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An alternative to airborne droplet transmission route of SARS-CoV-2, the feco-oral route, as a factor shaping COVID-19 pandemic

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ABSTRACT

The Chinese scenario, a rapid increase in the frequency of SARS-CoV-2 infections and sudden decline, is uncommon worldwide. Enormous differences in COVID-19 severity among individual countries are the striking findings of the pandemics. It has been demonstrated that a mild course of COVID-19 is associated with gastrointestinal symptoms, less inflammatory response, and better prognosis. The presence of SARS-CoV-2 was observed longer in the gastrointestinal tract than in respiratory swabs, promoting feco-oral transmissions and mild virus attenuation. The spread of the pandemic and its severity might, consequently, depends on the dominant environmental route of infection and emerging immunity. We hypothesize that the feco-oral SARS-CoV-2 transmission may help to achieve the long-term immunity against COVID-19, since it enables the continuous contact with viral antigens in the gastrointestinal tract, resulting in lower mortality rate. To conclude, countries producing rice through traditional methods developed rapidly emerging long-lasting population immunity, possibly through increased SARS-CoV-2 antigen exposure in the gastrointestinal tract. Our hypothesis brings attention to this potential route of herd immunity against SARS-CoV-2 which warrants further investigation in the future.

Introduction

From January 2020 on, news came from China about the rapid increase in the rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infections. The apogee of infection incidents was recorded on February 12, 2020. Notably, it was followed by a sudden and sharp decline in newly recorded cases in China. Despite alarming epidemiological reports from Europe and both Americas, currently the infections with SARS-CoV-2 in China still oscillate around several dozen newly recorded daily cases and mainly concern people from outside the region initially affected by the pandemic. Meanwhile, coronavirus has underwent numerous mutations, including those in the S protein's amino acid composition, that may modify the immune response. These mutations, however, had no impact on China's epidemic progression. Furthermore, the high efficacy of Chinese coronavirus vaccine was not confirmed in other national studies which might indicate higher and more robust Chinese population immunity against SARS-CoV2 [1]. One can therefore assume that the permanent Chinese residents, who did not have clinical signs of infection, went through asymptomatic disease or acquired permanent herd immunity, including also new SARS-Cov2 strains through an unknown manner. It cannot be ruled out that this process was partly influenced by many years of direct relationships between intermediate hosts and inhabitants of the Far East, leading to mild symptomatic or asymptomatic contact with the virus. However, epidemiological data from the alarmingly intense start of the COVID-19 pandemic in the Wuhan region, indicates that the herd immunity emerged later. Van Tan attributed the successful combat against the Vietnam epidemic to such measures as early preparedness, contact tracing, isolation and mass PCR screening, coupled with timely border closure, physical distancing, and community adherence [2]. On 21.01.2022, the mortality rate in China and other Southern East Asian countries was three or fewer deaths per 1,000,000 inhabitants, whereas

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in 25 countries in Europe it exceeded 1000 deaths per 1,000,000 inhabitants, despite the application of safety measures analogous to Vietnamese. Similar epidemiology as in China was reported in other rice producers in Southern East Asia and Africa (Table 1). The severity of the global COVID-19 in more affected countries required further studies on the impact of factors that may be responsible for a different pandemic course. A few issues seem to be of particular epidemiological importance. First, the reported milder course of COVID-19 in patients with a form of isolated infection limited to gastrointestinal symptoms [3-6]. The second is the natural, common source of potential exposure to feco-oral virus transmission as an alternative to inhalation. The exposure to feco-oral transmission is essential in countries where the contact with wild animals is scarce and a watery environment remains the only potential source of contact with the virus [7]. Gundy et al. recently confirmed that water temperature, acidity, and organic contamination might substantially alter the SARS-CoV-2 properties, enabling direct oral contact while omitting the respiratory tract [8]. This article aims to analyze whether and how clinical and environmental factors, as well as oral antigen transmission may influence the clinical course of COVID-19 and stimulate population immunity to SARS-CoV-2.

