

Downward trend in the indices of death rate in the Covid-19 pandemic: Evaluating alternative hypotheses

Milind Watve^{1*}

Sonali Shinde²

Pratima Ranade²

1. Former Professor, Indian Institute of Science Education and Research, Pune, India

*For correspondence: milind@iiserpune.ac.in, milind.watve@gmail.com

2. AbasahebGarware College, Pune, India

Abstract:

In the ongoing Covid-19 pandemic, in the global data on the case fatality ratio and other indices reflecting death rate, there is a consistent downward trend from mid-April to mid-August. The downward trend can be an illusion caused by biases and limitations of data or it could faithfully reflect a declining death rate. A variety of explanations for this trend are possible, but a systematic analysis of the testable predictions of the alternative hypotheses has not yet been attempted. We state six testable alternative hypotheses, analyse their testable predictions using public domain data and evaluate their relative contributions to the downward trend. We show that a decline in the death rate is real; changing age structure of the infected population and evolution of the virus towards reduced virulence are the most supported hypotheses and together contribute to major part of the trend. The testable predictions from other explanations including altered testing efficiency, time lag, improved treatment protocols and herd immunity are not consistently supported, or do not appear to make a major contribution to this trend although they may influence some other patterns of the epidemic.

Keywords: Covid-19, case fatality rate, infection fatality rate, evolution of virulence, evolutionary medicine

Introduction

A consistent global trend in the current Covid-19 pandemic is that of decreasing case fatality rate(CFR). Whether this is an illusion created by some biases and limitations of data collection and if not, what are the possible alternative causes of the decline is the question we address in this paper. In an on-going epidemic, an estimate of true death rate is rather difficult for several reasons. Nevertheless, a number of indices can reflect death rates with some limitations. The case fatality rate, a cumulative index of the number of deaths attributed to the virus divided by the confirmed positive cases so far, is most commonly used^{1,2}. This index has shown a decline in global data [1,2]. (Note that we use square brackets for citing public domain data, sources being listed at the end). However, being cumulative, this index is less sensitive to time trends and is dominated by the phase having more number of cases. We therefore use two other ratios here which are more faithful to the time trend, although somewhat more sensitive to stochasticity.

The ratio of the number of new deaths in a day (ND) to the number of new cases registered (NC) on that day (ND/NC) is one index and the ratio of ND to the number declared recovered (NR) on that day (ND/NR) the other. The two ratios complement each other's limitations and therefore, when used together, assuming that all cases are diagnosed, reflect on the death rate more reliably. The main limitation of these ratios is because of the time lag between the day of diagnosis and the day of death or recovery. In a growing epidemic the number of new cases is likely to have increased during this lag making ND/NC an underestimate of true death rate. But for the same reason ND/NR can be an overestimate of the death rate. Therefore, if there are no other sources of biases, the true death rate can be captured between the range of the two ratios quite reliably. When the rate of transmission (R_t) in the population at a given time is constant, ND/NC is a consistent underestimate and ND/NR a consistent overestimate. However, if and when R_t increases, ND/NC will tend to decrease and ND/NR tend to increase. On the other hand, if R_t is decreasing, ND/NC will tend to increase but ND/NR may decrease. If both the ratios are changing in the same direction, it's a robust indication of a change in death rate irrespective of R_t.

It can be seen in the global picture that from mid-April to mid-August, both the ratios show a consistent monotonic decline although not quite linearly [1-3] (figure 1). The ND/NC ratio was close to 10 in mid-April, which came down to between 2 and 2.5 by mid-August.

ND/NR also declined in similar proportion. So among the recorded global data there is a 4 to 5 fold difference in these indices between mid-April and mid-August.

