Reflections on some very nasty little things (episode 2)

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Episode 2 : How do you identify you are facing a new disease ? How do you build a diagnosis kit ?

Disclaimer : *I am a Digital Architect at Microsoft Consulting Services who worked as an oncologist in a past life, pioneering stem cells research and biomolecular engineering (cell sorting, genetically modified cells, cell culture …) to transplant blood stem cells. The content and the opinions expressed herein are my own personal opinions and do neither officially (or unofficially) represent my employer's views in anyway nor are intended to convey the views of Microsoft Corporation.*

Do you remember how it all began? Early phases of the outbreak

Thanks to Michael Jackson for this lovely song (Do you remember the time…). Yes, I am generation X :)

What was about to be named COVID19 started by mid-november 2019 [**source**] but was not recognized at that time as being a pneumonia caused by a new pathogen. Since then, one to five cases were reported daily in Wuhan, Hubei region with pneumonia-like symptoms in some cases, or only-mild non specific symptoms (like those caused by common cold).

The issue there, is the well-known "low signal" issue. How can you identify in the flow of patients, coughing, sneezing, blowing their nose a new disease "in disguise", different from the common cold or the flu ? You have to wait for the signal to grow clearer.

"[…] *Following the pneumonia cases of unknown cause reported in Wuhan and considering the shared history of exposure to Huanan seafood market across the patients, an epidemiological alert was released by the local health authority on Dec 31, 2019, and the market was shut down on Jan 1, 2020. Meanwhile, 59 suspected cases with fever and dry cough were transferred to a designated hospital starting from Dec 31, 2019. An expert team of physicians, epidemiologists, virologists, and government officials was soon formed after the alert*. […]" [source "**The Lancet Journal**"].

A cluster of cases of Viral Pneumonia of Unknown Etiology (VPUE) was reported to the Chinese Center for Disease Control (CDC) on 29th of December 2019 and initially observed on 21st December 2019 [**source**]. Experts sent to Wuhan, decided to monitor a specific clinical presentation {1) fever with or without a recorded temperature; 2) radiographic evidence of pneumonia; 3) low or normal leukocyte count or low lymphocyte count during the early stage of disease; and 4) no improvement or

worsening symptoms after 3 to 5 days of antimicrobial treatment per standard clinical guidelines}. So now VPUE had a "face", a clinical presentation definition, hence ready for a better signal measurement [**source**].

One important key date is 25th December… Yes it is Christmas for all Christians in the world, but Santa Claus brought us some bad news: first man to man infection pattern confirmed as Health Care Professionals from Wuhan have been infected.

By the 2nd of January 2020, the signal was strong enough for researchers to identify they were facing a new disease, a viral infection, that could lead to severe viral pneumonia with a high Case Fatality Rate (CFR) around 15% as 6 of the patients in the 41-people cohort did die at that time (this had been kept secret at that time). Clinical presentation was very alike SARS-COV (outbreak in 2003). Interestingly enough, the 1st patient of this cohort (came to the hospital on 1st december 2019) had not link with the Wuhan wetmarket (like other 13 patients from this 41-people cohort) [**Source**].

But a lot of things had improved since 2003, among which:

1. China is now more opened to the world from an economic and political standpoint. In 2003 (first SARS outbreak) it was the 6th largest economy in the world and was not quite yet the "factory of the world". In 2019, China is the 2nd largest economy in the world and clearly it is the "factory of the world" and a lot of global supply chains rely on chinese factories.
2. From a political standpoint, the chinese government **reacted fast and immediately with bold actions**. It informed the international bodies (such as the World Health Organization). The measures introduced by China to contain the outbreak at its sources were unprecedented! They confine tens millions of people with strict confinement measures.
3. Sequencing technologies have improved a lot and were ready to give an accurate profile (gene sequence) of this new pathogen. Months in 2003, turned to Weeks or even Days in 2019/2020.
4. Information technologies have also reached a global spread, allowing almost transparent communications, and international teams cross collaboration. Social networks were also used at a global scale, by experts and common people.
5. Scientific communities, doctors, researchers, institution did also learn (not all alas!) from the SARS outbreak in 2003. They are more collaborative and share more information, spreading the news at a faster pace.

And things went very fast indeed… but somehow not fast enough to be able to contained the pandemic.

The initial laboratory screening results from patients were negative for 26 common respiratory pathogens (influenza A and B virus, adenovirus, rhinovirus, enterovirus, and other common respiratory viruses) so researchers were quite sure there was a new pathogen in town.

