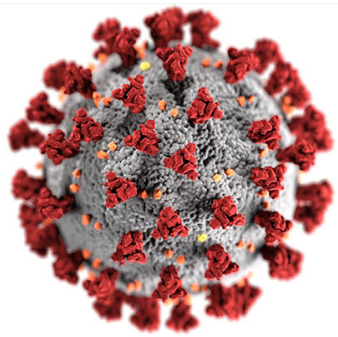
Amsterdam UMC
University Medical Centers



VU VRIJE UNIVERSITEIT AMSTERDAM

Transparency is essential in research under pressure: lessons from a pandemic

Lex Bouter

2021-02-11 Wetenschappelijke visie op de crisis – KAMG Congres 2020 – LM Bouter – 30 minuten (incl. 10 minuten Q&A)

Content

- **Research under pressure:**

  Less time and higher stakes can hamper research integrity

- **Importance of transparency:**

  Open Science modalities can improve research quality

- **Lessons learned from the pandemic:**

  Base policies on best public health, economical, behavioral evidence

2

Although I'm an epidemiologist I'm not a public health expert and know not much of infectious disease epidemiology.

I'll mainly talk on research quality which is my current field but will also dwell on public health and health policy issues.

Acknowledgements

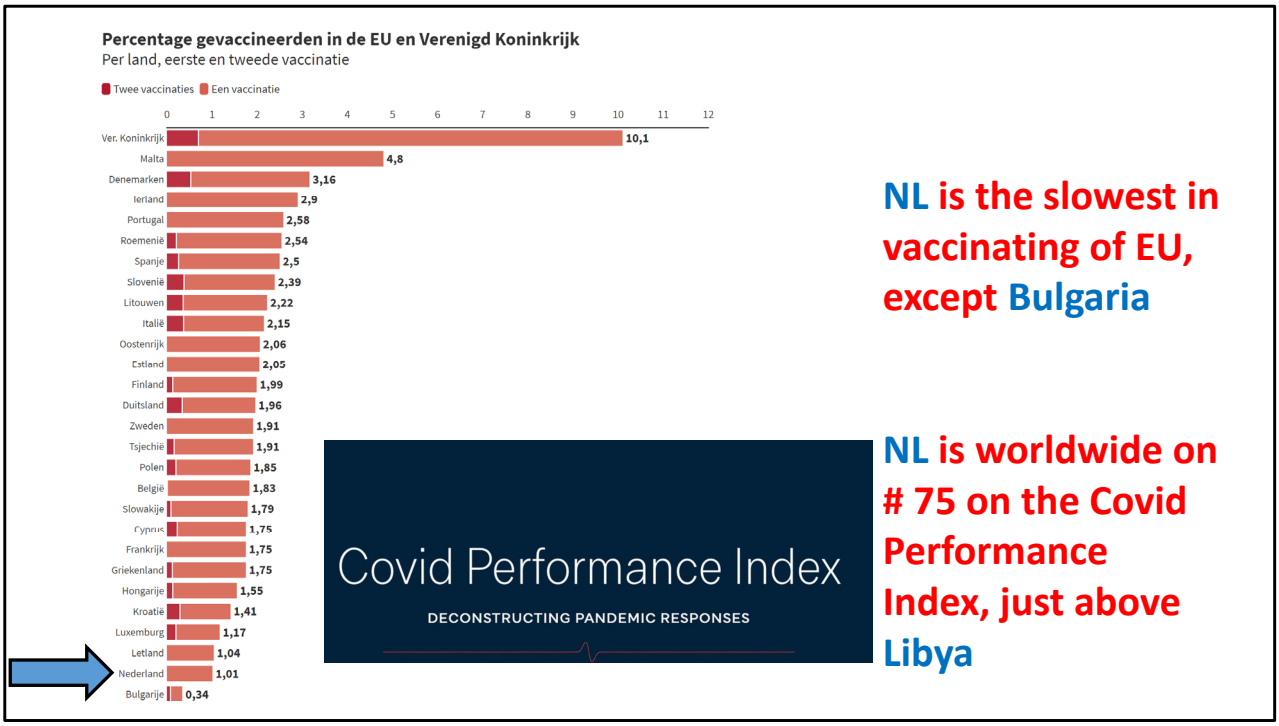
Trisha Greenhalgh

Gowri Gopalakrishna

I would like to acknowledge these two great sources of inspiration for this lecture.

Professor **Trisha Greenhalgh** – University of Oxford
"Give me back my fact": How can social science help us survive a post-truth pandemic?
Campaign for Social Science Annual SAGE Lecture 2020 on 10 December 2020
https://www.youtube.com/watch?v=3mNTDii3oJI&feature=emb_logo&ab_channel=CfSocialScience

Dr **Gowri Gopalakrishna** Amsterdam University Medical Centers
"Science in A Pandemic: is Open Science helping or hurting research integrity?
3rd Netherlands Research Integrity Network Research Symposium on 2 December 2020
https://www.nsri2020.nl/
https://research.vumc.nl/en/persons/gowri-gopalakrishna



Please let me be clear about my position from the start: I'm grateful for the enormous decication of health care and public health workers and many researchers but I'm critical about how The Netherlands is handling the Covid pandemic and the quality and transparency of Covid research worldwide.

