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A malaria vaccine for travelers and military personnel: Requirements and top candidates

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ABSTRACT

Malaria remains an important health threat to non-immune travelers with the explosive growth of global travel. Populations at high risk of acquiring malaria infections include once semi-immune travelers who visit friends and relatives, military forces, business travelers and international tourists with destinations to sub-Saharan Africa, where malaria transmission intensity is high. Most malaria cases have been associated with poor compliance with existing preventive measures, including chemoprophylaxis. High risk groups would benefit immensely from an efficacious vaccine to protect them against malaria infection and together make up a sizable market for such a vaccine. The attributes of an ideal malaria vaccine for non-immune travelers and military personnel include a protective efficacy of 80% or greater, durability for at least 6 months, an acceptable safety profile and compatibility with existing preventive measures. It is very likely that a malaria vaccine designed to effectively prevent infection and clinical disease in the non-immune traveler and military personnel will also protect semi-immune residents of malaria-endemic areas and contribute to malaria elimination by reducing or blocking malaria transmission. The RTS,S vaccine (GlaxoSmithKline) and the PfSPZ Vaccine (Sanaria Inc) are the leading products that would make excellent vaccine candidates for these vulnerable populations.

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1. Introduction

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The cornerstone of malaria prevention has included prophylaxis with drugs, insecticide-treated bed nets and mosquito repellants; however, despite their high efficacy, these interventions are only partially successful in curtailing the disease's global impact. The World Health Organization has set a strategic goal to license a vaccine by 2030 with protective efficacy of at least 75% against clinical malaria for at-risk groups in malaria-endemic areas [1,2]. In the past 40 years, many institutions across the world, including the United States (U.S.) Department of Defense (DoD), have made tremendous progress toward developing an effective human malaria vaccine for at-risk populations worldwide and breakthroughs have been significant in recent years [3,4]. The exciting recent data on the top two vaccine candidates, RTS,S and PfSPZ Vaccine, suggest that an effective vaccine to protect certain target groups of semi-immune and non-immune individuals may be licensed in the near future.

Global travel has accelerated the potential risk of being infected with malaria parasites among non-immune travelers, underscoring the importance of highly efficacious preventive interventions. In 2013 alone, over 1 billion international tourists traveled worldwide [5], and extrapolating from data on U.S. travelers, 50% traveled for leisure, 27% visited friends and relatives, 11% traveled as part of their occupation and 5% for education purposes [6]. Sub-Saharan Africa, which is considered to have a relatively high intensity of malaria transmission, welcomed an estimated 36.2 million travelers in 2013, representing a 5% increase from the previous year [5,7]. In 2014, the total number of international tourists who visited sub-Saharan Africa increased by 3% despite the Ebola Virus Disease outbreak in West Africa [8]. Asia and the Pacific region, where rates of malaria transmission are relatively lower, experienced a 6% increase in international travelers, and received a total of 248 million visitors in 2013 [5]. In 2013, an estimated 36.5 million travelers visited countries in Central and South America, where malaria transmission intensity is low [5]. International tourist arrivals are forecasted to steadily rise by 3.3% per year from 2010 to 2030, translating to an increase of approximately 43 million travelers per year and reaching 1.8 billion by 2030 [5]. Data is scarce on estimates of the number of children or elderly persons who travel internationally, but travel data for U.S. residents estimated that 7% of

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travelers were children [9] and 9% were 65 years of age or older [10]. There is a critical need for effective protective measures with the continuing growth of international travel to malaria endemic regions [5]. In this article we will discuss non-immune populations who are at a particularly high risk of acquiring malaria infection – these are international travelers and military personnel. Non-immune travelers are individuals who depart from countries which are malaria-free or have low rates of malaria transmission and visit or temporarily reside in regions with ongoing malaria transmission for leisure or work. These groups would greatly benefit from a vaccine to protect them against malaria infection.

