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HYPOTHESIS

The impact of the global distribution of bats on mortality in COVID-19 patients

Andrej Egorov, Julia Romanova[#]

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[#] *Corresponding author*: Julia Romanova, e-mail: jr.romanova@gmail.com

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated in November 2019 in China and quickly spread throughout the world causing a disease named COVID-19. An analysis of the epidemiological data on morbidity and mortality caused by SARS-CoV-2 shows that, in some countries, namely Belgium, UK, France, Italy, the Netherlands, and Spain, an increased case fatality rate (CFR) was noticed compared to the rest of the world. The CFR, calculated as the number of deaths from the total number of the cases, ranges in these countries from 10.22% to 15.8% according to the Center for Evidence-Based Medicine (CEBM). At the same time, in the countries of Central and Northern Europe, this parameter varies between 3.78% and 4.94%. This significant heterogeneity in CFR between countries has not been given a convincing explanation yet. It was found that the precursor of SARS-CoV-2 is a virus circulating in bats in China. The mutations that occurred in this virus altered its receptor specificity, thereby enabling viral infection in humans. Bats are highly resistant to viral infections due to their robust interferon system and a reduced level of inflammatory reactions. Viruses replicate in these animals up to high titers without any substantial harm to their health. As a result, bats represent a large reservoir of viruses with the potential to infect other animals, including humans. The infection of people with bat (or human) betacoronaviruses can lead to the formation of memory B-cells that provide an accelerated antibody response to cross-reactive epitopes upon subsequent infection. The early emergence of neutralizing antibodies in SARS-CoV-2 patients correlates with the severity of the disease and the likelihood of a fatal outcome. The antibody-dependent enhancement (ADE) of infection/disease known for various viruses, including SARS-CoV-1 and MERS-CoV, may be a possible cause of this phenomenon. In this article, we suggest a close connection between the distribution areas of bats carrying SARS-CoV-1-like viruses and the CFR from COVID-19.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the family *Coronaviridae*, subfamily *Coronavirinae*, genus *Betacoronavirus*. Coronaviruses are widespread among mammals and birds and cause respiratory, intestinal, neurological diseases as well as hepatitis [1]. The subfamily *Coronavirinae* includes 4 genera: *Alfacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltakoronavirus*. The disease caused by SARS-CoV-2 is named COVID-19.

Coronaviruses enter the cell using the S protein, a glycoprotein that forms viral spikes, which are the main targets for neutralizing antibodies [2]. The S protein consists of two subunits: the variable S1, comprising a receptor-binding site, and the more conserved S2, which is responsible for the fusion of the viral and cell membranes. The receptor for SARS-CoV-1 and SARS-CoV-2 viruses is the membrane-bound angiotensin-converting enzyme 2 (ACE2), and for the Middle East respiratory syndrome coronavirus (MERS-CoV), it is the dipeptidyl peptidase-4 (DPP4) [3]. The affinity of SARS-CoV-2 for ACE2 is 10–20-fold higher than that of SARS-CoV-1 [4], which contributes to the increased transmissibility of the virus in humans.

In the majority of patients infected with SARS-CoV-2, the disease is asymptomatic or causes mild respiratory symptoms. However, almost 55% of symptomatic patients develop respiratory failure approximately by the eighth day of the disease, associated with bilateral multilobal pneumonia [5]. In 29% of these patients, pneumonia progresses to a severe stage with the development of a cytokine storm and acute respiratory distress syndrome (ARDS) often leading to a fatal outcome [5-7].

Like SARS-CoV-1 and MERS-CoV [8, 9], SARS-CoV-2 infection causes increased secretion of cytokines and chemokines, such as interleukin-1β (IL1β), interferon-γ (IFNγ), IFNγ inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), IL4, and IL10. In patients with a more severe form of infection, requiring intensive therapy, high levels of IL2, IL7, IL10, granulocyte-macrophage colony-stimulating factor (GMCSF), IP10, MCP1, macrophage inflammatory protein-1α (MIP1α), and tumor necrosis factor-α (TNFα) are observed in plasma

indicating a cytokine storm [5, 10]. Based on postmortem examination of deceased patients, the virus is found not only in alveolar epithelial cells but also in alveolar, lymph node and spleen macrophages [11].

