Title: Should obstetricians working in non-endemic countries care about emerging tropical diseases? A review

Running title: Emerging tropical diseases in pregnancy

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Abstract:

Due to migration and travels, obstetricians are increasingly faced with a globalized setting and should adapt their daily clinical approach to the modifications of tropical infections epidemiology.

This paper is focused on five emerging infectious diseases, namely Chagas disease, HTLV-1 infection, malaria, schistosomiasis and Zika virus infection, having a high prevalence in migrant populations and which can affect international travelers. These diseases frequently pass unrecognized since they are characterized by few symptoms during pregnancy, however they may cause a relevant maternal, fetal and neonatal impact. Specific diagnostic and treatment options are available but are rarely used during routine obstetrical practice.

Introduction

Infections in pregnancy can have a particularly relevant impact on both maternal and neonatal health. When we mention infections in pregnancy we usually refer to the TORCHS complex: *Toxoplasma*, Others (*Human Immunodeficiency Virus* - HIV, *Hepatitis B Virus* - HBV, *Hepatitis C Virus* - HCV, *Varicella Zoster Virus* - VZV, *Parvovirus B19*), *Rubella Virus*, *Cytomegalovirus*, *Herpes simplex virus I/II* and syphilis. A serological screening for most of these infections is generally offered to pregnant women in middle and high-income countries.

The recent expansion of migration and international travel is greatly changing the epidemiology of infectious diseases, and the global burden of tropical diseases is increasing even in low endemicity countries.(1, 2) The first report on the health of refugees and migrants in the WHO (Wolrd Health Organization) European Region has recently shown that prolonged periods of inadequate nutrition and lack of care during migration makes primarily women vulnerable. A marked trend for worse pregnancy-related indicators among refugees and migrants is also reported.(3) Tropical diseases are frequently asymptomatic or paucisymptomatic and are poorly known by physicians working in non-endemic countries. Although

some of these infections have a potential risk of causing a negative impact on pregnancy outcome if not correctly diagnosed and treated before or during pregnancy, they are not usually targeted by screening protocols.

We decided to focus this paper on Chagas disease (CD), HTLV-1 infection, malaria, schistosomiasis and Zika virus (ZIKV) infection. These five infectious diseases have been selected because of their high prevalence in immigrant populations, their potential relevant fetal and neonatal impact and the availability of reliable diagnostic and treatment options to manage them during pregnancy or in the immediate post-partum. For some of them, the cost effectiveness of antenatal screening has already been proven.(4-7)

The data we will describe are summarized in the tables (*Table 1, 2)*. We created maps using mapchart.net© and then modifed with Microsoft Paint©, to visualize the geographical distribution of each disease.

Chagas disease

CD, so called in honor of the physician Carlos Chagas who discovered the etiological agent *Trypanosoma cruzi* and the related clinical manifestations, is transmitted to humans by infected triatomine.(8) The presence of competent vectors is limited to continental Latin America, the reason why CD is also known as "American trypanosomiasis" (*figure 1, panel A*).(9) Transmission may also occur through blood transfusions, organ donations, unsafe use of needles, ingestion of food contaminated by triatomines feces and from mother to child during pregnancy or very rarely by breastfeeding.(10, 11) After vector-borne transmission, vertical transmission is currently the main transmission modality. It is responsible for 22.5% of new cases globally and for almost all cases in non-endemic countries and in Latin America vector-free areas.(12) In the absence of diagnosis and effective treatment, people affected by CD often remain asymptomatic for some decades until the development of irreversible consequences, namely cardiomyopathy, megacolon and megaesophagus which occur in about 30% of cases.(13)

Because of rural-to-urban migrations initially, and intercontinental migrations after, CD has rapidly spread worldwide. Recent epidemiological studies estimate that 238,091 infected people reside in the United

States(14) and 68,000-120,000 are currently living in Europe,(8) notably in Spain (about 47,700 estimated affected subjects applying the seroprevalence estimates provided by the PAHO to the number of Latin American migrants) and Italy (3,000-5,000 estimated affected subjects(15)). Despite the fact that diagnosis in chronically infected adults can be easily performed using commercially available serological tests to detect IgG for *T. cruzi*, less than 10% of CD cases in Europe are diagnosed.(16)

