

Appendix 9: Malaria: evidence review for newly arriving immigrants and refugees

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ABSTRACT

Background: Migrants coming from malaria endemic areas are at risk for developing symptomatic disease, particularly in the first three months after arrival. Malaria, especially falciparum malaria, can be associated with severe disease and even death. This review was undertaken to determine whether Canadian primary care practitioners should routinely screen for malaria, in adult and child migrants from low to middle income endemic countries.

Methods: We performed a systematic search for evidence on the burden of disease (prevalence, morbidity, and mortality), risk identification, screening, and treatment of malaria. The quality of the evidence was assessed and ranked using the GRADE approach.

Results: There were no clinical trials demonstrating value of routine screening for malaria. Epidemiologic data on prevalence of asymptomatic parasitemia in migrants is limited and there are very few studies examining the risk of progression to symptomatic disease in those who test positive by screening. North American data, although limited for Canada, documents the risk of malaria, including severe malaria, for migrants, and the disproportionate malaria risk in migrant children. Malaria risk is highest for those migrating from endemic areas of Africa. Individuals who develop fever within 3 months of leaving a malaria-endemic area should be tested for malaria and, if positive, should be treated according to the Canadian Guidelines.

Interpretation: There is insufficient evidence at this time to recommend routine malaria screening of migrants. However, migrants that have resided or travelled in malaria endemic areas are vulnerable to acute malaria, particularly within the first 3 months of arrival. Canada requires better malaria surveillance, particularly related to malaria cases in migrant populations. More research is needed on the utility of malaria screening, including follow on studies to determine the risk of development of symptomatic malaria.

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Box 1: Recommendations on Malaria from the Canadian Collaboration for Immigrant and Refugee Health:

Do not routinely screen for malaria.

Be alert for symptomatic malaria in febrile migrants who have travelled to or resided in malaria endemic regions in the previous 3 months, particularly in those from sub-Saharan Africa and perform timely diagnostic inquiry and testing (RDT and thick and thin malaria smear).

Basis of recommendation

- **Balance of benefits and harms:** Individuals from malaria endemic regions, particularly migrants from sub-Saharan Africa, remain vulnerable to acute *P. falciparum* malaria for the first three months after arrival. However, there are no clinical trials demonstrating value of routine screening for asymptomatic malaria, prevalence data remains poor, there is some uncertainty of the performance of malaria screening tests in asymptomatic individuals, and there is no local transmission of malaria in Canada. Thus the focus of the recommendation is on timely diagnosis and treatment of symptomatic malaria, where medications are effective and harms from side effects are minimal.
- **Quality of evidence:** Low
- **Values and preferences:** The Guideline Committee attributed more value to avoiding burden and cost from routine screening given the absence of clear evidence of high prevalence of *P. falciparum* and uncertainty of performance of screening tests in asymptomatic individuals and determined malaria was best dealt with by primary care practitioners remaining alert for signs and symptoms of malaria and performing timely clinical diagnostic inquiry and treatment to address symptomatic individuals.

The cases

Two sisters, aged 3 and 5 years, presented to the emergency department with fever two weeks after immigration from Nigeria. They did not appear unwell, and were sent home from the emergency department after bloodwork, including malaria smears, was drawn. They were recalled when smears were reported positive for both.

Nduwimana, a 25 year old man originally from Burundi, arrived as one of 224 individuals to Quebec from a Tanzanian refugee camp. He and his family were resettled in a smaller community of 60,000 persons. Within three weeks of arrival he developed mild flulike symptoms and presented to the local emergency department where thick and thin smears were sent.

Subsequent review of the smear at a reference laboratory demonstrated *P. falciparum* with a parasitemia of 1.3%.

