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Opinion of the Helmholtz Initiative

"Systemic epidemiological analysis of the COVID-19 epidemic"

In the coming week, the Federal Chancellor and the Minister Presidents of the Federal States will discuss Germany's next steps to address the COVID-19 epidemic. One key question revolves around the criteria, timeline, and measures for gradually returning to normal life without running the risk of placing excessive demands on the healthcare system in terms of treating infected citizens. The process of answering this question must take into account a wide range of factors and resolve potential conflicts of interest without having access to a solid, verified knowledge base.

By publishing this position paper, we aim to provide an evaluative perspective on the current situation as it relates to the COVID-19 epidemic from the standpoint of systemic immunology and epidemiology at Helmholtz. Our statements are intended to provide support from a relevant professional perspective for the upcoming decisions on Wednesday, April 15, regarding the extent to which measures to limit personal contact in Germany are to be maintained, reinforced, or rolled back. **These decisions will be guided by the overarching objective of gradually easing contact restrictions without jeopardizing the intermediate targets that have already been achieved, or losing control of the virus.**

This paper is based on analyses of epidemiological data currently available in Germany and the Federal States conducted using mathematical models. It applies internationally recognized approaches for modeling and analyzing epidemiological data, such as those used by Imperial College, London (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30243-7/fulltext). We seek to provide a specific assessment of the situation for Germany as a whole as well as for the Federal States and selected cities. **A generic approach has been intentionally applied in selecting the models, foregoing unnecessary assumptions in order to make assertions that are as robust and reliable as possible.** As a method, mathematical modeling aggregates the available knowledge, enables interpretations of it, and supports the systematic and objective weighing of arguments that are an inherent component of decision-making processes.

It is generally agreed that the slowdown in the spread of the virus we are now seeing in Germany can be attributed to compliance with the contact restriction measures currently in place.

In this respect, the situation in Germany is developing along a similar path to the one analyzed in China (https://science.sciencemag.org/content/early/2020/04/07/science.abb4557).

This trend is clearly demonstrated by the development of the time-dependent reproduction number (Rt). The Rt variable is determined by the characteristics of the infection processes and specifies the average number of people infected by someone who has contracted the disease. Results from related analyses appear robust, as they have been independently reproduced by various groups using different methods (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/2020-04-08-de.pdf?__blob=publicationFile; https://stochastik-tu-ilmenau.github.io/COVID-19/germany; http://secir.theoretical-biology.de/).

All analyses indicate that the current Rt value is around 1 for both Germany as a whole and for the individual Federal States. As these estimates indicated that the Rt value was between 3 and 5 at the beginning of the pandemic, a current value of 1 **indicates that measures to restrict contact have already been highly successful.**

The trend we are seeing in the above analyses leads us to expect that Rt will continue to gradually decrease if current measures are maintained. However, this conclusion is theoretical in light of the knowledge that is currently available and the assumptions it necessitates and therefore cannot be truly proven. It is based solely on the observation that Rt does not appear to have reached saturation yet. The Easter holiday involves a particularly high degree of uncertainty when it comes to assessing the development of Rt in relation to time, as the number of cases reported each day are atypical. Some of the Federal States reported no new cases on Good Friday, which has resulted in an artifact in the current evaluation of how Rt is developing. Due to the uncertainties surrounding reporting over Easter, we recommend that the development of Rt not be assessed on the basis of figures that are updated daily and that decisions be made according to the situation as it stood on April 10; that is, the day on which newly reported figures from April 9 were received.

The reliability of model-supported forecasting regarding the further progression of the epidemic depends to a significant degree on the assumptions underlying the models and the parameters selected for the models. While a quantitative retrospective analysis is reliable, a quantitative assessment of the long-term forecasts produced by the models will not be possible given the inevitable uncertainties in the models. Nonetheless, it is justifiable to use the models to identify **qualitative scenarios** regarding how the spread of the virus could impact society and the healthcare system based on different packages of selected measures

(https://www.medrxiv.org/content/10.1101/2020.04.08.20056630v1, https://www.ndr.de/nachrichten/niedersachsen/Max-Planck-Institut-Kontaktverbot-noch-14-Tage,corona2102.html).

We believe that the analyses based on data and supported by models point to three scenarios. These scenarios only consider the effects contact restrictions have on COVID-19 infection rates and discount all other effects resulting from these restrictions.

Scenario 1: Contact restrictions are eased to the extent that Rt once again increases to values over 1. In this case, the activity of the infection would inevitably take off again and **severely overwhelm the healthcare system** within a few months. Germany currently has around 10,000 beds available in intensive care units (ICU) (https://www.intensivregister.de/#/intensivregister). In this scenario, the number of ICU beds required to treat patients would be much higher. Models vary in terms of the number of ICU beds required but agree on the prediction that the healthcare system will be severely overwhelmed. The same trend can likewise be observed across all models: The more the applicable restrictions are relaxed without introducing other accompanying measures, the sooner the load on the healthcare system will reach its peak, and the higher the peak will be.

