditis rarely occurs in the acute phase, but becomes a main cause of death. Almost all patients enter the indeterminate (asymptomatic) phase and up to 30% of the patients develop chronic symptoms years to decades after infection. Manifestations of the chronic phase include heart failure, such as arrhythmia, cardiomyopathy, and thromboembolism, which lead to sudden death.

Chagas disease now becomes a global concern because a multitude of people migrates into and out of the endemic areas of Latin America. In particular, the unawareness of Chagas disease by both of the patients themselves and the physicians in the non-endemic areas makes diagnosis difficult. Therefore, the estimate of the prevalence of Chagas disease is largely dependent on the limited epidemiological data. In this review, the current situations of and the efforts against Chagas disease in non-endemic countries are summarized.

### Chagas disease in the US and Canada

The burdens of Chagas disease in the US have been estimated by applying seroprevalence figures of country of origin to the relevant immigrant populations: 300,167 persons with *T. cruzi* infection, 30,000–45,000 with cardiomyopathy, and about 300 with congenital infections per year (Table-1)\(^5\). These estimates suggest the potential risks for Chagas disease in the US, due particularly to blood transfusion and congenital infection. In fact, *T. cruzi* transmission via transfusion has been reported in the US and European counties\(^6\). The source of infection was found to be exclusively platelet concentrates. There is no report suggesting the occurrence of transmission by red blood cells (RBC) or frozen plasma products. Therefore, transmission by RBC or frozen plasma products seems unlikely, although such possibilities cannot be ruled out. In 2007, the American Red Cross and Blood Systems Inc. introduced screening of ALL donated bloods for Chagas disease using the Ortho EIA kit (Ortho Clinical Diagnostics Inc., NJ) that has been approved by the Food and Drug Administration (FDA). A second serologic test kit (Abbott PRISM\(^\text{Tm}\) Chagas Assay, Abbott Laboratories, Abbott Park, IL) was also approved by the FDA in 2010. There is no report of the blood-borne transmission of *T. cruzi* since 2007.

Although the data for seroprevalence of Chagas disease has not yet been available, the highly suspected cases for vector-borne transmission of *T. cruzi* have been reported in Louisiana, Texas, California, Tennessee, and Mississippi\(^7\)-\(^12\). As for the congenital infection, the Centers for Disease Control and Prevention (CDC) have reported the detection of the blood-circulating parasite in a boy, whose mother recently has moved to the US from Bolivia and had previously been diagnosed as Chagas disease\(^13\).
In Canada, the Canadian Blood Service has implemented pre-donation questionnaire followed by targeted screening for the risk group\(^{14}\). The risk group comprises those who or whose mothers were born in Latin America and those who received transfusion or lived in these areas. In 2011, a case of congenital transmission was reported\(^ {15}\). A mother of this donor was found to be seropositive, likely being infected via transfusion from 1978 to 1983.

In 2010, FDA issued the guideline for prevention of *T. cruzi* transmission via whole blood and blood components intended for transfusion\(^ {16}\). The Potential donors are primarily asked “Have you ever had Chagas disease?” and the person who answered “Yes” are indefinitely deferred for blood donation. One–time testing of each donor using a licensed test for anti-\(T. cruzi\) antibody is implemented for all donors and the person who are nonreactive are ready for blood donation. Donors who are repeatedly reactive using a licensed test are indefinitely deferred for blood donation. FDA highly recommends that blood and blood components donated by