Introduction

In 2006 malaria caused active disease in 250 million people and one million deaths worldwide.¹ A large proportion of Canada's new immigrants and refugees come from malaria endemic countries (Figure 1). Symptoms of malaria are non-specific,² including fever and a constellation of symptoms ranging from mild illness to fulminant organ failure and death. *P. falciparum* is the most virulent species with an overall 1% case fatality rate³ that increases to 10-20% or higher for those with severe disease, defined by high parasitemia or end organ damage.^{3,4} Most imported malaria cases, particularly those due to *P. falciparum*, present within three months of leaving an endemic area.⁵⁻⁷ Canadian health care providers may have difficulties with malaria diagnosis and treatment due to the rarity of the disease and unfamiliarity with laboratory diagnosis and clinical management.^{3,8} As well the drugs for treatment may not be readily accessible in pharmacies across the country. These delays, which may be compounded by unfamiliarity of the ill migrant with the Canadian healthcare system, can lead to severe disease and even death.^{5,7,9,10} This review was undertaken to determine whether Canadian primary care physicians should routinely screen for malaria, in asymptomatic adult and child migrants from low to middle income endemic countries.

Methods

We used the 14-step method developed by the Canadian Collaboration for Immigrant and Refugee Health.¹¹ A Clinician Summary Table was used to highlight the population of interest, the epidemiology of disease, population-specific considerations and potential clinical actions (Appendix 2). We constructed a logic model to define the clinical preventive actions (intervention), outcomes, and key questions.

Search strategy for systematic reviews and guidelines and population-specific literature

In consultation with a research librarian, search strategies were devised to identify pertinent literature on the prevalence, diagnosis, screening and treatment of malaria (Appendix 1). The following databases were searched from January 1, 1996- January 1st, 2008: Medline, Medline in Process, Cochrane Database of Systematic Reviews, Database of Reviews of Effectiveness, Embase, CINAHL, and Healthstar.

