COVID STRATEGY: Systematic Concentric Circle Testing Methodology

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ABSTRACT

The WHO statement “Testing, Testing Testing!!!” has crucial value in the process of defeating the infection and terminating the SARS-CoV-2 pandemic crisis.

When the vaccine finally becomes available, a massive vaccination program will need to be applied at a general population level. However, until the introduction of a program of vaccination and development of effective treatment, systematic testing remains a decisive factor for success.

As in 7th of April, there are more than 600.000 possible unidentified infected worldwide if we apply the 3.4% mortality rate to the number of deaths (70.533 deaths, 1.287.169 confirmed, 1.857.131 estimated). [1]

The mortality rate is calculated extracting the number of deaths from the number of confirmed infected. Starting with 2.3 on 20th February 2020 in China, the mortality rate in 7th of February reached 5,47%.

The continuous increase of mortality is reasonable explained by the incorrect number of the infected, due to lack of testing. Because of inefficient testing, we don’t know exactly how many are infected.

The lockdown conditions are decreasing the infectivity rate (R0) from 2.2-2.4 to 0.67. [2] However, it is obvious that there are specific group of people who are candidates to become super-spreaders, which in case of being unidentified infected will infect large number of people even if the nonpharmaceutical contra measures are taken.

The solution is to address this group with a proper testing strategy and to continue to enlarge the testing areas systematically and continuously.

The description of the testing methods with advantages and disadvantages has been analysed in multiple situations and there are numerous related articles published in science journals and publications. None of the testing methods have themselves been individually proven as being generally effective and applicable; a combination of them may amplify the advantages and minimize the disadvantages of each.

This paper proposes an effective combination of three imperfect testing methods as a solution for a testing strategy, and as a basis for rationalizing and coordinating medical, social, economic and political measures [3,4]. Areas can be cleared of infection and coalescing of areas will help remove the threat.

The rationality for this is based on several empirical assumptions:

- The entire population cannot be tested at the same time.

- The higher the number of people that are tested, the more asymptomatic or mildly symptomatic infection carriers will be identified.

- Testing lower numbers will result in the underestimation of the extent of spread of the infection, and possible overestimation of the mortality rate.

- The accuracy of the testing method will influence the effectiveness of diagnosis.

- The number of infected will influence the impact on the medical care systems. However, not all those infected on testing will require medical care, nor intensive care.

- Logistic and economic conditions may determine the level of care.

- The role of the medical system is crucial, and what is available may be inadequate.

Could the problem (number of infected patients, and consequent drain on resources), or the solution (prevention, testing and identifying the infection, but better focus of isolation and medical treatment) be the answer?

AIM

The strategy proposed, aims to provide an effective testing solution required to limit the magnitude and duration of the epidemic, while preserving the functionality of the essential services.

