Suppressing the epidemic with repeated cycles of mass testing, isolation, and peaceful periods

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TRANSLATION NOTICE

THE ORIGINAL DOCUMENT IS IN HUNGARIAN, AT
https://docs.google.com/document/d/1_kFuwlvG2Jo99UC222bdzWt5-pMKt4TQ4_kO6z7qxuE/edit#

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We consider it important that the rules for controlling the epidemic are followed by everyone - our proposals and our work do not replace them. For more current information, visit https://koronavirus.gov.hu/ website.

Our goals

- investigate and expand the boundaries of the PCR sample pooling procedure for epidemiological purposes (important: not for diagnostic purposes using a reduced standard).

  There may be ways to use it (official bodies are entitled and able to do this):

  - Plan A: regular screening + isolation of the whole country (if adequate resources are available and this is the optimal way)

  - Plan B: make available for any other epidemiological activity the developed mass screening methods (if Plan “A” is not optimal epidemiologically or otherwise, or does not have sufficient resources for it)

- Make it available to the world in English as soon as possible so that any country may apply our results; i.e. publish.

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Contact: suppress-covid19-pandemic@googlegroups.com **Attention, this is a public mailing list!**
Web: https://sites.google.com/a/torokcsalad.hu/poroly/

Thanks to those who helped, help and recommend others for consideration:
- Dr. Ferenc Nagy, Director General of the Szeged Biological Research Center, Academician
- Endre Csóka, Pál Erdős Prize-winning mathematician, Rászi Alfréd Mathematical Research Institute at the Lovász-Barabási-Nešet Sync member of a research group. He specializes in graph theory, probability calculus and mechanism design.
- dr. Péter Török, family doctor, winner of the civic section of the Hungarian Silver Cross of Merit
- dr. Biologist researcher Viktória Lázár, Fellow of the Human Frontier Science Program, Israel Institute of Technology

International examples: which countries have already embarked on this path or similar:
- Germany: https://aktuelles.uni-frankfurt.de/englisch/pool-testing- of SARS-CoV in the samples 02-Increases-Worldwide body capacities Alemany-times-over /
- Israel: https://www.medrxiv.org/content/10.1101/2020.03.26.20039438v1
- UK: https://twitter.com/PaulFreemont/status/1242893427831967745
- USA: https://jamanetwork.com/journals/jama/fullarticle/2764364
- Korea: http://www.koreabiomed.com/news/articleView.html?idxno=7966
- Romania: http://www.dspbihor.gov.ro/2020/04/Informatii%20publice/Comunicate%20de%20presa/Comunicat%20de%20presa%2010042020_2.pdf

English:
- Medium.com: https://bit.ly/2RtwSCW
- Interactive model: https://bit.ly/349p9PA
- G doc: https://bit.ly/2xOvGTK

Executive and press summary

Temporary video summary in Hungarian: https://www.youtube.com/watch?v=yq_OG_HgXho In

In short, the point is:

- *(near) total population screening (e.g. via PCR pooling every 1-5 days) + **isolation of infected [groups]** for a few weeks*
- *repeated whole-country screening after 15-30 days (this could be even longer via competent epidemiological surveillance),*
- *repeated for a few months.*

What can be achieved with this? With proper caution, life can be restarted virtually risk-free (if the doubling time is reduced too much, [monitored via hospital admissions] simply the next round of screening should be brought forward at most), and deaths can be kept to a minimum: deaths can stop at as few as 290 people [in Hungary, according to our model]. The advantage of this method is that it works even if the PCR tests are only 85% accurate:

***The PCR-related part of the feasibility is an important task, because although some parts have already been tested abroad and at home (March 31 afternoon news), the scale and accuracy is still an issue. The task is to further specify this operation, to provide the necessary materials and capacities, and to organize and implement it for the population.** This is a very big task. Therefore, we recommend this plan to the Hungarian official bodies: they also have competence and financial resources in other fields. It is our mission to make this proposal, so elaborate that we can say for our part: it is worth trying to overcome the epidemic!*