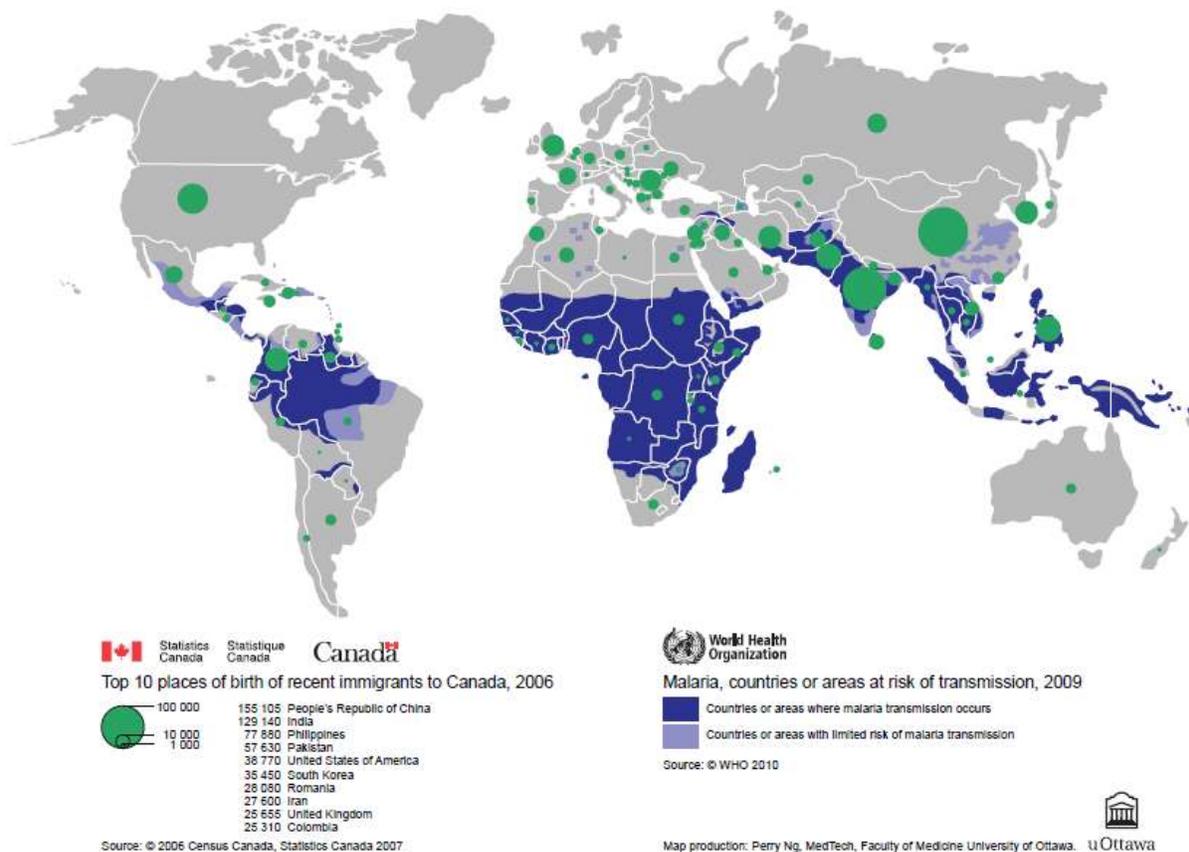


Figure 1: Map of migrant source countries and overlay of malaria endemicity.

The following websites were searched for surveillance data on malaria in migrants and guidelines on malaria: CMA Infobase, Public Health Agency of Canada, US National Guideline Clearinghouse, US CDC: Centers for Disease Control and Prevention, World Health Organization, and Australian Society for Infectious Diseases. In addition, we searched for surveillance data provided through the Canadian Malaria Network (www.travelhealth.gc.ca), the Public Health Agency of Canada Online Surveillance Report (www.phac-aspc.gc.ca/dsol-smed/index.php), the Center for Disease Control and Prevention, Domestic Malaria Branch (P Arguin), and the GeoSentinel Surveillance Database (www.istm.org/geosentinel/main.html). Three initial literature searches were conducted. The first search identified pertinent systematic reviews, meta-analyses and guidelines relating to malaria in immigrant and refugee

populations. The second search was identical but identified articles relating to the general population. The third search identified articles about malaria and the immigrant/refugee population which addressed population-specific concerns including: 1) baseline risk/prevalence in comparison to the Canadian-born population; 2) risk of clinically important outcomes; 3) genetic and cultural factors (e.g. preferences values, knowledge); and 4) compliance variation. This third search was not limited by article type or study methodology. Eligible articles were each appraised by two reviewers for relevance to malaria, epidemiology, screening, diagnosis and treatment.

A further search for evidence was conducted on the efficacy of treatment of falciparum malaria with Coartem® (artemether & lumefantrine), Malarone® (atovaquone/proguanil), and quinine plus doxycycline or

tetracycline. The databases Medline, Embase, and Cochrane Database of Systematic Reviews were searched from January 1, 2003-June 1, 2009. An updating search was conducted on Medline, Embase, and Cochrane Database of Systematic Reviews from January 1, 2007-December 31, 2010 yielded 443 articles. No articles that changed the position of the reviewers on their recommendations were found.

Synthesis

We synthesized evidence from systematic reviews and recent trials for treatment efficacy using the GRADE summary-of-findings tables, which assesses both relative and absolute effects of interventions. We also appraised quality of evidence for each outcome using the GRADE quality assessment tool, which assesses study limitations, directness, precision, consistency, and publication bias across all studies (Box 2).

Results

The initial searches resulted in 1,421 articles, of which 101 articles were selected for detailed appraisal. Initial searches for malaria screening in immigrants and refugees provided many retrospective and prospective reviews of screening in asymptomatic migrants, many related to refugees.¹²⁻¹⁵ Some of these articles provided recommendations on screening for malaria in migrants from endemic areas, however none reported a systematic review methodology. The search for treatment of malaria yielded 247 records, including two systematic reviews.^{16,17}

What is the burden of malaria in immigrant populations?

