Feature Global Health

# Covid-19: Why Germany's case fatality rate seems so low

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# Re: Covid-19: Why Germany's case fatality rate seems so low

Dear Editor,

I am German and lived in Germany for 29 years, but have spent the last 23 in the NHS. I have been reflecting a lot on this. There are many plausible explanations and you see it often in German patients coming to England: They expect a scan and a test for everything. Diagnostics is huge in Germany and there is a huge diagnostics industry (and huge manufacturing, too). Reason: Financial reward to practices is high for diagnostics, but low for consultations. Many other reasons could be contributing, two particularly spring to mind: Society controls each other, Germans are happy to challenge their neighbours for not toeing the line. Not a very polite habit, but very effective. Secondly, hospital wards are not open, they are sub-devided in 1-2 bedded rooms with hand sanitisers outside each and everyone (already 30 years ago, when I started working there). However, to finish this little reflection, I think none of this matters. Personally, I believe there is a little country in Europe that may provide the answer: Portugal. Portugal, besides Germany and Austria is the only country in Europe with comparably low death rates and certainly much much lower than Spain. Portugal locked down early. I have spoken to my Portuguese friend, a stroke specialist in Faro, Algarve. Their equipment status is much worse than ours, PPE is often little or not available. The only face masks he has is the ones that his wife got in a pharmacy early in January, before everything ran out. However, all this seems relatively un-important compared with the early lock down. Finally, as our medical chief officer rightly comments, it is much too early to draw conclusions. And while we count every Coronavirus death we forget all the other deaths we may be causing or missing by focussing solely on COVID-19. Imagine, if we soon enter a deep recession with all the consequences on tax receipts and NHS funding we may see many other conditions we are no longer able to fund treatment for that may be indirectly caused by the lockdown. So, it is very early days in a time that could have consequences for many years to come and influence mortality rates in the future to a much bigger extent than ever anticipated. And the Germans will feel the consequences of a deep global recession deeply, because nobody will buy a new luxury car if they have not got the cash.

#### Competing interests: No competing interests

**19 April 2020** Martin Kittel General Practitioner and Locality Lead for East Berks CCG 27 Meadow Way, Dorney Reach, Maidenhead, SL6 0DR

#### **Re: Covid-19: Why Germany's case fatality rate seems so low: Is nutrition another possibility**

**Dear Editor** 

We read with interest the Global Health feature "Covid-19: Why German case fatality seems so low" as compared to most of the other European countries (1). The author proposed several explanations including an early and large testing of the population. Most current debates focus on the differences among countries, but little attention has been given to regional differences.

We used Worldometer to assess death rates as this tool provides detailed information on deaths at the regional level

(https://www.worldometers.info/coronavirus/country/germany/). The current death rate per million people in Europe shows different trends. Germany has a low death rate (48 deaths, April 17, 2020), but Austria (46), the Czech Republic (18), Poland (8), Slovakia (1), the Baltic States (from 2 to 27) and Finland (14) have similar or lower rates. On the other hand, Belgium (479), France (275), Italy (367), Spain (423) and the UK (202) have far higher rates. The low-rate countries have used different guarantine and/or confinement methods and none have performed as many early tests as Germany. Thus, although the German approach is very important, other factors may also be significant. Large differences exist when assessing death rates within a country. In Germany, Bavaria started the earliest tests but was and still is the most affected region. Death rates per million range from 8 in Mecklenburg-Vorpommern to 87 in Bavaria. In Switzerland, the French and Italian speaking cantons have a far higher death rate than the German-speaking ones (Office fédéral de la santé publique, Switzerland, https://www.bag.admin.ch/bag/fr/home.html). In high-rate countries such as Spain, large variations also exist within the country, but the numbers range from 50 in Ceuta to over 1,000 in Madrid.

Most diseases exhibit large geographical variations which frequently remain unexplained despite abundant research (2). Covid-19 will not be an exception. Though the more relevant factors are likely to be seasonal variations, the immunity, crossimmunity and the intensity and timing of measures (3), other factors like environment or nutrition should not be overlooked.