A correlation between the disease severity and the early development of an antibody response was found in patients during the SARS-CoV-1 outbreak in 2003. In patients with a severe form of the disease, who required additional oxygen and hospitalization in the intensive care unit (ICU), the antibodies emerged as early as on the 4th day post symptoms onset with early seroconversion (<16 days) and high IgG antibody titers [12, 13]. In these patients, the disease outcome was more often fatal. In milder cases, specific antibodies emerged 2–3 weeks after infection, with seroconversion occurring on average in 20 days [13-15]. Antibody titers in asymptomatic patients were low, and seroconversions were rare.

Similarly, in patients infected with SARS-CoV-2, the severity of the disease was positively correlated with antibody titers [5]. In patients admitted to the ICU, the emergence of neutralizing antibodies was recorded as early as 5-14 days after the onset of symptoms [16].

One of the reasons for the early antibody response may be the presence of memory B-cells formed during a previous infection with antigenically related viruses. It is known that betacoronaviruses can induce cross-reactive antibodies against each other. For instance, over the course of a human coronavirus OC43 infection, antibodies against SARS-CoV-1 were induced and vice versa [17, 18]. Neutralizing antibodies to the MERS-CoV virus that occurred in 2012 were found in the sera of patients recovered from SARS-CoV-1 disease [17, 19], and neutralizing antibodies to SARS-CoV-2 were revealed in the sera of healthy donors in 3% of all cases [16].

It is known that in SARS-CoV-1 patients, antibodies to the S protein can enhance the pathology due to antibody-dependent disease enhancement (ADE) [20]. An immunodominant B-cell epitope in the S protein (597-603 aa) was mapped utilizing post-infection sera of patients recovered from SARS-CoV-1. Antibodies specific to this epitope elicited not only neutralizing but also enhancing effects on infection in non-human primates [21]. The ADE phenomenon is known for various viral infections. In the late 1960s, vaccination of children against respiratory syncytial virus (RSV) led to the hospitalization of 80% of children with severe respiratory disease, with two children dying. It has been suggested that the cause of this disastrous vaccination result was the development of ADE [22, 23]. ADE is also described for dengue virus, influenza virus, and Ebola virus [24-27].

The principle of the ADE lies in binding of the anti-S antibodies to the S protein on the viral surface, followed by docking of the immune complex to the surface of immunocompetent cells (monocytes, macrophages, or B-cells) through the interaction of their Fcγ receptor (FcγR) with the Fc fragment of the antibodies [28]. Therefore, the virus can infect macrophages bypassing ACE2 receptor. The interaction of neutralizing antibodies with the receptor-binding site of the SARS-CoV-1 S protein has also been reported to induce conformational change with the subsequent activation of the fusion protein, enabling the infection of macrophages and leading to transcription of virus genome [29, 30]. Although the infection of macrophages does not lead to productive virus replication, their interaction with the virus causes a skew towards proinflammatory M1 macrophages (Fig. 1).

Accumulation of M1 macrophages in the lungs leads to the increased production of chemokines, such as MCP1(CCL2) and IL8(CXCL8), which cause lung infiltration by proinflammatory leucocytes. As a result, there is a sharp increase in inflammation in the lung tissue, accompanied by hypercytokinemia and the development of ARDS [31, 32]. This process has been shown to depend on the concentration and affinity of anti-S antibodies. ADE occurred at suboptimal concentrations of antibodies or, in the case of their low affinity, when the virus was insufficiently neutralized [33, 34]. Neutralizing anti-S antibodies decreased the virus titer in macaques, at the same time significantly increasing pulmonary pathology [31]. A reduction in pathology was achieved by blocking FcγR [31]. Therefore, immune complexes played a key role in the development of ADE, and the observed organ failure in the cases of severe infection was caused not by excessive virus replication but rather by the hyperactivation of the innate inflammatory response [14].