Hypothesis

We hypothesize that the feco-oral route of SARS-CoV-2 is an alternative to the commonly known airborne droplet transmission route. Our hypothesis is based on the following observations: (i) striking differences in COVID-19 severity among individual countries, depending location with relation to the rivers, and differences between standing and streaming water, (ii) mild course of COVID-19 associated with gastrointestinal symptoms, less inflammatory response, and better prognosis, (iii) the presence of SARS-CoV-2 observed longer in the gastrointestinal tract than in the respiratory swabs. Considering these observations, the spread of the pandemic and its severity might depend on the dominant environmental route of infection and emerging immunity. The clinical significance of our hypothesis is that the feco-oral SARS-CoV-2 transmission may help to achieve the long-term immunity against COVID-19, since it enables the continuous contact with viral antigens in the gastrointestinal tract, resulting in lower mortality rate. Hence, the feco-oral route might be a factor shaping the COVID-19 pandemic. The hypothesis presented in this article is showed in the Central Figure.

Association between systemic inflammation and COVID-19.

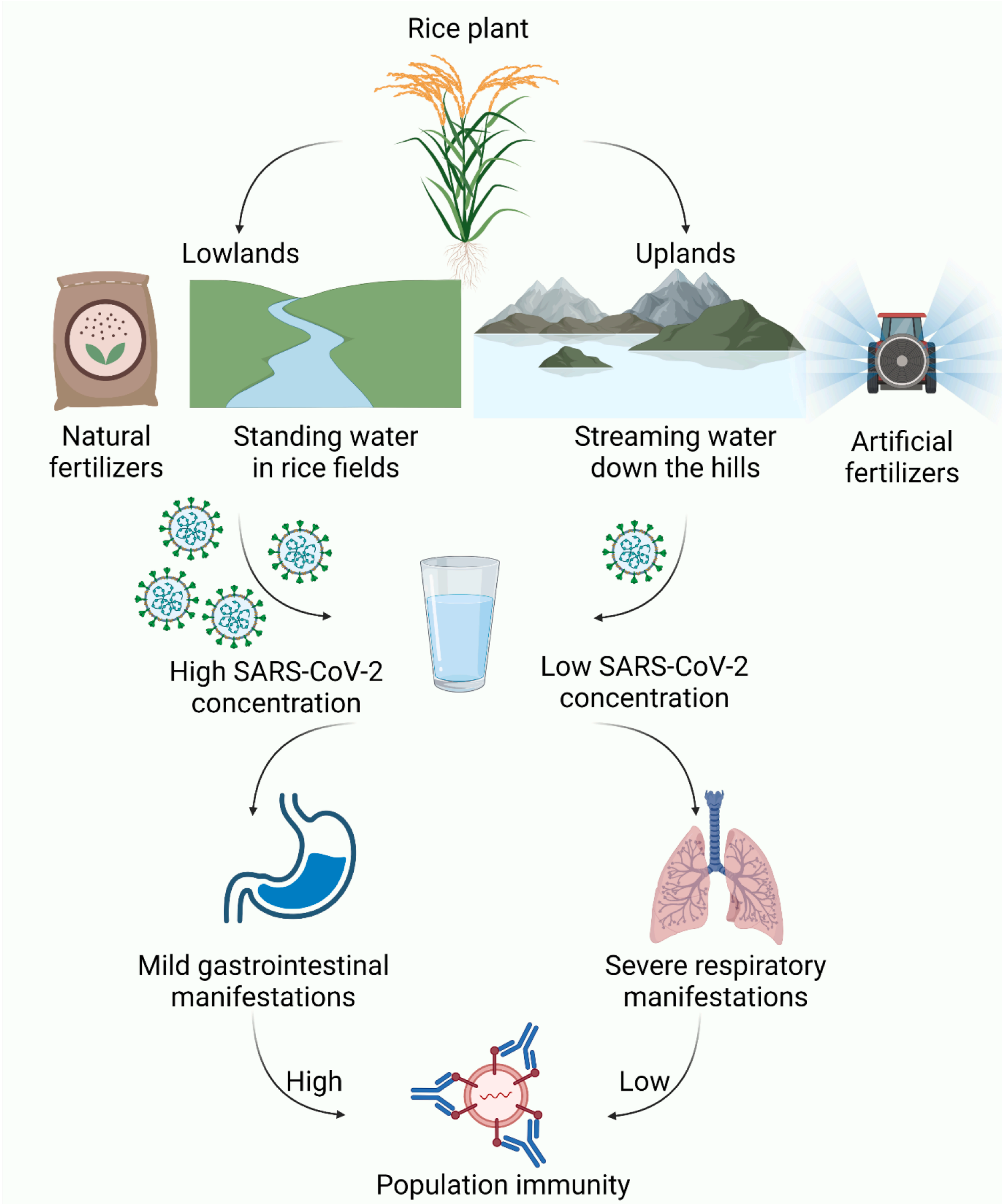
Since the epidemic outbreak, it has been postulated that SARS-CoV-2 originated from bats, pangolins, and raccoon dogs [9]. Initially, it was thought that the disease was spread by ingestion of contaminated products, but direct contact transmission via airborne or airborne droplets was later confirmed among humans [7]. The risk of infection is the greatest in confined spaces, especially in clinics, hospitals, airplanes and ships. The virus causes severe acute respiratory symptoms with shortness of breath, fever and weakness. Another form of COVID-19 is gastrointestinal infection with accompanying nausea, vomiting, and diarrhea that affect 8.8–38.7% of cases [3,4]. Previously, we demonstrated that abnormal sodium storage