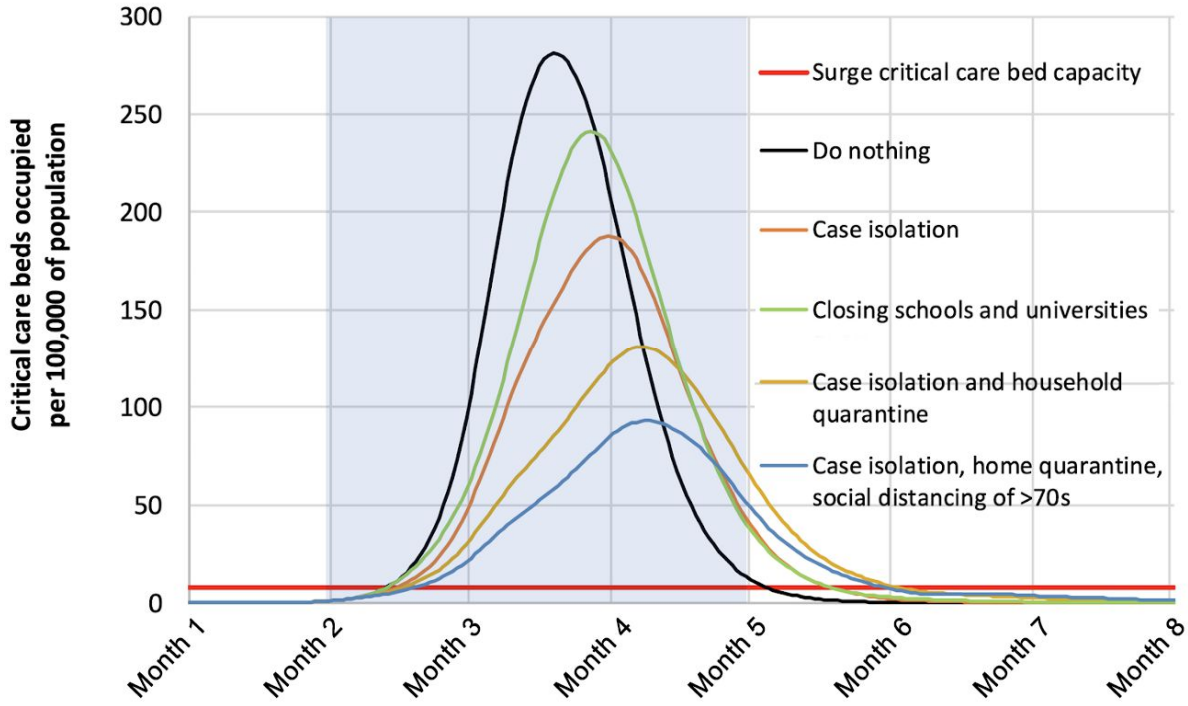
DESCRIPTION

The SARS-CoV-2 pandemic is dramatically challenging the medical systems all around the world. The extremely high infectivity rate, even before the symptomatic stage and the general ease of cross-infection, in conjunction with a significant number of asymptomatic or low and minimally symptomatic patients, causes tremendous difficulty in establishing a clear situational awareness as to the number and distribution of the individuals infected.

The macroeconomic and social effects are unprecedented, affecting the availability of necessary resources to manage the special and unique situation.

In order to prevent the development of the expansion of the pandemic, the identification of those infected is crucial. This is followed by case isolation, which is the base for reducing the dimensions of the epidemic (Figure 1).

Fig 1: The peak need for ICU beds dependent on social distancing measures



Modified from Ferguson N et al. Impact of non-pharmacological interventions (NPI's) to reduce CoVID-19 mortality and healthcare demand [5]

Indiscriminate dramatic social distancing measures are nothing else but an attempt to manage the absence of an efficient solution for identification of the cases*.[*6]

The non-availability of an efficient single method of testing to be applied at the populational level is the main difficulty, and many nations are utilising several methodologies and strategies in order to understand the magnitude of the situation.

The proposed strategy requires introduction of an objective, coherent, systematic, efficient and effective testing methodology with the purpose of triggering the additional adequate measures required to limit the expansion and to reduce or eliminate the epidemic.

A "door to door" population testing strategy has low chances of success, because there is a high risk for the tested population to be infected by the potential carriers from the untested population. Moreover, the costs, logistics, and administrative requirements of testing the entire population could be predicted as very difficult,

almost impossible to be achieved.

This strategy proposes a narrowed testing methodology, guided by precise criteria, based on the population at risk, the gravity of evolution, the functionality of the essential services, and the characteristics of the transmission and virulence of the epidemic.

The testing process will follow the model of several concentric circles in expansion, starting with well-defined circle centres: the medical system; the suspected voluntary isolated patients; the essential services; the population at risk for severe outcome; security and emergency systems; and the transportation of persons and mobility of goods.

TESTS AVAILABLE

1. Temperature screening

Clinical COVID-19 is associated with a high temperature ($T \geq 38°C$). This is easy to measure using a variety of digital electronic thermometers. However, it is very non-specific, and usually only presents when the other "flu-like" symptoms are already present. For this reason, although of assistance in the clinical disease screen, it does not pick up those who are asymptomatic, but may be carrying the virus, and absence of pyrexia will not confirm the absence of infection.

2. IgM/IgG antibody detection method

IgM/IgG Assay method, based on the immune response of the infected body, reveals the presence of the virus, and the stage of infection (at the beginning, the middle or at the end). With a level of accuracy described at around 85% [7;8], the method is fast, the results are available in 20 minutes on site, without special lab requirement, at significantly less cost.

The IgM/IgG testing method is limited not just by the level of accuracy but also by the presence of the IgG and IgM. In SARS CoV-2 infection, the IgM is detectable after 7-10 days from the infection, and IgG within 10-14 days. Considering this disadvantage, the IgM/IgG detection should be used as a triage method, revealing, with 7-10 days delay, the infectivity picture at the systemic level. The test therefore cannot be used for absolute initial entry screening.

The overall testing sensitivity has been reported as 88.66% and specificity of 90.63% [9], although there is some variability between authors. At the systemic level, an assumed accuracy of 85% after 7 days from the infection is below of all the related published results, but still acceptable and usable in a coherent strategy.

