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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

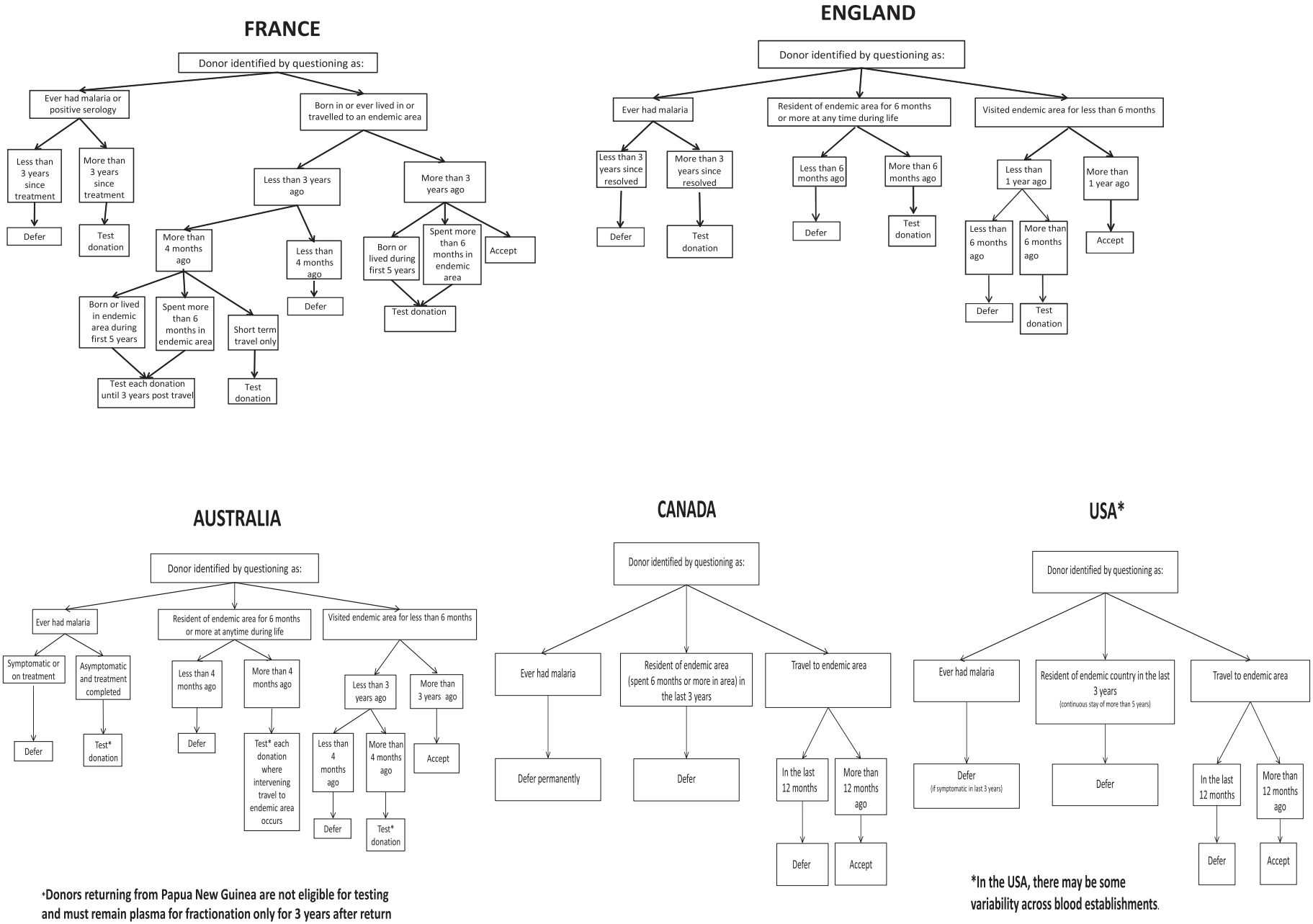

Fig 1. Algorithms for donor selection for testing for *Plasmodium* species antibodies in France, the UK, and Australia and for deferral in Canada and the United States.

immunoassay and, after stopping later that year, recommenced in 2001 with the Lab 21 assay as well as an IFAT. The IFAT was dropped in 2003. In Australia, selective testing with the Lab 21 assay started in 2005.

Donor Selection Criteria

In Australia and England, a single national blood supplier is responsible for blood collection. In France, there are 2 suppliers (the Etablissement Francais du Sang (EFS) collects >99% of units), which have the same policy. In Canada and the United States, there can be some variation in policy with different suppliers.