On 3rd of January 2020, the sequence of novel β-genus coronaviruses (2019-nCoV) was determined from specimens collected from patients in Wuhan by scientists of the National Institute of Viral Disease Control and Prevention (IVDC).

On 7th of January 2020, this novel coronavirus was confirmed to be the pathogenic cause of this VPUE cluster, and the disease has been designated "Novel Coronavirus-Infected Pneumonia" (NCIP). [**source**].

Information technologies played also a major role for international cross team collaboration as complete sequence of the new virus have been shared on the internet, obviously communicated to the World Health Organization(WHO), and made available so other teams (such as Pasteur Institute in France) could develop their own virus detection PCR-kits.

Data availability. The new *Betacoronavirus* genome sequence has been deposited in **GISAID** under the accession number EPI_ISL_402119, EPI_ISL_ 402020 and EPI_ISL_402121.

How did they build a detection test for this new pathogen ?

They had a clinical definition of the VPUE, a clinical presentation, the disease had a "clinical face". Now how can you give the new pathogen a "molecular face" when you ignore what you are looking for? How do you build a detection kit, which is highly critical to be able to qualify and quantify the early stages of the Pandemic?

Based on clinical evidence (similarity with SARS-COV 2003), researchers had the intuition they were looking for a new kind of coronavirus. How to confirm this intuition ?

Polymerase Chain Reaction (PCR)

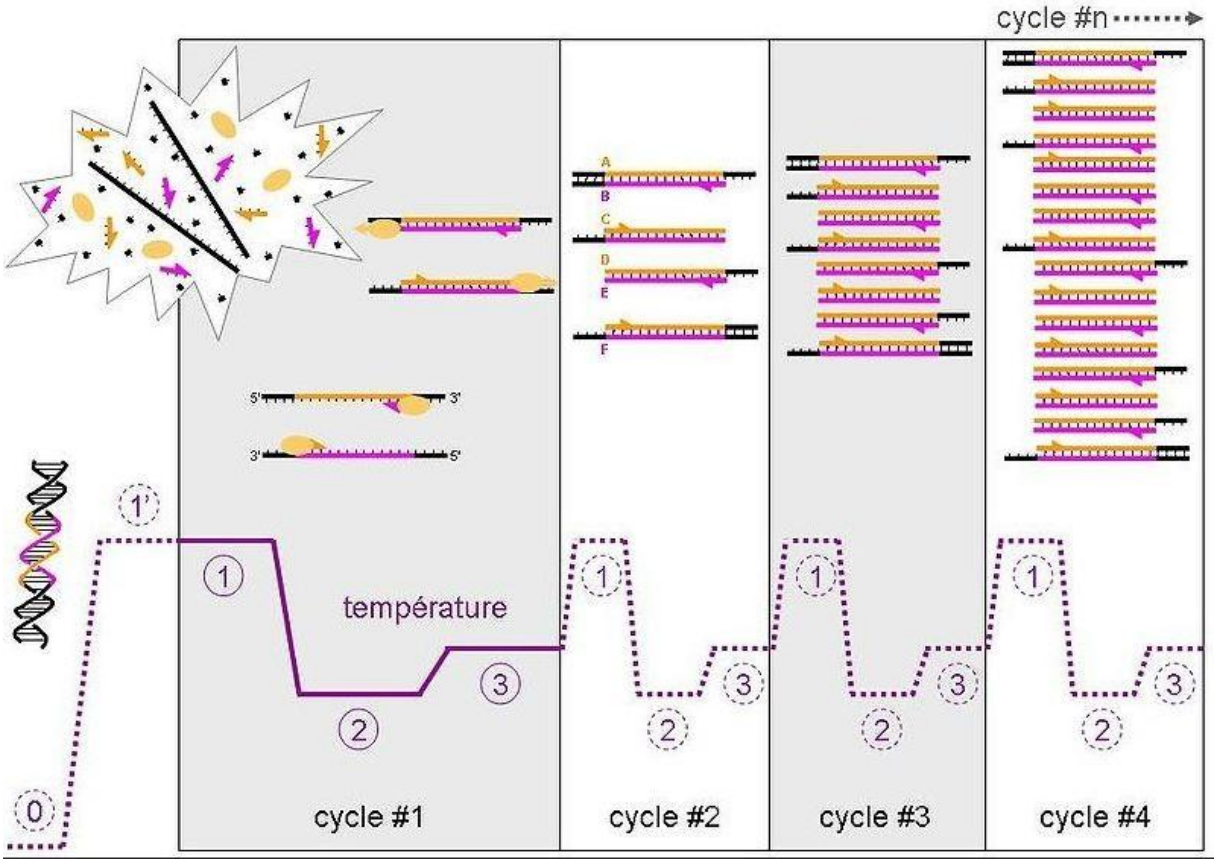
PCR is an acronym you are used to as "famous COVID19" tests are based on PCR (RT-PCR to be accurate).