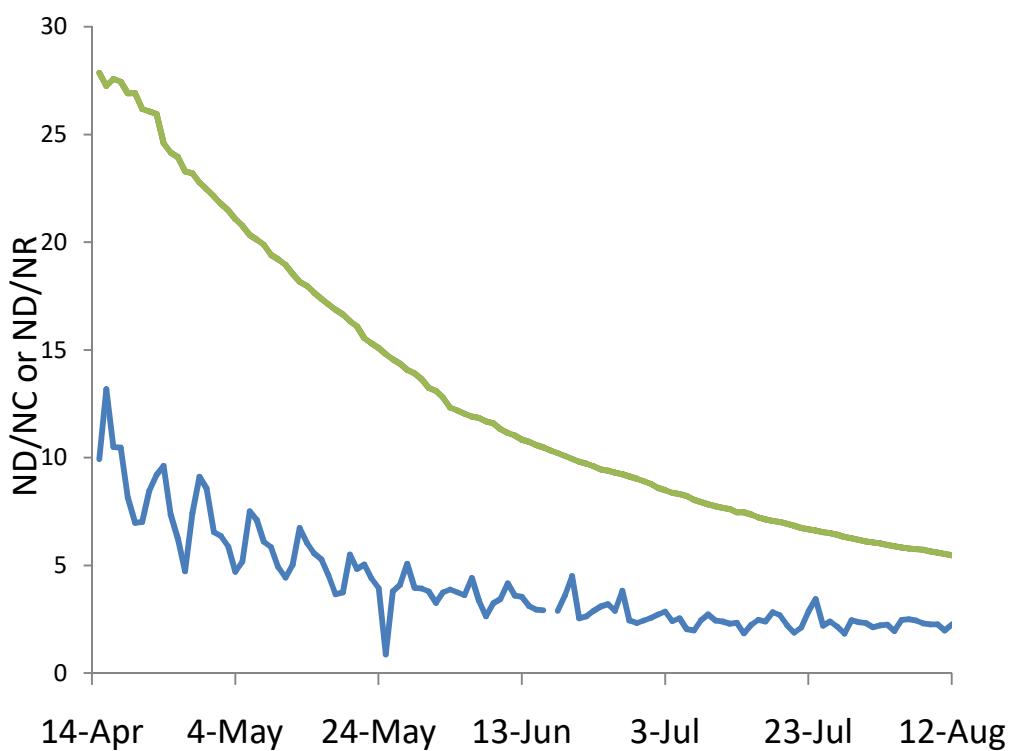


Figure 1: Consistent monotonic decline by a factor of 4 to 5 in the ND/NC (blue line) and ND/NR (green line) ratios expressed as percentages between mid-April to mid-August.

It is suspected with reasonable support that not all deaths have been on record and so are a number of cases. It is well recognized from the early phase of the epidemic that CFR is a substantial underestimate of the infection fatality rate (IFR)[7]. There have been a number of attempts to estimate the IFR which are consistently smaller than CFR. However, the methods of estimating IFR vary, the IFR estimates are spatially and temporally fragmentary and therefore plotting time trends in IFR is not possible. If we assume that the bias in CFR is more or less constant over time, the time trend in CFR may reflect the time trend in IFR as well. However, it is quite possible that the bias itself has an increasing or decreasing time trend. Therefore it is necessary to test for a temporal trend in the bias as well. Although IFR data are too fragmentary to plot a time trend, it is possible that even IFR has been declining with time. The IFR estimates till June were between the ranges of 0.09 to 1.6 % with a mean of 0.68%³. However, later serosurveys have made a substantial difference in the perspective. Assuming that seropositivity represents a recent infection by SARS-CoV-2, the estimate of the number of infections increases substantially^{4, 5}. Therefore it is possible that even IFR is

much smaller than estimated earlier or is declining considerably in time similar to CFR. We will examine this possibility in greater details while evaluating the alternative hypotheses.

While underreporting of deaths has also been a serious problem, the attempts to estimate the extent of underreporting have revealed that death underreporting has been disproportionately smaller than case underreporting^{5, 7}. Therefore any correction for the reporting bias will reveal a death rate much lower than the CFR indices. Owing to greater awareness and greater availability of testing facility the death underreporting is expected to have declined with time. On the other hand when the epidemic spreads and the numbers of new cases increase exponentially, the efficiency of contact tracing is likely to decrease and the case underreporting may increase with time. Therefore with time, the net bias is likely to over-report rather than underreport death. If the CFR is decreasing instead of increasing in spite of the possible bias, it is more likely to represent a true decline. It is therefore necessary to examine and evaluate comparatively all possible explanations for a true or illusionary decline in the death rate. Using CFR along with the ND/NC and ND/NR ratios, wherever appropriate, we will first list the possible explanations, examine the differential testable predictions and evaluate their relative contributions in the declining trend. Further, since the different explanations are not mutually exclusive, we explore the possibility of their interactions.

The alternative hypotheses:

A. We first consider the possibility that the downward trend is illusionary for one or more of the following reasons.

(i) Time lag in diagnosis and death: Because of the inevitable but unpredictable time lag, by the time deaths are recorded, the number of cases might have gone up and therefore the indices of death rates are an underrepresentation of true death rate. This may be a contributor to the appearance of a declining trend.

(ii) In later phases of the pandemic, increased testing detected more asymptomatic or mild symptomatic cases bringing down the death rate on record: It is possible that the decreasing death rate is an illusion created by increased testing which detects many asymptomatic cases which were being missed during the early days of the pandemic. The assumption behind this explanation is that the death rate was always as low as it is apparent today. The alarming death rates projected in the initial phases of the epidemic were a result of the limited and/or biased data in hand. The IFR calculated from recent serosurveys is of the order of 0.02 to

0.07 %^{5, 6, 8}. If this was the true death rate right from the beginning, then the social implication is serious. The perceived severity of the infection was the basis on which a number of measures were imposed by different state administrations throughout the world, which have seriously affected the livelihood of a large population in different parts of the world. If people develop an impression that it was a false alarm, they may lose trust in international and national health authorities including WHO. This may have serious long term consequences. Therefore it is extremely important to evaluate this possibility carefully.

