Statement

German Network for Evidence-based Medicine

Berlin, 20.02.2020

COVID-19 - Where is the Evidence?

When the first coronavirus infections were reported in China at the end of December 2019, it was hardly foreseeable that a worldwide pandemic would develop from this outbreak. Initially, it was thought that the spread of SARS-CoV-2 could be halted by isolating those infected and quarantining suspected cases. It is now clear that the virus will spread worldwide despite all the drastic measures taken so far. No epidemiologist still believes that isolation and quarantine can completely eliminate the virus.

The question that urgently needs to be addressed in the present situation is therefore not how we can eliminate the virus, but rather how we can ensure that it causes as little damage as possible. Here, direct damage caused by deaths, the absence from work, or the overloading of health care systems must be weighed against indirect damage, such as the consequences of social isolation and economic stagnation. In the following, an attempt will be made to present the ambiguities and lack of evidence for the measures currently under discussion and those being implemented. The core message is the need to obtain reliable data through research on the current situation to inform future similar events.

COVID-19 – Morbidity

Currently, in many countries, including Germany, Austria and Switzerland, the number of diagnosed cases doubles approximately every 2 to 2 ½ days [1]. Projections predict that the capacities of clinics and hospitals responsible for the care of patients in German-speaking countries will be exhausted by the beginning of April at the latest [2]. It is uncertain whether the measures currently taken will have a favorable effect on this scenario. The increase in new cases could at least be slowed down in China, South Korea and Singapore, where significant suppression measures were taken [1,2].

COVID-19 Lethality

There are no reliable figures on the lethality of COVID-19, but it is certain that simply dividing the number of detected diseases by the number of deaths leads to a substantial overestimation of the so-called "case fatality rate" (CFR). According to real-time data from the Center for Systems Science and Engineering at Johns Hopkins University, there were 218,824 infections and 8,810 deaths confirmed by the rapid PCR test as of March 19, 2020 [3,4]. This would correspond to a CFR or lethality of 4.0%. However, this figure is subject to several errors:

- In the majority of cases, COVID-19 takes the form of a mild cold or is even symptom-free. Therefore, it is highly unlikely that all cases of infection are recorded, in contrast with deaths which are almost completely recorded. This leads to an overestimation of the CFR. According to a study of 565 Japanese people evacuated from Wuhan, all of whom were tested (regardless of symptoms), only 9.2% of infected people were detected with currently used symptom-oriented COVID-19 monitoring [5]. This would mean that the number of infected people is likely to be about 10 times greater than the number of registered cases. The CFR would then only be about one tenth of that currently measured. Others assume an even higher number of unreported cases, which would further reduce the CFR.

- The widespread availability of SARS-CoV-2 tests is limited. In the USA, for example, an adequate, state-funded testing facility for all suspected cases has only been available since

Anschrift: Schumannstraße 9, 10117 Berlin • Telefon: +49 (0)30-30833661 • Telefax: +49 (0)30-30833662
E-Mail-Adresse: kontakt@ebm-netzwerk.de • Internet: www.ebm-netzwerk.de

11.3.2020 [6]. In Germany as well, there were occasional bottlenecks which contribute to an overestimation of the CFR.

- As the disease spreads, it becomes increasingly difficult to identify a suspected source of infection. As a result, common colds in people who unknowingly had contact with a COVID-19 patient are not necessarily associated with COVID-19 and those affected do not go to the doctor at all.
- An overestimation of the CFR also occurs when a deceased person is found to have been infected with SARS-CoV-2, but this was not the cause of death.
- On the other hand, an error that leads to an underestimation of the CFR is that every case is counted from the time of diagnosis, but at this point it is not yet clear whether the patient will survive. The cumulative deaths would therefore have to be compared with the number of known illnesses at the time at which the disease first manifested itself in the deceased, i.e. the number of illnesses about 14 days before the date of death, assuming that those affected die on average two weeks after illness onset. The CFR would then range between 5 and 15% depending on the country [7].

In addition, CFRs vary widely from country to country. This may be due to an incomplete coverage of cases, e.g. due to differences in testing procedures and capacities, as well as differences in the ability to provide high-quality intensive care. For example, of the 35,713 confirmed cases in Italy, 2978 (as of 19.3.2020 [3]) died, corresponding to a CFR of 8.4%, while in Germany only 28 of 12,327 died (CFR 0.2%). However, in contrast to Italy, Germany is only at the beginning of the exponential expansion and the intensive care capacity limit does not yet play a role in Germany. The widely divergent figures make it clear that it is not yet possible to reliably estimate the CFR.