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of immigrants</th>
<th>No. of estimated patients</th>
<th>Pre-donation questionnaire</th>
<th>Blood screening</th>
<th>Other implementations</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>USA *</td>
<td>22,843,939</td>
<td>300,167</td>
<td>Yes</td>
<td>Mandatory for all donors</td>
<td>One–time screening. Negative blood is used for transfusion</td>
</tr>
<tr>
<td>Canada †</td>
<td>374,305</td>
<td>5,779</td>
<td>ND</td>
<td>Mandatory for at-risk donors</td>
<td>Negative blood is used for transfusion</td>
</tr>
<tr>
<td>Europe ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>1,445,751</td>
<td>39.985–65.258</td>
<td>Yes</td>
<td>Mandatory for at-risk donors</td>
<td>Negative blood is used for transfusion</td>
</tr>
<tr>
<td>Italy</td>
<td>440,000</td>
<td>5.520–7.081</td>
<td>Yes (regional)</td>
<td>In progress</td>
<td>National guidelines for transplantation available</td>
</tr>
<tr>
<td>UK</td>
<td>400,000</td>
<td>14,000</td>
<td>Yes</td>
<td>No.</td>
<td>All at-risk donors are deferred for donation</td>
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<tr>
<td>France</td>
<td>208,395</td>
<td>2,166</td>
<td>Yes</td>
<td>Mandatory for at-risk donors</td>
<td>Negative blood is used for transfusion</td>
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<tr>
<td>Portugal</td>
<td>83,000</td>
<td>850</td>
<td>ND</td>
<td>In progress</td>
<td></td>
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<tr>
<td>Sweden</td>
<td>58,196</td>
<td>1,118</td>
<td>Yes</td>
<td>No.</td>
<td>Donors having &gt; 5 year stay in endemic areas are deferred</td>
</tr>
<tr>
<td>Germany</td>
<td>58,000</td>
<td>935</td>
<td>ND</td>
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<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>38,133</td>
<td>1,982</td>
<td>ND</td>
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<td>Netherlands</td>
<td>35,211</td>
<td>480</td>
<td>ND</td>
<td>Not provided</td>
<td></td>
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<tr>
<td>Switzerland</td>
<td>35,000</td>
<td>3,000</td>
<td>Yes</td>
<td>Mandatory for at-risk donors</td>
<td>Negative blood is used for transfusion</td>
</tr>
<tr>
<td>Austria</td>
<td>7,552</td>
<td>140–180</td>
<td>ND</td>
<td>Not provided</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan †</td>
<td>240,101</td>
<td>3.148</td>
<td>Yes</td>
<td>At-risk donors consented to the examination</td>
<td>Negative blood is only used for plasma products</td>
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<tr>
<td>Australia †</td>
<td>116,430</td>
<td>1,871</td>
<td>Yes</td>
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<td>Negative blood is used for transfusion</td>
</tr>
<tr>
<td>New Zealand †</td>
<td>6,315</td>
<td>101</td>
<td>Yes</td>
<td>Mandatory for at-risk donors</td>
<td>Negative blood is used for transfusion</td>
</tr>
</tbody>
</table>

The data are based on the ref\(^ {17}\).
* Adopted from ref\(^ {5}\)
† Infection rate was adopted from ref\(^ {20}\)
‡ Countries where the data are available are listed.
ND: not available.
repeatedly seropositive persons should be traced back to 10 years and that the relevant bloods and blood products must be destroyed. Thus, donor deferral in the US is based on the evidence of seroreactivity, as well as the personal history of Chagas disease.

Chagas disease in Europe and Oceania

Europe hosts more than 2 million of legal Latin American immigrants and therefore has a substantial burden of Chagas disease (Figure-3). An attention also should be paid for a hidden population of illegal immigrants. Spain hosts the largest Latin American communities with about 1.5 million people, as Spanish is the most common language in Latin America. Seroprevalence figures of the country of origin to the relevant immigrant populations have been applied to the European countries (Table-1). More than 80% of the immigrants are hosted by 3 countries, Spain, Italy, and UK and the estimated 86,000 persons with T. cruzi infection live in these countries.

Because the vectorial transmission does not occur in Europe, almost all Chagas patients are detected among the immigrants; hundreds of cases of domestic infections caused by transfusion, organ transplantation, and congenital transmission have been reported. Preventive measures against the transmission, however, vary among the countries. Regarding prevention via transfusion, a systematic screening for identifying at-risk donors is conducted in France, Spain, Sweden, Switzerland, and the UK. The UK adopted most strict settings for blood donation; blood, cells, and organs of at risk-donors, who or whose mothers were born in South America or Central America including Southern Mexico but excluding Caribbean countries and donors who received transfusion or lived continuously for 4 weeks or more in these areas must not donate their blood. The person who returned from endemic areas and are subsequently found nonreactive to T. cruzi antibody using validated test for at least 6 months after their return can be considered discretionarily for donation. Similarly to the US, Spain, France, and Switzerland implement mandatory screening of blood donors at risk for T. cruzi infection. Donors who were judged as negative are able to donate blood. In non–European countries, Australia and New Zealand have established the similar guidelines. In Sweden, persons who lived more than five years in endemic areas are automatically deferred for donation, irrespective of country of origin. Italy and Portugal are going to develop guidelines for the blood transfusion service.

Screening of congenital infection with T. cruzi is also not implemented in most of non-endemic countries. The epidemiological surveillance for pediatric Chagas disease in Barcelona, Spain and Geneva, Switzerland was conducted between 2004 and 2012 and detected 45 cases of congenital infection, whose mothers were all born in Latin America. Majority of mothers (41 of 45 cases) originated from Bolivia, clearly suggesting that Bolivia is a Chagas disease “hotspot.”

Chagas disease in Japan

Historically, many Japanese have settled in Latin America, especially in Brazil, Peru, and Bolivia, before and after the World War II. In 2014, of 240,000 Latin American immigrants, the majority is the Japanese diaspora (Nikkei) from Brazil. Because the occurrence of the domestic life cycle of triatomine bugs is not officially reported in Japan, as well as in European countries, these immigrants and their offspring are typically the risk group. Based on the seroprevalence figures of the country.
of origin\(^5\), the estimated 3,148 of 240,101 immigrants in 2014 live with *T. cruzi* infection in Japan (Table-1).