A little bit of history. In 1983, Karry Mullis invented a new DNA amplification procedure through Polymerase Chain Reaction (PCR). It is an enzymatic reaction that can 1) select a specific DNA fragment 2) amplify it thousands, millions time (*i.e.* create million copies of the specific DNA fragment) as the copy of DNA follows a power law. So it is very sensitive technique that can detect very small quantity of DNA in a sample… basically, it turns a weak signal into a huge highly visible signal.

The three phases of a PCR cycle. PCR works through cycle with 3 phases:

- 1) **Open the molecular doors, the denaturation phase:** Denaturation of DNA around 95°C, the well-know double helix structure becomes loose, providing space for polymerase enzyme to anchor on a single-strand of DNA.
- 2) **Bind your DNA Polymerases to the DNA Strands, the hybridation phase:** Hybridation of the DNA around 50°C-60°C. We are using specific DNA Primers, which are small portion of DNA with a specific sequence. We have one forward primer (5'-3') and one reverse-primer (3'-5') (remember in 1st episode - "read/daer" as both strands are mirrored). Both primers are selected so they demarcate the DNA portion we want to amplify. So specific forward primer and reverse primer will bind to the DNA at very specific chosen locus. This is what we call hybridation.
- 3) **Let your DNA polymerases do the job, the elongation phase:** Elongation of the DNA around 72°C. Each strand (forward and reverse) will be elongated (they will serve as a matrix/mold) to reconstruct the original double-stranded DNA. For this the TAQ-polymerase is used. Interestingly, it comes from a thermophilic bacteria identified in 1969 in the biggest geyser of the Yellowstone Park (USA). This TAQ-polymerase is stable and can do the job at 72°C (its preferred temperature). TAQ-polymerase will consume the nucleotides (A,T,G,C) to synthetize new complementary DNA strands, using the 2 single-strand DNA as a matrix/mold.
- **Do this again and again…the amplification process.**

Before the 1st cycle of PCR, let's assume you only had one copy of the specific DNA you wanted to amplify. At the end of the 1st cycle, you now have 2 copies (thanks to TAQ-polymerase). So.. let's do it again and again.. 2 copies, 4 copies, 8 copies… Yes IT Guys know it by heart .. well up to 65536 :)… But with PCR we go far beyond 2^16 (*Yes, I listened to Michael Jackson and also had a Sound Blaster 16 Express bus sound card!*). to get millions of copies. That's the magic of PCR for which you need to know the DNA Portion you want to amplify… 2 primers (forward and reverse)… TAQ-Polymerase… Nucleotides… and a PCR cycler… 1st cycle lasts 20 minutes, then other cycles can last 90 seconds… 45 cycles produce trillions of copies of the specific DNA fragment you wanted to amplify.



Cool explanation **here** and **here** with animated analogy with elastics!

What about RT-PCR ? Remember in **Episode 1**, we explained that SARS-COV2 is a retrovirus, its genetic information is coded on a single-strand RNA. So this needs to be turned into a double-strand DNA with a **R**everse **T**ranscriptase first before you can do regular PCR. Hence the RT-PCR name, used to amplify genes from retroviruses.

How do we select the gene to identify the new pathogen?

In **Episode 1**, we also discussed about the mutations of retro-virus mentioning that despite a higher "mutability", there were still quite stable genes in such viruses.

So we need to identify a molecular target that is:

- Stable enough, so our detection test can remain relevant despite possible mutations of the new pathogen. The risk here, by selecting a mutating gene (less vital to the virus replication cycle), is that after a few mutations, our detection test will generate "false negative" and miss detection of genuine COVID19 patients.
- Specific enough, so our detection test is accurate enough to detect SARS-COV2, and not any other existing coronavirus, like those responsible for winter common cold. If it was the case, then your test will generate "false positive".