Germany, Austria, the Czech Republic, Poland, Slovakia, the Baltic States and Germanspeaking Swiss cantons exhibit lower Covid-19 mortality rates than France, Italy, Spain, and the French and Italian speaking Swiss cantons. Obesity, a risk factor of mortality in Covid-19, suggests the importance of nutrition. Diet differs considerably between low or high mortality countries. Nutrition may therefore play a role in the immune defense against Covid-19 and may explain some differences seen in Covid-19 across Europe. A Mediterranean diet more common in Italy, France and Spain does not appear to be protective. Foods with potent antioxidant or anti angiotensin-converting enzyme activity - like uncooked or fermented cabbage (4-6) - are largely consumed in countries like the low death rate European countries, Korea and Taiwan, and might be considered in the low prevalence of deaths. Understanding the within and between country differences in Covid-19 will be of paramount importance in understanding Covid-19 risk and protective factors, and will eventually help to control the epidemics.

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None of the authors have any conflict of interest to declare

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**18 April 2020** Jean J Bousquet MD W Czarlewski, H Blain, T Zuberbier, JM Anto Charité Hospital, Berlin 373 avenue Occitanie

## Re: Covid-19: Why Germany's case fatality rate seems so low

Dear Editor

A rate comprises two numbers: a "numerator" - number of incidents; divided by a background number, the denominator. For them to be meaningful, you have to understand what both numbers mean.

When it comes to Covid-19 fatality rates, both numerator and denominator are far more slippery than you might imagine.

Take the deaths. The UK government has been reporting deaths that occur in hospital, in people who have tested positive for Covid-19. Died somewhere else, not in hospital? Not counted. Died in hospital but not tested, or a false negative? Not counted. Died in hospital of something else, but had had a positive Covid-19 test (false positive or incidental finding) - not really a Covid-19 death, but counted as one, anyway.

We've also started to receive data on death certification. But anybody who works in epidemiology knows how unreliable death certificates are - especially if (as has been reported) there is pressure on doctors, from some coroners not to include Covid-19 without a test. When health protections teams deal with an outbreak of cases in a care home, for example, they want a few tests done, to confirm that the virus is circulating in the home. But once that's been confirmed, there really isn't any point in doing any further testing - if other residents have symptoms suggestive of Covid-19, you should assume that's what they have. With a sensitivity rate of only 70-80%, who would believe a negative test result? The negative predictive value isn't good enough to be confident. But if the coroner insists that if they didn't test positive you shouldn't put Covid-19 on the medical certificate of the cause of death (MCCD), it's easier just to put "bronchopneumonia" or similar... So those cases won't be counted either.

All of which means that the number of Covid-19 deaths is far from clear. It doesn't mean that the data are useless - but you have to understand their limitations.

So if getting the numerator - the number of Covid-19 deaths - clear isn't as straightforward as you'd think, how about the denominator?

The denominator used is, often, the number of cases. But how do you know how many cases you've got? In the UK, cases are people who are admitted to hospital, who test positive for Covid-19. We've already established that the test isn't perfect. The RT-PCR tests are highly specific for SAR-CoV-2 RNA (although they don't distinguish between viable, potentially infectous virus, and "dead", non-viable fragments of RNA). But many patients don't have virus particles present on the swabs done - and getting a good nasopharyngeal swab is not straightforward. So the sensitivity rate is estimated at 70-80% at best.[1] And remember - in studies in China and elsewhere, a considerable number of people had very minor illness or were asymptomatic. One of the first UK cases demonstrates this - he was unwell, but not so unwell as to curtail his normal activities, including a few days skiing. Which is partly how he came to infect so many other people.[2]

So if you only count people who are sick enough to be admitted to hospital, and who get offered the test, you will miss a lot of people. They will have had the infection, perhaps passed it on to others, but they won't count as cases. They'll also be a lot sicker - ill enough to be admitted - and therefore most likely to die. Which explains why early estimates of the case fatality rate were so high.

So, when you compare the UK's and Germany's "case fatality rate" - are you comparing like with like?

Just imagine, for a moment, that the same percentage of the population in Germany and England is infected; and the same proportion die; and that both systems identify deaths in a similar way, so their numerators will be similar. But if Germany tests twice as many people the denominator will be twice as large, and the rate will be half the UK rate. But what matters is that the same proportion of the population got infected and the same proportion of those infected died.

What you really want to know is not the case fatality rate, where caseness is such a slippery concept, but the infection fatality rate - which can only ever be estimated.

If you want to compare populations you need to compare true numbers. You could, for example, compare the number of deaths with the number of people in the population - the Covid-19 fatality rate (not the case-fatality rate). You would also want to take differences in demographics into account. Death rates increase significantly at older ages, for example; so if you were to compare, say, Italy (with a relatively elderly population), and Syria (with a very young population), you'd expect a much higher

death rate in Italy, simply because of the demographics. It wouldn't indicate that the disease, per se, were more serious in Italy; or that medical treatment in Syria is better. (These things could be true, of course; but it could just be the demographics affecting the fatality rates.) You have to use methods such as age standardisation before such comparisons are meaningful.

