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Review

A systematic review and meta-analysis of the prevalence of *Leishmania* infection in blood donors

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ABSTRACT

Background: The risk of transfusion transmitted leishmaniasis (TTL) from apparently healthy persons or asymptomatic individuals, should not be ignored. Lack of a comprehensive review, encouraged us to design a systematic review with meta-analysis approach to assess the prevalence of *Leishmania* infection in healthy blood donors.

Methods: For this purpose, 6 English databases (PubMed, Scopus, Web of Sciences, Science Direct, EMBASE and CINAHL) were browsed from January 1990 to July 2016.

Results: Due to significant heterogeneity, the random-effects model was used (I^2 = 98.04% and 94.68%, for serological and molecular methods, respectively). A total of 496 papers were found through searching in which 17,816 apparently healthy blood donors were examined for *Leishmania* infection. The weighted overall prevalence of *Leishmania* infection in this group was estimated 4% (95% CI = 2–7) and 8.7% (95% CI = 4.2–14.3) using serological and molecular methods, respectively.

Conclusions: High serological prevalence does not justify widespread donor screening. Leukodepletion filters would substantially decrease the risk of TTL, hence they are potentially proposed in endemic areas specifically for high-risk recipients. To better enlighten the epidemiological aspects of *Leishmania* infection in blood donors, it is suggested to perform high-level stewardship and more precise studies with regard to involved risk factors.

Contents

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1. Introduction

Visceral leishmaniasis (VL) is a vector-borne infection caused by an obligate intracellular protozoa belonging to family Trypanosomatidae (order Kinetoplastida) and genus *Leishmania*. The disease differs around the world, depending upon clinical manifestations and causative agents [1]. Based on formal reports, the annual incidence of VL cases is 0.2–0.4 million worldwide, mostly (more than 90%) in six countries, including: Bangladesh, India, Brazil, Sudan, South Sudan and Ethiopia. Death as a result of VL is approximately 20,000–30,000 cases per year, and if left untreated, it reaches to 100% [2]. *Leishmania* (*L.*) *infantum* in the Mediterranean basin, West Africa, and South America (*L. infantum chagasi* (or *L. infantum* MON 1)) is the agent of zoonotic visceral leishmaniasis (ZVL), and dogs are the only confirmed primary reservoir of infection. *L. donovani* causes anthroponotic VL in the Indian subcontinent and eastern Africa [3]. The protozoa transmit to humans or animal vertebrate hosts through the bite of infected female sandflies namely *Lutzomyia* and *Phlebotomus* in the New World and Old World, respectively [1]. Alternatively, transmission of *Leishmania* via blood transfusion has also been documented [4,5].

Notwithstanding rigid surveillance on blood supply and blood products, concerns remain about transfusion-transmitted infections (TTI) on donated bloods [4,6–9]. The risk of transfusion transmitted leishmaniasis (TTL) from seemingly healthy persons or asymptomatic individuals whom called carrier for parasite, should not be neglected [5,10]. This probable transmission route, could be imposed intangible economical wastages on societies, particularly where VL is endemic [10]. Since VL is often without any sign in immunocompetent individuals of endemic areas, it is very difficult to estimate accurately the risk of transmission by blood transfusion and it could remain a dilemma for transfusion safety [4]. It has been reported that under general storage period in blood bank, for at least 25 days after blood donation, the parasite could survive in human RBCs, depending on the kind of storage [10,11]. Recently, TTL has been approved in experimental studies with hamsters, mice [12,13] and dogs [14,15].

During recent decades, several papers have been published regarding prevalence of *Leishmania* infection in seemingly healthy blood donors and blood products using serological and molecular techniques throughout the globe. Lack of a comprehensive review, encouraged us to design a systematic review with meta-analysis approach to assess the status of *Leishmania* infection in apparently healthy blood donors.

2. Materials and methods

2.1. Search strategy

To evaluate the prevalence of *Leishmania* infection in seemingly healthy blood donors, a systematic review and meta-analysis was conducted. For this purpose, six English databases (PubMed, Scopus, Web of Sciences, Science Direct, EMBASE, and CINAHL) were searched from January 1990 to July 2016 (Supplementary Fig. S1). Search strategy was performed using medical subject headings (MeSH) terms in Scopus and PubMed. Furthermore, we used several keywords including: "*Leishmania*"; "Leishmaniasis"; "Blood donors"; "Blood Pack"; "Prevalence"; "Seroprevalence" and "Epidemiology" alone or combined together using "OR" and/or "AND". The reference list of selected full-text papers were also meticulously checked manually to find articles not retrieved by the database searching.

2.2. Study selection and data extraction

According to inclusion criteria, only cross- sectional and case-control papers that estimated the prevalence of *Leishmania* infection in apparently healthy blood donors and blood packs using serologic or molecular methods, were qualified to be included in this systematic review. The papers that studied the prevalence of *Leishmania* infection in groups except of blood donors and blood packs, were excluded immediately. The retrieved records were precisely reviewed by two reviewers (M. Foroutan and S. Khademvatan) to assess the eligibility for inclusion, and any contradiction was resolved by consensus. Afterwards, the required data were recorded using a data extraction form on the basis of the country, year of publication, first author, study population or sample size, the exact number of positive samples, diagnostic method (serologic or molecular), cut off value or antibody titer for serological techniques, primer with details for molecular methods, main findings or suggestions, and reference. The PRISMA protocol (preferred reporting items for systematic reviews and meta-analysis) was followed to report our finding [16].

2.3. Meta-analysis

The meta-analysis procedure was performed as formerly described [7,17–22,77]. Briefly, we estimated the prevalence and 95% confidence interval (CI) every included study. The findings of the meta-analysis were represented by a forest plot diagram which shows estimates of prevalence and their respective CIs of individual studies with the summary measure. Cochran's Q and I^2 statistics, were applied in order to analyze the heterogeneity. I^2 values of 25%, 50% and 75% were considered as low, moderate, and high heterogeneity, respectively [23]. Besides, publication bias and small study effects were estimated using funnel plot based on Egger's regression test. According to results obtained from heterogeneity test, in case of pooling the estimations, either Der Simonian and Laird's random-effects method or Mantel-Haenszel's fixed-effects method were used. Furthermore, we conducted meta-regression test to assess the association between prevalence, the year of publication, and the sample size. Analysis was carried out with STATA statistical software.

3. Results

A total of 496 papers were found through searching in six English databases and ultimately 20 articles were met to be included in this systematic review and meta-analysis, as shown in supplementary Fig. S1. The results of included papers according to type of diagnostic methods, have been summarized in Tables 1 and 2. Due to significant heterogeneity, the random-effects model was