accelerates inflammatory mechanisms [10]. Other authors also showed that specific populations with the tendency towards civilization diseases and sodium retention states are predisposed for more severe courses of COVID-19 [11]. Since race and ethnicity have significant impact on the frequency and severity of civilization diseases, these factors may further contribute to frequency and severity of COVID-19 in ethnically diverse populations [12]. Starko et al. has presented an interesting hypothesis that aspirin contributed to the incidence and severity of infections during the influenza epidemic in 1918–1919, likely also due to increased sodium retention and subsequent pulmonary oedema [13]. Recently, adverse effects of commonly used drugs, such as non-steroid anti-inflammatory drugs which induce sodium retention has been also reported [14]. A common pathogenetic mechanism of COVID-19 in various organs is the virus-induced and ACE2 receptor-mediated process of microvascular damage and inflammation. This process includes macrophage mobilization and activation, exaggerated local and systemic renin-angiotensin-aldosterone system activity, reactive oxygen species production, activation of internal and external coagulation pathways. Finally, inflammatory response resulted in pulmonary and systemic formation of neutrophil extracellular traps that may be triggered by both sodium-induced inflammation and SARS-CoV2 infection [14]. This leads to disseminated microcirculation damage, acute respiratory distress syndrome (ARDS) and death. The severity of inflammatory changes in the lungs in COVID-19 seems to be associated with the selective pulmonary localization of angiotensin-converting enzyme (ACE) receptors. Hence, the long-term use of ACE inhibitors reduces the number of symptomatic forms of influenza A and possibly also COVID-19 [14-16]. Altogether, pre-existing systemic inflammation seems to modify the course of COVID-19, and factors affecting this inflammation, such as diet, may modify it.