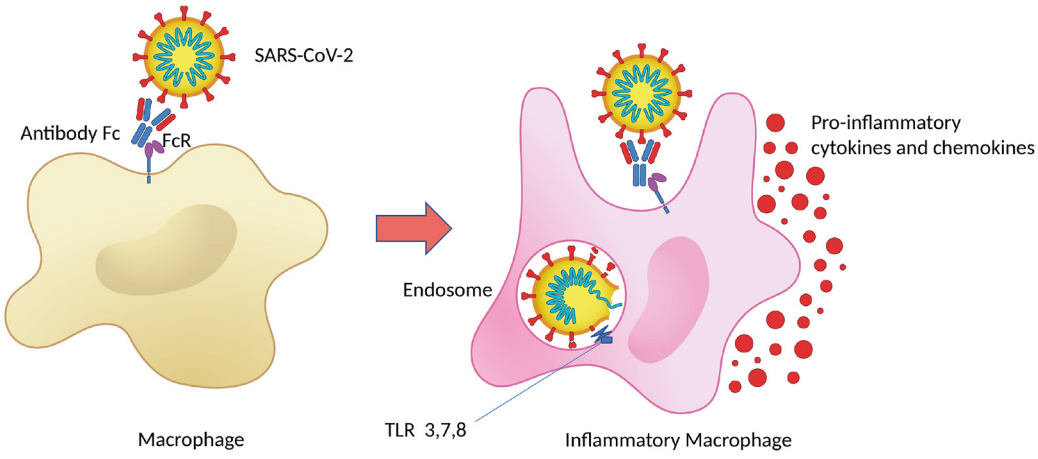

Fig. 1. Mechanism of the antibody-dependent enhancement of infection/disease (ADE).

It can be assumed that over the course of the COVID-19 disease ADE underlies the complications that occur in cases with an early development of the antibody response due to the presence of memory B-cells – potential producers of antibodies to the S protein of antigenically related coronaviruses.

Attempts to identify the host of SARS-CoV-1 in China have shown that a closely related virus circulates in horseshoe bats belonging to the genus *Rhinolophus*, the family *Rhinolophidae*, and the order *Chiroptera* [35, 36]. The genome sequence of the first SARS-CoV-2 strains shares up to 86.9% sequence identity with that of the bat-SL-CoVZC45 coronavirus previously isolated in China [37]. The SARS-CoV-2 S protein shares between 75.7% and 97.7% sequence identity with that of other bat coronaviruses [38, 39]. Consequently, people who come into contact with bats may have antibodies or memory B-cells that recognize SARS-CoV-2 antigens due to past infections with antigenically related coronaviruses that caused mild or asymptomatic disease.

Bats are used for food in southern China and other countries in this region. Live bats are commonly sold in markets and are used for cooking in restaurants in southern China. This practice significantly facilitates the contact between bats and other animals and leads to infection in humans [20]. The presence of elevated antibody titers to viruses close to SARS-CoV-1 in people associated with live animal markets confirms the fact that people are infected with viruses from bats [40]. The ADE effect may explain the increased number of severe COVID-19 cases with a fatal outcome in China among people associated with such markets [5]. After the 2002/2003 SARS-CoV-1 outbreak, the evaluation of coronaviruses distribution in the world has identified bats as a natural reservoir of coronaviruses not only in China but also in Europe, America, and Australia [41].

Bats are the only representative of mammals capable of active flight. Flight is associated with enhanced cellular metabolism and increased body temperature (up to 41°C in some bats), which increases the risk of damage to genomic DNA. The evolution of bats made it possible to prevent inflammatory reactions by weakening the cytoplasmic sensors of abnormal DNA and DNA pathogens, such as stimulators of IFN genes (STING) as well as by reducing the level of inflammatory cytokine production, for example TNFα [42, 43]. Due to a decrease in the intensity of protective inflammatory responses, the sensitivity of bats to virus infection increased, which was compensated by the development of more effective antiviral measures, such as high constitutive expression of INF and unique interferon-stimulated genes (ISGs). Due to the powerful IFN response system and the ideal regulation of inflammatory responses, bats have acquired high resistance to viral infections [42, 43]. RNA viruses replicate in these animals to high titers and persist without causing significant harm to their health. As a result, a large number of bats act as a source of viral infections in humans and other animals. These include dangerous infections, namely coronaviruses (SARS-CoV-1, MERS-CoV), filoviruses (Ebola and Marburg viruses), and henipaviruses (Hendra and Nipah viruses) [44]. The emergence of the SARS-CoV-2 infection in 2019 is another striking example. Humans, who have a less sophisticated mechanism for inflammation control than bats, may develop a pathological response of the innate immune system, such as a cytokine storm and ARDS.

