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Letter to Editor

# Why Did They Not Die?

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## Letter to Editor

By 1992, Francis Black published an article that investigated the question in the tittle (Why did they die?). The article suggested that the low genetic diversity of the indigenous populations helped to explain why infectious diseases threatened the survival of vulnerable indigenous groups distributed in the Amazon region of Brazil [1]. At that time, only traditional methodological tools were available to explain the influence of the genetic similarities within families residing in isolated indigenous communities. The emerging knowledge of the Human Leukocyte Antigen (HLA), Class I Major Histocompatibility Complex (MHC) A and B loci genes could explain the higher risk of infectious agents in indigenous populations compared to that of urban population groups [1].

Colonization brought violence, slavery and diseases to natives inhabiting the Brazilian territory. Indigenous population numbers were drastically reduced, although surviving groups did maintain enough population growth to keep these populations demographically viable [2,3]. The contact with novel infectious agents, particularly with measles and influenza, led to a high mortality and devastating social changes in the community [1].

Isolated population groups do not generally have endemic viruses, but epidemics can occur with the occasional introduction that can infect many susceptible persons [4]. The entry of new infectious agents may be due to the demographic modifications of small groups. The lack of genetic diversity within these populations is a common explanation for the occurrence of epidemics with high mortality rates [4]. In contrast, only a few genetic traits and genes have been shown to be involved in the mechanisms of susceptibility among indigenous population groups. The decrease in the number of epidemics among indigenous peoples in the recent past is also important to consider, and this was caused by an improvement in the access to health care [3].

The recent emergence and rapidly spread of the RNA virus, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, which infects the respiratory tract, reinstated the concern for these vulnerable population groups, particularly the indigenous peoples from the Amazon region of Brazil. The history of past epidemics caused the health authorities to rapidly take action [5,6].

Seroepidemiological investigations are underway among urban groups in Brazil, but few of these investigations are being pursued in indigenous peoples. Recent results [7] have showed an extensive presence of antibodies against SARS-CoV-2 in the population of Xikrin do Bacajá (prevalence of 74.5%). The continuing surveillance of populations have determined that the prevalence of antibodies among six indigenous groups in the state of Pará (Asurini do Koatinemo, Araweté, Parakanã, Munduruku and Kararaô) ranges from the absence of antibodies to close to 80% (A C R Vallinoto ongoing investigation). One single death associated with COVID-19 (coronavirus disease 2019) was reported in an elderly chief of the village in Xikrin do Bacajá; among the other 742 infections undergoing investigations, there were five deaths in Munduruku and one in Parakanã.

Similar to the general question from Black's original article, these facts now pose a main question against all the odds: why did they not die?

Updated data on the COVID-19 pandemic in indigenous peoples in Brazil, reported in the Epidemiological Bulletin of the Special Secretariat for Indigenous Health – SESAI (http://www.saudeindigena.net.br/coronavirus/mapaEp.php), show that to date 51,709 cases of SARS-CoV-2 infection have been confirmed in the 34 Special Indigenous Health Districts (DSEI), with only 762 deaths (mortality rate of 1.47%); below the national average for urban populations (2.8% - https://covid.saude.gov.br).

It is possible that a low heterogeneity among the indigenous peoples, as compared to the trihybrid Amazonian populations [8], is associated with a poor response to infectious agents and diseases. Until the 1990s, our associates at the genetic laboratory were using protein polymorphisms, and it was quite evident that there were different manifestations of Hepatitis B virus (HBV) and *Chlamydia* exposure, infection and agent/host interactions resulting in persistence among the different indigenous groups [9,10]. The urban communities showed a different response when communities were tested for both agents.

A high exposure to both agents also results in high levels of persistence of the infectious agents. However, it also showed that a low exposure to the agents caused higher levels of persistence and vice versa, as shown in Table 1. For instance, Tiryió had a low prevalence of exposure to HBV and *Chlamydia*, but these areas maintained medium and high levels of persistence of HBV and *Chlamydia*, respectively. The nature of the agents (virus *vs.* bacterium) have different genetic complexities, and different infectious agents can be more or less virulent, possibly by avoiding the immunological responses in individuals. These agents can cause different degrees of outcome severity, which can be different from what was expected.