2. Non-immune travelers, deployed military and international organization personnel at risk for acquiring malaria

The risk of acquiring malaria is determined by multiple factors such as the location of the destination, season, transmission intensity, duration of travel, and use of personal protection. Specific groups of travelers may be at a higher risk of malaria parasite exposure based on these factors. Nearly half of all global trips are made by adventure tourists [11], who travel for an average duration of 8 days but typically experience greater exposure to the natural environment, resulting in higher risk of bites from infective mosquitoes. Business or occupational travelers to malaria endemic regions are generally well-informed but adherence to chemoprophylaxis is often poor [12]. Travelers who volunteer for international organizations or the Peace Corps are at increased risk for acquiring malaria because they work in the field and reside in rural areas for 6 months or longer [13]. Foreign service personnel and their family members who are stationed at diplomatic posts in malarious regions are also at increased risk for acquiring malaria [12,14]. Migrants who previously lived in malaria-endemic regions or countries, have resided in non-malarious countries for several years and who then travel to their respective homelands to visit friends and relatives (VFR travelers) are disproportionately affected by severe *Plasmodium* infections [15–18]. Persons who live in areas with high intensity malaria transmission develop naturally acquired immunity from repeated exposure to the parasite so that in early adulthood, they develop a certain level of protection against malaria and during an acute malaria infection may have only mild clinical symptoms. However, this state of semi-immunity is partial and wanes within months of living in malaria-free countries or regions with very low malaria [18]. The VFR traveler remains at risk for malaria infection though they tend to develop less severe disease than the non-immune travelers [18]. Children born to once semi-immune VFR travelers are particularly vulnerable to malaria infection because they have no innate protection and a low percentage of this group accesses pre-travel consultation and/or complies with the health care providers' personal protection recommendations. Another large segment of the population at increased risk for malaria infection is the growing number of in-country travelers who visit rural areas and reside in malaria-free capital cities and regions, such as Nairobi, Kenya, the major cities of South Africa such as Pretoria, Johannesburg, Cape Town, Durban, Sun City, Richards Bay, and highland areas in sub-Saharan Africa at 2000 meters elevation above sea level or higher, where *Plasmodium falciparum* epidemics are infrequent [19].

Military personnel from the international community deploy worldwide to execute combat and security operations to promote regional stability, engage in humanitarian missions and participate in peacekeeping operations (Table 1). Throughout history, military personnel have served in areas where they can potentially acquire malaria, and outbreaks have significantly impacted military operational capabilities and readiness.

The current anti-malaria strategies used by military include chemoprophylaxis and personal protective measures to prevent mosquito bites by wearing insecticide impregnated uniforms, sleeping under bednets, and applying insect repellent. In addition, mosquito control can be used in long-term and humanitarian operations, but may not be possible in contingency operations [20–22].

3. Malaria in travelers

Many international travelers continue to acquire malaria while visiting countries where the disease is endemic, and over 10,000 persons per year are reported to become ill with malaria after returning from travel [23]. It is possible that malaria cases may be underreported because information is derived from systems which rely on passive reporting [23]. Data collected from the EuroTravelNet sites from 2008 to 2012 showed an increase in the number of imported malaria cases attributable to travel to sub-Saharan Africa by persons who emigrated to malaria-free regions in Europe and traveled back to their countries of origin to visit friends and relatives, also known as VFR travelers [24]. A rising trend in the number of imported malaria cases has been observed in the U.S. since 1973; in 2012, 1683 cases of imported malaria were reported and nearly 80% were acquired from sub-Saharan Africa with a majority of the cases coming from Nigeria, Sierra Leone, Ghana, and Liberia [15]. Among the imported malaria cases who reported the purpose of travel, 54% were VFR travelers, 8.2% traveled as part of their occupation, 7.2% were involved in missionary work, 4.2% were students or teachers, and 2.9% were tourists [15]. Chinese travelers represent approximately 13% of worldwide travelers and China is actively engaged as an industrial, manufacturing, and development partner of numerous African countries [25]. Consequently, imported malaria has become increasingly recognized in China, with 808 reported cases in the Zhejiang province from 2005 to 2014, and at least 70% were acquired after travel to Africa primarily among businessmen [26].

Despite the abundant availability of effective malaria preventive interventions such as chemoprophylactic medications, insecticide-impregnated bed netting, and insect repellants, the CDC's National Malaria Surveillance System has continuously received 5–10 reports of malaria-related deaths in the U.S. annually [15,27,28]. A majority of the deaths have occurred among VFR travelers who took suboptimal chemoprophylaxis regimens or did not use malaria protective measures [28]. Additionally, travelers who fall ill during travel may find it difficult to access reliable medical care, and those who develop malaria upon returning home may be treated by medical personnel unfamiliar with malaria, resulting in delayed diagnosis.

4. Malaria among deployed military members

In the last century, malaria historically caused greater loss of manpower than combat-related injuries during deployments to tropical regions [29]. In 1972 the number of malaria cases among U.S. military personnel sharply decreased from over 4000 per year [30] to less than 50 annually [31–33], but malaria has remained a militarily relevant infectious disease negatively impacting operational readiness among deployed forces. Deployed forces to malaria-endemic regions have experienced outbreaks, and noncompliance with personal protective measures had been a recurrent risk factor associated with these outbreaks. During the deployment of 30,000 U.S. military troops to Somalia from 1992 to 1993, *P. falciparum* malaria was diagnosed in 48 personnel whose onset of illness occurred while still in-country; over 200 military service members developed symptoms after their return to the U.S. [34–36]. The risk factors for developing clinical malaria were failure

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