COVID-19 teaches humanity a lesson: what do epidemiological data reveal about our learning curve? PART I - SARS-CoV-2 virus biology overview.

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ABSTRACT

This paper is split in two separate, yet essentially interrelated parts. In this *PART I* 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.

In the *PART II*[71] of the paper we will 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.

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 the 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 virus 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], which in case of SARS-CoV-2 virus has not been clarified yet with certainty. 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 SARS-CoV and MERS-CoV viruses, both severe pathogens with their demonstrated case fatality ratios (CFR) of 9.6% and 34% respectively[4], prompted the WHO 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 over 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 connected to unparalleled costs to societies, yet met with various degrees of 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. These data are vital to understanding where communities are on the continuum of COVID-19 cumulative incidence and prevalence and how NPIs can be redesigned in order to minimize their negative impacts during their possible future implementations.

This paper is split in two separate, yet interrelated parts. The PART I is a concise overview of the SARS-CoV-2 virus biology, which offers comprehensive background information for the interpretation of data analysis presented in the next part. PART II is then based on the analysis of observed epidemiological data submitted to WHO. There we will attempt to point out some frequently unappreciated biological facts such as the role of the natural global (herd) immunity in this pandemic mitigation process. In relation to natural herd immunity we will also critically examine the present use of SARS-CoV-2 vaccines, in addition to emphasizing more realistic aspects of COVID-19 morbidity.

The virus biology overview

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped virus belonging to the genus of single-(+)-stranded RNA *Betacoronaviruses* of family *Coronavidae*. It has 29891–base pair (bp) sized genome[5] containing 14 open reading frames translating into an estimation of 27 proteins[6]. The virus preferentially exploits Angiotensin-Converting Enzyme 2

(ACE2) receptor in conjunction with the Transmembrane Serine Protease 2 (TMPRSS2) found primarily on epithelial cells in many organs, but especially in lung and colon tissues. Once bound to the cell the TMPRSS2 activates the viral spike protein bound to the cell's ACE2 receptor, which then cleaves the ACE2 receptor permitting viral internalization within the host's tissue cells[7]. The host proteases are responsible for activating (or priming) the viral spike protein. However, in the absence of serine protease on host's cells the virus still can enter its target cell using the endocytic pathway within the endosomal-lysosomal compartments including processing by lysosomal cathepsins[8]. Murgolo and colleagues (2021) [8] also mentioned two recent publications finding immune CD14+ primary monocytes from healthy human donors readily susceptible to SARS-CoV-2 infection[9,10]. Given the minimal expression of ACE2 receptor in monocytes, Murgolo et al., (2021) [8] found these observations rather surprising. It follows that understanding which viral entry pathway is prevalent in specific cell types and in particular human populations is paramount to understanding the SARS-CoV-2 biology.

Once inside the cell, the virus begins to reproduce. The SARS-CoV-2 virus is characterized by very high rates of replication. The original wild type strain, which began the pandemic was shown to produce in naso-pharyngeal swabs titers as much as 1000 times higher than SARS-CoV virus indicating its increased rate of infectiousness. In addition, SARS-CoV-2 viral loads were shown to peak earlier, five days after the onset of symptoms in comparison with SARS-CoV, which peaked seven to ten days after the onset of symptoms[11]. It is tempting to hypothesize that such unprecedented rates of replication of SARS-CoV-2 might possibly be attributed, at least in part, to the regulatory elements residing within the 5' and possibly 3' UTR region of its + strand RNA genome, with the 5' UTR promoter region, being the most likely candidate. Sola et al. (2015), also noted potentially important regulatory elements for coronaviruses being located in the 3' UTR [57,58]. As a result, the viral replication-transcription complex (RTC), responsible for both the transcription and replication of the viral genome, might not be able to carry out its (yet naturally limited) proofreading activity. This situation would lead to an extra load of genomic mistakes, and thus, to a very high viral mutability, as observed by the unusual number of different SARS-CoV-2 variants already described.

