Nucleic acid (PCR) and antibody (IgG) tests: the course of SARS-CoV-2 infections in the German population unveiled

Michael Günther[a,b], Robert Rockenfeller[c], Harald Walach[d,e]

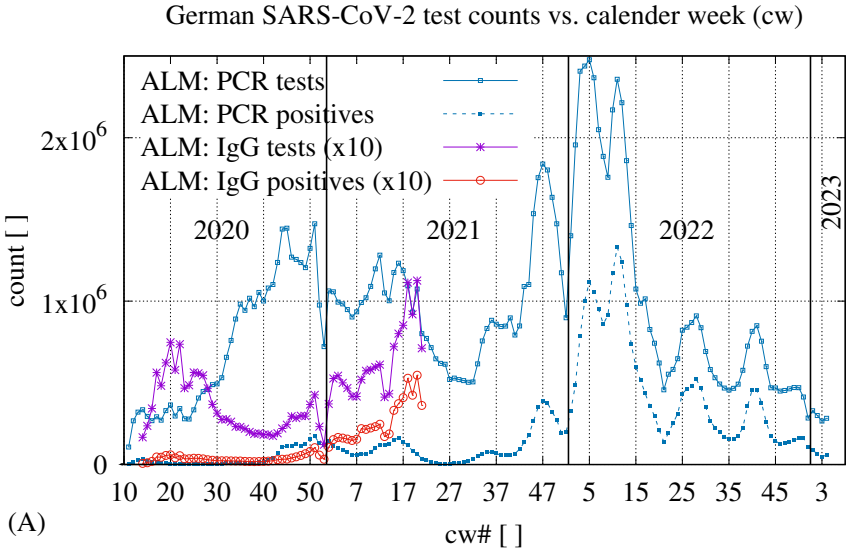
[a] *Computational Biophysics and Biorobotics, Institute for Modelling and Simulation of Biomechanical Systems, Universität Stuttgart, Nobelstraße 15, 70569 Stuttgart, Germany*
[b] *Friedrich–Schiller–Universität, 07737 Jena, Germany*
[c] *Mathematisches Institut, Universität Koblenz Universitätsstraße 1, 56070 Koblenz, Germany*
[d] *Change Health Science Institute, 4053 Basel, Switzerland*
[e] *Next Society Institute, Kazimieras Simonavicius University, Vilnius, Lithuania*

Abstract

In early 2020, the World Health Organization (WHO) endorsed (real-time quantitative, reverse transcription) polymeric chain reaction (PCR) test assays as the world-wide gold standard to check individuals for being 'infected' by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In Germany, the consortium of authority-accredited laboratories (ALM) that covered about 90% of all PCR tests, likewise conducted serological mass tests for IgG antibodies, at least until late May, 2021. We analysed the time courses of PCR and IgG tests in terms of their respective weekly positive fractions. We related them to each other on the grounds of the basic idea that a SARS-CoV-2 infection, as assumed to be indicated by a positive PCR test, should evidently be followed not later than two weeks after infection by the detection of IgG antibodies in the blood. We found that the time course of the IgG-positive fraction as measured by ALM in their labs can be well reproduced by the cumulative sum of the likewise ALM-measured PCR-positive fraction, until two weeks before the IgG value in question, only requiring a proportionality factor of 0.135. The straight-forward conclusion is that only 13.5% of those who where tested PCR-positive actually got infected by SARS-CoV-2. In a second analysis, we took a multiply confirmed value from the literature, namely, the approximative, empirical factor of 10 (in Germany) between one positive PCR test and the number of actually infected persons, to also estimate from solely PCR-positive numbers the fraction of infected in the whole German population. The time course of this fraction of infected runs always a few percent below the ALM-measured IgG-positive fraction. Both courses align well at the end of 2021. At the turn into 2022, the Robert-Koch-Institut (RKI) reported the IgG-positive fraction to have reached 92%, which is almost perfectly matched by the corresponding (extrapolated) ALM value (90%), and close to our conservative estimation (85%) of the infected fraction. Methodologically, we propose the PCR-positive fraction to not only constitute an adequate but a superior replacement for the hitherto used term 'incidence', which has commonly been reported by the RKI as the absolute number of PCR positives normalised to some (arbitrarily chosen) population size. Data-content-wise and remarkably enough, no effect whatsoever of the SARS-CoV-2 mass vaccination campaign (having started on 27/12/2020) can be distinguished in the time courses of the positive fractions, whether measured or estimated.

Key words: infectious disease; epidemic dynamics; CoViD-19; serology

Email address: s7gumi@uni-jena.de (Michael Günther)