This low access to diagnosis is mainly related to the absence of large-scale screening programs, despite the WHO recommendations to globalize the efforts for CD control and elimination.(1) Two previous studies have already demonstrated that CD screening in Latin American migrants at primary health-care centers in Europe is cost-effective (4, 5) and another has recently reported that universal screening in the US is cost saving even at $60 per woman screened.(6) Nevertheless, only three autonomous communities in Spain (Catalonia, Galicia and Valencia) and one region in Italy (Tuscany) are currently testing pregnant women coming from CD endemic areas.(17)

T. cruzi seroprevalence among pregnant women varies between different countries of origin, reaching up to 70% in people living in some rural areas of Bolivia and 18% in people emigrated from Bolivia to Europe.(8, 18) In Italy, CD seroprevalence ranging between 3.9 to 17.1% among Latin American migrants is reported.(19)

Congenital fetal infection occurs in about 4% of chronically infected mothers in non-endemic areas.(20) Since benznidazole and nifurtimox are contraindicated during pregnancy, mother-to-child transmission (MTCT) can be prevented only through treatment of childbearing age infected women before conception.(21-23) However, diagnosis in asymptomatic infected pregnant women is critical to set up correct management and treatment of newborns. Congenitally infected newborn are often asymptomatic at birth (40-100% of cases).(24) For these reasons, all neonates from women with CD have to be tested at birth using parasitological or molecular direct test and then followed-up using serology until 9-12 month of age to assess the clearance of maternal anti *T. cruzi* antibodies. If congenital infection is confirmed following a positive direct test or due to persistence of positive serology beyond 9-12 month, the infant should receive

a specific antiparasitic treatment (benznidazole or nifurtimox).(25) Breastfeeding is contraindicated only in acute phase of the disease, reactivated disease resulting from immunosuppression, or bleeding nipples. In these cases, thermal treatment of milk before feeding the infant may be considered.(26)

While efficacy in adulthood assessed through sero-reversion is disappointing (usually less than 20%), antiparasitic treatment of infected children within the first year of life is effective in almost 100% of cases. (27)

Considering that CD serology is widely available in high income countries, more efforts should be done to detect silent infections in high risk populations and prevent irreversible sequelae in infants.

Pregnant or childbearing age women eligible for CD screening are:

1) native women from continental Latin America (*figure 1*, *panel A*);
2) women whose mother was native from continental Latin America;
3) women who have travelled to continental Latin America and carried out an activity at risk such as: visiting or living in rural areas; spending the night outdoors/in a tent/in rural houses made with vegetable matter like straw and wood; drinking unpasteurized fruit/sugar cane juices;
4) women who have undergone blood transfusions in continental Latin America.

HTLV-1 infection

HTLV-1 (Human T-Cell Leukemia/Lymphoma Virus type 1) was the first oncogenic human retrovirus discovered. As documented for the more familiar HIV, HTLV-1 persists lifelong in $CD4^+$ lymphocytes, but while the first virus induces the death of infected cells, the second is rather associated with the proliferation and transformation.(28) Approximately 90% of HTLV-1 infected people are asymptomatic carriers that can inadvertently infect other individuals throughout their life.(29) In the remaining 10%, HTLV-1 can induce an aggressive lymphoproliferative malignancy of peripheral T cells (notably the adult T-cell leukemia/lymphoma – ATLL – that give the name to the virus), or an incapacitating neurological disease

known as HTLV-1-associated myelopathy/tropical spastic paraparesis, or inflammatory affections like uveitis and dermatitis.(28) Furthermore, the subclinical immune suppression HTLV1-related is responsible for an elevated rate of opportunistic coinfections, such as crusted scabies, tuberculosis and severe strongyloidiasis.(30)

Globally, HTLV-1 prevalence is difficult to define because not homogeneous. According to the European Centre for Disease Prevention and Control (ECDC), HTLV-1 is endemic in the south-west of Japan, in the Caribbean islands, in South America and in equatorial Africa, while in Europe the only concerned country is Romania (*figure 1, panel B)*. In high endemicity settings, the HTLV-1 seroprevalence in adults is at least 1–2%, reaching 20–40% in specific clusters.(31) Contrariwise, there are only sporadic epidemiological data concerning seroprevalence in non-endemic countries. A study conducted in northern Italy among migrant population reported a seroprevalence of 0.3%(32) comparable to data obtained in a cohort of migrant pregnant women in Spain.(33)

HTLV-1 transmission occurs through sexual intercourses (more often from male to female than vice-versa), blood transfusions, organ donations, unsafe use of needles, and from MTCT which is considered the main route of transmission globally.(28)

