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Is glucose-6-phosphate dehydrogenase deficiency more prevalent in Carrion's disease endemic areas in Latin America?

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) is a cytoplasmic enzyme with an important function in cell oxidative damage prevention. Erythrocytes have a predisposition towards oxidized environments due to their lack of mitochondria, giving G6PD a major role in its stability. G6PD deficiency (G6PDd) is the most common enzyme deficiency in humans; it affects approximately 400 million individuals worldwide. The overall G6PDd allele frequency across malaria endemic countries is estimated to be 8%, corresponding to approximately 220 million males and 133 million females. However, there are no reports on the prevalence of G6PDd in Andean communities where bartonellosis is prevalent.

Dear Editor,

Glucose-6-phosphate dehydrogenase (G6PD) is a cytoplasmic enzyme with an important function in cell oxidative damage prevention. Catalysation of the first reaction in the pentose phosphate pathway by G6PD promotes detoxification of free radicals, protects the cell against hydrogen peroxide-induced damage and assures an oxidative balance profile within the cell [1]. Erythrocytes have a predisposition towards oxidized environments due to their lack of mitochondria, giving G6PD a major role in its stability [2]. G6PD deficiency (G6PDd) is the most common enzyme deficiency in humans; it affects approximately 400 million individuals worldwide. Human migration could explain the presence of G6PDd with varying frequencies in populations worldwide. However, the overall G6PDd allele frequency across malaria endemic countries is estimated to be 8%, corresponding to approximately 220 million males and 133 million females [3].

G6PDd is a frequent phenomenon in Latin America, although the prevalence of G6PD and the extent of its clinical consequences have not been reported in the region [4]. In Peru, there is one published study on the prevalence of G6PDd in a small population in the Amazon region which finds that 2 of 79 males and 1 of 43 women were affected by the deficiency [5]. However, there are no reports on the prevalence of G6PDd in Andean communities where bartonellosis is prevalent.

This enzymatic deficiency provides the affected individuals with a certain degree of protection against malarial infections even though the exact mechanism has not been described. Some authors postulate that the mechanism involves an increased sensitivity to phagocytosis of *Plasmodium* infected erythrocytes due to high levels of oxidative stress [6]. For this reason, G6PDd is more prevalent in endemic regions with malaria and areas where consanguinity is high given its hereditary patterns [4].

In Peru, over last 10 years, there have been reports of over 200 000 cases of methaxenic diseases such as bartonellosis, dengue and malaria. Piura and the Amazons are two departments endemic to both *Bartonella* and malaria [7]. The lack of information regarding the prevalence and incidence in Amerindian communities poses an important public health problem. Previous studies have associated an increase in the incidence of bartonellosis with El Niño period of 1995–1999 due to the elevated ambient temperature and precipitation rates. El Niño watch has issued a warning after assessing a very likely return of El Niño throughout 2015–2016 [8].

Bartonellosis is caused by *Bartonella bacilliformis* (*B. bacilliformis*), a facultative intracellular aerobic Gram-negative coccobacillus, causing the so-called Carrion's disease,

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a human infection prevalent in areas inhabited by low-income Andean communities of Peru, Ecuador and Colombia. Along with *Plasmodium* spp., *Babesia* spp. and *Anaplasma marginale*, *Bartonella* is one of the few infectious agents that include the parasitization of erythrocytes as part of its pathogenicity [9]. Carrion's disease is considered an emergent and truly neglected tropical disease. Its incidence is 12.7/100 person-years in general population, however in children under 5 years it increases to 38/100 person-years. Carrion's disease is transmitted through the bite of female sand-flies *Lutzomyia verrucarum* [10] and has two different clinical presentations and three stages: the acute phase also known as primary or Oroya fever, is characterized by fever, headache, myalgias and anemia. During this phase, there is a massive erythrocytic invasion causing hemolytic anemia and sepsis. It constitutes the most severe stage given that there is a mortality rate of 44%–88% if no treatment is administered. Those that survive the acute phase can go on to develop a chronic or verrucous phase of Carrion's disease. This stage is characterized by an asymptomatic period for weeks or months that are later associated with verrucous eruptions known as 'Verruga peruana'. These lesions are similar to hemangiomas; they bleed easily and are often pruriginous [10,11].

In order to invade the mammalian erythrocyte, there need to be an interaction between the ligands on the surface of *Bartonella* spp. and the receptors on the erythrocyte cell surface. In *B. bacilliformis* case, it has been identified that the initial erythrocyte adhesion is mediated by its flagella. However, studies have shown that both *B. bacilliformis* and *Plasmodium falciparum* may have two common pathways involved in the entry mechanism. These include a sialic-acid independent pathway mediated by erythrocytic receptor band 3 and a sialic-independent pathway mediated by the glycophorin proteins A, B and C on the erythrocytic cell surface. Furthermore, monoclonal inhibition *in vitro* studies of said receptors have shown a decrease in the rate of erythrocytic invasion for both pathogens [9].

Moreover, G6PD activity is markedly reduced in older erythrocytes. This renders mature erythrocytes more vulnerable to the physiologic oxidant stress and that is produced by parasitization, hence there is an increased susceptibility to phagocytosis [6]. Wouldn't *B. bacilliformis*, an intraerythrothytic parasite, be affected by the same principle? Could this mechanism bring forth a new theory regarding *B. bacilliformis* protection in G6PDd individuals the same way it has been theorized for *Plasmodium* spp.?

G6PDd and bartonellosis are both contemporary research fields that have not been fully studied in Peru due to the lack of funding. It is important to emphasize that up-to-date studies on the prevalence of G6PDd in endemic regions with *Bartonella*, will ultimately provide beneficial information for disease control. Additionally, this information could provide the groundwork for new associations related to the oxidative states of erythrocytes in G6PDd patients that have proven to be protective in individuals with malaria. Departments of Peru endemic to both malaria and *Bartonella*, such as the Amazons and Piura, will be key to investigate those links.

There are still many unknown aspects of the physiopathology of bartonellosis, such as its entry mechanism, the molecular pathways it uses, and if an enzymatic deficiency has any implication, among others. Furthermore, there is no data regarding the prevalence of G6PDd in regions affected by neither malaria nor other methaxenic diseases. Given that there is evidence that the entry mechanism is similar between *Plasmodium* spp. and *Bartonella* spp., and both are endemic in regions such as the departments of Piura and Amazonas, it would be important to know whether an enzymatic deficiency has any influence on *B. bacilliformis* the same way it has for *Plasmodium* spp.

Therefore, it begs the question, is there any association between Carrion's disease and G6PDd?

Conflict of interest statement

We declare that we have no conflict of interest.

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