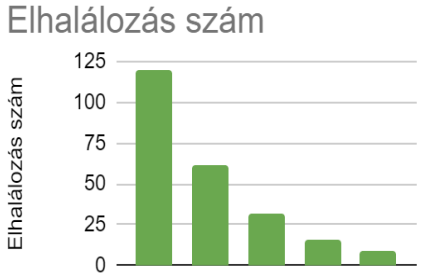
In response to the further spread of the COVID-19 epidemic, many Western states have changed their treatment strategy: instead of accepting an expected mortality rate, focusing on the flattening of the curve, and eventually reaching herd immunity [via vaccination or otherwise], they are setting a goal similar to that of Asian states: eradicate the epidemic. We follow this sentiment.

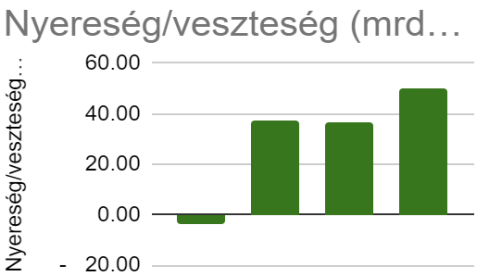
There are several ways to achieve this goal: a vaccine, a cure, or the isolation of those infected. While we wait for the first two, complete mass testing is needed at first; followed by rapid targeted testing to isolate infected people. In this way, we have saved human lives, and it is possible for the non-infected to operate the economy and society as soon as possible. We propose an implementation of the “at first” mass testing measures here.

According to our model, the total social savings are HUF 3-4 billion per day [in Hungary], as with proper caution life can be restarted essentially risk-free (if the doubling time is reduced too much, the next screening round must be brought forward at most), and deaths can be reduced to a minimum: up to 290 people the number of deaths may stop.

Mass testing is therefore one of the keys: a relatively inexpensive solution is to put available PCR equipment in order. There have been practical obstacles to effective mass measurements so far, but with the solution described in this paper, we provide a realistic solution to test the Hungarian population in days (this may be needed every 14-30 days for the next 2-5 months) - and quickly isolate infected patients to avoid viral transmission.

With our proposed solution, the number of deaths could be kept below 300, and the decline in GDP could be reduced by HUF 120-130 billion over a few months, even according to the most modest calculations (if the assumption is that the decline in GDP would be only 3.2%).





[Y axis: deaths,
X axis: round of testing???, ~1 month]

[Y axis: Money saved (billion HUF),
X axis: round of testing???, ~1 month]

Both elements of the proposal are simple - and neither is new:

1. Mixing samples from multiple (5-64) people: sample pooling

https://en.wikipedia.org/wiki/Group_testing
https://www.medrxiv.org/content /10.1101/2020.03.26.20039438v1
https://www.google.com/search?q=PCR+sample+pooling

In a screening sample (**saliva sample**) instead of a single person, **we test a community of 5-64 people - a couple of families or members of the work environment.** The idea may seem very simple, but the magnitude change between 1 and 5-64 in the present situation testing the population in under 5 days vs. 75 days is of fundamental importance. Also in costs: 0.9 billion (pool 64), 15 billion (pool 5) or 45 billion (traditional method). [numbers are in HUF]

It is also conceivable to use pooling in other ways, for example:

- When entering the country, e.g. Simultaneous screening of 64 truck drivers.
- Regular workplace screenings when many people work in one airspace.

2 Nationwide screening repeated every 14-30 days for a few months

If we test over and over again and isolate the infected (for a few weeks until they can become infected), we practically always jump back to a very early point in the exponential curve. This iterative method should be used to prevent re-outbreaks from internal sources. Thus, it is worth dealing with the situation for 2-5 months, from which time other methods (5-minute screening, vaccine, personal identification of vulnerability) are expected to provide no other solution to the problem.