Two main hypotheses attempt to explain the higher susceptibility of Native Americans to emerging infectious agents when compared with non-native populations. The immune memory hypothesis




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**Table 1:** Genetic background influence of isolated populations of the Amazon region of Brazil: different modulation of exposure and persistence levels of HBV and *Chlamydia**.

| Infection | Exposure level | Persistence level | Exposure (%) | Persistence (%) | Indigenous Community |
|---|---|---|---|---|---|
| **Hepatitis B virus** | | | | | |
| | Low | Medium | 6.4 | 3.2 | Tiriyó |
| | | | 5.1 | 3.1 | Assurini do Trocará |
| | | | 0 | 5.6 | Kikretun |
| | Medium | Low | 22 | 0.6 | Munduruku |
| | | | 17.9 | 0 | Yamamadi |
| | Medium | High | 26.3 | 14.2 | Wayana-Apalai |
| | | | 12.3 | 7.5 | Yanomami |
| | | | 24.2 | 11.3 | Surui |
| ***Chlamydia*** | | | | | |
| | Low | Low | 20.4 | 3.3 | Munduruku |
| | Low | Medium | 27.7 | 7 | Arara Laranjal/Kurambê |
| | Low | High | 11.5 | 33.3 | Tiriyó |
| | Medium | Low | 55.9 | 1.9 | Kokraimôro |
| | | | 61 | 4 | Asurini do Kuatinemo |
| | Medium | Medium | 47.1 | 6.2 | Cinta-Larga |
| | High | Low | 90.7 | 2.6 | Awa-Guajá |
| | High | Medium | 81 | 5.9 | Parakanã |
| | | | 81.5 | 9.5 | Xikrin |
| | High | High | 75.8 | 10.1 | Kubenkokrê |
| | | | 87.6 | 21.1 | Yanomami |

*Adapted from references #9 and #10.

suggests that the lack of exposure during childhood would increase the susceptibility to infection and disease [11]. There is a theory that a low genetic variability observed in HLA would lead to less diverse phenotypes for disease-resistance in the host. In fact, Amerindian populations have an unusual evolutionary history and a different demographic pattern compared to other populations in the world, and genetic studies with mitochondrial DNA, HLA, other autosomal markers and X and Y chromosomes suggest that they have a low genetic diversity but a high interpopulation diversity compared to other populations located elsewhere [12]. However, these findings are based on studies that used small sample sizes for the Amerindian populations in the lands of the lower Amazon River. The genetic investigation of 11 Amazon River lowland groups and among three south-central Brazil populations [13] identified profiles for the genetic variability of the HLA genes (with a large number of alleles and some with a frequency very different from other regions of the world) that differed from the profiles of the other genes previously analyzed.

These findings support the evidence that selection favors different sets of alleles in different locations, which can lead to a greater differentiation among populations, and that balancing selection in HLA genes would simultaneously increase the intrapopulation polymorphism and interpopulation differentiation in the Native American population.

Therefore, more in-depth genetic studies are needed to explain the response to SARS-CoV-2 infection observed among the indigenous people in the Amazon.

A third point of view that should be investigated is the increased level of the inflammatory response in COVID-19 patients, which is an important mechanism in the development of the disease. The lack of diverse responses in the population could contribute to not having severe cases of the disease and the low mortality seen among the indigenous groups in the state of Pará.

Several other variables are inherent to epidemics in virgin soil populations, and these include famine, overcrowding, warfare, psychosocial stress and social chaos. These factors may contribute the most to the mortality observed from novel infectious agents in indigenous groups [3]; however, they have not been observed thus far. The understanding of the interaction of genetic and environmental elements is crucial for understanding the innate and adaptive immunological responses, and there could be possible impairment of these factors among isolated indigenous people.

One major reason for the devastating epidemics of emerging infectious diseases among indigenous peoples of the Amazon region of Brazil may be the low genetic diversity in these populations. However, the expected high number of COVID-19 deaths and social chaos were not observed, but these were seen in previous epidemics of variola, measles and influenza. Perhaps a low genetic diversity may also help overcome the inflammatory response secondary to COVID-19. Finally, epidemics in virgin soil populations need further investigation, as the emergence of SARS-CoV-2 requires new insights and a different explanation compared to previous epidemics.

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