This method would provide the possibility to identify those patients who had been infected, but if

asymptomatic would still be a source of infection, and at a strategic level. would provide a high statistical value.

The IgM/IgG testing provides the advantage of revealing the already immune subjects who could be used to maintain the functionality of essential services, with the special emphasis on the health care system, as well as all other essential services, as they would have significant immunity. Moreover, at the end of the present epidemic wave, an extensive and complete immunity map, would be essential for strategic vaccination plan (if will be available), and for adapted strategies in front of potential future waves.

"The antibody detection offers vital clinical information during SARS-CoV-2 infection. The findings provide strong empirical support for the routine application of serological testing in the diagnosis and management of COVID-19 patients." [8]

3. **Real-Time Polymerase Chain Reaction Test (RT-PCR)**

Real time RT-PCR is a nuclear-derived method for detecting the presence of specific genetic material from any pathogen, including a virus. Originally, the method used radioactive isotope markers to detect targeted genetic materials, but subsequent refining has led to the replacement of the isotopic labelling with special markers, most frequently fluorescent dyes. With this technique, scientists can see the results almost immediately while the process is still ongoing; conventional RT-PCR only provides results at the end.

While real time RT-PCR [10] is now the most widely used method for detecting coronaviruses and is the only method recognized as providing the standard testing method, many countries still need support in setting up and using the technique. It is costly and time consuming, (at least 4 hours for the method, with additional time for transportation of the samples to the lab – up to 48 hours). It is not yet effective for extensive application due to the infrastructure requirements (limited number of labs), biosecurity during the transportation, and cost.

The method is also affected by errors depending of preanalytical and analytical sets of conditions

Performance of the COVID-19 RT-PCR test against the expected results are: Positive percent agreement 40/40 = 100% Negative percent agreement 50/50 = 100% (95% CI: 91.24% - 100%). There is correspondence between development of viral load during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, clinical course and positivity of (real time) reverse transcription polymerase chain reaction (rRT-PCR) assays[11].

4. **Epidemiological investigation**

This method alone is meant for and is effective at the beginning of the epidemic in order to identify all the possible carriers, and not in the situation when the virus is already present in the general population.

The method of epidemiologic investigation is meant to identify the contacts of the confirmed infected patients, has shown limitations and inefficiency, due to the rapid spread of the infection.

During the time of investigation, the secondary contact circle and then the tertiary circle, become sources and start to spread the infection, even before the investigation reaches them. Consequently, there is a high probability of missing contacts who would then become the sources of new infections. Extensive epidemiological investigation is not efficient anymore in this stage of a pandemic where the infected are already possible present everywhere, due to the high level of infectivity and general receptivity.

Functional and economic impact of isolation measures for the suspects without the confirmation of the infection affects the efficiency of the entities to which they belong, which, in the case of medical personnel or the essential services and security or emergency intervention personnel will dramatically impact the essential services themselves (i.e. hospitals). [6]

Only narrowed and limited investigation triggered by the IgM/IgG testing strategy, completed by the standard RT PCR confirmation will prove the value and necessity of this method.

Table 1. Testing methods parameters

Parameters	**RT PCR**	**IgM/IgG**
Time of detection	Dependent of Limit of detection	IgM 7 days IgG 14 days
Sensitivity	Gold Standard depending on preanalytical and analytical errors	88.66
Specificity	Gold Standard depending on preanalytical and analytical errors	90.63
Type	Quantitative	Qualitative
Significance	Presence of the infection	Stabilization Presence of infection Immunity
Time	Up to 48 hours	20 Min
Applicability	Infection confirmation	Systematic triage method Immunity map

Table 2: Applicability, advantages and disadvantages of the Methods

	Method	Advantages	Limitations	Application
1	IgM / IgG	Fast, affordable, mobile, repeatable	Low level of accuracy (sensibility sensitivity) Late reliability (7-10 day from the infection) Not for use for initial diagnosis	Large scale triage 85 % of infections
2	RT-PCR	Standard test	Time consuming, Expensive special infrastructure	Narrowed and precise confirmation of the suspects identified by the previous methods
3	Epidemiological Investigation	Identification of the possible infected (contacts of the confirmed infected)	High rate of subjectivity, Needs Lab confirmation Time consuming	Narrowed to define the primary contacts of the positive finding from the IgM/IgG triage and the confirmed infected

A testing strategy based exclusively on achieving 100 percent testing accuracy is unachievable and ineffective.