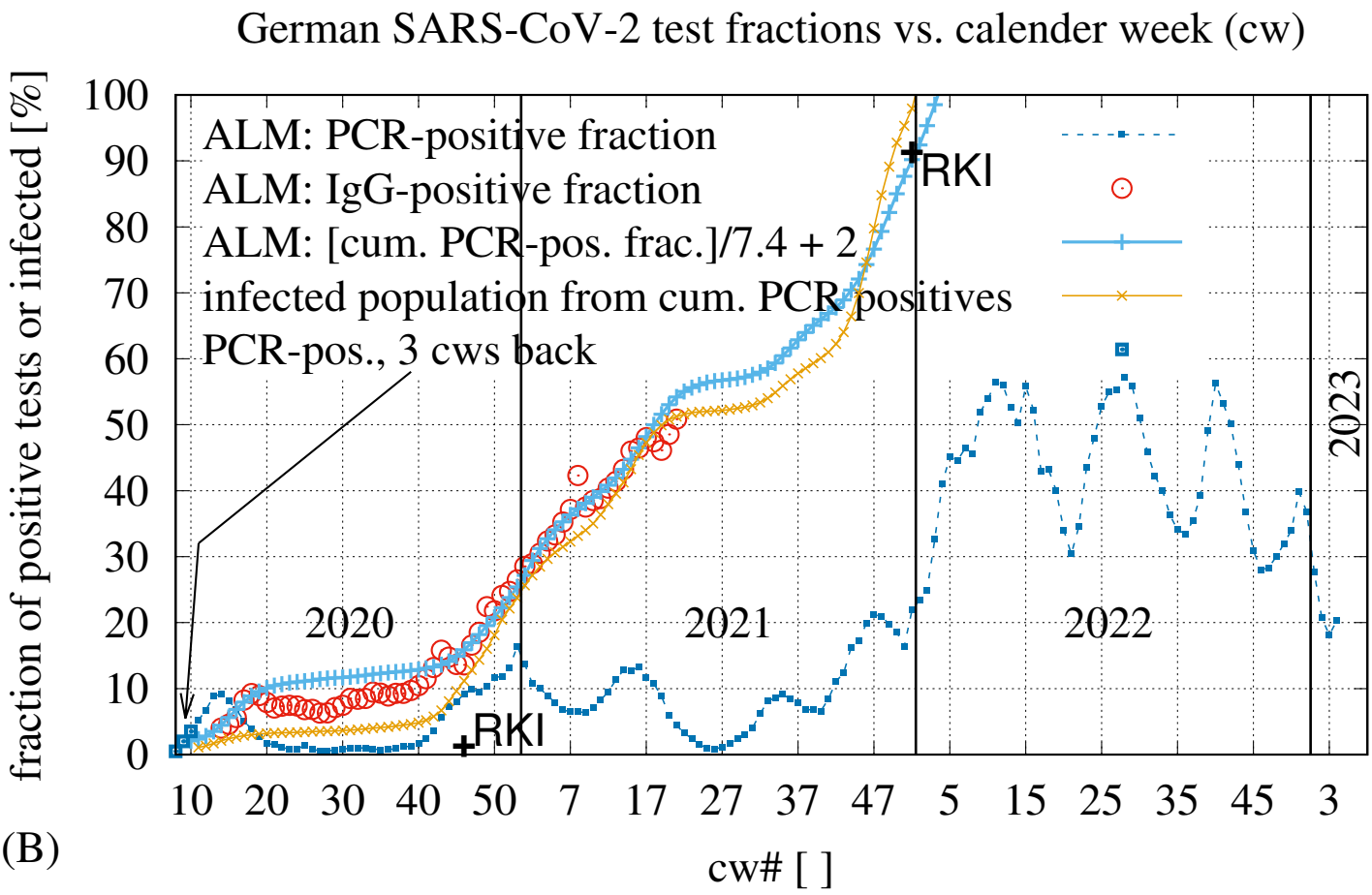


Figure 1: (A) Absolute numbers (taken from [1]; still available at [2], however, IgG data only discontinuously and until CW number cw53(2020)) of both PCR (mucous; *small hollow squares*) and IgG antibody (serological; *asterisks*) tests for SARS-CoV-2 carried out weekly by ALM in Germany 2020-2022, and their positive portions (*small solid squares* and *circles*, respectively); for better visibility, IgG counts are multiplied by ten.
(B) Fractions (ALM-measured, given in percent) of both positive PCR ($F_{PCR,cw} \cdot 100\%$, *small solid squares, dashed line*) and IgG ($F_{IgG,cw} \cdot 100\%$, *big circles*) tests, i.e. the respective ratios of positive portions and absolute numbers of tests carried out. Also shown (details: see main text): the scaled cumulated sum $\sum_{i=0}^{cw-2} F_{PCR,i}$ of past values (until two CWs ago) of PCR-positive fractions providing a fit to the time course of the ALM-determined IgG-positive fraction ($F_{IgG,cw} \cdot 100\%$ fitted according to Eqn (1), *thick line with plus signs*), three back-extrapolated data points (at cw8(2020)-cw10(2020)) to estimate the initial course (*thick hollow squares*) of the PCR-positive fraction $F_{PCR,cw}$, as well as the estimate of the fraction of SARS-CoV-2-infected (i.e. carrying IgG antibodies: $F_{infec,cw} \cdot 100\%$ according to Eqn. (2), *thin line with small crosses*) in the entire German population, calculated from the cumulated sum $\sum_{i=0}^{cw} N_{PCRpos,cw}$ of all PCR-positive persons since the start of ALM measurements (in cw11(2020)). Additionally, two RKI-reported [3, 4],[5, 6] IgG-positive fraction values of the entire population are plotted (*thick plus signs*).

1. Introduction

Detecting (through amplification) specific nucleic acid sequences of viral gens by carrying out (real-time quantitative, reverse transcription) polymeric chain reaction (PCR) tests from mucosal swabs in a group of selected persons provides a representation of the presence of 'the virus' in this group's 'collective mucous membrane'. Virus presence in an individual's mucous membrane can trigger the production of membrane-bound IgA antibodies. Moreover, if 'the virus' can breach the mucosal barrier, it can invade a single person's organism; in this case, the person gets infected. As a natural consequence, the immune system of the infected responds with a multitude of processes, one of which is the production of further IgA and, delayed, IgG antibodies (plus another three types: IgD, IgE, IgM), which then all circulate in the blood. Taking data on SARS-CoV-2 infections as a recent virus example, in more severe illness cases, IgG antibodies are first detectable about two weeks after the instant of infection, i.e. during the second week after onset of symptoms [7]; in milder cases, it takes up to four weeks after infection [8, suppl. fig. 1]. IgG antibodies then remain easily detectable until half a year later at least [9], and even longer as a rule. Accordingly, in the course of an epidemic virus spreading in a population, the fraction of persons within the population who have IgG antibodies in their blood indicates what percentage of the population were infected in the past (year). In other words, if a *group* of persons within a population is selected randomly and *tested for IgG antibodies*, the *fraction* of this group *showing IgG antibodies* in their blood (i.e. being *IgG-positive*) *reflects* the sum of all those *infected* in the population until two weeks before (probably even until seven days before [10]).

