COVID-19 mitigation strategies and overview on results from relevant studies in Europe.

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ABSTRACT

In December 2019, the first patients in Wuhan, China were diagnosed with a primary atypical pneumonia, which showed to be unknown and contagious. Since then, known as COVID-19 disease, the responsible viral pathogen, SARS-CoV-2, has spread around the world in a pandemic. Decisions on how to deal with the crisis are often based on simulations of the pandemic spread of the virus. The results of some of these, as well as their methodology and possibilities for improvement, will be described in more detail in this paper in order to inform beyond the current public health dogma called "flatten-the-curve".

A comprehensive literature review of publications on the SARS-CoV-2 outbreak, previous epidemics and related forecasting and containment strategies was conducted.

There are several ways to model an epidemic in order to simulate the spread of diseases. Depending on the timeliness, scope and quality of the associated real data, these multivariable models differ in the value of used parameters, but also in the selection of considered influencing factors. It was exemplarily shown that epidemics in their course are simulated more realistically by models that assume subexponential growth. Furthermore, various simulations of the COVID-19 pandemic were presented in an European perspective, compared against each other and discussed in more detail.

It is difficult to estimate how credible the simulations of the pandemic models are. Whether a model works well in reality is largely determined by the quality and scope of its underlying data. Past studies have shown that countermeasures are able to reduce reproduction numbers or transmission rates in epidemics. In addition to that, the presented modelling study provides a good framework for the creation of subexponential-growth-models for assessing the spread of COVID-19.
INTRODUCTION

On 30.03.2020 the SARS-CoV-2 virus arrived almost everywhere. Nevertheless, there is disagreement about the measures to be taken against Covid-19 around the world, while the news report frightening incidents. Why is it so difficult for countries to find a common consensus on how to tackle the pandemic?

Virus pandemics spread across national borders with a time lag. Therefore, while some countries are at an early stage of the crisis, as evidenced by the low number of new infections confirmed daily, other populations in the world may already be much more seriously affected. China and South Korea, for example, are already planning to return to normal life (1,2), but elsewhere the situation is becoming increasingly dramatic. These differences result in an inhomogeneous data situation; in addition, different fundamental conditions of countries make it difficult to mutually compare situations. Creating simulation models that allow a (realistic) prediction of the pandemic virus spread is a difficult task. The basic theories on which such models are based are as old as they are complex. Thus, with this thesis I would like to contribute to the understanding of these and to present results from previous publications relevant to this topic.

Scientists are not only making a special contribution to the general public by informing them about the dangers and ways to protect ourselves from them, but they also support politicians all over the world. At the moment, it is becoming clear how valuable scientific skills and experience are for assessing the situation and making quick decisions.
RESULTS

A concept to mitigate the effects of the virus pandemic is being widely covered by the media. This is the current public health dogma "flatten-the-curve". This can be explained without further elaboration: the number of seriously ill persons should be kept low so that the national health system does not collapse due to a lack of beds in the intensive care units of the hospitals (ICUs). The outbreak of the disease in society is to be "slowed down", and the mortality rate is to be kept low.

Using epidemiologic models as basis for the assumption

The concept "Flatten-The-Curve" is based on the frightening result obtained by comparing the results of statistical, epidemiological simulations of the pandemic with the number of intensive care beds available in the country. Many of them conclude that without effective countermeasures, a collapse of the health system is to be expected.

A model frequently used for simulating directly transmitted infectious diseases is the so-called "SIR" model. This model is based on the 2nd Nobel Prize winner (who was awarded for his findings on malaria) for Medicine/Physiology, Robert Ross, as well as to the former researchers Hilda Hudson and Kermack/McKendrick.

The SIR model assumes that during an epidemic, every person goes through the three states, S: "susceptible", I: "infected" and R: "recovered".

Since the number of people in each stage depends on the dynamics of the epidemic and thus on the time during the epidemic, the SIR model can be described mathematically with differential equations (3), which will not be discussed in detail in this work.

It is often assumed that every epidemic initially spreads exponentially. Due to the initially small number of cases detected, the spread normally goes unnoticed. However, experience has shown that epidemics slow down in the course of their spread and no longer show exponential growth (4). This observation will be discussed in more detail in the following study. For its understanding, however, further foundations are necessary.

