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Apparent difference in fatalities between Central Europe and East Asia due to SARS-COV-2 and COVID-19: Four hypotheses for possible explanation

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ABSTRACT

The comparison of the numbers of cases and deaths due to SARS-CoV-2/COVID-19 shows that people in Central Europe are much more affected than people in East Asia where the disease originally occurred. Trying to explain this difference, this communication presents four hypotheses that propose the following reasons for the observed findings: 1) Differences in social behaviors and cultures of people in the two regions; 2) Possible outbreak of virulent viruses in Central Europe due to multiple viral infection, and the involvement of immuno-virological factors associated with it, 3) Possibility of corona resistance gene mutation occurring among East Asians as a result of long-term co-evolution of virus and host, and 4) possible involvement of hygienic factors. Direct or indirect supportive evidences for each one of our hypotheses are presented and experimental approaches for their evaluation are discussed. Finally, we suggest that the dynamics of the pandemic also shows that the problems of the new coronavirus can be overcome due to people's awareness of the epidemics, rational viral diagnostics and a high level of medical care.

Introduction

The new coronavirus SARS-CoV-2, causing an infectious disease named COVID-19 has caused a major pandemic with more than 13 million people infected and more than 570,000 already dead [1,2]. Its momentum is disrupting the economy, society, and healthcare systems, filling hospitals with patients, emptying public spaces, and drawing people away from work and friends.

Due to the test strategy used in nearly all countries, “people infected with SARS-CoV-2” or simply named “COVID-19 cases” are usually people with clinical symptoms or contacts to infected people. The number of infected people without clinical symptoms is therefore unknown. Further testing, including antibody tests, will most likely reveal that much more people around the world have been infected than the number of defined cases of COVID-19. This may upset modern societies on a scale never seen before. On the other side, it may be assumed that these infected people might contribute to herd immunity and slow down further spread of the virus, provided their antibody response is longer lasting and has neutralizing potential. These aspects need further experimentation and proof.

In the 21st century, information (including scientific and technological knowhow) circulates around the world instantly. The world has entered an era where the traffic of people, economic goods, money, but also viruses and other microbes seems to be nearly unlimited. Therefore, after the outbreak of the new coronavirus epidemics in China, the transport of the virus to other parts of the world, particularly to Europe, was fast and efficient.

Of particular note is the striking difference in the extent of medical impact caused by SARS-CoV-2 in Eastern Asia versus Central Europe [3,4]. This difference is prominent, when i) the number of infected persons with clinical symptoms, ii) the ratio between infected people with clinical symptoms and the total population of the countries, iii) the number of deaths, or iv) the death ratios of infected people with symptoms are compared between Eastern Asia and Central Europe. In this communication, we compared selected countries from Central Europe and East Asia with respect to the medical impact of SARS-CoV-2 and COVID-19. Based on this analysis, we propose four hypotheses that might explain the observed differences. For each one of these hypotheses, we present direct or indirect evidences to support them. None of these hypotheses by itself can explain the observed differences.

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Table 1
Coronavirus cases and deaths in Central Europe and East Asia.

Country	Population (millions)	GDP	Cases	Deaths	Cases /1 million	Deaths /1 million	Deaths /Cases (%)
USA	327.09	62,689	1,236,987	72,241	3,737	218	5.8
Spain	46.69	30,733	250,661	25,613	5,359	548	10.2
Italy	60.62	34,321	213,013	29,315	3,523	485	13.7
UK	67.14	42,580	194,990	29,427	2,872	433	15.0
France	64.99	42,953	170,551	25,531	2,613	391	14.9
Germany	83.12	47,662	167,007	6,993	1,993	83	4.1
China	1427.64	9580	82,881	4636	58	3	5.5
S. Korea	51.17	33,320	10,804	254	211	5	2.3
Japan	127.20	39,304	15,078	536	119	4	3.5
Taiwan	23.72	25,008	438	6	18	0.3	1.3

Data of population for each country were obtained from the World Population Prospects (2019 Revision from WHO, https://w.globalnote.jp/post-1555.html). Nominal GDPs per capita in the world are expressed in US$ based on 2018 IMF statistics. Tot Cases/1M Pop and Deaths/1M Pop = Total cases and Deaths per nation's total population (per million people), respectively. As of 6 May 2020 (https://www.worldometers.info/coronavirus/).

