Published in final edited form as:

Transfusion. 2011 November ; 51(11): 2398–2410. doi:10.1111/j.1537-2995.2011.03158.x.

Deconstructing the Risk for Malaria in United States Donors Deferred for Travel to Mexico

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Abstract

Background—More than 66,000 blood donors are deferred annually in the U.S. due to travel to malaria-endemic areas of Mexico. Mexico accounts for the largest share of malaria travel deferrals, yet it has extremely low risk for malaria transmission throughout most of its national territory, suggesting a suboptimal balance between blood safety and availability. This study sought to determine whether donor deferral requirements might be relaxed for parts of Mexico without compromising blood safety.

Study Design and Methods—Travel destination was recorded from a representative sample of presenting blood donors deferred for malaria travel from six blood centers during 2006. We imputed to these donors reporting Mexican travel a risk for acquiring malaria equivalent to Mexican residents in the destination location, adjusted for length of stay. We extrapolated these results to the overall U.S. blood donor population.

Results—Risk for malaria in Mexico varies significantly across endemic areas and is greatest in areas infrequently visited by study donors. Over 70% of blood donor deferrals were triggered by travel to the state of Quintana Roo on the Yucatán Peninsula, an area of very low malaria transmission. Eliminating the travel deferral requirement for all areas except the state of Oaxaca might result in the recovery of almost 65,000 blood donors annually at risk of approximately one contaminated unit collected every 20 years.

Conclusion—Deferral requirements should be relaxed for presenting donors who travelled to areas within Mexico that confer exceptionally small risks for malaria, such as Quintana Roo.

Keywords

Plasmodium; malaria; blood donor; deferral; malaria travel; transfusion transmitted disease; Mexico

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The authors have no conflicts of interest or other financial involvement to declare.

Introduction

Transfusion-transmitted malaria (TTM) is a potentially lethal outcome of blood transfusion, but one which is uncommon in the United States. On average, the last two decades have seen less than one case of TTM per year, representing a rate of < 0.1 per 10^6 red cell transfusions.^{1,2,3} TTM prevention currently relies on exclusion of donors who might present risk for malaria infection. Based on requirements and recommendations of the FDA⁴ and the AABB (formerly the American Association of Blood Banks),⁵ the deferral period is three years for those who report a history of malaria infection or of prior residence in a malaria-endemic country as defined by the Centers for Disease Control and Prevention (CDC),⁶ whereas it is one year for donors with travel to parts of countries considered endemic for malaria by CDC.

The number of presenting or productive donors with non-zero risk for harboring malaria parasites is essentially unknown, as is the relative likelihood for infection across the different malaria deferral categories. However, empirical evidence in the U.S.^{1, 2, 7} and other countries^{8, 9, 10, 11} clearly implicates donors from Sub-Saharan Africa in cases of TTM over the last 3 decades. While many of these donors were improperly accepted due to an error during health history screening, others were rare biological outliers whose semi-immune status allowed for *Plasmodium* parasite carriage for several years. This occurred most often with *P. falciparum* and also with *P. malariae*, a more benign species known to remain undetected for decades.¹²

In contrast to those with long-term residence in Sub-Saharan Africa and a few other highly endemic areas, donors reporting routine travel to malarial areas appear to confer relatively low risk for transmitting malaria to recipients of blood products. In fact, over a 28- year period, only one donor out of 32 implicated in TTM cases was a native-born U.S. resident on routine travel.^{1,2,7} While denominator data that would allow for accurate risk comparisons across the different deferral categories are lacking, there can be no doubt that the one-year deferral period for short-term travelers has a significant impact on blood availability. A recent analysis by our consortium estimates that annual deferrals by U.S. blood centers might surpass 150,000,¹³ and unpublished data suggest that several times that many might self-defer.¹⁴

To assess the risk that donors who report a travel history requiring malaria deferral might actually be infected with malaria parasites, our prior study detailed the travel destinations of a representative sample of blood donors with malaria travel deferral.¹³ Using public data sources on imported malaria in the U.S.¹⁵⁻²⁰ and on numbers of travelers to different countries and regions,^{21,22} we developed region-specific risks for malaria infection that suggested a 1000-fold greater risk for travelers to Africa versus Mexico. Traveler risk to Mexico was estimated as roughly 1 in 800,000 for those who visited an area triggering malaria deferral. We concluded that these data supported the relaxation or elimination of the year-long deferral period for travel to Mexico, with a negligible marginal increase in risk balanced by the recovery of tens of thousands of donors annually.¹³

Given the large number of deferrals following travel to Mexico, and the long-term trends in malaria incidence there, this manuscript reports a follow-up analysis focusing only on this country. Mexico is a country of low and declining risk for malaria, one where the remaining areas of natural transmission are characterized as scattered foci in rural areas populated by indigenous inhabitants.²³ Though firm data are unavailable on how many U.S. tourists visit any given location within Mexico, U.S. malaria surveillance figures support the interpretation that most travelers visit areas with very low risk for malaria. For each year from 2000 to 2007, an average of ≈ 6 and a maximum of 11 U.S. residents have acquired

malaria in Mexico that was diagnosed following return to the U.S.,^{7,15-20,24} out of an average of roughly 20 million visitors annually with at least an overnight stay.²² Furthermore, a disproportionate share of these malaria cases occurred in Mexican citizens now residing in the U.S.,²⁵ so the risk for routine, U.S.-born travelers appears exquisitely low.