Although in most nations the IgM/IgG is not recognized as having strategic benefit, this strategy uses it as an effective epidemiologic triage tool, in order to effectively prioritize the entire testing strategy.

At the NATO level, a surveillance question was addressed to all representatives of the medical services, related to the usage of IgM/IgG in their countries. From 20 responders, just one admitted that the IgM/IgG could be use as orientation test at the end of quarantine but is not officially recognized. None of the 20 responding nations are not recognizing the IgM/IgG method as reliable, and they are not including it in any official strategy.

METHODOLOGY

The ***systematic concentric circle*** methodology consists of simultaneous testing, using the IgM/IgG Antibody Method (Assay method), as a base, starting with special initiation points considered as the centres of testing circles followed by enlarging the circles using the below described methodology. The method does not require a laboratory, can be applied on site by a technician, and requires 20 minutes for getting the results.

The rapidity, simplicity, mobility and affordability would compensate for the level of accuracy.

It will be possible that many of the possible infected individuals will be prevented within a very short time from further spreading the infection in the most sensitive parts of the society first, followed by broadening the testing until the ending of the epidemic.

The systematic and continuous sustained testing inside the described circles will eventually merge and clear the seven days retroactive maps, and the circles will be expanded, and will eventually merge at the entire society level.

Those individuals with an IgM positive reaction, will be considered as having very high chance of current infection, which will be confirmed with RT PCR. Those with an IgG positive reaction, are considered to have immunity against the disease following the symptom free quarantine period.

The same confirmation with RT PCR will be applied also to all their primary contacts made in the previous seven days, based on the epidemiological investigation. All the primary contacts of the confirmed infected, will be tested with RT PCR.

The IgM/IgG test as the triage method, will provide a 7 days retrospective map used by the epidemiologic investigation to identify the primary (direct) contacts. Just the primary contacts will be tested using the RT PCR. This will provide a real, current, updated map of the infection, but at significantly reduced cost.

The testing strategy needs to be accompanied by the other measures in order to be effective: protective measures, social distancing, narrowed and effective quarantine and treatment including partial, voluntary or legally enforced lockdowns.

The methods will have specific use aimed at specific processes.

Triage: **IgM/IgG rapid**

Expansion: **Narrowed epidemiologic investigation**

Confirmation: **RT-PCR**

The combination of the three methods should be applied simultaneously in 6 circles which will expand, until

confluence.

The strategy should be applied as a continuous, consistent and coordinated process. It will be essential that the testing strategy be accompanied by medical, social, economic and political adapted measures.

1. **Hospitals**

   The medical personnel and the administrative personnel will be tested before and after each shift. [12]. *In this case, 85% of those who are asymptomatic or when they are presenting mild and unspecific symptomatology but carrying the virus over the previous 7 days will be limited from continuing to spread the infection, through earlier detection.*

   Those who are tested positive will be isolated and tested with real time PCR for confirmation. The level one 7-day retroactive contact circle of these persons will be considered suspects and tested with RT PCR.

   The medical personnel also are tested after finishing their workday. Within the hospital a source may infect his/her contacts in consecutive moments, so the IGM will be detectable in consecutive moments. As the IgM/IgG method is a retroactive triage for mapping the infection, the repetitive tests will increase the accuracy of the method and will increase the chances of detection of the infection within the shortest time possible.

2. **The patients**

   All new patients arriving at the hospital will be tested in a triage area before entering the hospital. Any patient with a positive test result will follow the pathway and protocol for the infected patients.

   Thereafter, the first contact circle of these identified carriers/infected patients will be tested as well (family, friends...). This measure will dramatically decrease the chance of infection within the hospital and will increase the chances to identify the existence of the infection in a part of society.

   The hospitals should be considered the priority centre of systematic concentric testing strategy [12] because:

   - The medical personnel are the most exposed at risk

   - The infected medical personnel could be the most effective source of infection for the most endangered population (patients with comorbidities)

   - The risk of infection is higher than in general population

   - Effective reducing the risk of infection of the hospitals

- Effective early detection of infection of the hospitals

- Effective early diagnostic of the incoming patients

- Effective detection/clearing of the infection inside the contact's circles

- Effective motivation of the medical personnel. Ensuring the continuity of testing among medical personnel will exponentially raise the morale and the sense of security of this very vulnerable group

The result consequent to this screening will be fewer patients both admitted to hospital, and the contacts, will be increased cleared hospitals and contact circles .