These countries' policies have a number of features in common (see Fig 1). All rely on screening questions to identify at-risk donors, have deferral periods for risk travel (shorter with selective testing), a more stringent policy for residency than short-term travel, and donors can donate plasma for fractionation immediately (in Australia) or after an initial deferral period (6 months in England and the United States, 4 months in France, rarely done in Canada for operational reasons). For a detailed review of policies in other countries, see Reesink et al [8].

The greatest divergence between policies is testing vs not testing. Countries with testing policies test former residents of endemic areas at least once no matter how long since they immigrated, whereas countries relying on deferral presume any infections will resolve within 3 years. The criteria differ in a variety of other ways such as the definition of a former resident of an endemic country. In England, donors are eligible for testing after a minimum of 6 months deferral period after leaving the risk country but a 4-month deferral period in France and Australia. In England, short-term travel is defined as within the last 12 months, whereas in France and Australia within the last 3 years. In France, former residents of endemic areas are tested on each donation until 3 years have passed since last travel, whereas in England and Australia, the first donation is tested no matter how long since last returning from travel and only repeated after subsequent travel. Donors with a history of malaria are tested in France, England, and Australia, permanently deferred in Canada, and deferred for 3 years in the United States. In Australia, donors with travel to Papua New Guinea are not eligible for selective testing and are restricted to plasma for fractionation for 3 years. Indeed, none of the countries in this report have identical policies.

Pathophysiologic Basis for Policy

Strategies aim to delay donation until parasitemia is resolved (deferral strategies) or antibodies can be detected (testing strategies). As the clinical manifestations vary by *Plasmodium* species and immune status of the host, effectiveness of these strategies depends on the probability of a donor infection, the likelihood of infection with particular species, and likelihood of semi-immunity.

Transfusion policy considers the duration before symptoms appear and/or infection resolves, and for selective testing, also the duration before antibodies are detectable. *P. vivax* and *P. ovale* infections may be milder and can relapse for 6 to 11 months (occasionally longer) posing a small risk of asymptomatic infection after travel. *P. malariae*, also milder, usually resolves within a few months but may last several years in people without prior exposure [6,45]. The incubation period is as little as 6 days for *P. falciparum*, about 2 weeks for *P. vivax* and *P. ovale* and up to 2 months for *P. malariae* [6,7]. Travelers from nonendemic countries generally have no prior exposure and will nearly always develop symptoms; thus, this risk is largely captured by a short deferral period and antibodies are usually detectable within weeks postinfection.

There is no clear consensus on the minimum testing embargo period with selective testing, but it should comfortably exceed the antibody window period of 7 to 14 days. In France where community cases are predominantly *P. falciparum*, a 4-month period as recommended by the Council of Europe (CoE) is supported by identification of nearly all infections within this time. Australia is mandated to CoE guidelines and therefore applies the 4-month period. In England, 6 months is applied as advised by their expert standing committee.

The predominant transfusion risk is from former residents of endemic areas as they can develop semi-immunity with repeated exposure and can harbor asymptomatic infection. Once living in a nonendemic area, these individuals usually resolve their infection within 2 (*P. falciparum*) to 3 years (*P. vivax* or *P. ovale*), although *P. malariae* infection can persist indefinitely [6] and the situation for *P. knowlesi* is currently unknown. Importantly, infection from all species can persist well beyond the norm [7,46].

Countries may be challenged with all species, but malaria is approached as a single disease for operational reasons; thus, parasitemic donations may occur from time to time with deferral. Progressively stringent deferral policies for travel, residency, and history of malaria are consistent with the pathophysiology of malaria. The time frames of 1 year, 3 years, and life are more than enough for most infections but will miss a significant proportion of persistent infections in semi-immune donors and very rarely travelers [45]. Testing strategies are also very conservative in ensuring that antibodies have ample time to develop, and most infections would be symptomatic in the deferral/component restriction times allowed. Unlike deferral, testing strategies can potentially identify all infections by deliberately having no time limit for testing former residents of endemic countries, limited only by the ability to identify the risk donors and the sensitivity of the assay used.

Surveillance Data

Travel and Country of Birth Data

Figure 2 shows the number of visits per 10000 residents to regions of the world where malaria is endemic. France and the UK have similarly high rates of travel to Africa where most malaria cases originate (primarily *P. falciparum*). Only Australians have any substantial travel to Oceania (also higher risk, both *P. falciparum* and *P. vivax*), primarily Papua New Guinea. However, travel within regions varies. For example, 42% of UK residents' Africa travel was to South Africa, whereas the most common destinations for people living in France were Senegal and Madagascar, which together accounted for 35% among malaria-endemic countries in Africa. Table 1 shows some similarities in trend for the number of people born in malaria-endemic countries per 10000 residents in each country.