To develop risk estimates for malaria infection in blood donors that are independent of the travel destination within Mexico for overall U.S. travelers, this manuscript adopts an alternate method that derives donor risk from malaria risk figures for the local populations of the areas visited. Specifically, we recorded destination(s) of travel within Mexico for the same cohort of deferred donors described in the earlier analysis,¹³ and used malaria surveillance indicators developed by the Mexican Ministry of Health for the same areas during the same time frame as a measure of potential malaria risk faced by blood donors deferred for travel to Mexico. Because the Mexican morbidity data reflect risk for year-round residents, we adjust the donor risks for duration of exposure. To provide a basis for selective alterations to current deferral requirements for Mexico, we disaggregate the results by state, since distribution of risk across the country varies significantly.

Materials and Methods

Source of data on presenting US blood donors deferred for travel to malaria-endemic areas in Mexico

Six blood centers participating in the *Retrovirus Epidemiology Donor Study – II* (REDS-II) program sponsored by the National Heart, Lung and Blood Institute (NHLBI) provided data for this analysis. These centers represent geographically and demographically diverse populations and collectively account for > 8% of annual allogeneic blood collections in the U.S.³ The REDS-II blood centers include the Blood Centers of the Pacific (BCP), San Francisco, CA; Blood Centers of Wisconsin (BCW), Milwaukee, WI; Hoxworth Blood Center, University of Cincinnati (HOX), Cincinnati, OH; the Institute for Transfusion Medicine (ITxM), Pittsburgh, PA; the American Red Cross, New England Region (NEARC), Dedham, MA; and the American Red Cross, Southern Region (SARC), Douglasville, GA. Each center retrieved blood donation records from the first sixty donors deferred for malaria travel in either the even-numbered (BCW, ITxM, SARC) or odd-numbered months (BCP, HOX, NEARC) throughout 2006 to ensure that seasonal patterns in travel were captured. Data were recorded on donor demographics, date of presentation, dates of travel in malaria-endemic regions, and the destination country or countries with malaria risk for up to 5 countries. Countries were ranked by malaria risk,^{26,27} and specific locations triggering malaria deferral were recorded verbatim from the blood donation records for the two countries with highest risk for malaria. This analysis reports only on the subset of donors for whom Mexico either was the only country visited with malaria risk or was the country with the highest risk. Deferral records lacking the destination country or the date that deferral began were excluded from the analysis.

Estimate of annual deferrals of U.S. blood donors for malaria-risk travel to Mexico

The proportion of malaria travel deferrals that were allocated to Mexico for the six REDS-II centers was used to estimate the annual number of malaria travel deferrals associated with Mexico for U.S. donors overall. Annual data on allogeneic donations and malaria travel deferrals were recorded and summed across all centers, and each center's contribution to national estimates was weighted by its share of the collective REDS-II malaria travel deferrals. Based on their aggregate contribution of 8.07% of US allogeneic donations,³ the blood centers' estimates for malaria deferrals were multiplied by 12.4 to extrapolate to the US overall. These figures have been updated from the earlier manuscript¹³ to account for the

availability of U.S. donation data from 2006,³ which increases the projections of U.S. deferrals for malaria travel from 150,537 to 161,105. When a donor reported more than one trip with a visit to a malaria-endemic area, the most recent trip was chosen for analysis. When more than one geographic region within Mexico was visited, the donor's visit was allocated to the area of higher risk for malaria infection, based on Mexican public health data. Donor's travel destination was assigned to the smaller administrative unit possible between state- and county-level destinations. Donors for whom location within Mexico was not available were assumed to represent randomly missing data and were accounted for by proportional weighting for those donors who did report location, for each of the six blood centers.

Criteria for malaria travel deferral to different areas of Mexico

For U.S. travelers, risk for malaria infection is described by the Centers for Disease Control and Prevention on a country by country basis,⁶ and by FDA requirement this information is used as the basis on which donor acceptability is determined.⁴ For the time frame of this study—donor presentation during 2006 and donor travel during 2005-2006—the description of malaria risk in Mexico was as follows:

Risk in rural areas, including resorts in rural areas of the following states: Campeche, Chiapas, Guerrero, Michoacán, Nayarit, Oaxaca, Quintana Roo, Sinaloa, and Tabasco. In addition, risk exists in the state of Jalisco (in its mountainous northern area only). Risk also exists in an area between 24° N and 28° N latitude, and 106° W and 110° W longitude, which lies in parts of Sonora, Chihuahua, and Durango. No malaria risk exists along the United States-Mexico border. No malaria risk exists in the major resorts along the Pacific and Gulf coasts.⁶

The specific job aids or work instructions provided for health historians of each REDS-II blood center might have differed in detail during 2006, but the referent for each center would have been the foregoing text from CDC. Figure 1 shows a map of Mexico, with those states named in the above excerpt shaded in grey. Depending on the specificity of information provided by donors with travel to Mexico, as well as on the detail of information available in reference materials for health historians, travel to one of the shaded states during 2005-2006 might not have necessarily triggered a deferral. It would, however, at a minimum require consultation with support documentation to exclude travel to a malaria risk area in order for the donor to be judged acceptable to donate.

