Reply to the Editor's and Reviewers' comments on:

The Effectiveness of Testing, Vaccinations, and Contact Restrictions for Containing the Covid-19 Pandemic

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Summary

We thank the editors and referees for their excellent comments. Revising the paper to address them has allowed us to substantially improve our paper.

The largest adjustment was warranted with respect to the sensitivity of rapid tests. We fully agree that our calibration appears optimistic in light of the studies that have come out since our submission. We therefore verified that our results and conclusions are not affected when repeating the simulations under a much lower sensitivity of rapid tests. For that, we added a robustness check with sensitivities that are derived from more recent sources, relying on the progression of viral load over the course of an infection and rapid test sensitivity with respect to different viral loads. These new sensitivities are on average significantly lower than those in our main specification. We are happy to report that even the most conservative estimates lead to only a minor decrease in the estimated role of rapid tests.

The remaining comments have allowed us to improve our text significantly to be clearer and better referenced. We also updated our citations for papers that we cited as pre-prints and that have been published in the meantime. In our view the text has become clearer, more legible and better referenced as a result.

We now address the comments by the Editors and Reviewers in turn.

Editors

The title should have a clear, precise scientific meaning and should not contain a colon. Where possible, the title should be read as one concise sentence.

We changed the title from "The Effectiveness of Strategies to Contain SARS-CoV-2: Testing, Vaccinations, and NPIs" to "The Effectiveness of Testing, Vaccinations, and Contact Restrictions for Containing the Covid-19 Pandemic"

Reviewer 1

The authors of the manuscript presented here have used mathematical models to examine the impact of different measures to contain the SARS-CoV-2 pandemic. Using epidemiological data from Germany, the contribution of rapid antigen testing is considered in particular.
The topic studied here is of great importance for the control of the coronavirus pandemic. The presentation of the scientific methodology is sufficiently detailed, especially with the supplementary materials. It allows the reader to follow the research process in detail. However, I noticed a significant deficiency when reviewing the submitted work. Therefore, the manuscript should definitely be revised again before publication: A crucial point of the authors is to point out the special benefit of a rapid test strategy. However, for the calculation of the corresponding influencing factors in their mathematical model, the authors simplify, specifically, the sensitivity of rapid antigen tests in an unacceptable way. In the development of the mathematical model, apparently only the knowledge available a few months ago on the performance of rapid antigen tests was taken into account. This is evident from literature references mentioned above. In part, incorrect references are also used, especially for the assumption of the high sensitivity of the rapid tests. For example, reference No. 74 explicitly does not refer to rapid antigen tests, but to an immunological laboratory test method (Quidel SARS Sofia antigen FIA). Especially in light of the benefit of rapid antigen tests described by the authors, it should be considered that many of the commercially marketed tests show only extremely poor performance. This has recently been demonstrated by several publications:

- Comparative sensitivity evaluation for 122 CE-marked rapid diagnostic tests for SARS-CoV-2 antigen, Germany, September 2020 to April 2021, Scheiblauer, Heinrich and Filomena, Angela and Nitsche, Andreas and Puyskens, Andreas and Corman, Victor M and Drosten, Christian and Zwirglmaier, Karin and Lange, Constanze and Emmerich, Petra and Müller, Michael and Knauer, Olivia and Nübling, C Micha, Eurosurveillance, 26, 2100441 (2021), https://doi.org/10.2807/1560-7917.ES.2021.26.44.2100441

- Assessment of SARS-CoV-2 rapid antigen tests, Özcürümez, Mustafa, Katsounas, Antonios, Holdenrieder, Stefan, von Meyer, Alexander, Renz, Harald and Wölfel, Roman, Journal of Laboratory Medicine, vol. 45, no. 3, 2021, pp. 143-148. https://doi.org/10.1515/labmed-2021-0036

Especially in the case of a mass application of antigen tests, it is therefore to be expected that products with lowest sensitivity will also be used in the general population. The authors should at least model this with an alternative calculation and discuss it accordingly. Such an improvement would increase the importance of this manuscript enormously.