MTCT is mainly caused by a prolonged breastfeeding in the postnatal period thus even transplacental and perinatal transmission may also occur.(34) A high level of HTLV-1 proviral load in milk and in blood cells as well as high HTLV-1 antibody titers in the serum and long duration of breastfeeding (longer than six months) are the major risk factors.(35) Intrauterine or peripartum transmission has rarely been reported, while no case of transmission via saliva has currently been published. Infected newborns frequently develop the complications of chronic HTLV-1 infection during their life, notably ATLL, while patients infected in adulthood are more likely to develop inflammatory diseases.(36)

Unlike HIV, effective treatments to reduce HTLV-1 viremia are not available but diagnosing infection during pregnancy can allow to implement strategies to reduce the MTCT from 15%–20% to 2%–3%.(34) Mainly, infected mothers should avoid long-term breastfeeding, preferring formula milk feeding, frozen-thawed

breast milk or short-term breastfeeding (≤ 3 moths) as recommended by Japanese guidelines.(37) Some authors also suggest a cesarean section to minimize the risk of perinatal transmission(30), but currently no guidelines indicate this recommendation.

Nowadays, the only guidelines recommending a serological antenatal screening are the Japanese guidelines for obstetrical practice.(37) After the refusal of the National Screening Committee to introduce HTLV-1 antenatal screening in 2017 in United Kingdom, two English authors demonstrated that at a cost of £1.37 it could be cost effective also in the UK setting.(7)

Pregnant women eligible for HTLV-1 screening are:

1) women native from high prevalence countries (*figure 1*, *panel B*);
2) women whose mother comes from one of the high prevalence countries;
3) women who have undergone blood transfusions in a high prevalence country;
4) women with an HTLV-1 affected partner.

Malaria

According to WHO, in 2018 around 220 million cases of malaria occurred worldwide, most frequently in sub-Saharan Africa where approximately 25 million pregnant women are at risk of *Plasmodium falciparum* infection every year (*figure 1, panel C*).(38) The main route of malaria transmission is vector-born transmission, mediated by the female specimen of mosquito *Anopheles*. Uncommonly, parenteral transmission and vertical transmission may occur. Compared with non-pregnant women, pregnant women more frequently experience a severe disease, inducing cerebral malaria and respiratory complications (pulmonary edema and acute respiratory distress syndrome).(39) Parity-specific immunity, as well as age-associated immunity, plays an important role in controlling the infection during consecutives pregnancies in high and stable transmission areas.(39) Pregnancy-induced changes in immunity and splenic function particularly predispose primigravidae to severe malaria.(39) Severe anemia is the main determinant of malaria-related maternal and perinatal morbidity and mortality. Miscarriage, intra-uterine growth

restriction (IUGR), preterm delivery, stillbirths, low birth-weight (LBW), congenital infection and neonatal death have all been associated to infection acquired during pregnancy.(39) Parasite placental sequestration can also induce congenital malaria and reduce transplacental transfer of maternal antibodies and infant cellular immune responses to several other infectious diseases.(40) Furthermore, if anti-malarial drugs do not achieve placental therapeutic levels, sequestered parasites may be intermittently released and cause recurrent maternal infection.(41)

In addition to the classical acute symptomatic malaria, people coming from high endemicity countries may present a subclinical and submicroscopic infection, normally detectable only through molecular techniques like Polymerase Chain Reaction (PCR) or Loop Mediated Isothermal Amplification (Lamp).(42) This special condition is related to their “semi-immunity” or “premunition”, an immunological state resulting from repeated parasite expositions, which control but does not eliminate the infection.(43)

Available data reported that more than one in four pregnant women in high-transmission and one in fifteen in low-transmission African settings have evidence of placental infection at the time of delivery, even if the women were symptomless and malaria was acquired several months before.(39)

Despite the prevalence of submicroscopic malaria among asymptomatic African immigrants being rather high, between 5% and 9%(42, 44), currently Italian guidelines recommend screening for malaria in asymptomatic migrants only if splenomegaly and/or thrombocytopenia are present.(45) Contrariwise, American CDC “Domestic Refugee Health Guidelines” recommend malaria PCR screening in all asymptomatic pregnant refugees originating from Sub-Saharan Africa and not receiving a pre-departure therapy.(46)

Regardless of local legislation, literature data suggest malaria screening in pregnant women coming from high endemicity countries, especially if visiting friends and relatives in the previous months. Preferentially, screening should be performed with molecular methods such as Lamp which have high sensitivity. Microscopy remains essential for confirmation and definition of parasitemia. Infected patients should receive antimalarial treatment based on severity, *Plasmodium* species and gestational age.(47)

Pregnant women eligible for malaria screening are native women from high incidence malaria countries (mostly Sub-Saharan countries, *figure 1*, *panel C*) newly arriving in low endemic countries or who may have been travelling in the last few years (e.i. in the last five years) in their country of origin or in another endemic country.

