The art of “DIVI-nation” – predicting tomorrow’s ICU capacities from today’s infection numbers

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Abstract

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Introduction

The German center for disease control, the "Robert Koch Institute" (RKI), consistently speaks of a "dynamic" situation when talking about epidemiology of the SARS COV 2 virus and public health threats related to it. Following the developments and analyzing data for this third paper in a row I can truly confirm this statement. I had concluded my recent analysis of test strategy impact on case numbers with a warning that local health administrations would be overwhelmed by their contact tracing tasks if the strategy would not be adapted, and when I had the chance to post my results this scenario had almost become reality. Indeed, the national test strategy was adapted as one of the countermeasures – too late, unfortunately, to prevent a temporary collapse of the tracing system that is still ongoing.

Today the picture is completely different, with a continuously increasing number of SARS COV 2 positive patients on intensive care units, increasing the burden on health system, while hospital staff had already suffered from a high workload and stressful work conditions throughout the country before Corona. Currently the situation still seems to be manageable but the unprecedentedly high number of reported cases per day pushed the level of public concern to new dimensions. Part of the problem is the difficulty to correctly interpret the data we are seeing, owing to the various aspects I have highlighted in my previous papers. Daily reported infections are in tenfold dimension of what we saw during the first wave, yet at the same time we know that the numbers are not comparable.

We see our scientific fortunetellers, the modelists, back to the stage, showing how we are inevitably doomed to perdition by combining exponential growth models with fixed hospitalization and fatality rate estimates, ending up in apocalyptic death toll projections. What I have been missing to date is a reasonable attempt to relate the two relevant data sources we have, the public infection surveillance monitoring and the German registry on intensive care units (DIVI), in a systematic way. Herewith I am presenting my personal approach to bridge this gap, hoping to contribute to a realistic and adequate resource planning for our hospitals facing the challenge.

In the following I am going to review the different steps I have taken to construct suitable forecast models for the number of patients with COVID 19 diagnosis in ICU on a specific day. As a second step I have assessed the validity of these models by comparing predicted vs. real-life numbers during a follow-up period after the dataset used for construction. Finally, I am going to take a closer look on the interaction between different variables recorded and published by the German registry on intensive car (DIVI), aiming to clarify some obvious inconsistencies and thus allow for a better understanding how increasing SARS COV 2 infections translate into decreasing resources.

Objectives

The main objective of this study was to construct a valid predictor model for COVID 19 patient burden on ICUs based on public infection surveillance data as published by the German center of disease control (RKI).

Data

This manuscript is based on daily reports of confirmed COVID 19 cases in Germany using the dataset available on https://npgeo-corona-npgeo-de.hub.arcgis.com. Timeseries on COVID patients and ICU capacities were downloaded from the official website of the "DIVI" registry, maintained by the German interdisciplinary association for intensive and emergency care (DIVI): http://www.intensivregister.de/.

As highlighted on the registry website there were several important changes in reporting requirements that show an immediate impact on the data. An obligation for all units to report their capacities was introduced on 16 April 2020, which led to a subsequent stabilization of the number of reporting units after that date. To control at least partly for the effect of a varying number of reporters, all time series data were multiplied with the quotient of actual and maximum number of reporting intensive care units, thus ameliorating the fluctuations observed in the raw data especially before 16 April 2020.

The data used for model construction cover a timeframe from 20 March to 30 November 2020. Due to daily updates by local health authorities the RKI data are sometimes adjusted retrospectively. My construction dataset (DIVI and RKI data) represents the status of 12 December 2020. The validation dataset comprises all data available for 2020 from both sources, last updated 06 January 2021.

Methods and parameter selection

Like in the two precursor papers on COVID 19 I am mainly resorting to linear regression models and descriptive statistics for analyzing the available datasets [1] [2]. All calculations and graphs where done using the statistical package "R version 4.0.0 (2020-04-24) – 'Arbor Day'", published by "The R Foundation for Statistical Computing" (2020).