A number of authors reported increased COVID-19 disease burden among racial/ethnic minority populations in the United States[12,13,14]. Primarily cultural and socioeconomic factors were implicated because racial/ethnic minorities and poor people in urban settings tend to live in more crowded conditions and are more likely to be employed in public-facing occupations. In addition, some racial/ethnic minority populations are marked with a disproportionate burden of underlying comorbidities such as diabetes, cardiovascular disease, asthma, HIV, morbid obesity, liver disease, and kidney disease[13,20]. The latter suggests that a predisposition to the severity of this respiratory disease by genetic or epigenetic factors in some populations cannot be ruled out. Moreover, consistent gender differences in response to the disease have been reported in China, Brazil, other parts of South America and many countries of Europe[19,20]. In Wuhan city death rate from coronavirus were 2.8% among infected Chinese men as opposed to 1.7% of infected women[15,19]. Higher propensity in Chinese men to smoking coupled with an increased incidence of comorbidities such as type 2 diabetes, high blood pressure and obstructive pulmonary disease[16,17] are typically implicated. However, disproportionately higher distribution of ACE2 receptors in pulmonary tissues of Chinese men might potentially also be important[18]. In addition, the TMPRSS2 gene encoding a type II transmembrane serine protease (TTSP) was shown to be regulated by androgens and is highly expressed in prostate epithelium[8]. The TMPRSS2 gene–related activity and nasal epithelium expression was also shown to be significantly higher in Afro-American men indicating that higher nasal epithelium expression of TMPRSS2 may contribute to the higher burden of COVID-19 among Black individuals[13]. This supports the view that a consistent biological phenomenon might also be operating in some populations and especially in men, accounting for higher case fatality rates observed in some countries[19].

The SARS-CoV-2 virus is spread predominantly via inhalation of virus laden particles, through respiratory droplets exhaled by an infectious individual in close proximity, or particles being mixed within an aerosol cloud dispersed within a closed area (public transport, aircraft cabin, shopping malls, etc) [2,23]. As reviewed in W. Joost Wiersinga et al. (2020) [2], prolonged exposure to a contagious infected person, or briefer exposures to individuals who are contagious when symptomatic or pre-symptomatic is associated with higher risk for transmission. Contagion was shown to be significant within the first five days of COVID-19 symptom onset, infectiousness

dropping off rapidly after that. For some SARS-CoV-2 variants (strains), brief exposures to asymptomatic contacts are less likely to result in transmission[21,27-30,47] likely because asymptomatic cases are associated with lower titers at peak replication, faster viral clearance and thus a shorter infectious period[25]. Nevertheless, some SARS-CoV-2 variants, for example the so called "Czech Strain" spreading across the Czech Republic between September and November 2020, and characterized by a combined deletion of amino acids 69 and 70 of the S protein gene, together with N439K substitution, was distinguished by extremely high virus titers, yet minimal and unremarkable clinical presentation in most of the individuals tested. It led to a rapid spread of the contagion; a situation very similar to the "Delta" variant that started circulating in Europe in the spring of 2021.

As noted above, clinical presentation and COVID-19 outcome might be directly proportional to the initial load of inhaled viral particles. In support of the Gangelt study findings[24], breathing and coughing by an individual with COVID-19 with a high viral load was estimated to release large number of viruses, ranging from thousands to millions of virus copies per cubic meter depending on air circulation and microdroplet formation process. However, the estimated infectious risk posed by a person with typical viral load who breathes normally was low[32]. The community transmission rates were estimated to be around 1%, and in common household 5-10%. At board meetings and during choir rehearsal transmission rates as much as 75% have been reported[28,32,34,35]. The contribution of individuals to infection transmission appears to be highly skewed; a small proportion transmits lots of infection, while the majority transmits relatively little[33]. Likewise, the results of Riediker and Tsai (2020) [32] modelling study on COVID-19 aerosol transmission suggest that only few people with very high viral load pose an infection risk in poorly ventilated closed environments. However, in addition to the load of the virus the variant type has an impact on the transmission e.g. Delta variant is more than two times transmissible as the original form[59].