The gastrointestinal form of coronavirus infection

SARS-CoV-2 can enter ACE 2-expressing cells in lung alveolar type 2 cells and the small intestine's surface cells and cause either pulmonary, or gastrointestinal symptoms, or both of them [17]. The high overall ACE activity in the lungs is related to high sodium storage states, cytokine storm, abnormal coagulation, and abnormal angiogenesis. On the contrary, the severity of disease in COVID-19 with affinity to gastrointestinal tract does not correlate with comorbidities or age, indicating that exclusively the pulmonary mechanisms triggered by SARS-CoV-2 lead to severe, sometimes fatal course of the disease [3,18-20]. Despite the persistence of negative PCR swabs from the nose and throat, some publications point out that orally transmitted COVID-19 is associated with an increased risk of asymptomatic infections [12,21]. The appearance of the virus in the aquatic environments is responsible for gastrointestinal infection and probably does not impede the contraction of SARS-CoV-2 in ACE2 alveocytes [13], but modifies the abnormal

Table 1
Top 10 rice-producing countries above seven million inhabitants with dominant classical rice cultivation method and mortality rate below 8 per 1 million (M) inhabitants.

Country	Total population (M)	Mortality rate (per 1 M inhabitants)	Upland rice (%)	Rice production (x 1000 t)	Rice consumption (x 1000 t)
Cambodia	16 865 946	0	17%	9 327	5 716
Laos	7 342 600	0	14%	4 002	2 008
Burundi	12 113 660	0.2	10%	67	No data
Tanzania	60 805 840	0.3	Negligible	2 621	1 178
Vietnam	97 896 395	0.4	8%	44 974	21 391
Taiwan	23 844 332	0.4	3%	Together with China	Together with China
Thailand	69 911 903	1	11%	32 620	13 605
Papua New Guinea	9 054 372	1	No data	No data	No data
China	1 439 323 776	3	0	208 239	135 024
Benin	12 356 551	7	54	234	603



Central Figure. Hypothetical association between the feco-oral route of SARS-CoV-2 transmission and high population immunity, resulting in lower mortality due to COVID-19. Figure created with BioRender.com, licensed version.

response of the respiratory system. Earlier reports, especially in adults with gastrointestinal symptoms, indicated the possibility of transmitting the infection via the fecal-oral route. Guan et al. showed that in a group of 1,099 patients, pulmonary infection is associated with a more severe course of COVID-19 than gastrointestinal infection [4]. Therefore, it can be assumed that gastrointestinal infection symptoms are more frequent in a population of people with mild or asymptomatic infections than in severe pulmonary forms of the infection. The coexistence of pulmonary and gastrointestinal COVID-19 has also been described, with a reduced intubation rate and death compared to isolated respiratory coronavirus infection [3]. Laszkowska et al. concluded that the slower course of this form of the disease results from a longer period from the onset of symptoms to hospital admission and lower inflammatory markers profiles [3]. It is possible that gastrointestinal symptoms transmit the disease phenotype with a weaker immune response, thus improving treatment outcomes, but delaying virus clearance, which may extend the time of virus excretion and infection of other healthy people. On the contrary, in a meta-analysis of 6686 patients Mao et al. showed a significant association between gastrointestinal symptoms (abdominal pain) and an increase in alanine aminotransferase (ALT) aspartate aminotransferase (AST) in patients with severe COVID-19 [22]. Guan et al. showed that ALT and AST were elevated in some patients with COVID-19, and the rate and extent of ALT and AST elevation in severe pulmonary infection were higher than those in non-severe ones [4]. Experimental and clinical studies also showed that the development and progression of ARDS are associated with abnormal liver function tests (LFT) [23,24]. There are no reports of deaths during COVID-19 with gastrointestinal involvement without ARDS and no evidence of isolated SARS-CoV-2 damage to liver cells. Together, all these facts may confirm that the LFT increase is not due to gastrointestinal viral infection, but due to the coexistence of severe pulmonary involvement or its progression. It is unclear, whether the virus obtained from the aquatic environment can cause respiratory re-infections or whether the process of shortening SARS-CoV-2 virus survival after intestinal passage described by Gundy et al. can be considered as a natural pathway of the virus attenuation process [8,25].