The DIVI registry as well as the RKI infection monitoring database offer a variety of parameters that could be used as predictor or outcome variables. With respect to outcomes there are basically three possibilities to focus on, the number of occupied beds, the number of available beds, or the number of ICU patients tested positive for SARS COV 2. Although the number of beds seems to be the most relevant in terms of capacities, there are several reasons to interpret these data with caution as discussed in more detail below. It may be assumed that almost every patient admitted to an intensive care unit since start of the registry received a PCR test, suggesting that the number of test positives among ICU patients is probably the most reliable and stable outcome to choose with the additional benefit of an immediately plausible connection to the overall number of infections. In addition, this parameter should not have been significantly affected by the various changes in reporting requirements introduced by the registry administrators since March.

With respect to predictors, there is a choice between number of cases based on the date of report or based on the day of first symptoms. The latter is available as an actual date reported for part of the cases or it is again imputed by the day of reporting, meaning that either no clinical information was available or that the person indeed had no clinical symptoms. For clinical purposes, the date when a new case is reported is generally not relevant, so the decision to work with data based on date of first symptoms is a logical consequence. However, the practice of imputing start of symptoms might make sense for the RKI, as they use this for calculating their estimate of the current reproduction rate. For any attempt to construct prediction models it might rather be harmful, as the imputation sort of blurs the picture of the true situation on a given day. With the increase of test activities, the number of patients without clinical information, i.e. without a confirmed date of first symptoms, has increased to more than 50%. Fortunately, the RKI dataset contains a variable allowing for separation of cases with confirmed and imputed start of symptoms, so I could use this information to assess the impact before deciding for the final predictor.

Apart from using the raw data it would also be possible to use a variety of aggregates or derivates, such as cumulative numbers, incidence rates, etc. However, there is no need for working with derivates while the original variables already provide good enough results, so I started with the infection counts as reported.

Results

Prediction interval

My first construction step was a series of analyses to identify the optimal time interval between predictor and outcome variables. Obviously, the number of confirmed infections cannot validly predict the number of hospitalizations on the same day, since some time will pass between a patient getting ill and a condition so serious, that intensive care is required. The timespan between predictor and predicted outcome will also decide on the usability of the approach, since a predictor model will not make much sense if it just allows for a one-week projection.

To find the best candidate, I applied a method I already used in “Hunting the Tiger”, when investigating the correlation between mobility and infection rate [2]. I started with parallelized time series of outcome (test positive ICU patients) and predictors (recorded infections) and then shifted the two series against each other with one day increments, thus producing an increasing offset between predictor and outcome. For each step I calculated correlations between predictors and outcome, hoping that an optimum would reveal itself in terms of a clear maximum. Figure 1 provides a graphical representation of the results as curve plots for each predictor variable. Besides the total number of recorded infections and the number of recorded infections with confirmed start of symptoms I have also included the moving 7-day-average of the latter to eliminate the obvious weekly swings, that are not present in the outcome variable.

Luckily all three curves indeed show a clear maximum in the region of 30 days offset, which as a prediction interval offers some practical value. As suspected, the data without imputation clearly show higher correlations than the imputed data, and the averaged data give a slightly better result than the raw data. I therefore decided to proceed using the seven-day moving average as a predictor and considering only cases with confirmed start of symptoms. The maximum correlation was observed with a correlation coefficient of .94 at a 32-days offset, so the prediction interval was fixed to 32 days for subsequent calculations. I would like to add, that while I have worked on these analyses, I have updated the datasets several times which shifted the peak by one or two days back and forth occasionally. Still the optimum always remained in the region of 30 days between outcome and predictor.