Imported Cases

Figure 3 shows reported cases of malaria per million residents with the highest rate in France, somewhat lower in the UK and Australia and lowest in Canada and the United States. Table 2 shows the region of origin/residence (when known). Malaria was mainly acquired in Africa, although for Australians sometimes in Papua New Guinea (Oceania). Figure 4 shows the breakdown of imported malaria cases by species (when known).

Synthesis of Surveillance Data

A key strength of the available data is that international malaria surveillance is a World Health Organization priority, and data collection is coordinated from most endemic countries. However, for transfusion policy, the data have a number of limitations. First, in some countries, the focus of surveillance is on *P. falciparum* and to some extent *P. vivax*, whereas other species are often not reported. Although these are the most prevalent species and responsible for most severe illness, transfusion policies strive to address all risk, including from rare species, which may have severe consequences for immunocompromised recipients. Second, reporting is frequently incomplete, and fever in developing countries reported as malaria often lacks laboratory confirmation and speciation [3]. Third, some degree of underreporting of imported cases exists due to failure to report, misdiagnosis, and patients not

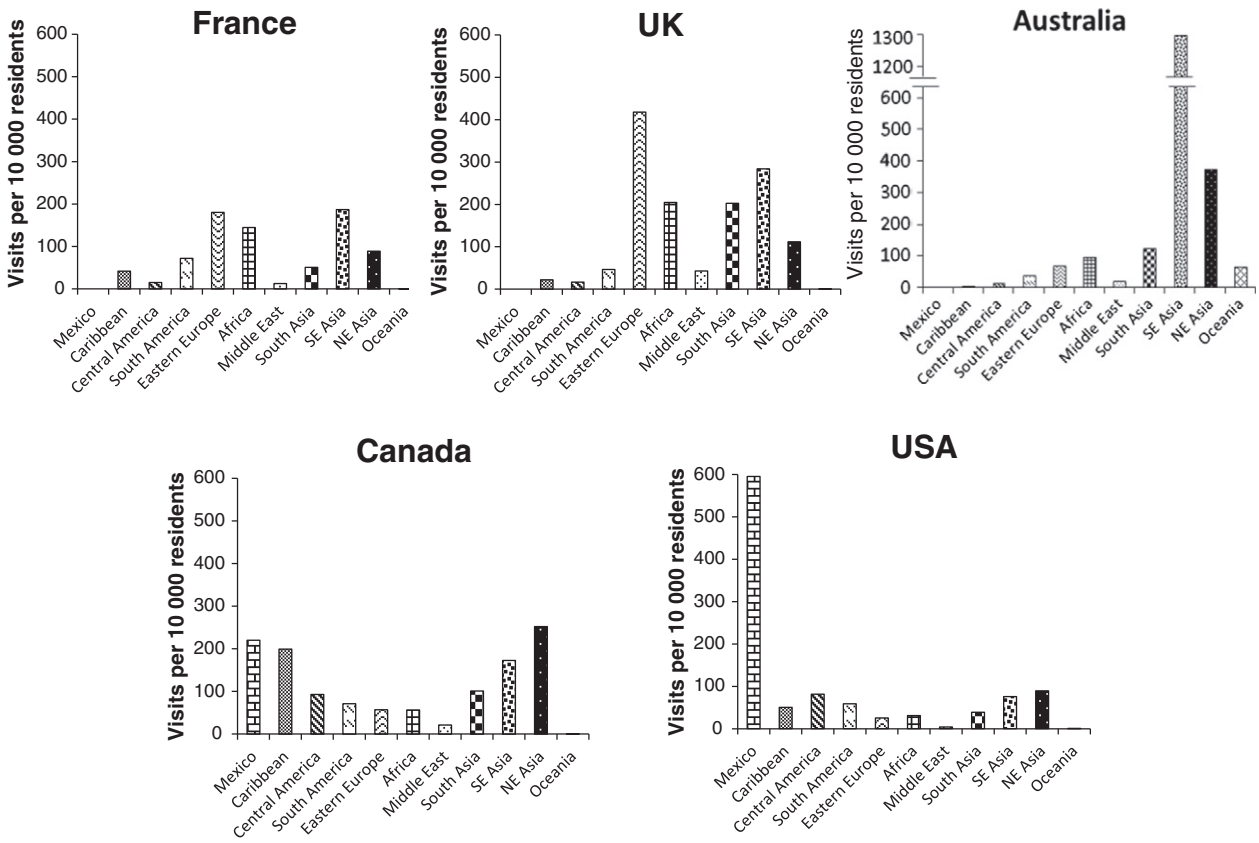

Fig 2. Number of visits to malaria-risk regions per 10000 residents in France, the UK, Australia, Canada, and the United States. Travel data from WTO (2011) [16] expressed per 10000 residents [18].