Epidemic in Europe

The beginning of the epidemic in Europe took place in Italy on 31, January 2020. Then, it quickly spread to the whole of Europe. In Poland, the map of cases in the vicinity of the biggest Polish city - Warsaw, the place of the highest number of coronavirus infections, showed a strikingly different infection rate pattern than in the surrounding counties. Five regions with the highest infection number in the low reach of the Vistula River, were compared to five regions with the highest number of infections in the upper reach. Hence, the reach to the river in Warsaw could have had a significant impact on the number of COVID-19 cases. On April 21, 2020, 575 and 256 infections were found in the high and low reach of the Vistula, respectively. On 24, October 2020, during the second wave of the pandemic in Płock, placed in the lower reach of the river, the new incidence rate per 1000 inhabitants was 1.26, while in Radom placed in the upper reach of the Vistula River it was 2.23 [26]. The observed differences prompted the assessment of the frequency of coronavirus cases in individual European countries, depending on their location concerning the largest European river, the Danube. On April 22, 2020, the new incidence rate per 1,000 inhabitants in the countries located along the Danube ranged between 2.00 in Slovakia, through 1.76 in Austria, 0.83 in Serbia, 0.43 in Romania, 0.19 in Hungary, to only 0.13 in Bulgaria. These data were interpreted by comparing Austria and Switzerland, two neighboring countries that are socially, economically, and geographically similar. In Switzerland, the incidence rate was 3.42, nearly double that of Austria. This comparison with Polish data allowed for the formulation of a working hypothesis that the rivers flowing through large agglomerations during epidemics carry a factor that may favorably modify the frequency of symptomatic infections and the symptom severity. In Switzerland, great European rivers begin their reaches in sparsely populated mountain areas. It can be assumed that in their upper reaches, viruses that are excreted by patients with saliva, feces, and urine, due to sparse population, fast-flowing streams and rivers, rocky, non-filtering ground and usually deeply localized wells in the mountain areas, have little chance of fast perfusion into the deep waters. By flowing through large agglomerations in lowland areas, despite wastewater treatment processes, viruses have an increased chance of getting into deep water and then to the places of water intake. This process is probably facilitated when the intake sources are located in better filtering soil. Hence, in Austria, particularly few cases were observed at the beginning of the epidemic in Vienna and the adjacent lowlands, compared to the country's mountain areas. The impact of flowing rivers on the COVID-19 epidemic severity is confirmed by the incidence statistics in Belgium and the neighboring Netherlands. The incidence rate on April 19, 2020, in Belgium was 3.3, and in the Netherlands 1.9 where the mouths of Rhine, Moselle, and Scheldt, three major European rivers are located. At the other end of the continent, greater differences in epidemic intensity were found in the same period between Portugal and Spain, where these rates were 1.8 and 4.04, respectively [27]. In Portugal, unlike in Spain, the entire population was vaccinated against tuberculosis. The vaccine is a well-known immunostimulant and was suspected to be a reason for the milder COVID-19 course in Portugal [28]. However, this hypothesis does not explain the significant differences in the epidemic severity between individual cities in Portugal. It may result from the fact that the largest river Tagus has been flowing through Madrid, the biggest Spanish agglomeration and in Lisbon flows into the Atlantic Ocean. Interestingly, in Lisbon with 0.5 million inhabitants, 4,896 COVID-19 cases were diagnosed on April 21, 2020. In turn, in Puerto, which is less than 240,000 residents, located on the Douro River, flowing through more sparsely populated areas, 12,500 cases were confirmed [29]. The observed differences in the incidence of COVID-19 in Portugal reduce the likelihood that the tuberculosis vaccine is associated with the increased resistance to the coronavirus [30]. They were, more likely, related to different water contamination contents of rivers flowing through both cities. Undoubtedly, the airborne droplet route plays the main role in spreading of SARS-CoV-2 and the overall infection frequency, so that tourism, trade, and periodic lockdowns have determined the ultimate infection rate. However, the association between the vicinity to the river and course of SARS-CoV-2 infections might also have contributed to differences in infection rates.