You can try the recurrence frequency for different cases here [interactive spreadsheet in English]:
https://docs.google.com/spreadsheets/d/1zcW2pyTVRbVr6L1rUjr2S-u_d883GZfZ9LsYZuDMCvs

The vision for the proposal is therefore:

- **After the first full testing isolation, we keep border crossing to minimal and only for (group-)tested individuals**

- **The iterative method is used to prevent a second wave from internal sources. This can be omitted as soon as a drug, vaccine or accurate rapid test becomes available.**

Brief description of the practical solution

[specific to Hungary, population ~9.8 million]

1. We need 200-250 PCR instruments capable of detecting fluorescent signals. This is available in the country, either through rent or other measures. Where are such devices located? At economic operators, research laboratories, clinics, hospitals.
2. There is a need for practical PCR protocol, tailored to the current situation and policy goals. The optimum of accuracy and testing capacity must be sought, because in this case accuracy is not the primary consideration, ie it should be optimized for epidemiological screening, not for medical diagnostic purposes (see below: the model is also effective with 80% accuracy, but obviously more accurate, a up to a certain level of expenditure).
3. Available machines need to be staffed 24/7.
4. We must organize a process that looks like this, according to current knowledge [Hungarian, flow chart of sample collection and processing] : https://docs.google.com/drawings/d/1ZrrucnKxQf33jzSfyVQfAUsEj4zdO8IvtRqHKUjd2wE/edit and that all the details of procurement, training of manpower, logistics, etc. The main elements of this are the following -- and this part of our proposal is not covered in detail, but we entrust to the Hungarian state bodies. The following is not fully considered, however, our professional consultations so far have found the proposal to be feasible overall. It is therefore necessary to organize:
    a. the purchase and distribution of sample containers,
    b. the identification of samples (eg mobile phone numbers on a paper, associated with identification of containers)
    c. the, professional and safe group sampling,
    d. the transport of samples to PCR machines,
    e. primary (sms) notifications, and secondary, legal mandatory quarantine notification for
    f. the procurement of supplies and reagents for PCR machines
    g. the serious isolation of persons currently infected, ie quarantine actually observed by authorities. Within this, the isolation or retesting of people belonging to vulnerable age groups or groups, as well as the care of entire groups, will be important here, as the system signals entire families.
5. Using 200 machines we can do daily 200 * 8 * 94 test, ie 150,400 measurements [source of numbers?]. A negative measurement of 64 people at once tells you immediately that none of them are infected. With this speed, we could test 64 * 150 400 = 9 625 600 people in one day! Positive samples [may] require additional measurements, but the mathematical methods presented here can be used [English!] to keep the number of tests required below 200,000, even when identifying those infected.
6. Thereafter, this scan of the entire population should be repeated every 14 to 30 days. The frequency depends on the doubling rate and the accuracy of the PCR measurement.

Here is the model, we suggest you make a copy and experiment with it, we welcome suggestions: https://docs.google.com/spreadsheets/d/1zcW2pyTVRbVr6L1rUjr2S-u_d883GZfZ9LsYZuDMCvs

END OF HAND TRANSLATION, BELOW IS PURELY GOOGLE TRANSLATE, AS IS, FROM HUNGARIAN TO ENGLISH

Q: What are some issues with this plan?

The lack of all kinds of material is starting to be a problem internationally, given that many countries have embarked on a similar path at once.
At first, the availability of the Covid-19 test kit seemed to be the most serious concern. Of these, for pool 64, 1,563 the country needs units for a full population scan. It is expected that by the time of the next scan, global production capacity will be sufficient, but the first round is questionable, according to our experts. What we do know is that yesterday (March 27) there were still 500 kits in stock at one source in South Korea. Production also takes place at home, but we do not know the capacities.

What is even a bottleneck: RNA isolation as a work phase. This is another serious task. We can work on the solution ourselves, and we are happy to hand it over to the state actor. In principle, the protocol described here or analogous to it should be used for all PCRs:
https://www.medrxiv.org/content/10.1101/2020.03.26.20039438v1 In

all laboratories used for this purpose, positive + negative controls
must first be run , and the system must be set up. If the PCR method is not robust enough (this will become apparent on the fly), it can be confusing that each PCR instrument is a little different. This would be preceded by a mandatory first setup attempt.

Question: It is a known problem that the PCR test only detects 80-95% of cases. What is the solution to this?