In August 14 2013, Japanese Red Cross Society (JRCS) and the Ministry of Health, Labour and Welfare of Japan announced that one male blood donor, who and whose mother have originated from Latin America, was found to be seropositive for Chagas disease. Retrospective analysis revealed that this patient had already donated his blood 9 times and these blood products had been delivered to 8 medical institutions and used for 11 recipients. Fortunately, there was no secondary infection investigated so far; 5 of 11 recipients were finally traceable and they were found to be negative.

Nowadays, JRCS provides awareness poster and counter display for at-risk donors of Chagas disease (Figure-4) and is implementing a questionnaire to those who or whose mother originated from Latin America and those who have stayed more than 4 weeks (in total) in Latin American countries\(^22\).

Bloods from at-risk donors who consented to being enrolled in the epidemiological surveillance are tested using the Ortho ELISA kit and the positive bloods are permanently excluded. At present, the blood of the negative donor is only used for fractionation into plasma derivatives in Japan.

Epidemiological surveillance by JRCS to identify...
the prevalence of Chagas disease is now underway. Recently, a case of congenital transmission was reported. A 13-year-old boy who was born to a Bolivian mother in Japan was hospitalized due to severe constipation. His family is a Bolivian Nikkei and used to live in endemic areas. He was diagnosed using the Ortho ELISA kit, PCR using a standardized T. cruzi-specific primer set, and the haemoculture; all of testing showed positive to T. cruzi infection. His mother was also found to be seropositive for T. cruzi.

How do we prepare for Chagas disease in Japan?

**Diagnosis based on clinical symptoms:** Because of the absence of triatomine bugs in Japan, vectorial and food-borne transmissions are negligible. In addition, donated blood is becoming secured by introduction of a questionnaire to donors from Latin America. Therefore, the risk groups should include those who were born or grown in Latin America or born to a Latin American mother, or who temporarily lived in Latin American countries; particularly, Bolivian immigrants are at highest risk for Chagas disease according to seroprevalence. Because Chagas disease patients inhabiting in Japan seem largely asymptomatic or chronic, physicians should take Chagas disease into account for a person with the following conditions.

1. A person who is of Latin American origin and has abnormalities of cardiac electrogram or constipation.
2. A person who was born to a mother of a Latin American origin and has typical manifestations of Chagas disease as above.
3. A pregnant woman of a Latin American origin.

The condition (1) may be pointed out by a routine health checkup for foreign employees. By contrast, the conditions (2) and (3) may be unnoticeable. Therefore, pediatricians and obstetricians, in particular, should keep those possibilities in their minds.

**Differential diagnosis:** When an outpatient is suspected of Chagas disease, physicians should consult nearby experts; consultation to the experts at Department of Parasitology, Tropical Medicine, or Medical Biology in the Medical Universities is helpful. Differential diagnosis using authorized kits and diagnostic PCR should be carried out. Because the improvement of awareness of Chagas disease and the establishment of a systematic medical care system including differential diagnosis and chemotherapy are still lacking in Japan, further implementation in terms of better control of Chagas disease is necessary.

**Chemotherapy and recent advances in drug development for Chagas disease**

Two drugs, benznidazole and nifurtimox, are currently available but not a silver bullet. In the acute phase of infection, where T. cruzi can be detected in the blood, both drugs are effective. By contrast, the treatment of asymptomatic or chronic Chagas disease without detectable parasitemia in the blood is still a matter of debate, because the cure rates in these phases are considerably inferior to the acute phase. In Bolivia, chemotherapy is only conducted in the patients who possess the parasites in the blood (personal communication). During treatment, severe side effects including rash, peripheral neuropathy for benznidazole and anorexia, nausea, vomiting, weight loss, and abdominal pain for nifurtimox may appear, which often results in discontinuation of chemotherapy. Nifurtimox is available from the Drug Service of the Research Group on Chemotherapy of Tropical Diseases in Japan.

Thus, the development of new, truly effective drugs for Chagas disease is required. Recently, two compounds, ravuconazole and posaconazole were offered to the prospective, randomized clinical trials (phase II) in endemic areas. Both compounds have been developed as an antifungal agent, which are a potent inhibitor of fungal ergosterol biosynthesis. Unfortunately, both of compounds were well tolerated but did not show the comparable effects to benznidazole.

**Conclusion**

In non-endemic countries, Chagas disease cannot be regarded as a fire on the other side of the river. Due particularly to the prolonged indeterminate phase and subsequent incurable damages to vital
organisms in the chronic phase, Chagas disease is being recognized as a lifetime, deadly disease, like AIDS, in endemic areas. Therefore, not only clinical treatment but also social supports for both patients and their family are undoubtedly needed.

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