Hayward et. al showed that the reported rate of influenza infection rate is influenced by its severity [31]. Similarly, the infection rate with SARS-CoV-2 is likely underreported in patients with less typical and less intense symptoms due to the lack of testing, which may lead to the discrepancy between the number of patients diagnosed and the actual number of people with antibodies in the population. This is why the mortality rates better reflect population immunity than new cases, which are more indicative of the symptomatic respiratory infections frequency.

Impact of physicochemical factors on biological properties of coronaviruses

Gundy et al. showed that the inactivation of coronaviruses in water is related to its temperature and depends on the level of organic matter and antagonistic bacteria [8,25]. The time it takes for the virus titer to drop by 99.9% (T99.9) shows that in tap water, the coronaviruses are inactivated much faster in 23 °C (10 days) than in 4 °C, where they survive over 100 days. Coronaviruses are dying out quickly in wastewater, where the T99.9 value ranges from 2 to 4 days [8]. Interestingly, in the water at 4 °C, there is an increase in the initial viral titer, which can be attributed to the tendency of the viruses to aggregate in room temperature and disaggregate at low temperatures. It has also been shown that the higher levels of suspended solids in the water provide coronaviruses with additional protection against inactivation [25]. According to World Health Organization data, coronaviruses are stable in stool and urine at room temperature for at least 1–2 days [8]. In addition, the natural process of attenuation of the viruses in the gastrointestinal tract occurs more intensely in the presence of low pH [8,25]. Epidemiological, clinical and experimental study by Gundy et al. demonstrated some similarities between the polioviruses and the coronaviruses [8]. For instance, poliovirus infection in humans begins with the inflammation symptoms in the respiratory tract and evolved to the next phase of nervous system damage. Both groups of viruses are spread by airborne droplets, but infection through poliovirus ingestion is also possible [8]. In the case of diseases caused by coronaviruses, inflammation mainly affects the respiratory system. Recent studies indicate that accompanying severe nervous system changes exceed the commonly recognized temporary impairment of smell and taste [32,33]. Both viruses can also cause symptoms of gastrointestinal infections [3,5,6,18]. Hence, it is likely that similar to poliovirus, SARS-CoV-2 can be transmitted via feco-oral route.