https://twitter.com/LexBouter/status/1355191148403429378

https://interactives.lowyinstitute.org/features/covid-performance/

Positions researchers can take

1. Remain in the Ivory Tower:

   focus on knowledge production

2. Be available as expert on request:

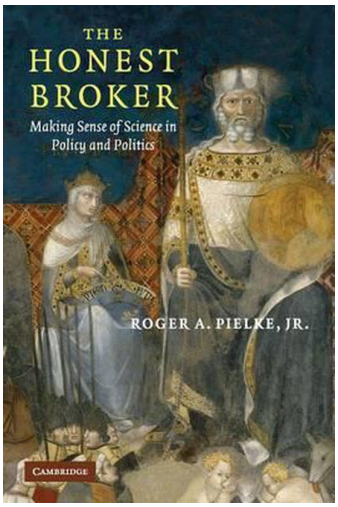
   answer questions based on knowledge

3. Be an activist:

   (mis)use expertise as advocate of specific policy option

4. Act as honest broker:

   use expertise to clarify policy options



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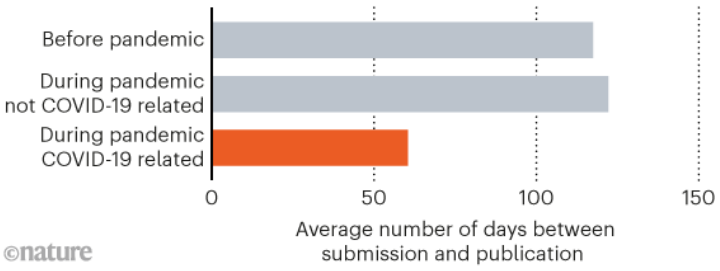
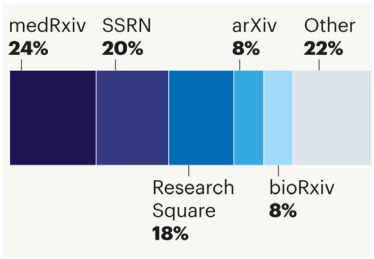
The author of this interesting book pleas for option 4 and I agree that this is the best when the issue is really important (like in the Covid pandemic) although in daily life I usually act according to option 2.

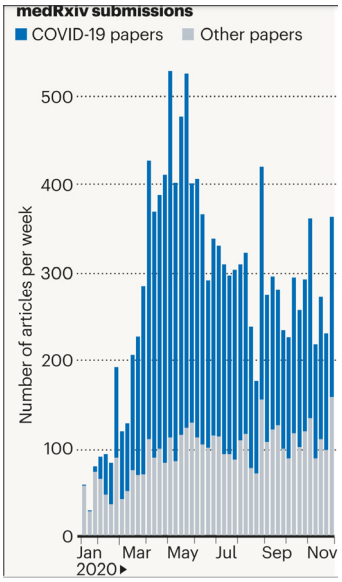
Pielke, R.A. (2007). The Honest Broker: Making Sense of Science in Policy and Politics. Cambridge: Cambridge University Press. doi:10.1017/CBO9780511818110

Rapid review



Rise of preprints

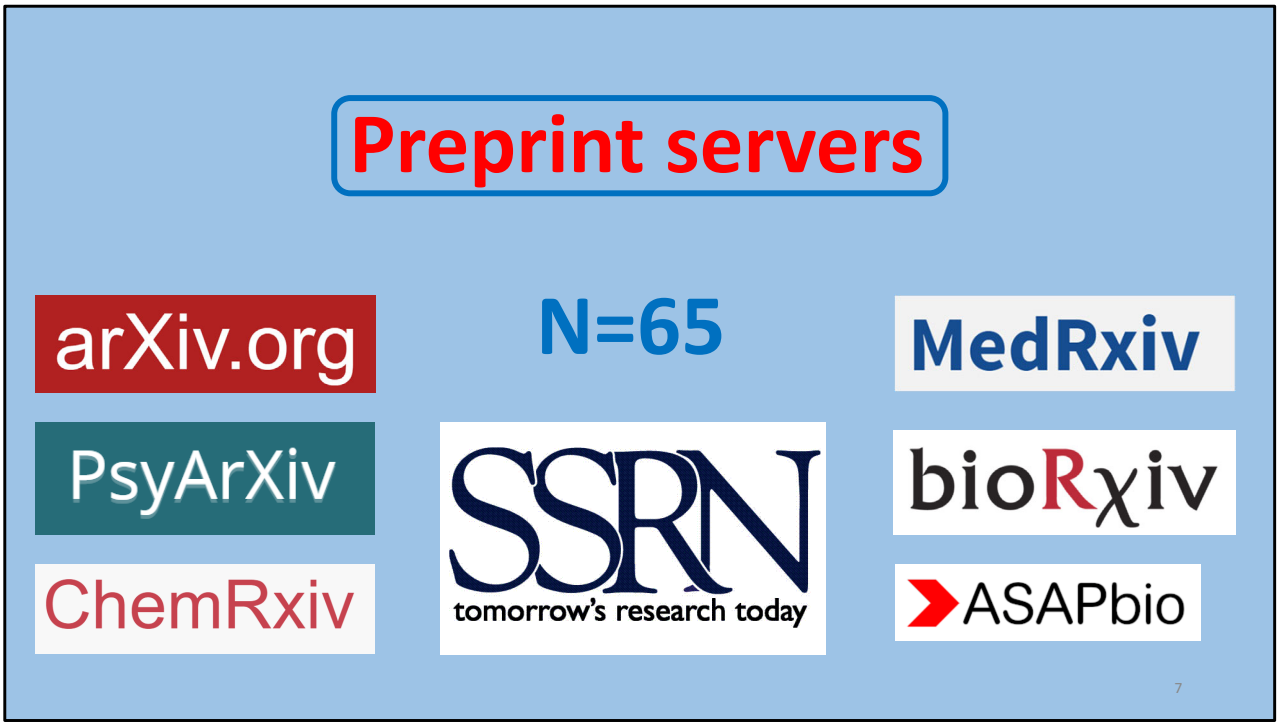




The COVID pandemic led to a surge of preprints and halved waiting time in regular journals.