seeking treatment due to mild symptoms or social reasons. For example, in France, the true number of cases is estimated to be approximately double the number reported [33]. In addition, there is a need for mandatory reporting of cases of imported malaria and malaria as a transfusion transmitted infection (TTI) by country of origin of the infection and *Plasmodium* species as these details are often not available.

In spite of their imperfections, the data are informative and several key points are clear. By far, the highest incidence of malaria is in sub-Saharan Africa, although risk varies within Africa depending on the country traveled to, destinations within the country, seasons of travel, living conditions, and precautions taken; consequently, the rate of visits will not translate neatly into risk. Nevertheless, there tend to be more imported malaria cases in countries with more visits to high-incidence parts of the world. All countries have some imported cases due to *P. falciparum* and *P. vivax*, and a few due to *P. ovale* and *P. malariae*; therefore, there is some risk due to at least 4 species in each of the 5 countries. The larger number of community cases in France as well as the frequent occurrence of transfusion-transmitted malaria (TTM) before testing suggests higher risk consistent with higher travel and immigration from Western Africa. *P. vivax* may present more risk in England

Table 1
Number of people born in malaria-risk regions per 10000 residents of France, the UK, Australia, Canada, and the United States

	Country of residence				
Region of origin/residence	France	UK	Australia	Canada	United States
Africa					
North Africa	2.1	<0.1	0.02	0.1	0.1
West Central Africa	52.1	52.1	7.7	25.3	16.9
East Central Africa	15.8	63.8	27.0	45.2	15.1
Southern Africa	11.4	63.4	82.0	18.0	3.8
Asia					
North East Asia	15.5	28.6	173.4	191.7	86.9
South East Asia	31.5	42.6	286.5	208.2	118.5
South Asia	14.3	253.5	205.7	260.0	76.3
Latin America and Caribbean					
Mexico	1.4	1.7	1.4	20.3	379.4
Caribbean	10.6	1.0	0.2	26.2	48.6
Central America	0.7	1.0	5.1	23.9	96.6
South America	19.4	21.4	23.4	75.5	83.3
Oceania	<0.1	0.5	13.1	0.1	<0.1
Middle East	4.9	40.5	53.9	65.9	21.3
Eastern Europe	40.4	13.9	15.5	10.9	6.0

Data obtained from national census Web sites [19-23] for 2011. For the United States, missing data were estimated from previous years.

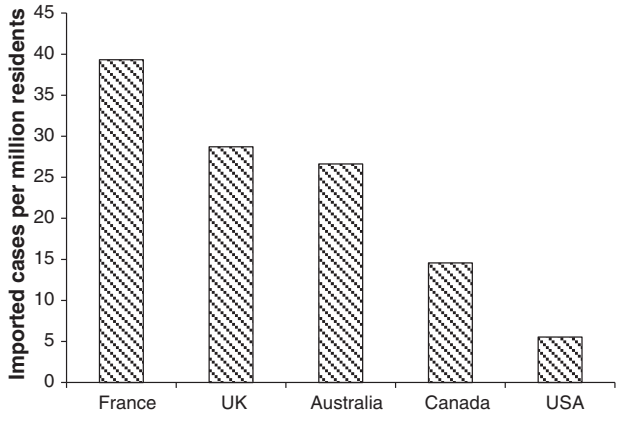

Fig 3. Reported cases of imported malaria per 1 million residents in France, the UK, Australia, Canada, and the United States. Year of data: United States, France, and UK: Year 2011 [32,33,35]; Australia: July 1, 2009, to June 30, 2010 [34]; Canada: personal communication from the Public Health Agency of Canada.