Yes, it is very important that this is not a test of diagnostic accuracy and responsibility, in a legal, medical or scientific sense. We do not diagnose, we treat an epidemic: they determine probability. This will reduce - not eliminate - the epidemic. We are reducing deaths, relieving doctors, the health care system, society and the economy.
Try the model at 80%, adjust the test frequency and number of duplication days:
https://docs.google.com/spreadsheets/d/1zcW2pyTVRbVr6L1rUjr2S-u_d883GZfZ9LsYZuDMCvs/You
can see that 80% effect may also mean that if 20% of the population does not show up at sampling, it could also mean that the PCR test is not 100%, or its addition - but obviously it would be better to be more accurate, up to a certain level of input during the measurement. After all, if we filter with 80% accuracy, we have to run a filtering cycle more often, or we may have to apply stricter distance-keeping practices. At the same time, it is a manageable problem.
On the other hand, it is important that if we take a work or residential community (several families in the neighborhood) into a pool, and 2-3 people are expected to be infected here, the accuracy is exponential: in case of 2 infected we will have 96% accuracy, in case of three infected 99.2 %. If the test base is 90% accurate, then the same numbers will be: 99 measurements will be 99% accurate

for 2 infections, 99.9% for three infections. This would mean reducing the number of unrecognized cases from 100,000 to 100. If there are 5,000 patients in the country right now, it's 5.

At the same time, there is a need to develop this PCR protocol in a practical way, optimized for the present situation and purpose. The optimum of accuracy and throughput must be sought, because in this case, accuracy is not the primary consideration, but accuracy can be degraded for the whole process.

At the same time, a forum based on a plasma-based test was launched:
https://groups.google.com/forum/#!topic/suppress-covid19-pandemic/5FF8Dz-nsX4

Question: What restrictions should be introduced during the measurement?

It is necessary to decide on the extent to which it is worth imposing an exit or exit ban in a geographical area for the duration of the full screening. The aim is to prevent people who have not yet been screened but become infected from infecting people who are already producing a negative test.

Important: the total curfew does not guarantee that the geographical area tested is 100% virus-free, ie it will remain infected afterwards, and our method provides a treatment for this as well. There are two known reasons for the residue:

- Transfection from objects, airspace.
- Due to the false negatives of the PCR measurement indicated by the German experience.

Question: How many main common patterns are the optimum? 5? 10? 15? 64?

Forum: https://groups.google.com/forum/#!topic/suppress-covid19-pandemic/Qkzule-GjJE

This is a practical matter of biology and lab work that we can't decide. What we do know is that the Germans use pools of 10, the Israelis used 64 - that's more of a lab than such an industrial scale, it may not be scalable to the size we're targeting.
Overall, this is an issue where professionals outside of us need to get the most out of the situation by pushing the boundaries, relocating standard options (accuracy, flawless work), and increasing the throughput of the entire system (hundreds of labs) by optimizing for tight resources (materials, tools , live labor, etc.).

Question: Managing 5-64-fold false positives

Forum: https://groups.google.com/forum/#!topic/suppress-covid19-pandemic/Qkzule-GjJE

If a sample already has 1 positive, the group's test result it will be positive, but that doesn't mean we give the other 4-63 people the feedback that they need to be quarantined - unnecessarily. As in this paper is available, a very minimal number of additional tests must be performed using appropriate mathematical methods to tell which of the 64 people are infected.

In any case, it is an important task to optimize the effort to minimize false positives and the expense: when will it be optimal to use PCR machines (and system capacity) to “release these people from quarantine” and how much burden will be placed on the sampling and evaluation process? by striving for this. The optimum also depends on the availability of test kits, the load on the system, and the value of a person’s loss of value creation - and the risk that the second measurement will be a false negative. This is an optimization task.

Question: Regularly repeated screenings - how often?