Kwon D. How preprint servers are blocking coronavirus research. Nature 2020; 581: 130-1. https://www.nature.com/articles/d41586-020-01394-6

Else H. Covid papers: a torrent of science. Nature 2020; 588: 553. https://www.nature.com/articles/d41586-020-03564-y



The idea of preprints is immediate release of research reports to enable pre-submission peer review by colleagues in the field, flagging priority and quick dissemination (not always a good idea).
Preprint servers are digital platforms with typically no or minor upload criteria and weak monitoring functions.

https://arxiv.org/
https://chemrxiv.org/
https://www.biorxiv.org/
https://psyarxiv.com/
http://asapbio.org/

List of 65 preprint servers at
https://docs.google.com/spreadsheets/d/17RgfuQcGJHKSsSJwZZn0oiXAnimZu2sZsWp8Z6ZaYYo/edit#gid=0

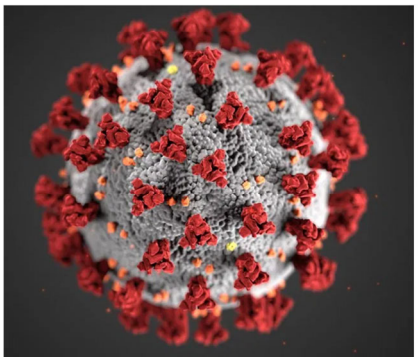
YouTube video 'What are preprints?'
(https://www.youtube.com/watch?time_continue=9&v=2zMgY8Dx9co)

Malički M, Jerončić A, ter Riet G, Bouter LM, Ioannidis JPA, Goodman S, Aalbersberg IJJ. Preprint servers' policies, submission requirements, and transparency in reporting and research integrity recommendations. JAMA 2020; 324: 16: 1901-3.
Malicki M, Jerončić A, Bouter B, ter Riet G, Ioannidis JPA, Goodman SM, Aalbersberg IJ J. Preprint servers' policies, submission requirements, and transparency in reporting and research integrity recommendations. Research Square (25 January 2021) (https://www.researchsquare.com/article/rs-153573/v1)

Chalmers I, Glaziou P. Should there be greater use of preprint servers for publishing reports of biomedical science? F1000Research 2016; 5: 272

Hydroxychloroquine-COVID-19 study did not meet publishing society's "expected standard"

Lancet, NEJM retract controversial COVID-19 studies based on Surgisphere data



Didier Raoult

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Not all went well but a small proportion of the Covid-19 papers was retracted: to date about 80 in total.
There is little evidence that preprints fared worse than regular publications. In fact there is some research that suggests that manuscript change very little when promoted from preprint to accepted peer reviewd publication.

Some cases were very prominent in the media, the most wellknown example being that of the antimalarial drug hydroxychloroquine as a "miracle cure" in the treatment of Covid 19.
It first appeared as a preprint then a journal publication as a result of a seriously flawed study by the by now infamous French scientist Didier Raoult, on the basis of clinical observations among 24 patients with multiple co-morbidities. Suffice to say the study, with multiple grave errors from methodological flaws to data mismatch, to patient safety concerns made headline news. Resulting in the former US president claiming it as a cure for Covid. Later publications denying that based on dubious data: Lancet and NEJM had to retract these flawed analyses, although that didn't stop later publications from citing them as genuine information.

https://retractionwatch.com/retracted-coronavirus-covid-19-papers/

https://retractionwatch.com/2020/04/06/hydroxychlorine-covid-19-study-did-not-meet-publishing-societys-expected-standard/
https://retractionwatch.com/2020/06/04/lancet-retracts-controversial-hydroxychloroquine-study/
https://www.nytimes.com/2020/06/14/health/virus-journals.html
https://www.the-scientist.com/features/the-surgisphere-scandal-what-went-wrong--67955?_ga=2.70401744.1931656756.1608568714-1790261732.1608568714
https://www.sciencemag.org/news/2021/01/many-scientists-citing-two-scandalous-covid-19-papers-ignore-their-retractions?utm_campaign=SciMag&utm_source=JHubbard&utm_medium=Facebook

This preprint led to a lot of heated discussions and detailed peer reviews on Twitter and lenghty articles in both scholarly and lay media.
The paper suggested that the case fatality rate would be in the range of that of influenza and not as high as many thought.
There turned out to be some methodological flaws and a number of unsubstantiated policy recommendations.
Many MedRxiv comments, Tweets, PubPeer comments and magazine articles put fair and unfair criticisms on the table.
Within a two weeks an improved preprint was uploaded although the debate on the interpretation was not settled.
The debate was complicated by the fact that right wing activists and some politicians used this study to emphasize their point that draconic measures where not justified.
While this was a good example of the self-corrective resilience of the research system it was a bad example of interaction between scientists and policy makers plus general public – a media storm with one famous scientist at its core.

https://www.medrxiv.org/content/10.1101/2020.04.14.20062463v2

https://www.medrxiv.org/content/medrxiv/early/2020/06/08/2020.05.13.20101253.