3. Isolated suspects

The voluntary isolated suspects are tested with real time PCR only should they develop specific symptoms. If they remain asymptomatic during the isolation period, they are released from isolation and they will have the similar freedom of movement as that of the general population, as is already the case in most countries (movement limitations, social distancing), but will still be allowed to leave the isolation for defined circumstances.[6]

Systematic testing of the isolated population with the Assay Method will identify 85% of those infected, and after PCR confirmation they will be quarantined and treated.

The patients with negative results will be tested again at the end of the isolation period, before being considered as the general population.

Ths measure will decrease the chances of infection from this highly potential source of infection by up to 85%.

4. Population at risk of severe disease

There is a known population at risk defined as the candidates for the ICU and for death caused by COVID19 [13]

Individuals above 65 years of age, especially those with comorbidities, are subject to special restrictions and measures in many countries.

A weekly systematic testing program could be feasible for this special population category, due to the need for early diagnostic and more effective therapy

- The aged often live in pairs of two in families, or in nursing homes with many possible cohabitants, having consequently, a multiplying risk of infection. The early detection would decrease the risk of

overloading the hospitals and most important will decrease the pressure over the ICU capabilities

- Predictability of the number of severe cases will support a proper readiness of the system to face and solve the situation [4]

5. Essential services: water, power, gas, communication, food, administration

The employees running the essential services are exposed to the same risk of infection as the general population is, by living with their families. Added to this, they are in permanent contact with their colleagues and other persons during their work time. Therefore, they can import or export the infection to and from their families and to and from their institution or general population.

The rapid IgM/IgG test will decrease the risk of infection and in a slightly longer term will also enhance the effectiveness of the essential services being delivered.

Daily tests will increase the accuracy, by its repetition.

On the other hand, a positive test will allow an early detection of the risk and effective measures to coup the bridge in bio security of the services.

Furthermore, a positive result will trigger the testing in the primary contact circle of contacts, enlarging the circles of clearing process in general population.

The same combination with epidemiological investigation and RT PCR will be applied.

6. Security and emergency services: police, firefighters, military

The principle is identical with the previous category.

Moreover, the risk of receiving or spreading the infection is higher, due to the specificity of their mission, interacting randomly with general population (many of whom are not obeying the rules of isolation or escaping from the quarantine with high risk of positive infection)

7. Mobility of persons and goods:

Systematic testing of all the travellers and transporters: ground, air or maritime, at origin and at destination and at the borders. This measure will prevent the import-export of the infection.

The testing should be also applied at all borders.

Furthermore, the measure will add a sense of security to the mobility of goods.

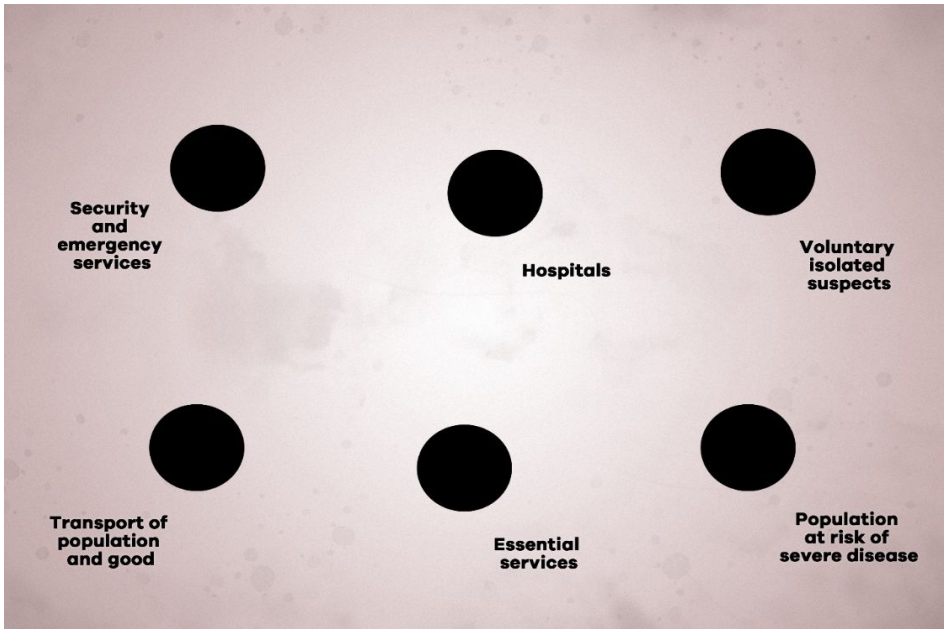
RESULTS / ENDPOINTS

With the expansion of all the described circles of this concentric testing strategy, the circles would merge at some point, having as a result, due to a coherent and narrowed mass testing strategy:

