COVID-19 teaches humanity a lesson: what do epidemiological data reveal about our learning curve? PART II - Non-pharmaceutical interventions and Herd immunity.

Paul Kauler[1*], Mohammad Amin Kerachian[2] and Sona Pekova[3]

October 18, 2021

[1] Eco-Scientific Consultants, Montréal, Canada, e-mail pkauler@ecoscientific.ca
[2] McGill University Faculty of Medicine | MUMS, e-mail amin.kerachian@mail.mcgill.ca
[3] Tilia Laboratories, Czech Republic, e-mail sona.pekova@tilialaboratories.cz

*Corresponding author

ABSTRACT

This paper is split in two separate, yet essentially interrelated parts. In the *PART II* of this paper we attempt to objectively assess the effect of the use of public health intervention measures, as a tool to mitigation of the spread of SARS-CoV-2 virus. Our analyses are based on observed epidemiological data submitted to the World Health Organization (WHO). We noted that the use of strict non-pharmaceutical interventions (NPIs) was only one of two options at the beginning of the world pandemic public health authorities had at their disposal in order to mitigate the spread of the novel disease. Governments at large chose the implementation of severely restrictive interventions. However, as the pandemic progressed our scientific knowledge base indicated that COVID-19 was a predominantly mild disease. In addition, here we document quite early establishment and progress of the global (herd) immunity throughout affected populations, which the epidemiological data in all countries we looked at clearly indicated. The continuous implementation of strict NPIs therefore became redundant and unnecessarily imposed enormous social hardships and economic costs, which far exceeded their benefits. Moreover, with time it became obvious that the use of lock downs, various social distancing measures and confinement met with various degree of success falling short of expectations, yet their implementation widely continued.

Using publicly available mortality data we also followed the temporal development throughout the pandemic of the COVID-19 Infection Fatality Ratio (IFR) in number of selected countries. It started up very high only during the first several months of the pandemic, then mortalities commenced continuous consistent slide as the pandemic continued, in many countries dipping towards and staying below 0.1%. The COVID-19 IFR observed in twenty two countries followed up throughout 2021 averaged 0.17% (median 0.145%) and poorly correlated with incidence.

Due to the undeniable progress of natural herd immunity within all human populations throughout the pandemic, and because of the inherent difficulty interpreting confounded epidemiological data, without carefully designed relevant longitudinal studies we question the generally accepted notion of effectiveness of COVID-19 vaccines. Much of the evidence in support of vaccine effectiveness is blurred by the underlaying immunological history of, by now substantial proportion of the population already exposed to the pathogen hence mounting its own natural immune response. Using publicly accessible epidemiological and mortality data we found little evidence to suggest that present vaccination efforts would be effective. However, our analyses seem to suggest that population resilience to COVID-19 might be related to the intensity of exposure of population in question to the pathogen regardless of current vaccination efforts.

In the *PART I*[71] of the manuscript we present a concise overview of the SARS-CoV-2 virus biology. Here we point out the two possible mammalian cell internalization pathways, explore virus replication and the potential genetic and epigenetic predisposition of certain vulnerable human population groups. We also discuss the virus transmission and the resulting broad range of clinical outcomes particularly in relation to some described variants of the coronavirus.

After almost two years of the pandemic, in humans COVID-19 turned into a predominantly mild disease with asymptomatic presentation in ~ 40% or more of the general population. In Canada asymptomatic, mild symptomatic to moderate symptomatic presentations of the disease were noted in 99.5% of the population. Only 0.5% of Canadians exposed to the coronavirus required hospitalization.

The adaptive immunity to COVID-19 is reviewed. We point out that likely due to the robust innate and cell-mediated immune response to the coronavirus in most patients re-infections by the same strain of the virus are rare. If they do occur, they might be exhibited by an asymptomatic or mild disease presentation. This may not be the case during exposures to a different strain of the SARS-CoV-2 virus however. In addition, we noted that the level of seropositivity at the population level might not be informative of a population immuno-protective potential as it likely reflects only the instantaneous rate of infection incidence, which in mild cases is associated with this virus relatively rapid clearance.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2, initially named novel coronavirus 2019 (2019-nCoV), was first reported in December of 2019 in Wuhan city of Hubei province in China. Due to its peculiar biology resulting in its very high pandemic potential and today's human populations' interconnectedness the virus has spread rapidly and uncontrollably throughout the globe. The still ongoing pandemic has since been reported from over 200 countries, territories and areas. By June 13, 2021 in its weekly epidemiology report World Health Organization (WHO) documented total of 175 333 154 officially reported cases and 3 793 230 deaths attributed to this respiratory disease.

The 2019-nCoV, (now SARS-CoV-2) virus belongs to enveloped β-coronaviruses exhibiting genetic similarity to SARS-CoV virus, an agent causing SARS (Severe acute respiratory syndrome) and MERS-CoV responsible for MERS (Middle eastern respiratory syndrome). All three coronaviruses have previously been suggested to originate from bats and might have been transferred to humans through an intermediate animal host [1,2,5]. As opposed to previous human respiratory disease pandemics however, since the beginning of the world COVID-19 emergency SARS-CoV-2 virus has polarized societies and divided the scientific community itself. This is likely due to the coronavirus peculiar etiology, which results in wide range of clinical disease presentations ranging from predominantly asymptomatic and mild through moderate to severe and even fatal outcomes. In addition, given that both SARS-CoV-2 and Influenza viruses have demonstrated their ease of person-to-person transmission through the respiratory droplet route with both diseases also sharing similar clinical presentation, including fever and respiratory symptoms that range from mild forms such as cough, to severe lung infections, many tended comparing COVID-19 to a trivial seasonal flu[3]. On the other hand, because of the agent's relatedness to SARS-CoV and MERS-CoV viruses, both severe pathogens with their demonstrated case fatality ratios (CFR) of 9.6% and 34% respectively[4], the WHO was prompted to declare the coronavirus disease 2019 (COVID-19) a public health emergency of international concern on January 30, 2020.

As the first COVID-19 cases began appearing in many places all around the world, most respective countries responded swiftly. With no known safe and effective pharmaceutical treatment available, no vaccine developed and with rapid escalation of the epidemic under way leading to shortages of medical supplies, hospital beds and ICUs filling rapidly, following China's example most countries resorted to implementing strict public health measures in the form of non-pharmaceutical interventions (NPIs) to control the spread of the disease. These efforts however, often greatly politicized, were associated with unparalleled costs to societies, yet met with various degrees of disease mitigation success. As the pandemic has dragged on, and in many countries still with no end in sight, there is an urgent need to review COVID-19 epidemiological data based on population-level incidence, the spectrum of the disease, and the proportion of the community with protective herd immunity to SARS-CoV-2 virus acquired so far.

In order to address this need we present this paper in two separate, yet interrelated parts.
The PART I is a concise overview of SARS-CoV-2 virus biology, which offers comprehensive background information for interpretation of data analysis presented here. In this PART II of the paper, which is supported by analysis of observed epidemiological data we will attempt to highlight some frequently unappreciated biological factors such as the role of the global (herd) immunity in this pandemic mitigation process in addition to emphasizing more realistic aspects of COVID-19 morbidity.

Public Health Intervention Measures

The initial implementation of non-pharmaceutical interventions (NPIs) in the spring of 2020 was the only option the world community had at its disposal in order to respond to the deepening COVID-19 public health crisis, which at the time appeared to be propagated by a severe pathogen. The social distancing measures, as they were called, resulted in unprecedented wide-spread lock downs, the implementation of severe travel restrictions or in the international and domestic travel being completely banned. Stay-at-home orders, limitations of gatherings, curfews, closures of schools, businesses and halt of all non-essential services in many countries was enforced. In addition in many countries wearing of personal protective equipment (PPE) such as face masks anywhere outside one's residence was recommended or enforced. In many countries entire cities or communities were shut down and border control with symptom screening conducted. For many travellers in numerous countries or provinces this was followed by the requirement, once upon reaching their destination, of costly isolation and lengthy quarantine regardless of presence or absence of COVID-19 symptoms. In China for example, the sheer scale of cordon sanitaire across Hubei Province in the early 2020 was unprecedented. On January 23, a series of major actions were taken by the Chinese government, shutting down entire cities or communities, banning international or domestic travel, conducting border control with symptom screening, and implementing mandatory isolation often times with a 28-day long quarantine fully, or in part in designated health care facilities[60,61,63]. Following China's example by March 2020 similar drastic measures began to be implemented in other countries and areas like Spain, northern Italy and throughout much of Europe.

In the early stages of the COVID-19 pandemic such measures did show some promise flattening first wave incidence curves in the US, Canada (**Fig.1**), Czech Republic (**Fig.12**), UK[26], just to name a few. In the US, Ayanian JZ, (2020)[66] reported that between March 19 and April 7, 2020, 42 states and the District of Columbia issued statewide public health measure orders. These orders have included stay-at-home or shelter in place order, closure of nonessential businesses, closure of public schools, and prohibition of large social gatherings.[67] To promote physical distancing, the state orders have been coupled with federal guidance for individuals to remain 6 feet or more apart and wear face coverings while outside their homes, as well as practising consistent hand hygiene. In two bordering counties of 2 contiguous states - Illinois and Iowa Lyu and Wehby (2020)[68], compared cumulative cases of COVID-19 infections. Illinois implemented a statewide stay-at-home order on March 21, whereas Iowa did not issue such order. During the week prior to Illinois' stay-at-home order, the bordering counties in Illinois and Iowa had similar rates of COVID-19 infections. One month after the Illinois order was implemented, the Illinois counties were estimated to have significantly fewer cases of COVID-19 than the adjoining counties in Iowa.[66,68]. The investigators estimated that the Iowa counties with a population of approximately 462000, without a stay-at-home order, after 1 month experienced up to 217 excess of COVID-19 cases[68].

In Wuhan, vigorous and multifaceted measures of containment, mitigation, and suppression were temporally associated with improved control of the COVID-19 outbreak in that almost 12 million city. Pan et al.[63] suggest that this series of measures resulted in substantial reduction of incidence where the daily confirmed case rate per million people increased from 2.0 before January 10, to 162.6 by the end of January when strict measures began to be implemented. The rate then decreased to 77.9 between February 2 and 16 and to 17.2 after February 16[64], and the R_t of the epidemic declined to below 1 within weeks[65]. When R_t decreases below 1 for a given disease in a given place, disease spread slows and the epidemic has the potential to be controlled in that area.

The choice of public health intervention measures is typically based on research and experience gained in the 20th century Influenza pandemics. In the US, for example, earlier and more sustained school closures and cancellations of public gatherings were associated with significantly lower mortality during the 1918/1919 H1N1 Influenza Strain A pandemic[69,70]. It must be pointed out however, that the much feared and in mainstream media in relation to COVID-19 frequently publicised 1918/1919 Influenza pandemic was estimated to be associated with substantially higher mortalities (IFR of 0.8%)[72] across wide, primarily younger socially and economically active age population spectrum[73]. On the other hand COVID-19 mortalities are documented to be much lower, seriously affecting mostly much smaller proportion of vulnerable primarily older individuals with comorbidities. In their early New Zealand modelling study Wilson et al., (2020)[72] with remarkable accuracy projected COVID-19 IFR to fall somewhere between 0.17 and 0.29%. Indeed, twenty two selected countries between January 3 and October 3, 2021 reported data yielding a mean IFR estimate of ~0.17% (**Table 1**). In addition, morbidity of some SARS-CoV-2 virus variants of concern (VOC) such as the feared British strain B.1.1.7 (Alpha) with its demonstrated increased morbidity and hospitalization rates for more diverse younger patients did not increase the strain-induced COVID-19 infection fatality ratios over 0.3% in Canada (**Fig.5**), Czech Republic (**Fig.13**) or in the UK (**Fig.15**).

As severe and complete, as the public health interventions during the first wave in many countries were, after their relaxation COVID-19 positive cases still continued trickling in throughout the summer. In Czech Republic, for example, after gradual reopening of the society in

Country	*Mean IFR %*	*Min*	*Max*	*SD*
Norway	0.03	0	0.17	0.035
Denmark	0.04	0	0.16	0.046
Netherlands	0.05	0.01	0.14	0.040
Finland	0.06	0	0.18	0.046
Sweden	0.08	0	0.41	0.084
UK	0.09	0.01	0.3	0.088
France	0.11	0.02	0.29	0.077
Belgium	0.11	0.02	0.32	0.082
Austria	0.12	0	0.26	0.076
Canada	0.12	0.05	0.31	0.057
Czech Republic	0.14	0	0.28	0.064
USA	0.15	0.08	0.24	0.039
Iran	0.15	0.07	0.33	0.050
Italy	0.18	0.04	0.34	0.077
Philippines	0.20	0.06	0.52	0.110
Germany	0.21	0.05	0.45	0.128
Spain	0.24	0.02	0.9	0.211
Brazil	0.27	0.10	0.42	0.084
Ukraine	0.29	0.14	0.46	0.086
Slovak Republic	0.33	0.02	0.79	0.191
Hungary	0.35	0.04	0.78	0.177
Poland	0.35	0.16	0.88	0.148
Mean IFR :	***0.167%***	*0.04%*	*0.41%*	
Median IFR :	***0.145%***	*0.02%*	*0.32%*	

Table 1 - The comparison of COVID-19 Infection Fatality Ratio (IFR) in 22 selected countries between January 3, 2021 and October 3, 2021. The official weekly incidence and mortality statistic submitted to WHO was compiled and used in the present analysis (see text for discussion and methodology).

May of 2020 following very mild COVID-19 first wave, that country continued reporting on the average 992 cases per week prior to the August 30, 2020 run up to a very high first peak of the second wave (**Fig.11,12**). Therefore through the initial implementation of very strict health intervention measures the SARS-CoV-2 virus from the Czech population was never eliminated. Spain was another European country, which opted for the implementation of very intensive public health intervention measures in the form of complete lock downs and severe restriction at the great social and economic cost to its populace. The Spanish State of Emergency finally ended on May 9, 2021, yet after 17 months of hardships in Spain SARS-CoV-2 virus continues to be firmly established (**Fig.16**), the same holds for the UK (**Fig.14**). Similarly, during their epidemiological assessment of the situation in Brazil, William Marciel de Souza et al., (2020)[20] noted that the implementation of non-pharmaceutical interventions in that country offered only mitigation at best, the sought suppression of the pandemic in Brazil using painful NPIs was never accomplished. Finally, Since the pandemic debut in Wuhan, China has imposed very strict, almost draconian measures on its citizens. Almost two years later China is still smoldering, continuously coping with isolated outbreaks averaging around 150-300 or more cases per week, which are likely to continue for many more years, if not decades to come. In reality, through the almost two-year implementation of non-pharmaceutical interventions to mitigate COVID-19 little was accomplished.