An important indicator used to assess the risk of epidemic spread is the effective reproduction number $R_t$. This indicates the average number of secondary infections per primary infection, i.e. how many more people are infected by an infected person at a given time.

If the value $R_t$ falls below 1, the epidemic decreases, above 1 the epidemic picks up speed.

Another key figure that should not be confused with the one just mentioned is the so-called "basic reproduction figure" $R_0$. It indicates how quickly an epidemic can spread at the beginning when all people in a population are susceptible to infection. To determine this important parameter, it is important to know the underlying "agent", its transmission and pathogenicity precisely and as generally as possible.
Trying to find a value of $R_0$ for the Covid 19 pandemic online, one encounters different values, which vary greatly from 1.4 to 3.9 \((5-9)\). To calculate the effective reproduction number, the basic reproduction number must already be known. To understand why this second one varies so much, one must understand what influences it. In the classical SIR model, the reproduction number at the beginning of a pandemic, i.e. at time $t = 0$, is calculated as follows:

$$R_{t=0} = R_0 = \frac{\beta_0}{\gamma}$$

$\beta_0$ is the initial transmission rate and $\gamma$ the rate at which infected persons recover. $R$ is a ratio of new infection rate to recovery rate and therefore dimensionless. The transmission rate $\beta$ is generally calculated by the product of the contact rate $C$ times the probability $p$ with which contact between infected and susceptible persons leads to virus transmission, but in more complex models other influencing factors can be taken into account.

$$\beta = C \cdot p_{I\rightarrow S}$$

The determination of both reproduction numbers is therefore always based on certain assumptions which are mathematically described in a model that can be based on different types of growth. This can be exponential (as most commonly used), or other growth processes, e.g. logistic or linear. These growth processes can be tested and compared with the presented SIR model.

**Estimating the effective reproduction number correctly**

In a publication by Chowell et Al \((4)\), published in October 2016, for example, the dynamics of epidemics were examined using various basic concepts Advanced SIR models were used to determine how the predicted number of cases and the number of reproductions change over time and differ when exponential growth is assumed on the one hand and subexponential/polynomial growth on the other in a generalized growth model. In the course of this, three models were created and mathematically formulated, which consider different aspects:

**Model 1** takes into account a certain degree of clustering within society. This influences the way epidemics spread. Taking this into account, model 1 postulates that all people live in total $C$ households of a certain size $H$ and each household is part of a, to a certain degree, networked community. In the subsequent mathematical simulation of the model, it could be seen that a larger number of people in the community leads to more infected people, which is logical. It was also seen, however, that under the assumption of a subexponential/polynomial growth, the effective reproduction number decreases as the epidemic progresses.

**Model 2** considers a reactive change in human behaviour, with a resulting time-dependent change in the transmission rate. This is achieved by introducing a parameter $q$, which influences the transmission rate $\beta$. The results were similar: Behavioural changes in society lead to a decrease in the reproduction number towards 1.
Figure 2: Results of the study of model 2: Simulation of the case incidence (a) and the reproduction number (b) over time of the pandemic spread (increasing generation number). Situation without countermeasures: \( q = 0 \). Change of behaviour (\( q > 0 \)) leads to a rapid decrease of the effective reproduction number (here: \( R_g \)) towards one. Source: (4).

Model 3 assumes that the population is unevenly, i.e. inhomogeneously mixed. For this purpose a parameter \( \alpha \) is introduced in the mathematical formulas. The smaller it is (\( \alpha < 1, \alpha \to 0 \)), the more it reduces the simulated epidemic spread. As suspected, this model also behaves like the one mentioned above. Higher inhomogeneity of society, lowers \( R \) more drastically over time.

Subsequently, all approaches were combined into one concept and the results were compared with real, historical data. The following conclusion could be drawn: Models that assume exponential growth estimate the effective reproduction number to be higher than actually proven. In comparison, models such as the one presented, which does not assume exponential growth, calculate the case number and effective reproduction number \( R_t \) in the advanced course of an epidemic, more realistically (see Figure 3, Figure 4).

Comparing the results with the situation at the end of March 2020, shown in Figure 5, it can be seen that at this point in time, the curve for new cases in some countries begins to deviate from the exponential growth that would be linear-diagonal. Assuming that many previous simulations have only considered exponential growth, this is a positive signal. It could mean that the effective reproduction number, as mentioned in the study, is actually lower than previously assumed.