What matters is that you know what's going on in the population, and you can take the appropriate steps to control it. For now, the main question is whether the so-called "social distancing" measures and shielding of the vulnerable are working. If they are, the effective reproduction number (Re) will drop. Once it is below one - so that each case on average infects fewer than one other person - the incidence will fall; and then the case numbers will fall... Death rates are a clumsy proxy for incidence, because deaths generally occur weeks after infection, so there will be a considerable lag.

Peter English.

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Competing interests: No competing interests

**17 April 2020** Peter M B English Public Health Physician N/A - this is a personal response Surrey, UK @petermbenglish

#### Re: Germany does not have a lower COVID-19 death rate

Dear Editor

I am not sure how sensitive disease is to semantic construction but if Italy is in Western Europe and Gemany in Middle Europe [1] we still find that they inhabit roughly the same latitudes, with Italy being slightly further east (both at its most westerly and most easterly points). Moreover, Germany still has a lower death rate whatever its location. I think this is perhaps not a very helpful speculation.

[1] Dominique Valeyre, Jean-Philippe Derenne, 'Germany does not have a lower COVID-19 death rate', 16 April 2020, <u>https://www.bmj.com/content/369/bmj.m1395/rr-9</u>

**Competing interests:** AgeofAutism.com, an on-line daily journal, concerns itself with the potential environmental sources for the proliferation of autism, neurological impairment, immune dysfunction and chronic disease. I receive no payment as UK Editor

**17 April 2020** John Stone UK Editor AgeofAutism.com London N22 @JohnStone32

#### Germany does not have a lower COVID-19 death rate

Dear Editor,

Germany has a number of COVID-19 cases in the same order as France, Italy and Spain, respectively 125 298, 98076, 159 516 and 169 496 on April 14, 2020. In contrast, the number of deaths is low as compared to the other three countries: 2669 versus 14 967, 20 465 and 17 489. Ned Stafford in this journal (1) explained this difference by the German nation's early and high level of testing, including that of milder cases in younger people and an earlier intervention by German authorities: closing schools and retail businesses, banning gatherings of people and promoting contact restrictions. These measures were well adapted to the situation but they cannot explain the amplitude of the differences in lethality between countries.

Indeed, it is a striking feature of day by day observation of the epidemics in the different countries of Europe that geography is to be considered. Specifically, western countries appear to face a more deadly situation. In order to verify this fact, we sliced Europe into 3 zones: western, middle and eastern.

Western Europe includes the British Islands (Ireland and United Kingdom), Benelux (Belgium, Netherlands, Luxembourg) and the Latin countries (France, Italy, Spain and Portugal), plus small countries or entities (Isle of Man, British Channel Islands, Andorra, Monaco, San Marin and Vatican City). The overall population is approximatively 280 millions. COVID-19 killed 72 021 people in this area.

Middle Europe includes Scandinavia (Norway, Denmark and Sweden), Baltic countries (Estonia, Latvia, Lithuania) and Finland, central Europe (Poland, Slovakia, Czech Republic, Austria, Hungary and Germany) and the Balkans (Slovania, Croatia, Kosovo, Bosnia and Herzegovina, North Macedonia, Serbia, Montenegro, Albania, Greece, Bulgaria and Romania) with a population of 240 millions. COVID-19 killed 5997.

Eastern Europe includes Bilarus, Ukraine, Russia, Moldavia, Azerbaidjan, Armenia and Georgia with a population of 217 millions. The death toll was 397.

The differences between these zones are too important to be due to some flaw. A twelve fold number of deaths between countries situated west and east of the Alps and of the Rhine cannot be fortuitous.

Germany, with a population of 80 millions, has a number of deaths similar to the other 160 millions of the middle Europe area (3038 versus 2859), meaning that the casualty rate was twice that of the average of the other countries. Since the medical and political status of the other countries is not homogeneous, the death toll difference cannot be explained only by a better or worse management of the situation.

(1) Stafford N. Covid-19: Why Germany's case fatality rate seems so low. BMJ. 2020 Apr 7;369:m1395. doi: 10.1136/bmj.m1395. No abstract available.

#### Competing interests: No competing interests

16 April 2020

Dominique Valeyre MD PhD Jean-Philippe DERENNE AP-HP, hôpital Avicenne; INSERM UMR 1272, Université Sorbonne Paris Nord 125 rue de Stalingrad, Bobigny, FRANCE

### Re: Covid-19: Why Germany's case fatality rate seems so low

Dear Editor

If the early statistical indicators for mortality rates in Germany are borne out (following due analysis and correction for differences in reporting methodology) there is one glaring difference in how the German population habitually responds to viral symptoms.