We would like to thank the reviewer for these insightful comments. First of all, we agree that the references we used have become outdated in the meantime. Note that we submitted the original manuscript in early September 2021; the analysis had been finalised in June of last year. Indeed, in the light of the additional evidence, the numbers we use for test sensitivity appear to be in the upper part of plausible values. We have followed your suggestion and report detailed robustness analyses in the paper and its appendix.
Before describing our changes, we would like to thank you for pointing out that the test analysed in Smith *et al.* (*1*) is not a rapid test. While this is true, the crucial feature in Smith *et al.* (*1*) is that the paper reports the sensitivity over the course of an infection. We have not found a comparable study. Getting this profile right is important particularly in the beginning

of an infection, as we detail shortly. At that point, the differences between different methods to assess test sensitivity by timing within an infection are relatively small.
On page 3 of the paper, we cite the references you pointed out (numbering of references relates to this document) and note that we conduct a robustness analysis:

Specificity and sensitivity of these tests is set according to data analyzed in Brümmer et al. *(2), Scheiblauer* et al. *(3), and Özcürümez* et al. *(4); sensitivity depends on the timing of the test relative to the onset of infectiousness as in Smith* et al. *(1). We analyse robustness to different assumptions in Appendix B.12.*

We followed your suggestion and ran additional analyses with more conservative assumptions on the sensitivity of rapid tests. The results are very robust. We write in the main text on page 8:

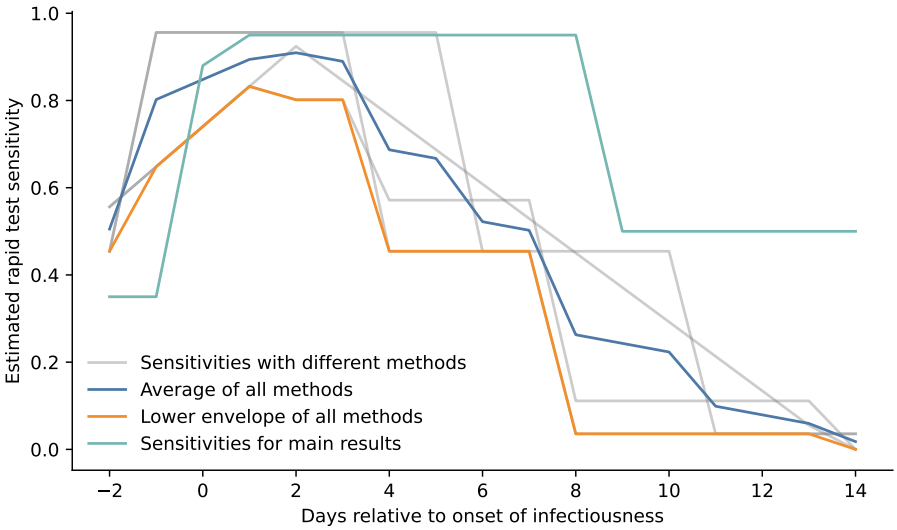
In Appendix B.12, we provide a detailed analysis of whether our results are robust regarding the sensitivity parameters we assume for rapid tests. Even if we take a pessimistic stance, the effect is only reduced from 42% to 38%.

The robustness is due to the fact that over the course of an infection, the largest differences between the parameters we use in our main analysis and those based on imputing values from other studies are found during the later stages of an infection. Uncovering an infection that was previously undetected at that stage does not have a large effect on subsequent infection dynamics. Our whole analysis in Appendix B.12 reads as follows:

Our main results are based on rapid test sensitivities read from clinical trials. Recent studies showing that the actual sensitivity of rapid tests may be lower than that (e.g., 3).
This section shows that our results are robust to making less favorable assumptions on rapid test sensitivity. We proceed by describing several possible ways of calibrating rapid test sensitivity profiles based on recent studies. Since none of these methods is inherently better than the others, we make simulations with two sensitivity profiles: The average over all methods and the lower envelope over all methods using recent studies.
Both profiles imply lower sensitivities of rapid tests than used in our main results. This is especially true during the later stage of an infection. However, the main results stay very robust. The original result was that rapid tests, seasonality and vaccinations are responsible for 42%, 43% and 16%, respectively. With the average profile, the effect of rapid tests decreases to 41 %. With the lower envelope profile, which is an extremely unfavorable assumption, it becomes 38%.
The effect of rapid tests on infection dynamics strongly depends on when *an infection is detected. Earlier detection means that it is more likely that the infection has not yet been discovered for a different reason (e.g. due to the onset of symptoms) and that the infected person can be isolated before spreading the disease to others.*
The sensitivity of rapid tests depends on the viral load in the respiratory tract. It is low at the beginning of an infection (especially before the onset of infectiousness), high in the first few days of infectiousness and then gradually decreasing towards the end of infectiousness.