Discussing the biology of SARS-CoV-2 virus in the PART I of this paper[71] we pointed out notable peculiarities in this virus etiology. In particular, its predominantly asymptomatic and mild symptomatic expression complicates the typical syndromic identification of cases, and in addition to its pre-symptomatic and early symptomatic viral shedding confounds input variables for routine modelling and interpretation of epidemiological data. This makes efficient implementation of NPIs difficult[31] or unrealistic. Hellewell et al. (2020)[75] found that the possibility of controlling COVID-19 through isolation and contact tracing decreased with increasing proportion of transmission that occurred before symptom onset. The results of that study were aligned with conclusions of Hao-Yuan Cheng, et al., (2020)[31]. In their study the investigators suggested aggressive social distancing and proactive contact tracing might be necessary to block the transmission chain of COVID-19. However, Nande et al. (2021)[76] showed that it is very difficult for interventions which only target transmission outside the house to effectively control the COVID-19 outbreaks. This is because social distancing confines individuals to their households without additional precautions. Unless these interventions reduce the vast majority of contacts, ongoing transmission in households combined with occasional spillover to other households means that the epidemic may continue to increase long after social distancing begins. They also found that the relative contribution of household and external contacts to transmission was a critical determinant of the overall outcome of social distancing interventions, and that number of contacts alone was not very informative for predicting intervention efficacy. They concluded that it is not possible to predict the effect of an intervention that differentially affects household and external contacts by simply estimating the proportional reduction in the total R_t.

The Costs of Interventions

The continuous drastic social distancing measures so heavily relied upon throughout the world come at a cost however, very high cost. They are inevitably linked to economic destruction, enormous stress and psychological traumas imposed on citizens through isolation resulting in many forms of social disharmony, often even in increase of suicides in addition to resulting loss of education opportunities for children and youth, and enormous hardships imposed on country's population by reduction of access to, or even complete closure or elimination of essential services. Unlike the obvious and frequently in mainstream media publicized numbers from the hospital ICUs the silent hardships and suffering of vast majority of citizens in countries enforcing such measures have largely gone unnoticed and unreported. The shattered lives, relationships, livelihoods and artificially induced starvation of millions around the globe cannot possibly be completely documented.

Based on lock down experiences that were recorded in response to previous epidemics, a relatively recent review of the literature concluded that quarantine measures could have negative psychological effects, including symptoms of posttraumatic stress, stress, anxiety, and depression[77]. Marielle Wathelet et al. (2020)[78] based on a large nationwide study found high prevalence of self-reported suicidal thoughts and severe self-reported distress, depression, anxiety, and stress among quarantined students in France. Wang et al (2020)[79] found that students in China were at a greater risk of stress, anxiety, and depression in response to the COVID-19 outbreak than older adults. The rates of mental health disorders among students in France however, were consistent with preliminary data reported among the Chinese general population during the initial stage of the COVID-19 epidemic[79] indicating that this problem is not limited to young people. Serious psychological distress was reported by 13.6% of US adults in April 2020 vs 3.9% in 2018[80]. The reported prevalence of serious psychological distress among US adults was 13.6% in April 2020 and 13% in July 2020. Persistent distress increases risk of psychiatric disorders. High prevalence at both time points suggests that the pandemic's longer-term disruptions are important drivers of distress[81].

Secondary consequences of social distancing may increase the risk of suicide. A substantial body of evidence demonstrates that loneliness and social isolation present major risks for premature mortality comparable with other risk factors. This includes excess deaths through surge in stress-related diseases in addition to increased risk for premature mortality through suicides[84]. Variety of economic, psychosocial, and health-associated risk factors may be involved, such as economic stress, social isolation, decreased access to community and religious support in addition to imposed barriers to mental health treatment[82]. Trauma and abuse are well-established risk factors for suicide[83]. In Quebec, Canada suicide-prevention billboards were put up throughout the Montreal subway system (**Fig.18**) during the past year of COVID-19 pandemic because of increased risk of suicide attempts in that city's public transit system. During COVID-19 pandemic stay-at-home orders have led to major concerns about increases in domestic violence[83]. Indeed, by March 25, 2021 seven women had been murdered in seven month as a result of domestic violence in the Canadian province of Quebec alone - a notable acceleration of domestic violence from the pre-pandemic years likely due to confinement.

As if chronic stress and anxiety due to confinement were not enough, in addition the economic impact due to the implementation of public health measures is severe. Pandemic-related job losses especially in travel-related industry, sector traditionally employing migrant workers supporting their families in poorer countries, means less money is being sent home. This compounds already bleak situation in many countries of South America, and Asia. In the Caribbeans where entire island communities relied on tourism for sustenance situation is catastrophic. Acute hunger was expected to affect 270 million people worldwide by the end of 2020, an 82% increase since the coronavirus disease 2019 pandemic began, according to the United Nations World Food Programme (WFP)[85].

At the beginning of the pandemic apparently WHO was aware of this, and in its Epidemiology Report #50, appropriately cautioned the governments against taking disproportionate measures as part of their non-pharmaceutical interventions:

"WHO reiterates that measures that restrict the movement of people during this outbreak should be proportionate to the public health risk, short in duration and reviewed regularly as more information about the virus, the disease epidemiology and clinical characteristics becomes available."

The initial stand of WHO was in accordance with International Health Regulations (IHR) proscribing unnecessary interference with international travel and trade, while also requiring respect for the human rights of travellers. States must impose the “least restrictive” measures necessary to safeguard public health[86]. In addition, as Gostin and Wiley (2020)[87] pointed out physical distancing raises profound questions of culture, faith, and family. Coming together affords comfort during times of crisis. At the same time, physical distancing affects rights, including liberty, privacy, and freedoms of speech, religion, and assembly. How are the fundamental values of health and human rights balanced in times of crisis? [87] They asked.

As the COVID-19 pandemic progressed through the first wave, with time it became clear that SARS-CoV-2 virus was not so severe pathogen as initially feared. Nevertheless despite of the clear recognition by the scientific community that in 80-91%[37,38] of the population COVID-19 produces only mild or asymptomatic courses, in reality severe restrictions on citizenry all around the world continued being enforced. In Canada for example, according to the Public Health Agency of Canada, by January 23, 2021 Canada recorded cumulative 743058 confirmed positive cases of which only 39819 (5.3%), required hospitalization. In other words, total of 94.7% of official COVID-19 cases in Canada were mild or asymptomatic. This however does not include the estimated ten times more individuals (i.e.~7430500 of Canadians) who were by January 23, 2021 exposed to the virus yet because of mild or asymptomatic course of their COVID-19, or thinking it was just another seasonal flu chose not to be tested. It follows that in Canada only about 0.5% of COVID-19 infected individuals required hospitalization and 99.5% of Canadians exposed to the coronavirus passed through the COVID-19 disease either completely asymptomatic or with predominantly mild symptoms. Canadians showing moderate symptoms still successfully recovered from their disease at home with no extra burden to the Canadian medical system. At the same time however, this same large number of coronavirus-exposed individuals played an exceedingly important role in the formation of nations' global (herd) immunity. Through their exposure to the disease they began mounting their own immune response to the SARS-CoV-2 virus.

Progress of Herd Immunity Throughout the Pandemic

Since the beginning of COVID-19 health crisis in numerous publications function of the global (herd) immunity in relation to this novel respiratory disease was surmised. Few attributed any major significance to it however. It is our understanding that initially even some countries like UK and Sweden contemplated incorporating the attainment of herd immunity by their nations into their national strategy to combat the epidemic. UK soon abandoned this approach in favour of reliance on strong interventions such as severe restrictions and lock downs. Sweden remained one of few countries successfully balancing public health with individual rights safeguarding the fundamental values of health, human rights and dignity of its citizens thus minimizing damages described above.

From the collection of national COVID-19 incidence data submitted to WHO the effect of attained herd immunity in individual countries did not become evident until well into the second wave of the epidemic. Of the several selected countries we looked at in this publication Czech Republic (Czechia) together with Slovakia were the first countries whose epidemiological data clearly demonstrated the effect of herd immunity in this pandemic. Both countries experienced significant sharp peak of incidence on November 1st, 2020 (**Fig.11,12**), which was then followed by a steep drop as the virus began hitting more and more individuals already immune to the strain driving this first peak. Clearly, there was no “flattening” of the curve due to the implementation of strict NPIs predicted by standard SEIR modelling. Interestingly, in Czech Republic and

Slovakia the run up of the second wave for unknown reasons was observed to be very steep (**Fig.11**), and just as steep as the infection cycle became so was the Czech and Slovak populations' natural immune response to it.

In other countries natural population immune response to SARS-CoV-2 virus soon followed, in Spain on November 8th, 2020 (**Fig.16**), in Sweden on December 20/January 10th, 2021 (**Fig.6,9**), in the USA (**Fig.1,2**), and Canada (**Fig.1,4**) on January 10th, 2021, in Germany (**Fig.6,7**) on December 20/January 10th, 2021 and in the UK (**Fig.14**) on January 10th, 2021. Importantly, in all these countries sharp increases in COVID-19 confirmed cases at the end of the 2020 and the beginning of 2021 were followed by sharp incidence declines not predicted by SEIR modelling. In addition, few increases and crashes in COVID-19 incidence correlated with the implementation of NPIs. Finally, all initial sharp declines of incidence occurred prior to any initiation of government mass vaccination program, or in case of the January 10, 2021 incidence crashes prior to any significant vaccination coverage (see below).

The evolution of COVID-19 epidemiology in Czech Republic is remarkable for two other reasons. First, in Tilia Laboratories we have sequenced by Next Generation Sequencing (NGS) a representative sample of positive cases from each of the three peaks of the second Czech incidence wave. Our sequencing data confirmed that each of the three distinct peaks was driven by a genetically different strain of SARS-CoV-2 virus. This in turn suggests the biological mechanism of herd immunity formation within the Czech population in relation to the SARS-CoV-2 virus. We propose specifically in the relation to the SARS-CoV-2 virus that the acquisition of natural herd immunity in a population to one variant of the virus may not confer resistance to other genetically distinct strains of the same virus. However, a continuous exposure of a population to additional strains of the virus might lead to continuous evolution and refinement of adaptive immunity within majority of individuals so that in the end during active infection it forms sufficiently diverse clonal pool of memory CD4+/CD8+ T-cells and B-cells together with IgG producing plasma cells for the organism to become completely protected against more and more diverse strains of the pathogen. Such robustness of immune response against COVID-19 can never be achieved by artificial vaccine alone because its neutralizing antibody is developed against a single epitope (viral spike protein domain, for example) or in case of polyclonal antibody vaccine to a limited number of epitopes. Achieving sufficiently diverse set of polyclonal antibodies and polyclonaly diverse pool of activated CD4+/CD8+ T-cells is only possible through natural herd immunity and might be key in combatting the SARS-CoV-2 virus, which was documented to be exploiting multiple internalization pathways[8]. This appears to be clearly reflected in the pattern of the Czech COVID-19 second wave epidemiology profile. In case of humoral response, there is no need for all IgG antibodies to be neutralizing. A large naturally formed clonal pool of differentiated B-cell plasmablasts likely is a mixture of neutralizing and non-neutralizing antibody producing cells. With each additional exposure to different strain(s) of SARS-CoV-2 virus the natural diversity of produced neutralizing and non-neutralizing immunoglobulins increases and so does the capacity of an organism for semi-permanent or possibly permanent resistance formation (**Fig.11**).

The second interesting observation gained from the Czech COVID-19 epidemiology stems from its unusually elevated incidence profile (**Table 2**). Despite the implementation of very strong NPIs by the Czech government throughout the entire second wave between September 2020 and June 2021, after normalizing the raw incidence data in order to bring them to a common baseline (see **Fig.1**, **Table 2** for methodology), the comparison of Czech incidence with Sweden shows ~ 29-fold higher Czech incidence over similarly populated Sweden. While we cannot explain the reasons for this, the substantially higher incidence of COVID-19 cases in Czech Republic apparently led to more intense exposure of the Czech population to SARS-CoV-2 virus. By July 2021 156% of Czech population (i.e. 56% of the population must have been exposed at least twice) was exposed to multiple strains of the pathogen and likely began mounting its diversified immune response to multiple strains of the coronavirus. It might be still too early arriving at any conclusions at this time, but at the time of writing this paper it appeared that by July 2021 the Czech population might have substantially approached its semi-permanent or permanent immune protection through its herd immunity. This is in contrast to neighbouring Slovak Republic where only 70% of its population was exposed to the coronavirus and began mounting its delayed immune response. Despite similar epidemiological profiles both countries shared till July 2021 this appears to be evidenced by subsequent division and reversal in the evolution of Czech and

Slovak COVID-19 epidemiology profiles on September 5, 2021 (**Fig.11**).

	Relative Incidence Magnitude		
	Mean Peak height	***Relative Magnitude***	***# of Peaks***
Czech Republic	0.04027	503.4	3
UK	0.00183	22.9	2
Sweden	0.00139	17.4	3
Germany	0.00053	6.6	2
Spain	0.00047	5.9	2
USA	0.00008	1.0	1
Canada	0.00008	1.0	2

Table 2 - The second COVID-19 wave (September 2020 - June 2021) average incidence peak magnitude comparison. The *Mean Peak Height* is expressed as the number of infections / 100000 of population / Km^2. The raw number of cases is spread over territory with epidemiologically significant population density. Hence sparsely settled areas of Canada, Sweden, UK and continental USA are excluded. Only surface area of continental USA, and continental Spanish territory is considered.