After the emergence of SARS-CoV-2 in late 2019, PCR testing [11] for virus-specific genetic material in mucous (nasopharyngal) membranes became a world-wide diagnostic gold standard. It is noteworthy that PCR tests merely scan for *presence of* and not *infection with* viruses. Still, it can be assumed that there exists a virus-characteristic likelihood that an individual becomes infected, if virus material is detected in its mucous membrane. Therefore, the population's IgG-positive fraction should be *in proportion to* the sum of all individuals having been tested PCR-positive in the past until two weeks before the IgG testing. However, this only applies if any PCR-positive person has only been tested positive *once* during an analysed time period; in other words, positive *cases* should approximately equal *persons*. Studying the PCR-IgG relation and its quantitative proportion is important, because PCR-test positives were taken as proxy for the number of potentially infected, and used to derive public health policy measures. As a side note, two factors can be identified to increase the number of false positive PCR tests. First, a study [12, p. 6] ascertained in 2020, that the screening part of the Charité's PCR test assay tagged *water* controls positive at CT values in the range 36-38. Second, based on the Bayesian law of conditional probability, the relative amount of false positives naturally rise in times of low SARS-CoV-2 prevalence, due to the finite specificity of PCR tests. In addition, it is established that there is no infectiousness of infected individuals above PCR test cycle thresholds (CT) of 30 [13, 14], whereas practice was to run tests with CTs up to 40 [15, 16].

In a nutshell, a PCR test takes a *snap shot* of a body's *present exposure* to some virus-specific genetic material at the outer surface, the shield, of the body. Considering common epidemiological wording, the PCR-positive fraction can thus be interpreted as a normalised incidence. Contrary to the definition of 'incidence' used in the German Infection Protection Act (§ 28a(3) "Infektionsschutzgesetz"), this fraction does not depend on the actual number of tests conducted and thus constitutes a more robust measurand for the occurrence (frequency) of infection events. An IgG test, then again, reflects a body's immune response (its *memory*), behind the shield, to some virus' *past invasion*. Again in common epidemiological terms, the IgG-positive fraction is equivalent to the normalised prevalence of SARS-CoV-2 (immunity responses) in a population. In this study, we examine to which extent the PCR-positive (normalised) incidence (a snap shot) in the German population after emergence of SARS-CoV-2 corresponded to IgG-positive (normalised) prevalence (the memory), based on data provided by the same authority-accredited labs. Eventually, we use this cross-checked information contained in the time courses of lab-reported PCR

and IgG tests (and two parameter values from the literature) to estimate the time course of the fraction of SARS-CoV-2-infected persons within the entire German population.

2. Methods and Results

We have checked the relation between the sum of past positive PCR and presently positive IgG test counts in the specific time period from mid March 2020 until the end of 2021 in Germany. The data were taken from a webpage [1] at which a medical lab consortium (*Akkreditierte Labore in der Medizin e.V.*, Berlin, Germany; short: ALM) of German test labs reported their results on weekly counts of PCR and IgG tests, respectively, both absolute numbers and positive portions. The consortium continuously ran about 90% of all PCR test data in Germany [2]. The time course of these counts are plotted in Fig. 1(A), resolved by calendar weeks (CWs; numerical symbol: cw); here, cwX(Y) denotes CW X in year Y, e.g. cw10(2020) the tenth CW in 2020. The corresponding weekly ratios of positive test counts and all those carried out, i.e. the fractions of positive tests (PCR and IgG), are plotted as percentages in Fig. 1(B): the small squares connected by a dashed line represent the ALM-measured data of the PCR-positive fraction, and the big circles symbolise the ALM-measured data of the IgG-positive fraction. Also plotted is the scaled sum of past values of the PCR-positive fraction (thick line with plus signs in Fig. 1(B)), which fits (reproduces) the ALM-measured IgG-positive fraction by a simple model estimate. To be more precise, for each given CW – at which the IgG fraction is sought to be reproduced – the past PCR-positive fractions are summed until two CWs before. The sum is then scaled with (multiplied by) a factor P_{PCR} of proportionality, and an offset $O_{IgG,0}$ (fraction: 0.02, percentage: 2%) is added to the sum, which reflects the value of the IgG-positive fraction being unknown before the time of start of summation, and makes the sum match the first IgG-positive fraction value (0.04) collected at cw14(2020). Expressed as a formula, this simple model estimate of the IgG-positive fraction in CW number cw from the (past) PCR-positive fractions is

$$F_{IgG,cw} = O_{IgG,0} + P_{PCR} \cdot \sum_{i=0}^{cw-2} F_{PCR,i} \quad . \tag{1}$$

Here, $F_{PCR,i} = \frac{N_{PCRpos,i}}{N_{PCR,i}}$ is the PCR-positive fraction in each CW i before number cw (exactly, until $cw-2$), $F_{IgG,cw} = \frac{N_{IgGpos,cw}}{N_{IgG,cw}}$ is the IgG-positive fraction in any CW, where $N_{PCR,cw}$, $N_{PCRpos,cw}$, $N_{IgG,cw}$, and $N_{IgGpos,cw}$ are the weekly PCR and IgG counts, respectively. The ALM reported their first PCR data point in cw11(2020). To capture the full width of the 'first SARS-CoV-2 wave', the PCR-positive fraction $F_{PCR,cw}$ was linearly back-extrapolated for three weeks (cw8(2020): 0.005, cw9(2020): 0.02, cw10(2020): 0.035; see 'PCR-pos., 3 cws back' in Fig. 1(B)), assuming that there were very low to vanishing levels of the PCR-positive fraction until cw7(2020). Consequently, $i = 0$ in Eqn. (1) corresponds to cw8(2020). The still non-vanishing initial IgG-positive fraction value of 2% may be an indicator that this actually pretty insignificant initial condition of the PCR-positive signal has not been exactly correct, or it might also be simply due to the percentage of false-positive IgG tests.