Rather, the mechanisms defined in individual hypotheses seem to interact and thus cause the overall effect observed. We are aware that additional mechanisms, not covered by our analysis, may also contribute to the pandemics.

Facts

For the analysis of the difference regarding the number of infected people and the death tolls due to COVID-19 between Central European and East Asian countries, we have chosen Italy, Spain, France, Germany and UK from Central Europe and China, South Korea, Japan, and Taiwan from South East Asia. Mongolia and North Korea were excluded, since not sufficient information was available from both countries. For comparison, the United States, which have the highest number of infected and dead people due to COVID-19, were included into our analysis.

Table 1 first shows the populations and GDPs, in order to help estimating the scale, medical level, and affluence scale of the selected countries. It is obvious that East Asia is one of the most densely populated areas in the world. It can also be seen that there is not much difference with respect of the GDPs, except for China. However, China's GDP has grown rather rapidly in recent years, and it is certain that it will reach the economic level of the other countries sooner or later.

Table 1 also shows COVID-19 cases and deaths in Central Europe and East Asia. The numbers of cases (most of them with clinical symptoms) in Central European countries ranged from 1993 to 5359 per million people, whereas those of East Asian countries were in the range of 18 ~ 211. The ratio between the two was about 32. These numbers depend on the number of tests performed in individual countries, as well as on differences in the test strategy, resulting in a certain degree of uncertainty. To get a more precise picture of comparison, COVID-19-related deaths per nation's total population (per million people) were calculated based on the total population of each country. As seen in Table 1, the numbers of Central European countries were in the range of 391–548 deaths/million people, with the only exception being Germany's lower number of 83. In contrast, deaths/million people in East Asian countries were in the range of 0.3–5, i. e. they were nearly 150 times lower than the values found for Central European countries. Importantly, also the death rate of infected people seems to be much lower in East Asian countries, compared to the Central European countries (except Germany).

The relatively lower number of infected people as well as COVID-19-associated deaths in Germany seems to be due to strong differences in the percentage of infected people with clinical symptoms between the south and north of Germany (Table 2). It seems that measures taken after the first cases in Bavaria (a large state in the South East of Germany, which was first hit by the pandemics) were successful to prevent a strong spreading on the long run. Germany had the advantage to be affected by COVID-19 later than China and Italy. Getting valuable information from other countries was essential for slowing down and partially restricting the pandemics in Germany. Furthermore, the relatively high availability of equipment for intensive care reduced the death rate of infected people. Importantly, the picture of inhomogenous distribution of the disease and associated deaths as seen for the whole of Germany is also seen when the spreading of infections and deaths is analyzed within Bavaria, the state being affected the most (Table 2). The detailed analysis of cases and deaths in districts points to hotspots of infection and death, from which the neighbouring areas seem to be reached out. This results in an overall picture with a relatively high number of cases and deaths in the hotspot (Tirschenreuth) that far exceeds the average number of cases / population and deaths / population of total Germany. The immediate neighbouring districts in the

Table 2
Coronavirus cases and deaths in selected States within Germany and districts within Bavaria.

Localization	Population	Cases	Cases /100,000	Deaths	Deaths /100,000	Deaths /Cases (%)
States:						
Bavaria	13,076,721	44,265	338	2153	16.4	4.8
Bad. Württ.	11,069,533	33,287	300	1542	13.9	4.6
Meckl.-Vorp.	1,609,675	726	45	19	1.1	2.6
Schlesw.-Holst.	2,896,712	2938	101	123	4.2	4.1
Bavarian districts:						
Tirschenreuth	72,504	1122	1547	129	177.8	11.4
Wunsiedel	73,178	627	856	36	49.2	5.7
Neustadt/WN	94,352	782	828	62	65.7	7.9
Oberallgäu	155,362	172	110	7	4.5	4.2
Main-Spessart	126,365	147	116	6	4.7	4.0
Regensburg	193,572	436	225	14	7.2	3.2