Herd Immunity and Artificial Vaccinations

Since the beginning of the world health crisis many hopes were placed on the development and administration of vaccines, so much so that number of countries states and provinces rapidly implemented the use of "vaccine passports". This confidence in artificial vaccination programs in relation to SARS-CoV-2 virus is surprising however, since due to the peculiar biology of this pathogen the use of vaccines is wrought with risks and uncertainties. Apart from numerous anticipated side effects of vaccines, which might be experienced by some individuals, the most obvious challenge a vaccination program might encounter is due to the well known SARS-CoV-2 virus rate of mutagenesis. The second, frequently overlooked, uncertainty stems from the administration of vaccine to individuals who have already unknowingly mounted their natural immune response due to prior exposure to the pathogen. Typically vaccines are developed for disease prevention, and thus tested on naïve subjects. Vaccines are not intended to be administered to already exposed and naturally immunized individuals. Rarely have they been deployed at such a grand scale in the face of expanding epidemic where much of the target population have already been exposed to the pathogen and began forming its own immune response to it, as it is the case with the SARS-CoV-2 coronavirus.

The Canadian vaccination program began on December 14, 2020. By December 27, 2020 ~5393000 Canadians have already been exposed to COVID-19 infection however. Substantially delayed by the Canadian NPIs, through the exposure to the pathogen circulating within the general population by August 1, 2021 in Canada ~14290000 individuals have already begun forming their natural immune response to COVID-19. It is logical, and has been widely documented that most of exposures to SARS-CoV-2 virus primarily occur in dense urban centres[20,63]. Yet, it is the residents of these large cities, already mostly naturally immunized through prior exposure, that are being encouraged, sometimes by the threat of implementation of "vaccine passports" coerced to undergo additional artificial vaccination. This way the Canadian vaccination program has largely focussed primarily on immune individuals within its cities.

With the administration of vaccine to individuals who have already mounted their adaptive immune response to a pathogen through their previous exposure the possibility of antibody cross-binding and antigen competition is real[88]. Outcomes of such interactions at the molecular level were not clinically tested and are difficult to predict especially at such high virus mutation levels as we experience with SARS-CoV-2. In addition, as we know, in vast majority of asymptomatic and mild symptomatic COVID-19 outcomes recovery and virus neutralization might be accomplished without the formation of neutralizing antibodies likely due to extensive involvement of naturally robust innate and cell-mediated immune response[71]. The potential interference of vaccine-produced monoclonal antibodies with T-Cell Receptors (TCRs) on surface of activated CD4+/CD8+ T-cells, Dendritic Cells (DC) and other Antigen Presenting Cells (APC) have never been evaluated.

In Canada with its population of 38 million inhabitants, between December 14, 2020 and July 3, 2021, there were 18.4 million partial vaccinations and 5.5 million full vaccinations carried out[89]. During this period there were 551243 COVID-19 positive cases involving unvaccinated individuals, 27461 cases of

SARS-CoV-2 infections, which occurred to individuals receiving one single dose of vaccine and 2811 individuals were infected after receiving both vaccine doses (**Table 3**)[89]. It follows that full vaccination with two doses of vaccine might not protect against SARS-CoV-2 virus infection. The interpretation of

	Unvaccinated	**Single dose**	**Two doses**
No. of confirmed cases	551243	27461	2811
No. of hospitalizations	27763	2280	217
No. of fatalities	5836	543	82
Proportion hospitalized	5%	8.3%	7.7%
Proportion dying	1.06%	1.97%	2.91%

Table 3 - Numbers of Canadian COVID-19 cases for unvaccinated, vaccinated with a single dose, and fully vaccinated with two doses between December 14, 2020 and July 3, 2021. Also notice that vaccination program in Canada predisposed individuals to more severe outcomes.
Data: Public Health Agency of Canada[89]

number of infections for vaccinated cases must be made with caution however. All 551243 of infected unvaccinated individuals were at risk of infection throughout the entire period between December 14, 2020 and July 3, 2021. Not so for vaccinated individuals since they received their vaccination sometimes between these two dates, hence the risk of exposure to SARS-CoV-2 virus for vaccinated individuals was much shorter. It follows that the numbers of fully vaccinated, yet not protected and infected individuals are much higher than officially reported. Moreover, as stated above, in Canada vaccination program focuses on very high proportion of individuals already immunized through prior exposure to the virus. It is difficult to separate the already naturally immunized, subsequently vaccinated individuals from the vaccinated naïve subjects. Hence potentially this increases the number of failed vaccinations even further.

Misinterpretation of confounded epidemiological data by country's health authority in relation to mass vaccination program is not unique to Canada. For example, Athalia Christie et al. (2021)[97] in their US Morbidity and Mortality Weekly Report compared COVID-19 case incidence, hospital emergency department visits, hospital admissions and deaths by age group during November 29 - December 12, 2020 (pre-vaccine) period with the same between April 18 - May 1, 2021 (vaccine) period for age stratified sample of COVID-19 patients. The investigators concluded that comparing the 2-week pre-vaccination period with 2 weeks in late April, declines in ratio for the four variables mentioned above for older (> 65 years) patients to younger (18-49 years) patients were significantly greater among older adults, who had higher vaccination coverage, than among younger adults, who had lower coverage.

There are at least two serious problems with the interpretation of these observations however. First, the choice of this age stratified patient sample intuitively suggests that comparison of much younger, socially and economically active group of patients just after reopening of the society following several months of restrictive health intervention measures will inevitably predispose the younger group to greater risks of secondary attack through increased activity and exposure as opposed to much older, largely sedentary seniors. Second, an interpretation of dropping incidence together with the other three variables in wake of crashing January 10, 2021 incidence peak, which occurred in numerous other countries concurrently despite differing vaccination efforts (and as we suggest in this paper, primarily due to the exposure of large segment of the US population to the pathogen rendering majority of Americans by January 10, 2021 resistant to the prevalent strain through mounting of their own natural immune response) renders any link to vaccination effort questionable. The development of the prevalent COVID-19 epidemiological profile in North America throughout the pandemic (**Fig.1**) might clarify this situation better. Both countries in parallel engaged in similarly intensive vaccination efforts, yet Canada has experienced a significant run up to the second incidence peak of the second wave driven by the British strain (B.1.1.7) "Alpha" by April 18, 2021. The US peak was much reduced. While the vaccination efforts in both countries were similar, by April 18, 2021 the US population has approached 95% natural population exposure to the pathogen as opposed to only 30% exposure for Canadians. Lastly, not least importantly, neither of the US and Canadian intensive vaccination efforts was able to prevent the third incidence wave in August of 2021. The development of present epidemiological situation in the UK (**Fig.14**), a country engaged in one of the most intensive vaccination efforts in Europe, adds even more uncertainty to the vaccination issue. It follows that without additional well designed comprehensive studies, the present epidemiological evidence does not support the notion of effectiveness of COVID-19 vaccination efforts.

Herd Immunity and the IFR

True severity of a disease can be described by its *Infection Fatality Ratio (IFR)*. It estimates the proportion of deaths caused by the disease among all infected individuals. In situations where not all infections can be accounted for, such as in the case of COVID-19, which is characterized by very high proportions of asymptomatic and very mild disease presentations, a surrogate measure - *Case Fatality Ratio (CFR)* is frequently used instead. Case fatality ratio (CFR) is defined as the proportion of individuals diagnosed with a disease who die from that disease. It is therefore a measure of severity among detected cases[90]. CFR cannot be assumed to reflect the true severity of COVID-19 disease however.

The COVID-19 incidence reported to WHO by individual countries' health authorities, as well as the Canadian weekly reports referred to here, are based on officially reported cases only, thus substantial proportion of the extent of the pandemic remains hidden and underestimated due to unreported asymptomatic and mild cases. In order to convert Case Fatality Ratio (CFR) to Infection Fatality Ratio (IFR) in our paper a multiplication factor of 10 is used. Factor of 10 is a conservative estimate derived from numerous cross-sectional and serological studies and well approximates the true extent of the epidemic within general population encompassing asymptomatic fraction of COVID-19 cases[46,52,53,74].

The IFR calculations in this paper are based on the assumption that today's resulting COVID-19 fatality is an outcome of a diagnosis reported three to four weeks earlier[26,76], therefore to establish instantaneous infection fatality ratio the following IFR model was used:

$$F_{IFR} = \frac{f_{(t)}}{(C_{(-28)} + C_{(-21)})/2 \times 10} \times 100$$

Where:

F_{IFR} = this week's Infection Fatality Ratio %
$f_{(t)}$ = number of new COVID-19 fatalities recorded in the past week
$C_{(-28)}$ = number of new cases recorded 28 days ago
$C_{(-21)}$ = number of new cases recorded 21 days ago
10 = asymptomatic / mild outcome multiplication constant

In scientific literature numerous approaches to calculation of IFR were noted. They were primarily based on surveillance modelling of reported cases[72,91,94,95], serological surveys[92] or to a lesser extent on cross-sectional population surveys[24]. Often the IFR estimates were marked with high variance ranging from 0.1% to 1.0%[93]. Besides the heterogeneity of population age structure encountered in these studies, like SEIR modelling, many surveys based on reported cases and serological surveys may have been confounded. Great degree of uncertainty exists due to underestimation of number of asymptomatic cases, which in many populations were documented to reach as much as 50-85% of the COVID-19 cases[26,71]. The extent of the pandemic was thus greatly underestimated, while its severity overestimated to yield meaningful IFR estimates. Serological surveys are prone to similar degree of uncertainty since large proportion of asymptomatic individuals recover without developing detectable antibody titers in addition to frequent sampling bias of sub-sampled populations not being representative of the general population. This initially might have led to overestimation of IFR in some general populations, for example in France (IFR of 0.5-0.7%)[95], in China (IFR of 0.66%)[94]. In addition, most of such IFR estimates attempted during the initial stages of the pandemic were likely affected by increased COVID-19 mortalities due to initial unfamiliarity with the disease leading to mis-diagnosis and/or subsequent mishandling of severe cases within clinical settings (see below). It follows that initial COVID-19 severity estimates were much higher than the pandemic mean, since the COVID-19 IFR did not remain constant throughout the development of the pandemic and continued dropping with time.

In this paper, using a simple analysis of officially reported to WHO epidemiological data by seven countries we document the general trend of IFR evolution throughout the pandemic. We assumed improvement of the reliability of reported incidence to WHO by mid-March 2020 together with an improvement of the reporting of COVID-19-related mortalities by the beginning of April 2020 yielding consistent reliable epidemiological data suitable for our purpose. Two countries, Spain and UK were still making some corrections to their reported data submission at a later date. We therefore omitted analysis of Spanish data prior to June 28, 2020, and British data prior to August 23, 2020.

USA, Canada, Germany, Sweden, Czech Republic, UK and Spain show very similar pattern in their IFR development throughout the pandemic. It generally can be separated into three distinct periods:

1) ***Excessive mortalities*** resulting from the initial exposure of naïve, vulnerable population to the pathogen. The severity of COVID-19 in the early weeks of the first wave is documented for five countries in their respective epidemiology profiles (**Fig.2,4,7,9 and 12**). Since April 5, 2020 notice in the US (**Fig.2**), Canada (**Fig.4**), Germany (**Fig.7**), Sweden (**Fig.9**) and Czechia (**Fig.12**) the initial COVID-19 fatalities were excessive (blue dots). In the UK and Spain the pattern would have been similar, however, due to the unreliability of initially reported incidence and/or mortalities in these two countries the data were omitted from our analyses. In addition to mis-diagnosis, mishandling of severe cases and shortage of crucial medical supplies and equipment during the first wave of the epidemic, the delays in hospital admissions and overwhelming of the medical system are likely causes of these initially very high fatality ratios. Furthermore, initial under reporting of cases within the first weeks of the health emergency have diminished the denominator in our model resulting in artificially inflated IFR. Hence the IFR estimates in this region of the graph (blue dots) are pictured for illustration purposes only and by no means represent the actual morbidity of COVID-19.

2) ***Summer IFR bottoms out*** - during the second phase of the epidemic at the end of the first wave, in most countries we examined with the exception of the USA, the COVID-19-related fatalities generally showed bottoming trend in the summer of 2020 (**Fig.4,7,9 and 12**). In the autumn of 2020 this was followed by a turn around with increasing COVID-19 mortalities during the run up to the first peak of the second wave (red dots). During this period apparently still primarily vulnerable population only slowly continued mounting its global immune response to SARS-CoV-2 virus through exposure to the pathogen. In the US, likely due to super-spreading mass protests following the murder of George Floyd on May 25, 2020 since the summer the IFR trajectory remained more or less constant throughout the epidemic with a slight continuous dropping trend (**Fig.2,3**).

3) ***Consistent continuous drop in IFR*** - in most of the seven countries past the first incidence peak of the second wave the second wave IFR trailing edge became apparent (orange dots in **Fig.5,8,10 and 13**). It was characterized by a continuous steady drop in IFR. Apparently the explosive incidence run up to the first peak of the second wave resulted in equally robust population immune response. As the coronavirus began hitting more and more resistant individuals within the respective populations, the increasing population resilience was accompanied with a steep incidence decline (crash). The IFR began following

this decline commencing consistent continuous drop despite some subsequent occasional COVID-19 incidence increases. The steady progression of COVID-19 fatality ratio decline throughout the pandemic in all countries we looked at lends support to the notion of advancing herd immunity within populations.

For unknown reasons in Spain the pattern of dropping IFR was delayed well until April 2021 (**Fig.16,17**) Canada has experienced some up tick in IFR after June 23, 2021 (**Fig.5**). This is quite unusual since the increase in the Canadian IFR was not matched by any corresponding increase in the COVID-19 incidence. The same was true for the German IFR (**Fig.8**). This mysterious June irregularity in IFR was also exhibited in the US (**Fig.2,3**), Sweden (**Fig.9**) and in Czech Republic (**Fig.12,13**) as a consistent increase of IFR data scatter at times of low incidence. Unlike in Sweden, which otherwise exhibited strikingly similar COVID-19 incidence pattern with Germany (**Fig.6**), in Germany the onset of dropping IFR past the first peak of the second wave was substantially delayed. In addition, despite much lower magnitude of the COVID-19 incidence in Germany (**Table 2**), we also see substantially elevated German infection fatality ratios in comparison with Sweden (**Fig.8**). There might be several explanations for this, such as much higher German population density, older population age structure, and/or different handling of cases at the clinical level (higher propensity for intubation for critically ill patients in German hospitals, for example).

Conclusions

To our knowledge this is the first publication, which using publicly available epidemiological data attempts to document the role of the natural global (herd) immunity in the mitigation of the COVID-19 pandemic. Our analysis of epidemiological data from eight selected countries suggests that the first signs of herd immunity were discernible as early as November, 2020 and that its progress towards achieving broad population resilience against COVID-19 might depend on the magnitude of natural population exposure to different variants of the pathogen.