As we wrote, this VPUE had a clinical presentation that was very close to the SARS 2003 outbreak. Researchers then focused on the known genes of SARS-COV which was the pathogen of this first SARS outbreak. SARS-COV had a quite stable gene coding for a specific protein which function was to package/structure/stabilize the genetic payload of SARS-COV into a helical ribonucleocapsid. This protein is inside the virus' envelope so it is not exposed to the immune system of the infected host (so it cannot be used for immunological testings, we shall discuss it later on). This nucleoprotein plays a major role during the assembly of the virion in the infected cell's cytoplasm, once every parts of the retrovirus have been produced and need to be assemble, as it has obvious interactions with the viral genome (it packages it) and envelope proteins (to anchor it within the envelope). This critical role could also explain its stability, as any kind of mutation of the NP gene could be "deadly" to the virus, compromising its ability to replicate. Meaning that only viruses with stable and working NP gene could thrive and survive (Darwinian selection of virus variants).

NP Gene is a good candidate for RT-PCR. It seemed that with the NP gene, first identified and sequenced in SARS-COV (1), researchers had a good candidate for RT-PCR amplification to detect SARS-COV2. Researchers tested the presence of the NP gene within biological samples collected on this 41-people cohort and found it to be present in every samples. This could become one specific virus presence detection test based on RT-PCR.

As the SARS-COV2 genome has been fully sequenced, other specific target might have been identified, and specific primers synthetized for these specific cases. But once again, when selecting your molecular amplification target, be specific to avoid "false positive", but not too specific (especially on a mutating region) to avoid "false negative" in the near future. The current RT-PCR test used in France has been designed by the "Pasteur Institute", and have been available quite early to test our population. However, the public health policy approach was not in favor of massive testing at that time (we shall discuss this in another chapter below). This test demonstrated a few false negative tests: At least one resident has been tested negative and presented the full clinical presentation of COVID19 a few days later.

There is a good article **here** that explains "recent advances and perspectives of nucleic acid detection for coronavirus" (it is also the title of the article).

