Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Highlight

There will be blood☆

Keywords:
Malaria
ABO blood group system
Anaemia
Auto-antibodies

At some point during the recent years, the German language evolved a new word. Technically, it does this all the time, as computer programs tirelessly comb through electronic texts to feed the *Duden*, the ultimate Teuton authority for things to be recognised as official words, in order to adapt to modern times.[1] *Energieeinsparverordnung* (instruction for energy saving) for example has apparently good admission chances,[2] so does Low-Carb-Diät (rather obvious), and altogether, they are a surprisingly accurate sociological readout. Which would in turn explain the emergence of *fremdschämen*, a term which describes a sensation of "vicarious embarrassment", or more concretely, the sensation that arises upon the realisation that one belongs to the same phylogenetic twig as a species, which hoarded toilet paper and set radio towers on fire when confronted for the first time of their lives with a demo version of a global threat. But these are mere fads compared to other deep-rooted, everlasting absurdities, such as the influence of far distant rocks and giant gas balls on our daily chances to conclude the financial deal of our lives, or find our soulmate.

Now, astrology has the arguable merit to have been around for a few centuries, but it turns out that in some places, horoscopes do nowadays not only exist for Gemini, Scorpio and friends, but also for more biologically relevant phenomena – that is to say, blood groups. The latter refer to the copious amount of proteins anchored on the surface or crossing the lipid bilayer of red blood cells (RBCs/erythrocytes). They tend to be glycoproteins, as well as polymorphic, and their diversity is due to variations in oligosaccharide or amino acid sequences and combinations [1]. To date, there exist 38 official systems according to the International Society of Blood Transfusion (ISBT), which is pretty much the Duden of blood groups, aiming "to develop and maintain guidelines for blood group antigen and allele nomenclature for use in Transfusion Medicine and related sciences".[3]

As many certainly remember from their first contact with the notion of allelism during high-school biology class, the poster child of blood groups is the ABO system, discovered in 1900 by the Austrian physician Karl Landsteiner, who noticed that blood from different individuals would often agglutinate upon mixing [2]. Landsteiner was awarded the Nobel Prize in Physiology or Medicine in 1930, ironically around the same time that the *blood type personality theory* emerged under ethically questionable conditions in national-socialist Germany, and got quickly picked up by Japanese social psychologists in order to demonstrate the superiority of some races.

Over the years, and a few lessons from History, the belief mutated into a more harmless version. Nowadays, despite opposing scientific findings, the belief that the ABO blood type dictates personality and compatibility with other people is widespread in Japan, Taiwan and South Korea [3]: blood type O individuals are said to be natural leaders, type A are hard-working and serious, while type B are more creative, and AB somehow bipolar.[4] There are daily horoscopes for blood groups, and it is common to indicate the blood group of a celebrity, just as much as of a fictional character in games, manga, and anime.

No need to blame only the famous Japanese pop-culture here though, as intriguing convictions regarding the power of oligosaccharide-spiked red cells exist all around the globe. Without surprises, a society obsessed with healthy nutrition did not take long to come up with the concept of a *blood type diet*, obviously entirely devoid of any scientific evidence [4], telling O to ingest meat, A tofu, and B liquorice tea.[5] However, unlike the shiny dots in the night sky, blood types *do* actually predict a few things about an individual, notably their susceptibility to certain infections: indeed, blood group components can serve as receptors and co-receptors for various pathogens, or get hijacked for uptake, signalling, and adhesion [1]. Noroviruses for instance, the leading cause for acute gastroenteritis, require the expression of blood group antigens on gut epithelial surfaces for successful infection [5,6], the hepatitis B virus seems to have a preference for blood group A [7], the tastes of the human immunodeficiency virus (HIV) are still under debate [8], and an extremely detailed

☆ Article highlight based on "Effects of IgG and IgM autoantibodies on non-infected erythrocytes is related to ABO blood group in *Plasmodium vivax* malaria and is associated with anemia" by Luiza Carvalho Mourão et al. [15].

[1] https://www.duden.de/ueber_duden/wie-kommt-ein-wort-in-den-duden.

[2] And this is also why I got banned from using German during the "describe it with one single word" round when playing TimesUp.