Estimated risk for malaria infection in U.S. travelers to different areas of Mexico

Population-adjusted risk measures for year-round Mexican residents at the state level are available from 8 endemic states which together account for 98.5% of reported cases in 2005.²⁹ County-level risk measures were derived from malaria case counts at the county level for 2005³⁰ and the 2005 census population figures for each county.³¹ State- and county-level risk measures for year-round Mexican residents were used as a proxy for potential malaria risk which U.S. residents might face during travel to the same areas, appropriately adjusted for duration of exposure. Donors eligible for inclusion in this study - those deferred during calendar year 2006- reported travel that occurred during both 2005 and 2006. Mexican surveillance data from 2005 only are used to develop risk estimates due to unavailability of 2006 county-level malaria surveillance data. To evaluate longitudinal trends in malaria incidence in Mexico, and to establish any significant changes in the amount or distribution of malaria subsequent to the period used for our study, we referenced several years of publicly available Mexican government surveillance data.³²

Duration of exposure was estimated by calculating donor reported dates for beginning and ending of exposure in risk areas. This measure was available for donors from 3 of the 6 blood centers, and it was not possible to distinguish donors who simply reported the duration of their entire trip versus the proportion who correctly provided dates only for the portion of travel subject to deferral due to presumed malaria risk. After reviewing the distribution of results, we chose a uniform duration of exposure (7 days) that encompasses over 70% of those donors with both start and end dates recorded.

Transfusion risk from blood donors with deferrable travel to Mexico

Transfusion risk is defined in this manuscript as the risk that a donor might be accepted for donation while asymptotically parasitemic, which we assume is equivalent to the risk that a donor might become infected with malaria while on travel in Mexico. Our risk estimates assume the absence of any deferral period for travel to Mexico, which means the donor could be found acceptable to donate the very day upon return from travel. Because the risk for asymptomatic malaria infection diminishes with increasing interval between return from travel and date of presentation - $\approx 50\%$ of *P. vivax* infections manifest within the first month and 70% within the first 3 months,¹³ the actual risk from abolishing the deferral for Mexico might be even lower than we estimate.

Results

Malaria travel deferrals to Mexico for REDS-II donors and extrapolation to U.S. annually

The six REDS-II centers reported a total of 13,007 deferrals for travel to malaria-endemic areas by U.S. residents in 2006 (Table 1), of which 2,160 were sampled for further analysis. The required data were available for 2,108 of these (97.6%), of which 885 donors were deferred for malaria travel to Mexico. Based on weighting that is proportional to each blood center's malaria deferral count, extrapolating to the U.S. yields an estimated 66,554 deferrals annually for malaria travel to Mexico. The change from 870 donors deferred for travel to Mexico in the earlier analysis¹³ derives from changing from a macro-regional to a country-based analysis, for which Mexico was the country of higher risk.

Risk for malaria infection in US travelers to Mexico

Population-adjusted risks for malaria at the state level are shown in Table 2, supporting the characterization of risk areas within Mexico as mostly scattered foci rather than large swaths of the national landscape, and demonstrating that most residents of endemic areas face very low risk for malarial illness. First, of the 2.8 million Mexican residents living in risk areas, fewer than 10% reside in areas with an annual risk for malaria greater than 1 per 1000 (an API, or Annual Parasite Index, of 1 means one case is reported per 1000 residents). Even in these regions – Durango, Chihuahua, and Sonora in the Northwest, and Oaxaca in the South--, the population at risk represents a small proportion of each state's population, and the number of counties with cases is low compared to each state's overall number of counties. Although the risk faced by residents of these 4 states is large relative to residents of the other endemic states, this elevated risk is confined to a very small fraction of the population. For Quintana Roo and 4 other states, which collectively account for 53 reported cases, the risk is < 1 per 10,000 residents per annum.

Table 3 contextualizes the malaria risks across states in 2005 within a long-term trend of increasingly lower malaria risk in fewer and more circumscribed geographic areas. Compared to 1985, when more than 133,000 cases were reported from all but two Mexican states,³³ the number of cases declined by 95% by the year 2000, and within the last decade has been reduced by an additional 60%. Active transmission of *Plasmodium* parasites is now limited to 115 counties distributed across 10 states, down from 234 counties in 16 states in

2000, and applies to less than 3% of the population of > 100 million. The country has not reported a malaria fatality in more than 10 years (data not shown), and the number of cases of *falciparum* malaria –the most malignant species, and at constant risk for importation from neighboring countries —has been reduced to zero for 3 consecutive years. Across those areas with active transmission, risk is non-uniform, with two states—Chiapas and Oaxaca—accounting for > 75% of all reported cases in each of the last five years.

Risk for malaria infection in US donors deferred for travel to Mexico

Table 4 combines the results for travel destination within Mexico reported by the REDS-II donors with the proxy risk attached to the identified locations. Overall, the information provided by a large majority of donors (85%) was sufficient to identify location of travel at least to the state level. For more than half of the remaining donors (N=69, 7.8%), information on location was either altogether lacking or insufficiently specific (“went horseback riding, visited ruins, drove through rural area”) to exclude potential exposure to malaria, thus triggering deferral; records were no longer available for another 60 donors (6.8%). The adjusted distribution in Table 4 and the calculations based on them assume the distribution of travel by the 15% missing was random, and locations for these observations were re-allocated according to the proportion missing for each blood center. Notably, more than 9 of 10 donors in this analysis provided sufficient detail on their travel destination(s) within Mexico to identify both state and county visited.