Schistosomiasis

Schistosomiasis, also known as bilharziasis in honor of the physician Theodor Bilharz who first described the parasite in humans, is a tropical disease caused by five different species of schistosomes.(1) The infection transmission requires the contact of the human host with fresh water contaminated by both parasites and cercariae, in which the parasite completes its life cycle.(1)

According to WHO data, schistosomiasis is endemic in over 70 tropical and subtropical countries and afflicts almost 240 million people worldwide, mostly school-age and young adult populations in sub-Saharan Africa. Other moderate-high endemicity countries are Philippines, Yemen and Brazil (*figure 2, panel A*).(1) A recent meta-analysis reported a schistosomiasis seroprevalence of 18% among migrants coming from endemic countries, reaching 24% in Sub-Saharan African migrants.(48) Several studies conducted in Italy showed a prevalence ranging from 7% up to 20% among newly arrived Sub-Saharan African migrants.(2, 49) In addition to imported cases, European autochthonous transmission of schistosomiasis is not a remote possibility, considering that many cases of autochthonous infection have already occurred in Corsica(50) and transmission can potentially occur in Sardinia too, where the intermediate host is present.(51)

Infected people normally present an asymptomatic or paucisymptomatic parasitosis. If unrecognised and untreated, chronic infections lead to irreversible urogenital or hepato-intestinal sequelae in around 10% of cases.(52)

Epidemiological studies on maternal schistosomiasis are currently scarce, but it is estimated that about 40 million child-bearing age women are infected worldwide.(53) Animal models and human case reports suggest a deleterious effect of infection on maternal, fetal and neonatal outcomes, mainly related to

maternal anemia and undernutrition.(53) AS for other infectious diseases, the burden of schistosomiasis is more pronounced in primigravid mothers and tends to decrease with gestational age. Moreover, pregnancy-related Th2 polarization may exacerbate clinical features, inducing larger granuloma lesions and more severe morbidity.(54) Finally, a transplacental transmission has anecdotally been reported.(53) *S. haematobium* may cause genital lesions called "female genital schistosomiasis" a clinical condition associated with infertility, symptoms of sexually transmitted infections and increased risk of acquiring HIV. (55)

Both European and Italian National Guidelines concerning health checks on newly arrived migrants recommend *Schistosoma* spp serology in all migrants who have lived or traveled in endemic areas and treatment of seropositive subjects.(45, 56)

Given the absence of teratogenicity and fetal toxicity evidence in animal models and accidentally exposed pregnant women, the WHO has recently expressed in favour of administration of praziquantel in pregnancy.(57) Praziquantel treatment seems to have no significant effect on birth weight but it is safe and effective, and it can improve future gestations outcomes.(57, 58) Hence, schistosomiasis screening in high risk patients should be considered.

Pregnant women eligible for schistosomiasis screening are those coming from high endemicity countries (*figure 2*, *panel A*), mainly sub-Saharan Africa.

Zika virus infection

ZIKV is an arthropod-borne flavivirus transmitted by *Aedes* mosquitoes and causing clinical manifestations in approximately 20% of infected people.(59) During recent years, it has rapidly spread and caused outbreaks across the American continent but also in Africa, Southeast Asia, and the Pacific Islands (*figure 2, panel B*).(60) ZIKV infections acquired in pregnancy can induce the Congenital Zika Syndrome (CZS) characterized by severe cerebral fetal abnormalities, namely ventriculomegaly, microcephaly and intracranial calcifications.(61) A significant number of fetuses suffering from IUGR have also reported,

although positive and especially negative predictive values of fetal ultrasound in ZIKV infection are not optimal.(62) The reported percentage of fetuses or infants with possible Zika-associated birth defects is 8%, 5%, and 4% in the first, second, and third trimesters respectively among completed pregnancies with confirmed ZIKV infection (positive nucleic acid tests).(63)

The epidemiological impact of ZIKV infection on pregnancy outcomes has been so important that the WHO declared the state of global public health emergency on February 2016 and some authors suggested adding a Z to the classic TORCHS complex.(64)