(iii) The age class of patients changed: Covid 19 is known to cause disproportionately higher deaths in the elderly⁸⁻¹⁰. So if the age class distribution among the infected population has changed substantially during the course of the epidemic, if more of the younger age class are infected in the later phases of the epidemic, there would be an apparent decline in the indices of death rates although the age specific death rates haven't changed.

B. An alternative possibility is that the downward trend in death rate is real and because of one or more of the following reasons.

(i) Increased efficiency of treatment regime: It is possible that the treatment efficiency, particularly for the patients needing critical care has improved, which effectively brings down the death rate.

(ii) Increased immunity in the population: It is a common pattern in all epidemiological models that the proportion of susceptible individuals in the population declines as the epidemic progresses. This leads to a reduction in the rate of growth of the epidemic (R_t). Although classical epidemiological models do not incorporate severity of infection, one may speculate that the severity of disease among the infected population may also reduce as the population becomes more immune.

(iii) The virus progressively lost its virulence: A number of evolutionary epidemiology models indicate the possibility that progressive evolution of a newly invading virus leads to reduced virulence. There are multiple possible reasons for natural selection to favour variants of the virus with lower virulence. In the context of SARS-CoV-2, we will examine this possibility theoretically as well as with epidemiological and genomic data.

We would now comparatively evaluate the alternative hypotheses for the apparent decline in the indices of death rate using data from public domain.

Sources of data: We use data from sources available in the public domain, mainly from WHO, CDC and other open sources giving raw data as well as patterns seen in it. This includes Worldometer [3], Our World in Data [2], and Covid19India [4]. The data sources are listed at the end of the article and specifically cited in the text with square brackets as appropriate. There are certain inevitable limitations in the data. Data collection from different countries has subtle differences in the method of collection and accordingly some inevitable biases. We use pooled global data whenever available but some numbers are not available from all countries. For example, data on the number of tests performed is not available globally. Furthermore some countries report the number of tests performed and others report the number of individuals tested. The two are not interconvertible and their implications can be different. Whenever, getting global figures is not possible, we take the four countries with maximum number of cases reported so far, namely the United States, Brazil, India and Russia and perform country specific analysis.

Testable predictions and evaluation of the hypotheses:

A(i): We have already argued above, while explaining the choice of indices that if the time-lag between diagnosis, death and recovery leads to under or overestimates of death rates. Simultaneous use of two ratios, ND/NC and ND/NR can resolve the issue (fig 1). Since in the global data we see a consistent decline in both the ratios, it is unlikely to be an illusion created by the time lag effect. Further along the course of the epidemic, Rt has been declining globally¹². When Rt is declining, ND/NC tends to be overestimated. A decline in ND/NC in spite of a declining Rt is a robust indication of a true decline. Therefore the time lag bias alone is unable to explain the consistent decline in ND/NC.

A(ii): If we assume that the death rate was always low but in the initial phases of the epidemic, it was recorded on the higher side because of inadequate testing and contact tracing, it is possible that symptomatic cases were much more likely to be tested than asymptomatic cases. As the testing facility and efforts taken for contact tracing increased gradually, a greater proportion of asymptomatic cases are likely to have discovered leading to an apparent drop in the death rate. It is expected that if the testing effort effectively increased, the proportion of positives among the tested should have decreased. In contact tracing, the number tested is expected to increase with the number of positive cases found at a given time. Therefore rather than the absolute number of tests or the number of individuals tested, the

ratio of number of tests to number of positives in a short time frame is a better indicator of the effective testing effort.