Figure 3: Comparison of both concepts (subexponential growth = GGM, left) and exponential growth (EXP, right) based on real data on Spanish flu in 1918, HIV in Japan and Ebola in West Africa in 2014. Source: (4), Supplementary material S4.
Figure 4: Comparison of the deviation of both concepts to reality by means of a comparison with data from 21 data sets on epidemics in the past. Source: (4), Supplementary material S5.

Figure 5: The trend curve of weekly confirmed new cases of the disease compared to the total number of people with the disease in each country. Logarithmic scaling, therefore distorted representation of the case numbers. Modified according to: Covid-19 Trends by Aatish Bhatia & Henry Reich, Data provided by Johns Hopkins CSSE, Status: March 29, 2020.

For the sake of completeness, reference should be made to the model known as “SEIR”. Here, the incubation time is also taken into account as another possible state (“Exposed”). If this is higher, this
reduces the number of patients at the peak of the epidemic, but extends the period of high exposure for the clinics, since "herd immunity" is reached later.

– In a study published in 2012 by the BKK (German Federal Office for Civil Protection and Disaster Assistance), the results of the modelling of a hypothetical SARS epidemic are found. The effect on the total population (80 million) is simulated. In the study it is assumed that without measures, one infected person will infect an average of three others (initial reproduction number: \( R_0 = 3 \)).

With effective intervention (curfews, closure of universities/schools) this rate is reduced to 1.6. Countermeasures are assumed from day 48 to 408 since the first infected person was detected and the rate with hospitalized patients requiring intensive care is assumed to be between 20 and 30 %. Furthermore, it is determined that the mortality rate at the age of 60 years is 50 % and a mild course of the disease occurs in 5 % of cases.

The simulation comes to the conclusion that at the peak of the epidemic about 1.1 million patients need intensive care. Of these, an estimated 23890 are available under normal conditions in Germany (10). In comparison with other countries such as Italy or Great Britain, this is a relatively high value, but according to the study results, the health care system would still collapse under the burden.

In this model, the incubation period during which an infected person is not yet infectious is not taken into account. For Covid-19 this is estimated to be about 5.2 days (11).

An essential factor that makes prognostic simulations more credible is knowing which countermeasures to spread, how well they work. However, since there are few general, evidence-based publications and no databases on this subject, assumptions must be made.

The study presented by the German Federal Office BKK estimates the reduction of \( R_0 \) through school closures, the prohibition of events and home quarantine at -46.6 %. For comparison: Reports (non-peer-reviewed) from China even estimate a reduction of as much as -91.71 % due to the very drastic measures against Covid-19 in Wuhan (12,13). Calculations from Spain claim that the transmission of influenza can be reduced by a maximum of 20 % by closing schools without curfew (14). This contrasts with observations from Russia, which showed that school closure during the flu season reduces the daily contact rate (≠ Reproductive index \( R_0 \)) with individuals by 53 % for students and 19 % for workers (15). Only the results of these studies should be mentioned. These are not directly related to the current or future situation. However, it can be seen from the data that measures taken appear to be effective against the spread of infectious diseases.

– The fact that science is currently exerting enormous influence on political decisions is shown by a recent publication by Imperial College London, which caused the governments of Great Britain and the USA to rethink their course against the virus (16). The author and one of the directors of the renowned university, Neil Ferguson, is probably the English equivalent of the German doctors Drosten and Kekulé, to whom politics in this country is currently listening.

The ICL publication paints a gloomy picture of what lies ahead for the UK. Without going into the economic consequences, it is based on the so-called "NPI measures" (Non-Pharmaceutical-Measures) taken in the USA in 1918. Measures to contain the Spanish flu.

The effectiveness of such "NPIs" is tested in the study using a statistical model which assumes exponential epidemic growth for the UK. The results will be presented in more detail below. The model assumes a reproduction number of \( R_0 = 2.4 \), a 0.9 % general death rate of tested AND untested infected persons (Infection-Fatality-Rate, short: IFR), a mean hospitalization rate of of 4.4 % among infected persons and an incubation period of 5.1 days.
Furthermore, it is assumed that symptomatic patients are 50% more infectious than asymptomatic patients, while a distribution parameter is additionally introduced to take into account "individual infectivity". As shown in the excerpt below, the authors make the proportion of hospitalized infected persons dependent on the age of the person.