Duration of exposure was estimable for 284 donors, and the distribution was bi-modal. Nineteen percent of donors reported a duration of exposure of 0 days, which reflects day trips to risk areas. Another 24% reported 7-day stays in areas with malaria risk. The median and mode both were 7 days, and the mean was 7.4 days. Together, 73% of the 284 donors reported a duration of exposure of 7 or fewer days, and this duration was accordingly used to estimate the risks for malaria infection, discussed below and shown in Table 4.

A significant majority --72%-- of REDS-II donors were deferred for travel to the state of Quintana Roo. Located on the Yucatán Peninsula, Quintana Roo draws heavy numbers of tourists arriving by both plane and cruise ship. As indicated in Table 3, the number of malaria cases reported in Quintana Roo has been reduced by > 95% over the last decade, and in 2005 (Table 2) only 2 of the 8 counties in the state had any cases. The information provided by travelers to Quintana Roo was sufficiently detailed to identify location at the county level for 98% of the donors deferred for travel to that state (Table 4). Risk for infection in donors with travel to Quintana Roo is derived from a weighted summation of location risk (county-level for 98%, state level for 2%) multiplied by the number of U.S. donors extrapolated from the REDS-II donors (Table 5). From these calculations, two figures stand out. First, 81% visited areas with zero risk for malaria in 2005 (Table 4 and Figure 2), mostly in the area of Cancún, Playa del Carmen, and other coastal areas of the northern third of the state. Second, after adjusting for duration of exposure (see above), we would expect the projected number of 47,939 donors deferred annually for travel to Quintana Roo to acquire malaria infection at a rate of 0.0080 per year, or one infection every 125 years. This estimate assumes no significant alteration in the degree or distribution of risk within the state, both of which seem reasonable inferences based on the number of cases reported statewide during 2006-2009 (Table 3).

Following Quintana Roo, the states responsible for the second- and third-largest number of donor deferrals also represent very low risk travel. Both Guerrero and Nayarit account for > 6% of travel deferrals to Mexico, but Guerrero reported no more than 3 cases of malaria (either 0 or 3, depending on the source) in 2005, and travelers to both states overwhelmingly reported travel destinations in counties with zero malaria cases throughout 2005 (see Figure 3 for Nayarit). Accordingly, the > 8,400 U.S. donors projected to have been deferred for

travel to these two states would be expected to acquire 0.0007 infections altogether, or one per 1,400 years.

Continuing in like fashion across all the states responsible for donor deferrals, the results indicate that 76% of donors did not enter an area with even one malaria case in 2005, and the weighted average location risk for all deferred donors is 0.2091 infections per 1,000 year-round residents. Adjusted for duration of exposure, this estimate implies roughly a 1:250,000 malaria risk for U.S. donors deferred for travel to Mexico. Given the 100-fold risk gradient across states shown for Mexican residents in Table 3, the donor risk categorized at the state level gives similar results. In fact, 81% of the risk attributed to donors deferred for travel to Mexico (0.2170 infections annually, or roughly one case per 4.6 years) is for travel to the state of Oaxaca, a risk associated with only 1,847 donors. Omitting them from the analysis, the remaining 64,707 donors collectively incur risk for malaria infection of roughly one per 20 years. Inclusion of Oaxaca yields an estimated 0.2676 expected infections in 66,554 deferred donors per year, or roughly one infection every 3.7 years.

These frequencies can be understood as the maximum theoretical risk from fully repealing the donor deferral for travel to Mexico, which assumes that all donors present for donation immediately upon return. Given that 50% of vivax malaria infections in U.S. travelers become symptomatic within one month and 70% within 3 months,¹³ the actual risk under the expected distribution of intervals between return and presentation would likely be quite a bit lower. Moreover, as discussed below, imputing to U.S. travelers a prorated risk for malaria infection equivalent to Mexican residents almost certainly overstates risk by a significant, albeit unquantifiable amount.

It is noteworthy that donors were deferred for travel to 19 states, plus the Federal District (Mexico City), whereas only 13 states are listed by name in the Yellow Book. To be sure, these occurrences represent a small minority, but some of the states responsible for deferrals (Baja California Sur, Colima) had not reported a malaria case in several years.

Discussion

While blood centers in the U.S. have previously expressed concern that the donor deferral for malaria risk in Mexico reflects a poor balance between risk averted and impact on blood availability,³⁴ no systematic effort had been undertaken to quantify either metric in a joint assessment of safety and availability. Our consortium's first analysis suggested that the risk for malaria infection associated with travel to Mexico might be low enough that the current 1-year deferral period could be scaled back with negligible impact on blood safety. Given the apparent size of the population of willing donors turned away following travel to Mexico, there are indeed significant potential gains in blood availability to be weighed in the assessment of risk and benefits that might follow any change in donor eligibility requirements. To address the potential concern that our estimates for malaria risk in U.S. travelers to Mexico might not have been based on accurate estimates of population at risk, we sought an alternate measure for malaria risk that was independent of U.S. traveler patterns overall. The results presented herein support the conclusions from the original paper, while providing a more nuanced perspective on donor travel patterns and attendant malaria risk.