There is limited data on screening of migrants. Since 2009 Citizen and Immigration Canada has screened refugees from East Africa, utilizing antigen rapid detection tests (RDTs) 48-72 hours prior to departure and treating all positives. During 2009 and the first nine months of 2010, a total of 3384 Canada-bound refugees were screened and 3.7% tested positive (unpublished data, Citizenship and Immigration Canada). The prevalence in Canada-bound refugees from other areas and non-refugee migrants is not known, as they are not screened pre-departure. Published reports of malaria prevalence from screening protocols in new migrants have variable malaria prevalence, from 6.8-64% in African migrants, mostly refugees, with much lower prevalence from other malaria areas.^{6,12-14,18-20} There are limited numbers of follow-on studies that determine the risk of development of active, symptomatic malaria after screening, suggesting a risk of 20-40%.^{12-14,20}

The burden of symptomatic malaria in Canadian migrants is not easy to ascertain. Although the Public Health Agency of Canada receives reports of 350-1000 imported malaria cases per year, the reason for travel in these cases is not reported. Of the 150 malaria cases requiring parenteral therapy reported from June 2001 through January 2010 to the Canadian Malaria Network, 20.6% (31) occurred in new migrants. Among immigrant cases, 64.5% (20/31) were children, compared to 26.7% (40/150) of malaria cases overall. All but one migrant case originated from Africa, with one case in a recent Karen refugee from northern Thailand.⁷ In Alberta, new migrants accounted for 20.7% (79/382) of malaria cases over 10 years (unpublished information, Alberta Health and Wellness). Data compiled from three Canadian tropical medicine clinics (GeoSentinel Surveillance Network Sites in Montreal, Ottawa and Toronto), reporting mostly illness in adults, from Jan 2006 through October 2010 found migrants comprised 15.1% (22/146) of malaria cases, with children accounting for 6.8% (10/146) of all cases and 27.3% (6/22) migrant cases; overall 60% of childhood cases occurred in migrants (D. Freedman, GeoSentinel Surveillance Network, Birmingham, Ala.: personal communication, 2010). In the US, migrant malaria accounted for 7.9% (362/4597) of all malaria cases from 2005-2007, and from 2007-2008 there was an over-representation of childhood migrant cases with 66.3% migrant malaria cases occurring in children compared to approximately 20% of all malaria cases (P. Arguin, Surveillance Reports to Domestic Malaria Branch, Centers for Disease Control and Prevention, Atlanta, Ga.: personal communication, 2010).^{5,21} Most non-surveillance studies report on refugee movements or case series among specialty clinics.^{6,22,23} One Canadian case series from British Columbia found that 28.6% of pediatric cases occurred in immigrants (42 cases in 40 children).²⁴ These data confirm the occurrence of symptomatic malaria, including severe malaria, in new migrants, and highlight the disproportionate malaria burden in migrant children.

Does screening for malaria decrease related morbidity and mortality?

Screening Tests

Microscopic diagnosis with Giemsa stained thick and thin blood smears have traditionally been the gold standard to diagnose malaria and the level of parasitemia. These tests are inexpensive and ubiquitous,²⁵ but time-consuming and rely on significant expertise, seldom readily available in laboratories outside of malaria endemic areas. Rapid diagnostic tests (RDTs) detect

antigens from lysed parasite infected red blood cells, with results available within 5-20 minutes. These tests have the advantage of portability and ease of use. The usual lower detection limit is <100 parasites/ul, with sensitivity declining at lower levels of parasitemia.²⁵ A non systematic review of RDTs concluded that the sensitivity of RDTs for diagnosing falciparum was 95.3% (95% CI: 93-97); this dropped to 89.2% (CI:75-97) for 100-500 parasites/ul. The specificity for *P. falciparum* was 94.2% (95% CI:93-95). However, the ability to detect vivax malaria was not as robust, with a sensitivity of only 68.9% (95% CI:66-72) and a specificity of 99.8% (95% CI:99-100).²⁶ PCR-based assays are also used to diagnose malaria and have lower detection limits, ranging from 0.02-0.7 parasites/ul, however, this significant improvement in detection levels is offset by the cost, institutional support required, limited accessibility and greater time required for test results.²⁷

In Canada, there are many regions where laboratories are unaccustomed to diagnosing malaria by microscopy. The technology, convenience and affordability make RDTs a viable alternative option for most Canadian health laboratories.