What can be said with great reliability, however, is that deaths primarily occur in older people, mainly elderly people with pre-existing cardiovascular and pulmonary conditions. In an analysis published in February 2020 by the Chinese Center of Disease Control, 81% of COVID-19 deaths were in people over the age of 60 [8]. None of the 416 children <10 years were among those who died. However, the CFR was 0.6% even for those <60 years old.

The numbers in Italy are somewhat different. Only one person under the age of 50 died, while almost 60% of deaths involved people over the age of 80 [9].

In contrast to COVID-19, for example, almost 50% of deaths in the 1918/19 influenza pandemic affected those aged between 20 and 40 [10].

Concomitant diseases also represent a significant risk factor. In the Chinese study, 67.2% of those who died had at least one chronic concomitant disease, most frequently hypertension (39.7%), cardiovascular disease (22.7%), diabetes mellitus (19.7%), and chronic respiratory diseases (7.9%) [8]. Persons without pre-existing or concomitant diseases had a CFR of 0.9%. Here again, COVID-19 differs markedly from the 1918/19 influenza pandemic, in which many young people died without any major concomitant diseases [10].

In summary, the damage caused by COVID-19-associated premature deaths is considerable and is very likely to increase dramatically. However, the CFR of 0.2% currently measured for Germany is below the Robert Koch-Institute's (RKI) calculated influenza CFRs of 0.5% in 2017/18 [11] and 0.4% in 2018/19 [12], but above the widely accepted figure of 0.1% for which there is no reliable evidence. More threatening than the CFR of COVID-19 itself therefore is the absolute number of deaths to be expected if the disease continues to spread at doubling rates of two to three days. From the perspective of evidence-based medicine (EbM), however, all these figures are of limited use if the total mortality of the

population, or the total burden of disease caused by influenza-like infections and their CFRs are not available as reference values.

Effectiveness of non-pharmacological interventions (NPI)

At this point, the main focus of this paper will be on the currently practiced and planned measures of "social distancing", i.e. state interventions ranging from the closure of educational institutions to a complete curfew.

As a historical example of the effectiveness of NPI, we refer to the different reactions of American cities to the 1918 influenza pandemic. In St. Louis, drastic measures were taken three days after the first cases of influenza occurred to contain the spread of the virus (closure of schools, churches, theatres, bars, cancellation of public events, etc.). In contrast, in Philadelphia a large parade was held after the outbreak and effective containment measures were not implemented until two weeks later [13]. The consequences were dramatic: in St. Louis the death rate peaked at 31/100,000 inhabitants, while in Philadelphia it rose to 257/100,000 inhabitants, resulting in a collapse of the health care system. The total number of deaths in St. Louis reached 347/100,000 inhabitants, about half that of Philadelphia (719/100,000 inhabitants) [13]. It is completely unclear, however, whether the experiences from the 1918/19 influenza pandemic are transferable to COVID-19. The fact that, at that time, the deaths were mainly among young people, and that neither hygiene standards nor medical care in 1918/19 are comparable with today, rather indicates that this is not the case.

Beyond the (rather questionable) conclusions drawn from the historical example, there is little evidence that NPIs for COVID-19 actually lead to a reduction in overall mortality. A Cochrane Review from 2011 found no robust evidence for the effectiveness of border control screenings or social distancing. However, this was mainly due to a lack of studies and poor study quality [14]. A systematic review from 2015 found moderate evidence that school closures delay the spread of an influenza epidemic, but at high cost. Isolation at home slows down the spread of influenza but leads to increased infection of family members [15]. It is questionable whether these findings can be transferred from influenza to COVID-19.

It is completely unclear how long the NPIs must be maintained and what effects could be achieved depending on their duration and intensity. The number of deaths might only be postponed to a later point in time, without any change in the total number. In contrast to seasonal influenza, we do not know how SARS-CoV-2 will continue to behave, whether the approaching spring in the northern hemisphere will lead to a natural halt to the spread of the virus, or whether the virus will continue to spread continuously and indefinitely until a large part of the population has been infected and become immune. The latter currently seems more likely.