The table presents selected data on Covid-19 for Germany, based on data released from the Robert Koch Institute, a federal agency for disease control, on May 10th 2020. The data show that the two most southern states, Bavaria and Baden-Württemberg have much more cases of Covid-19 and Covid-19-related deaths (both in absolute numbers and per 100 000 people) than the two northern states Mecklenburg-Vorpommern and Schleswig-Holstein. Within Bavaria, there are very strong differences between Tirschenreuth (one of the hotspots of Covid-19 in Germany, located in the north east of Bavaria on the border to the Czech republic) and its directly neighbouring districts Wunsiedel (in the north) and Neustadt/Waldnaab (Neustadt/WN) (in the south), compared to districts that are more distant to the hotspot (Oberallgäu in the north west corner, Main-Spessart in the south west corner and Regensburg in the center of Bavaria). Taken together, these data show the high efficiency of SARS-CoV-2 for spreading from a site of initial infection, but also the efficiency of adequate countermeasures taken. Abbreviations: Bad. Württ. = Baden Württemberg; Meckl.-Vorp. = Mecklenburg-Vorpommern; Schlesw.-Holst. = Schleswig-Holstein.

north and south show about half the cases / population and less than half the deaths / population than the hotspot, whereas districts distant of the hotspot are characterized much lower numbers. This picture points to strong initial effects from local infection events, but, importantly, it also indicates that further spreading had obviously been prevented through adequate measures.

Since the data on the number of COVID-19-caused deaths in each country gave reliable data that showed strong differences between East Asian and Central European countries, we tried to explain these differences by four intercalated hypotheses.

Hypotheses

General view

Given the host-virus relationship, it is necessary to consider factors affecting both virulence of the pathogens and the resistance of the hosts to virus infection. Several aspects might be involved in the difference. For example, Lippi et al. investigated potential reasons for the noticeable difference in COVID-19-associated mortality rates between Asian and European populations from clinical and demographic aspects in Italy versus China [5]. These authors confirmed that a higher burden of comorbidities, male sex, and older age may be considered substantial determinants of enhanced risk of death in Italy compared to China. Similarly, in New York City where the highest number of deaths is recorded compared to other states in the United States, factors such as high population density, the possible super spreaders of virus, the degree of poverty between races, and the lack of insurance have become important issues [6].

Specific hypotheses

Hypothesis # 1: socio-behavioral aspects determine the observed differences

Hypothesis #1 is based on the difference in social behavior and customs of people in each area, i.e. in Europe and South East Asia. This might explain the difference to some extent. When comparing the lifestyles of European countries with that of Asia, the first noticeable difference is the closeness of direct human contact. In Asia, bowing is the mainstream greeting, and even with the spread of Western culture, shaking hands is still not very common. Of course, besides handshaking, there can be no hugs or kisses that are popular in Western culture (if any, those are performed only after building a very close relationship). It is easy to imagine that these common actions in Western societies help to spread respiratory viruses like SARS-CoV-2 very efficiently. These differences between Europeans and Asians, considered from a perspective of the social science might be very important in the progress of the pandemic.

There is also a marked difference in obesity between Westerners and Asians, mainly due to differences in food culture. In addition, people wear shoes indoors in Western societies, while it is strictly forbidden to do so in East Asia. Although the weight of this habit in preventing virus infection is not clear at this moment, this difference indicates that Asians very clearly distinguish between outdoor and indoor in daily life. The habit of wearing a mask in case of a cold or fear of it also seems quite Asian-specific. Thus, it is very likely that differences with respect to these actions play an important role in the spread of infection.

Evidence supporting hypothesis #1. Social distancing has been proven to avoiding new corona infections, and is a drug-free means of controlling de novo infections. Shaking hands, kissing, and hugging are not allowed during social distancing. In favour of our hypothesis #1, the switch from European style of close contact to the Asian style during social distancing is regarded as an essential part of successful slowing down and preventing further infections with SARS-CoV-2.

Hypothesis # 2: the differences are determined by virological aspects

Potential effects of repeated infection on the severity of the clinical outcome, contributions of antibody-mediated enhancement of infection to the severity of disease, as well as genetic changes of the virus due to mutation of its RNA genome might be underlying the observed effects.