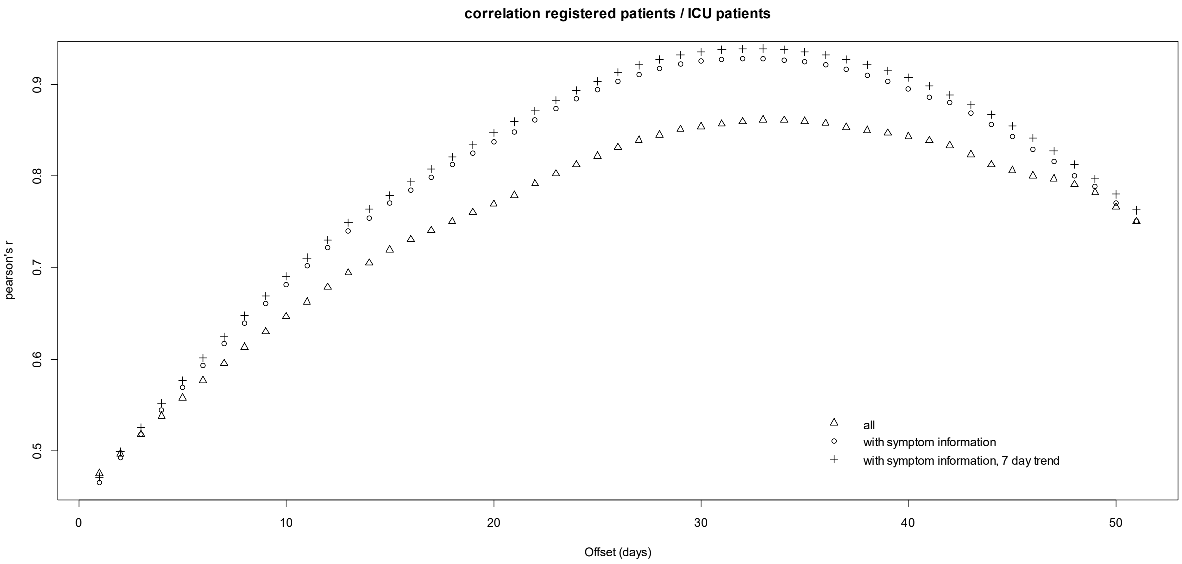


Figure 1: Correlation ICU patients and selected predictors with increasing offset

Model construction

Having identified suitable parameters and the most promising prediction interval the predictor model to be constructed was defined. A linear regression model was computed predicting the number of test positive ICU patients according to DIVI registry from the moving seven-day average of patients with known date of disease onset according to RKI surveillance data 32 days ago. The model yielded an adjusted R squared of .877 with a coefficient estimate of .58 and an intercept of 336.87.

Since the RKI dataset not only provides totals but also a breakdown of infections by age groups, I was curious to see if the model could be improved by using a breakdown by age groups as predictors instead of the total number. This would be a plausible assumption in view of the commonly accepted fact that the risk for a severe cause of disease grows with increasing age. For model construction I likewise used the seven-day moving average of patients with confirmed disease onset date only. The model summary is provided below:

```
Call:
lm(formula = ICU ~ age_1 + age_2 + age_3 + age_4 + age_5 + age_6)

Residuals:
    Min      1Q  Median      3Q     Max 
-490.67 -230.69   13.33  163.04 1004.89 

Coefficients:
             Estimate Std. Error t value Pr(>|t|)    
(Intercept) 387.79843   37.27451  10.404  < 2e-16 ***
age_1       -58.36291    8.26613  -7.060 2.06e-11 ***
age_2         1.78244    1.73506   1.027    0.305    
age_3         2.75074    0.42458   6.479 5.80e-10 ***
age_4        -0.40401    0.93297  -0.433    0.665    
age_5         3.80199    1.66088   2.289    0.023 *  
age_6         0.03688    0.75644   0.049    0.961    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 317.6 on 224 degrees of freedom
  (6 observations deleted due to missingness)
Multiple R-squared:  0.9385,    Adjusted R-squared:  0.9369 
F-statistic:   570 on 6 and 224 DF,  p-value: < 2.2e-16
```

The age groups 1 to 6 correspond to the categories as reported by the RKI, with age 1 = < 4 years, age 2 = 5 - 14 years, age 3 = 15 - 34 years, age 4 = 35 - 59 years, age 5 = 60 - 79 years, and age 6 = 80+ years. A subsequent ANOVA showed that the age groups 2 and 6 did not explain a significant amount of variance within the all-age-groups-model, so a simplified third model was calculated omitting these predictors. The reduced-age-groups-model yielded an adjusted R square of .9371 without much change to the coefficients as reported above.