[3] https://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/.

[4] https://jw-webmagazine.com/blood-type-in-japanese-culture/.

[5] https://www.health.harvard.edu/blog/diet-not-working-maybe-its-not-your-type-2017051211678.

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list of pathogens and their blood type connection can be found in a review by Laura Cooling [1]. It is noteworthy that this connection exceeds often the stage of simple binding between host and pathogen: some microorganisms have learnt to stimulate antibodies against blood group antigens, in order to manipulate the immune system, while blood group antigens can function as decoy receptors, as to prevent the pathogen from accessing its target tissue [1].

In terms of infection rates and disease severity however, the best-studied cases are naturally intra-erythrocytic pathogens, first and foremost malaria.[6]

At this point, it is important to point out that, although the disease is usually associated with the parasite *Plasmodium falciparum* as the automatic culprit, the *Plasmodium vivax* variant is geographically more wide-spread and responsible for almost three-quarters of malaria cases in the Americas [9,10]. There are significant differences in regard to disease pathogenesis, elicited immune response, and life cycle of the two species. Notably, *P. falciparum* merozoites are mainly found in mature RBCs, while *P. vivax* prefers their immature precursors, reticulocytes. Fittingly, another crucial difference is the requirement of the Duffy antigen specifically for *P. vivax* infection [9,11].

To date, most studies, including on ABO groups, have focused on *P. falciparum*, considered for a long time the more virulent of the two species, and causing most malaria cases on the African continent [9]. A recent meta-analysis by Degarege et al. concluded that non-O blood groups had a higher risk of severe *P. falciparum* infection, with no further differences between A, B and AB types [12].

One possible molecular mechanism seems to be the process of "rosetting", the adhesion of infected RBCs to uninfected erythrocytes, which is strongly correlated to severe malaria through complications such as microvascular congestion and the ensuing tissue damage and organ failure. Evidence points towards the blood group A trisaccharides and *P. falciparum* RIFIN molecules as binding partners, with more candidates on the cell surfaces and in the host serum awaiting further investigation for potential therapeutic applications [13].

A few studies also point towards a *P. vivax* – ABO system connection: one of them found for example that the proportion of blood group O individuals was three times higher in *P. vivax* compared to *P. falciparum* infections [14].

Érika M Braga's team addresses in this issue of *Microbes & Infection* not only the relation of *P. vivax* with ABO blood groups, confirming the increased susceptibility of group O individuals, but in addition tackles an important yet often neglected complication of malaria infection, which is anaemia [15]. Direct destruction of RBCs upon the release of parasites and perturbed erythropoiesis would be obvious explanations for anaemia, if it weren't for the fact that much more uninfected than infected RBCs are actually removed – in *P. vivax infection*, the ratio is of 34 [16]. Oxidative stress and lipoperoxidation, leading to 4-hydroxynonenal production, have been invoked as a potential mechanism [17], but Braga's group speculated already in a concise review from 2014 that host immune mechanisms, and an excessive immune response might play a part in malaria associated anaemia pathogenesis, especially upon *P. vivax* infection, which elicits strong inflammation. The authors pointed out that complement activation is systematically increased in malaria, and an insufficient upregulation of regulatory elements could lead to autologous complement-mediated lysis. Moreover, autoantibodies can emerge from cross-reactive antigenicity between host and parasite, or molecular mimicry by the pathogen [16].

Before long, Braga's group provided experimental evidence for the presence of high levels of auto-antibodies against RBCs in *P. vivax* patients with severe anaemia. In addition, they showed that opsonisation with IgG antibodies from anaemic patients of healthy erythrocytes increased their phagocytosis and decreased their membrane flexibility [18]. The study in question did not address yet an additional difference between blood groups regarding the risk to develop anaemic and the involvement of auto-antibodies, as hinted soon by another investigation revealing that *P. vivax* infected individuals of blood type O showed lower levels of haemoglobin and haematocrit compared to type O patients [19].