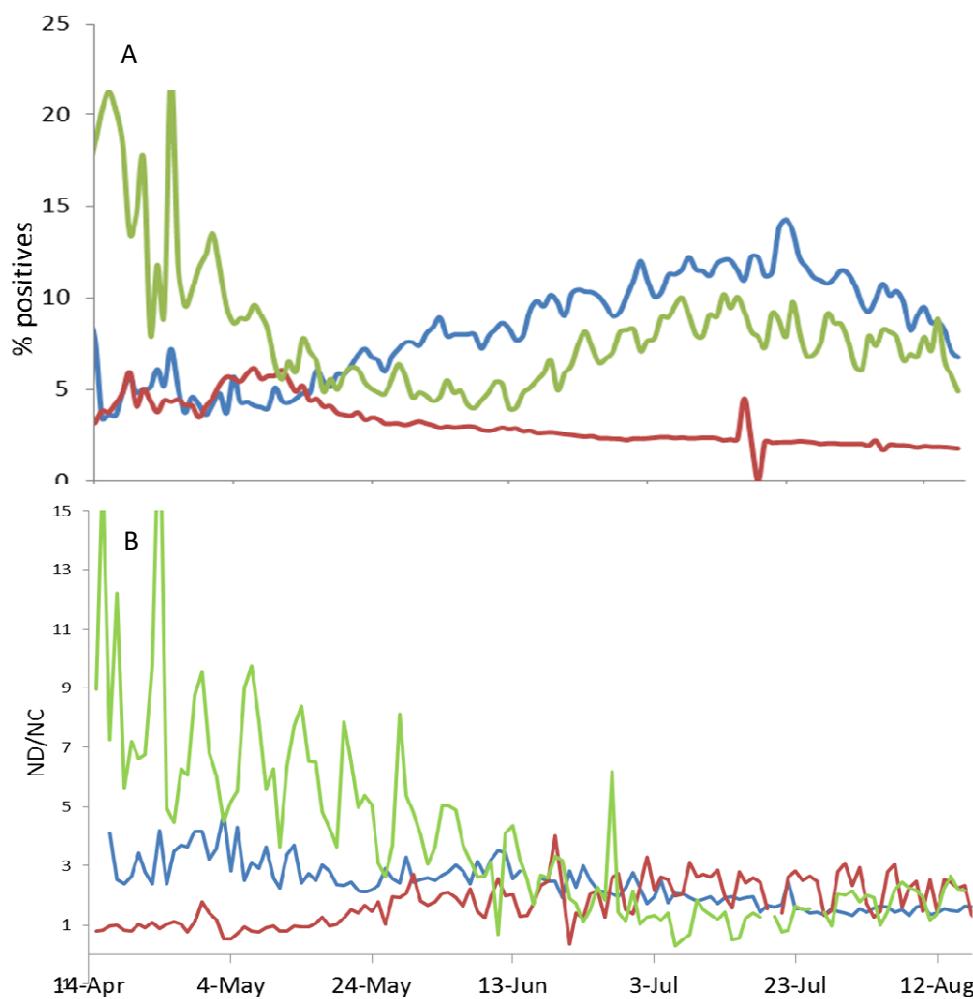
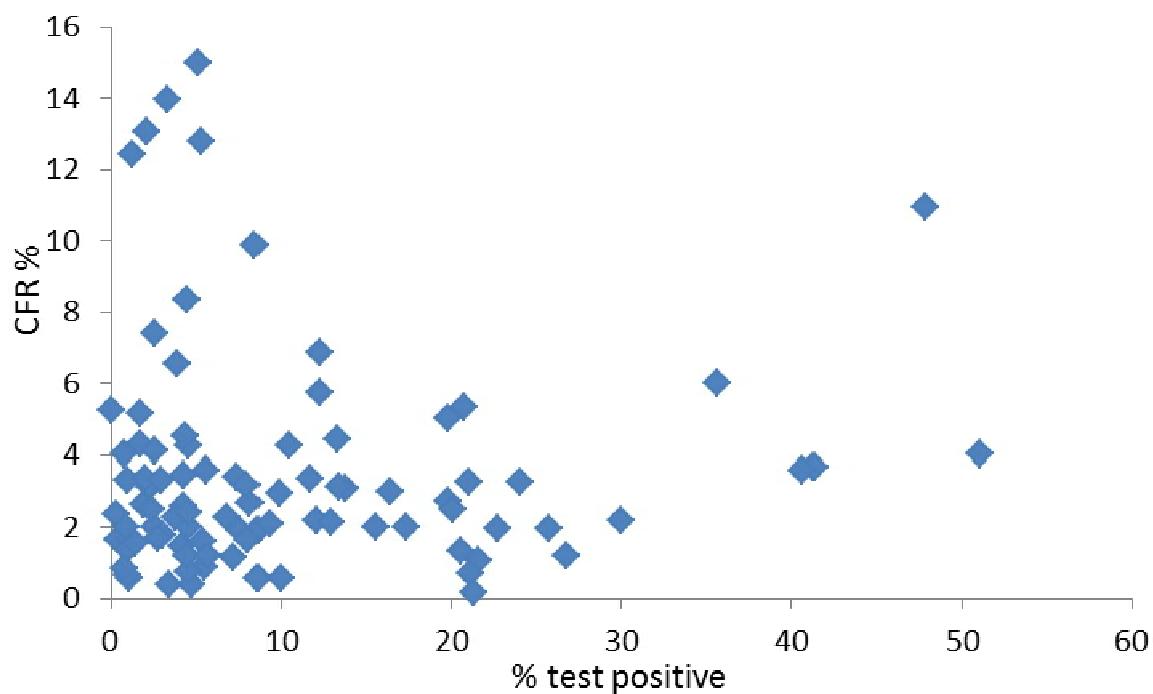


Figure 2: Time trends in the proportion of positives detected per day during the testing effort (A), which inversely reflects the testing efforts and the ND/NC ratio (B). Since global data on testing are not available, we use the countries with maximum number of cases reported so far. This includes United States (green line), India (blue line) and Russia (red line). Testing data for Brazil was not available throughout the period. By the hypothesis under test, the direction of the trend in B should mimic the trend in A.