We also characterized the dynamic nature of SARS-CoV-2 virus infection fatality ratio (IFR) since the beginning of the health emergency. Using a relatively simple model and epidemiological data reported by 22 countries we confirmed the SARS-CoV-2 virus infection fatality ratio to be ~0.17% (Median IFR

~ 0.145%) for majority of the general population during the last seven months of the pandemic (**Table 1**). This value is well aligned with conclusions of other IFR modeling[72,91], as well as serological studies[92].

From the overwhelming biological and epidemiological evidence we have examined in both parts of this publication, it became evident that COVID-19 is a mild disease for vast majority of human population[71]. For the minor segment of vulnerable population with comorbidities (~0.5%) who are at risk of developing serious, severe or critical disease manifestations resulting in respiratory failure, septic shock, or multiple organ dysfunction, failure and death it is a preventable disease since in most cases these vulnerable individuals are easily identifiable and can easily be separated from the non-vulnerable majority.

At the beginning of the world COVID-19 health emergency in the spring of 2020 it was difficult to ascertain the true morbidity of this pathogen and the reliance on non-pharmaceutical interventions was logically the only option the world community had to mitigate the disease. Within a short span of time, however, our knowledge base substantially expanded and it became evident that SARS-CoV-2 was a predominantly mild pathogen. It became everybody's personal experience that the lack of political will often fueled by sensation-hungry mainstream media campaigns prevented this recognition. Reliance on confounded modeling and ineffective severely damaging strict social distancing measures continued to the detriment of humanity. With time, plethora of scientific literature pointed out the shortcomings of such approach and highlighted the need for the use of randomized design cross-sectional and longitudinal epidemiological studies and the use of multiplication factors in order to improve our understanding of SARS-CoV-2 virus epidemiology and to determine the true extent of the pandemic. These rigorous and promising scientific approaches, despite their utility were rarely attempted.

In October article published in JAMA,Cutler and Summers (2020)[96] discussed the economic costs of the coronavirus in their appropriately titled contribution, "The COVID-19 Pandemic and the $16 Trillion Virus". Now we would like to close our two-part review paper with a question: was the COVID-19 public health emergency the result of a $16 trillion virus, or a $16 trillion response to a predominantly mild respiratory disease?

FIGURES

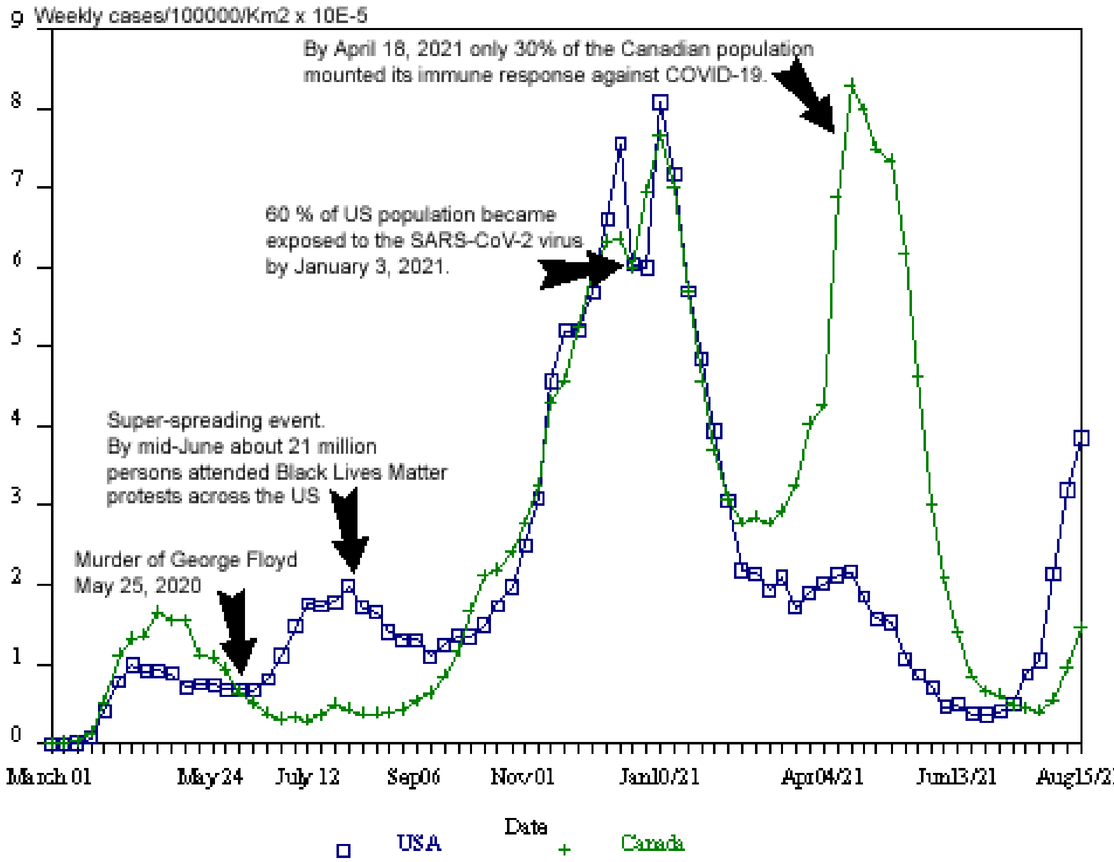

Figure 1 - The evolution of COVID-19 epidemiology in North America between March 1st 2020 and August 15th 2021 expressed as the weekly number of confirmed cases per 100000 per Km^2. In Canada and in the continental USA only the surface area with population density > 10 individuals per Km^2 was considered in the analysis. This highlights the epidemiologically significant population density in each country bringing both populations to the same baseline making direct comparison and superimposition of epidemiologically significant data possible. Notice in particular the similarity of the incidence profiles in both countries clearly indicating the SARS-CoV-2 virus behaving as one single panmictic population unit throughout the entire North-American continent. This apparent congruence ended on February 21, 2021 when marked separation in both curves occurred likely due to differences in level of attained herd immunity in the US and Canadian populations. By April 18, 2021 95% of Americans had been exposed to the coronavirus and began mounting their immune response to it as opposed to only 30% of Canadians.

Data: WHO weekly epidemiology reports

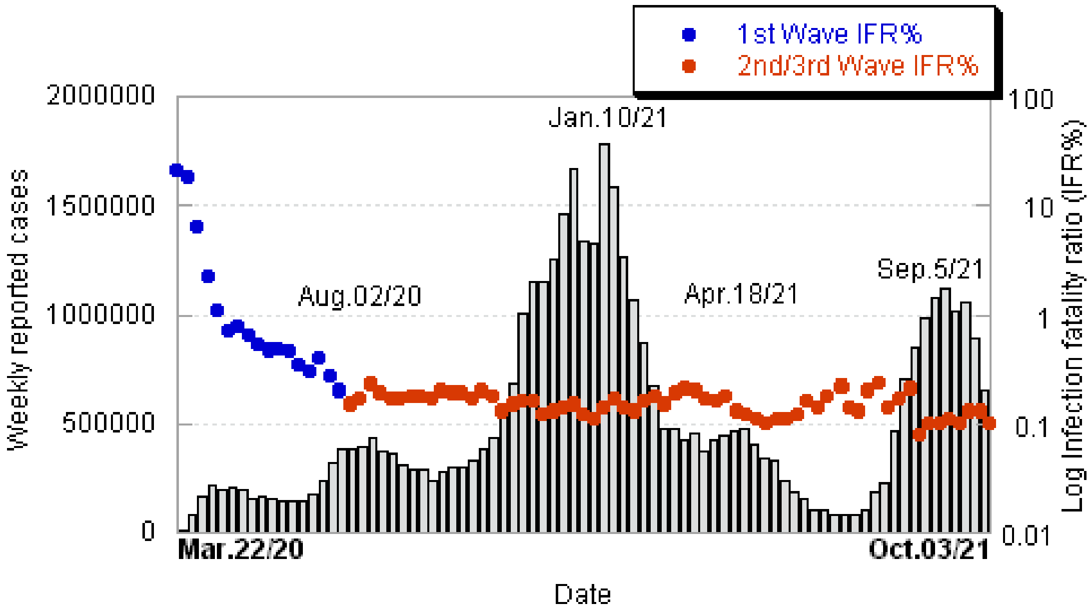

Figure 2 - The number of weekly reported new cases in the USA between March 22, 2020 and October 3, 2021 plotted together with superimposed evolution of the Infection Fatality Ratio (IFR) throughout the COVID-19 epidemic. At the beginning of the pandemic unprepared and initially overwhelmed US medical system exhibited very high COVID-19 mortality rates (blue dots). The 20.9% IFR on March 22, 2020 commenced consistent and continuous slide throughout the first wave however, finally stabilizing at a summer and second wave equilibrium (red dots). Mortalities of 0.2% were reached sometimes around July 12, 2020. Since then the IFR continued its slide as the US epidemic progressed exhibiting only minor fluctuations following prevalent incidence rates (see **Fig. 3**). By October 3, 2021 already ~130% of the US population had been exposed to the pathogen (excluding vaccinations) and began mounting its natural immune response to a number of SARS-CoV-2 variants.

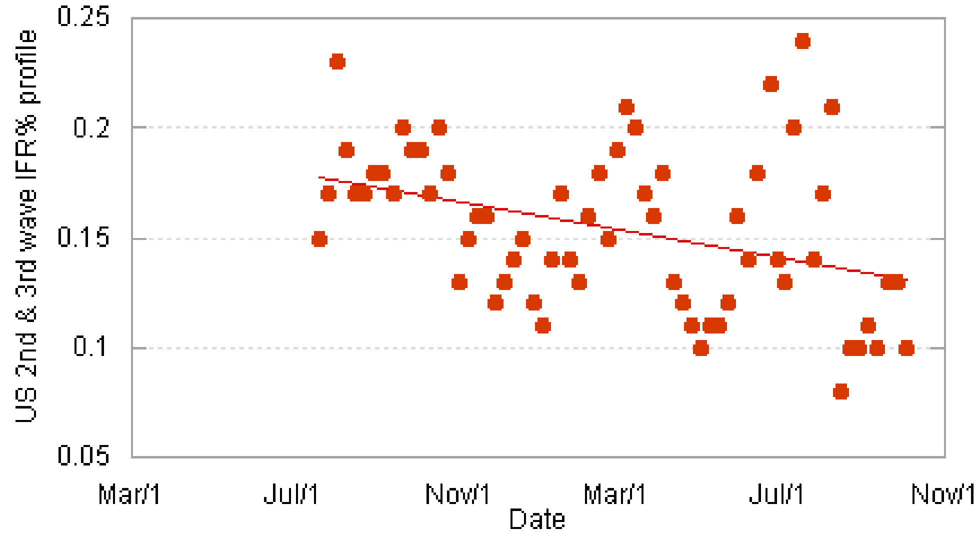

Figure 3 - Despite Black Lives Matter organised mass protests which resulted in super-spreading events and increases in COVID-19 incidence across the US, the summer and second wave mortality remained relatively stable. It fluctuated mostly below 0.2% throughout the rest of the pandemic. Interestingly, we see a substantial increase in COVID-19 mortality scatter as the US vaccination program began at the end of December 2020. In other countries some IFR scatter was seen to be associated with relaxation of NPIs (**Fig.12**), however the magnitude of the mortality scatter seen in the US appears to be unique among all countries we looked at.

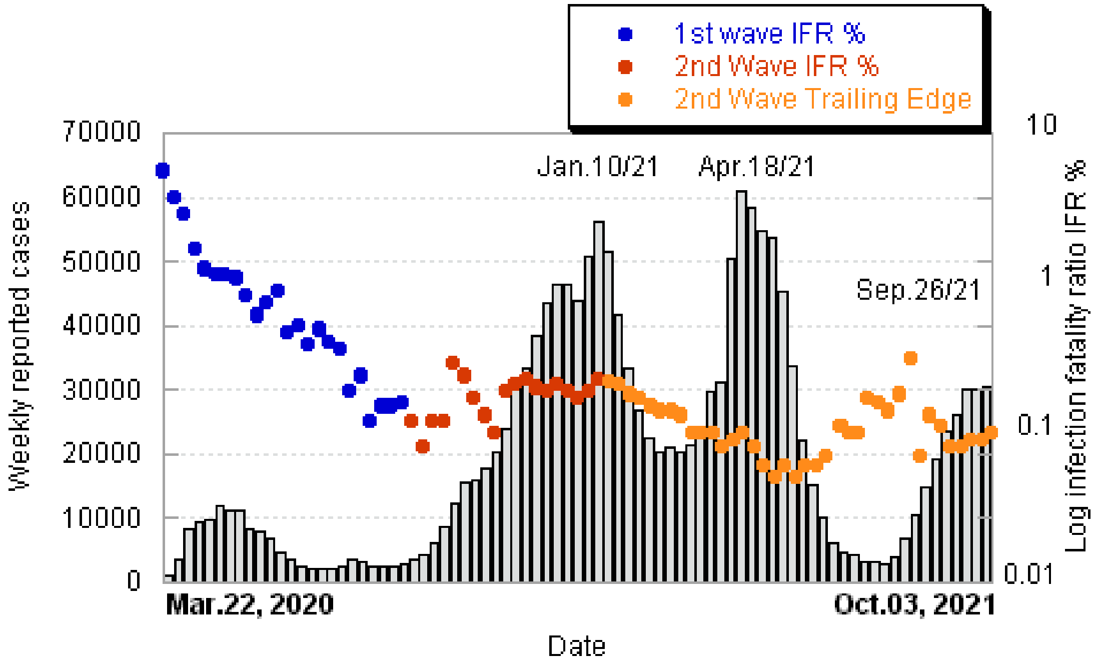

Figure 4 - The COVID-19 incidence in Canada expressed as the number of weekly reported cases between March 22, 2020 and October 3, 2021 (gray bars). Data is plotted together with superimposed evolution of the IFR for the same period (blue, red and orange dots). The Canadian IFR was estimated to be 5.58% on March 22, 2020 subsequently dropping to the Canadian summer and second wave equilibrium of 0.19% on July 26, 2020. It then remained fluctuating around 0.2% for the remainder of the pandemic. By October 3, 2021 ~43% of Canadians were already exposed to the SARS-CoV-2 virus and began mounting their own natural immune response to it.