Evidences supporting hypothesis #2. In Italy, the death toll from the new coronavirus was 25,085 by the April 22, the third highest in the world after the United States and Spain. Of these, more than 10,000 people were confirmed to be infected among medical staff. This finding shows that inadequate protection of medical staff from infection is a major issue. Many of the doctors who died were practitioners. They were fighting the new coronavirus without adequate protective equipment (sometimes due to unavailability of material) or underestimation of the contagiousity of the new virus, driven by the strong wish to help their patients. Thus, it is highly likely, especially during the medical collapse, that these doctors will have got infections repeatedly from the infected patients one after another. So the question is what would be expected if a person is infected with coronavirus multiple times.

Under the conditions of in vitro experiments, the degree of virus-induced cytotoxicity (that is, the severity of symptoms) is clearly proportional to the multiplicity of input (amount of virus inoculated). In other words, the greater the amount of virus (or the more frequently the virus infection takes place), the faster (and more strongly) the degree of cell damage (symptoms) appears. The more contagious and infectious the virus, the more difficult it is for the host to control its replication and spread. This explains the effect of high virus doses very well. The enhancing effect of repeated application of lower doses of virus is more complex, but there exist interesting examples in the literature. Using a challenge model by infecting mice repeatedly in short intervals with low doses of influenza A virus, Song et al. reported that compared to a single high-dose infection, mice that received repeated low-dose challenges showed earlier morbidity and mortality and more severe disease [7]. Mice developed higher viral loads, more severe lung pathology, and greater inflammatory responses and generated only limited influenza A virus-specific B and T cell responses. Although several pathways could contribute to higher viral loads in mice that received influenza A virus repeatedly, the authors suggested the possibility that the inflammatory response elicited by the first dose of influenza A virus damaged the mucosal barrier, thus allowing the virus given as a second or third dose to penetrate more deeply into the lungs. Higher viral loads will lead to the induction of stronger cytokine storms. These data are in agreement with clinical findings in humans, where high-risk individuals were exposed to multiple small doses of HBV, as well as in the woodchuck model, in which animals were repeatedly exposed to small quantities of infectious HBV [8]. In both cases, viral infection was molecularly evident and there were detectable virus-specific CD8-T cell responses but undetectable virus-specific antibody responses.

As to repeated infections, another possibility is also considered that is involvement of the antibody-dependent enhancement (ADE), which is a well-known phenomenon in the field of viral immunology. First, let's assume the situation of the individual who received a coronavirus infection followed by a second one. One week or so after initial infection, antibodies against the virus are elicited, and the second virus reacts with this antibody causing more serious effects. This phenomenon to increase viral infectivity and virulence has been observed with many viruses including several coronaviruses, HIV, Zika virus and mosquito-borne flaviviruses (dengue virus and Yellow fever virus). Indeed, Olsen and colleagues have shown antibody enhancement of infection with one of the animal coronaviruses, feline infectious peritonitis virus by a subset of specific monoclonal antibodies, especially those directed against specific sites on the spike protein [9]. Similarly, Wang et al. generated monoclonal antibodies against SARS-CoV spike proteins and found that these antibodies promoted SARS-CoV infection [10]. ADE has received the most attention from the perspective that it might be an obstacle in development of vaccines against the new corona. Further

studies are necessary to experimentally verify whether the effects of repeated infections alone or together with the ADE are involved in the enhancement of viral pathogenicity.

These aspects may be particularly relevant for a limited number of people such as medical staff. Therefore, in addition to that, the emergence of more virulent virus due to mutation of the virus during the course of superinfection might also be assumed. RNA viruses are, in general, highly susceptible to mutations, and the base substitution rate, which indicates the degree of change, is estimated to be $7 + 2 \times 10^{-4}$ nucleotide substitutions per site and per year on average in case of Transmissible gastroenteritis virus (TGEV), an enteropathogenic coronavirus. This rate falls in the range reported for other RNA viruses [11]. In addition, it is also known that coronavirus changes considerably easily due to gene recombination or part of gene loss (deletion). For example, the new strain of canine respiratory coronavirus identified in 2017 is reported to be a recombinant of the existing canine and bovine coronaviruses [12]. In addition, it has been known that the deletion of part of the spike gene has caused the emergence of a PRCV from the ancestral porcine gastroenteritis virus [13]. It is possible that the doctor who actually examined many infected patients could be exposed to the coronavirus repeatedly, and among the multiple virus strains infected, more virulent virus strains suitable for spread may be selected and prevailed, at least initially.