Historical and literary data on immunization in the course of earlier epidemics

In the early 1950s, Koprowski invented the first effective oral polio vaccine using attenuated polioviruses [34]. Then, Sabin developed another live oral polio vaccine [35]. The attenuated polio vaccine replicates very fast in the intestine, the primary poliovirus entrance site, but cannot replicate in central nervous system cells. A single dose of oral polio vaccine produces immunity in about 50% of recipients, but three doses resulted in protective antibodies in more than 95% of recipients. The question arises whether this type of virus entry also leads to the emergence of immunity and whether repeated exposures to the SARS-CoV-2 in the gastrointestinal tract leads to the gradual increase of antibody titer, similarly to oral poliovirus vaccination. Moreover, remote descriptions of early vaccination development in other ancient epidemics suggest that a beneficial scenario for patients carrying the SARS-CoV-2 is also possible. During the aforementioned epidemics in China and India, the smallpox virus obtained from crushed scabs from convalescents was applied to mucous membranes or directly into a skin wound, following scarification. This procedure usually led to mildly symptomatic infection and long-term immunity. The vaccination with viable virus omitting air droplets transmission resembles coronavirus infection introduced to the digestive system by viruses fixed in aquatic environments. The procedure is similar to a more composed mechanism of obtaining immunity in ancient India, where brahmins applied a few drops of Ganges water, together with smallpox virus, into the skin wound [36,37]. In the 1950s and 1960s, two epidemics of smallpox were observed in Gdańsk and Wrocław [38]. Apart from isolation, sick patients and contact subjects were re-vaccinated. After a few months, both epidemics were brought under control, and doctors reassessed the re-use of the smallpox vaccine in patients, concluding that the procedure was associated with a favorable prognosis for individual patients and contributed to a faster end of the epidemic. At the time, no randomized methods were known. Hence, this assumption should be treated with caution, and the only possible conclusion was that there were no reported side effects when the vaccine was re-used even in symptomatic patients [38]. The procedure resembles the positive impact of the repeated oral polio vaccines and is consistent with the well-known boosting effect of other re-vaccinations. In "The Plague," Albert Camus presented the plague epidemic that decimated the population in Oran in the 1940s. The epidemic began in April with the mass death of rats leaving the sewers, and by the end of April, people started dying too. The end of the epidemic was heralded in December by the reappearance of rats in the streets and an increasing number of recoveries among humans. There are two specific local epidemiological determinants to consider when evaluating these events. The first is the practice of fertilizing land using human feces, commonly used in Sub-Saharan regions. The second is the heavy seasonal rainfalls in Northern Africa, usually lasting from October until late January. These factors may have caused the occurrence of pathogens in the drinking water or fresh vegetables, contributing to a gradual increase in population immunity. This mechanism resembles the relationship between a lower incidence of COVID-19 in people living at the lower reaches or mouths of European rivers. Fertilization with human waste is an old method currently used in south-east Asia, including China and other countries, mainly with low domestic product. If the fecal-oral route of transmission leads to long-lasting immunity in the population, then the single-peak or no peak epidemic course in all countries from Table 1 may also result from the same phenomenon. Prolonged and repeated contacts of the local people with the virus might lead to population immunity, increased vaccination efficacy, and limit the disease spread only to foreigners. Contemporarily used vaccines against COVID-19 consist of inactivated virus particles that have been grown in culture and then are killed using physical or chemical methods, while still stimulating immunological response or using prepared DNA or mRNA to produce immunoglobulins against SARS-CoV-2 proteins. Therefore, the presence of a virus capable of replication is not required for the development of immunity. Currently, parenteral application of vaccines is widely used but previous experiences with the poliovirus [34] and influenza [39,40] indicate that the repeated exposure to viral antigens in the gastrointestinal tract might also be effective.

Rice cultivation and COVID-19 mortality

All countries with a mortality rate below 8 deaths per 1 million inhabitants and a population of over 7 million are also major rice producers and consumers in the world (Table 1). In all but Benin countries, rice cultivation on lowlands is the dominant method by far. Standing water in rice fields creates a favorable environment in which the virus or its antigens can be found for a long time. The way rice is grown in these countries is primarily based on human labor. Moreover, the classical way of growing rice – the Chinese planting method – means that rice is exposed to human excrement and virus is suspended in the water environment at each stage of production. In China, Laos, Vietnam, Tanzania, and Cambodia (countries with 0–3 mortality rates), bat guano is widely used as fertilizer. It cannot be excluded that the fecal-oral route infections occur not only in crop fields, but also later during rice consumption contaminated with the viral antigens. On the contrary, among the other large rice producers Guyana, Uruguay, Indonesia, the mortality rate for COVID-19 is much higher than seven and achieves as much as – 285, 251, 146 deaths per 1 million inhabitants, respectively. A higher proportion of upland rice production, mechanical and non-classical rice cultivation methods are commonly applied in these countries. All these measures decrease the possibility of gastrointestinal SARS-CoV-2 infection in the population.

Conclusions

In the Far East, SARS-CoV-2 is a common pathogen responsible for mild, oligo- or asymptomatic gastrointestinal infections. The emergence of new mutants, transmittable via the respiratory tract, increased infection severity, particularly in subjects with civilization diseases, often associated with sodium retention. Countries producing rice through traditional methods developed rapidly emerging long-lasting population immunity, possibly through increased SARS-CoV-2 antigen exposure in the gastrointestinal tract. The clinical significance of our hypothesis is that the feco-oral SARS-CoV-2 transmission may help to achieve the long-term immunity against COVID-19, since it enables the continuous contact with viral antigens in the gastrointestinal tract, resulting in lower mortality rate. These observations warrant prompt investigation of the impact of gastrointestinal viral transmission on immunity.

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Consent statement/Ethical approval

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Declaration of Competing Interest

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