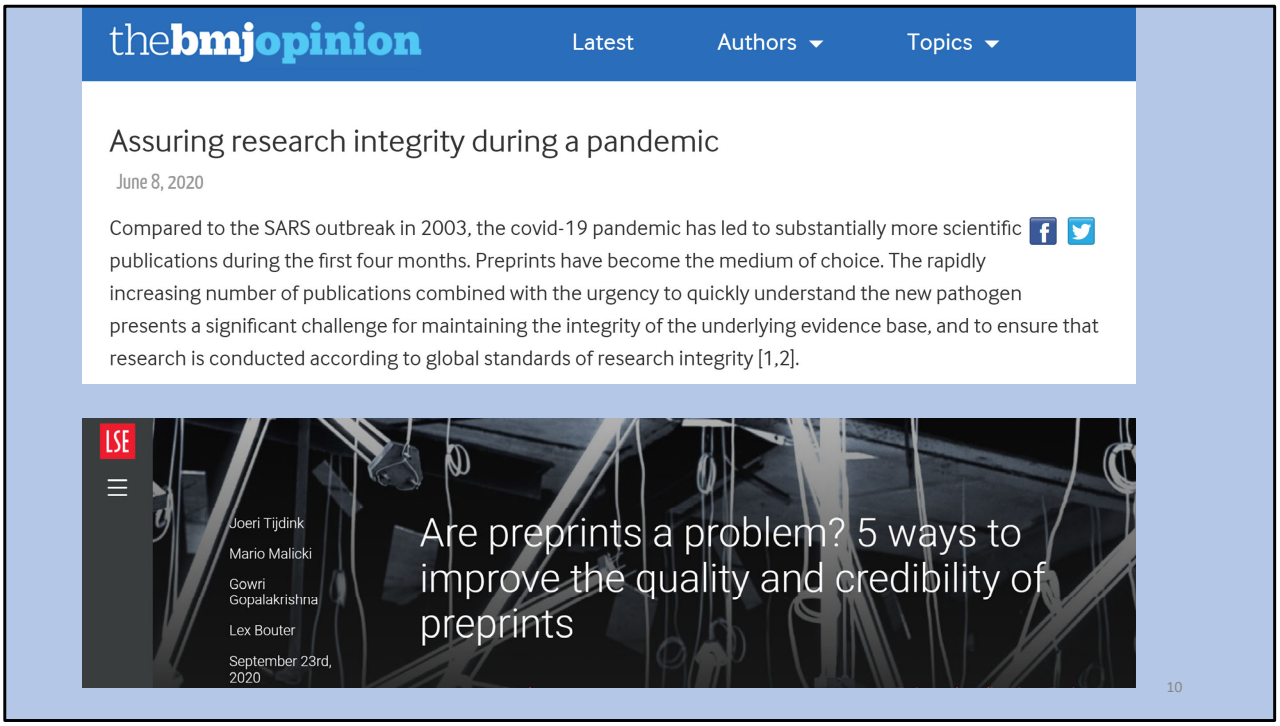
full.pdf

https://undark.org/2020/06/11/john-ioannidis-politicization/

https://www.buzzfeednews.com/article/stephaniemlee/stanford-coronavirus-neeleman-ioannidis-whistleblower

https://www.washingtonpost.com/dc-md-va/2020/12/16/john-ioannidis-coronavirus-lockdowns-fox-news/

https://www.youtube.com/watch?v=cwPqmLoZA4s&list=PLQtY8p5blBAjsMEGBe7aafyM9EoQ9lYnQ&ab_channel=JourneymanPictures



We explored in these blogs how the pressure affects research integrity and how peprints can be improved.

Gopalakrishna G, Bouter L, Mayer T, Steneck N. Assuring research integrity during a pandemic. BMJ Opinion. Published online: 8 June 2020. (https://blogs.bmj.com/bmj/2020/06/08/assuring-research-integrity-during-a-pandemic/)
https://blogs.bmj.com/bmj/2020/06/08/assuring-research-integrity-during-a-pandemic/#content

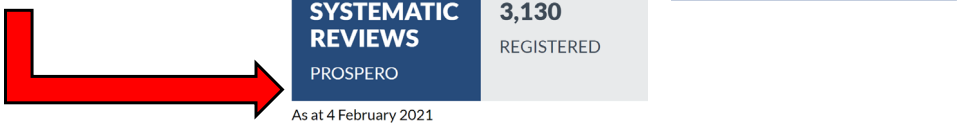
Tijdink J, Malički M, Bouter L, Gopalakrishna G. Are preprints a problem? 5 ways to improve the quality and credibility of preprints. LSE Blogs, 23 September 2020. (https://blogs.lse.ac.uk/impactofsocialsciences/2020/09/23/are-preprints-a-problem-5-ways-to-improve-the-quality-and-credibility-of-preprints/)

Dinis-Oliveira RJ. COVID-19 research: pandemic versus “paperdemic”, integrity, values and risks of the “speed science”. Forensic Sciences Research 2020; 5: 174-187. (https://doi.org/10.1080/20961790.2020.1767754)

https://connect.biorxiv.org/relate/content/181
https://retractionwatch.com/retracted-coronavirus-covid-19-papers/
https://undark.org/2020/10/29/opinion-all-prints-preprints/

Avoidable research waste

1. Improve preprint quality
2. Improve study quality
3. Improve reporting quality
4. Avoid redundancy
5. Better balance between pharmalogical and other interventions



Preprint quality

https://blogs.lse.ac.uk/impactofsocialsciences/2020/09/23/are-preprints-a-problem-5-ways-to-improve-the-quality-and-credibility-of-preprints/

Full list of recommendations: https://osf.io/w4ydg/?pid=eb6wv

Malički M, Jerončić A, ter Riet G, Bouter LM, Ioannidis JPA, Goodman S, Aalbersberg IJJ. Preprint servers' policies, submission requirements, and transparency in reporting and research integrity recommendations. JAMA 2020; 324: 16: 1901-3.