Relative benefits and harms of treatment

Based on data from pre-departure treatment protocols of asymptomatic African refugees to Australia and the US, there has been a reduction in migrant malaria cases.^{22,23,28} Of concern, however, there have also been reports of failures, often thought to be due to problems with completion of therapy or delays in departure following therapy.^{29,30} In contrast, the efficacy of treating symptomatic malaria is well documented.^{3,4} The World Health Organization recommends artemisinin combination therapy, such as CoArtem[®], as first line treatment for *P. falciparum* malaria,⁴ however, these drugs are not licenced or available in Canada, where atovaquone / proguanil (Malarone[®]) or quinine plus doxycycline (clindamycin in pregnancy or under the age of 8 years) are recommended. Diagnosis and management for symptomatic individuals should be as per the Canadian malaria guidelines.³

In summary, although detecting and treating asymptomatic parasitemia may decrease malaria morbidity and mortality, there are no clinical trials demonstrating the benefits and harms of routine screening, and a paucity of data preclude the establishment of the true risk of developing symptomatic malaria in migrants to Canada.

Clinical considerations

Citizenship and Immigration Canada (CIC) began screening for malaria in 2009 using malaria rapid diagnostic testing (RDT) on all refugees destined to Canada from East Africa 48-72 hours prior to departure. When a positive RDT is found, treatment is provided with a full course of Coartem[®] (artemether and lumefantrine). For lactating women or for children under five kg a combination of artesunate and amodiaquine is used. For pregnant women quinine is used. Australia follows the same protocol as Canada, while the USA provides presumptive treatment with Coartem[®] to all persons except those who are pregnant, lactating, or under 5 kg, who are tested with a RDT and treated if positive.

It is important to remember that the majority of individuals migrating from areas of malaria risk, particularly sub-Saharan Africa, will not have received pre-departure malaria screening. As well, even those who have undergone screening, including those who have received therapy, may still develop malaria especially within the first 3 months after migration. Many new migrants to Canada are unfamiliar with the health care system and those from malaria endemic countries may be accustomed to having access to malaria therapy, without a physician visit or prescription. The perceived cost of medical care may also be a barrier to receiving care,³¹⁻³³ along with health care providers unfamiliar with malaria diagnosis and management.⁸ Depending on the area of relocation, effective drugs for malaria treatment may not be readily available. These factors may delay detection and treatment, therefore increasing the risk of severe malaria disease.⁷

Numerous studies have also documented the increased risk of malaria, including severe malaria, in more distant migrants and their children returning to visit friends and family (VFR) in malaria endemic countries.^{5,7,9,21,34-36} Practitioners can take the opportunity to introduce the future malaria risk and the need to seek pre-travel advice for recommendations on malaria prevention and management.

Recommendations of other groups

Canada has malaria prevention and treatment guidelines,³ but they do not address screening immigrants and refugees. In the US, there are CDC Technical Instructions addressing treatment of refugees pre-departure. These technical instructions recommend post-arrival presumptive therapy for those who missed pre-departure therapy.³⁷ In Australia there are guidelines for malaria screening in refugees from Africa who have

resided or travelled through a malaria endemic region. These guidelines advocate screening with both thick and thin smear and RDT, and recommend treatment instituted by or in consultation with a specialist infectious disease service.³⁸

The cases revisited

The family (Case 1) was recalled when blood smears showed *P. falciparum* at 2.5 % for Oluwadoyinso, and 0.1% for her sister, which when repeated had risen to 23 and 4.5%. Timely diagnosis and treatment is essential to prevent progression to severe malaria. Availability of a rapid screening tests (RDT), and awareness of the importance of keeping suspected malaria cases until the results are known may have prevented severe malaria in one sister.

Nduwimana (Case 2) had very mild symptoms and due to the difficulty in interpreting the thick and thin smear in a smaller community hospital, he was initially sent home without treatment. This missed diagnosis might have been averted if the testing laboratory had also used an antigen detection test for malaria. The case highlights the problems with the lack of expertise in interpreting blood smears and the utility of confirmatory testing.