Transmission from inanimate surfaces is difficult to interpret without knowing the minimum dose of virus particles that can initiate infection[2], however, normally transmission through contact with inanimate objects (fomites) is less likely. It may become important in closed settings

like hospitals, hotels, airports, railway stations or cruise ships. Droplet spread via face-to-face contact still remains the primary mode of transmission[2,31].

COVID-19 is exhibited in broad spectrum of clinical courses ranging from totally asymptomatic, very light to severe and even fatal outcomes while in vast majority of the infected population (80-91%) initially it produced primarily asymptomatic and relatively mild disease symptoms[37]. In these cases the disease caused mild to moderate symptoms of upper respiratory tract such as sore throat, dry cough or fever or some combination of the three[37]. With increasing age there was an observed shift toward an increase of number of symptoms together with more severe complications leading to severe pneumonia, acute respiratory failure, life-threatening sepsis and even death[2]. In an early study of 44672 patients with COVID-19 in China, 81% of patients had mild manifestations (non-pneumonia or mild pneumonia), 14% had severe manifestations (dyspnea, and/or lung infiltrates >50% within 24 to 48 hours), and 5% had critical manifestations (defined by respiratory failure, septic shock, and/or multiple organ dysfunction and failure) [38]. In general, much older patients with COVID-19 are at higher risk of developing severe and critical disease than younger adults[36] and case fatality ratio (CFR) was found to be elevated among those with pre-existing comorbid conditions such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, or cancer[38]. Only approximately 2% to 5% of individuals with laboratory-confirmed COVID-19 were younger than 18 years with a median age of 11 years. In addition, children with COVID-19 have milder symptoms that are predominantly limited to the upper respiratory tract, and rarely require hospitalization[2,39]. As the pandemic continued to develop however, the SARS-CoV-2 virus continued to mutate producing by the autumn of 2020 varieties characterized by somewhat differing clinical presentations. In Czech Republic for example, the second wave, which started in September 2020 with the so-called “Czech Strain” as mentioned above, entered a series of incidence fluctuations characterized by three distinctive peaks (**Fig.1**). Our sequencing data (unpublished) confirmed that each peak was driven by a different strain of SARS-CoV-2 virus, and was then accompanied with different predominant clinical presentation in the COVID-19 patients. As the COVID-19 second wave in Czechia continued, higher severity progressively shifted towards younger patients with more severe outcomes requiring more intensive medical attention. This was especially true for the last, third

peak of the second wave, which was driven by the British variant 202012/01 (B.1.1.7). Interestingly, heavier clinical presentation of the British strain did not appear to be associated with increases in COVID-19 mortality at the population level (**Fig.2**).

COVID-19 is a predominantly mild disease

Presence of large proportions of asymptomatic cases is characteristic for COVID-19. Numerous studies documented asymptomatic individuals in different populations ranging in proportions from 0-85%[26]. Seungjae Lee et al., (2020) [40] in North Korean community treatment center found 80.9% (95% CI, 77.2%-84.6%) of patients with SARS-CoV-2 to be asymptomatic. On Diamond Princess cruise ship the proportion of asymptomatic cases was estimated to be 17.9% (95% CI 15.5–20.2%) [41], while on naval vessel USS Theodore Roosevelt Payne DC et al., (2020) [42] found 18.5% (44/238) of infected crew asymptomatic. Patel MC et al., (2020) [43] documented 37% asymptomatic cases during an outbreak in a US skilled nursing facility. In a German community of Ischgl 85% of residents were infected with COVID-19, yet showed no symptoms[44], and in Italian municipality Vo' Lavezzo E et al., (2020) [45] documented 42.5% (95% CI 31.5-54.6%) asymptomatic cases. Another large-scale population survey carried out in Spain estimated broad community proportion of COVID-19 asymptomatic cases to be at 40% of Spanish incidence[46].