Model validation

For all model construction steps I have described in the previous sections I used a dataset obtained on 12 December 2020 and restricted to the period from 20 March 2020 (start of the time series data made available by the DIVI registry) to 30 November 2020. The numbers show an excellent model fit to the data which was even improved by moving to the more complex approach with separated age groups. However, the model coefficients proposed by the age group models seem suspicious. Two age groups seem to have a moderating effect, especially age group 1 (children < 4 years) dominates the equation with a strong negative weight. However, there is no logical explanation why more children tested positive would lead to less patients on ICU.

My main objective was to see how well the DIVI numbers could be predicted using regression models, so my next step was using data before and after the construction data set to investigate the behavior of the models derived. Figure 2 compares real life data from the DIVI registry (solid line) to predicted values from all three models described in the previous section over the complete year 2020 (last updated 06 January 2021).

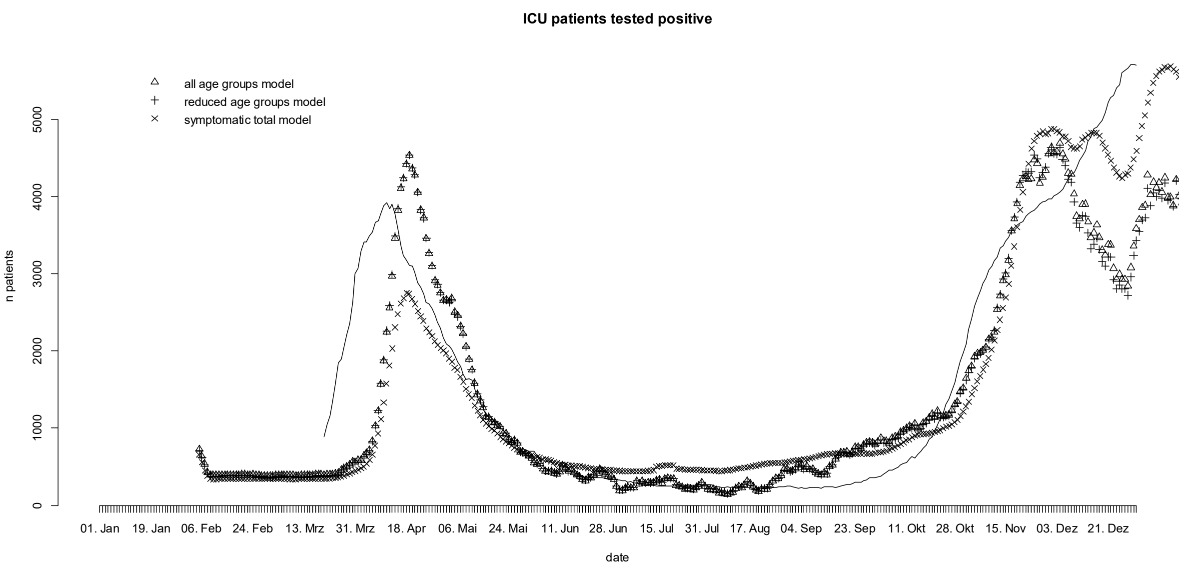


Figure 2: SARS COV 2 positives on ICU - real vs. predicted

The graph illustrates that both age-group-based models, which yield almost identical results, show a better match to the earlier phase of the pandemic, the first wave between March and May. However, they clearly fall behind the symptomatic-total-model in terms of predicting the number of ICU patients beyond the construction data set. The improved model fit achieved by separating the age groups came at the price of diminished predictive power and thus is in fact an over-fitting reducing the generalizability of the model. The total number of infections with confirmed disease onset proved to be the better predictor.

The question remains why the model would underestimate the situation in the beginning of the pandemic. Considering the continuous evolvement of test capacities over the year the probable answer is that the overall detection rate for symptomatic SARS COV 2 carriers was lower during the first wave than during the second wave of the pandemic. Every patient arriving at an ICU since establishment of the registry was tested and every test-positive patient was registered as a COVID 19 patient, which makes these data highly reliable. On the other hand, public surveillance data suffer from an unknown number of unreported cases and various changes in test strategy not considering representativity aspects. Consequently, a reversed predictor model from ICU patients back to patients with symptoms might also provide a better impression of the situation in spring. This approach is illustrated with Figure 3, where total numbers of patients with confirmed disease onset are estimated back from ICU cases (triangles). The estimates are compared to the actual numbers according to the RKI database (solid line).