Here, Mourão et al. combine all three elements, confirm previous findings, and add a layer of molecular mechanisms to the process. They demonstrate that the IgG antibody response of *P. vivax* patients in general is greater against type O than type A erythrocytes, and that anaemic patients in particular exhibit more IgM antibodies against type O. Furthermore, IgG antibodies from anaemic individuals also lead to a greater increase in RBC membrane rigidity, and to more phagocytosis especially of type O erythrocytes [15]. This raises a plethora of new intriguing questions: what boosts the auto-immune response specifically against blood group O RBCs, and if it is potentially triggered by *P. vivax*, and if there is a connection with the patient's blood type, to cite a few.

Without doubt, the overall interest in blood ties with infections is just as topical as ever. Fifteen years ago, some studies associated the ABO system with severe respiratory diseases, and found type O to be more resistant against severe acute respiratory syndrome (SARS) [20]. At the moment of writing (in confinement), a retrospective case study on 2173 patients with COVID-19 and confirmed SARS-CoV2 tests from Wuhan and Shenzen (China) is pending as a pre-print on medRxiv, pointing towards a higher risk for group A, and a lower risk for group O, for contracting COVID-19 [21].

Obviously, the information should be handled not with a pinch, but a handful of salt, in times where rumours and shaky evidence about the effectiveness of the antimalarial drug hydroxychloroquine against COVID-19 prompted people to swallow aquarium cleaner with a fatal outcome.[7] Thus, this is *no* reason to send out only type O family members to do all the shopping, nor hunt them down for their blood. Just in case.

1. Biosketch of Dr. Erika Martins Braga

Dr. Erika Martins Braga is a Full Professor of Parasitology at the Universidade Federal de Minas Gerais (UFMG), Brazil. She received her B.A. degree in biology in 1990 and her Ph.D. in parasitology from the same university in 1997. She has been the head of the Malaria Laboratory of the Parasitology Department at UFMG since 1997. Her research is focused on two distinct approaches: study of the immune response in human malaria and study of the diversity of avian malaria parasites in wild birds. She has spent the last 25 years studying the humoral and cellular immune responses among different populations in the Brazilian endemic Amazon region. Her current research interest includes the study of immunological mechanisms which determine anaemia in patients infected by *P. vivax*.

[6] https://www.who.int/news-room/feature-stories/detail/world-malaria-report-2019.

[7] https://www.npr.org/sections/coronavirus-live-updates/2020/03/24/820512107/man-dies-woman-hospitalized-after-taking-form-of-chloroquine-to-prevent-covid-19?t=1586344071746.

2. Interview with Dr. Erika Martins Braga

2.1. What was your motivation to investigate the association between ABO blood groups and the severity of Plasmodium vivax *infection?*

The ABO blood group system has been associated with severe disease in *P. falciparum* infections, pointing that individuals with A phenotype are at a higher risk to develop severe illness compared to type O phenotype. However, this protective effect of blood group O observed in *falciparum* malaria has never been demonstrated in malaria caused by *P. vivax*. Since immune response, life cycle and disease pathogenesis are different for both *P. vivax* and *P. falciparum*, we postulated that ABO blood groups influence clinical outcomes of *Plasmodium* infection in different manners. Because anaemia is one of the major complications of *P. vivax* infection, which is thought to arise from the destruction of both infected and non-infected red blood cells (RBCs), we decided to test *in vitro* mechanistic evidence in favour of higher susceptibility to healthy RBCs destruction by autoantibodies from *P. vivax*-infected patients from blood group O compared to patients of the blood group A.

2.2. What was your first reaction when you faced the results? Did you expect them?

We were very pleased when we evidenced that IgG antibodies purified from anaemic patients can increase nRBCs membrane rigidity, an effect that is most pronounced in O erythrocytes, promoting *in vitro* phagocytosis. We demonstrated for the first time a possible association between ABO blood groups and the potential removal of nRBCs mediated by autoantibodies in *P. vivax* malaria.

2.3. How will the project go on?

Although we have demonstrated that IgG has a greater effect on membrane rigidity of O nRBCs, we still do not understand how this immunoglobulin induces such effect. It is possible that the binding of antibodies to O-type erythrocytes induces a strong modification on the cell membrane, impeding cell cytoskeleton distortion and leading to a decrease in membrane deformability. Thus, further investigation should be carried out to assess this issue.