Conclusion and research needs

Malaria is common in immigrant and refugees to Canada and other non-endemic countries. Few migrants from endemic areas are currently screened prior to arrival, and plans to expand refugee screening will still leave many non-refugee migrants at risk of developing malaria after arrival in Canada. Awareness must be raised among Canadian health care providers to suspect the diagnosis, order the appropriate tests, and treat cases appropriately to prevent morbidity and mortality. PCR is the best diagnostic screening tool, but lack of availability and high cost, make it impractical at present. RDTs have the most utility, particularly considering the limitations of thick and thin smears in real world applications. Treatment is justified due to reported transformation to symptomatic malaria and risk of adverse outcomes, including death.

Canada requires better malaria surveillance, particularly related to malaria cases in migrant populations. More research is needed on the potential utility of PCR testing, including follow-up on studies to determine the risk of development of symptomatic malaria.

Key points

- Do not routinely screen, but be vigilant for symptoms of malaria.

- Migrants that have resided or travelled in malaria endemic areas are vulnerable to acute malaria, particularly within the first 3 months of arrival.
- Malaria symptoms (malaise, myalgia, headache, fever) are non-specific and may not be readily recognized as symptoms of malaria by primary care practitioners. Delays in the diagnosis and treatment of *P. falciparum* may lead to severe disease and even death.
- Canada requires improved malaria surveillance, as well as more research related to the utility of screening immigrants and refugees.

Box 2: Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence (www.gradeworkinggroup.org)

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and could change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

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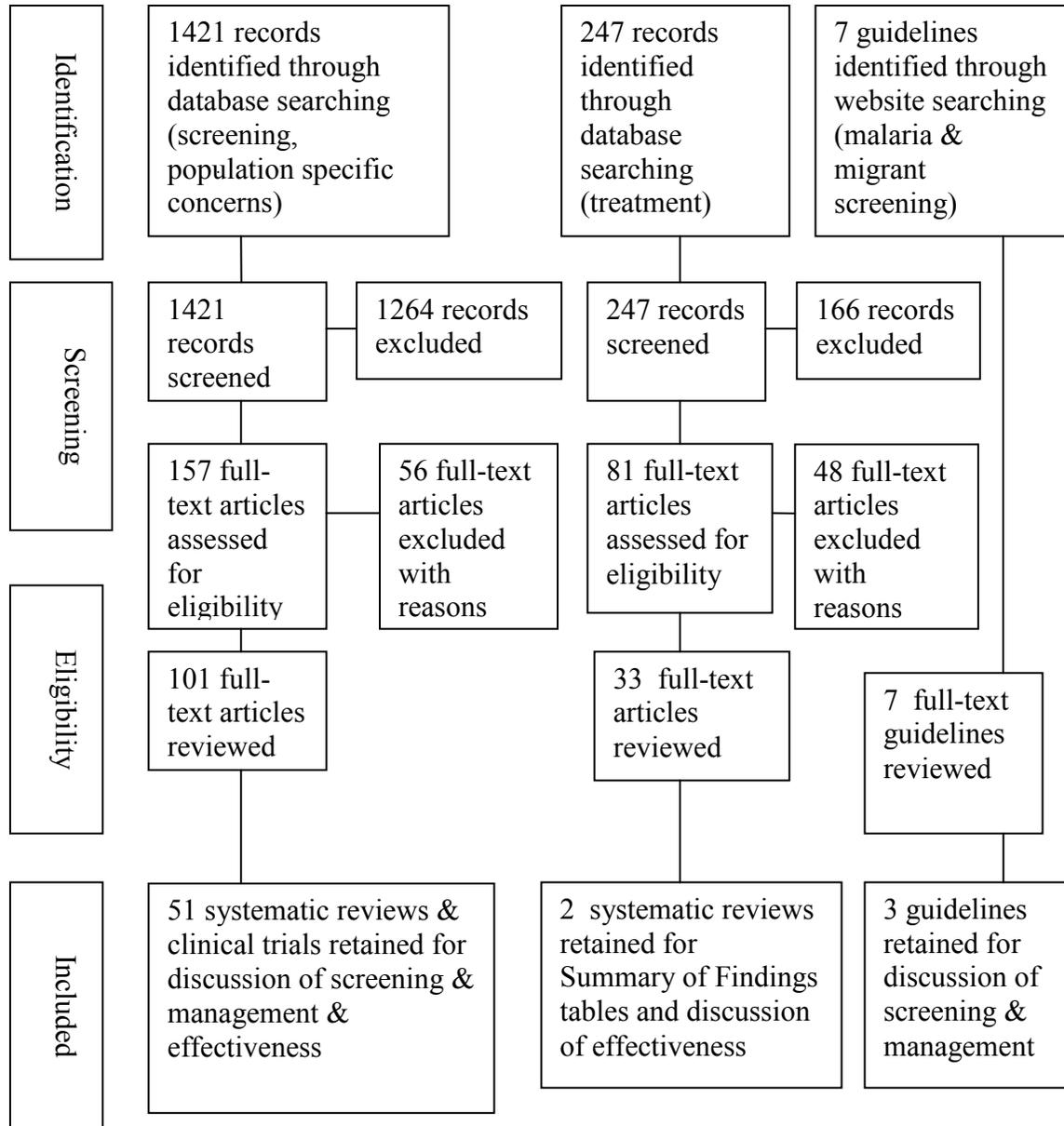
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Clinical preventive guidelines for newly arrived immigrants and refugees