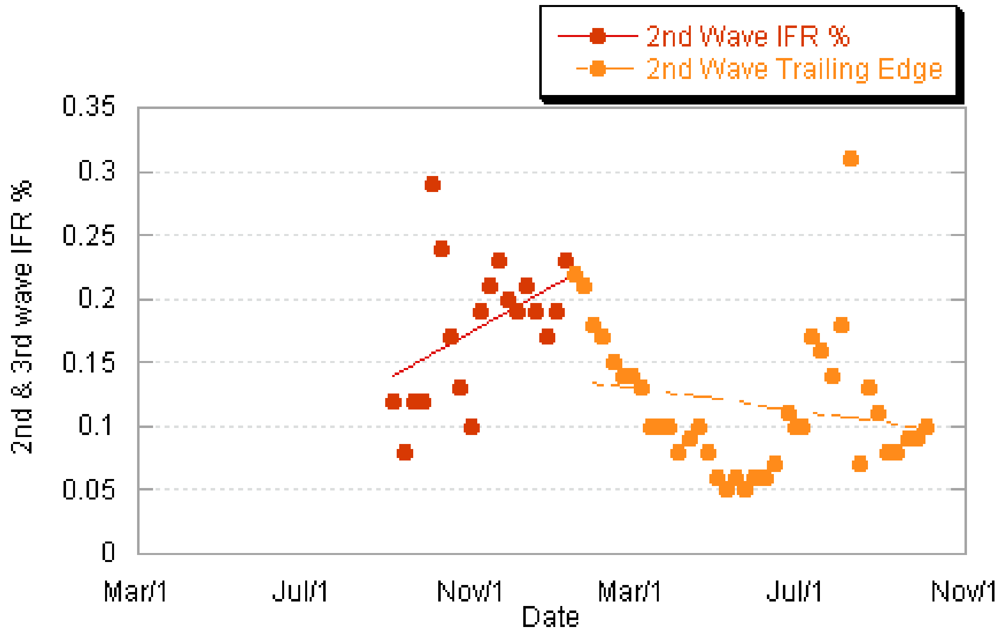

Figure 5 - This graph represents the progression of the Canadian IFR in the summer and 2^{nd} wave, between July19, 2020 and January 10, 2021 (red dots) and then throughout the continuation of the 2^{nd} wave, between January 17, 2021 and August 15, 2021 (orange dots). It ends in the third wave by October 3, 2021 (orange dots). Together with the US and Canadian incidence the Canadian IFR commenced sustained drop in January of 2021 (orange dots). The COVID-19-linked fatalities falling trend was maintained despite pronounced second incidence peak driven by the strain “Alpha” (B.1.1.7) at the end of April 2021. The consistent rise in IFR in June/July 2021 is unexpected, as it is not matched by any increase in incidence. It might be linked to the Canadian vaccination efforts (see **Table 3** and text for discussion).

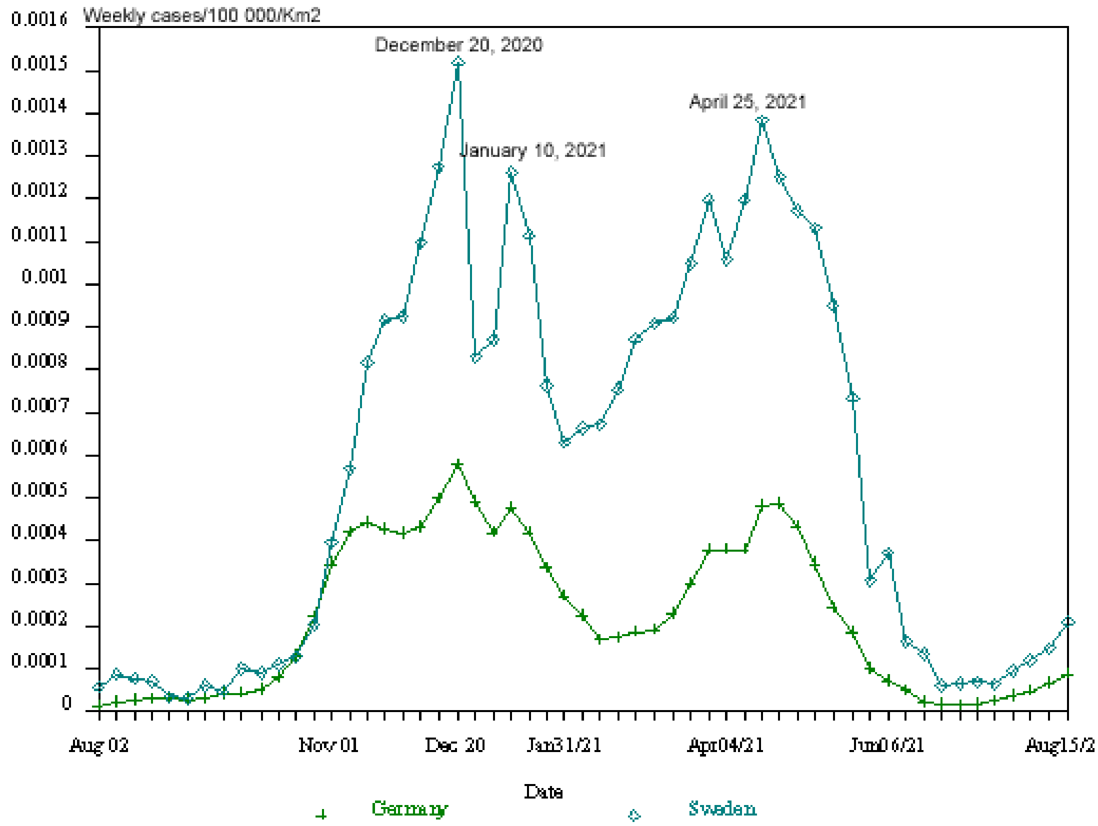

Figure 6 - Two European countries with, for unknown reasons, strikingly similar evolution of COVID-19 epidemiology were Sweden and Germany. For direct comparison the raw reported epidemiological data is expressed as the weekly number of cases per 100000 of population per Km^2 of epidemiologically significant population density. Only the second wave of the epidemic with its distinctive peaks and valleys between August 2, 2020 and August 15, 2021 is imaged here.

Data: WHO weekly epidemiology reports.

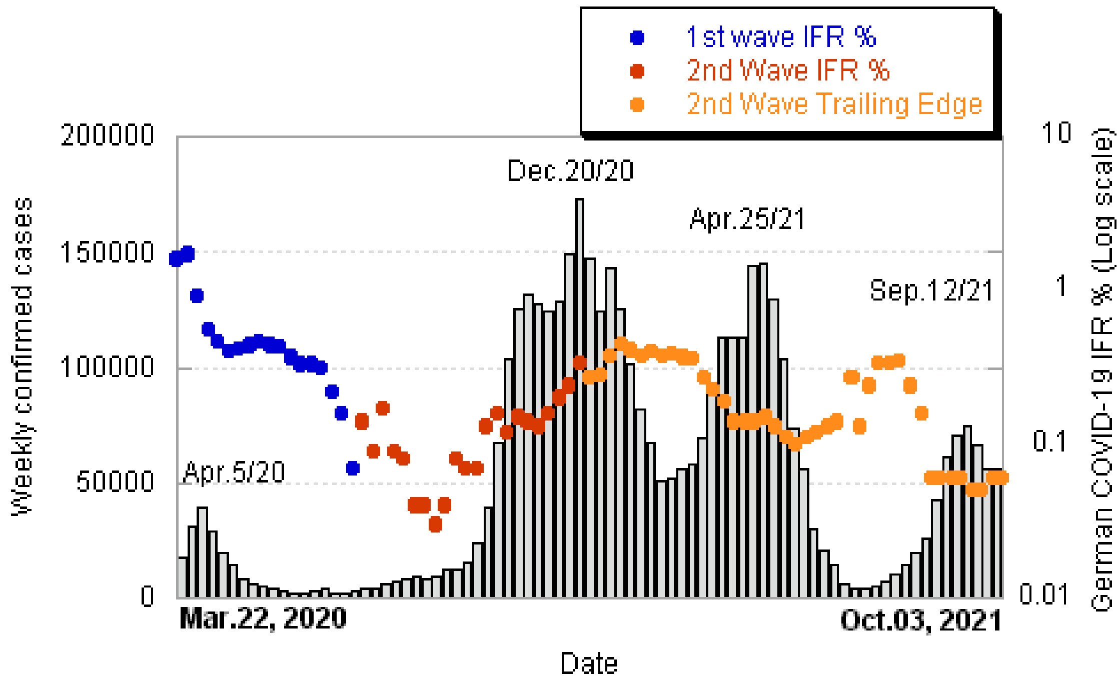

Figure 7 - The evolution of COVID-19 pandemic in Germany between March 22, 2020 and October 03, 2021. Raw data of weekly reported new cases (gray bars) is plotted together with the log-transformed course of the German Infection Fatality Ratio (IFR) (blue, red and orange dots). Germany experienced very high IFR fluctuations throughout the pandemic despite the implementation of very strict non-pharmaceutical interventions possibly due to high strain on its medical system. Similar profile could also be expected in countries with aging population structure, or engaging in particular clinical practices such as intubation of critically ill patients. Germany shares with Canada the mysterious rise in mortalities throughout the summer of 2021 (**Fig. 5**). This rise in fatalities coincides with low COVID-19 incidence prior to the onset of the third incidence wave. Due to very strict public health intervention measures implemented in Germany, by October 3, 2021 only ~ 51% of Germans were exposed to the pathogen and began mounting their natural immune response to it.

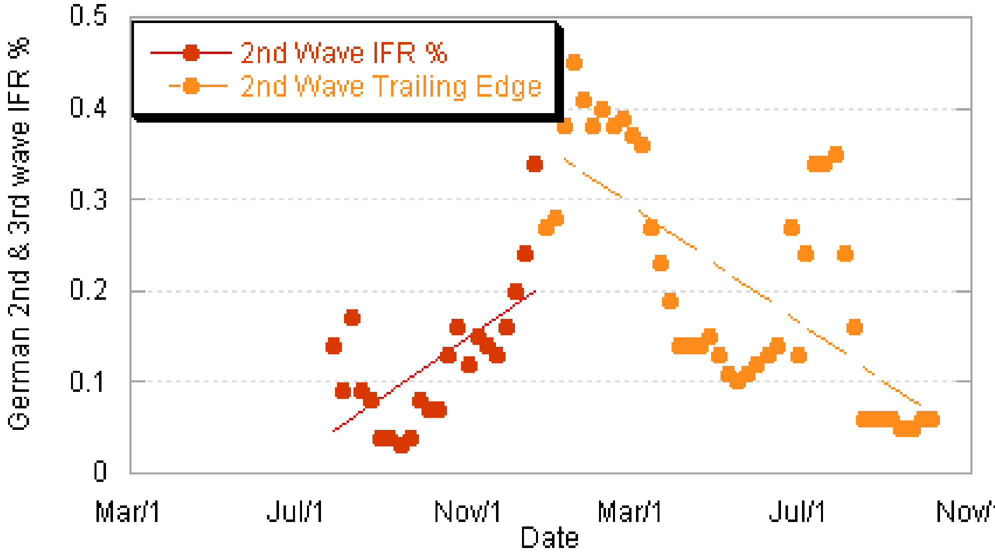

Figure 8 - The course of the German COVID-19 IFR during the summer, second and third incidence wave of the pandemic between July 5, 2020 and December 20, 2020 (red dots) and December 27, 2020 and October 3, 2021 (orange dots). In Germany the COVID-19 induced mortality tends to follow more closely the prevalent disease incidence. In this densely populated country this possibly might be due to the strain on the country's medical system, yet the IFR exhibits consistent drop throughout the epidemic dipping below 0.1% during the third incidence wave in the autumn of 2021.

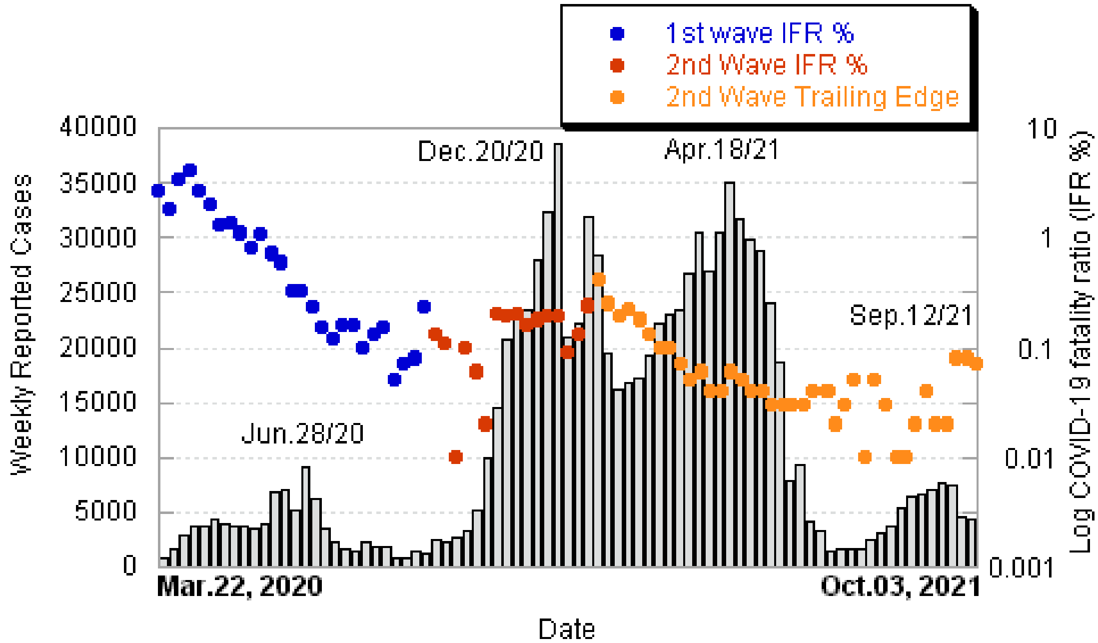

Figure 9 - The evolution of COVID-19 epidemiology in Sweden between March 22, 2020 and October 3, 2021. The total number of weekly reported cases (gray bars) is plotted together with the log-transformed corresponding IFR for the period (blue, red and orange dots). As more Swedes mounted their herd immune response to COVID-19 throughout the epidemic, the Swedish IFR continues its slide towards 0 regardless of reported case incidence increases. For unknown reasons this trend is broken in the summer and autumn of 2021. The rise in COVID-19 fatalities over summer of low COVID-19 incidence is shared by a number of countries engaged in intensive vaccination efforts. On October 3, 2021 ~115% of Swedes have already been exposed to the coronavirus and began mounting their natural immune response.