Table 2
Number of reported community cases of malaria and rate per 100000 residents by region of acquisition

Region of acquisition	Country of residence									
	France		UK		Australia		Canada		United States	
	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate
Africa	1745	2.757	1090	1.738	n/a		138	0.400	1144	0.367
Central	643	1.016	70	0.112	n/a		55	0.159	101	0.032
East	14	0.022	134	0.214	n/a		n/a		213	0.068
North	10	0.016	n/a		n/a		n/a		32	0.010
Southern	60	0.095	55	0.088	n/a		9	0.026	3	0.001
West	1,011	1.597	811	1.293	n/a		55	0.159	746	0.239
Unspecified	7	0.011	20	0.032	n/a		19	0.055	49	0.016
Asia	48	0.076	351	0.560	58	0.256	34	0.099	363	0.116
Asia (other)	11	0.017	8	0.013	n/a		1	0.003	32	0.010
Asia (South)	37	0.058	n/a		58	0.256	33	0.096	329	0.106
Asia, unspecified	n/a		343	0.547	n/a		n/a		2	0.001
Latin America and Caribbean	95	0.150	4	0.006	n/a		22	0.064	140	0.045
Middle East	n/a		1	0.002	n/a		1	0.003	1	0.000
Oceania	n/a		2	0.003	115	0.507	n/a		7	0.002
Other country	n/a		n/a		168	0.740	n/a		n/a	
Unknown	n/a		229	0.365	73	0.322	301	0.872	265	0.085
Total	1888	2.983	1677	2.675	414	1.824	496	1.438	1920	0.616

Year of data: United States, France, and UK: Year 2011 [32,33,35]; Australia: July 1, 2010, to June 30, 2011 [34]; Canada does not produce a national report per se, region of acquisition data are presented for the province of Québec and the city of Toronto [36] and the national total from the Public Health Agency of Canada.

and Australia, and *P. vivax* relevant travel and immigration are from different parts of the world (the India subcontinent and Papua New Guinea). Genetic variability in relapsing strains is possible [46].

Imported cases are proportionately more frequent among recent immigrants, whereas most short-term travel is to low-risk areas associated with fewer imported cases. Some common travel such as to Mexico/Central America from Canada and the United States and to Indonesia from Australia is predominantly to coastal resorts and cities with virtually no risk, also shown in US risk modeling [47,48]. The greatest operational impact is from deferral of these low-risk travelers, whereas in many, but not all countries, the former residents of endemic countries comprise comparatively few donors, but the bulk of the risk.

Travel and surveillance data are mainly collected to support public health policy generally addressing risk in people already exposed to a pathogen. In this context, policies that partially address risk are seen as beneficial. However, safety of blood products is guided by pharmaceutical principles in which the imperative is to avoid doing harm in people who otherwise have no exposure. With public expectation of zero risk, partially addressing risk is seen as doing harm. Transfusion policy requires quite stringent data for which existing data fall somewhat short. Because of the inherent uncertainty of the true number of imported cases, the true distribution of species, and what constitutes risk travel, considerable judgment is required, often evoking some aspect of the Precautionary Principle [49].

Transfusion-Transmitted Infection Cases

Table 3 shows all documented transfusion-transmitted cases of malaria since 2002. There were 7 cases in the United States, 3 in France, 1 in England, and none in Australia or Canada. In all cases, the donor had lived in Africa, but most did not have recent travel history. Four donors from the United States and 1 in France reported a history of malaria. All transfusion-transmitted cases involved *P. falciparum*, except 2 US cases that involved *P. malariae*. All donors except the most recent one in

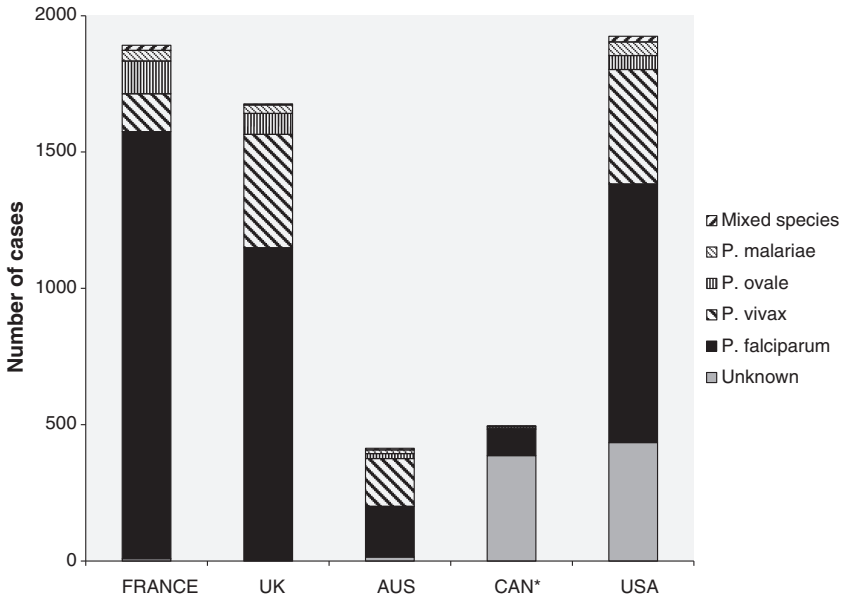

Fig 4. Reported community cases of malaria by species.