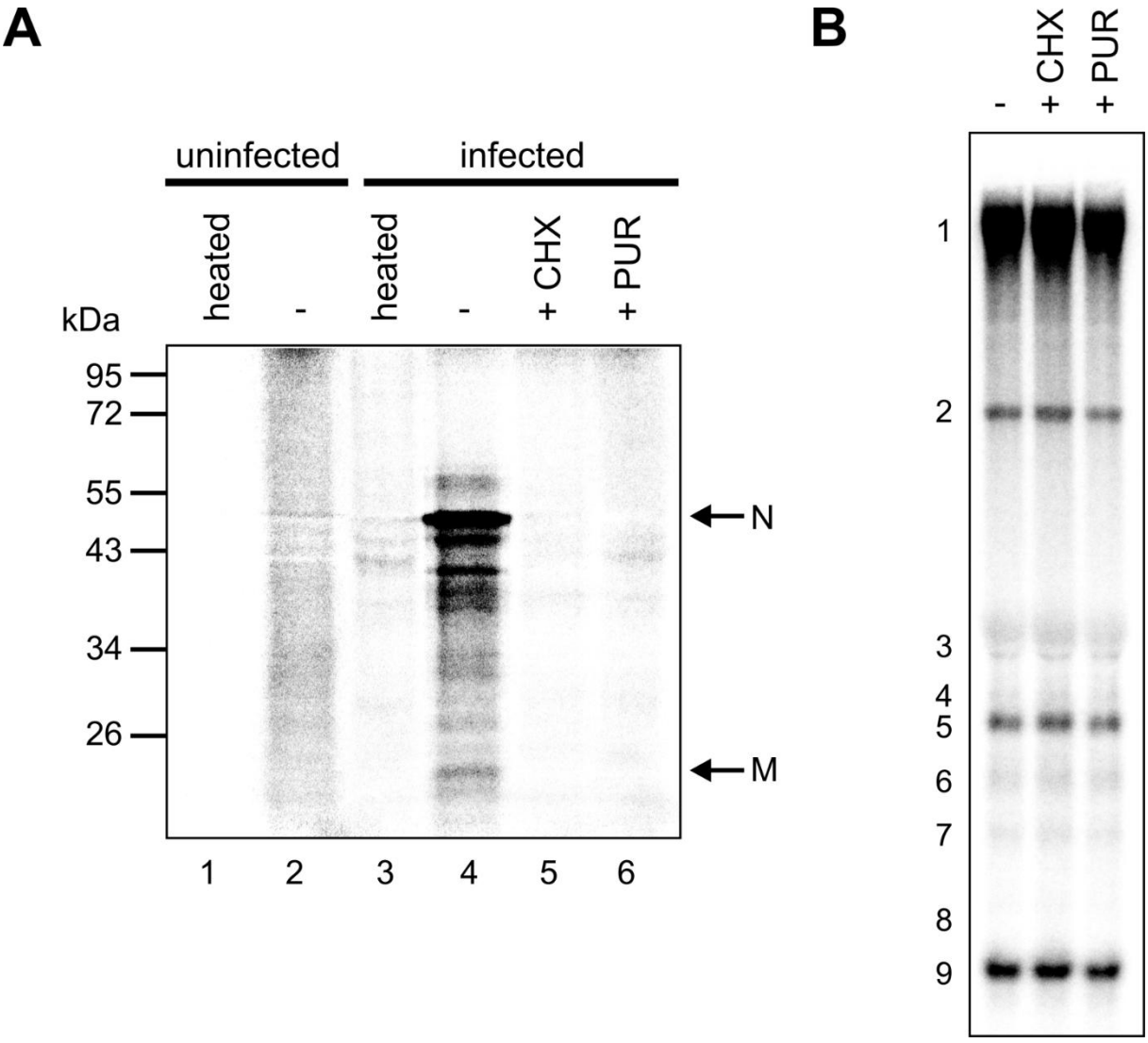
Different kinds of tests

Virus direct detection

The RT-PCR test is the reference test. Different RT-PCR kits might be available, targeting different regions of the SARS-COV2 RNA (we just discussed about the NP gene).

You can read this paper SARS-COV2 RT-PCR Protocol **here**. Do It Yourself RT-PCR testing :) You can order reagents, and kits **here** (just kit-ding^^).

What is important to understand, is that **the (RT)-PCR test confirms that you have virus "particles" circulating in your body**, it detects through amplification and then electrophoresis (once you have amplified the specific portions of the SARS-COV2 RNA, you will make then migrate into an electrophoresis gel, and depending on the size/weight of the RNA portion, and the time of the migration, it will position itself at a specific position on the electrophoresis gel 2D matrix).



Electrophoresis after RT-PCR (**source**).

A little bit of economic perspective. (RT)-PCR is a sensitive test that requires a few hours to complete. Its price is around $20-USD (Operational Expenditure without the laboratory technician time) while the PCR-cycler itself is between $5000-USD for very simple models, up to $100'000+ USD (Capital Expenditure). I have even heard of something like 400'000 euros, but was unable to find the reference. This is important to know when your politics talk about "massification of tests"; it has a high cost. Furthermore, still from an economic standpoint, every test, requires specific reagents which might undergo supply disruption that will limit your capacity to do PCR tests (even

if you have the cash to pay for it… does it remind you about the mask supply as well ?… Maybe another article later on).

Indirect virus detection

These are immunological tests. These tests do no look for traces of viral particles, they look for the presence of antibodies you did produce to fight the (SARS-COV2) viral infection. The famous Immuno globulin (IgX) molecules. Let us focus on 2 particular IgX which are the IgM and IgG.

- IgM is found mainly in the blood and lymph fluid, is the first antibody to be made by the body to fight a new infection. So we can detect IgM against the virus in the early phases of infection with a peak that can last up to a few weeks.
- IgG is the most abundant type of antibody, is found in all body fluids and protects against bacterial and viral infections. It is produced later and provides long-term antiviral (antipathogen) protection. To see if a vaccine for Hepatitis-B has been successful, we dose the IgG targeted against the antigen (a molecular subset of the Hepatitis B virus which proved to stimulate the immune system) of Hepatitis-B.

Most of these tests are based on the ELISA (which is the lovely acronym for Enzyme-linked immunosorbent assay… but this second definition does not give you the desire to write a letter to Elis..A). Regarding HIV infection, the first test is an ELISA test, and then if positive, it is confirmed using RT-PCR.

So.. If you have IgM and not IgG, your infection is very fresh. If you have both, you might be recovering from the acute phase of the infection. If you have IgG only, you were exposed to the pathogen in the past, did recover, and now have (hopefully) a mid to long term protection. You are note naive anymore (from an immunological standpoint) to the new pathogen.

Immunological ELISA test are currently being developed and are planned to serve to validate the "Go Decision" for deconfinement. Guys with IgG only are the best candidates. Issues are:

- do you really want to test all your population with a $10 USD kit ?
- these tests need a blood sample. For those who remember the vaccination campaign for AH1N1 flu in 2009… you see the logistic nightmare to draw blood samples from millions of people to do ELISA.