According to US guidelines(65), symptomatic women with possible ZIKV exposure should undergo concurrent ZIKV serology and PCR for viral RNA on serum and urine as soon as possible, within 12 weeks after the symptom onset. Because of the overlap of ZIKV and Dengue virus epidemiology and the consequent risk of false-positive ZIKV IgM results, a Dengue serology should be simultaneously performed. Antibody cross-reactivity may also be observed in individuals who have been vaccinated against yellow fever or other *flavivirus*, so an unexpected serological positivity should be interpreted with caution. Demonstration of viremia is conclusive and not rare in infected women, considering that it persists three times longer during pregnancy, probably because of a further viral replication in the placenta or fetus.(66)

Contrariwise, asymptomatic pregnant women with recent possible ZIKV exposure, but without ongoing possible exposure, are not routinely tested in the US.(65) However in other countries such as Italy, testing is recommended in asymptomatic and symptomatic pregnant women returning from affected areas or reporting sexual contact with a partner recently exposed in affected areas.(67)

Although the lack of an effective therapy to prevent congenital infection or mitigate pre and post-natal CZS, testing is currently considered using a shared patient-provider decision-making model. ZIKV screening should be offered to women with relevant epidemiological exposure (*figure 2, panel B*), according to WHO recommendations.(68) Male partner's travel in endemic countries should be considered as a risk factor for pregnant women in case of unprotected sexual contact, due to the possibility of ZIKV sexual transmission. Protected sexual intercourse are in this case recommended for the duration of pregnancy.(69)

Pregnant women eligible for ZIKV screening are:

1) women who have travelled to areas below 6500 feet (2000 meters) where ZIKV mosquito transmission is ongoing, during pregnancy or within 2 months before getting pregnant;
2) women who have had unprotected sex with their partner who has travelled to endemic areas during the woman's pregnancy or up to 3 months before her getting pregnant.

In case of confirmed ZIKV infection, serial fetal ultrasounds should be offered to assess fetal neuroanatomy and fetal growth should closely monitored. Moreover, newborns should be tested, evaluated and followed during the first months of life for the possibility of post-natal CZS appearance.(70)

Conclusions

The five emerging tropical diseases described in this paper mostly fulfill the criteria for being considered for screening in asymptomatic people, namely a high prevalence, a significant clinical impact and the availability of diagnostic tools and treatment (or at least management) options and favorable cost-effectiveness profile. Given the recent epidemiological changes, we should consider adopting public health policies that include an implemented screening strategy for pregnant migrants and travelers. The period of pregnancy could be used to diagnose infections transmissible to the newborn, but also potentially and silently affect other family members. Increasing screening and notification efforts is essential to quantify the true burden of these infections in high-income and low-endemicity countries, and consequently to inform evidence-based policy decisions. Undoubtedly, achieving these goals primarily requires guaranteed health access for all pregnant women, regardless of their country of origin, social status or administrative situation.

Disclosure of interests:

We don't have any conflict of interest to declare.

Contribution to Authorship: L,Z. conceived and planned the review and performed the systematic analysis of literature. S.G. and G.M. wrote the manuscript. B.B., I.C., M.T., M.D.T., V.S. and A.B. critically reviewed the discussed manuscript.

Ethics approval : N/A.

Funding : This article has been supported by funds of "Ministry of Education, University and Research (Italy) Excellence Departments 2018-2022" Project for the Department of Experimental and Clinical Medicine and funds of "Finanziamento alla Ricerca di Ateneo ex 60% 2019" University of Florence, Florence, Italy.