In the calculation table of our model, estimates can be set that determine the frequency of repetition of measurements. This will be mainly determined by the extent to which the distance habits of the population push out the doubling of the infection. The more they are pushed out, the less often the measurement has to be repeated.
The mathematician for epidemiological modeling is not currently on our team, butthe Operational Staff they are in. With their competence, a more optimal procedure can also be developed, as well as a way to monitor the spread of the epidemic with smaller sampling and thus delay the time of new full measurements with smaller area screenings + isolations. Our model does not cover this, but after the first round of screening, experts competent in this field will have time to develop this direction as well.

Question: What else can be improved on this?

Lot. It was just a step or two down the road, a continuation of previous ideas. We stand on the shoulders of giants. We hope you add your own ideas and better methods emerge. A few ideas:

You can change the filtering target area: We filter the

- whole country first, and then filter the faster-spreading areas more often based on the resulting image, thus reducing the frequency of full re-filtering (reducing the efficiency of nodes in a network sense).
- If there are few resources (human, material), then in the first round it is possible to search for target areas based on some logic,
- or to check by sampling (also using sample pooling, ie the measured points are a group of 5-64 people). distribution and further filter where it appears necessary. Obviously you have a risk, but it’s much better than nothing, and you can specifically calculate the optimum.

Can be developed on PCR pooling itself, protocol, PCR pre- and post-process.

There is another huge room for improvement in the evaluation of the PCR tests. The raw output is a time series which has much more information in it than what we generally use. Instead of just checking whether the fluorescent signal crosses a certain threshold after a certain number of cycles, machine learning will help us much better exploiting the information from this time series. Accordingly, our final pooling algorithm will not assume that the output of a test is binary but it is a probability or a signal strength.

The frequency of screening can also be optimized: initially iterating every 3-5 days, minimizing the number of infections in several rounds, and then thinning it. The advantage of this is that deaths can be minimized, as the first few iterations return to an early point in our exponential function, so that increases in the number of infected days in future waiting days are nominally lower than if we were moving at a later stage of the function.

Biological and Equipment Background

PCR measurements can determine whether a particular piece of DNA (base sequence) is present in any sample that contains DNA or RNA. In the current epidemic, we are looking for a piece of RNA characteristic of the COVID-19 virus in human saliva. Screening usually requires enough kits to examine 100 samples, in the Hungarian situation a full population scan requires 1563 packages of 100 in the case of 64 pools.

The PCR measurement is 90-95% accurate according to German experience. Concept: when a measurement method recognizes as healthy a sample that comes from a person who is actually sick, it is called a “false negative” (the reverse of this: it indicates a healthy person as a patient - this false positive). Current PCR measurements give a false negative of 5-10%. This is probably due to the virus hiding in the deeper regions of the throat.

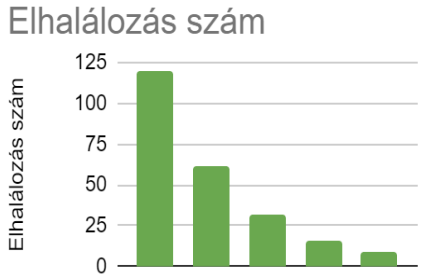
Wikipedia writes more about PCR here:
https://en.wikipedia.org/wiki/Polimer%C3%A1z-l%C3%A1ncreakci%C3%B3

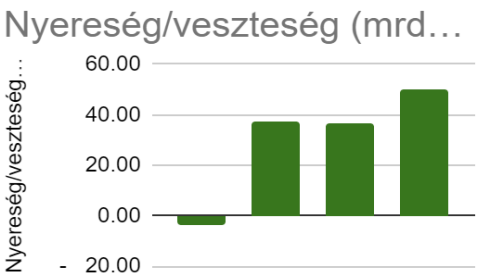
You can read about PCR sample pooling for Covid-19 here :
https://www.medrxiv.org/content/10.1101/2020.03.26.20039438v1

Calculations, modeling

The most urgent implementation of the first round of screening is clear based on current international examples. There is no question to be examined about the model either. There is time to make further decisions in the next period, two examples of which are shown below, and we recommend putting real further modeling in the hands of competent experts in this field and shaping it according to future visible data - essentially ordering more screening rounds. .