- Early diagnosis
- Efficient and more predictable epidemic limitation in time and amplitude
- Effective isolation of the infected persons
- Decreased pressure on the medical system and ICU
- Functional hospitals
- Functional essential services
- Effective security and emergency response system

Graphic representation of the testing strategy in evolution

Fig 1 The 6 Target Circles for an area



The dark colour represents the uncertain presence of the infection

The lightening evolution of the dark black to gray, represents the increasing level of the cleaning in the target circle.

Fig. 2 Target circle (i.e. Hospital) before Testing

Systematic test beginning (white spot)

Measures for clearing the infection (lighter gray colour), identifying the primary contact circles (small dark black circles)

Continuing the testing process in the hospitals, testing the contact circles (white spot in the small dark circles

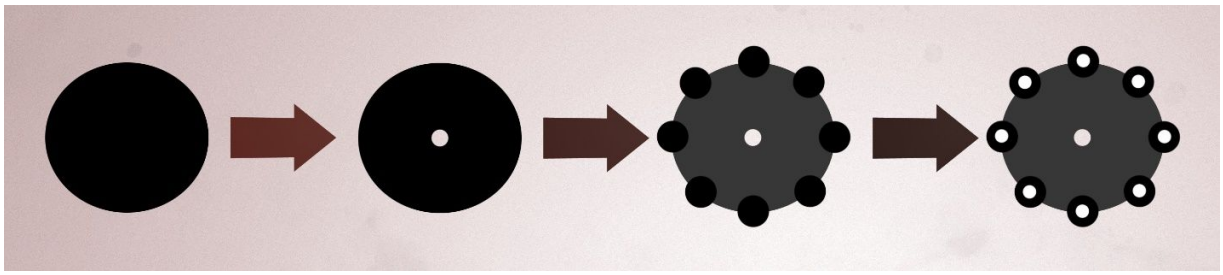


Fig. 3 Continuing the testing process in the hospital identifying the extended contact circle (smallest, peripheric dark spots) Expansion- Sustaining the expansion of testing (in the target circle and the peripheric contact circles)

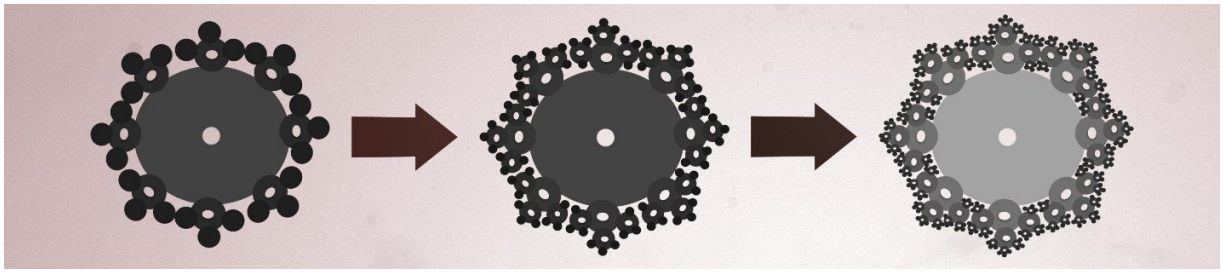


Fig.4 Populational effect of expanding of the 6 testing circles with (decreasing infections) the concentric circle testing strategy