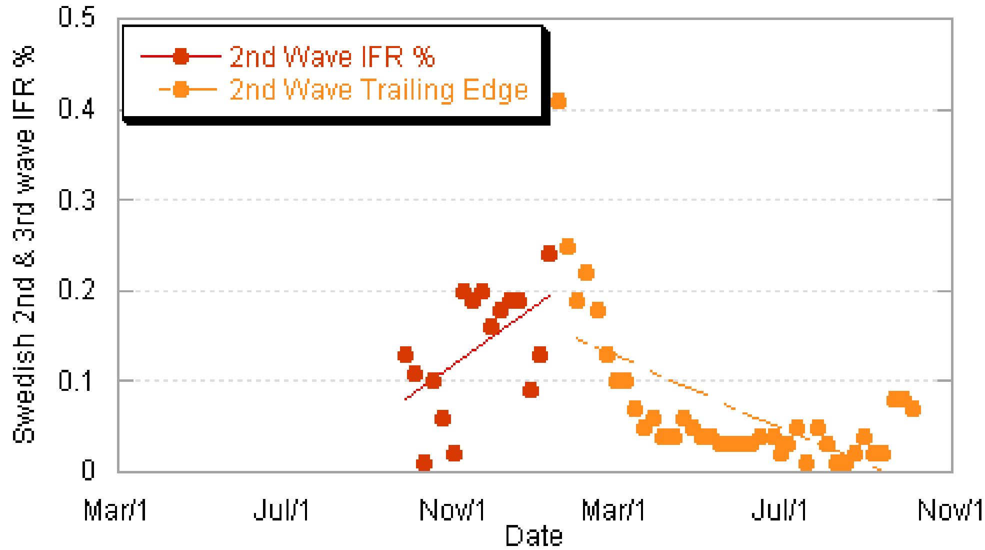

Figure 10 - Swedish COVID-19 Infection Fatality Ratio during the summer, second and third wave of the pandemic. While its course shows some similarity to the German profile, it remained quite low often fluctuating much below 0.1%. Data represent the IFR during the summer and the beginning of 2nd wave, July 5, 2020 to January 3, 2021 (red dots). This is followed by the 2nd wave trailing edge between the January 10, 2021 peak and October 3, 2021 (orange dots). The mysterious up tick in mortalities in the summer and autumn of 2021 is clearly seen in Sweden as well.

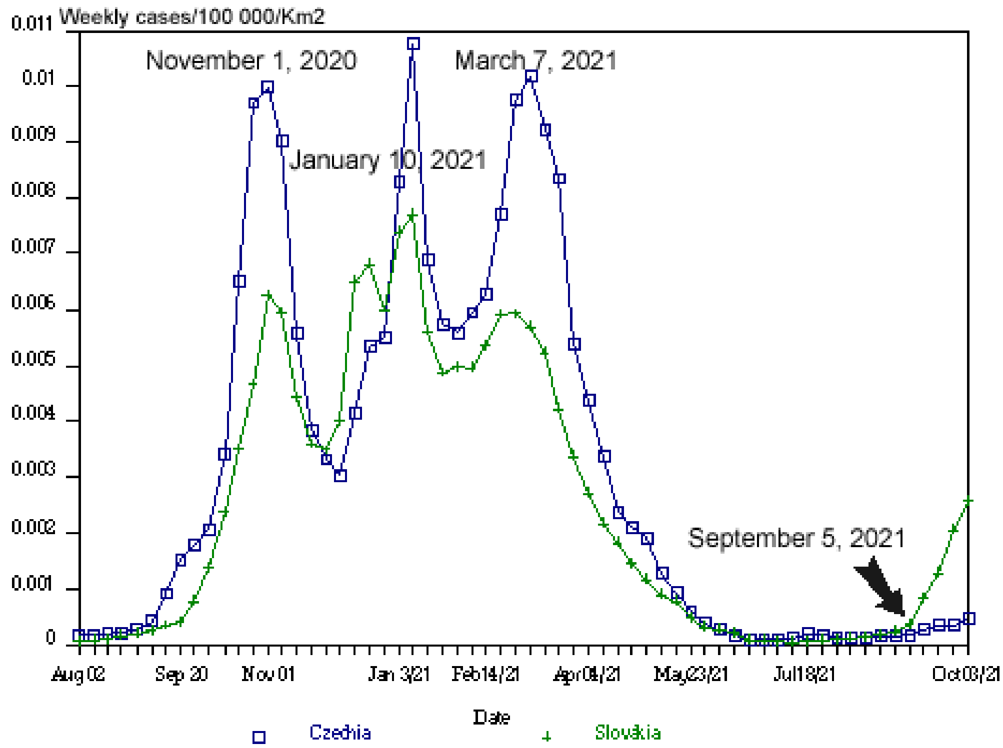

Figure 11 - Czech Republic (population 10.7 million) shares remarkable temporal similarity of its COVID-19 epidemiology with neighbouring Slovakia (population 5.5 million). In order to bring the epidemiology in both countries to the same baseline for comparison both graphs are expressed as the weekly number of confirmed cases per 100000 per Km^2. Notice the magnitude of peaks closely matching the population size of both countries. By September 5, 2021 (arrow) ~157% of the Czech population and only ~72% of Slovaks became exposed to the coronavirus and began mounting their natural immune response to the pathogen. Apparently the Czech high exposure level to the virus was sufficient to significantly enhance the population resilience to the disease as evidenced by the reversal of the Czech and Slovak incidence lines during the run up to the third incidence wave on September 5, 2021.

Data: WHO weekly epidemiology reports.

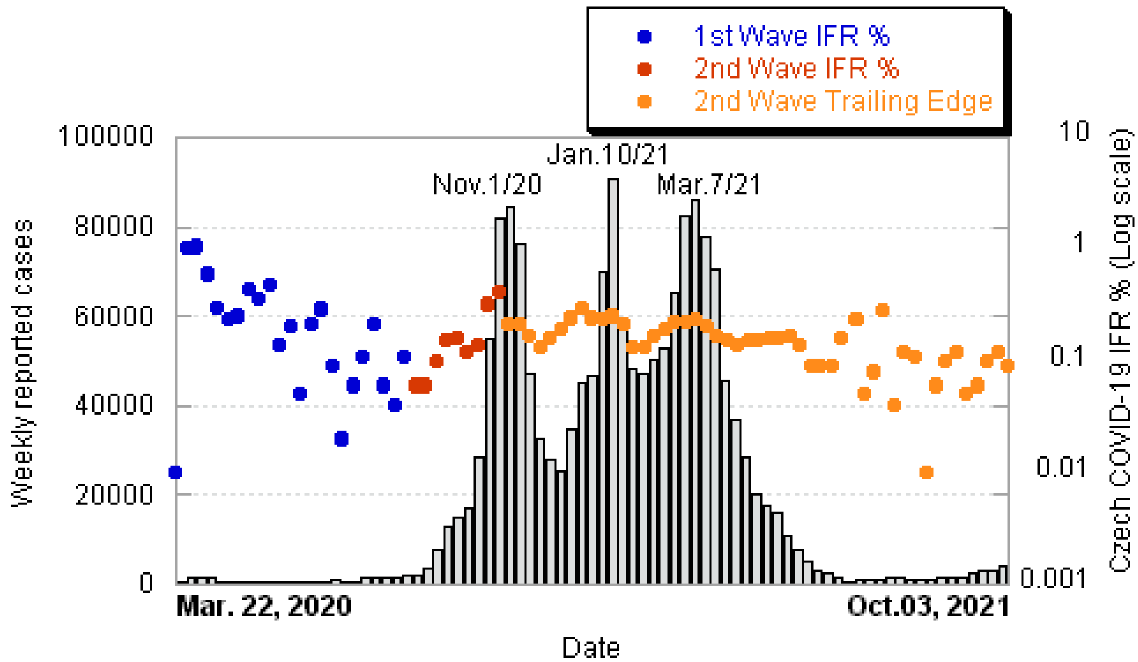

Figure 12 - The COVID-19 evolution throughout the pandemic in Czech Republic between March 22, 2020 and October 3, 2021. The raw weekly incidence data (gray bars) is plotted together with corresponding log-transformed Infection Fatality Rate (IFR) (blue, red and orange dots). Notice the persistent second wave incidence fluctuations despite maintenance of strict social distancing measures in that country. Moreover, the second wave fluctuations in incidence are matched by only minor IFR profile changes. The COVID-19 IFR began consistent continuous slide after the first 2nd wave peak on November 1, 2020 (orange dots), see also **Fig.13**. By October 3, 2021 over 158% of Czechs became exposed to the virus and began mounting their own natural immune response to a number of SARS-CoV-2 virus variants.

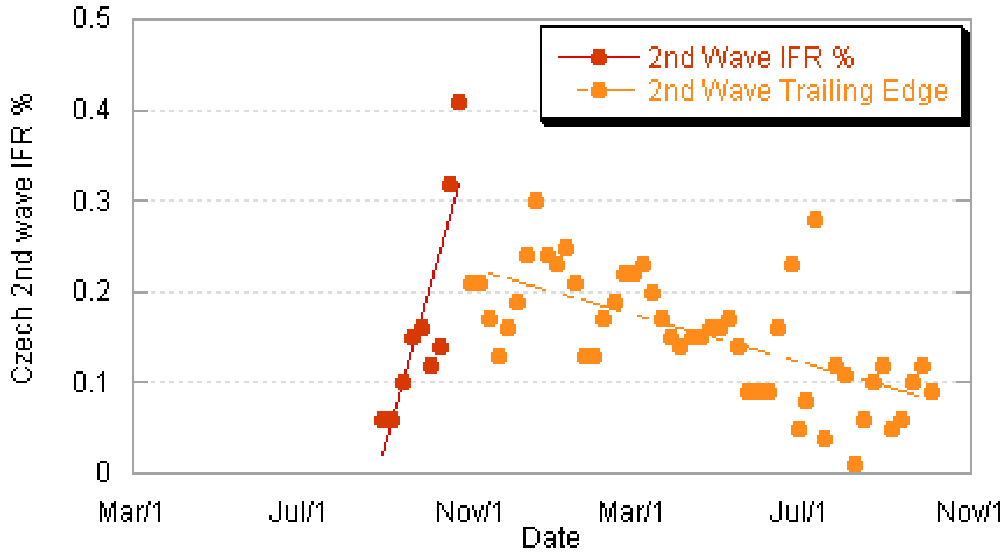

Figure 13 - The evolution of the COVID-19 infection fatality rate (IFR) in Czech Republic (Czechia). The data covers period between Aug 30 and November 1, 2020 (red dots) and the remainder of the 2nd wave and its trailing edge between November 1, 2020 and October 3, 2021 (orange dots). Like in Canada, Germany and Sweden in CR we can also notice the temporary mysterious up tick in COVID-19 mortalities associated with summer 2021 low incidence.

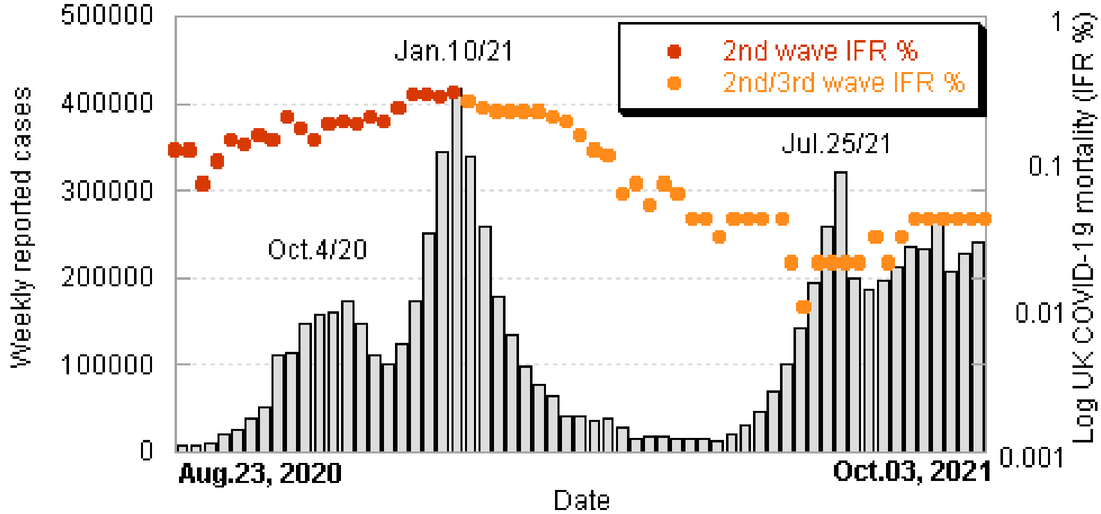

Figure 14 - The COVID-19 incidence and its corresponding infection fatality ratio (IFR)development in the United Kingdom during the second and third wave of the pandemic between August 23, 2020 and October 3, 2021. In the UK the second wave January 10 peak was ascribed to the British SARS-CoV-2 variant B.1.1.7. Interestingly, the January 10 incidence peak was seen in numerous other countries (see **Fig. 2,4,12**) not reporting this variant at the time. Despite the variant B.1.1.7. being associated with more severe clinical presentations of the COVID-19 disease the UK IFR did not exceed 0.3% (**Fig.15**). Notwithstanding the intensive British vaccination efforts, after easing of the harsh NPIs in June of 2021 Britons experienced a run up to substantial and persistent 3rd incidence wave of COVID-19 cases rasing doubts about the effectiveness of global vaccination efforts. By October 3, 2021 approximately 115% of the UK population has already been exposed to a number of SARS-CoV-2 virus variants and began mounting their natural immune response to them.

