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The Epidemiology of Imported Malaria and Transfusion Policy in 5 Nonendemic Countries

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ABSTRACT

Addressing risk of imported malaria is complicated by 5 human species of *Plasmodium*, semi-immunity in donors with long-term exposure, increasing travel and immigration, changing risk in endemic areas, and limitations of screening assays. To gain insight into policy formulation, we have compiled epidemiologic data from 5 countries with different policies involving either deferral (the United States and Canada) or selective testing (France, England, and Australia). The greatest risk is from semi-immune former residents of endemic areas, but the greatest impact on sufficiency (donor loss) is from low-risk short-term travel. France and the UK have the highest rates of travel to Africa where most malaria cases originate. The UK has substantial travel to the Indian subcontinent where *Plasmodium vivax* cases are more common, and Australia, to Southeast Asia and Papua New Guinea. In the United States and Canada, malaria risk travel is more often to lower risk areas such as Mexico and the Caribbean. Each country has imported cases, predominantly *Plasmodium falciparum* and *P. vivax*, although data are incomplete. Transfusion-transmitted malaria has been rare over the last 10 years, generally involving *P. falciparum*, but there were 2 US cases of *Plasmodium malariae*. Uncertainty due to limitations of epidemiologic data and reliance on donors' answers underpins much of the complexity of policy formulation. Variability in policies between countries reflects not only epidemiologic differences but also operational considerations, donor demographics, regulatory approaches, and public pressure to react to rare transfusion-transmitted malaria cases. Testing reduces the operational impact of addressing the very small risk from travelers and offers improvement over deferral by testing all former residents of endemic areas. Notwithstanding current international regulatory requirements, policies have "evolved" through a series of additions and revisions as concerns and issues arose, with resultant variability in donor selection criteria.

Contents

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International travel and migration from developing to developed countries have become common place, with potential exposure to tropical diseases [1,2], some of which can be transmitted by blood transfusion. Worldwide, there are approximately 207 million acute cases of malaria per year, more than 80% of which occur in Africa [3]. Malaria is characterized by cyclic fever due to *Plasmodium* parasites. There are 5 species that infect humans. The most lethal, *Plasmodium falciparum*, accounts for approximately 90% of cases especially in sub-Saharan Africa. Most other cases involve *Plasmodium vivax*, found in many of the same areas as well as more temperate regions [4]. *Plasmodium ovale* and *Plasmodium malariae* are rare but are reported in many of the same areas [5,6]. A fifth species, *Plasmodium knowlesi*, is primarily found in macaques but has infected a small number of people in Asia [7]. The life cycle of *Plasmodium* species requires both mammalian (human) hosts and mosquito vectors. During a blood meal, infected female anophelene mosquitos inoculate humans with the parasites, which mature in the liver, multiply in many cycles of red blood cell invasion and infection before some blood stage parasites differentiate to finally yield circulating sexual forms that are infective for the mosquito and so complete the cycle.

In nonendemic countries, policies to address imported malaria risk are an important part of blood safety. Risk from transfusion may be addressed by deferring donors for long enough post-travel to either develop symptoms or resolve the infection, or by testing at-risk donors after a shorter deferral period [8]. The first country to implement selective testing was France in 1986 [9], followed by England, initially in 1997 for a short period and then permanently in 2001 [10] and Australia in 2005 [11] as well as several other countries. In Canada and the United States, at-risk donors are deferred for varying periods of time depending upon perceived levels of risk [12-15].

Decisions about malaria risk policy are complex and consider a range of factors including the epidemiology of the parasite and ensuing infection, donor demographics, sufficiency of the blood supply, acceptability of assays, regulatory environment, ability to implement a strategy, and potential benefits of change. Individual countries have described their experience with selective testing [9-11] and deferral [12-15], but no publications compare these factors in countries with testing vs deferral strategies. We have compiled data from both publicly available and internal sources to compare the background epidemiology of imported malaria and the specific risk reduction strategies in 3 countries that have selective testing (France, England, and Australia) and 2 countries that rely on donor deferral (United states and Canada) to gain further insight into policy for travel related infections.

Methods

Travel and Country of Birth Data

Visits to malaria-endemic countries in 2011 were extracted from the World Tourism Organization (WTO) tables [16]. Most countries report data to the WTO with some exceptions, notably Ivory Coast and Kenya. Countries traveled to were classified as malaria endemic or nonendemic based on the Centers for Disease Control (CDC) Yellow Book [17], then grouped into regions. The number of visits was divided by the number of residents (eg, the number of visits to Africa from France divided by the population of France) [18]. Visits per 10 000 residents were plotted in bar graphs for each of the 5 countries. The country of birth of residents of France, the UK, Australia, Canada and the United States were obtained from national census Web sites [19-23], classified and grouped similarly, and expressed as number per 10 000 residents.

General Population Malaria Cases

The number of imported cases, species, and country of origin reported to public health departments were obtained from national reports [24-36]. For Canada, the number of cases was provided by the Public Health Agency of Canada (Personal Communication, H. Zheng, Public Health Agency of Canada—July 18, 2012); species and country of origin, from the Québec Department of Public Health (province of Québec only) and the City or Toronto (country of origin for Toronto, ON, cases) [36]. Data concerning transfusion transmitted cases in the past 12 years were obtained from the CDC Malaria Reports [24-32], from published reports for England [37] and France [33,38], and from the investigators.

Testing Data

France, England, and Australia test for malaria antibodies using the Lab 21 Malaria Total Antibody EIA (Trinity Biotech [UK] Ltd, Kentford, Suffolk, UK) [39]. Supplemental testing on samples identified as antibody repeat reactive is primarily for donor management and counseling purposes. In France, a *P. falciparum* indirect fluorescent antibody test (IFAT) is used. In England, 2 additional immunoassays are used (Pan Malaria Antibody Celisa; Cellabs, Brookvale, Australia and Malaria Ab; Dia.Pro, Milan, Italy) together with an in-house *P. falciparum* IFAT. Donors with serological reactivity in any of the confirmatory assays are tested for malaria DNA using an in-house reverse transcription polymerase chain reaction. In Australia, an immunochromatographic assay for antigens is used (BinaxNOW ICT malaria pf/pv test; Binax Inc, Scarborough, ME) and a malarial PCR assay (artus Malaria PCR kit CE; Qiagen GmbH, Hilden, Germany).

Transfusion Safety Policies

Testing

Testing approaches have been previously reviewed [40,41]. In brief, direct parasitic and antigen detection methods lack the required sensitivity to reliably identify semi-immune individuals who characteristically have very low parasite loads. The IFAT was for many years considered the "gold standard," but newer EIA-based methods such as the Lab 21 assay using recombinant antigens lend themselves to high-throughput systems with similar if not better sensitivity, at least for *P. falciparum* and *P. vivax* [10,42-44]. The Lab 21 assay is prepared from *P. falciparum* and *P. vivax* recombinant antigens and detects other species via cross-reactivity, albeit with lower sensitivity [39]. In France, an IFAT was implemented in 1986 [9] switching to the Lab 21 assay in 2012. In England, selective antibody testing commenced briefly in 1997 using a microplate