Using this principle, a testable prediction of this hypothesis is that there should be a positive correlation between the proportion of positives among the tested and the death rate on record as represented by ND/NC. This relationship can be tested in the temporal trends in global data or focal countries. Unfortunately global data on the number of tests are not available. In country level analysis of the focal countries we find different and mutually inconsistent

patterns. In the US, the proportion of positives has decreased with time showing an increased testing effort. The ND/NC ratio has decreased and the two trends are compatible to the hypothesis being tested. However in India the proportion of positives has an upward trend till the third week of July, reversing later. But the ND/NC ratio has been decreasing monotonically though slowly which contradicts the hypothesis. In Russia the proportion of positives has decreased but the ND/NC ratio, which was always much smaller than the global average, has increased marginally. Thus across the focal countries, the time trends in the relationship between proportion of positives and ND/NC ratio are contradictory and inconsistent. Across 91 countries for which the testing data at least as recent as July 2020 was available at the time of analysis [5], we do not find a positive correlation between the proportion of positives and CFR which was expected if testing efficiency was the main factor deciding the apparent CFR.



population vis-a-vis the registered cases. This is attempted using a variety of methods, at different locations and different phases of the epidemic. So a rigorous comparative analysis is not possible. Grossly, while the estimated seroprevalences during the trials completed by April are all less than 10 % with only one exception from Iran⁴, the July and August trials have this estimates in the range of 15 to 57 %^{6, 7, 12}. In areas where a comparison of the fold increase in cases to fold increase in seroprevalence during the same period is possible, in some countries such as in US [8]^{13,14} and Brazil¹⁵ the ratio of the rise in seroprevalence to rise in cases declined with time. In the 10 areas of serosurveys in the US, in the first round the ratio of seroprevalence to case prevalence ranged between 6 and 24 which came down to between 2 and 7 by the third round [8]. In southern Brazil while the seroprevalence increased by 4.6 fold between 13th April and 11th May. If we assume that the average trend in Brazil applies to the sampled are, the cumulative cases increased by 7.52 fold¹⁵. But in many other countries the fold increase in seroprevalence is observed to be far greater than the increase in cumulative cases. In India from mid-May to end-July or mid-August, the cases increased by 16 to 27 fold whereas in the same period seroprevalence increased by 31 to 78 fold^{6, 7, 16, 17}. In Pakistan, between the serosurveys from mid-April to first week of July the cases increased by 20 fold and seroprevalence by 37 to 43 fold¹⁸. In Switzerland, weekly seroprevalence data from early May to mid-June show that in 5 weeks the cumulative number of cases increased by only 2.5 %, but seroprevalence increased by 125 %¹⁹. Collectively there is no consistent evidence that the overestimation bias in the CFR and ND/NC ratio reduced with time. Therefore the hypothesis that the downward trend is caused by a greater bias in the earlier phases of the epidemic and gradual removal of the bias subsequently is not supported by evidence.

There is one more reason to suspect that globally the proportion of undetected cases has not decreased but actually may have increased in time. If a large proportion of cases were asymptomatic and therefore unrecorded, contact tracing and isolation as an elimination strategy wouldn't have worked anytime anywhere^{20, 21}. Models of elimination by contact tracing and isolation have shown that only if the undetected cases were less than 10 to 50 %, new infections can be effectively reduced²². In the initial phases of the pandemic, i.e. in February for China and late March and early April for 19 other countries, the contact tracing and isolation strategy appears to have worked successfully resulting into substantial decline in the new cases for a large number of countries (figure 4). In the later phases of the epidemic hardly any country, including the same countries that achieved good success earlier, could

show comparable success of the contact tracing and isolation strategy. If the proportion of undetected cases was as high as it is today, it looks impossible to achieve the remarkable success. As the proportion increased in later phases, the contact tracing and isolation strategies might have lost their effectiveness. Compatible with this suggestion early estimates of asymptomatic cases are within the limits required by the model²³ whereas later estimates are far greater^{6,7,16-18}.