Scenario 2: Contact restrictions and other accompanying measures are selected with the result that Rt remains around 1. This strategy would correspond to an immediate easing of restrictions in a careful, controlled manner along with the introduction of suitable accompanying measures. This approach would track the impact of the measures by continually monitoring how epidemiological parameters develop so Rt could be kept as close as possible to the target value of 1 based on adjustments to the measures. The aim of this feedback-based strategy would be to keep the healthcare system stable and capable of treating patients. However, this statement should also be viewed with caution, as estimates regarding the numbers of patients who would then require treatment – and therefore the resulting Rt value – are determined by some of the uncertainties in the models described above. Moreover, the sensitivity of the system and the delay in the time it takes for changes in the measures to have an impact on the numbers of cases could lead to the system overreacting. Nevertheless, we expect that the Rt value can be adequately tracked if the feedback principle is suitably configured, despite the uncertainties in the models. **The main drawback of this scenario is that the contact restrictions necessary to keep Rt around 1 and the heavy burden on the healthcare system could last for several years.** According to forecasts produced by various models, achieving full immunization of the population would take an excessively long time and lead to a high number of fatalities.

(https://www.medrxiv.org/content/10.1101/2020.03.26.20044214v1.full.pdf; https://www.medrxiv.org/content/10.1101/2020.04.04.20053637v1).

This assertion holds true even if there is a high number of unreported cases (https://www.medrxiv.org/content/10.1101/2020.04.08.20056630v1) and the assumption that those infected have long-term immunity – which is yet to be proven – is correct.

Scenario 3: Contact restrictions remain in place for the time being and are supported by accompanying measures with the result that Rt falls significantly below 1 on a long-term basis. This would correspond to a continuation of contact restrictions, which should be supported by further measures. In this case, it can be assumed based on estimates from various models that the virus would spread at a significantly reduced rate within society. The models vary with respect to the estimated time required to effectively reduce the number of new infections to an adequately low target value. Optimistic estimates indicate that this would take several weeks. **The stricter the measures, the more quickly the target value could be attained.** Once the target value has been achieved, the measures could be gradually lifted. However, suitable measures would still have to be applied to prevent a new outbreak. A significantly **expanded testing strategy** would be indispensable in this context so new cases could be detected early on at the local level and effective countermeasures could be taken as necessary. Established and practiced tracing systems must follow a consistent isolation strategy when new cases occur to prevent the epidemic from flaring up again. At the same time, the population should be rigorously tested to detect antibodies against the virus. This would make it possible to determine the rate of infection and identify individuals who are no longer at risk of infection for the time being.

A f**inal evaluation of these scenarios** makes it clear that scenario 3 would be ideal from an epidemiological standpoint. This scenario can be expected to let us return to normal life in the near future while maintaining an enhanced level of vigilance. We believe that scenario 1 is inadvisable as this would result in the healthcare system being severely overwhelmed and would lead to very high numbers of fatalities. However, we cannot recommend scenario 2 at this point either, given that the current state of knowledge mapped in the models indicates it would take several years for the entire population to become immune without outpacing the capacities of the healthcare system. In light of the considerable collateral damage that long-term, moderate restrictions to social activities would cause in social, economic, and political terms, intensive contact restrictions that are limited in terms of time, as described in scenario 3, appear to be the preferable approach – even if a definitive evaluation would need to go beyond the epidemiological subject matter discussed here.

The imposed contact restrictions have reduced the Rt value to approximately 1 in just three weeks. They have also established a high level of awareness of the problem among the population and created a strong sense of solidarity along with very high acceptance of the precautionary measures. Looking ahead, there is the potential that this increased willingness among the population could be used to decrease Rt to the point that the epidemic becomes controllable over the long term. This could be achieved with approximately three more weeks of contact restrictions as described in scenario 3. **We believe that easing the measures at this point and being forced to reintroduce them later on comes at a high risk: It would likely be more difficult to communicate the necessity of resuming the measures to the population later on than simply continuing them now.**

The available forecasting models are improving incrementally and allow the situation to be reassessed on a daily basis according to the described feedback method, which applies an Rt target value of well below 1 in scenario 3. These models also make it possible to identify potential ways of easing existing measures or introducing accompanying measures. This process can also be carried out specifically for each Federal State (http://secir.theoretical-biology.de). **Over these three weeks, additional measures should then be planned with respect to how tests and contact tracing can be stepped up in conjunction with what will then be a significantly lower number of new cases so the spread of the virus can be kept under control despite the easing of measures.**

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