A model calculation by the COVID-19 working group at Imperial College predicts that the implementation of radical NPIs - as currently planned or already implemented - could lead to a second, equally severe pandemic wave in autumn 2020 if the NPIs are relaxed after three months [16]. Alternatively, an "on-off strategy" could be pursued, which would have to be sustained until about 60-70% of the population has acquired the disease and become immune, and herd immunity has developed. However, this would mean that drastic NPIs would be in force at intervals for two thirds of the time over the course of an entire year [16].

Possible indirect damage from COVID-19 and NPIs

There is also little evidence of the possible indirect damage of the pandemic. In any case, the damage caused by the pandemic goes beyond the death toll. The disease not only places a serious burden on

the health care system with possibly reduced or worse care for patients who are not ill with COVID-19, but also leads to major absences from work.

On the other hand, the current NPIs have massive effects that go far beyond the economic slump and the fall in stock prices. What are the psychological and social effects of social isolation? How many foreign caretakers do not want to or are no longer able to work with our elderly people in need of care because of the border closures and the requirements for coronavirus protection, such as the 14-day quarantine after returning home, and what are the consequences? How many jobs will be lost? How many companies will collapse? Whom will the economic consequences hit hardest? Will the NPIs contribute to greater social disparities?

Closing schools may reduce transmission rates among children, but will it really help to stop the pandemic and, most importantly, reduce death rates? Won't children meet outside of school, keep parents from working in the absence of childcare, and then visit grandparents - putting at risk the very group of people who most need protection?

At this stage, it is impossible to assess whether the unhindered rapid spread of the disease, or the delay of its spread and therefore prolongment of the total period of illness, would cause greater damage. Damage which may also have indirect effects on health, quality of life, and life expectancy.

Where is the evidence?

Many questions remain unanswered. On the one hand, the media confronts us daily with alarming reports of an exponentially increasing number of ill and dead people worldwide. On the other hand, the media coverage in no way considers our required criteria for evidence-based risk communication.

The media is currently communicating raw data, for example, there have been "X" infected persons and "Y" deaths to date. However, this presentation fails to distinguish between diagnoses and infections. The cases reported by the media are diagnoses; the total number of infected persons is not known. This would require a complete testing of a representative sample of the population.

The presentation of diagnosed cases without reference values is misleading. For example, only raw data are reported for individual countries, states or regions, without reference to population size. The data could refer to 100,000 inhabitants in each case.

Data is provided without the necessary reference values. For example, it is said that "there are 10,000 cases so far". Also, the naming of raw data without reference to other causes of death leads to an overestimation of the risk. In Germany about 2,500 people die every day. The data on deaths by Covid-19 should therefore be reported in the context of either the daily or weekly overall deaths in Germany. A reference to deaths from other acute respiratory infections would also be appropriate.

Statements that COVID-19 causes the death of predominantly elderly and sick people should be contextualized with a comparison to the people who die from other acute respiratory diseases.

We must consider the extent to which it is ethically justifiable to report on individual cases of severe illness in the media without contextualizing them in the overall spectrum of illness and death.

Moreover, there are considerable inconsistencies in the available data. It remains unclear why Italy in particular experienced such an explosive spread with many deaths, nor why the epicenter is wealthy Lombardy rather than one of the poorer regions of Italy. It is certainly not possible to dismiss this event

simply by rebuking poorer medical care, and furthermore Italy does not appear to lack of testing capacities.

The figures from China are not very credible. It seems very unlikely that the "containment" in a country with 1.4 billion people works so well that suddenly no one is infected anymore (25 new infections in the whole country on March 18, no new infections on March 19) [3]. And what happens if the NPIs are relaxed? Infection rate, virulence, and pathogenicity of the virus do not change due to the containment. The spread will pick up speed again after containment is lifted, as predicted in the report of the Imperial College [16] and continue exponentially until about 60 to 70% of the population is infected and is then immune. Or has this status already been reached in China? In that case, 3,217 deaths (as of March 19) [3] in relation to 1.4 billion people would be far below the annual influenza death rate, which we have accepted so far without drastic NPIs.

The few deaths so far in, for example, Germany and Austria also tell a different story. Are there simply more tests conducted for SARS-CoV-2 than for influenza? In 2017/18, 25,100 people died of influenza in Germany [12]. This death rate corresponds to 5 million infected people based on the CFR of 0.5% calculated by the RKI for 2017/18. According to the RKI report on the epidemiology of influenza in Germany in 2017/2018, the influenza season lasted 15 weeks, from the 52nd calendar week of 2017 to the 14th calendar week of 2018 [11]. In order to reach 5 million within 15 weeks, the number of infected people would have to double every 4.4 days. This is similar to what we are now seeing with SARS-CoV-2 and differs only in that we did not measure it for influenza. In any case, there were no reports in 2017/18 that our health care system was overburdened, even though all 25,000 fatal flu cases presumably received medical treatment before their deaths, most of them certainly in a hospital or even in intensive care.