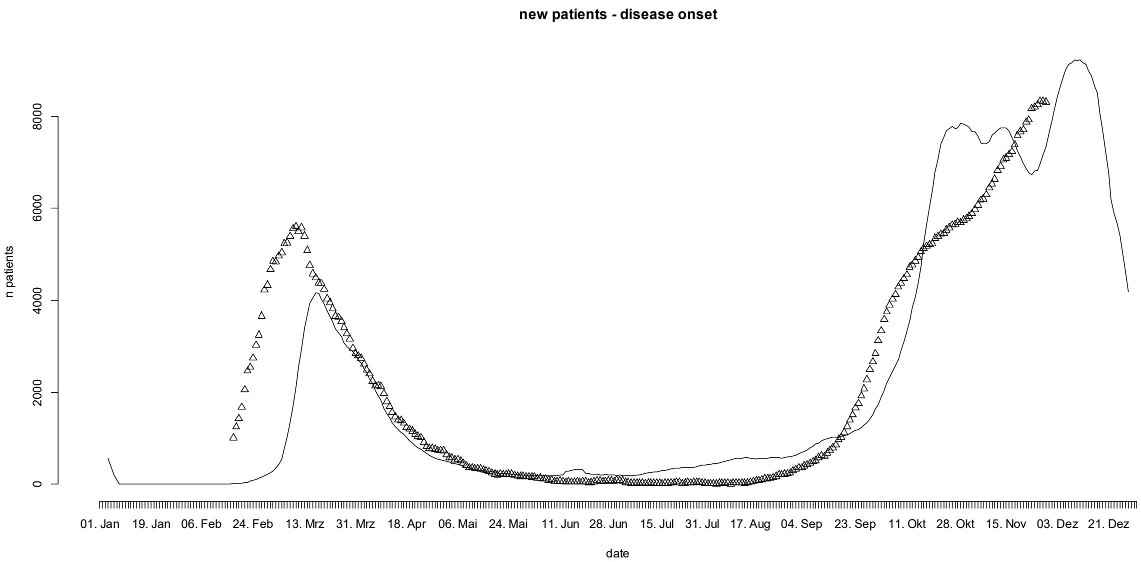
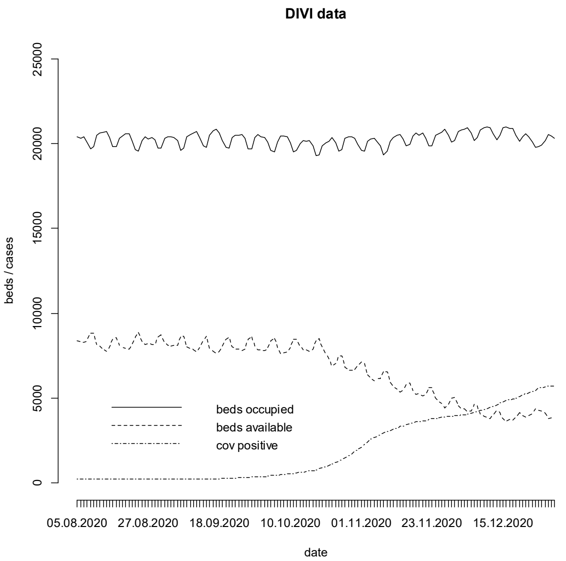


Figure 3: Patients with known disease onset per day - real vs. predicted

Interestingly the graph supports what I had stated as a hypothesis in “Hunting the Tiger”, in that the “true” wave of infections had already started earlier and reached its’ peak before the German public became aware and initiated systematic tracing and countermeasures [2]. Unfortunately, the DIVI data only allow for a limited look into the past, it would have been interesting to see how the curve slowly built up and when the pandemic effectively started in Germany. Anyway, I have computed the difference between reported and estimated numbers from 17 February 2020 (earliest available estimates) to the day before changing the national test policy (18 May 2020, compare <<referenz>>) and resulted in an estimated number of at least 96,480 symptomatic COVID 19 patients undetected during that period. As the graph shows the majority of those would have occurred between mid and end of February, weeks before any public awareness of something concerning going on.