According to the classical models of virulence evolution of the virus, multiple infections select for raised virulence. To explain why so many people are dying of COVID-19 in New York City, sequence analysis of the viral genome has been performed. According to Zimmer, the virus mainly came from Asia through a small number of infected individuals in California, while in New York, more than 100 people initially brought the virus mainly from Europe, suggesting as if the European type viruses are more virulent in its pathogenicity and infectivity than the Asian type [14]. A number of studies have supported that through collective actions leading to common good production and immune system impairment, viral cooperation can lead to increased levels of virulence. Researchers around the world have already sequenced over 3000 more of SARS-COV2, finding some of which carry distinctive mutations. Very recently, mutation has suggested to be directly linked with functional changes in viral pathogenicity. Yao et al. have characterized the functional properties of 11 viruses isolated from COVID-19 patients, all of which have at least one mutation. Importantly, these viral isolates show significant variation in cytopathic effects and viral load, up to 270-fold differences, when infecting Vero-E6 cells [15]. Based on more molecular virological studies, Tan et al. proposed that SARS-CoV-2 can be divided into two major lineages (L and S). Intriguingly, the S and L lineages can be clearly defined by just two tightly linked SNPs at positions 8782 (*orf1ab*: T8517C, synonymous) and 28,144 (*ORF8*: C251T, S84L). *orf1ab* encoding replicase/transcriptase is essential for viral genome replication and might also be important for viral pathogenesis [16]. However, there was no evidence so far that this mutation produced a more virulent form of the virus. Moreover, the data examined up to now are still very limited, and follow-up analyses of a larger set of data are needed to have a better understanding of the evolution and epidemiology of SARS-CoV-2. Thus, further virological studies must focus on the relationship between differences in nucleotide sequences and infectivity/ pathogenicity of viruses since there is no firm evidence, so far, of the existence of European strains of the coronavirus or its pathogenicity being more virulent than the Asian strains.

Hypothesis # 3: the differences can be explained by evolutional aspects

Human hosts and their virus have co-evolved for millions of years, during which viruses have adapted to defense system of its host by regulating pathogenic mechanisms. Therefore, the possible genetic change and resulted selection of people living in East Asia should also be considered from an evolutional perspective. Thus, the difference in viral susceptibility and mortality of East Asian people to SARS-CoV-2 could also be explained if people living in East Asia may have evolved to be more resistant to viral infections, including those of novel corona viruses.

Evidences supporting hypothesis # 3. In East Asia, especially in China, agriculture started about 13,000 years ago, maybe 3000 years ahead of Europe. This led to an explosive increase in population, urbanization, and population density with the supply of abundant food. As a matter of course, acute viral infections such as measles, rubella, mumps, which could not be established until then, are believed to have taken roots in the human population (in the case of measles, it requires a population more than 250,000 to settle). Unlike today, Asia had long been much richer than Europe before the Industrial Revolution.

Under the over-crowded and chaotic conditions, East Asians must have experienced overwhelmingly with many plagues including several zoonoses due to the encounter with strange animal species. It is natural to consider that such epidemics are related to the change, choice, and evolution of the people who live there. East Asians may have evolved to become more resistant against infectious agents in general including coronavirus. It is possible that difference of the past plagues could contribute to a difference in the susceptibility (and thus, pathogenicity) between Europeans and Asians against present new corona. Present COVID-19 is apparently derived from bats directly or via vector animals, and its appearance is closely related to Chinese food culture. Given this, it is not strange to consider the possibility that this area had been hit by coronavirus infections similar to this time before long ago. In fact, the country experienced similar endemics, SARS and MERS only 18 and 8 years ago, respectively. This suggests that coronavirus infection itself is one of the most likely candidates for East Asian selection and evolution among the past plagues.