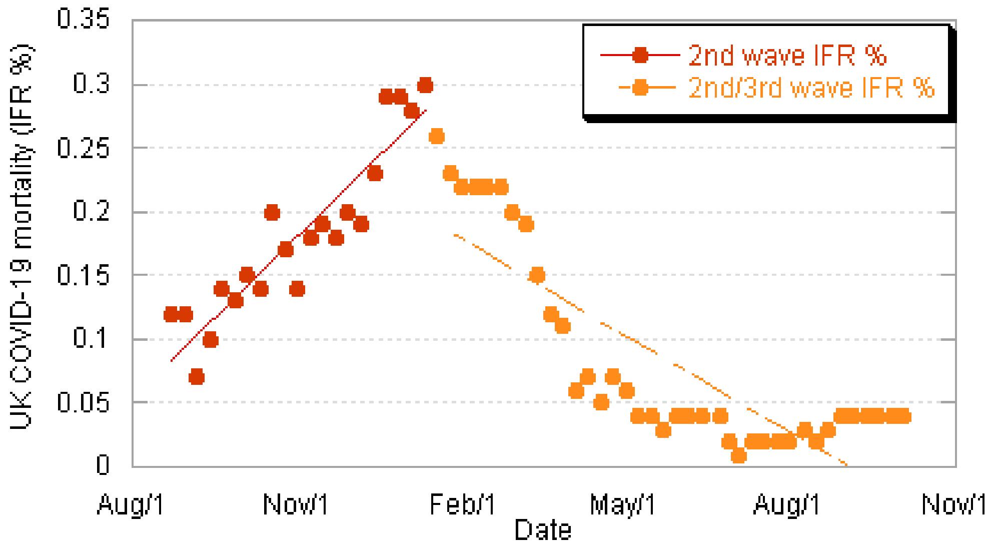

Figure 15 - The course of the British COVID-19 infection fatality ratio (IFR) between August 23, 2020 and October 3, 2021. The UK IFR commenced a sustained drop right after the second wave January 10 peak and remained very low even after all social distancing measures were lifted and the third wave peaked on July 25, 2021.

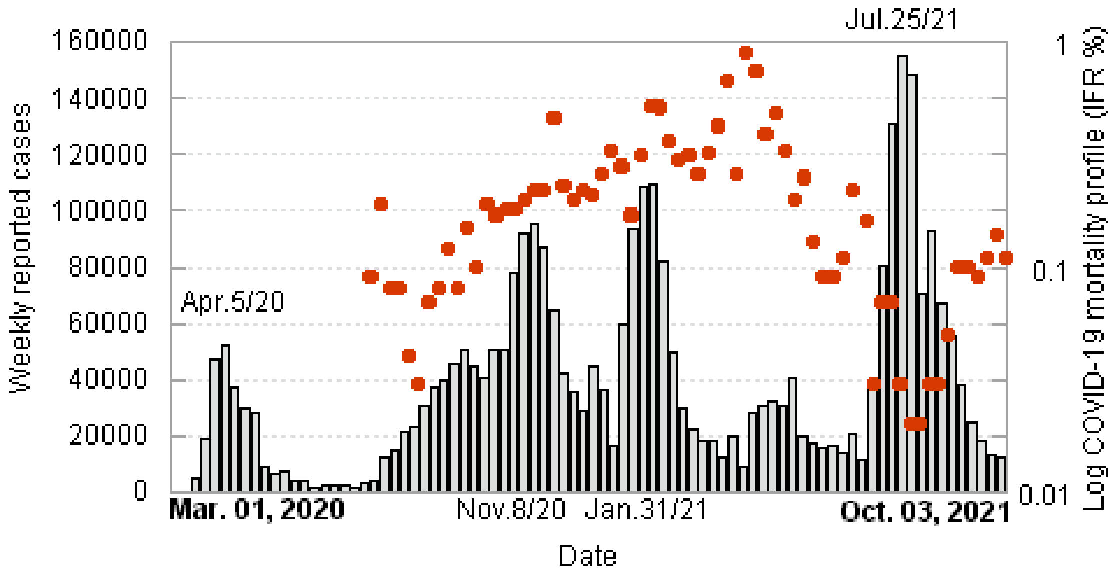

Figure 16 - The developments of COVID-19 pandemic in Spain between March 1, 2020 and October 3, 2021. Here weekly incidence of confirmed positive cases (gray bars) is plotted together with log-transformed changing profile of the COVID-19 characteristic infection fatality ratio (IFR) (red dots) in that country. Despite the repeated use of lock downs and severe restrictions including an intensive government vaccination program the SARS-CoV-2 virus was never eliminated from the Spanish population and continues to remain established. By October 3, 2021 approximately 107% of the Spanish population has already been exposed to the coronavirus and began forming its natural global immune response to a number of circulating virus variants.

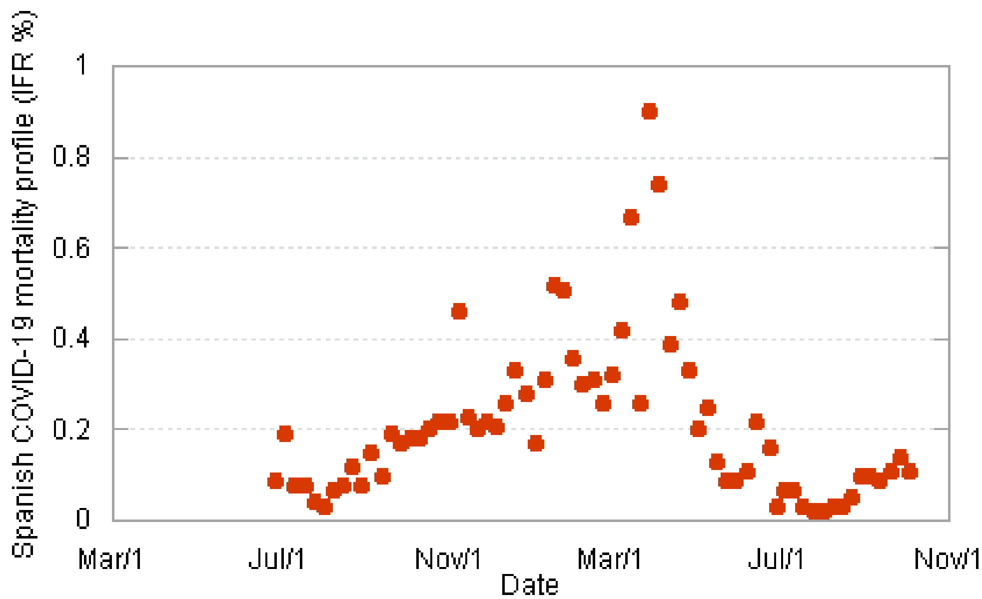

Figure 17 - The profile of Spanish COVID-19 infection fatality ratio (IFR) between June 28, 2020 and October 3, 2021. The plot comprise only the period for which reliable data was available. Despite the implementation of very strict non-pharmaceutical interventions at very high social and economic costs to citizens by the Spanish authorities, at the beginning of 2021 Spain had recorded one of the highest mortalities in Europe.

Figure 18 - The implementation strict social distancing measures and confinement resulted in very high social costs including an increase in the risk of suicide. In Canada during the COVID-19 pandemic billboards were put up by the Montreal Transit Commission (STM) in a suicide prevention effort likely in order to mitigate the heightened risk of suicides taking place in that city's transit system.

REFERENCES

1 Carlos del Rio and Preeti N. Malani, 2020. COVID-19 - New Insights on a Rapidly Changing Epidemic. JAMA. 2020;323(14):1339-1340. doi:10.1001/jama.2020.3072

2 W. Joost Wiersinga et al. 2020. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review.
JAMA. 2020;324(8):782-793. doi:10.1001/jama.2020.12839

3 Xiaoyan Song et al. 2020. Comparison of Clinical Features of COVID-19 vs Seasonal Influenza A and B in US Children. JAMA Netw Open. 2020;3(9):e2020495. doi:10.1001/jamanetworkopen.2020.20495

4 David L. Swerdlow, and Lyn Finelli. Preparation for Possible Sustained Transmission of 2019 Novel Coronavirus: Lessons From Previous Epidemics.
JAMA. 2020;323(12):1129-1130. doi:10.1001/jama.2020.1960

5 Zhou P, Yang X-L, Wang X-G, et al. 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273. https://doi.org/10.1038/s41586-020-2012-7PubMedGoogle ScholarCrossref

6 Gordon DE, Jang GM, Bouhaddou M, et al. 2020. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020;583(7816):459-468. https://doi.org/10.1038/s41586-020-2286-9PubMedGoogle ScholarCrossref

7 Hoffmann M, Kleine-Weber H, Schroeder S, et al. 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.e8. doi:10.1016/j.cell.2020.02.052PubMedGoogle ScholarCrossref

8 Murgolo N, Therien AG, Howell B, Klein D, Koeplinger K, Lieberman LA, et al. (2021) SARS-CoV-2 tropism, entry, replication, and propagation: Considerations for drug discovery and development. PLoS Pathog 17(2): e1009225. https://doi.org/10.1371/journal.ppat.1009225

9 Pontelli MC, Castro IA, Martins RB, Veras FP, La Serra L, Nascimento DC, et al. Infection of human lymphomononuclear cells by SARS-CoV-2. bioRxiv. 2020.

10 Codo AC, Gastão Davanzo G, de Brito Monteiro L, de Souza GF, Muraro SP, Virgilio-da-Silva JV, et al. Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF_1alpha/Glycolysis_Dependent Axis, e435. Cell Metab. 2020;32:437–46. pmid:32697943

11 Roman Wölfel et al., 2020. Virological assessment of hospitalized patients with COVID-19. Nature 581:465-469, https://doi.org/10.1038/s41586-020-2196-x.

12 Monica Webb Hooper, Anna María Nápoles et al., 2020. COVID-19 and Racial/Ethnic Disparities. JAMA. 2020;323(24):2466-2467. doi:10.1001/jama.2020.8598

13 Supinda Bunyavanich, Chantal Grant, and Alfin Vicencio, 2020. Racial/Ethnic Variation in Nasal Gene Expression of Transmembrane Serine Protease 2 (TMPRSS2).
JAMA. 2020;324(15):1567-1568. doi:10.1001/jama.2020.17386

14 Harvey V. Fineberg. 2020. The Toll of COVID-19.
JAMA. 2020;324(15):1502-1503. doi:10.1001/jama.2020.20019

15 D. Di Mascio, A Khalil, G Saccone et al. 2020. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am.J.Obstet Gynecol MFM 2020;2(2):100107.

16 I. Huang, MA Kim, R. Pranata, 2020. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - a systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr. 2020;14(4):395-403.

17 Zhao Q, Meng M, Kumar R, et al., 2020. The impact of COPD and smoking history on severity of COVID-19: a systematic review and meta-analysis.
J. Med. Virol. 2020. https://doi.org/10.1002/jmv.25889.

18 Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W., 2020. Single-cell RNA expression profiling of Ace2, the putative receptor of Wuhan 2019-nCoV. 2020;10.1101/2020.01.26.919985 %J bioRxiv:2020.2001.2026.919985.

19 Catherine Gebhard et al., 2020. Impact of sex and gender on COVID-19 outcomes in Europe. Biol. Sex Diff. 2020 11:29 https://doi.org/10.1186/s13293-020-00304-9.

20 William Marciel de Souza, Lewis Fletcher Buss, Darlan da Silva Candido et al., 2020. Epidemiological and clinical characteristics of the COVID-19 epidemic in Brazil. Nature Hum. Behav. | VOL 4 | August 2020 | 856–865 https://doi.org/10.1038/s41562-020-0928-4

21 Chu DK, Akl EA, Duda S, et al; COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020;395(10242):1973-1987. doi:10.1016/S0140-6736(20)31142-9PubMedGoogle ScholarCrossref

22 Chia PY, Coleman KK, Tan YK, et al; Singapore 2019 Novel Coronavirus Outbreak Research Team. Detection of air and surface contamination by SARS-CoV-2 in hospital rooms of infected patients. Nat Commun. 2020;11(1):2800. doi:10.1038/s41467-020-16670-2PubMedGoogle ScholarCrossref

23 Ye Shen, Changwei Li, Hongjun Dong et al., 2020. Community Outbreak Investigation of SARS-CoV-2 Transmission Among Bus Riders in Eastern China. JAMA Intern Med. 2020;180(12):1665-1671. doi:10.1001/jamainternmed.2020.5225

24 Hendrik Streeck et al., 2020. Infection fatality rate of SARS-CoV2 in a super-spreading event in Germany. Nature Communications (2020) 11:5829 https://doi.org/10.1038/s41467-020-19509-y

25 M. Cevik et al., Lancet Microbe 2, e13 (2021)

26 The Royal Society 2020. Reproduction number (R) and growth rate (r) of the COVID-19 epidemic in the UK:methods of estimation, data sources, causes of heterogeneity, and use as a guide in policy formulation.
https://royalsociety.org/_/media/policy/projects/set-c/set-covid-19-R-estimates.pdf. Accessed December 5, 2020.

27 Chaw L et al., 2020. SARS-CoV-2 transmission in different settings: analysis of cases and close contacts from Tablighi cluster in Brunei Darussalam. MedRxiv
https://doi.org/101101/2020.05.04.20090043.

28 Cheng HY et al., 2020. Contact tracing assessment of COVID-19 transmission dynamics in Tiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med. https://doi.org/10.1001/jamainternmed.2020.2020.

29 Park SY et al., 2020. Coronavirus disease outbreak in call center South Korea. Emerg. Infect. Dis. 26,1666-1670. https://doi.org/10.3201/eid2608.201274.

30 Luo L. et al., 2020. Modes of contact and risk of transmission in COVID-19 among close contacts. MedRxiv. https://doi.org/10.1101/2020.03.24.20042606.

31 Hao-Yuan Cheng, et al., for the Taiwan COVID-19 Outbreak Investigation Team. 2020. Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset
JAMA Intern Med. 2020;180(9):1156-1163. doi:10.1001/jamainternmed.2020.2020

32 Michael Riediker and Dai-Hua Tsai, 2020. Estimation of Viral Aerosol Emissions From Simulated Individuals With Asymptomatic to Moderate Coronavirus Disease 2019
JAMA Netw Open. 2020;3(7):e2013807. doi:10.1001/jamanetworkopen.2020.13807

33 Lloyd-Smith JO et al., 2005. Superspreading and the effect of individual variation on disease emergence. Nature 438:355-359, https://doi.org/10.1038/nature04153.

34 Hijnen D, Marzano AV, Eyerich K, et al. SARS-CoV-2 transmission from presymptomatic meeting attendee,Germany.EmergInfect Dis.2020;26(8).
doi:10.3201/eid2608.201235PubMedGoogle Scholar

35 Hamner L, Dubbel P, Capron I, et al. High SARS-CoV-2 attack rate following exposure at a choir practice—Skagit County, Washington, March 2020.