While Ferguson used Chinese data in a preprint paper from the beginning of March to calculate hospitalisation rates as shown in Table 1 (17), the figures in the study now published look somewhat more threatening, since it also takes into account the situation in Italy (see Table 2).

Online simulation tools have also been published, one of which was developed by a research group led by Richard Neher at the University of Basel. With this tool, (SEIR) simulations can be easily visualized in a browser. By default, the hospitalisation rate (severe-cases) is given there as follows, but it can be adjusted individually. The underlying model uses data on health care and demography of a given country. However, parameters are not (yet) adapted to current knowledge (as of 29.03.2020, (10)). In order to adjust the simulation in the appendix to more recent data, we have therefore changed the parameters for the proportion of severe cases according to the ICL paper as it can be seen in Figure 6.

In summary, the third assessment of the online tool shown is probably the most pessimistic, as it is based so far only on data from countries particularly affected by the crisis. It has been shown that a collapse of the health care system quickly pushes up the death rate. The ICL, on the other hand, predicts a lower probability of hospitalisation and severe courses of disease in older patients (80+).

It should be noted that the two important parameters, R₀ and IFR, are currently undergoing continuous correction and also vary widely between different online simulations. In contrast to many
other simulations, the Oxford Centre for Evidence Based Medicine, for example, estimates the death rate at a significantly lower level and also corrected the prognosis downwards based on the figures from Germany (IFR = 0.4, as of March, 29, 2020) (19).

ICL study results

The scientists first compared the effects of various very realistically defined measures. Among them:

- Doing nothing
- Isolate cases of disease
- Isolate cases of disease and house quarantine
- Closure of schools and universities
- Isolate cases of disease, domestic quarantine and social distancing from 70+

They concluded that, although a combination of measures is comparatively more effective, the effectiveness of all the measures described is not sufficient to reduce the transmission rate $R_0$ sufficiently and prevent the system from collapsing. This picture is consistent with the estimates and calculations of the studies mentioned at the beginning (14,15). This procedure is commonly referred to as "mitigation" strategy.

![Figure 7: Comparison of measures to reduce intensive care bed occupancy in the event of a Covid 19 pandemic. The simulation for Great Britain showed that ICU capacities will not be sufficient despite the measures presented. Source: (18)](image_url)

The researchers see the only way to get the transmission rate $R_0$ from the specified original value of 2.4 to near or below 1 as a combination of drastic measures, whereby a complete "lockdown", as is currently the case in parts of Austria, is considered a (temporarily) safe option. The two remaining scenarios therefore envisage the following countermeasures:

- Isolate cases of disease, domestic quarantine and general social distancing
- Isolate cases of disease, domestic quarantine, closure of schools and universities and general social distancing
However, the results in Figure 8 also show that drastic measures for a limited period of five months only postpone the pandemic to a later point in time into winter and do not mitigate it. Successful herd immunisation with a vaccine therefore remains necessary in this case.

Since this strategy, known as "suppression", is ultimately not an option, the researchers propose a special protocol instead:

- Permanent case isolation with subsequent quarantine up to a limit of 50 Covid-19 intensive care patients per week and school closures, as well as general social distancing from a limit of 200 intensive care patients/week

The researchers show in their simulation that it would be possible to maintain intensive care units for normal operation in this way. It should be mentioned in this sense that the duration of the prevention measures depends to a large extent on how well one manages to reduce $R_0$. Assuming that the current reproduction number is 2.0 and that the alternating measures would be sufficient to reduce the value permanently, the study calculates that the proposed protocol would have to be adhered to in Great Britain for just under 16 months. There are already differing opinions as to the feasibility of this strategy.