Bats live in colonies of up to hundreds of individuals. Animal nests are often located in parks and in the immediate vicinity of residential buildings. Bats secrete viruses with feces, in which the amount of virus can reach $2.4x10^8$ copies/g [45]. All species of bats in Europe are protected by the European Union Directive on the Conservation of Natural Habitats and Wild Fauna and Flora [46] and the Agreement on the Conservation of Populations of European Bats [47].

Of the four known genera of coronavirus, only two were found to circulate in bats: *Alfacoronavirus* and *Betacoronavirus*. Since 2010, alfa- and betacoronaviruses are constantly detected in Italian bats [48-50] and, therefore, in the provinces of Piedmont and Liguria, up to 26% of the bat colonies are infected [51]. In 13 regions of Spain, an examination of 576 individual bats of various species led to the identification of 14 new alpha- and betacoronaviruses [52]. In the Netherlands, betacoronaviruses were isolated from 211 bats, mostly of *Pipistrellus* genus, in 31 settlements. Their colonies are widely distributed in urban areas. The infection rate of bats with coronaviruses was found to be 16.9% in the Netherlands [53] and 37.9% in France [54]. However, the distribution of coronavirus-carrying bats is heterogeneous. Therefore, in Germany, when studying 653 bats in three regions, coronaviruses were found much less often, only in 1.4-3.1% of cases [55]. The most frequently detected viruses in bats in Germany were astroviruses of *Astroviridae* family, from 25.8% to 65%.

In many European countries, including Italy, Spain, France, and Bulgaria, SARS-CoV-1-like betacoronaviruses were isolated exclusively from horseshoe bats of the genus *Rhinolophus* [51] as well as in China, thereby confirming the specificity of this host for SARS-CoV-1-like viruses. Fig. 2 shows the distribution of *Rhinolophus* bats – carriers of SARS-CoV-1 – in the world. It is important to note that, in addition to China and Southeast Asia, this genus of bats is widely represented in Southern Europe and Middle East but it is absent in Northern Europe.

When comparing the mortality rate of COVID-19 according to the Center for Evidence-Based Medicine (CEBM) (Table 1) with the distribution areas of *Rhinolophus* bats that carry SARS-CoV-1-like viruses, it is clear that an increased mortality from COVID-19 (with CFR higher than 10) [56] is observed in countries where these bats are widespread, such as Spain, France, Italy, the Netherlands, and the UK. In countries where *Rhinolophus* bats – carriers of SARS-CoV-1-like viruses – have not been detected, the mortality rate is significantly lower (the CFR is 4-6). Therefore, we assume that high CFR in COVID-19 patients may be associated with the preexisting non-protective immunity to related coronaviruses in people living in the areas that are natural habitats of infected bats. Among the countries of Northern Europe, Sweden