Impact on ICU capacities

With the previous analyses I have demonstrated that it is indeed possible to establish a mathematical model relating public surveillance data and test-positive ICU patients counted by the DIVI registry, and that the model can be used to predict developments within a timeframe of approximately one month. However, understanding how these numbers impact available intensive care capacities remains a problem. The first, intuitive expectation would be that COVID 19 adds on top of the pre-existing hospitalization numbers since it is a new disease and other reasons for hospitalization continue to prevail. This would imply that each additional COVID patient on ICU occupies an additional bed while the number of free beds decreases by one. A glance at the charts presented on the registry homepage immediately shows that the connection is obviously not as simple as that. Until a change in the reporting requirements from 03 August 2020, neither the number of occupied ICU beds nor the number of free beds shows a visible reaction to the number of ICU patients tested positive at the same time [3]. After the date mentioned the number of free beds seems to show more of the expected behavior but the number of occupied beds still only shows a very minor increase. Figure 4 compares the three curves of interest after 03 August 2020, once for the numbers as reported and once with additional correction for “weekend effects”, i.e. using the seven-day moving average.



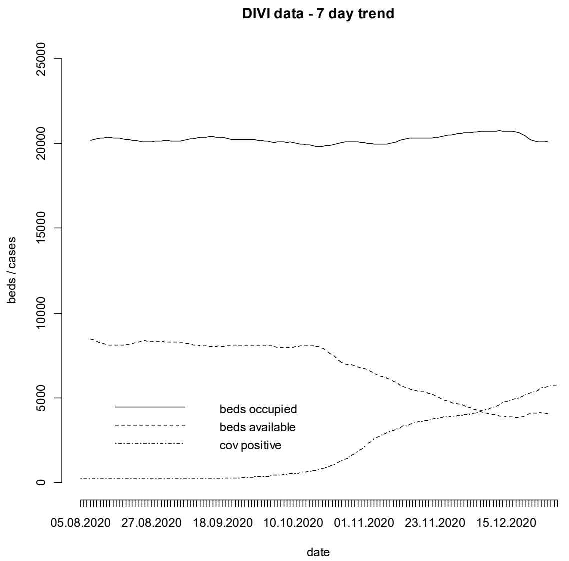


Figure 4: DIVI time series after AUG 03

For quantifying these observations, I calculated correlations between the three variables using the seven-day trend:

```
               occupied       free cov_positives
occupied      1.0000000 -0.6038367     0.5067826
free         -0.6038367  1.0000000    -0.9902834
cov_positives 0.5067826 -0.9902834     1.0000000
```

The Pearson coefficients confirm an almost ideal 1:1 correlation between COVID positives and free beds while the relation to the total number of occupied beds is only moderate. A regression model predicting the increase of total beds occupied from the number of test positives on ICU yields a coefficient of 0.063, meaning that it takes almost 16 additional test positives on ICU to occupy one additional bed there, although at the same time each test positive seems to take away almost exactly one bed from the total capacities reported. The preliminary resume is that although the total number of COVID 19 patients on ICU can be projected from public surveillance data to a certain degree, this number does not translate directly into occupation of ICU capacities. A more profound understanding of the putative inconsistencies in the DIVI data is required, which I am going to defer to the discussion section below.

Discussion

Predictability of COVID 19 cases on ICU

The main objective of this study was to investigate the relationship between data from the German DIVI registry on ICU capacities and infection surveillance data hosted by the RKI. A model predicting the number of test positive ICU cases from infection cases registered with confirmed disease onset about one month ago yielded the best compromise between high model fit (nearly 90% explained variance) and predictive power in the validation phase. However, even though the results prove that the number of patients with confirmed disease onset is a more robust predictor than the total number of infections, the predicted curve as presented in Figure 2 still moves away from the empirical curve in the periods before and after the construction dataset.