The value $P_{PCR} = \frac{1}{7.4} \approx 0.135$ is our primary and major parameter finding, determined by least-squares fitting Eqn. (1) to the ALM-measured IgG-positive fraction through asking for P_{PCR}, while leaving $O_{IgG,0}$ fixed to the value 0.02. That is, only one in every 7.4th ALM-detected PCR-positive person proved (statistically) to be IgG-positive in an ALM lab at least two weeks after having tested PCR-positive. Note that the latter sentence is an *inference* based on a specific *assumption*, which we make here due to our lack of knowledge of the criteria that determined the selection of persons for being IgG-tested: We assume that the latter were all, or mostly at least, among those having been PCR-tested. For that, it is important to realise that contrary to many other countries, the standard test in Germany was a PCR test conducted on mucosal swabs; IgA tests conducted on saliva were also acceptable, but rarer. IgG tests were usually conducted after PCR tests had been positive, and on blood. Hence, IgG tests are in the vast majority of cases a sub-population of PCR-positive test cases. In other words, with this *assumption* kept in mind,

only about 13.5% of all PCR-positive persons were actually infected by SARS-CoV-2, according to the ALM data. With this P_{PCR} value, the model estimate $F_{IgG,cw}$ by Eqn. (1) (thick line with plus signs in Fig. 1(B): 'ALM: [cum. PCR-pos. frac.]/7.4 + 2') fits the ALM-measured data points of the IgG-positive fraction (circles in Fig. 1(B): 'ALM: IgG-positive fraction') well. This estimate further allows to extrapolate beyond ALM's terminating IgG measurements in cw21(2020), namely, until the model-estimated fraction $F_{IgG,cw}$ reaches 1 at the beginning of 2022.

Another basic parameter value has been found here. During the vaccination campaign of the first half of 2021, the fraction of people showing IgG antibodies in their blood increased by 1.1% per week, which is the approximate slope of a least-squares-fitting straight line through the last 12 circles in Fig. 1(B) until cw21(2021). Yet, the slope (likewise from least-squares fitting) of the observed IgG fraction curve *before* the start of the vaccination campaign (end of 2020, circles in Fig. 1(B) from cw45(2020) through cw52(2020)), which was caused by solely natural infections, was even *steeper*, namely, 1.8% per week.

In a last methodical step, we estimated the time course of the fraction $F_{infec,cw}$ of SARS-CoV-2-infected persons *within the entire German population* ($N_{pop} = 83.5 \cdot 10^6$ inhabitants in Germany). For this, we transferred the statement "For any positive PCR test, there are actually about 10 SARS-CoV-2 infections.", which recapitulates empirical findings in Germany [17, p. 59: $U_{infec} \approx 10$] and Switzerland [18, SEROCoV-POP: $U_{infec} \approx 11$], into a simple phenomenological formula:

$$F_{infec,cw} = O_{infec,0} + \frac{U_{infec}}{R_{ALM}} \cdot \frac{\sum_{i=0}^{cw} N_{PCRpos,cw}}{N_{pop}} \quad . \tag{2}$$

Here, the entire population's SARS-CoV-2-infected fraction $F_{infec,cw}$ is assumed to depend on the initial value ($i = 0$) at cw11(2020) of the infected fraction ($O_{infec,0} = \frac{O_{IgG,0}}{2} = 0.01 = 1\%$ as a simple guess), the empirically known approximate number U_{infec} of infections per positive PCR test (value chosen: 10), and the parameter R_{ALM} (value chosen: 0.9) that accounts for the ALM having continuously run about 90% of all PCR tests in Germany [2]. The chosen value $U_{infec} = 10$ is, by the way, fully consistent with the ratio $\frac{\text{infection fatality rate (IFR)}}{\text{case fatality rate (CFR)}} \approx 10$ that can be determined for Germany from CFR ≈ 0.025 [19, r_{PF} in tables 3, 4], and IFR $\approx 0.0021 \ldots 0.0025$ [20, 'Germany' in table 4]. The phenomenological model estimate of the time course of the German population's SARS-CoV-2-infected fraction $F_{infec,cw}$ according to Eqn. (2) is plotted as a thin line with small crosses in Fig. 1(B). From November 2020 on, $F_{infec,cw}$ generally lies in a range 2...6% below the ALM-measured IgG-positive fraction, along with its fitted estimate $F_{IgG,cw}$ (Eqn. (1)), only to eventually exceed from cw46(2021) on the extrapolated (towards the end of 2021) fit $F_{IgG,cw}$ of the ALM-measured IgG-positive fraction. At the turn of 2021 into 2022, extrapolated $F_{IgG,cw}$ shows a value of about 90%, which almost perfectly coincides with the value of 92% given by the Robert-Koch-Institut (RKI) [3, 4], while the estimated SARS-CoV-2-infected fraction has reached its theoretical maximum of $F_{infec,cw} = 1$ (i.e. 100%). The steep $F_{infec,cw}$ slope towards the end of 2021 owes, numerically, to the peak of the count of PCR-positive tests around cw47(2021) (Fig. 1(A)). The infected fraction (seemingly) reaching 100% therefore indicates that lately in autumn 2021 the number of PCR tests must have deviated from the number of persons tested. The corresponding multiple testing per person has also been suggested as a phenomenon in [19, sec. 3.3; tables 5, 6]. Accordingly, the $F_{infec,cw}$ slope steepening and its crossing of $F_{IgG,cw}$ cannot be seen a reliable finding. In any case, taking $F_{IgG,cw} = 0.9$ in cw52(2021) as a guide (and the course of the $F_{infec,cw}$ estimate until about cw43(2021)), the fraction of Germans having been SARS-CoV-2-infected at least once must have reached approximately 85% at the end of 2021, which is a guess slightly more conservative than reported by the RKI (92%).