In literature number of issues have been raised about estimation of proportions of asymptomatic cases obtained in earlier studies. Sometimes there was lack of follow up on presumably asymptomatic individuals who developed symptoms later. Other times selection bias was implicated, or sensitivity of serologic assays used during studies was questioned. However, reliable estimates of COVID-19 asymptomatic case proportions show quite consistent pattern in general community asymptomatic ratios typically approaching or exceeding 40% of officially reported incidence. As it was demonstrated in the German Gangelt study by Streeck et al., (2020)[24] the interpretation of results from studies on proportions of asymptomatic cases carried out under certain well-defined conditions such as super-spreading events or confinement of persons on board of ocean vessels are wrought with complications and might be confounded. Such environments may inevitably lead to increase of secondary transmission not representative

of the general community rates and the increase in concentration of infectious inoculum present in such environments may skew the true proportion of asymptomatic cases. Similarly, despite a real possibility of increased potential for nosocomial transmission, many studies on COVID-19 proportion of asymptomatic cases were carried out on patient cohorts in hospitals, during outbreaks in skilled nursing facilities and senior residences, and in designated health care facilities used in many countries to provide institutional quarantines of infected, or presumably infected individuals. In these institutions, as it could be expected, the proportion of asymptomatic cases typically were found to be quite low. Possibly due to increased chance of secondary infections unnaturally acquired in such facilities, reviews of proportion of asymptomatic cases such as that of Buitrago-Garcia D et al., (2020), which included many of such studies found overall proportion of asymptomatic individuals in the vicinity of only 20% (95% CI 17%–25%)[47]. This figure however, might not reflect the true natural incidence of asymptomatic cases in the general community.

In addition to frequently observed high proportions of asymptomatic cases, the prevalent clinical presentation of COVID-19 in general population also was found to be relatively mild. By the week of March 27, 2021 the Canadian incidence published by the Public Health Agency of Canada[48] was documented to reach 962019 of officially reported positive cases resulting in 51402 hospitalizations. It follows that 51402/962019 = 0.053; i.e. we see 5.3% rate of COVID-19 hospitalization in Canada. The remaining 94.7% of virus tested positive cases passed through asymptomatic, mild to moderate disease presentation from which patients have successfully recovered at home without the additional burden to the Canadian medical system. Moreover, we also know that due to passive public reporting in many countries because of predominantly asymptomatic and mild disease presentations, the official incidence statistics is underestimating the true number of exposures. From numerous serological studies SARS-CoV-2 virus exposures had been conservatively estimated to be as much as 10 times higher than the number of officially reported cases[46,49,53,74]. It follows that in reality, the above Canadian hospitalization ratio actually holds at 0.5%, hence COVID-19 is asymptomatic or mild to moderate disease for 99.5% of the Canadian population.

COVID-19 and adaptive immunity

We also know that documented re-infections of individuals who once passed through the COVID-19 disease caused by the same strain of virus are rare; nevertheless, in Czech Republic many asymptomatic or very mild cases exposed to the initial wild type strain of the virus during the first wave in the spring of 2020 became re-infected by the prevalent strain of SARS-CoV-2 virus again in the autumn of 2020. After their re-infection the same patients were coming down with much heavier COVID-19 disease presentations. However, re-infections by the same strain of the virus usually result in much milder or asymptomatic disease course. Thus previously infected individuals do mount immune response to the same strain despite relatively low observed seropositivity within most populations. Neutralizing antibodies (NAb), memory B-lymphocytes, and CD4+ and CD8+ memory T cells to SARS-CoV-2 virus generated by infection, re-exposure or vaccination are key to acquisition of one's immunity. However, the magnitude of the antibody and T-cell response was observed to be discordant among individuals and is influenced by the disease severity[49]. Fan Wu et al. (2020) [50] found titers of SARS-COV-2–specific NAbs in their study subjects varying substantially and included ~6% of patients who recovered successfully from mild COVID-19 with NAbs below detectable limit. The NAb titers in patients appeared to be associated with age. Older patients had significantly higher titers of NAbs than younger patients in their study. It follows that the strength of patient's humoral response, hence his antibody titer within his blood stream proportionately increases with the disease severity and the number of symptoms displayed.