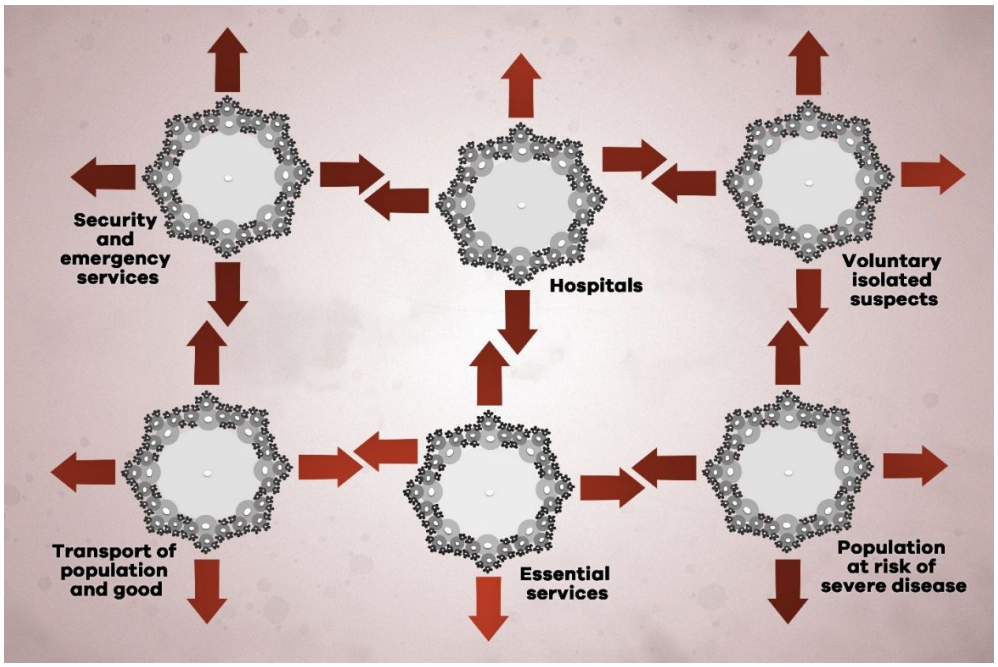
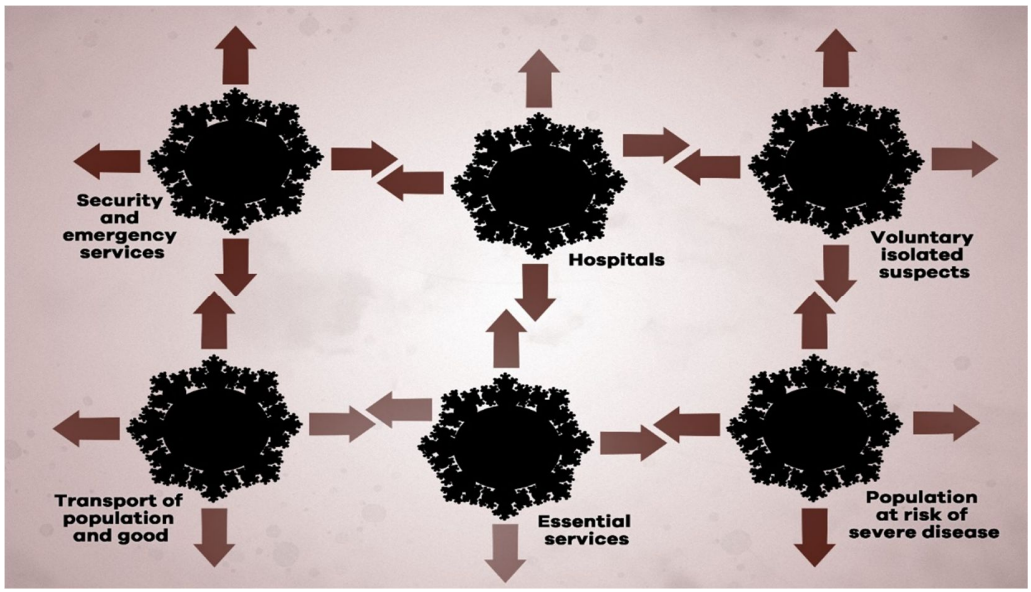


Fig.5 Populational effect of expanding of the 6 testing circles without (Increasing infections) the concentric circle testing strategy



The systematic testing process will progressively clear the defined circles. All the new infected out of the circles will enter the circles since they will become symptomatic, opening new contact circles. The expansion of the circles will increase the cleared areas and eventually the circles will reach each other and overlap, until the infection is eliminated at the society level.

Without the systematic testing strategy, the infection will follow the same pathway as the clearing without testing.

CONDITIONS FOR SUCCESS

In order to be efficient, the concentric systematic testing strategy should be strictly coordinated across the entire community. The testing process should start at the same time in all the defined circle centres.

The rapidity of testing, the mobility of the testing materials, the relative acceptable costs of the testing method, and the acceptable accuracy, are the main arguments in favour of the concentric systematic testing strategy.

This strategy would be effective combined with all the other measures, objectivising the epidemiologic investigations, and providing objective criterion for the narrowed and effective actions.

NOTE: The strategy is based on accepting usage at the low level of specificity (80%) and sensitivity (90%) of the method, compensated by the rapidity, mobility and affordability.