3. Discussion

In our view, the result of comparing the scaled cumulative sum of PCR-positive (past) fractions (shortly: PCR-positive sum) with the (present) IgG-positive fraction is astounding: Given the utter simplicity of

the summation model representing both the physiological (virus presence in membranes and serological antibody response) and the technological details (testing principles and procedures) behind both test signals, the match of the reproduction (fit: Eqn. (1)) gained by summing the PCR-positive signals to the directly observed time course of the IgG-positive signal might be considered almost perfect (Fig. 1(B)). The temporary over-estimation of the ALM-observed IgG-positive course by the (scaled) PCR-positive sum (Eqn. (1)) during the summer of 2020 may be explained by IgG concentration levels in the blood decreasing partly below the detection thresholds of the given and maintained IgG antibody test procedures in the labs, while the IgG information still remaining present in the once-infected bodies. This seems to be a reasonable explanation, as it is even more surprising that then, in the autumn 2020, the predicted PCR-positive sum 'hits' the observed IgG-positive course, and 'curves upward' during the 'second and third SARS-CoV-2 waves' into spring 2021 just to almost perfectly match the observed course with the 'correct' slope.

The result does definitely *not* imply that PCR testing can detect an individual's SARS-CoV-2 infection, as an ensemble's number of PCR-positive tests just indicates a *collective, on-average proportionality* between the fraction of PCR-detectable virus presence in the 'collective mucous membrane' and the fraction of carriers of IgG antibodies in the 'collective blood' of the ensemble members. Hence, infection can *definitely not* be ascertained in the individual case from a PCR-positive test, as the collective factor $P_{PCR} = \frac{1}{7.4} = 0.135$ of proportionality is clearly smaller than 1, and, moreover, a product in itself of multiple impacting proportionality factors. These factors are, for example, a practically irreproducible and time-dependent combination of pre-selection criteria of persons tested, individual sensitivities of persons with respect to virus presence (states of the immune systems), number of CT values chosen for PCR testing by a lab (or an authority) as the threshold for 'positive' results (in combination with several other methodical factors in PCR testing), as well as methods and detection thresholds (e.g. concentrations or 'optical densities') chosen in IgG testing. All these impacting factors are conflated in the two standard performance parameters of testing, namely, a test's 'sensitivity' and its 'specificity' (for a nice summary, see [21]). To sum it up, the factor P_{PCR} reflects the net probability of a person to get systematically infected if virus material can be (PCR-)detected in its mucous membrane; and this probability is about 0.135 (13.5%).

The performance parameter relevant to our findings is the overall specificity of PCR mass testing in Germany in 2020 and 2021. Irrespective of the sensitivity of PCR tests (so let us even assume it were 100%), by knowing that the mean weekly PCR-positive fraction (normalised incidence) in Germany from cw11(2020) until cw21(2021) (the period until termination of IgG testing by ALM) had been approximately 7%, and having found $P_{PCR} = \frac{1}{7.4}$ through our fitting, which together disclose a mean pre-test fraction (probability) of about 1% actually SARS-CoV-2-infected persons per week, a specificity of 93.5% explains that 6.5% of the actually 99% non-infected in mass testing have been tagged as 'false positives' by PCR mass testing, which in turn corresponds perfectly to direct checks for the specificity of PCR tests (see [22, p. 362]). This hence explains that only $\frac{1}{7.4}$ of the PCR-tagged 'positives' have actually been SARS-CoV-2-infected (as proven by IgG testing), namely, 1% SARS-CoV-2-infected ('true positive') persons in altogether 7...7.5% PCR-tagged 'positives'. In summary, our finding of $P_{PCR} = \frac{1}{7.4}$ is fully consistent with the observed (low: few percent) mean PCR-positive fraction and a Germany-wide PCR tests' specificity value of 93.5%.

In a recent analysis of this NAA-conditional mortality in Germany until mid 2023, some of the authors had estimated that no more than about 59,500 persons, out of about 115,500 tagged by the RKI, can be claimed to have potentially died due to SARS-CoV-2 in the full two year period 2020-2021 [19, sec. 4.2], thus, roughly only half of the number asserted by the RKI. Both this RKI number and the reasoning for its halving was based on accepting that a positive PCR test indicates 'being infected by SARS-CoV-2' (this is also implied within German legislation, i.e. the "Infektionsschutzgesetz"). As a consequence of our finding here, the claim must now be further reduced, namely, to only 13.5% of 115,500 deaths, i.e. roughly 15,600, would actually be causally attributable to SARS-CoV-2 infections through the two years 2020

and 2021. Accordingly, the question arises what other factors caused the undoubtedly manifest excess mortality in the flu seasons 2020/21 and 2021/22 [19, tab. 2] and could explain the difference, for 2020 and 2021 together, between the estimated 59,500 excess deaths in the PCR positives and the estimated 15,600 deaths among the actually SARS-CoV-2-infected? This question depends on how many of the remaining 86.5% of PCR-positive persons had not been infected by any virus at all, how many potentially only mildly by SARS-CoV-2 (leaving no detectable IgG traces in their blood), and how many perhaps by other types of viruses, with the above-given degree of non-specificity of PCR tests. Non-specificity can be well explained by regularly applying PCT test CT values up to 40 [15, 16], while it seems established (e.g. by the German Paul-Ehrlich-Institut, PEI [13]) that (i) specific information, whether no, mild, or severe symptoms of illness arose, gets lost above CT values of about 27 [15, p. 2, left col.], (ii) infectiousness practically vanishes for CT values increasing from 25 through 30 (i.e. the viral load in the mucosal barrier decreasing; $10^6 \frac{\text{copies}}{\text{ml}}$ correspond to a CT value of about 25) [16, 13, 14], and (iii) the probability of getting infected (i.e. the body and thus blood being invaded, partially with symptoms of illness) generally decreases with viral load.