After over a year of raging pandemic population seropositivity in many severely affected countries like Spain and Italy remained low and generally below 20%[51,52]. For most US states it remained below 10% and in a number of states below 1%. In the US it was rarely observed to reach over 20% (New York), only later dropping back again to below 20% level[53]. Since vast majority of COVID-19 disease courses is asymptomatic or mild (80-91%) the level of seropositivity within a population under study is expected to reflect this low number of severe outcomes accordingly. Second explanation for observed varying and low population seropositivity against COVID-19 in many countries is the timing of seroconversion in relation to

prevalent epidemiological picture within the population in question. The emergence of adaptive immunity in response to SARS-CoV-2 virus exposure occurs within the first 7 to 10 days of infection[54,55,56] with secretion of serum IgM and IgA antibodies by day 5 to 7 and IgG by day 7 to 10 from the onset of symptoms. In general, serum IgM and IgA titers decline after approximately 28 days, and IgG titers peak at 49 days slowly waning to below detection limits subsequently, as the short-lived antibody producing plasmablasts (B-cells) die following the viral clearance[49]. It follows that in the absence of second re-infection the NAb titer normally drops with time within the population thus the observed low seropositivity merely reflects the instantaneous rate of infection incidence rather than population's immuno-protective potential.

From the short overview of SARS-CoV-2 biology a few important points stand out:

- First, school closures, facial masks for children and especially vaccination of children are unnecessary and contribute little to controlling the spread of the disease, as consistently children have been associated with low burden of COVID-19 together with predominantly asymptomatic and very mild presentations of the disease.

- Second, 80-91% of general relatively healthy population handles COVID-19 well. Importantly, as we will see in PART II[71] of this paper it is this segment of the population, given the opportunity, plays a key part in formation of nation's natural global (herd) immunity.

- Third, it is the elderly and immunocompromised individuals with comorbidities, which are the most vulnerable who need most of the attention of health authorities.

- Fourth, together with the most vulnerable members of the society it is the health care workers and caregivers of elderly requiring special attention (for example frequent PCR monitoring) until nation's herd immunity becomes established, as they may be exposed to potentially significant viral loads in the course of their day to day work activities potentially becoming significant viral vectors.

- Finally, seropositivity monitoring for the presence of COVID-19 antibodies at the individual or population level might not be informative and not lead to definitive conclusions about nations' acquired resilience to the disease.

It the next, PART II of this paper we will attempt to point out some frequently unappreciated biological facts such as the significant role the natural population herd immunity played in the suppression of the SARS-CoV-2 virus. In addition, we will objectively examine the effects of

public health interventions on the mitigation of this pandemic. Finally, in relation to natural herd immunity in PART II we will also critically evaluate the use of the present SARS-CoV-2 vaccination programs, in addition to emphasizing more realistic aspects of COVID-19 morbidity.