Based on the recognition that traveler risk and donor acceptance might be only loosely associated, this analysis purposefully did not restrict its focus only to the donor population that entered an area in Mexico with active malaria transmission. While a donor who reports having entered a risk area is clearly excluded from donation, other donors who did not enter such an area but who cannot provide sufficient detail to exclude the possibility of malaria

exposure are also deferred. Thus, the critical population for the current analysis is the donor population who entered an area of Mexico that would trigger their exclusion from blood donation, independent of the level of risk they might have faced. As indicated in Table 4, a large majority (76%) of donors were deferred for travel to areas reporting zero malaria cases in 2005.

The discrepancy between risk areas described in the CDC Yellow Book and actual donor deferrals could have more than one explanation. First, the deferral of donors for travel to areas with no malaria could simply reflect the natural time lag between an area within Mexico having been determined to be free of active transmission, this information being published in the next version of the Yellow Book, and the newest version of the Yellow Book being integrated into blood centers' documentation for donor screening for malaria risk. Indeed, the version of the Yellow Book subsequent to the one referenced for this study removed four states from the list of those considered risk areas: Campeche, Guerrero, Jalisco, and Michoacán. A second, perhaps more important factor, might be the limited amount of detail available in the Yellow Book coupled with limited information provided by the donor him- or herself. Consider, for example, the fact that the state of Nayarit has reported nearly all its malaria from the same six counties –Huajicori, Acaponeta, Del Nayar, Rosamorada, Ruiz and Tepic-- between 2002 and 2005³⁰ (see Figure 3), but 85% of REDS-II donors were deferred for visiting Nuevo Vallarta and Sayulita in the county of Bahía de Banderas in the southern part of the state, where no malaria case has been reported since at least 1999.³⁰ A similar dynamic prevails in the states of Guerrero and Quintana Roo. The breadth of risk implied by the phrase “risk in rural areas” followed by a long list of states, implies that risk is incurred by any traveler who leaves an urban locale in any of those states, and a high lack of specificity is the result. The issue of timeliness of risk information could in theory be partly remedied by the online malaria risk map CDC has developed,³⁵ if subsequent iterations of this application were to provide more detailed or more recent information than the print version of the Yellow Book. In sum, while the information provided by the CDC is valuable in assessing risk, it is often insufficient to exclude the need for deferral for many presenting donors.

The risk estimates presented herein should be evaluated in terms of how realistically they reflect the actual risk incurred by deferred donors. The intent of this analysis, as with the prior one, was to develop a conservative model that ensured that risk estimates were not artificially low. We are confident that the first model is successful in this sense, most notably by its prediction of one case of TTM every six years from a routine traveler, whereas empirical observation has identified only one such case in the last 3 decades. We believe that the low risk estimates for travel to each state in the current analysis also are conservative and provide a significant margin of safety. This is probably best illustrated by the data from the state of Oaxaca, which is responsible for the largest share of cases within Mexico and the second-highest population-adjusted risk in 2005. Notably, less than 5% of the state's population lives in risk areas, and only 19 (3.3%) of the 570 counties reported cases in 2005 (Table 2). Combining census and reported malaria data,^{30,31} one sees that Oaxaca's 1,432 cases are scattered across 265 different towns or hamlets (out of 1249 in these 19 counties), which by simple arithmetic implies an average of 5 malaria cases per town or hamlet, each with mean population of 700 inhabitants. Altogether, the data suggest that the population-adjusted risk of 7.39 cases per thousand residents, or 1:135 residents annually, applies to a very small share of the population and the landscape of Oaxaca. If tourists to Oaxaca faced malaria risk equivalent to those of local residents, one should expect far greater numbers of U.S. tourists to return with malaria. Oaxaca accounts for roughly 1-2% of air traffic from the U.S. to Mexico,^{25,36} and is associated with 3% of the deferrals in the REDS-II cohort. If even 1% of U.S. overnight travelers to Mexico visit Oaxaca, stay one week, and face the malaria risk shown in Table 4, one would expect almost

24 malaria infections from this state alone, 4 times the average over the last 8 years for the whole country (200,000 travelers * 1:163 risk ÷ 52 for 1-week exposure = 23.6 infections). In sum, use of local resident risk as a proxy for traveler risk undoubtedly overstates the risk in our donor population.