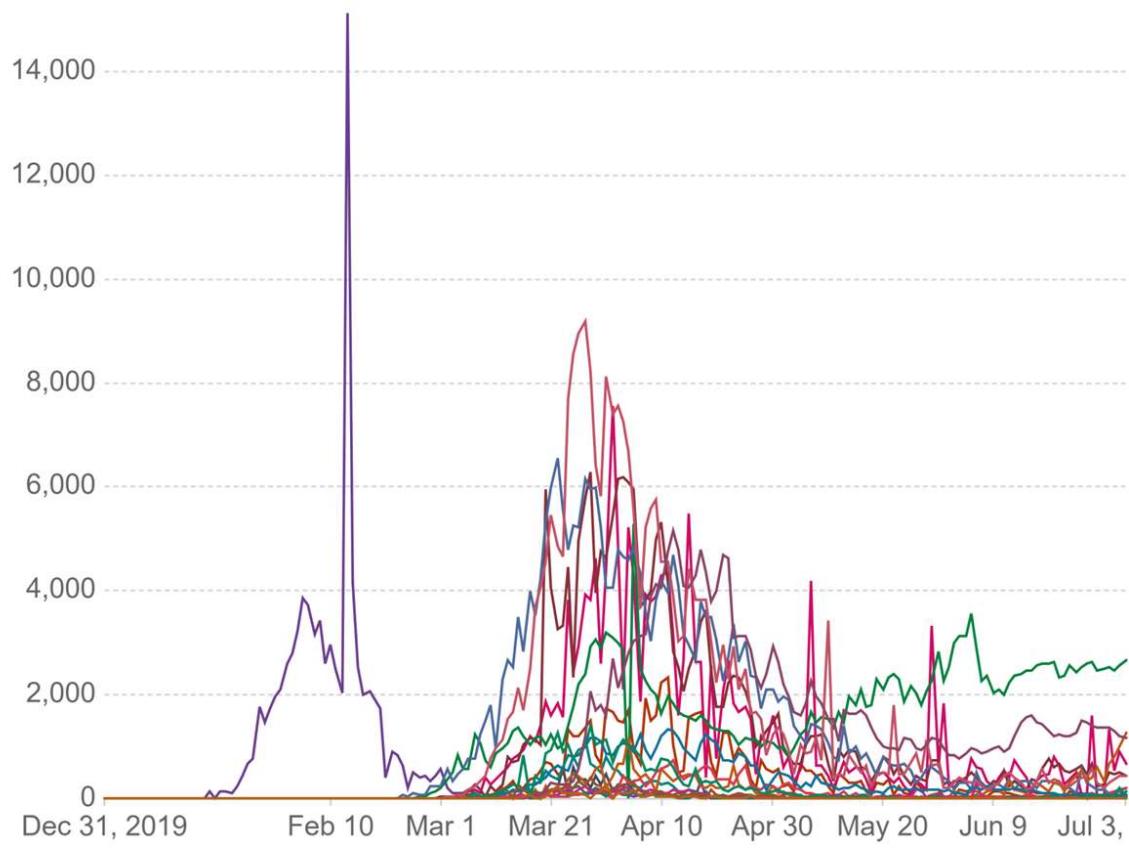


Figure 4: The time course of daily new infections recorded in 20 countries which achieved maximum success in controlling the viral transmission using contact tracing and isolation method. The success of this method requires that undetected cases are below a threshold. A comparable success of this method was not observed in the later phases, which might be attributable to the increased proportion of undetected cases.

The multiple lines of analysis fail to give consistent support to this hypothesis. Therefore CFR overestimation bias is unlikely to be a true explanation for the declining trend.

A (iii): The age class distribution among the diagnosed cases has evidently decreased with time in global data [6]. Also the differential case fatality across age classes is well known⁸⁻¹⁰.

Therefore it is very likely that at least qualitatively the changed age class distribution may explain the apparent decline in death rates. We need to estimate to what extent the changed age distribution explains the decline.

The > 65 age group has declined from 28% to 10 % among the infected population between mid-April to end-July during which time ND/NC in the registered cases declined by 75-80 % to remain at 20-25%. If we take a limiting assumption that all deaths are only in the > 65 group, the death rate would have declined by 64% to come down to 36%. By this assumption a changing age distribution explains a substantial part but not the entire reduction in death rate. This is a limiting estimate assuming all deaths are in the > 65 age class. The age class distribution of deaths is different in different countries since the age class distribution of the population itself is widely different. We can consider the other limit of the estimate by taking data from countries like India where the age class distribution of the population is dominated by the young classes. In the US, about 20% deaths were in the class < 65 and in India, 47% deaths were among the $< 60\%$ age class [9]. Considering that the 64 % reduction was only in the > 65 class, the expected decline is 51.2 % and 33.92 % in the two countries respectively. This indicates that changing age class distribution may explain a substantial part of the apparent decline in death rate but still leaves a considerable decline unexplained.