As is stated in the methodology, the lack of accuracy is assumed and repeated tests (twice a day, daily and weekly) will increase the chances to capture the misdiagnosed. However, they will continue to infect their contacts, medical personnel or patients. Correlating the positive testing from this new group of infected (85% will become positive) with the narrowed epidemiologic investigation, the undetected source will be identified with very high probability. However, the RT PCR should remain the standard method, and used only for confirmation of positive rapid tests

COST EFFECTIVENESS

Medical cost: How many tests could be bought by the saving of one ICU patient fewer per day, multiplying with the number of the patients who would not need ICU anymore as a result of this strategy?

Social and security costs: How much money would be spent for dysfunctional essential and security systems?

Economical costs How much money would be saved by the national economies for every day of shortening the medical emergency special crisis?

DISCUSSION

Reliable situational awareness is fundamental for the effectiveness of all plans and measures and should consider the necessity and reliability of objectivising the real expansion of the infection, but in different ways.

Existing strategies are developed and applied in stages, based on the extension of the infection, measured by the number of infected, the rate of infection and the fatality rate. [3]

It is reasonable to assume, without testing, that everybody should be considered as being possibly infected[10] (the blind theory). Therefore, everybody should be responsible to act as an asymptomatic infected person and be responsible for self-applying the protective measures to minimize spreading the infection. In this case the infection propagation would be blocked or significantly limited and after a certain time the epidemic would be terminated.

The weakness of this theory is given by the fact that it is relying on individual responsibility of all members of society which, has a very low chance of success, despite penalties applied to those who do not comply with the rules imposed by the authorities.

Applying the blind theory would make it impossible to objectivise a dimensional measurement of the phenomenon, and the real effects would be revealed by an ongoing number of patients with severe symptoms and the number of fatalities. [6]

The opposite would be to find all the infected with 100% accurate testing methods (the flash theory). This would only be successful if 100% accurate test methodology were to be available, affordable and time effective. Currently, the only available 100% accurate method is the RT PCR which requires special infrastructure (specialized laboratories), is inefficient in time and requires strict isolation of the subjects from the moment of testing to the moment of receiving the results.

Due to the length of the process, subjects who are subsequently proven to be uninfected, are at risk of becoming infected at any moment. Those initially confirmed uninfected, might become infected after sampling but before availability of the result and act as a “Trojan horse”, within the presumed cleared systems. Even should the tests be available, the method is impossible to be apply to and entire population. [6]

The concentric circle testing strategy

Based on the advantages and disadvantages of three imperfect methods, the strategy aims at amplifying the combined benefits and minimizing the limitations.

The principle of the strategy is:

Triage (IgM/IgG)

Confirm (RT-PCR)

Special and adequate protective measures for the medical professionals will reduce the primary contact circles.

Investigate (Primary/direct) contacts

Confirm (RT-PCR), systematically inside the expanding circles.

Social distance and protective measures will reduce the primary contact circles.

CONCLUSION

At present, the only objective markers of the evolution of the pandemic are the curves of the severe case rate (the total number of infected persons) and the rate of the new infections (case rate) which are subjective criteria, and the mortality rate (which is objective), in any given population. The total number of infected highly infected is dependent on the number of tests performed. The actions taken are reactive, adapted to these curves, despite tier inaccuracy.

Considering the medical systems as being at the front line of the effort, the availability of all medical personnel is essential. Preserving the limited human resources in the health systems is essential especially under the continuous increasing pressure in the pandemic situation. Based on the real data provided by this strategy, the managing process of human resources can be adapted in line with the situation. If the situation requires, then medical personnel could be kept involved, even if they are themselves have been exposed (asymptomatic infected, low symptomatic infected, even uninfected), and have appropriate active immunity. Special protocols should be developed for each situation. The effectiveness of the medical human resources strategy depends on the accuracy of the data.

The systematic application of the three imperfect methods in combination within the expanding circles described in this strategy, would provide a clear and objective picture as a base for the efficiency of the adapted medical, social, economic and politic emerging strategies.

The strategy provides an extensive immunity map based on the IgG positive results, which would add extra value and benefits (immune personnel do not need so much protection, prioritisation in vaccine supply, and they could become more professionally and socially active). [3;6]. The same could be applied to the greater community, allowing stores to reopen, and the community to re-integrate. This could have far-reaching economic benefits. This strategy also differs from the concept of “herd-immunity” which relies on an infection and recovery rate of >60% of the population but make no provision for maintaining services until that occurs.

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