Our estimated fraction of about 24% of SARS-CoV-2-infected inhabitants at the start of the German SARS-CoV-2 vaccination campaign on 27/12/2020 is remarkable, because the German authority for health surveillance, the RKI, suggested that maximally 2.8% [5] (ostensibly, not even more than 2% [6]) of all Germans had been IgG-positive "until November 2020", which leaves open which cut-off date for this percentage was used exactly. At the time the RKI reported, let us assume mid November (i.e. cw46(2020)), lab-observed data by ALM show about 15%, which is perfectly confirmed by the scaled cumulative PCR-positive sum, and our estimated German-wide fraction of cumulatively SARS-CoV-2-infected (IgG carriers) is about 11%. The discrepancy between the RKI-reported IgG-positive fractions and, on the other hand, ALM-observed IgG-positive fraction is striking, particularly as the ALM data were available to—and even commissioned by—the RKI. The low value of 2.8% may be explained by the IgG measuring method employed in the RKI-SOEP study (subjects' self-taking 'dried blood spots' [5]) being generally too insensitive.

Regarding the discrepancy between the ALM-observed IgG fraction and our generally lower estimate of the population's SARS-CoV-2-infected fraction, we could neither find information on the pre-selection of the ALM clientele tested for IgG antibodies (except for all tests being requested by physicians [2]), nor on the IgG testing method employed by ALM. It can only be speculated whether the lower (SOEP) instead of the higher (ALM) value was intentionally reported to boost the starting vaccination campaign. In any case, the ALM data basis is vast, relying on carrying out between 10,000 and 100,000 IgG tests every week (Fig. 1(A)), German-wide, but ALM suddenly stopped reporting after the fraction of IgG positives had reached 50% in cw21(2021). Yet remarkably, the RKI claim of the IgG-positive fraction of the entire German population at the end of 2021 is about 92% [3, 4], which almost perfectly aligns with *both* our extrapolation of ALM-based IgG-positive fractions from cw21(2021) onwards according to the ALM-fitting Eqn. (1) *and* our simple phenomenological model estimation of the entire German population's SARS-CoV-2-infected fraction according to Eqn. (2).

As a last consideration, we want to assess potential effects of the vaccination campaign on ALM-measured data and our model-based estimates. While it is well established that the anti-SARS-CoV-2 injections trigger an IgG response [23], it remains controversial whether [24] or not [25] they significantly decrease the infection rate (to which the PCR-positive fraction is assumed to be in some proportion). Consequently, we had no a-priori estimate on the timely development of the PCR-positive fraction during the year 2021. On the contrary, the only free parameter in Eqn. (1), P_{PCR}, as well as potentially the literature-derived parameter in Eqn. (2), U_{infec}, may be expected to actually carry some information on vaccinations. It is hence surprising to see an equally good agreement of the ALM-measured IgG fraction and our PCR-positive-derived estimation while using the *same* P_{PCR} parameter value *before and after* the start of the vaccination campaign at 27/12/2020. In particular, when looking at Fig. 1(B), neither is there a discontinuity in the slope of the ALM-*measured* IgG fraction at the start of 2021, the beginning of the vaccination campaign. At this point, one could argue that the vaccination campaign affected both the IgG-

and the PCR-positive fraction equally. However, as we have shown above, the slope of the IgG-positive fraction became *less* steep in the first half of 2021, when compared to the last weeks of 2020, *contrary* to what would be expected as a desired impact of the vaccination. Since, one would theoretically expect divergence of the two curves, the time course of the cumulated PCR-positive cases and the one of the IgG positives, due to the roll-out of the vaccination campaign. In an ideal world, the vaccination campaign would reduce PCR-positive cases, because it would reduce infection risk, and at the same time increase the number of IgG-positive individuals, because vaccines should convey increased collective immunity. None of this is visible in the data. Hence, we have to conclude that the vaccination campaign did not at all contribute to a reduction of infection, nor were (vaccinated) individuals less likely to be tested positive by PCR, nor did the number of infected (IgG carriers) increase more steeply until mid 2021 (during the first five months of the vaccination campaign).

4. Summary and Conclusion

The main finding from our analysis of ALM data on both nucleic acid amplification (PCR from mucosal swabs) and IgG antibody (serological) testing for SARS-CoV-2 in Germany during late March 2020 through summer 2021 is: Just 13.5% of the persons tagged SARS-CoV-2-positive in PCR tests got actually infected by SARS-CoV-2, as proven by carrying IgG antibodies. We conclude from our analysis: The IgG tests carried out by ALM had been *commissioned* by the RKI (subjected to the German ministry of health). Yet, the study was evidently stopped after cw21(2021) (or, at least, the 'public' reporting at [1]), and the ALM-measured IgG results published here have not been mentioned anywhere by the RKI. Transparency in communicating these data would be mandatory to not create the impression that the antibody monitoring was purposefully scrubbed as it did not conform with the official narrative of vanishingly low immunity against SARS-CoV-2 within the German population at the beginning of the vaccination campaign, and neither with the authority-claimed epidemiological impact of the vaccination campaign during 2021. On the contrary: The collective immunity was already high at the end of 2020 (about a quarter of the population carried IgG antibodies) and followed a time trajectory of its own, which was evidently determined by natural infections rather than by the vaccination campaign. Last, we propose to omit in the definition of 'incidence' the normalisation to the number of individuals within an arbitrarily chosen population (i.e. its size), but rather to normalise the number of positive tests to those conducted.

Competing interests

We have no conflicts of interest.

Acknowledgements

The readers of this article should be truly grateful to an attentive reader of "NachDenkSeiten", Ulf Martin, who prodded MG in a reader's letter [26] on 05/10/2021 to the ALM webpage [1] reporting the IgG data in a graphical panel, alongside with their PCR data in another panel. The readers should likewise be utterly grateful to a straight journalist, Boris Reitschuster, and a straight scientist, Stephan Luckhaus. The latter published a highly informative article [27] on seroprevalence—with, among other things, precious references and pointers to pretty hidden data sources, e.g. [17, 18]; some comments held also extremely valuable hints—on the former's blog page.