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484 *Table 1*

Infectious disease	Infectious agent	Pregnant women at higher risk	Effects of infection during pregnancy	Diagnostic test in pregnant women	Management	Benefits of screening and/or treatment	Guidelines recommending the screening	Cost-effectiveness
Chagas disease	*Trypanosoma cruzi*	1) Native women from continental Latin America; 2) women whose mother was native from continental Latin America; 3) women who have travelled to continental Latin America and carried out a risk activity; 4) women who have undergone blood transfusions in continental Latin America	MTCT in 5% of cases[71]	*T. cruzi* IgG	Newborns of seropositive women should be tested at birth, followed-up and treated preferably within one year of life in case of confirmed infection. Breastfeeding is usually allowed (see the main text)	Treatment is highly effective if performed within the first year of life; prevention of CD complications in women (treated after breastfeeding); prevention of transmission in subsequent pregnancies	Catalonia, Galicia and Valencia in Spain, and Tuscany region in Italy (all pregnant women coming from CD endemic areas)[17]	Cost-effective in Latin American migrants at primary health-care centers in Europe[4,5]; universal screening is cost-effective in US[4-6]
HTLV-1 infection	HTLV-1	1) Women native of high prevalence countries; 2) women whose mother comes from one of the high prevalence countries; 3) women who have undergone blood transfusions in a high prevalence country; 4) women with a HTLV-1 affected partner	MTCT via breastfeeding in 15-20% of cases[34]; increased risk of ATLL in vertically infected newborns[30]	HTLV 1-2 antibodies	Avoid long-term breastfeeding, preferring formula milk feeding, frozen-thawed breast milk or short-term breastfeeding (≤ 3 moths)[37]	MTCT rate reduced from 15-20% to 2-3%[34]	Japanese guidelines (all pregnant women in Japan) [37]	Universal screening is cost-effective in UK at a cost of £1.37 par test[7]

Schistosomiasis	*Schistosoma* spp (*Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*)	Native women from high endemicity countries	Possible exacerbation of chronic infections; increased incidence of LBW and prematurity[53]	*Schistosoma* spp antibodies	Treatment with Praziquantel during pregnancy or after childbirth	Prevention of chronic schistosomiasis complications; improvement of future gestations outcomes	European and Italian National Guidelines (all newly arrived migrants having lived or travelled in endemic areas)[45,56]	No studies

MTCT= Mother to child transmission; CD= Chagas disease; LBW= Low birth-weight; IUGR= Intrauterine growth restriction; Lamp= Loop mediated isothermal amplification; ZIKV= Zika virus; CZS= Congenital Zika Syndrome; VTP= Voluntary Termination of Pregnancy

Table 2

Infectious disease	Infectious agent	Pregnant women at higher risk	Effects of infection during pregnancy	Diagnostic test in pregnant women	Management	Benefits of screening and/or treatment	Guidelines recommending the screening	Cost-effectiveness
Malaria	*Plasmodium* spp (*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*)	Native women from high incidence malaria countries (mostly Sub-Saharan countries) newly arrivied in low endemic countries or who may have been travelling in the last few years (i.e. in the last five years) in their country of origin or in another endemic country	Increased incidence of LBW, IUGR, miscarriage, congenital malaria and stillbirth[39]	Molecular methods for detection of *Plasmodium* spp (e.i Lamp)	Antimalarial treatment based on severity, species and gestational age	Improvement of maternal, fetal and neonatal outcomes	CDC guidelines (all asymptomatic pregnant refugees originating from Sub-Saharan Africa not receiving pre-departure therapy)[46]; Italian guidelines (asymptomatic migrants presenting splenomegaly and/or thrombocytopenia)[45]	No studies
Schistosomiasis	*Schistosoma* spp (*Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*)	Native women from high endemicity countries	Possible exacerbation of chronic infections; increased incidence of LBW and prematurity[53]	*Schistosoma* spp antibodies	Treatment with Praziquantel during pregnancy or after childbirth	Prevention of chronic schistosomiasis complications; improvement of future gestations outcomes	European and Italian National Guidelines (all newly arrived migrants having lived or travelled in endemic areas)[45,56]	No studies

ZIKV infection	ZIKV	1) Women who travelled to areas where ZIKV mosquito transmission is ongoing, during pregnancy or within 2 months before; 2) women who have unprotected sex with their partner who has travelled to endemic areas during the woman's pregnancy or up to 3 months before	CZS in 8%, 5%, and 4% in the first, second, and third trimesters respectively among completed pregnancies with confirmed ZIKV infection[63]	ZIKV antibodies +and PCR on serum and urine	Serial fetal ultrasounds during pregnancy, possible amniocentesis and newborn follow-up	Possibility of VTP according to current legislation; CSZ early diagnosis and post-natal management	US guidelines (test recommended for symptomatic pregnant women only)[65] In Italy, testing is recommended in asymptomatic and symptomatic pregnant women returning from affected areas or reporting sexual contact with a partner recently exposed in affected areas[67]	No studies

MTCT= Mother to child transmission; CD= Chagas disease; LBW= Low birth-weight; IUGR= Intrauterine growth restriction; Lamp= Loop mediated isothermal amplification; ZIKV= Zika virus; CZS= Congenital Zika Syndrome; VTP= Voluntary Termination of Pregnancy