This document provides the review details for the CMAJ CCIRH Malaria paper. The series was developed by the Canadian Collaboration for Immigrant and Refugee Health and published at www.cmaj.ca.

Appendix 1: Figure 2



Appendix 2: Malaria Evidence Based Clinician Summary Table

Do not routinely screen for malaria.

Be alert for symptomatic malaria in febrile migrants who have travelled to or resided in malaria endemic regions in the previous 3 months, particularly in those from sub-Saharan African and perform timely diagnostic inquiry and testing (RDT and thick and thin malaria smear).

Prevalence: Published reports of malaria screening protocols in new migrants have indicated variable prevalence of malaria, ranging from 6.8-64% in African migrants, whom are mostly refugees. The prevalence is much lower from other malaria endemic areas.

Burden: The burden of symptomatic malaria in Canadian migrants is difficult to ascertain. Of malaria cases in Canada requiring parenteral therapy (June 2001-January 2010) 20.6% (31/150) occurred in new migrants; 64.5% (20/31) were migrant children, compared to 26.7% (40/150) of malaria cases in children overall.

Access to Care: Many new migrants to Canada are unfamiliar with the health care system. As well, they may be faced with health practitioners unfamiliar with malaria diagnosis and management. These factors may delay detection and treatment, therefore increasing the risk of severe malaria disease.

Screening Test: Microscopic diagnosis with thick and thin blood smears have traditionally been the gold standard to diagnose malaria and the level of parasitemia. Rapid diagnostic tests (RDTs) detect *P. falciparum* antigens from lysed parasite infected red blood cells, providing results within 5-20 minutes. These tests have the advantage of portability and ease of use.

Treatment for *P. falciparum* malaria: The World Health Organization recommends artemisinin combination therapy, such as CoArtem[®], as first line treatment for *P. falciparum* malaria, however, these drugs are not licensed or available in Canada, where atovaquone proguanil (Malarone[®]) or quinine plus doxycycline (clindamycin in pregnancy or under the age of 8 years) are recommended. Diagnosis and management for symptomatic individuals should be as per the Canadian malaria guidelines.

Special Considerations:

- Migrants that have resided or travelled in malaria endemic areas are vulnerable to acute malaria, particularly within the first 3 months of arrival.
- Malaria symptoms (malaise, myalgia, headache, fever) are non-specific and may not be readily recognized as symptoms of malaria by primary care practitioners. Delays in the diagnosis and treatment of *P. falciparum* may lead to severe disease and even death.
- Canada requires improved malaria surveillance, as well as more research related to the utility of screening immigrants and refugees.