Funding

The authors have not been funded for writing this paper. MG is currently supported as a biomechanics researcher by *Deutsche Forschungsgemeinschaft* (DFG) under grant SCHM2392/5-2.

References

[1] Anonymous, Graphical panels showing weekly counts of PCR and IgG tests, Corona-Diagnostik Insights provided through ALM Service GmbH, Berlin, Germany, by order of Akkeditierte Labore in der Medizin e.V. (ALM), Berlin, Germany, [in German]; not accessible anymore: https://www.corona-diagnostik-insights.de/daten-fakten/ (2021).

[2] Anonymous, ALM-Datenerhebung zur SARS-CoV-2-Testung der Labore, Akkeditierte Labore in der Medizin e.V. (ALM), Berlin, Germany, [in German]; last accessed 04/03/2024: https://www.alm-ev.de/aktuell/corona-themenseite/datenerhebung-alm-ev/ (2023).

[3] Gößwald, A, Corona-Monitoring bundesweit – Welle 2, Robert-Koch-Institut, [in German]; last accessed 04/03/2024: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Studien/lid/Factsheet-CoMoBu-Welle-2.pdf (2022).

[4] Gößwald, A, Informationen zur Studie "Corona-Monitoring bundesweit" (CoMoBu-Studie), Robert-Koch-Institut, [in German]; last accessed 04/03/2024: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Studien/lid/lid_node.html (2023).

[5] H. Neuhauser, A. S. Rosario, H. Butschalowsky, S. Haller, J. Hoebel, J. Michel, A. Nitsche, C. Poethko-Müller, F. Prütz, M. Schlaud, H. Wilking, L. H. Wieler, L. Schaade, A. Gößwald, T. Ziese, Nationally representative results on SARS-CoV-2 seroprevalence and testing in Germany at the end of 2020, Scientific Reports 12 (2022) 19492, https://doi.org/10.1038/s41598-022-23821-6.

[6] Gößwald, A, Corona-Monitoring bundesweit (RKI-SOEP-Studie) – Überblick zu ersten Ergebnissen, Robert-Koch-Institut, [in German]; last accessed 04/03/2024: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Studien/lid/Ergebnisse.pdf (2021).

[7] C.-C. Guo, J.-Q. Mi, H. Hie, Seropositivity rate and diagnostic accuracy of serological tests in 2019-nCoV cases: a pooled analysis of individual studies, European Review for Medical and Pharmacological Sciences 24 (19) (2020) 10208–10218. doi:10.26355/eurrev_202010_23243.

[8] G. Rijkers, J.-L. Murk, B. Wintermans, B. van Looy, M. van den Berge, J. Veenemans, J. Stohr, C. Reusken, P. van der Pol, J. Reimerink, Differences in antibody kinetics and functionality between severe and mild severe acute respiratory syndrome coronavirus 2 infections, The Journal of Infectious Diseases 222 (8) (2020) 1265–1269. doi:10.1093/infdis/jiaa463.

[9] M. C. Tejiokem, H. A. Abessolo, J. M. Nkodo, M. Ouethy, G. B. Mayaka, Y. Touha, U. A. Dikoume, J. B. Tchatchueng-Mbougua, D. C. Noumbissi, W. T. Ndjeukam, H. O. O. Mbarga, P. A. T. Ngoupo, C. Moussi, B. H. Garoua, R. Njouom, V. Richard, High seroprevalence of severe acute respiratory syndrome coronavirus 2 among healthcare workers in Yaoundé, Cameroon after the first wave of Covid-19 pandemic and associated factors, Influenza and Other Respiratory Viruses 18 (2) (2024) e13239. doi:10.1111/irv.13239.

[10] E. Bendavid, B. Mulaney, N. Sood, S. Shah, E. Ling, R. Bromley-Dulfano, C. Lai, Z. Weissberg, R. Saavedra-Walker, J. Tedrow, A. Bogan, T. Kupiec, D. Eichner, R. Gupta, J. P. A. Ioannidis, J. Bhattacharya, COVID-19 antibody seroprevalence in Santa Clara County, California, International Journal of Epidemiology 50 (2) (2021) 410–419. doi:10.1093/ije/dyab010.

[11] V. M. Corman, O. Landt, M. Kaiser, R. Molenkamp, A. Meijer, D. K. W. Chu, T. Bleicker, S. Brünink, J. Schneider, M. Schmidt, D. G. J. C. Mulders, B. L. Haagmans, B. van der Veer, S. van den Brink, L. Wijsman, G. Goderski, J. Romette, J. Ellis, M. Zambon, M. Peiris, H. Goossens, C. Reusken,

M. P. G. Koopmans, C. Drosten, Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR, Eurosurveillance 25 (3) (2020) 2000045. doi:10.2807/1560-7917.ES.2020.25.3.2000045.

[12] S. Etievant, A. Bal, V. Escuret, K. Brengel-Pesce, M. Bouscambert, V. Cheynet, L. Generenaz, G. Oriol, G. Destras, G. Billaud, L. Josset, E. Frobert, F. Morfin, A. Gaymard, Performance assessment of SARS-CoV-2 PCR assays developed by WHO referral laboratories, Journal of Clinical Medicine 9 (6) (2020) 1871. doi:10.3390/jcm9061871.

[13] R. L. Schlenger, Antigentests auf SARS-CoV-2: Was die Aussagekraft bestimmt, Deutsches Ärzteblatt 119 (51-52) (2022) A2297–A2031, in German; https://www.aerzteblatt.de/archiv/228979/Antigentests-auf-SARS-CoV-2-Was-die-Aussagekraft-bestimmt.

[14] D. B. Larremore, B. Wilder, E. Lester, S. Shehata, J. M. Burke, J. A. Hay, M. Tambe, M. J. Mina, R. Parker, Test sensitivity is secondary to frequency and turnaround time for COVID-19 screening, Science Advances 7 (1) (2021) eabd5393. doi:10.1126/sciadv.abd5393.