Table 3
Documented transfusion transmitted infections from 2002 to 2013

	Year	Species	Details
France			
West Africa	2012	*P. falciparum*	Emigrated 2 years ago History of malaria 13-15 years ago Tested negative on Lab 21
West Africa	2005	*P. falciparum*	Emigrated
West Africa	2002	*P. falciparum*	Emigrated 4 years ago
UK			
West Africa	2003	*P. falciparum*	Emigrated 15 years ago Last visited Africa 7 years ago
United States			
West Africa	2011	*P. malariae*	Emigrated 16 years ago No history of malaria No recent travel
West Africa	2010	*P. falciparum*	Lived in West Africa for 17 years No travel in last 4 years
West Africa	2009	*P. falciparum*	Emigrated 5 years ago Treated for malaria at age 12
West Africa	2009	*P. falciparum*	Emigrated to the United States as a child Presumed malaria as a child Recent travel 13-17 months ago
West Africa	2007	*P. falciparum*	Emigrated 5 years ago Presumed malaria 19 years ago
West Africa	2003	*P. falciparum*	Emigrated 1 year ago Treated for malaria 2 years ago
West Africa	2002	*P. malariae*	Emigrated 8 years ago

There were no transfusion-transmitted cases in Australia or Canada, 2002 to 2013. Data obtained from national reports [24-33,35].

France could possibly have been identified and their donations removed from inventory if selective testing had been applied.

In France, there were on average 3 to 5 TTM cases per year before implementation of selective testing, after which they were rare (1 in 1990, 1 in 1993, and 1 in 1998 [possible]) [9] due to testing and declining imported cases in travelers [33]. The case in 2002 involved a 19-year-old female donor from West Africa who lived in France for more than 4 years without symptoms unaware of a history of malaria. Her donation was accepted without testing in accordance with the policy at the time. The recipient developed malaria symptoms and died, and the donor was subsequently found to have low-level parasitemia (*P. falciparum*) and detectable antibodies. This case highlights the risk from early childhood malaria, which donors may not be aware of as adults. As a result of this case and survey data suggesting that donors had difficulty answering screening questions, the donor criteria in France were modified to stipulate being born in or living in an endemic country before the age of 5 years. They also began testing all former residents of endemic countries no matter how long ago (previously testing was not required after 3 years since last exposure) and testing for 3 years after last travel [9]. For the 2005 case, the donor met the criteria for donation without testing, which prompted revision of the questions to close a small loop hole. For both cases, the weak link was identification of a risk donor, not test failure. However, in 2012, a donor from West Africa who was negative for antibodies with the Lab 21 assay was implicated in transfusion transmission of *P. falciparum*. This donor was subsequently found to be positive on the Diamed assay and IFAT (1/40). To date, this is the only case of TTM attributed to failure of the Lab 21 assay [38].

In England, there have been 4 cases plus the 2003 case in Table 3 (5 in total) in the past 27 years [37]. All implicated donors were former residents of Africa, and the donor criteria at the time were correctly applied. The most recent case in 2003 involved a 38-year-old female donor from West Africa who emigrated 16 years earlier and last visited Africa 7 years before her donation. She was eligible to donate according to the criteria at the time. Similar to the 2002 case in France, this was a semi-immune donor with very long duration *P. falciparum* parasitemia. The criteria were then revised to include testing of the first donation from all individuals born in an endemic country, regardless of how long since they emigrated. In addition, CoE guidelines were revised to extend the definition of a "resident" to "6 months cumulative residency in a malaria endemic area at any time of life" from the previous definition of "spent a cumulative period of 6 months or more within the in the last 3 years in an endemic area," which was implemented in France, England, and Australia.