The deviation in the early phase is a clear and systematic underestimation. A plausible explanation for this observation could be that due to the limited test resources available in spring the rate of identified patients was lower than later during the year. At the other end of the scale, it looks like - once again - a change to the national test policy implemented on 11 November has brought some turbulence into the system which caused an artificial drop in numbers around that date [4]. However, the predicted maximum of 5,683 test positive ICU patients only deviates by .5% from the observed maximum of 5,713 patients. This result could probably be still improved if the model parameters are dynamically adapted, while I have remained with a static model derived from the construction dataset for validation purposes. Having such degree of security with a planning horizon of one month would in certainly justify the effort to use such models and keep the parameters up to date, which is not overly complex and can easily be automatized.

Estimated COVID 19 incidence in 2020

As stated before, the rate of existing COVID 19 patients registered during the early phase of the pandemic probably was considerably lower than later during the year, mainly due to lack of awareness and scarce test resources [1] [2]. I would therefore consider a reconstruction of infections during that period from ICU-data more valid than the actual public surveillance data and I have presented such reconstruction with Figure 3 above. I calculated a gap of nearly 100,000 symptomatic patients that had not been recognized appropriately. Furthermore, the expansion of test activities has increased the percentage of registered infections without confirmed disease onset to a level of more than 50%. Taking this as a benchmark, the total number of cases that could have been detected by the RKI under stable conditions would be in the region of 2 million. In addition, there is an unknown number of persons in touch with the virus, yet without being tested and registered. Assuming an under-recognition factor 5 to 10 as indicated by official sources would mean that 12 to 24 percent of the German population already have contracted the virus throughout the year. With 33,071 COVID 19 related deaths registered, the estimated infection fatality rate in 2020 would be nationwide in the region of .08% to .16% [3].

It is striking that the estimated peak of infections during the first wave is considerably earlier than the peak observable in officially registered infections. This observation supports the hypothesis stated in "Hunting the Tiger" that the measures taken by the German government did not show a significant impact on infection rates but only met with an already declining curve, probably best explained by seasonal effects [2]. Likewise, there does not seem to be an impressive effect of the lockdown measures implemented in November to bring down the infection rates. What we observe on the contrary is a further increase in December, which might owe to official recommendations to have a test before seeing the grandparents on Christmas. These might again have pushed the number of infections detected, which would fit the additional observation that we saw an even increasing percentage of test positives without clinical information despite a more restrictive national test policy.

My personal impression is that despite all good intentions the postulated governmental goal to bring infection rates down to 50 per 100,000 inhabitants will remain completely out of reach until March next year, when the seasonal decline sets in. I am not sure if it makes sense to keep the measures in place anyway, which is primarily done with the argument that the numbers would explode otherwise. To me it does not look like we are achieving much with that, the data indicate a fairly normal seasonal development as seen for other respiratory diseases, and I still wonder if a concentration of resources on protecting the most vulnerable groups and strengthening the capacities of our health system would not be more efficient than what we do today.

Impact of high rates of SARS COV 2 infections on ICU capacities

The number one question remains if the German health system will be able to deal with the challenge or not. To this respect the DIVI registry seems to convey contradictory messages, depending if you rather look at the number of ICU beds occupied or at the free capacities reported. The discrepancy has been observed by others of course, and to date the organizers of the registry seem to struggle with the correct interpretation. They even had to defend themselves against allegations to deliberately reduce intensive care capacities, which is clearly nonsense. However, the explanations provided like staff getting quarantined due to infections or increased efforts to take care of the COVID patients are still not completely convincing to explain why each new COVID patient seems to take exactly one free bed away, while it takes sixteen of them to occupy an additional one. Typically, the underlying reason for such observations is in the way the questions were asked and it seems to be the same story here.