Whether the predicted level of risk supports a complete or partial reversion of current deferral requirements for travel to certain parts of Mexico is a question that has been reviewed recently by policy makers.³⁷ In a discussion focused only on Quintana Roo, Mexico, the FDA Blood Products Advisory Committee recommended 17 to 1 in favor of allowing donation from donors with travel to that state. Our analysis reinforces this conclusion and supports extending a similar policy to other areas of Mexico with exquisitely low risk for malaria infection. Both within Quintana Roo and elsewhere, most donors reported travel to areas with zero reported malaria cases in 2005, and those that traveled to areas with theoretical risk generally incurred risks of very low magnitude. Specifically, 3 in 4 deferred donors were associated with areas that were malaria-free in 2005, and 85% of the remainder faced estimated one-week risks of < 1:640,000. Only the 3.5% of donors deferred for travel to Oaxaca, Chihuahua and Sonora faced potential risks that could be considered non-trivial. This finding replicates that from our consortium's first analysis, albeit here on a sub-national rather than global scale: The largest share of malaria travel deferrals is associated with travel to the area of lowest estimated risk. Just as Mexico reflects about a 1,000-fold lower risk than Africa, donors who visited Quintana Roo appear to have faced an average 1:115,661 (annualized) risk, compared to travelers to Oaxaca, with its estimated risk of 1:164, a 700-fold difference. Adjusting each for a one-week exposure, that leaves us with absolute risks on the order of 1 per 6 million for Quintana Roo vs. 1 per 8,510 for Oaxaca. Returning again to the earlier manuscript, the absolute traveler risk for Quintana Roo is < 8,000 times that of the estimated traveler risk to Africa. We believe that at a minimum Quintana Roo should no longer be considered a deferrable travel destination, and strong consideration should be given to extending such a measure to other locations in Mexico with very low malaria risk.

This study is subject to a number of potential limitations. First, donors from the REDS-II blood centers might have travel patterns that are not representative of U.S. donors overall. In fact, given the lack of REDS-II data from the southwestern U.S., one might assume that at least that region's donors could have a different amount of travel to Mexico or undertake travel of a different nature compared to REDS-II donors. While such data are sparse, a parallel study to this one was presented to the Food and Drug Administration's Blood Products Advisory Committee. Using 2008 deferral data from blood centers in the border states of Texas, Arizona, and New Mexico, the study found a similar percentage of donors deferred for malaria travel as was found in REDS-II donors (0.9% vs 1%), but found that a higher percentage were deferred for travel to Mexico (60% vs 42%). The distribution across states differed from that in REDS-II donors, with more deferrals for travel to border states Chihuahua and Sonora within Mexico (15% vs < 1%); however Quintana Roo still represented the state responsible for the largest share (37%) of deferrals. More broadly, the study suggested that a majority of border state donors are also deferred for visits to areas with very low risk (< 1:250,000 assuming 1-week exposure).³⁸

Another potential limitation is that location data were not available from 15% of the donors in this study who were deferred for travel to Mexico. To cause downward bias in our risk estimates, however, the missing data would have to be from donors with higher malaria risk while traveling to Mexico than other donors from the same blood center, an unlikely scenario. If anything, the missing data are likely to come from relatively low-risk travelers. Since by 2008, 100% of malaria in Mexico has been characterized as occurring in indigenous populations in scattered rural areas,²⁴ one should expect these areas to be visited

by the more adventurous and/or sophisticated traveler, who almost certainly would be able to name at least the state they visited. In any case, because the missing data are adjusted for by re-weighting the available data for each center, any difference in risk for donors across REDS-II centers is adequately accounted for.

A third concern might be that the reports of lower levels of malaria within Mexico could reflect diminished surveillance capacity rather than reduced malaria transmission. Available evidence, however, suggests this is not the case. Mexico accounts for < 0.5% of malaria cases diagnosed across all endemic countries in the Americas, yet carries out > 18% of all blood smears examined for diagnostic purposes.³⁹ A slide positivity rate that is a fraction of other countries' together with a higher proportion (36% vs 21%)⁴⁰ of cases found through active case detection confirms that Mexico's malaria surveillance is both robust and committed to identifying all potential cases of infection.

One final possible limitation is that our estimates for risk and benefits associated with modifying the deferral guidelines to Mexico are based on risk estimates from 2005 only, and detailed county-level data are not available from 2006 onward. This could have implications for the reliability of the estimates presented herein as well as for inferences applied to subsequent time periods. While 2/3 of the donors in our analysis actually traveled in 2006, we have no a priori reason to assume that reliance on 2005 malaria surveillance data prejudices our risk estimates. First, between 2005 and 2006, the overall number of cases declined from 2,966 to 2,413, the API declined from 1.06 to 0.90,²⁶ and three of the four states with the highest API in 2005 all reported fewer cases in 2006: Chihuahua from 181 in 2005 to 122 in 2006, Oaxaca from 1432 to 575, and Sonora from 29 to 17; Durango, ranked highest in risk in 2005, was only slightly higher in 2006, increasing from 114 to 121 cases. Going forward, one might be concerned that the lack of county-level data beyond 2005 could mean that any relaxation of deferral guidelines might not have recent surveillance data of a high level of granularity to support it. While the ideal scenario would involve the availability of real-time, town- or hamlet-level data, the data presented here are part of a long, downward trend in risk for malaria in Mexico, and most of the areas shown to be malaria-free (or very low-risk) in 2005 were also malaria-free, or low-risk for several prior years. Further, malaria case reports at the state level are currently available on a weekly basis, with only a two- to three-week time lag,³¹ so that any significant change in malaria transmission would likely become rapidly detectable. Unless the nature of donor travel patterns to Mexico were to be re-oriented towards risky travel in remote areas and away from beach resorts, the estimates of risk described in this analysis are likely to remain relatively stable.