FIGURES

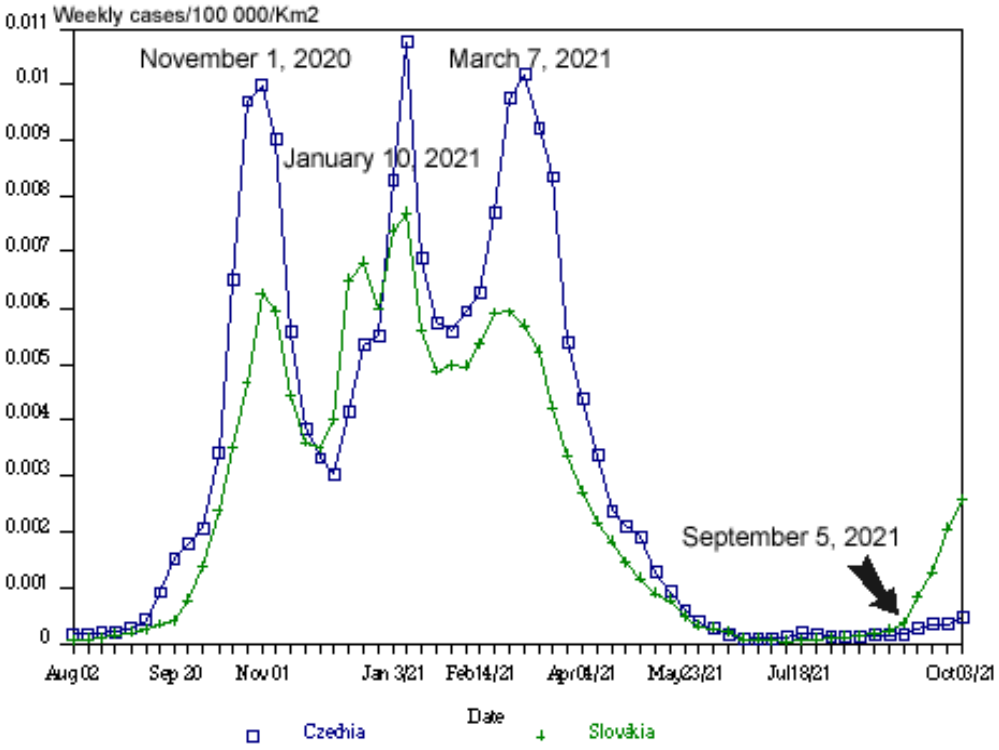

Figure 1 - Czech Republic shared remarkable temporal similarity of its COVID-19 epidemiology with neighbouring Slovakia. Here the second wave incidence fluctuations for both countries are pictured between August 2, 2020 and May 23, 2021, together with a run up to the third wave in Slovakia as of September 5, 2021. 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 of the population per Km^2. Notice the magnitude of peaks closely matching the population size of both countries. In addition, the significant 2^{nd} wave incidence fluctuations began prior to any vaccination efforts taking place and were unaffected by the continuation of strict NPIs in either country.

Data: WHO weekly epidemiology reports.

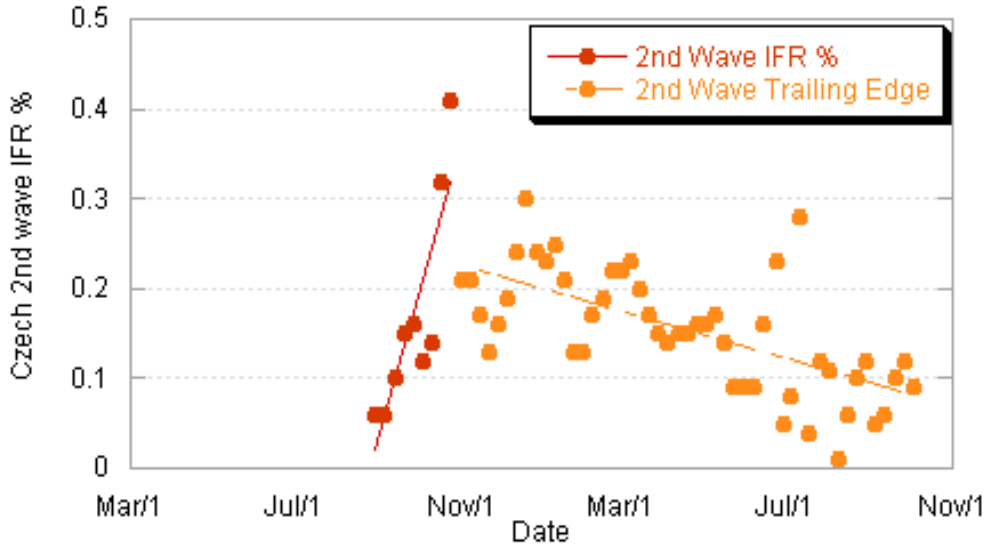

Figure 2 - The evolution of the COVID-19 infection fatality rate (IFR) in Czech Republic (Czechia). The data covers period between Aug 30 and November 1, 2020 (red dots) and the remainder of the 2nd wave and its trailing edge between November 1, 2020 and October 3, 2021 (orange dots). Notice unremarkable up tick in fatalities associated with the Czech third peak of the 2nd wave on March 7, 2021 which was primarily driven by the British variant B.1.1.7. Yet, this variant was associated with heavy clinical presentations of COVID-19 disease and substantial hospitalizations of younger patients.

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