Correctly chosen repetition frequency

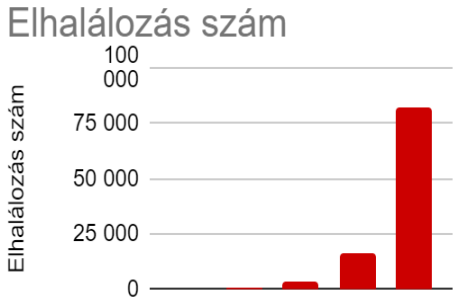


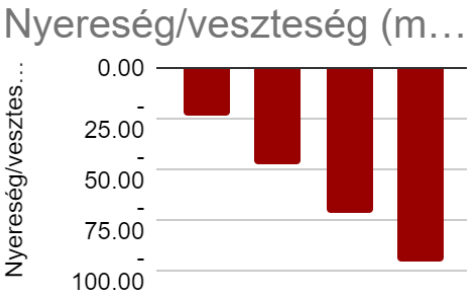


Model 1. Good parameters	No. infected people	days between full-scans	doubling rate of infections (days)	no. infected people after the scan	Number of deaths
Initial position	3 000	**14**	**3.8**	150	105
iteration 1.	1 928	14	3.8	96	67
iteration 2.	1 239	14	3.8	62	43
iteration 3.	797	14	3.8	40	28
iteration 4.	512			26	18
		56.00			262

Mortality rate: 3.5%
PCR filtration accuracy: 95%

Incorrectly selected repeat frequency





Model 3. Failed parameters	No. infected people	days between full-scans	doubling rate of infections (days)	no. infected people at the end of period	Number of deaths
Initial position	3 000	**21**	**3**	120	120
iteration 1.	15 360	21	3	614	614
iteration 2.	78 643	21	3	3 146	3 146
iteration 3.	402 653	21	3	16 106	16 106
iteration					4. 2 061 584 82 463 82 463

Death rate: 4% (Italian, British, German data comparison)
Filter accuracy: 96%

Facts, assumptions

Hungarian GDP (bn) EUR 42 662 billion
per day GDP: 117 HUF bn
Estimated GDP decrease: 3.2%

Daily damage (price of delay)

Human life: above percentage of illnesses, calculated on the basis of exponential quantity.
Material 3.74 HUFbillion

Issues, uncertainties - and solutions

PCR measurements will not take 3 hours. Solution: you need more machines.

Currently, RNA purification is more of a concern because this procedure precedes PCR and even the samples are not pooled. Therefore, according to our current process (April 4, 2020), we still have to work ten times as many units there.

If it's that simple, why don't others do it? But they do.

Learn more:
https://www.google.com/search?q=PCR+sample+pooling

Can mixing multiple samples cause the sample to be over-diluted and not indicate the measurement?

There are various competing solutions for this in the world, and currently the consensus is between 5 and 10, and there has also been a successful experiment with 64 samples.

Sources:
https://www.timesofisrael.com/to-ease-global-virus-test-bottleneck-israeli-scientists-suggest-pooling-samples/ (Thanks to you: Dr. Gergely J Szöllősi)
https: //
medium.com/@dinber19/more-with-less-using-pooling-to-detect-coronavirus-with-fewer-tests-8ba1a2cd8b67
https://www.medrxiv.org/content/10.1101/2020.03.26.20039438v1

A PCR challenges, professional remarks

"- contamination: PCR extreme contamination is dangerous, especially samples can contaminate each other
- real-time PCR because the result is also contaminating (PCR is molecularly sensitive), even better
- look at dimensional pooling (2D : square grid and row and column pools, but there is also a 5D pool, it identifies the patient with low transfusion)
- we don't know how much pooling reduces sensitivity, but it's true it's less interesting now
- it won't go without a robot already another time-scale put together)

But congratulations anyway OK!"

Sourcing and Service Sources

We encourage anyone who knows about a sourcing or service source to write to this: https://groups.google.com/forum/#!topic/suppress-covid19-pandemic/fCtldlUj4H4

topicIf you have a lab or rent a lab machine, please fill in this: https://forms.gle/FrLALdgr2mNsvZyy8