Malicki M, Jerončić A, Bouter B, ter Riet G, Ioannidis JPA, Goodman SM, Aalbersberg IJ J. Preprint servers' policies, submission requirements, and transparency in reporting and research integrity recommendations. Research Square (25 January 2021) (extended full version) (https://www.researchsquare.com/article/rs-153573/v1)

Weissgerber W, et al. Automated screening of COVID-19 preprints: can we help authors to inprove transparency and reproducibility? Nature Medicine 2021 (https://www.nature.com/articles/s41591-020-01203-7)

Other

Glasziou P, Sanders S, Hoffmann T. Waste in covid-19 research: A deluge of poor quality research is sabotaging an effective evidence based response. BMJ 2020;

369:m1847.
https://covid19evidence.net.au/news/
https://www.bessi-collab.net/
https://docs.google.com/spreadsheets/d/1NVO3hCHDzrfny3ByGtdoMww2WWGvo1itZKD8qcvRWvk/edit#gid=0
https://app.iloveevidence.com/loves
https://www.glopid-r.org/newsletter-13th-edition/covid-19-research-project-tracker/

Research findings must be trustworthy

1. *Transparency* is essential
2. *Open methods* and *open data*
3. *Prior probability*, *robustness* and ***replication***
4. *Study size* and *methodological quality*
5. *Consequences* of application of findings

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All these 5 points are also important when research is under time pressure and in the current Covid 19 pandemic the potential consequences (#5) are enourmous while there is little or no time for replication (#3).

So we better get it right immediately and that can be done by organize critical assessment alongside all phases of the study: the Red Team approach.

How to Assess Trustworthiness

1. What was the likelihood of the findings before the primary study was done? This is often referred to as the prior probability of the findings.

2. What was the study size and the methodological quality of the primary study? In other words: was the primary study precise and valid enough?

3. How many reproductions, direct replications and conceptual replications were performed? And what was their study size and methodological

quality? Which proportion of them was successful?

4. What are the stakes at issue? In other words: is another replication indicated before we can act upon the findings?

Peels R, Bouter LM. Replication and trustworthiness. Manuscript submitted for publication.

Bouter LM, ter Riet G. Empirical research must be replicated before its findings can be trusted. Journal of Clinical Epidemiology 2021; 129: 188-190.

A personal take on science and society

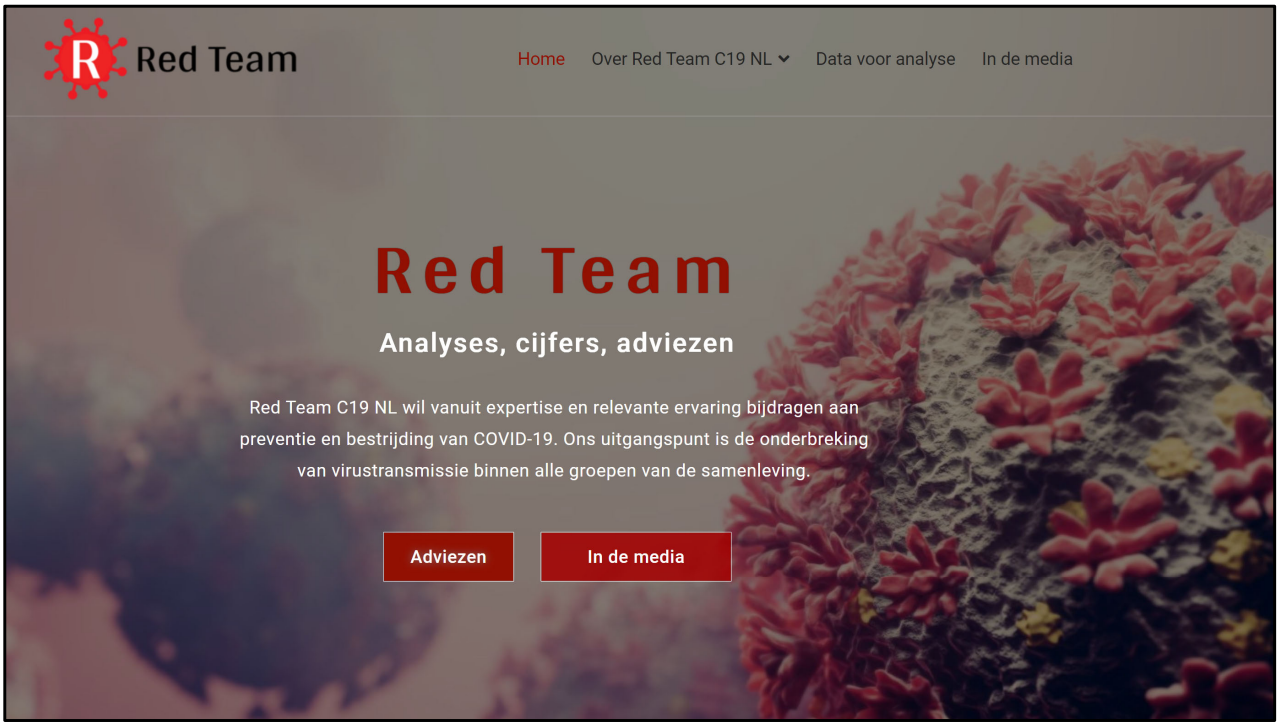
World view

By Daniël Lakens

Pandemic researchers – recruit your own best critics

As researchers rush to find the best ways to quell the **COVID-19 crisis**, they want to get **results out ultra-fast**. **Preprints** — public but unvetted studies — are getting lots of attention. But even their advocates are seeing a problem. To keep up the speed of research and **reduce sloppiness**, scientists must find ways to **build criticism into the process**.