Based on the preponderance of blood donor deferrals triggered by visits to areas of zero or very limited risk for malaria, we recommend the deferral policies for donor travel to Mexico be revised in a way that balances risk averted with the significant donor loss. While multiple permutations of new regulations might reasonably be considered, we believe the data from this analysis and available online are sufficient to inform these efforts.

Acknowledgments

The authors thank the staff at all six participating blood centers. Without their help, this study would not have been possible.

This work was supported by NHLBI contracts N01-HB-47168, -47169, -47170, -47171, -47172, -47174, -47175 and -57181.

Appendix

Appendix:

The Retrovirus Epidemiology Donor Study - II (REDS-II Study Group) is the responsibility of the following persons:

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Figure 1. States in Mexico where U.S. Centers for Disease Control reports risk for malaria, 2005-2006

Sources: Map adapted from INEGI;²⁸ Yellow Book Description from CDC.⁶ “Risk in rural areas, including resorts in rural areas, of the following states: Campeche, Chiapas, Guerrero, Michoacán, Nayarit, Oaxaca, Quintana Roo, Sinaloa, and Tabasco. In addition, risk exists in the state of Jalisco (in its mountainous northern area only). Risk also exists in an area between 24°N and 28°N latitude, and 106°W and 110°W longitude, which lies in parts of the states of Sonora, Chihuahua, and Durango. No risk along the United States-Mexico border. No risk in major resorts along the Pacific and Gulf Coasts.”

Figure 2.

Mexican State of Quintana Roo, with 2005 county-level malaria risk and general distribution of REDS-II malaria travel deferral destinations.

Source: Map adapted from INEGI;²⁸ malaria incidence derived from online county-level data on malaria cases³⁰ and population.³¹

Figure 3. Mexican State of Nayarit, with 2005 county-level malaria risk and destination location of large majority of REDS-II malaria travel deferrals.
Source: Map adapted from INEGI;²⁸ malaria incidence derived from online county-level data on malaria cases³⁰ and population.³¹

Table 1
Malaria travel deferrals to Mexico at 6 REDS-II Blood Centers, 2006*

	BCP	BCW	HOX	ITxM	NEARC	SARC	Total	Weighted Extrapolation to US
# travel deferrals	2,761	2,128	1,122	1,622	3,570	1,804	13,007	161,105
# travel deferrals sampled	334	353	356	359	360	346	2,108	
Deferrals to Mexico	123	230	159	119	130	125	885	66,554
% travel deferrals due to travel to Mexico	36.8%	65.2%	44.7%	33.1%	36.1%	35.8%	42.0%	41.3%
% MX deferrals with identifiable location	62%	98%	99%	92%	95%	52%	85%	

* REDS II participating centers included; Blood Centers of the Pacific (BCP), San Francisco, CA; Blood Centers of Wisconsin (BCW), Milwaukee, WI; Hoxworth Blood Center, University of Cincinnati (HOX), Cincinnati, OH; the Institute for Transfusion Medicine (ITxM), Pittsburgh, PA; the American Red Cross, New England Region (NEARC), Dedham, MA; and the American Red Cross, Southern Region (SARC), Douglasville, GA.

Table 2
Mexican population at risk and reported malaria cases at the state level, 2005

State	Population, 2005	Population at Risk, 2005	Number of counties reporting cases, 2005	Malaria cases, 2005	Population-Adjusted Risk* (and 95% CI**) for Malaria, 2005
Durango	1,554,948	14,126	3 of 39	114	8.07(6.71, 9.70)
Oaxaca	3,716,837	193,669	19 of 570	1,432	7.39(7.02, 7.79)
Chihuahua	3,432,518	33,126	8 of 67	181	5.46(4.72, 6.32)
Sonora	2,487,066	5,777	4 of 72	29	5.02(3.49, 7.22)
Tabasco	2,069,522	119,497	9 of 17	97	0.81(0.67, 0.99)
Chiapas	4,417,084	1,062,455	65 of 119	852	0.80(0.75, 0.86)
Sinaloa	2,771,148	559,254	10 of 18	208	0.37(0.32, 0.43)
Quintana Roo	1,091,496	127,808	2 of 8	11	0.09(0.05, 0.16)
Nayarit & other states	24,466,964	684,288	13 of 667	42	0.06(0.04, 0.08)
TOTAL	46,007,583	2,800,000	133 of 1,577	2,966	1.06(1.02, 1.10)

* Reported as Annual Parasitological Index (API), or number of cases reported per 1,000 residents

** Confidence intervals do not account for temporal or geographic variation, hence inference is to only the year 2005 and is specific to each state.