I will start with the easier one, the number of beds occupied. Taking the perspective of the reporter this should be easy to answer, either he or she knows it from the top of the head or will take a quick glance at a chart or list somewhere on the desk. So, given that the number is reliable and based on hard facts, why does not every COVID patient occupy an additional bed although the disease is a novel one? A plausible answer would be that the high-risk group for a severe course of COVID 19 is more or less the same as for most other diseases or incidents that might bring patients to an intensive care unit. This fits well to observations like the strange decline in admissions for cardiovascular diseases, which was attributed to people being scared to seek medical assistance as they fear nosocomial infections. Still, a heart attack or stroke is not a walk in the park, and I also do not believe that the measures taken to fight COVID 19 also protect from such diseases – rather the contrary. So, in my opinion the patients seen with COVID 19 on intensive care units today are in large parts the same that would have been seen there in absence of SARS COV 2, just for other reasons. Even though there are those exceptional fatalities among twenty-year-old athletes that are highlighted by the media, the typical COVID 19 death still is an elderly patient in fragile status with multiple comorbidities which makes it difficult to tell what the ultimate cause of death was. Those we have regrettably lost to COVID 19 might be those we would probably have lost to other causes this year without the virus, even though this is hard to accept for those left behind and each death still is a tragedy for family and friends. But as long as our health system maintains sufficient reserves to keep up a regular level of medical care for all indications – which we were able to do up to now – we will be able to avoid a high level of excess mortality as it was seen in countries, where the health system nearly or completely collapsed.

This brings me to the last and most important point, the data on free capacities. The way free beds are recorded via the DIVI registry was fundamentally changed beginning of August 2020 with the intention to allow for an easier and at the same time more precise assessment of available ICU capacities [4]. Before that date, the total available and occupied beds should be reported, and free capacities were calculated as the difference between number available and occupied. With the modification the reporter is now asked to directly estimate free capacities and the total number of available beds is calculated as the sum of (estimated) available and occupied beds. Moreover, the reporter is explicitly instructed to not only consider room and equipment but also staff available to operate the ICU bed.

Due to these changes the reporter now has a better chance to consider all those additional demands each COVID 19 patient brings to the hospital compared to other indications, such as increased safety measures, high intensity of care, unpredictable course of disease, risk of health staff getting infected, physical and mental stress for the caregivers. If these factors really add up to the simple formula “one COVID patient takes one free bed” could still be a question, yet as a rule of thumb it might work well enough and for sure the new approach reflects the true situation in German hospitals better than the previous one. I would not doubt for a minute that the emergency reported by more and more hospitals is real and that we are putting our health system to an unprecedented stress test. However, since this situation does not seem to be driven by an overall increase of patients but more by the special precautions and demands required for the care of COVID 19 patients, I wonder if a temporary re-organization of care could not be a way towards a more efficient management of the situation.

Dedicated treatment facilities as a potential stress relief?

While we are happily embracing large parts of the medieval arsenal for fighting the plague, such as quarantining or wearing masks, the idea of plague houses does not seem to have been seriously considered yet, at least I did not read about it. However, I think the additional burden caused by SARS COV 2 positive patients today is to a large part driven by the logistic and organizational efforts required to prevent nosocomial infections, while test positive and test negative patients are treated within the same facility. An alternative approach would be to concentrate all COVID 19 patients within public funded dedicated facilities, thus adopting the principal idea of “plague houses”. These could be either existing large general care facilities temporarily blocked, or emergency hospitals established during the first wave in July activated for that purpose. Compared to the current approach of scattering care for COVID 19 patients over all hospitals within a region this model could bring several advantages:

- Resources could be scaled up and down according to expected patient volume without consideration for competing indications
- Protective measures like controlled access, quarantining, and testing could be implemented more easily for dedicated treatment sites since the patients would not need to be separated from each other within the facility
- Completely separating SARS COV 2 positive patients from others immediately upon detection might lower the overall risk of nosocomial infections for patients and staff
- While other hospitals would be relieved rotational work models could be established for healthcare staff, so they might e. g. not have to work longer than one month in a row under the demanding conditions of a dedicated COVID 19 hospital
- Dedicated treatment sites would soon acquire a high level of expertise, would quickly adopt emerging new treatment strategies, and could contribute to focused research for further treatment approaches

I could imagine that the idea of separating the patients rather than lack of capacities was the main driver behind the spectacular construction of emergency hospitals within ten days in Wuhan, China at the very beginning of the pandemic. It might even have been one of the decisive factors that helped the country keeping the virus under control. For Germany, like for other western countries, the main problem would probably be a fair compensation model to guarantee an economic balance between hospitals that would dedicate to COVID 19 treatment to serve public interest, and hospitals relieved from that burden and able to perform financially more attractive elective interventions. It might still be worth looking into that, if only to be better prepared for the next pandemic to cross our way.

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