We thus need to calibrate a profile of rapid test sensitivities based on the number of days until or since the onset of infectiousness.
Unfortunately, such sensitivity profiles are not usually reported in studies. We thus need to create them by combining two types of studies: 1. Studies that report the viral load in terms of threshold cycle (Ct) values determined by PCR test (e.g. 5–9). 2. Studies that report the sensitivity of rapid tests for different Ct values (e.g. 2, 3).
It is natural to assume that the evolution of Ct values over time as well as the effect of Ct values on rapid test sensitivity are continuous functions. However, the results of the available studies are usually reported in a discretized way. This leads to multiple ways of calculating the sensitivity profiles. Some try to recover the underlying continuous functions using interpolation or regression, others simply use the discretized values.
For the calibration of Ct values over time we can either use discretized values for several time bins from (6) and (8). Alternatively, we can use linearized formulas for calculating sensitivities over time (5) and complement it with interpolations of data points from (8) in the pre-infectious stage. Throughout we assume that the Ct values of individuals who eventually develop symptoms and those who do not follow the same trajectory. This is in line with results by (9) and recent evidence that rapid tests excel at discovering asymptomatic cases (10).
For the mapping of Ct values to rapid test sensitivities, again we have two options. First, we can simply look up the discretized values for the three Ct bins provided in (3) (below 20, 25 to 30 and above 35). Secondly, we can use linear regression to estimate a continous mapping for the relationship by assuming that the Ct values of each bin are achieved exactly at the bin midpoints and that the relationship is linear.
In general, using discretized values can lead to an underestimation of peak sensitivities and an overestimation of very low sensitivities. This is because discretization is essentially a smoothing device. On the other hand, it has the advantage of simply working with published results, without introducing any tuning parameters or other assumptions.

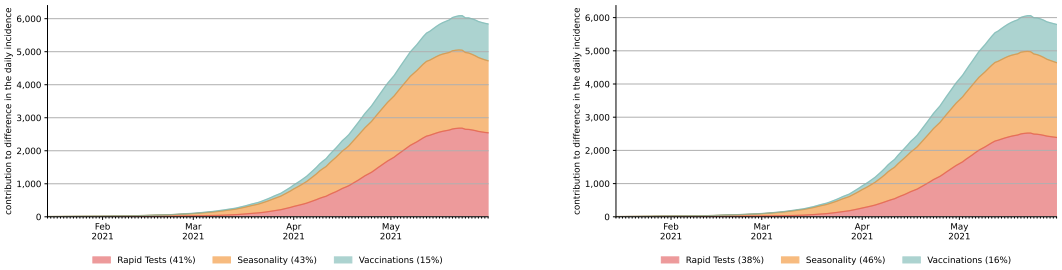
Figure I: Rapid test sensitivity profiles



Note: The figure shows estimated sensitivities of rapid tests over the course of an infection. The x-axis shows days relative to the onset of infectiousness. The y-axis shows the estimated rapid test sensitivities. The grey lines are the raw sensitivity estimates obtained with different methods of dealing with discretized data. The blue line shows their average and the yellow line their lower envelope. The turquoise line are the test sensitivities used for the main results of the paper.

Figure I shows that the updated sensitivity estimates are lower than the ones used for our original results, especially towards the end of an infection. However, the main results barely change. This is due to the fact that the differences are largest towards the later stage of an infection. Uncovering an infection that was previously undetected at that stage does not have a large effect on infection dynamics.

Figure II: Shapley decompositions for different values of rapid test sensitivity



(a) Shapley decomposition with average of sensitivity estimates

(b) Shapley decomposition with lower envelope of sensitivity estimates

Note: The figure shows updated versions of the Shapley decomposition in figure 3c. The decompositions are based on 20 model runs with different random seeds. The share attributed to each channel is rounded to the next full percentage point to acknowledge the remaining sampling uncertainty.

Furthermore, I recommend including a declaration of potential conflicts of interest in the manuscript. This may be particularly important in light of the significance of the findings from the study for the continued operation of industrial companies.

We have added such a declaration at the end of the paper:

Competing interests

The authors declare no competing interests.