36 Fan Wu, et al., 2020. Evaluating the Association of Clinical Characteristics With Neutralizing Antibody Levels in Patients Who Have Recovered From Mild COVID-19 in Shanghai, China. JAMA Intern Med. 2020; 180(10):1356_1362. doi:10.1001/jamainternmed.2020.4616.

37 Bi Q, Wu Y, Mei S et al., 2020. Epidemiology and Transmission of COVID-19 in Shenzen, China: Analysis of 391 cases and 1286 of their close contacts. Lancet Infect Dis 2020;S1473-3099(20)30287-5. doi:10.1016/s1473-3099(20)30287-5

38 Zunyou Wu, and Jennifer M. McGoogan, 2020. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention
JAMA. 2020;323(13):1239-1242. doi:10.1001/jama.2020.2648

39 Ankit B. Patel and Ashish Verma, 2020. Nasal ACE2 Levels and COVID-19 in Children
JAMA. 2020;323(23):2386-2387. doi:10.1001/jama.2020.8946

40 Seungjae Lee, Tark Kim, Eunjung Lee et al., 2020. Clinical Course and Molecular Viral Shedding Among Asymptomatic and Symptomatic Patients With SARS-CoV-2 Infection in a Community Treatment Center in the Republic of Korea
JAMA Intern Med. 2020;180(11):1447-1452. doi:10.1001/jamainternmed.2020.3862

41 Mizumoto K, et al., 2020. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill, 25. https://doi.org/10.2807/1560-7917.ES.2020.25.10.2000180.

42 Payne DC, et al., 2020. SARS-CoV-2 infections and serologic responses from a sample of US navy service members - USS Theodore Roosevelt, April 2020. CDC Morbidity and Mortality Weekly Report 69, 714-721. http://dx.doi.org/10.15585/mmwr.mm6923e4.

43 Patel MC, et al., 2020. Asymptomatic SARS-CoV-2 infection and COVID-19 mortality during an outbreak investigation in skilled nursing facility. Clin. Infect. Dis., ciaa763
https://doi.org/10.1093/cid/ciaa763.

44 Aerzteblatt. 25 June 2020 Antibody study: many citizens of Ischgl were infected.
https://www.aerzteblatt.de/nachrichten/114021/Antikoerper-Studie-Viele-Buerger-Ischgls-Waren-Infiziert

45 Lavezzo E et al., 2020. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. Nature. https://doi.org/10.1038/s41586-020-2488-1.

46 Nuria Oliver, et al., 2020. Assessing the Impact of the COVID-19 Pandemic in Spain: Large_Scale, Online, Self_Reported Population Survey.
J Med Internet Res. 2020 Sep; 22(9): e21319. doi:10.2196/21319.

47 Buitrago_Garcia D, Egli_Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. (2020) Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta_analysis.
PLoS Med 17(9): e1003346. https://doi.org/10.1371/journal.pmed.1003346

48 Public Health Agency of Canada. Canada COVID-19 weekly epidemiological report, 21 March to 27 March (Week 12). Published 1 April, 2020.

49 David S. Stephens and M. Juliana McElrath, 2020. COVID-19 and the Path to Immunity.
JAMA. 2020;324(13):1279-1281. doi:10.1001/jama.2020.16656

50 Fan Wu, et al., 2020. Evaluating the Association of Clinical Characteristics With Neutralizing Antibody Levels in Patients Who Have Recovered From Mild COVID-19 in Shanghai, China. JAMA Intern Med. 2020; 180(10):1356-1362. doi:10.1001/jamainternmed.2020.4616.

51 Percivalle E et al. 2020. Prevalence of SARS-CoV-2 specific neutralising antibodies in blood donors from the Lodi Red Zone in Lombardy, Italy, as at 06 April 2020.
Euro Surveill.2020;25(24):2001031.PubMedGoogle Scholar.

52 Pollán M et al.; ENE_COVID Study Group. 2020. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population_based seroepidemiological study. Lancet.2020;396(10250):535-544. PubMedGoogle Scholar.

53 Bajema KL et al. 2020. Estimated SARS-CoV-2 seroprevalence in the United States as of September 2020. JAMA Intern Med.doi:10.1001/jamainternmed.2020.7976Google Scholar.

54 Grifoni A et al. 2020. Targets of cell responses to SARS-CoV-2 coronavirus in Humans with COVID-19 disease and unexposed individuals.
Cell 181:1489-1501.e15. doi:10.1016/j.cell.2020.05.015 PubMedGoogle Scholar

55 Suthar MS et al. 2020. Rapid generation of neutralizing antibody responses in COVID-19 patients. Cell Rep Med. 1(3):100040. doi:10.1016/j.xcrm.2020.100040 PubMedGoogle Scholar.

56 Robbiani DF et al. 2020. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. Nature. doi:10.1038/s41586-020-2456-9 PubMedGoogle Scholar

57 Maria Romano 1,y , Alessia Ruggiero 1,y, Flavia Squeglia 1,y, Giovanni Maga 2
and Rita Berisio 1,* A Structural View of SARS-CoV-2 RNA Replication Machinery: RNA Synthesis, Proofreading and Final Capping Cells 2020, 9, 1267; doi:10.3390/cells9051267

58 Sola, I.; Almazan, F.; Zuniga, S.; Enjuanes, L. Continuous and Discontinuous RNA Synthesis in Coronaviruses. Annu. Rev. Virol. **2015**, 2, 265–288.

59 Christie A, Brooks JT, Hicks LA, et al. Guidance for Implementing COVID-19 Prevention Strategies in the Context of Varying Community Transmission Levels and Vaccination Coverage.
MMWR MorMortalWklyRep2021;70:1044–1047.DOI:http://dx.doi.org/10.15585/mmwr.mm7030e2

60 Alexandra L. Phelan, Rebecca Katz, and Lawrence O. Gostin, 2020. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance.
JAMA. 2020;323(8):709-710. doi:10.1001/jama.2020.1097

61 Jia Huang, Le Zheng, Zhen Li, et al., 2020. Kinetics of SARS-CoV-2 positivity
of infected and recovered patients from a single center. Nature Research,
Scientific Reports | (2020) 10:18629 | https://doi.org/10.1038/s41598-020-75629-x

62 Buntin MB. Social Distancing—What Would It Mean for It to Work? JAMA Health Forum. Published online April 15, 2020. doi:10.1001/jamahealthforum.2020.0474

63 An Pan, Li Liu, Chaolong Wang, et al. 2020. Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China.
JAMA. 2020;323(19):1915-1923. doi:10.1001/jama.2020.6130

64 David M. Hartley, and Eli N. Perencevich, 2020. Public Health Interventions for COVID-19: Emerging Evidence and Implications for an Evolving Public Health Crisis. JAMA. 2020;323(19):1908-1909. doi:10.1001/jama.2020.5910

65 Thomas V. Inglesby, 2020. Public Health Measures and the Reproduction Number of SARS-CoV-2. JAMA. 2020;323(21):2186-2187. doi:10.1001/jama.2020.7878

66 Ayanian JZ, 2020. Taking Shelter From the COVID-19 Storm. JAMA Health Forum. Published online June 3, 2020. doi:10.1001/jamahealthforum.2020.0689

67 Gostin LO, Wiley LF. Governmental public health powers during the COVID-19 pandemic: stay-at-home orders, business closures, and travel restrictions.
JAMA. Published online April 2, 2020. doi:10.1001/jama.2020.5460PubMedGoogle Scholar

68 Lyu W, Wehby GL. Comparison of estimated rates of coronavirus disease 2019 (COVID-19) in border counties in Iowa without a stay-at-home order and border counties in Illinois with a stay-at-home order.
JAMA Netw Open. 2020;3(5):e2011102. doi:10.1001/jamanetworkopen.2020.11102PubMedGoogle Scholar

69 Markel H, Lipman HB, Navarro JA, et al. 2007. Nonpharmaceutical interventions implemented by US cities during the 1918-1919 influenza pandemic.
JAMA. 2007;298(6):644-654. doi:10.1001/jama.298.6.644PubMedGoogle ScholarCrossref

70 Angel Desai, 2020. Twentieth-Century Lessons for a Modern Coronavirus Pandemic
JAMA. 2020;323(21):2118-2119. doi:10.1001/jama.2020.4165

71 Kauler P, Kerachian AM, and Pekova S. 2021. COVID-19 teaches humanity a lesson: what do epidemiological data reveal about our learning curve? PART I - SARS-CoV-2 virus biology overview. http://www.ecoscientific.ca/LessonI.pdf.

72 Wilson N, et al., 2020. Potential Health Impacts from the COVID-19 Pandemic for New Zealand if Eradication Fails: Report to the New Zealand Ministry of Health.
Prepared by COVID-19 Research Group, BODE, HEIRU, University of Otago Wellington, New Zealand.

73 Olson DR et al., 2005. Epidemiological evidence of an early wave of the 1918 influenza pandemic in New York City. PNAS 102(31):11059-11063.
www.pnas.org/cgi/doi/10.1073/pnas.0408290102

74 Fiona P. Havers, Carrie Reed, Travis Lim, et al., 2020. Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020.
JAMA Intern Med. 2020;180(12):1576-1586. doi:10.1001/jamainternmed.2020.4130

75 Hellewell J, Abbott S, Gimma A, et al; 2020. Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. Lancet Glob Health. 2020;8(4):e488-e496. doi:10.1016/S2214-109X(20)30074-7.

76 Nande A, Adlam B, Sheen J, Levy MZ, Hill AL (2021) Dynamics of COVID-19 under social distancing measures are driven by transmission network structure. PLoS Comput Biol 17(2): e1008684. https://doi.org/10.1371/journal.pcbi.1008684

77 Brooks SK, Webster RK, Smith LE, et al. 2020. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet. 2020;395(10227):912-920. doi:10.1016/S0140-6736(20)30460-8PubMedGoogle Scholar

78 Marielle Wathelet, Stéphane Duhem, Guillaume Vaiva, et al., 2020. Factors Associated With Mental Health Disorders Among University Students in France Confined During the COVID-19 Pandemic. JAMA Netw Open. 2020;3(10):e2025591. doi:10.1001/jamanetworkopen.2020.25591

79 Wang C, Pan R, Wan X, et al. 2020. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China.
Int J Environ Res Public Health. 2020;17(5):1729. doi:10.3390/ijerph17051729PubMedGoogle Scholar

80 McGinty EE, Presskreischer R, Han H, Barry CL. 2020. Psychological distress and loneliness reported by US adults in 2018 and April 2020.
JAMA. 2020;324(1):93-94. doi:10.1001/jama.2020.9740PubMedGoogle ScholarCrossref

81 Emma E. McGinty, Rachel Presskreischer, Kelly E. 2020. Psychological Distress and COVID-19–Related Stressors Reported in a Longitudinal Cohort of US Adults in April and July 2020
JAMA. Published online November 23, 2020. doi:10.1001/jama.2020.21231

82 Mark A. Reger, Ian H. Stanley, and Thomas E. Joiner, 2020. Suicide Mortality and Coronavirus Disease 2019—A Perfect Storm?
JAMA Psychiatry. 2020;77(11):1093-1094. doi:10.1001/jamapsychiatry.2020.1060

83 Christine Moutier, 2020. Suicide Prevention in the COVID-19 Era: Transforming Threat Into Opportunity.
JAMA Psychiatry. Published online October 16, 2020. doi:10.1001/jamapsychiatry.2020.3746

84 National Academies of Sciences, Engineering, and Medicine. Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System. The National Academies Press; 2020. https://www.nap.edu/read/25663/chapter/1

85 Bridget M. Kuehn, 2020. Pandemic Accelerates the Threat of Global Hunger.
JAMA. 2020;324(15):1489. doi:10.1001/jama.2020.20152

86 Alexandra L. Phelan, Rebecca Katz, and Lawrence O. Gostin, 2020. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance.

JAMA. 2020;323(8):709-710. doi:10.1001/jama.2020.1097

87 Lawrence O. Gostin and Lindsay F. Wiley, 2020. Governmental Public Health Powers During the COVID-19 Pandemic: Stay-at-home Orders, Business Closures, and Travel Restrictions
JAMA. 2020;323(21):2137-2138. doi:10.1001/jama.2020.5460

88 Abbas AK, Lichtman AH. and Pober JS, 1991. Cellular and Molecular Immunology. W.B. Saunders Publishers Company. ISBN 0-7216-3032-4

89 Canada COVID-19 Weekly Epidemiology Report, Week 28 (11 July to 17 July 2021).
Public Health Agency of Canada, published July 23, 2021.

90 WHO, 2020. Estimating mortality from COVID-19: Scientific brief.
World Health Organization, 4.August 2020, WHO-2019-nCoV–Sci_Brief-Mortality-2020.1-eng.pdf

91 Folkhälsomyndigheten, Public Health Agency of Sweden, 2020. The infection fatality rate of COVID-19 in Stockholm. Technical report #20094-2.
https://www.folkhalsomyndigheten.se/contentassets/53c0dc391be54f5d959ead9131edb771/infection-fatality-rate-covid-19-stockholm-technical-report.pdf

92 Lewis F. Buss, Carlos A. Prete, Claudia M. M. Abrahim, et al., 2020. Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic. Science (6526) 371:288-292 DOI: 10.1126/science.abe9728

93 WHO Weekly Epidemiological Report Update 36, published April 20, 2021

94 Verity R., Okell L.C., Dorigatti I., et al. (2020). Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 20:669-77
https://doi.org/10.1016/s1473-3099(20)30243-7

95 Salje H., Kiem C.T., Lefrancq N., et al. (2020). Estimating the burden of SARS-CoV-2 in France. Science, 369(6500):208-211. doi:10.1126/science.abc.3517.

96 David M. Cutler, and Lawrence H. Summers, 2020. The COVID-19 Pandemic and the $16 Trillion Virus. JAMA. 2020;324(15):1495-1496. doi:10.1001/jama.2020.19759

97 Athalia Christie et al., 2021. Decreases in COVID-19 Cases, Emergency Department Visits, Hospital Admissions, and Deaths Among Older Adults Following the Introduction of COVID-19 Vaccine — United States, September 6, 2020 – May 1, 2021. MMWR / June 11, 2021 / Vol. 70 / No. 23