B(i): If the decline in death rate was due to improved medical care, we would have seen a decline in death rate among the patient hospitalized and under critical care. Global trends show that there is substantial reduction in the proportion of patients under critical care but there is only a marginal reduction in the proportion of deaths among patients under critical care [3]. This coupled with the very limited success and inconsistent results of clinical trials of various Covid drugs make it unlikely that a major part of the decline is explained by improved medical care.

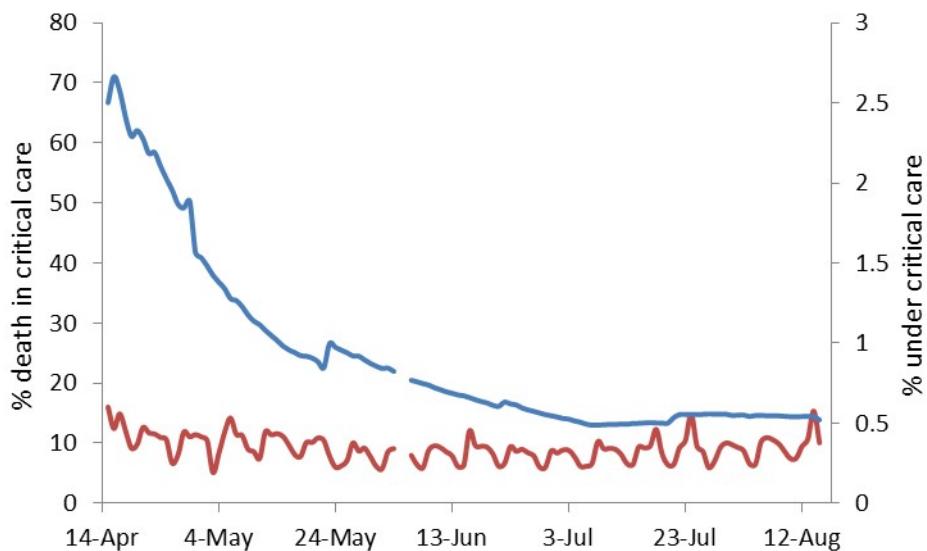


Figure 5: The time trend in global percent cases under critical care (blue line secondary axis) and percentage deaths under critical care (red on primary axis). The decline in death appears to be more due to decline in serious cases than due to success rate in treating serious cases.

B(ii): Going by the registered cases a very small fraction of the population is exposed to the infection to see any major population level immunity change. However, going by seroprevalence, a much larger fraction of the population appears to have been subclinically infected. As we discussed earlier in hypothesis A(ii) a large proportion of the asymptomatic and undetected infected population has either been there right from the beginning or has been increasing. We have already noted that the former failed to get support and the latter is more likely. It is possible that a substantial fraction of the population has indeed been exposed and presumably became immune. This immunity may be partially responsible for the reduced mortality. However, a critical question here is what made the large proportion of asymptomatic cases possible? If the virus was as virulent as initially apparent or perceived, the epidemic wouldn't have progressed to cause so many asymptomatic infections. The low mortality and mild clinical course therefore should be a cause, rather than a consequence of the increasing population immunity: low virulence or progressive loss of virulence permitting a high proportion of asymptomatic cases, which enabled the rapidly building population immunity, making the clinical course still milder. This could have been an autocatalytic process where reduction in severity of cases and population immunity facilitate each other.

The definition of immunity however, needs clarity here. By the classical concept, immunity should prevent or arrest viral invasion. If the large proportion of asymptomatic cases is because of increasing immunity which arrests viral invasion, we should see lower viral loads in asymptomatic cases as compared to the symptomatic and serious cases. This difference is not consistently observed across studies^{24, 25}. There is a large overlap in the viral loads of symptomatic or fatal versus asymptomatic cases and even in samples where there is a statistically significant difference, the effect size or the magnitude of difference is not very large. Therefore the difference between symptomatic and asymptomatic cases seems to be decided to a large extent by factors other than acquired immunity that arrests the infection.

B(iii): The concept that in the process of host-parasite coevolution, a pathogen often evolves towards reduced virulence is quite old, but evolution towards loss of virulence is conditional, not all pathogens appear to have reduced virulence when they coexist with a host population for a long time²⁶⁻³⁰. Many evolutionary epidemiology models for optimum virulence were built and the continued theoretical development was backed up by epidemiological³¹⁻³³ as well as experimental studies³⁴. With respect to the Covid-19 pandemic there are a multitude of reasons why evolution towards reduced virulence can be expected.