Although humans are a fairly homogeneous group of species as viewed from the genome, the diversity of the genome is well maintained. It avoids all human species from suffering the same disease and is a means of survival as a species, even if some disease prevails. Although plague and people have been closely linked, one of the causes of human diversity is infectious disease. Many genetic diseases are unfavorable to survival, but in some cases they are also advantageous for survival, and in some cases mutations have given the power to survive from the diseases that have hit the ground in the past. In East Asia, where agriculture was established early on and urbanization has been achieved, plagues have been rushing to people in a messy environment since ancient times. We believe that it should be worth considering that individuals with advantageous gene mutations have been selected in relation to various epidemics, and have reached the present day.

Several genes may be involved in the genetic predisposition to COVID-19, and the combination of multiple genes may be important for the severity of the infection. Among them, human leukocyte antigen (HLA) polymorphisms are associated with susceptibility to various diseases such as autoimmune diseases and infectious diseases. The composition ratio of HLA types varies greatly depending on the country and ethnic group. Since HLA is a protein of the immune system that is responsible for antigen presentation, HLA has been attracting attention in relation to disease susceptibility. Ellinghaus and colleagues performed GWAS on patients in Italy and Spain [17]. But, it was found that certain HLA types are unlikely to be associated with exacerbation of the novel coronavirus at least in Italy and Spain. Nevertheless, since HLA types, which are present only in Japan and other Asian countries, may show resistance to the novel coronavirus, further analysis is necessary.

The human Angiotensin-converting enzyme 1 (ACE1) gene on chromosome 17 has an insertion (I) or deletion (D) of a 287 base pair (bp) Alu repeat sequence in intron 16 [18]. Therefore, in the I/D polymorphism, there are three different genotypes, II, ID and DD. ACE1 is a metalloproteinase, which is a type I transmembrane glycoprotein. This protein plays an important regulatory function in the renin-angiotensin-aldosterone system (RAAS) and can convert angiotensin I (AngI) vasoconstrictor, which is inactive, to angiotensin II (AngII).

AngII is the core product of the RAAS system, and causes various biological reactions through the angiotensin receptors (AT1 and AT2) while ACE2 (Angiotensin invertase 2) is a homologue of ACE and is well known as a receptor for SARS-COV-2. However, the original role of ACE2 is to digest AngII into Ang1-7 polypeptides, and protect the heart, vasodilate, resist growth, and resist proliferation. Also, the activity of bradykinin can be enhanced by ACE2. Very recently, we showed a strong negative correlation that the numbers of SARS-CoV-2 infected cases and deaths due to viral infection decreased with increasing ACE1 II genotype frequency [19]. The serum ACE1 level was significantly higher in those with the DD genotype compared with those with either the ID or the II genotype [20], and viral infection may lead to suppression of ACE2 function and causes ACE1/ACE2 imbalance responsible for RAS over-activation and pulmonary shut-down [21]. This can further reduce the effects of ACE2, which counteracts the pathophysiological effects of Ang II produced by ACE1, and may worsen the pathology. In patients with the D allele, especially those with the DD genotype, higher risk of morbidity and mortality from sepsis, acute respiratory distress syndrome (ARDS) and certain heart, lung and kidney conditions probably due to inflammation, vasculopathy and coagulopathy induced by AngII [22] is reported. Thus, the ACE1/ACE2 imbalance predicts that COVID-19 patients with the D allele of ACE1, especially the DD genotype, have a higher severity and prevalence of COVID-19.

Further evidence for our hypothesis is provided by results obtained through the study of other viral systems. There are a few lucky people who have escaped infection while being exposed to HIV-1. Individuals homozygous for CCR5-Δ32 show perfect resistance to HIV-1 [23]. Infection with Yersinia pestis or smallpox virus were suggested as potential selective pressures favoring CCR5-Δ32 [24]. Only European or Central Asians have this characteristic and in Norway, CCR5-Δ32 allele frequencies reaches nearly 20%. Since AIDS, smallpox and plague are, by nature, independent infectious diseases that should be completely unrelated, it is very intriguing if these infectious diseases are linked by this mutant gene. Indeed, in 1999, Lalani et al. showed that poxviruses, can exploit chemokine receptors, especially CCR5 to infect some cell types, notably migratory leukocytes [25]. This further suggests a need searching for polymorphism and virological studies to see if there is a difference in the function of the ACE2 gene as a SARS-COV-2 entry receptor between Asians and Europeans.