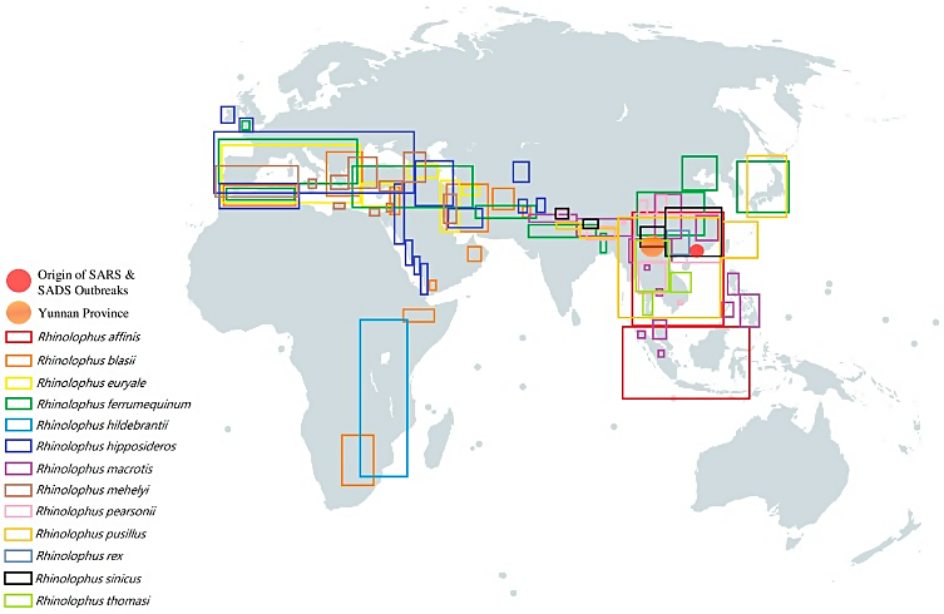

Fig. 2. Geographical distribution of *Rhinolophus* bats that carry SARS-CoV-1-like coronaviruses [41].

Table 1. Global COVID-19 Case Fatality Rates according to the Centre for Evidence-Based Medicine (April 30, 2020) [56].

Country	Number of deaths	Number of cases	Case fatality rate, %
Belgium	7844	49906	15.72
UK	28446	186599	15.24
France	24895	168693	14.76
Italy	28884	210717	13.71
Netherlands	5056	40571	12.46
Sweden	2679	22317	12.00
Hungary	351	3035	11.57
Spain	25364	247122	10.22
Indonesia	845	11192	7.55
Slovenia	96	1439	6.67
Egypt	429	6465	6.64
Philippines	623	9485	6.57
Iran	6203	97424	6.37
USA	68602	1188421	5.77
China	4633	82880	5.59
Denmark	484	9670	5.01
Switzerland	1473	29905	4.93
Poland	683	13937	4.90
Finland	230	5254	4.38
Germany	6866	165664	4.14
Austria	598	15597	3.83
Japan	487	14877	3.27
Estonia	55	1703	3.23

stands out, where no coronavirus-carrying bats have been detected, but a high mortality rate is observed (the CFR is 12). Besides the fact that Sweden was one of the few European countries without a lockdown, this phenomenon could be explained by recently published information that, in Sweden, the majority of lethal outcomes from COVID-19 are observed among immigrants from Syria, Iraq, and Afghanistan – the countries that are part of the distribution zone of SARS-CoV-1-like virus carrying bats [57]. A similar situation is in the UK, where patients belonging to minorities groups die from coronavirus infection 27% more often than the general population of the UK [58]. It should be noted that some areas of the UK are the natural habitats of bats of the genus *Rhinolophus* that carry SARS-CoV-1-like coronaviruses. Social reasons could not be excluded too.

Significant differences in the CFR of COVID-19 in various countries can be explained by a number of reasons

such as the BCG vaccination of population [59], vitamin D deficiency [60], as well as by political and social reasons. However, our hypothesis about the correlation between the population density of bats, which are a natural reservoir of various SARS-CoV-1-like coronaviruses, and the mortality rate from COVID-19 in some countries also deserves thorough consideration. Contact between humans and bats in countries with high population densities of the latter can lead to repeated asymptomatic infection during an individual's lifetime. The likelihood of such infection is low for children and young adults and increases with age, which is consistent with the data showing fewer deaths observed for patients under 20 years of age with the same frequency of diseases in different age groups. The resulting memory B-cells can lead to accelerated antibody production during a subsequent SARS-CoV-2 infection. Early emergence of low-affinity antibodies in COVID-19 may provoke the infection of macrophages and hyperinflammatory response of the innate immune system. Therefore, the presence of immunity to coronaviruses, gained in the course of previous infections, may have a damaging effect in individual patients depending on the presence of the memory B-cells to cross-reactive epitopes of antigenically related coronaviruses. The screening of healthy people for the presence of memory B-cells to SARS-CoV-2 antigens may be a way to assess the risk of COVID-19 severe complications.

CONFLICT OF INTEREST

The authors declare that there is no commercial or financial conflict of interest.

CITATION

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