In Australia, 4 cases of TTM were reported in 1960 plus the most recent case in 1991 [50] involving a donor infected with *P. falciparum* who had lived in Papua New Guinea. Since testing was implemented in 2005, no TTM cases have been reported; however, 2 "near misses" [51] involving donors who visited Papua New Guinea are notable. One donated about 4 months posttravel; the other made 4 donations between 5 and 13 months posttravel. Both had complied fully with prophylaxis and were diagnosed with relapsing *P. vivax* infections 1 to 2 months after their last donation, which had tested malaria antibody negative. However, no blood components from these blood donations were transfused, and given their antibody negative status and that symptoms occurred at least 20 days postdonation, the donors were likely not parasitemic at the time. Both donors had traveled to Papua New Guinea where relapse associated with a particular strain of *P. vivax* is more frequent. These cases demonstrated a previously unrecognized limitation of antibody screening, specifically that the potential for relapse cannot be predicted by a negative antibody test. It was considered that such cases were extremely rare, although a similar case was subsequently reported in England. As a precaution in 2009, the criteria in Australia were changed to exclude testing donors from Papua New Guinea, and they are restricted to donating plasma for fractionation only for 3 years (and reassessed thereafter). Reassuringly, monitoring since the change in criteria has failed to identify any further such cases.

In Canada, 3 TTM cases have been reported (in 1994, 1995, and 1997, all *P. falciparum*). The first 2 donors had a history of malaria, and as a result in 1995, the criteria were changed to permanently defer donors with a history of malaria. The third case involved a donor from Africa who met the criteria to donate [52]. In the United States, TTM cases have decreased since 1963. In the 1970s, many cases were attributed to military personnel returning from Vietnam. In 1994, the duration of deferral for travel to an endemic area increased from 6 months to 1 year. More recently, most cases have involved donors who emigrated from Africa [53]. Concomitantly, the proportion of cases related to *P. falciparum* increased, and to *P. vivax* decreased. *P. ovale* cases were

always rare, but 2 of 14 cases from 1990 to 1999 were attributable to *P. malariae* (plus the 2 recent cases shown in Table 3). In the analysis by Mungai et al [53], donors with *P. malariae* had 3 to 44 years from their last possible exposure (median, 8 years), which would not be addressed with a period deferral.

Although the direct impact of public pressure to achieve very low risk is difficult to assess, public confidence is integral to a transfusion service's mandate, and public scrutiny is constant. Transfusion-transmitted malaria has serious implications for the recipient, and its occurrence impacts negatively on public confidence. Single events provide limited grounds to modify policy as they are not necessarily predictive of future events and may never be seen again even without any revision of the policy. Transfusion-transmitted malaria cases have prompted modification of policies, often confined to the country in which they occurred, and could be viewed as a reflection of historical entrenchment of transfusion policy in which patches are applied rather than full revision.

Operational Feasibility

Table 4 shows the numbers of donations tested or deferrals in 2012. Although all policies require deferral periods for at-risk donors, with selective testing, the percentage of donors deferred is less (and shorter duration), but the percentage of donations for which the policy applies is similar or greater than for the United States or Canada. The highest percentage of donations tested was in Australia, and the lowest, in England. Among donations selected for testing, the repeat reactive rate ranged from 1.8% to 3.7% ($P < .001$). In France and England, approximately one quarter of repeat reactive donations were also positive with supplemental antibody testing. In England, 6 donations were positive for *Plasmodium* antigen in 2012, zero in Australia (antigen supplemental testing not routinely done in France). In England from 2010 to 2013, 14 (0.7%) of 1955 donations with reference serological activity were confirmed malarial DNA positive, all with residency risk and considered to be semi-immune [54]. In a US study of donors deferred for malaria risk, the Lab 21 EIA repeat reactive rate was 1.6%, but none were PCR positive [42]. Thus, very broad risk criteria identify most risk donors, and parasitemia is rare.

Table 4
Testing and deferral outcomes in 2012

Countries with testing policies			
	France	England	Australia
Whole blood donations	3053891	2043479	894359
No. of donations tested	184087 (6.0)[a]	36541 (1.8)[a]	120415 (13.5)[a]
No. of repeat reactive	3367 (1.8)[b]	1345 (3.7)[b]	2866 (2.3)[b]
No. of positive on supplementary antibody test	1051	453	–
No. of NAT positive	–	6	0
Countries with deferral policies			
	Canada	United States (estimate)[c]	
Whole blood collections	1161875	13643000	
No. of donors deferred			
Short-term travel	34648 (93.0)[d]	180245 (94.3)[d]	
Recent resident	1576 (4.2)[d]	10660 (5.6)[d]	
History of malaria	997 (2.9)[d]	260 (0.1)[d,e]	
Total	37221 (3.1)[f]	191165 (1.4)[f]	

[a] Percentage of donations tested.
[b] Percentage of donations tested that were repeat reactive.
[c] United States estimated from American Red Cross 2012 data.
[d] Percentage of malaria deferrals.
[e] Criteria at ARC were "malaria in past 3 years," elsewhere "malaria ever."
[f] Percentage of whole blood collections.

