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LETTER TO THE EDITOR

Unlikely influence of ABO blood group polymorphism on antibody response to COVID-19 mRNA vaccine against SARS-CoV-2 spike protein

We [1] and others proposed two possible mechanisms of the association between ABO blood groups and SARS-CoV-2 susceptibility/COVID-19 severity. The consensus is higher and lower risk for people in groups A and O, respectively. First, viruses can express A/B glycans on the spike protein, reflecting the ABO phenotype of the host cells in which they are produced, and natural antibodies can react to corresponding antigens and inhibit interpersonal infection, at least partially, resembling 'ABO-matched' and 'ABO-unmatched' transfusion (Figure 1). Second, lower serum levels of von Willebrand factor and factor VIII, essential for blood clot formation, could explain a lower risk of thrombosis, pulmonary embolism and venous thromboembolism in group O individuals. After reviewing the literature, Le Pendu et al. [2] concluded that the ABO polymorphism could play a role in the COVID-19 pandemic at the population level despite modest differences in risk between ABO groups.

In the recent issue of Vox Sang, Vicentini et al. [3] published a letter to the editor entitled 'Does ABO blood group influence antibody response to SARS-CoV-2 vaccination?'. The authors examined IgG titre against spike protein in 85 medical students who completed a full two-dose Pfizer/BNT162b2 mRNA vaccination and found no significant difference between ABO groups.

There are four main categories of COVID-19 vaccines: whole virus, protein subunit, viral vector and nucleic acid (Figure 2). An immune

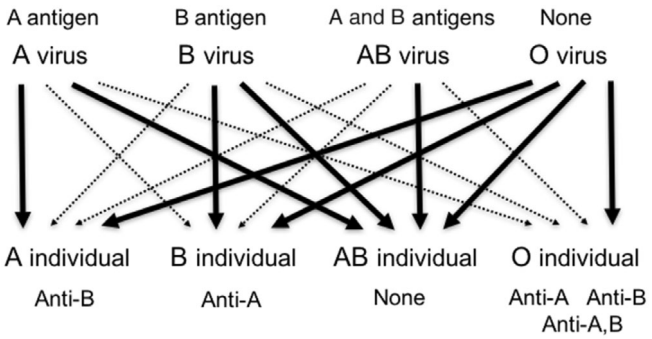

FIGURE 1 ABO-dependent inhibition of infection between SARS-CoV-2 viruses presenting different ABO phenotypes and individuals from groups A, B, AB and O. Solid and dotted arrows indicate infectivity without and with ABO-dependent inhibition, respectively. Inhibition is directional. Newly produced SARS-CoV-2 viruses exhibit the same ABO phenotype as the infected individual and are no longer neutralized (reproduced from Reference [1]).

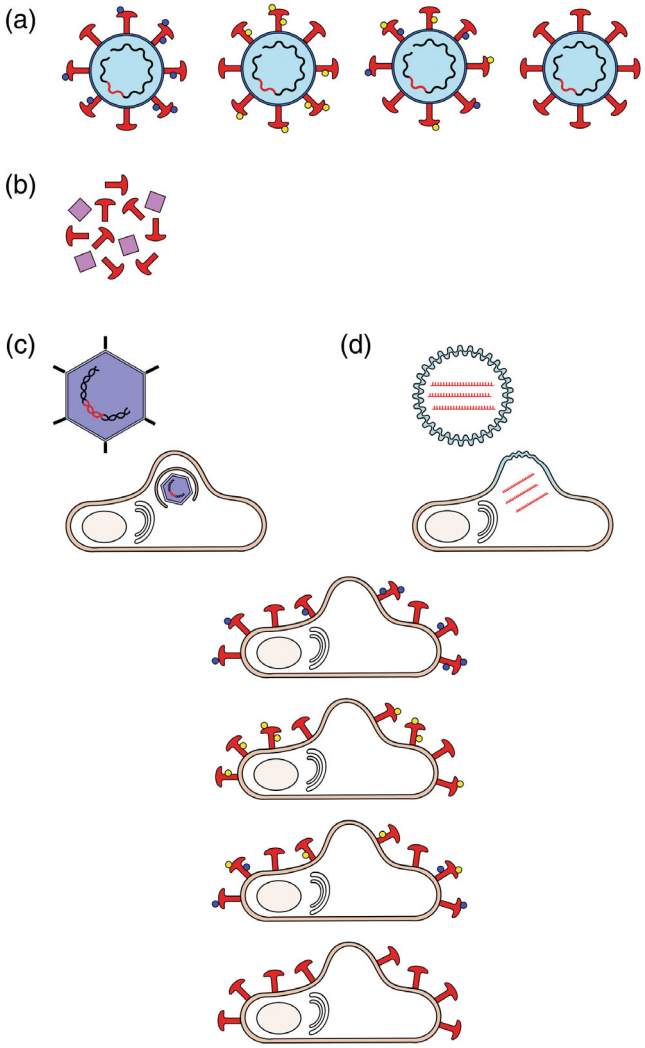

FIGURE 2 Four main categories of COVID-19 vaccines and the expected presence or absence of ABO blood group association. (a) *Whole virus*: A virus, B virus, AB virus and O virus are shown from left to right with the A and B glycans in blue and yellow circles. Natural antibodies can neutralize vaccinated viruses in an ABO-dependent manner. (b) *Protein subunit*: Protein subunit vaccines produced in bacteria or yeast do not carry the A/B glycan antigens. As a result, no ABO association is expected. (c) *Viral vector*: A harmless virus, such as the adenovirus, is used to introduce genetic instructions into the cells to produce the spike proteins. The cells can express the A/B-glycosylated proteins in the vaccinated individuals (A cell, B cell, AB cell and O cell are shown from top to bottom). No ABO-dependent inhibition is expected. (d) *Nucleic acid*: The mRNA case is shown, where mRNA molecules are embedded in lipid nanoparticles. No ABO-dependent inhibition is expected.

response is elicited, largely to the spike protein that viruses use to invade cells. When whole viruses are produced in human epithelial cells, they can be A/B-glycosylated and thus subject to ABO-dependent inhibition by natural immunity. However, those produced in cells with O phenotype can be used for universal vaccination, bypassing the inhibition. Protein subunits prepared for COVID-19 vaccination typically lack A/B glycosylation. Viral vectors, as well as nucleic acids, such as DNA and mRNA, induce spike protein expression on the cell surface. Although muscle cells do not express A/B glycans, the proteins can be A/B-glycosylated in other cell types depending on the ABO phenotype of the vaccinated individuals. However, these glycans do not cause ABO-related immune reactions because they are compatible. Consequently, ABO groups are unlikely to affect the anti-spike protein immune response. In contrast, the negative results of Vicentini et al. fit well with the natural immunity model to explain the ABO association with SARS-CoV-2 infectivity.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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