2.4. What is the take-home message of the article?

Anti-RBC IgG and IgM are increased in anaemic patients with acute *vivax* malaria and both antibodies can decrease the deformability of nRBCs, but only IgG can induce *in vitro* erythrophagocytosis. Such effects are enhanced in type O erythrocytes, suggesting that individuals from this blood group infected with *P. vivax* malaria may be more susceptible to develop anaemia.

2.5. Do you have a personal motto, quote or leading sentence?

"Nothing is worth more than this day. You cannot relive yesterday. Tomorrow is still beyond your reach." (Goethe).

2.6. What advice would you give to the young next-generation scientists?

Ask new and pertinent questions and do quality science. Never give up!

2.7. What is your favourite hang-out method after a tough day at the lab?

Relax with my family, preparing dinner all together.

2.8. In your opinion, what are the three most important (scientific) discoveries of the last decade?

It is a hard task to select three most important discoveries because in the last decade, scientists have made extraordinary progress to understand the different phenomena involving micro and macro perspectives, from our body to cosmos. Here are some of those important contributions:

- Editing genes: the identification of Crisp-Cas9 system.
- The significant expansion of the human family tree: numerous scientific advances aiming to understand our complex origin story.
- A vaccine and new treatments to fight Ebola: a hope for overcoming the Coronavirus global crisis.

2.9. If you could travel back in time – what historical personality would you like to meet and what scientific discovery to assist to?

As a parasitologist working with Malaria, I would like to meet Dr. Charles Louis Alphonse Laveran during his work in a military hospital in Algeria, which lead to the discovery of the malaria parasite. I would like to assist the microscopic observation of a drop of fresh blood taken from a malaria patient when, in November of 1880, he found inside the red blood cells, numerous pigment-filled moving bodies with flagella-like protrusions.

2.10. If you could travel forth in time – what eventual invention would you like to check out?

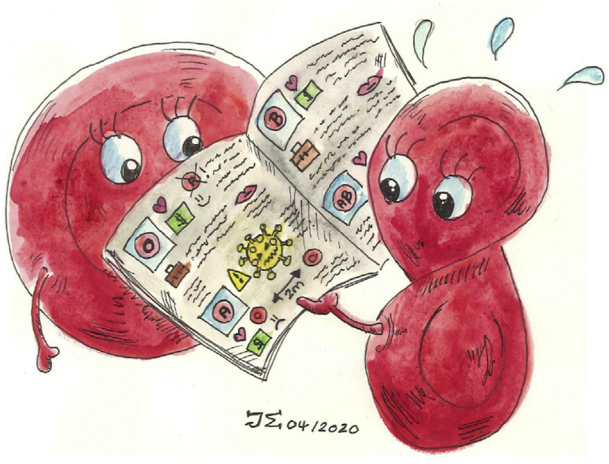
I really would like to check out a vaccine against malaria and new treatment perspectives that could be used to improve the lives of millions of people in endemic countries.

3. Background

- In 2018, 228 million cases of malaria and 405 000 deaths were indexed by the Wold Health Organisation (WHO)
- *P. vivax* causes about ¾ of malaria cases in the Americas
- One of the major complications of malaria is anaemia
- Several blood groups, including the ABO system, have been associated with the susceptibility to contract severe malaria

4. In a nutshell

- *P. vivax* malaria patients were sorted into an anaemic and a non-anaemic category based on a 11 g/dl haemoglobin level cut-off
- Both anaemic and non-anaemic patients display a greater IgG antibody response towards non-infected O than A erythrocytes
- Anaemic patients exhibited more IgM antibodies against group O then group A erythrocytes
- *In vitro,* addition of IgG or IgM antibodies from both patient classes increased the rigidity of group A and O erythrocytes
- Specifically, addition of IgG antibodies from anaemic patients led to a higher increase in rigidity of O erythrocytes compared to A erythrocytes
- Opsonisation by IgG antibodies from anaemic patients only increased the *in vitro* phagocytosis of both A and O erythrocytes, with a greater increase for type O phagocytosis rates



Declaration of Competing Interest

The author declares no conflict of interest.

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