Lakens D. Pandemic researchers - recruit your own best critics. Nature 2020; 581 121.



In the Netherlands a self-appointed Red Team provided unsollicited advice to the public health authorities, the ministry of health and the government with a view to constructively criticisize the Covid policies these organizations issued.

This cartoon emphasizes the different approaches of the official bodies and the Red Team: doing nothing without strong evidence versus acting on the evidence that is available.

A bit simplified we can say that the Outbreak Management Team mainly take the evidence-based management approach while the Red Team mainly follows an eclectic public health approach.

Evidence-based medicine

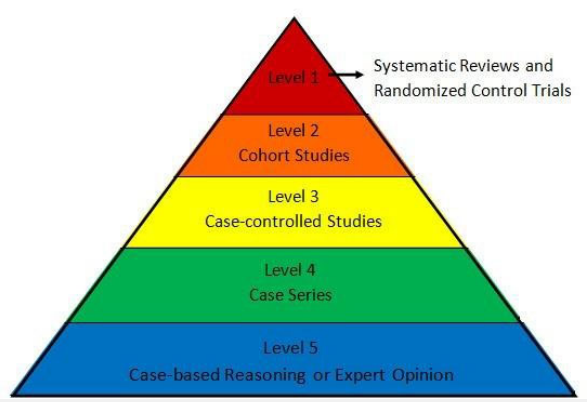
OMT

There is a ***hierarchy* of evidence** – with randomised controlled trials at the top

Good science is assumed to be defined by the use of ***correct methods***

Some methods are better than others

If participants are **randomized** in an experiment, that is **good science**; if they're not, it is less good science



Evidence-based medicine's hierarchy of evidence

OMT indicates the Dutch Outbreak Management Team that tried to follow the tradition of evidence-based medicine that relies strongly on RCTs and systematic reviews.

This means that they try to base their advise on high quality evidence only and often conclude that they cannot recommend a measure even when lower quality evidence suggests it to be effective.

Pragmatic public health

Red Team

There is ***no universally applicable hierarchy of evidence*** – though methods may be more or less fit for purpose

Good science is assumed to be defined by the use of **multiple methods**, adaptively and pragmatically, to build a *nuanced narrative of what has happened and why*

Theory is at least as important as method

The **narrative needs to *make sense*** and be plausible to the 'natives'

Pragmatic public health's real-world case study

The Dutch Red Team takes a more pragmatic public health strategy in which many types of research were considered and actions that seem to be the best were recommended.

OMT

GREAT BARRINGTON DECLARATION

- Covid-19 isn't as bad as claimed, especially for healthy under 60s
- The evidence base for interfering with people's lives is weak
- The economy should be prioritized over further lockdown

Red Team

JOHN SNOW MEMORANDUM

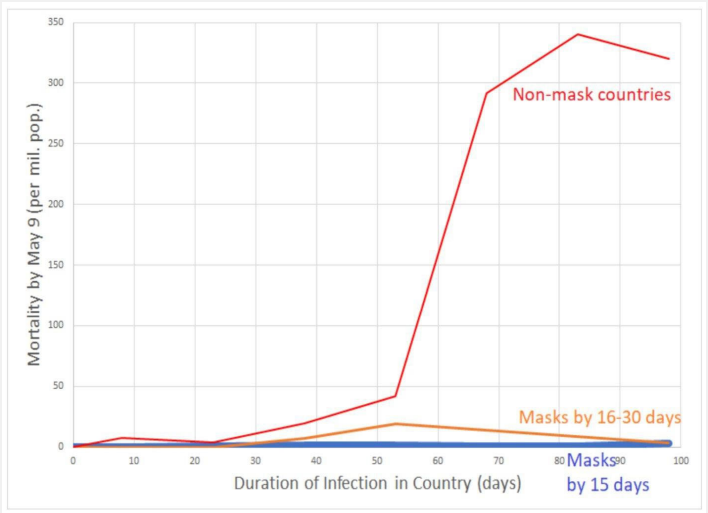
- Covid-19 is serious and sometimes deadly, also for those under 60
- The best way to save the economy is to address public health
- We all need to make compromises for the good of society

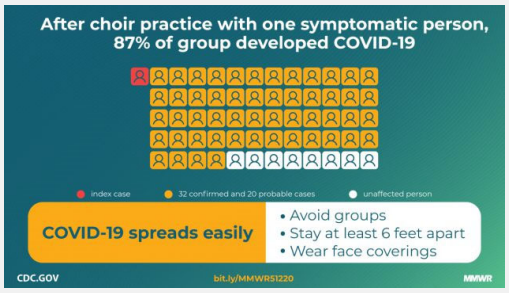
Both approaches are recognizable as forming the core of two alternatives researchers and self-nominated experts can sign.
Of course I exaggerate a bit the difference between OMT and Red Team for didactical purposes.

https://gbdeclaration.org/

https://www.johnsnowmemo.com/

IGNORED MASK STUDIES: TOO FAR DOWN THE "HIERARCHY OF EVIDENCE" ?