Besides, several other examples are available in the resistance to certain type infections and genetic mutations. Relationship between sickle cell anemia and malaria is well known [26]. Although less dramatic, it is speculated that the relationship between typhoid fever and cystic fibrosis, which is a recessive genetic disease commonly found in Europeans, is similar. There is also information regarding the relationship between human ABO blood type and disease, while AB type is strong against cholera and O type is resistant to tuberculosis [27]. However, our hypothesis suffers from the lack of analogous data available in other viral infections. In other words, if this theory is relevant, we should realize earlier that there is a difference in susceptibility and pathogenicity between Western and Asian people even in the case of other viral infections before this corona pandemic. Still, it is not impossible to explain with a claim that there was no report from the past because there was no appropriate viral pandemic involving Europe and East Asia in the past. If there is, it may be the Spanish Flu occurred at the beginning of the last century or some influenzas after that. However, in the case of Spanish Flu, it was before the identification of the influenza virus, and it was a special event taking place towards the end of World War I in Europe, so it is quite difficult to compare the difference in the pathogenicity of the influenza virus in both areas. Or is the new coronavirus indeed the first case to show such ethnic differences in terms of pathogenicity? It is hoped that this point will be answered when data in the comparative studies on new coronavirus infections in the United States, where many European and Asian immigrants live, will be accumulated in the very near future.

Hypothesis # 4. The differences are due to hygienic aspects

In relation to this natural selection of human traits about viral resistance, there are also some records on the relationship between hygienic condition and resistance to infectious diseases. It is generally accepted that Asia used to have a denser human population and to have lower hygienic conditions than Europe. Is corona's low pathogenicity for East Asians not related to the situation of Asia being less-hygienic than in Europe?

Evidence supporting hypothesis #4. A similar paradoxical seeming suggestion has been raised for childhood leukemia: the more often a child is infected during the first year of life, the less likely it seems to develop leukemia. Epidemiological studies performed by Kinlen [28], and Greaves and Wiemels [29] separately showed that high socioeconomic status and lack of contact with multiple infections early in life could be a risk factor. Based on these observations, zur Hausen and de Villiers made the following proposal by assuming the existence of a fairly universal lesser-known tumor virus such as TTV. Many viral infections during pregnancy and perinatal have a negative effect on the persistence and increase of this oncovirus. Intermittent viral infections, by inducing interferon, significantly reduce tumor virus load and reduce the risk of viral chromosomal alterations, prerequisites for malignant transformation [30].

Very recently, Katoh et al. reported a possible association between lower rate of fatality induced by coronavirus and immunization rate against encephalitis [31]. Artificial vaccines against Japanese encephalitis (JE) may result in relatively lower mortality rate in some countries. JE immunization is widespread or included in national programs in many Asian countries including China, South Korea, Japan, and Taiwan. In all of these countries, the fatality rate due to COVID-19 is very low when compared with countries that don't immunize against JE. Also, a similar hypothesis has been proposed that the inoculation of BCG vaccine may be effective against infectious diseases caused by the new coronavirus [32]. It is thus very intriguing to find out the reason why recipients are cross-protected against COVID-19 conferring lower fatality rate in the countries where immunization is performed against some infectious diseases such as encephalitis or tuberculosis. It will be important to explore the underlying mechanism, such as whether this can be explained by mere nonspecific activation of immunity.