Table 3
Malaria cases at national and state level and population at risk in Mexico, 2000-09

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Pop at risk (million)	50.3	54.7	54.7	54.7	2.8	2.8	2.8	2.8	2.8	≈ 2.8
Number of States Reporting 1 Malaria Case(s)	16	17	15	16	14	12	11	10	10	10
Number of Counties Reporting 1 Malaria Case(s)	234	202	189	177	148	133	NA	NA	115	NA
Number of <i>P. falciparum</i> cases	124	70	16	43	47	22	14	0	0	0
Individual States										
Campeche	36	57	54	21	4	1	0	0	0	0
Chiapas	3575	2522	2415	1757	1151	852	1349	1483	1136	1039
Chihuahua	695	404	420	259	184	181	122	148	185	438
Colima	0	1	0	0	0	0	0	0	0	0
Durango	171	136	104	79	52	114	121	46	38	42
Guerrero	161	88	24	7	3	0	0	0	0	0
Jalisco	50	29	11	6	5	2	2	2	10	8
Michoacán	135	52	21	2	7	0	0	0	0	0
Morelos	0	0	0	1	0	0	0	0	0	0
Nayarit	206	154	88	49	27	37	24	38	71	70
Oaxaca	654	285	260	699	1083	1432	575	369	804	896
Puebla	7	1	0	0	0	0	0	0	0	0
Quintana Roo	332	215	276	88	40	11	17	14	15	4
Sinaloa	790	616	664	377	513	208	98	108	76	72
Sonora	79	59	32	76	49	29	17	13	10	18
Tabasco	297	219	139	167	145	97	86	86	12	8
Veracruz	34	20	11	4	0	2	2	0	0	0
Yucatán	50	9	33	15	5	0	0	0	0	0
Total malaria cases	7,272	4,867	4,552	3,607	3,268	2,966	2,413	2,307	2,357	2,595

Table 4
Distribution of travel destination and estimated risk for acquiring malaria infection for 885 REDS-II donors deferred for malaria travel to Mexico, and projections to U.S. donors overall

State	Travel destination			Location risks		Projected U.S. Deferrals and Infections in Donors with Malaria Travel to Mexico		% of Total Estimated Risk
	Raw distribution	Adjusted distribution *	% assignable to county level *	% with travel to zero-risk area *	Estimated weighted risk, API ⁺	N Projected U.S. deferrals	Expected Infections in N Deferred Donors (and 95% CI **, 7-day Exposure	
Quintana Roo	63.8% (N=565)	72.0% (N=637.5)	98%	81%	0.0086	47,939	0.0080(0.0044, 0.0145)	3.0%
Nayarit	5.2% (N=46)	6.5% (57.1)	89%	89%	0.0076	4,295	0.0006(0.0004, 0.0009)	0.2%
Guerrero	4.9% (N=43)	6.2% (55.0)	97%	77%	0.0010	4,140	0.0001(0.0000, 0.0006)	0.0%
Oaxaca	2.3% (N=20)	2.8% (24.6)	49%	0%	6.1106	1,847	0.2170(0.1456, 0.3234)	81.1%
Sinaloa	1.8% (N=17)	2.6% (22.9)	67%	0%	0.1253	1,751	0.0041(0.0027, 0.0064)	1.5%
Jalisco	1.8% (N=16)	2.5% (21.7)	53%	53%	0.0450	1,718	0.0014(0.0002, 0.0105)	0.5%
Yucatán	1.8% (N=16)	2.3% (20.3)	79%	100%	0.0000	1,524	0.0(0.0, 0.0)	0.0%
Michoacán	1.5% (N=13)	2.0% (17.8)	43%	100%	0.0000	1,342	0.0(0.0, 0.0)	0.0%
11 other states & Mexico City	2.4% (N=21)	3.2% (28.1)	78%	51%	0.8942	2,117	0.0364(0.0226, 0.0587)	13.6%
Location unassigned	14.6% (N=129)							
Total	885		92% (814/885)	76% (673/885)	0.2091⁺	66,554	0.2676(0.2483, 0.2885)	

* Adjusted distributions are re-weighted according to the % missing for each center, as shown in Table 1.

⁺ API = Annual Parasitological Index, or number of cases reported per 1,000 residents per year

** Confidence intervals do not account for temporal or geographic variation of API, temporal variation in travel habits of US donors, or variation in donation habits of US donors.

Table 5
Detailed calculations fo risk estimates for travel to state of Quintana Roo

County (raw/adjusted N)	Estimated Resident Risk, 2005	% REDS-II MX donors	N Projected US deferrals	Expected malaria infections (and 95% CI ^{**}) in donors (7-day exposure)
Cozumel (N=8/8.136)	0.0000	0.92%	612	0.0000(0.0000, 0.0000)
Felipe Carrillo Puerto (N=1/1.938)	0.0306	0.22%	146	0.0001(0.0000, 0.0004)
Isla Mujeres (N=1/1.006)	0.0000	0.11%	76	0.0000(0.0000, 0.0000)
Othón P. Blanco (N=85/107.601)	0.0410	12.16%	8,092	0.0064(0.0034, 0.0119)
Benito Juárez (N=64/65.138)	0.0000	7.37%	4,902	0.0000(0.0000, 0.0000)
José María Morelos (N=0)	0.0000	0.0%	0	0.0000(0.0000, 0.0000)
Lázaro Cárdenas (N=0)	0.0000	0.0%	0	0.0000(0.0000, 0.0000)
Solidaridad (N=397/441.450)	0.0000	49.88%	33,198	0.0000(0.0000, 0.0000)
Unspecified location (N=9/12.149)	0.0861	1.37%	914	0.0015(0.0007, 0.0034)
Totals		72.0%	47,939	0.0080(0.0044, 0.0145)

* API = Annual Parasitological Index, or number of cases reported per 1,000 residents per year

** Confidence intervals do not account for temporal or geographic variation of API, temporal variation in travel habits of US donors, or variation in donation habits of US donors