A fundamental assumption behind this hypothesis is that the severity of symptoms and fatality is at least partly decided by the virulence of the virus. First of all, a virus that kills its host rapidly, gets less time to spread from the infected individual. Secondly the quarantine measures applied all over the world are likely to have created a selective force upon the virus. Since a symptomatic case is more likely to undergo testing and subsequently quarantined, a virulent variant causing more serious symptoms is more likely to be quarantined. A milder variant, that is more likely to result into an asymptomatic infection has a greater chance of escaping detection and subsequent quarantine and therefore has a greater chance of spreading in the host population. Thirdly, if virulence is tightly correlated to viral loads and thereby transmission success, the virulent variant can have a greater selective advantage²⁷⁻²⁹. If virulence does not have a direct correlation with infection intensity and pathogen transmission, it is likely to be selected against³⁵. If the viral loads are not consistently higher in serious cases, this advantage can be assumed to be marginal and not sufficient to compensate the quarantine disadvantage. One more possible interaction between the host resistance and pathogen virulence is mediated by the quantitative difference of the host response to mild versus virulent virus. At least some components of the immune response are expressed in proportion to the extent of invasion by the pathogen²⁸. In case of opportunistic

pathogens it is known that a benign presence among the microbiota does not elicit a strong host response, but when the same organism becomes invasive, a stronger response is elicited³⁶. If the host response is proportional to the extent of invasion, a milder virus may survive better in a more resistant host, while a virulent one may do better in a susceptible host. If this is true, host immunity and viral virulence are expected to interact in a positive feedback loop. As the population acquires greater immunity, a milder virus can experience a selective advantage. Thus there are multiple reasons why SARS-CoV-2 may have experienced a selective pressure for reduced virulence.

Rejection or quantitatively inadequate explanation by other hypotheses is an indirect support to the evolution hypothesis. But a true test of the hypothesis is to show evolutionary changes in the genome indicating reduced virulence. Close to 50,000 genomes have been sequenced in various parts of the world and as compared to the ancestral Wuhan virus there are on an average over 7 mutations per genome³³. So the mutation rate can be assumed to be sufficient to generate the required variation for natural selection. Among the single nucleotide mutations the high proportion of recurrent non-synonymous mutations suggests strong positive selection on the mutants³⁷. Genomic signatures of strong selection coupled with the declining death rates not explained completely by other hypotheses makes the evolution hypothesis more promising. One of the mutations, D614G is suspected to increase the cell adhesion but whether it affects the infectivity or virulence or both is not clearly known³⁹. On the contrary, there are many other mutations in the region of the spike protein S1, S2, and docking studies show that they reduce the stability of the host cell binding complex. Furthermore in a comparative study of four regions of India, the ones with lower average stability of mutants in the spike protein correlated negatively with local CFR⁴⁰. These mutations are likely candidates responsible for the loss of virulence. There are many other mutations in structural and non-structural proteins⁴¹ which are also likely to play a role in determining virulence. Virulence is a complex phenomenon and from previous studies it is apparent that a large number of genes may contribute to viral virulence¹². Unfortunately as yet we do not have sufficient knowledge linking specific mutations to their phenotypic effects. There is no standardized empirical test of virulence to examine the effects of specific mutations on virulence. Of more direct relevance is the observation that the mutational set observed among samples coming from symptomatic and asymptomatic cases is significantly different³⁶. This is the most direct indicator that the asymptomatic clinical course is likely to

be at least partly driven by changes in the viral genome. If the proportion of asymptomatic cases is increasing, mutations are very likely contributors to the trend.

In summary, the hypotheses A(i) and A(ii) fail to get any supportive evidence, B(i) does not appear to have made a strong contribution to the trend. A(iii), B(ii) and B(iii) are likely to be important causes of the decline in death rates, out of which B(ii) needs prior initiation by either or both the others. Therefore a combination of A(iii) and B(iii) are most likely the primary causes of the declining trend and a combination of both appears to be necessary to explain the trend quantitatively. The three are not mutually exclusive and in fact may interact with each other. The cause of changed age class in the infected population could be that the older age classes are being effectively protected by the prevalent preventive measures, but it is also likely that the virus has evolved to infect younger age classes. It is of particular relevance here that some of the mutants are disproportionately represented in different age classes³⁶. This is possible if certain mutants are more likely to invade younger age classes.

Viruses have short generation times and high mutation rates and therefore can evolve very fast. Evolution on the background of host physiology, immunity, behaviour, public health policies and available treatments should be an intrinsic part of epidemiological theories and models, which is likely to deepen our understanding of the disease process at different levels. Host-pathogen interactions are complex and range from genomic, molecular, cellular, physiological, immunological, behavioural, organismal, clinical, social and population level. Unfortunately owing to high degree of specialization in the field of biomedicine, the perceptions are highly fragmented. Broader perceptions are likely to bring in more insights. This needs substantial inputs from non-specialists to interpret the specialists' findings and develop more insightful perspectives in the field.

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