**DISCUSSION**

Whether a model works well in reality is largely determined by the quality and scope of its underlying data. Although the simulation models available today are already very comprehensively designed (some of them even include global traffic flows and demographics in their datasets (10,20–22)), an unmanageable number of influencing factors remain, which cannot all be taken into account mathematically. Depending on which model is used to determine the reproduction number, it will be lower or higher. If the growth curve begins to flatten out, it is probably worth adjusting the models and taking into account subexponential growth by assuming other growth processes as exponential growth, i.e. logistic growth or generalized growth, in order to realistically estimate $R_t$. The presented study (4) provides a good framework for such models to build on. Whether, and which measures are sufficient for a permanent reduction of the reproduction number has not yet been confirmed. It is a fact, however, that a relaxation of restrictions or non-compliance with rules increases the transmission...
rate and can quickly lead to a renewed rise in the curve in the worst case. Detection of such events through monitoring and rapid follow-up in case of occurrence offers potential to prevent this.

In China, South Korea and Singapore, it seems that the spread of the virus is well under control. Under the title „Response to COVID-19 in Taiwan - Big Data Analytics, New Technology, and Proactive Testing“ an interesting report on how data can be used to counteract the spread of the virus can already be found (23).

If the presumed high number of asymptomatic infections is confirmed and the number of fatal infections remains unchanged, this could reduce the IFR (Infection Fatality Rate) and thus also the simulation curves shown. Among other factors, this may be one reason why the IFR is lower in countries that rely on rigorous testing of many citizens for Covid-19 early on. Large-scale immunological antibody testing will provide evidence of the current status of herd immunity in populations.

It is difficult to estimate how credible the simulations of the pandemic models currently are, so it remains to be seen whether the spread of the pandemic can be effectively reduced by the measures taken. As the presented studies from the past have shown, countermeasures are basically able to reduce reproduction numbers or transmission rates in epidemics.

The principle that biotechnologists are so keen to use in the production of modern drugs when working with transgenic organisms is unfortunately playing against us all this time: exponential growth. This must be prevented.
APPENDIX

Enclosed is the result of the simulation for Germany for the period until the end of April 2021, which was created with the online tool provided by the Neher research group from Basel (10). This is based on the assumption that the development of a vaccine takes 12-13 months and is then quickly available.

According to this, the capacity of the intensive care units will not be exceeded by the number of serious cases until then (end of April 2021), or the overflow will be delayed. In the beginning, however, very tough measures will be necessary. It is assumed that hard measures such as social distancing will reduce the reproduction number by 75 % from the initially assumed 2.4 to 0.6. It is also assumed that it will increase again over time due to a beginning population dynamic after longer curfews. After four months with existing restrictions, measures will be eased and the transmission rate will continue to be maintained at -50 % until the end of April 2021.

Whether this assessment of the reproductive rate, IFR, as well as the effectiveness of countermeasures is realistic, will become apparent in the near future, when more data on the course and immunity in Germany and neighbouring countries will be available.

The hospitalisation rate of patients (severe-cases), as well as the proportion of persons requiring intensive care (critical-cases), was adapted according to the ICL paper from the UK (18). The result of the simulation can be seen in Figure 9.

| Date       | Limit the transmission rate by |
|------------|-------------------------------|
| 01/03/2020 | 0 %                           |
| 01/04/2020 | -75 %                         |
| 01/05/2020 | -70 %                         |
| 01/06/2020 | -65 %                         |
| 01/07/2020 | -60 %                         |
| Until      |                               |
| 01/11/2020 | -55 %                         |
| 01/01/2021 | -50 %                         |
Figure 9: Covid-19 simulation for Germany considering demography, hospitalisation and critical care statistics from ICL Paper (19), see Fig. 4 Right, baseline R0: 2.4, duration of intensive care: 10 days, number of ICUs: 24350, Severe = Hospitalised / Critical = ICU patients, countermeasures See Fig. 4 below, Simulation performed by using COVID-19 Scenarios
LIST OF ABBREVIATIONS:

- $R$: Reproductive number
- $R_0$: General reproductive number
- $R_t$: Effective reproductive number
- IFR: Infection-Fatality-Rate
- ICL: Imperial College London
- BKK: Bundesamt für Bevölkerungsschutz und Katastrophenhilfe
- ICU: Intensive-Care-Unit
- GGM: Generalized-Growth-Model (subexponential)
- EXP: Exponential

KEYWORDS:

COVID-19, SARS-CoV-2, Modeling, Epidemiology, Public Health, Forecasting, Epidemic spread, Mitigation, Countermeasures

DECLARATIONS:

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Not applicable.

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All data generated or analysed during this study are included in this published article [and its supplementary information files].

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The authors declare that they have no competing interests

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16