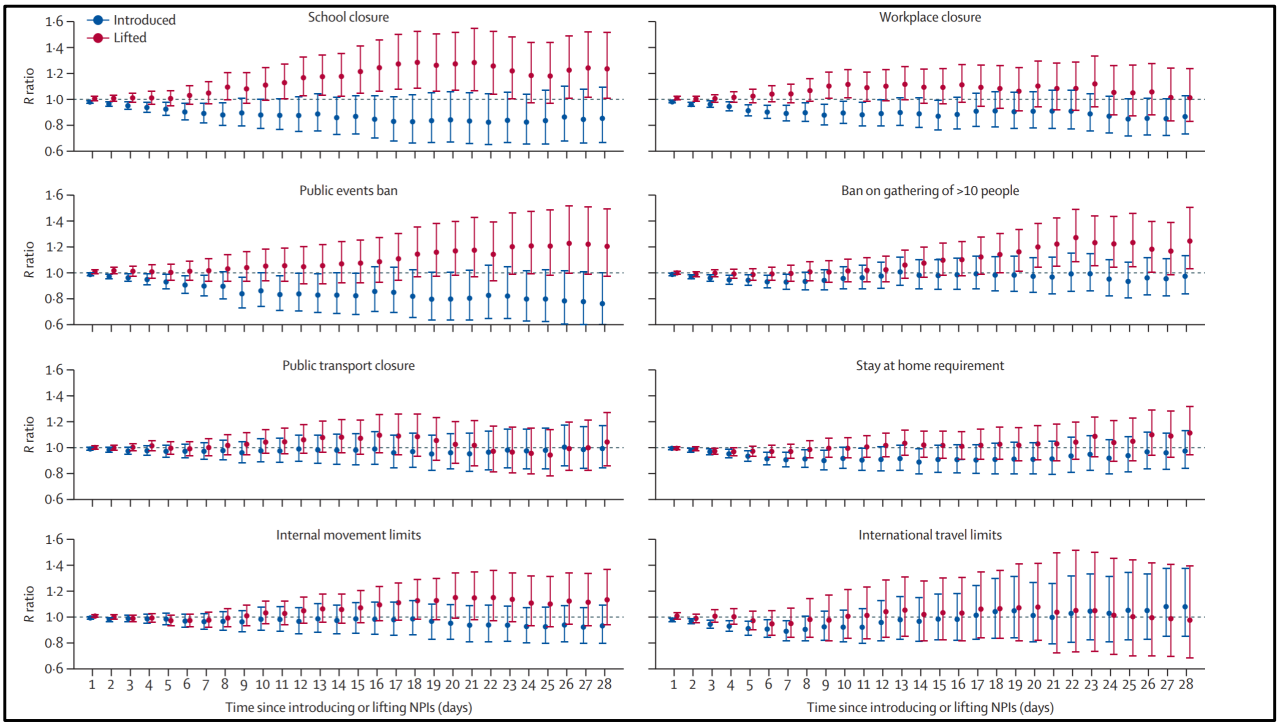
These are a few examples of non-RCT evidence that is quite convincing.

Greenhalgh T et al. Face masks for the public during the covid-19 crisis. BMJ 2020; 369: m1435

Leffler CT et al. Association of country-wide coronavirus mortality with demographics, testing, lockdowns, and public wearing of masks (Update June 2, 2020). https://www.medrxiv.org/content/medrxiv/early/2020/06/05/2020.05.22.20109231.full.pdf

Hammer L et al. High SARS-CoV-2 Attack Rate Following Exposure at a Choir Practice — Skagit County, Washington, March 2020. Morbidity and Mortality Weekly Report 2020; 69: 606-10.

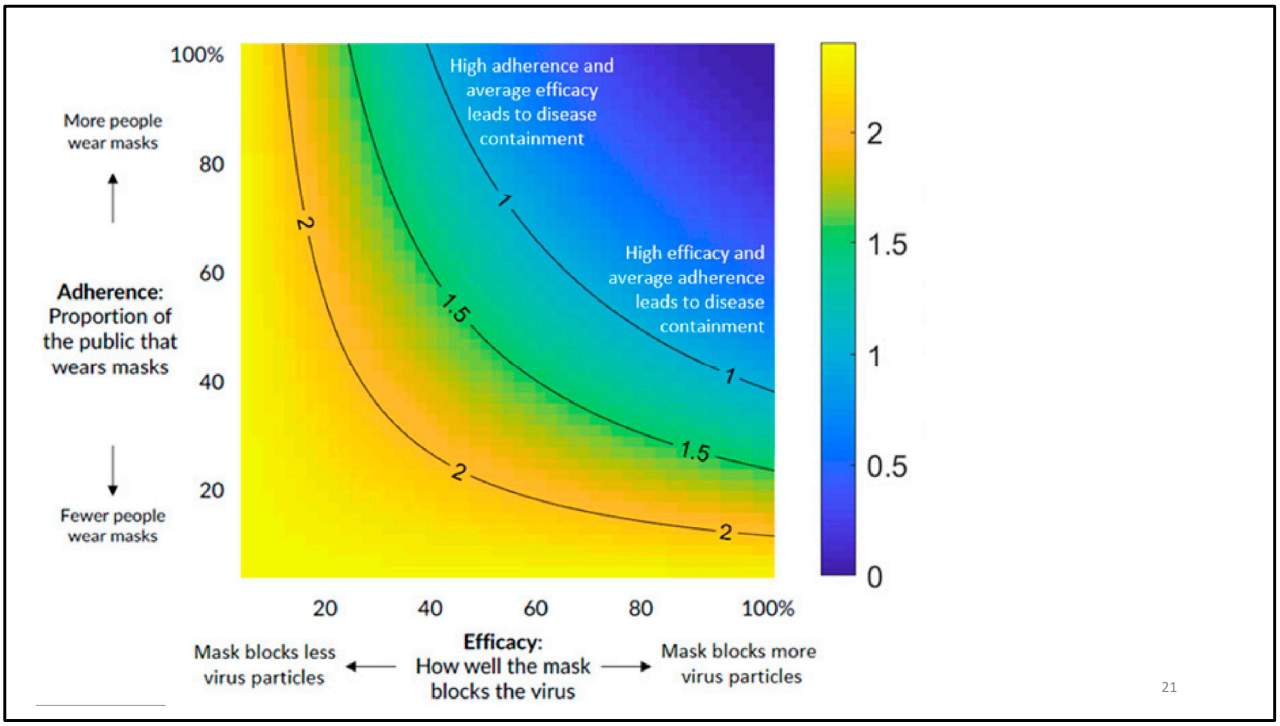
Anfinrud P et al. Visualizing Speech-Generated Oral Fluid Droplets with Laser Light Scattering. NEJM 2020; 382: 2061-3.