A comparison with this year's influenza activity could also be useful: According to the weekly report 11 of the RKI, laboratory diagnostics have confirmed 165,036 influenza cases so far this season. 23,646 cases have been hospitalized for diagnosed influenza, and 265 people have died of influenza [17].

The well-known epidemiologist John Ioannidis points out that coronaviruses that are the typical causative agents of common colds are responsible for millions of infections every year and that these common colds are fatal in up to 8% of older, multimorbid people with complications such as pneumonia [18,19]. The only difference to SARS-CoV-2 may be that we have never measured coronavirus infection rates in the population.

It is completely unclear whether SARS-CoV-2 will be subject to seasonal fluctuations like influenza, i.e., whether the spread will slow down or even come to a halt with warmer temperatures. It is also unclear whether the virus, like influenza viruses, is antigenically stable or whether it mutates so that permanent immunity cannot develop.

It is largely unclear to what extent the containment measures actually impact the course of the epidemic. The hints from Asian countries are only to a limited extent transferrable to Europe with its liberal attitude to life. And what happens if the NPIs are stopped? The projections from Imperial College are rather pessimistic and predict a second wave of the disease in late autumn, even if the current measures are maintained for three months. Alternatively, interval-like repeated NPIs for two thirds of the time over the course of an entire year would be necessary [16].

Furthermore, the question arises whether the population will build up herd immunity to the disease and when. Will the disease then possibly become a typical childhood disease, i.e., everyone who has not yet had it will at some point experience it and be protected from then on, or will there be seasonal outbreaks in the long run, like influenza? Is SARS-CoV-2 an antigenically stable virus or does it exhibit

high variability similar to the influenza virus? Whether and when there will be an effective vaccination is currently difficult to assess.

Conclusion

Overall, there is still very little robust evidence - neither on COVID-19 itself, nor on the effectiveness of the current measures. However, the serious threat posed by the COVID-19 pandemic cannot be disregarded, and NPIs - despite lacking evidence - are the only thing that can be done if we don't want to simply stand by and hope. Even with the most favorable assumption that the CFR will eventually lie well below 1% (mainly due to the failure to detect asymptomatic and mild cases) and that it will primarily affect the elderly and people with comorbidities, a high number of deaths must still be expected due to the rapid spread of the disease.

NPIs currently appear to make sense after consideration of the pros and cons, but they should not be conducted without meticulous accompanying research. Therefore, in addition to the undoubtedly necessary basic virological research, cohorts and registers must be established immediately in order to gather important scientific understanding for future pandemic situations. Among other things, examination of random samples of the entire population for SARS-CoV-2 makes sense in order to determine the true infection rate. In addition, it would be important to record the total burden of infection and disease caused by influenza-like illness and its consequences in a representative population sample, similar to what the British Flu Watch Cohort Study has done [20], for example, and which John Ioannidis strongly supports [18].

The public sector must provide sufficient research funding for such health care and public health research in order to better prepare for the future pandemic threats. The recent calls for proposals by the BMBF (D) and the FFG (A) address this need [21,22].

References

1. Lau R. Time-series COVID-19 confirmed [Internet]. 2020 [zitiert 2020 März 14];Available from: https://github.com/CSSEGISandData/COVID-19/blob/master/csse_covid_19_data/csse_covid_19_time_series/time_series_19-covid-Confirmed.csv

2. Thurner S, Klimek P. Coronavirus-Maßnahmen in Österreich eventuell zu gering, um Kapazitätslimits von Spitalsbetten zu vermeiden [Internet]. 2020 [zitiert 2020 März 14];Available from: https://www.csh.ac.at/csh-policy-brief-coronavirus-kapazitaetsengpaesse-spitalsbetten

3. Center for Systems Science and Engineering. Coronavirus COVID-19 (2019-nCoV) [Internet]. Johns Hopkins Univ.2020 [zitiert 2020 März 13];Available from: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

4. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect. Dis. 2020;S1473309920301201.

5. Nishiura H, Kobayashi T, Yang Y, Hayashi K, Miyama T, Kinoshita R, u. a. The Rate of Underascertainment of Novel Coronavirus (2019-nCoV) Infection: Estimation Using Japanese Passengers Data on Evacuation Flights. J. Clin. Med. 2020;9:419.

6. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Cent. Dis. Control Prev.2020 [zitiert 2020 März 13];Available from: https://www.cdc.gov/coronavirus/2019-ncov/testing-in-us.html

7. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect. Dis. 2020;S147330992030195X.

8. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. China CDC Wkly. 2020;2:113–22.

9. Istituto Superiore di Sanità. Sorveglianza Integrata COVID-19 in Italia [Internet]. 2020 [zitiert 2020 März 14];Available from: https://www.iss.it/documents/20126/0/Infografica_09marzo.pdf/1f62ad0a-e156-cf27-309d-26adcb1b52b4?t=1583782049035

10. Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. Emerg. Infect. Dis. 2006;12:15–22.

11. Bericht zur Epidemiologie der Influenza in Deutschland Saison 2017/18 [Internet]. Robert Koch-Institut; 2018 [zitiert 2020 März 17]. Available from: https://influenza.rki.de/Saisonberichte/2017.pdf

12. Bericht zur Epidemiologie der Influenza in Deutschland Saison 2018/19 [Internet]. Robert Koch-Institut; 2019 [zitiert 2020 März 17]. Available from: https://edoc.rki.de/handle/176904/6253

13. Hatchett RJ, Mecher CE, Lipsitch M. Public health interventions and epidemic intensity during the 1918 influenza pandemic. Proc. Natl. Acad. Sci. U. S. A. 2007;104:7582–7.

14. Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, u. a. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst. Rev. [Internet] 2011 [zitiert 2020 März 20];Available from: http://doi.wiley.com/10.1002/14651858.CD006207.pub4

15. Rashid H, Ridda I, King C, Begun M, Tekin H, Wood JG, u. a. Evidence compendium and advice on social distancing and other related measures for response to an influenza pandemic. Paediatr. Respir. Rev. 2015;16:119–26.

16. Ferguson N, Laydon D, Nedjati Gilani G, Imai N, Ainslie K, Baguelin M, u. a. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand [Internet]. 2020 [zitiert 2020 März 20]. Available from: http://spiral.imperial.ac.uk/handle/10044/1/77482

17. Buda S, Dürrwald R, Biere B. Influenza-Wochenbericht [Internet]. 2020 [zitiert 2020 März 19];Available from: https://influenza.rki.de/Wochenberichte/2019_2020/2020-11.pdf

18. Ioannidis J. In the coronavirus pandemic, we're making decisions without reliable data [Internet]. STAT2020 [zitiert 2020 März 19];Available from: https://www.statnews.com/2020/03/17/a-fiasco-in-the-making-as-the-coronavirus-pandemic-takes-hold-we-are-making-decisions-without-reliable-data/

19. Patrick DM, Petric M, Skowronski DM, Guasparini R, Booth TF, Krajden M, u. a. An Outbreak of Human Coronavirus OC43 Infection and Serological Cross-Reactivity with SARS Coronavirus. Can. J. Infect. Dis. Med. Microbiol. 2006;17:330–6.

20. Hayward AC, Fragaszy EB, Bermingham A, Wang L, Copas A, Edmunds WJ, u. a. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. Lancet Respir. Med. 2014;2:445–54.

21. BMBF. Förderaufruf zur Erforschung von COVID-19 im Zuge des Ausbruchs von Sars-CoV-2 - DLR Gesundheitsforschung [Internet]. Dtsch. Zent. Für Luft Raumfahrt EV - DLR

Gesundheitsforschung [zitiert 2020 März 20];Available from: https://www.gesundheitsforschung-bmbf.de/de/10592.php

22. FFG. Emergency-Call zur Erforschung von COVID-19 im Zuge des Ausbruchs von Sars-CoV-2 | FFG [Internet]. 2020 [zitiert 2020 März 20];Available from: https://www.ffg.at/ausschreibung/emergencycall-covid-19

In the name of the board

Prof. Dr. med. Andreas Sönnichsen

Chair of the German Network for Evidence-based Medicine

E-Mail: kontakt@ebm-netzwerk.de

The German Network for Evidence-based Medicine advocates that all citizens should receive health care that relies on best scientific evidence and informed decision-making. It brings together scientists from medical, nursing, and health sciences faculties, practicing physicians as well as representatives from other health professions (www.ebm-netzwerk.de). (www.ebm-netzwerk.de)