Here in the UK, Paracetamol (Acetominophen) is widely available across the counter, even in supermarkets, and in Germany it is a prescription-only medicine (PoM).

Even incidental paracetamol usage is widespread in the UK and questions concerning

potentially negative effects of antipyretic drugs remain largely unanswered, in terms of suitable prospective clinical studies conducted during viral pandemics.

The quote below, from the Journal of Thermal Biology, alludes to the possibility of a dysregulated cytokine cascade following antipyretic treatment. This phenomenon would be in keeping with the clinical presentation in some rapidly deteriorating cases. For most cases, individual susceptibility is undoubtedly multifactorial. However, in the absence of other predisposing illnesses, we must surely record what notional self-prescribed medication has been used in those patients showing high clinical susceptibility.

If it is considered possible that negative systemic effects from paracetamol arise, even within a single time-critical phase of the natural disease process, it follows that even modest self-prescribing must be clearly recorded for every admission, so that we are ultimately able to formulate a lucid research question and progress to a well-designed clinical study.

For the time being the question is whether suppression of fever may impact on:

'the temporal modulation of the stimulus induced generation of TNF-α, IL-1β and IL 6, early during the innate immune response, thereby obviating the risk of the potential harmful effects that could result from their dysregulated co-expression.' 'Fever: pathological or physiological, injurous or beneficial?' Journal of thermal biology Vol. 28, Issue 1, January 2003, Pages 1-13 <u>https://doi.org/10.1016/S0306-4565(02)00034-7</u>

Until such time as differences in mortality rates between different countries is explained purely by differences in reporting pathways and data-handling, we should consider that systemic differences in the treatment choices immediately available to patients may play a role in recovery times, rates of hospitalisation and fatality rates.

\*

#### Competing interests: No competing interests

**12 April 2020** Russell S. Malcolm Speciallty Doctor RLHIM/UCLH 60 Great Ormond St, London WC1N 3HR

#### Re: Covid-19: Why Germany's case fatality rate seems so



**Dear Editor** 

I can understand why Germany's case fatality rate is lower due to increased testing which detects more cases. But I have not yet seen a plausible explanation of why the absolute number of deaths is so much lower in Germany than in other countries. Perhaps your readers can shed some light in this?

Competing interests: No competing interests

**12 April 2020** John K Roberts Commercial Director Greenmeadow

# Re: Covid-19: Why Germany's case fatality rate seems so low

Dear Editor,

We read with interest "Covid-19: Why Germany's case fatality rate seems so low" [1] but we do not agree with the fact that the low Case fatality Rate (CFR) in Germany is partly due to the nation's early and high level of testing among a wide sample of the German population. This is not exactly related to testing as the case fatality rate is defined as the number of deaths in persons who tested positive for COVID-19 divided by number of COVID-19 cases.

If one compares, Italy and Germany, both countries have nearly similar testing (nearly 15000/million population) capacity. But case fatality as of now is 2.2 in Germany (statistics showed 2736 deaths from covid-19 had been recorded in Germany from 122, 171 confirmed cases) and 12.8 in Italy (statistics of 18 500 deaths from 147, 577 confirmed cases). It is true that fatality rate decreases as this ratio widens.

Other situations modify the CFR as below:

1. Rapid rate of spread of COVID-19 as seen in current outbreaks, and infection of a very large fraction of the population at a single point in time, overwhelming healthcare resources and also resulting in a decrease in quality of care and higher CFR.

2. The larger the number of quality ICU beds the better the survival rate of the patients admitted to a critical care unit. For example, Germany has the highest number ICU

beds/ per lakh population among all European Countries [3]. Health care capacity and capability factors, including the availability of healthcare workers, resources, facilities, and preparedness, also affect outcomes of CFR.

3. Asymptomatic people and people with mild disease usually remain undetected for COVID-19 and are left out of the denominator, leading to underestimation of the value in the denominator, which leads to overestimation of the CFR. Therefore, asymptomatic patients are not captured by screening.

4. Lack of availability of diagnostic reagents early in the outbreak, variations in surveillance intensity reservoir spill over events, stochasticity in the initial phase of the outbreak alter the denominator, but mortalities usually increase due to various reasons like lack of preparedness for unknown disease and management.