Some more non-randomized evidence on the impact of **introducing and lifting non-pharmaceutical interventions** on the reproduction number R which is quite informative altough not always easy to interpret..

Li Y et al. The temporal association of introducing and lifting non-pharmaceutical interventions with the time-varying reproduction number (R) of SARS-CoV-2: a modelling study across **131 countries**. Lancet Infect Dis 2020 Published Online October 22, 2020
https://doi.org/10.1016/S1473-3099(20)30785-4

But for assessing what the real contributions of non-pharmacological interventions are we need RCTs. This website keeps track of the emerging randomized evidence: https://www.bessi-collab.net/



Howard et al. An evidence review of face masks against COVID-19. PNAS 2021;118: e2014564118. (https://doi.org/10.1073/pnas.2014564118)

Bendavid E, er al. Assessing Mandatory Stay-at-Home and Business Closure Effects on the Spread of COVID-19. European Journal of Clinical Investigation 2021 (in press) (https://doi-org.vu-nl.idm.oclc.org/10.1111/eci.13484)

It is likely that social distancing plus face masks together can keep R (reproduction number) far under 1 IF the compliance with these measures would really be good (and the masks of at least acceptable quality).
For the face masks the figure shows that compliance is a strong determinant of effectiveness (they just don't work if you don't wear them).
The level of compliance may be driven by aspects of culture and adequacy of enforcement and oversight (which can be considered part of culture as well).
Levels of compliance differ strongly (due to differences in culture) between countries and between population groups within countries.
This is where high intensity measures come in: these are needed to compensate for poor compliance with low intensity measures.
The problem is that the high intensity measures have often harmful economical or

social side effects.

Lessons to be learned

- Look not at current level but at doubling time when growth is **exponential**
- Take **simple** measures, do that **quickly and** follow a pre-defined **road map**
- Be **transparant**, including about uncertainties, and very **consistent**
- Have a clear **command structure** and avoid decentral decision-making
- Avoid lenghty discussions, act **decisive**, and **enforce** measures taken
- **Collaborate** internationally and learn from other countries
- Base policies on **best** public health, economical, behavioral **evidence**
- What is best for **public health** is also best for the **economy** – ***NO DILEMMA***

22

Disclaimer: views from an interested outsider who happens to be an epidemiologist but not at all an expert on infectious diseases and outbreak management.

NL really needs to learn a few lessons: in Europe only Bulgaria was slower in organizing the vaccination campaign and on a ranking of Covid response of countries NL is #75 (just above Libya) – Top 5: New Zealand, Vietnam, Taiwan, Thailand, Cyprus

Gibney E. Whose coronavirus strategy worked best? Nature 2020; 581: 15-6.
Han E et al. Lessons learnt from easing COVID-19 restrictions: an analysis of countries and regions in Asia Pacific and Europe. Lancet 2020; 396: 1525–34.
Haug N et al. Ranking the effectiveness of worldwide COVID-19 government interventions. Nature Human Behaviour 2020; 4:1303–1312.
https://www.nature.com/articles/s41562-020-01009-0
Brauner JM et al. The effectiveness of eight nonpharmaceutical interventions against COVID-19 in 41 countries.

https://www.medrxiv.org/content/10.1101/2020.05.28.20116129v4.full.pdf

Michael Baker and Martin McKee. All countries should pursue a Covid-19 elimination strategy: here are 16 reasons why. The Guardian 28 January 2021. https://www.theguardian.com/world/commentisfree/2021/jan/28/all-countries-should-pursue-a-covid-19-elimination-strategy-here-are-16-reasons-why

Ranking the Covid response of countries:
https://interactives.lowyinstitute.org/features/covid-performance/

https://www.tweedekamer.nl/sites/default/files/atoms/files/20200930_gesprek_vws_redteam_presentatie_wim_schellekens_bert_slagter.pdf
https://debatgemist.tweedekamer.nl/debatten/redteam-wim-schellekens-en-bert-slagter

It's really wonderful what research contributed over the last year in the fight against the Covid pandemic. Especially the ultra-quick development of vaccines was impressive and that now seems the the essential game-changer.

I have been critical on both research and on policy. But I firmly believe that we need both– preferably in improved form – to navigate ourselves out of the crisis.

Yong E. How science beat the virus: and what is lost in the process. The Atlantic. December 14, 2020. https://www.theatlantic.com/magazine/archive/2021/01/science-covid-19-manhattan-project/617262/

Callaway E et al. COVID and 2020: an extraordinary year for science. Nature 2020; https://www-nature-com.vu-nl.idm.oclc.org/immersive/d41586-020-03437-4/index.html

Yin Y et al. Coevolution of policy and science during the pandemic. Science 2021; 371: 128-130. https://science.sciencemag.org/content/371/6525/128?rss=1