Reviewer 2

This is a comprehensive and important study that highlights the relevance of testing to stop the spread of the pandemic.
I cannot comment on the validity of the underlaying mathematical analysis, but I would like to comment on some assumptions made, which I think require further clarification or discussion.

1. They use contact-frequency from pre-pandemic diary data. Is this truly useful if behavior of people is already changed by the fact there is a pandemic?

Many thanks for this comment. Ideally, we would of course use real-time data. For example, several studies have used smartphone tracking data for this purpose. However, any such data are not detailed enough for our requirements because they do not provide any information about *who* is meeting with each other. These dimensions make up our contact networks, which are absolutely crucial.

Furthermore, note that we only use the pre-pandemic diary data as the starting point. Contact restrictions and individual behavior adjustments reduce contacts. These are active throughout the period of analysis and they vary with the strictness of measures. In order to do so, it is crucial to take the type of contact into account; see for example our analysis of potential school closures on Page 9. Closed schools mean that children have far fewer and parents have somewhat fewer contacts than without school closures.

Finally, the very good fit of our model to official infection rates across age groups increases our confidence that we manage to match actual meeting patterns. If we were far off for, for example, the number of work contacts, we would not be able to match either the infections of individuals during working age (35-59) or of those that mostly do not work anymore (60-79).

2. They state that susceptibility is dependent on age. This requires references and needs to be further explained. Also, younger populations are highly susceptible, they may just not contribute transmission as much. On that same note, infectiousness may not be independent of age

   Edward Goldstein, Marc Lipsitch, Muge Cevik, On the Effect of Age on the Transmission of SARS-CoV-2 in Households, Schools, and the Community, The Journal of Infectious Diseases, Volume 223, Issue 3, 1 February 2021, Pages 362–369, https://doi.org/10.1093/infdis/jiaa691

Many thanks for pointing this out, indeed we had not cited our key reference for susceptibilities by age group (*11*) in the main text. In fact, the paper you suggested (*12*) comes to similar conclusions: *"We found evidence that compared to younger/middle-aged adults, children younger than 10 years have significantly lower estimated susceptibility to SARS-CoV-2 infection, while adults older than 60 years have elevated susceptibility to infection."* The current version cites both papers on Page 1.

We base our assumption on infectiousness being independent of age on Jones *et al.* (*13*). That paper reports only slight differences in viral loads between German adults and children: "The least infectious youngest children have 78% (61, 94) of the peak culture probability of adults aged 45 to 55". Furthermore, they caution that these lower numbers may be due to different sample taking—such as the usage of smaller pediatric swab devices—rather than

actual lower viral loads and conclude that the differences, if existent, are likely not clinically relevant.

In fact, Goldstein *et al.* (*12*) reach similar conclusions, writing: *"There is limited evidence in the literature regarding age-related differences in infectivity, although point estimates in several studies suggest that infectivity may increase somewhat with age."* We are thus confident that different assumptions in the range of plausible values would not change our results in a quantitatively meaningful way.

3. It is not accurate that the vaccines stop transmission. This has to be adapted accordingly. Also, the authors should state which vaccines they based this analysis on, as in which ones were in use in Germany at that time and how does that affect the relative transmissibility as it cannot be assumed that all vaccines will have the same effect.

Many thanks, it is of course true that vaccines reduce transmissions, but do not stop them completely. We do not assume that, either. However, we have not been able to find data on the way in which this affects different population groups for the wild type and the α-variant.

In our model, we thus simplify the way vaccines reduce transmission risk. In particular, we assume that that 75% of individuals achieve sterile immunity through a vaccination while the remaining 25% remain fully susceptible. Firstly, the existing evidence supports the assumption that all four vaccines approved in the EU (Biontech/Pfizer, Moderna, Oxford/AstraZeneca and Johnson & Johnson) provide similar levels of protection in the first few months after vaccination against the wild type and the α variant (for details see Appendix A.1, starting on Page 4), which is the only time period and variant our simulations cover. Secondly, given the surprisingly good performance of rapid tests we tried to err on the side of being too optimistic with our modelling of vaccine performance. This is why we chose the perfect protection from vaccination for a large part of the population. Thirdly, reinfections are not a big issue for the time period that we look at. The incidences were small and the chance of more than one exposure to Covid are negligibly small. Thus, the value added by a probabilistic model of vaccination protection is very small for the period that we cover. At the same time, it comes at prohibitive computational costs.

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