As the aspect of nonspecific activation of immunity is considered as one possible mechanism that counteracts SARS-CoV-2 infection as well as the death rate of infected patients, it might seem worthwhile to ask the question whether the lower rate of infection and mortality due to SARS-CoV-2 in Germany, compared to other European countries, might be connected to differences in vaccination coverages. Unfortunately, such an analysis is difficult and has severe inherent limitations, as there is a very high degree of variability of vaccination coverage in Germany with respect to age, sex and geography [33]. This does not allow to consider Germany as one entity, but rather would require to focus on many different regions and groups, for which it seems difficult to obtain the required complete set of data. However, when the influence vaccination coverage for risk groups is compared between 11 European countries [34] Germany is only on place 10 among 11 – certainly not in favour for a more advanced immunization profile of the country. Furthermore, the analysis of the national vaccination calendars of France, United Kingdom, Italy, Spain, Sweden, Portugal and Germany [35] shows a large overlap of essential immunizations in these countries – a finding that is not in favour of assuming a specific aspect of immunization in Germany that might have a particular negative impact on SARS-CoV-2 infections and disease.

Conclusions

There is no doubt that Central Europe is much more affected by SARS-CoV-2 and COVID-19 than East Asia. The strong difference between East Asia and Central Europe cannot be explained by eventual

differences in the frequency of testing, as this would only affect the number of detected cases per inhabitants, but not the number of deaths.

Our four hypothesis raised for possible explanation of the observed facts, i. e. 1) Differences in social behaviors and cultures of people in the two regions; 2) Possible outbreak of virulent viruses in Central Europe due to multiple viral infection, and the involvement of immuno-virological factors associated with it, 3) Possibility of corona resistance gene mutation occurring among East Asians as a result of long-term co-evolution of virus and host, and 4) possible involvement of hygienic factors include cultural and behavioral differences among Central European and East Asian people, virological factors and even anthropological issues involving human evolution.

We are convinced that the behavioral difference in human contact in both areas of the world can be considered to have a very important influence on the spread of the SARS-COV-2, as seen by the impressive positive effect of social distancing on the control of COVID-19 in Europe. This shows that hypothesis # 1 seems to be relevant to a significant degree for the differences between East Asia and Central Europe. However, hypothesis # 1 cannot explain the complete picture observed, as it would only have an impact on the number of cases in relation to the population, but not on the death rate of cases. As the death rates per cases are also lower in East Asia compared to Central Europe, mechanisms suggested in hypothesis # 2–4 might also contribute to the overall effect. In addition, mechanisms not included into our hypothesis might play essential roles and await to be defined in the future.

Essential parts of our hypotheses for which we have no direct supportive information so far can be experimentally verified or falsified in the future. These so far unresolved aspects are i) the possible existence of more virulent strains of SARS-COV-2 in Europe, ii) the effects of repeated infections, possibly in combination with iii) ADE, iv) polymorphism of ACE2 or some other genes such as TMPRSS2 [36] and ACE1 [19,37], and their relation to the function of viral receptor.

COVID-19 positive cases are already over 5.3 million even at this point in total while number of people infected with SARS coronavirus-1 was only about 10,000. Considering its near-future expansion in developing areas such as Africa and South America, the new coronavirus may reach an even stronger impact than SARS-CoV-1. Moreover, this coronavirus is very easy to mutate due to its original properties. Taking these facts into account, this SARS-CoV-2 has the potential to persist in every corner of the world, has a great possibility of finding and adapting to the best environment in various climates and people's lives, and becoming established in human society.

However, the pandemics have taught us some essentials for counteracting in the future. At the beginning of the outbreak of COVID-19 in Europe, the initial response, especially the delay in response to outbreaks (clusters), demographics, social behavior and lower testing capacity, etc. were sometimes very problematic in response to COVID-19. These experiences allowed states that were hit later by the pandemics, like Germany, to adjust countermeasures. In Germany, the federal and local governments have been involved in the fight against COVID-19 from an early stage, and especially with an emphasis on looking for signs of early onset, PCR testing of very large numbers of samples for free, and isolation of defined cases. The medical system had time to be prepared and intensive care beds equipped with artificial respirators were reserved for COVID-19 and increased in number. The needed specialized staff was trained. Social distancing guidelines were introduced and widely followed. This resulted in slow-down of the pandemic.

Therefore, we can be confident, that even if European corona strains were more virulent than Asian strains, or if Europeans were more susceptible to coronaviruses, people can overcome the corona pandemic with proper countermeasures and management.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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