Operational feasibility balances safety benefits with the impact on sufficiency and practical constraints. Donor selection criteria that can be consistently implemented by screening staff result in broad definitions of risk and capture large numbers of donors. Donors sometimes fail to acknowledge risk, and a few at-risk donors will not be identified no matter how the questions are asked. Consequently, for both deferral and testing strategies, failure to identify at-risk donors is the main source of risk. It is also a reason for variability in policy between countries as each attempt to balance very inclusive criteria (dependent upon perceived risk in their donor population) with operational feasibility.

The 3 countries with the highest proportion of imported cases have implemented malaria antibody testing. In France, this was primarily to reduce risk. For England and Australia, safety could be achieved with deferral or restriction to plasma for fractionation. Selective testing was implemented to reduce the duration of deferral/component restriction of safe donors [43,11]. In England with broad ethnic diversity, deferral placed very real restrictions upon collections. Testing leads to significantly improved efficiency of "salvaged" fresh blood. For example, in Australia, more than 65000 red cell and 7000 platelet doses per annum were recovered due to early reinstatement of donors with negative antibody tests [11]. The availability of antibody assays suitable for high-throughput testing was an important consideration in Australia and would also be in the United States or Canada, should it be considered. In England, the availability of high-throughput testing was not essential initially, but it was once the system moved into the operational environment. In France, high-throughput testing was not available initially but became essential when the donor selection policy was broadened to include more testing of former residents of endemic areas. For most countries with developed transfusion services, donation screening has to be a fully automated process.

Regulatory Concerns

All 5 countries have published standards or guidelines, which address malaria risk. There are also regulatory requirements (the license to collect blood and produce blood products) consistent with the standards. The requirements of the regulator go beyond the standards to approval and monitoring of their application in a blood establishment. A regulatory or other body in each country must approve assays for donor/donation screening.

In Europe, the acceptability of selective malaria testing was influenced by the long history of successful risk reduction in France before development of CoE guidelines, which were then adopted by Australia. Selective testing in some form may become acceptable in the United States and Canada, but the Lab 21 assay is not being considered for licensure due to reliance on cross-reactivity to detect *P. ovale*, *P. malariae*, and *P. knowlesi* and sensitivity estimations based on small samples. All 5 countries have some risk from all 5 species, and to date, only 1 potential TTM case due to test failure has been observed. However, because of limitations of the data and rarity of infections, the data are insufficient to accurately quantify and compare the risk of *P. malariae*, *P. knowlesi*, and *P. ovale* across countries. Two recent *P. malariae* TTM cases in the United States show that the risk is likely low but not zero. No cases of TTM due to *P. knowlesi* have been reported. Different weighting of the importance of the ability to detect all 5 human *Plasmodium* species in the decision process reflects differing regulatory processes and criteria for acceptance as well as the inherent uncertainty of epidemiologic data. With deferral policy, there is the chance of a parasitemic donation beyond the deferral period; with selective testing, there is the chance that a parasitemic donation may be missed by the assay or too short a pretesting deferral period. Selective testing strategies offer risk mitigation beyond that of deferral by testing all former residents of endemic areas with the option to extend the posttravel period for which testing is done. However, all policies are still dependent

on the accuracy of the donor's answers to screening questions with some inevitable risk.

Conclusion

The uncertainty due to limitations of epidemiologic data and reliance on donor's answers underpins much of the complexity of policy formulation. Addressing malaria risk is further complicated by 5 species of *Plasmodium* with different pathophysiology and by semi-immunity in donors with long-term exposure, increasing travel and immigration, changing risk in endemic areas, limitations of screening assays, and rare events. In all 5 countries featured in this report, policies are based on the pathophysiology of malaria, further informed by lessons learned and information gained from cases of TTM. The considerable variability between countries reflects not only epidemiologic differences but also operational considerations, donor demographics, regulatory approaches, public pressure to react to rare TTM cases, and possibly variability in risk tolerance.

The greatest risk is from former residents of endemic areas, although most do not have active malaria. Conversely, the greatest impact on sufficiency (donor loss) is from very low-risk short-term travel. Although there are some differences in travel and the epidemiology of imported malaria between these 5 countries, it is not clear to what extent they necessitate different policies. Testing reduces the operational impact of addressing the very small risk from travelers with shorter deferral periods and offers significant 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. However, if policies were to be developed afresh, they would not necessarily be those which are currently in place. When countries reviewing their own policy examine the policies of others, they need to recognize and understand the substantive impact of historical context, country specific issues, and operational issues on policy development.

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