[15] A. Singanayagam, M. Patel, A. Charlett, J. Lopez Bernal, V. Saliba, J. Ellis, S. Ladhani, M. Zambon, R. Gopal, Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020, Eurosurveillance 25 (32) (2020) 2001483. doi:10.2807/1560-7917.ES.2020.25.32.2001483.

[16] A. Stang, J. Robers, B. Schonert, K. Jöckel, A. Spelsberg, U. Keil, P. Cullen, The performance of the SARS-CoV-2 RT-PCR test as a tool for detecting SARS-CoV-2 infection in the population, Journal of Infection 83 (2) (2021) 244–245. doi:10.1016/j.jinf.2021.05.022.

[17] Anonymous, Studie zur Untersuchung des Corona-Infektionsrisikos im öffentlichen Personen-Nahverkehr – Epidemiologischer Studienbericht, Tech. Rep. Version 3.0, May 10, 2021, Ministerium für Verkehr Baden-Württemberg (BWVM), Dorotheenstraße 8, 70173 Stuttgart, Germany, [in German]; last accessed 04/03/2024: https://vm.baden-wuerttemberg.de/fileadmin/redaktion/m-mvi/intern/Dateien/PDF/PM_Anhang/210510_%C3%96PNV_Studie_zum_Corona-Infektionsrisiko_im_%C3%96PNV.pdf (2021).

[18] A. Wisniak, S. Stringhini, H. Baysson, G. Piumatti, A. Flahault, I. Guessous, A. Richard, Seroprävalenz-Erhebungen als Marker der Immunität der Bevölkerung gegen SARS-CoV-2, Swiss Medical Forum 20 (2730) (2020) 422–427, [in German]; last accessed 04/03/2024: https://medicalforum.ch/de/detail/doi/smf.2020.08537.

[19] R. Rockenfeller, M. Günther, F. Mörl, Reports of deaths are an exaggeration: all-cause and NAA-test-conditional mortality in Germany during the SARS-CoV-2 era, Royal Society Open Science 10 (8) (2023) 221551. doi:10.1098/rsos.221551.

[20] J. P. A. Ioannidis, Infection fatality rate of COVID-19 inferred from seroprevalence data, Bulletin of the World Health Organization 99 (1) (2021) 19–33F. doi:10.2471/BLT.20.265892.

[21] J. Watson, P. F. Whiting, J. E. Brush, Interpreting a covid-19 test result, The British Medical Journal 369 (2020) m1808, Practice; with reference [19] to a test calculator ("Testing Wisely"): https://calculator.testingwisely.com/playground. doi:10.1136/bmj.m1808.

[22] R. J. Klement, P. S. Bandyopadhyay, The epistemology of a positive SARS-CoV-2 test, Acta Biotheoretica 69 (2020) 359–375. doi:10.1007/s10441-020-09393-w.

[23] J. Wei, N. Stoesser, P. C. Matthews, D. Ayoubkhani, R. Studley, I. Bell, J. I. Bell, J. N. Newton, J. Farrar, I. Diamond, E. Rourke, A. Howarth, B. D. Marsden, S. Hoosdally, E. Y. Jones, D. I. Stuart, D. W. Crook, T. E. A. Peto, K. B. Pouwels, D. W. Eyre, A. S. Walker, A. Lambert, T. Thomas, R. Black, A. Felton, M. Crees, J. Jones, L. Lloyd, E. Sutherland, E. Pritchard, K.-D. Vihta, G. Doherty, J. Kavanagh, K. K. Chau, S. B. Hatch, D. Ebner, L. M. Ferreira, T. Christott, W. Dejnirattisai, J. Mongkolsapaya, S. Cameron, P. Tamblin-Hopper, M. Wolna, R. Brown, R. Cornall, G. Screaton, K. Lythgoe, D. Bonsall, T. Golubchik, H. Fryer, S. Cox, K. Paddon, T. James, T. House, J. Robotham, P. Birrell, H. Jordan, T. Sheppard, G. Athey, D. Moody, L. Curry, P. Brereton, I. Jarvis, A. Godsmark, G. Morris, B. Mallick, P. Eeles, J. Hay, H. VanSteenhouse, J. Lee, the COVID-19 Infection Survey team, Antibody responses to SARS-CoV-2 vaccines in 45,965 adults from the general population of the United Kingdom, Nature Microbiology 6 (9) (2021) 1140–1149. doi:10.1038/s41564-021-00947-3.

[24] T. Braeye, L. Catteau, R. Brondeel, J. A. van Loenhout, K. Proesmans, L. Cornelissen, H. Van Oyen, V. Stouten, P. Hubin, M. Billuart, A. Djiena, R. Mahieu, N. Hammami, D. Van Cauteren, C. Wyndham-Thomas, Vaccine effectiveness against transmission of alpha, delta and omicron SARS-COV-2-infection, Belgian contact tracing, 2021–2022, Vaccine 41 (20) (2023) 3292–3300. doi:https://doi.org/10.1016/j.vaccine.2023.03.069.

[25] L. Ko, G. Malet, L. L. Chang, H. Nguyen, R. Mayes, COVID-19 Infection Rates in Vaccinated and Unvaccinated Inmates: A Retrospective Cohort Study, Cureus 15 (9) (2023) e44684.

[26] U. Martin, Leserbriefe zu "Zahlenchaos Corona" (reader's letter #17), NachDenkSeiten, [in German]; last accessed 04/03/2024: https://www.nachdenkseiten.de/?p=76627 (2021).

[27] S. Luckhaus, Ist die Mehrheit der deutschen Bevölkerung bereits gegen Corona immun?, Boris Reitschuster, [in German]; last accessed 04/03/2024: https://reitschuster.de/post/ist-die-mehrheit-der-deutschen-bevoelkerung-bereits-gegen-corona-immun/ (2021).