5. Substantial numbers of infected persons in the move/travel population compared with the total population leads to substantial uncertainties in calculation and lower number of observations and diagnosis.

6. Active surveillance, quarantine, and especially strong social distancing efforts will decrease the transmission and ultimately affect the CFR. Proactive contact tracing and containment might not be employed in a desired manner, resulting in a smaller denominator and inflating CFR.

7. Number of deaths relative to the number of confirmed cases of infection is not a true representative of the actual death rate as other factors like comorbidly and age, etc, are also contributory factors for deaths. For example, the overall older age distribution in Italy relative to that in China may explain, in part, the possible higher average case-fatality rate in Italy. The presence of these comorbidities might have increased the risk of mortality independent of COVID-19 infection.

8. Estimates of CFR are likely to increase if a longer delay between onset of illness and death is considered.

9. Number of mutations during the pandemics may also decrease the virulence and alter the fatality and transmission rate. As the predominant strains may vary from countries to country.

10. Virulence: study based on structural analysis of the virus particles suggests SARS-CoV-2 has a much higher affinity for the receptor needed for cell entry than the 2003 SARS virus [2], providing a molecular basis for the high infectiousness of SARS-CoV-2.

Lastly, we must understand that the outbreak is just over 3 months old. There is a great

need of continued surveillance, with transparent and accurate reporting of patient characteristics and management protocols for better understanding the global epidemiology of COVID-19.

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Competing interests: No competing interests

#### 11 April 2020

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## Re: Covid-19: Why Germany's case fatality rate seems so low

Dear Editor

Mass testing for SARS-CoV-2 has shown, time and again, that it initially gives a falsely low case fatality rate (diluting effect). However, this may give a false sense of security or be calm before the storm, because as the number of confirmed cases pile up, during the course more and more patients are admitted to hospitals. A building up of critically sick patients with COVID-19 in ICUs ultimately starts showing up as an increased fatality rate starting from two weeks up to many months later on. As of today (11 April 2020) is 2.07% (1), with critical cases case (2).

Russia and Turkey are following the example of Germany by mass testing for SARS-CoV-2, and they are now showing more critically sick patients with a dynamically increasing case fatality rate of 0.75% and 2.12% respectively (1-2).

- 1. https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates/
- 2. https://www.worldometers.info/coronavirus/

#### Competing interests: No competing interests

**11 April 2020** Muhammad Yousuf Physician Fouad Yousuf PO Box 22490 MC 1443 Division of Internal Medicine, Department of Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia.

# Re: Covid-19: Why Germany's case fatality rate seems so low

Dear Editor,

The triumvirate at daily UK government COVID-19 press conferences struggles to explain the low case fatality rate in Germany (compared to other European countries). It is too early for definite answers, but this important article summarises the most plausible and frequently discussed hypotheses: (1) The high rate of community testing in decentralised PCR laboratories all around Germany, (2) the relatively low age and fitness of bank holiday weekend skiers that returned infected from the Italian and Tyrolian alps and (3) the relative early lockdown compared to other European countries. [1]

There are other obvious explanations that should have been mentioned in this article: (4) The high number of ICU beds in Germany (the highest number per population of all EU countries with far more spare capacity than in the UK). [2] (5) Many ICUs for treatment of patients with infectious diseases in Germany have negative pressure rooms; this will decrease the number of hospital infections (among staff and other patients). [3]

Personally, I would also bet on (6) the relative high level of personal hygiene and cleanliness in Germany [4], as well as (7) home remedies like eucalyptus oil inhalations, which are recommended by German guidelines for the treatment of respiratory tract infections [5] and widely used in clinical practice. Most German families have a hot water steam inhaler in their cupboard. If mild cases of COVID-19 are treated more efficiently at home, this may reduce the number of hospital admission (and fatality).

My British wife, who is an experienced general adult and mental health nurse, finds it curious, when I treat myself with the steam inhaler that I inherited from my late mother.

We both had the pre COVID-19 flu in October 2019 that came along with fever and a dry cough. I had my inhalations and recovered within a few days, whereas my sceptical wife was coughing for 3 weeks (we are both non-smokers). This is an anecdotal observation and there is no research about eucalyptus oil inhalations and COVID-19.

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5 Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (2019) S2k-Leitlinie der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin zur Diagnostik und Therapie von erwachsenen Patienten mit Husten [free download at: <u>www.awmf.org</u>]

#### Competing interests: No competing interests

#### 10 April 2020

Ulrich Müller-Sedgwick Consultant Psychiatrist London & Cambridge (UK)

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