So massification at the national scale without "population sampling" is just an utopia, or a dystopia (we shall discuss this hereafter).

So, how could we diagnose COVID19? And what for? Available strategies?

Officially, the sole "way" to diagnose COVID19 (the disease caused by SARS-COV2 virus), is the RT-PCR which has a cost, and which might be difficult to generalize due to reagent partial supply chain disruption. **In particular, RT-PCR is the sole way to diagnose it in its very early stages when people are asymptomatic, or for people who will remain fully asymptomatic during the whole infection.**

As seen above, new kinds of test will be made available which are based on indirect detection of the virus, and the French Government envisions to use them to make targeted deconfinement decisions.

When you ask the question "how we diagnose COVID19" (the name of the disease caused by SARS-COV2 virus), the right question to ask immediately after is what for ? Which also relates to the pandemic phase we are in.

Early stages of the Pandemic

In an ideal world, we would have been able to test/screen massively during the initial phase of the outbreak in order to identify asymptomatic contaminant people, to trace the pandemic epidemiology, and be able to isolate them from other people to contain the pandemic and slow it down.

This massive testing is also critical to quantify the pandemic kinetics, among which the R(0) (basic reproduction rate), to monitor the "Case Fatality Rate" (which is distinct from the mortality rate, and always above as we underestimate the number actual number of infected people), the demographic of the pandemic, its epidemiological spread pattern… Which are key elements to be able to forecast its impact, and do the capacity management of the healthcare system accordingly.

As we can test 1.6 billion people at once (or 67 million people), this has to be "massively" done around the outbreak initial localization. And this has been somehow the strategy adopted by many countries, starting with China, and the Hubei region.

However, as we have seen in the introduction (Remember the time…I can't put this song out of my head now), it took roughly 1 month to identify the new disease and have a working detection test… during the moon new year celebration in China with massive population displacement visiting families and relatives.

Massive testing has not been massive enough (and there is no way to do it at the right scale, and velocity) and soon before Wuhan was locked down, hundreds of contaminated people were traveling in China and abroad spreading the COVID19.

So the massive testing strategy missed its containment objective… and it was doomed to miss it anyway given the circumstances (high density of population, new year celebrations with lots of travels, new disease in disguise, inertia of the system - which has been really very reactive- compared to the pandemic kinetics with a R(0) between 2 and 3).

Acceleration phase and generalization of the pandemic

We are clearly in that phase now, in many many countries around the world (have a look to **www.bing.com/covid**). So how should we behave, what is the right strategy? Is massive testing still a solution, and a solution to what?

Identify sick people to monitor the evolution of individual clinical situation. We need to diagnose people in order to monitor the evolution of their clinical situation and admit them in the hospital, and even in Intensive Care Unit, if needed. But do we need RT-PCR for that? Remember the time….(oh no…) of VPUE. First decision was to give the new disease a presentation frame, with list of symptoms. Since then, COVID19 exhibited new kinds of symptoms to be added to this "clinical presentation" (diarrhea, anosmia, agosia, leukopenia…). Most of these symptoms can be identified/collected through a simple anamnesis (medical interview), these if you need further examinations, you can do blood analysis and look for some biomarkers, and you can do a chest scanner to check the lungs' status.

Since RT-PCR costs a lot, let us have a probabilistic approach to diagnosis. If it presents like COVID19, it is likely to be COVID19. As long as you are not facing serious conditions with Acute Distress Respiratory Syndrome, just stay home (in your bedroom, to avoid contaminating your family… wear a mask, wash you hands whenever you have to touch something, disinfect home exposed surfaces 4 times a day).

There is no need to generalize RT-PCR testing for the general population. Clinical presentation should be enough in most of the cases.

Whom should benefit from the RT-PCR tests ? RT-PCR should be then reserved to people with serious clinical conditions (among those the elders and people with comorbidities), to make sure we are going the choose the appropriate therapeutics.

RT-PCR should be also reserved for Health Care Professionals (HCP) presenting alike symptoms to make sure it is COVID19, and not a flu, or common cold. So we shall not confine, so desesperately need Health Care Professionals for wrong reason. Even for COVID19 positive HCP, the current protocol in France is to confine them in their homes for at least one weak, and to allow them to go back to work after 48 hours being asymptomatic. RT-PCR might confirm low viremia and enable the recruitment of previously contaminated HCP workforce possibly sooner.

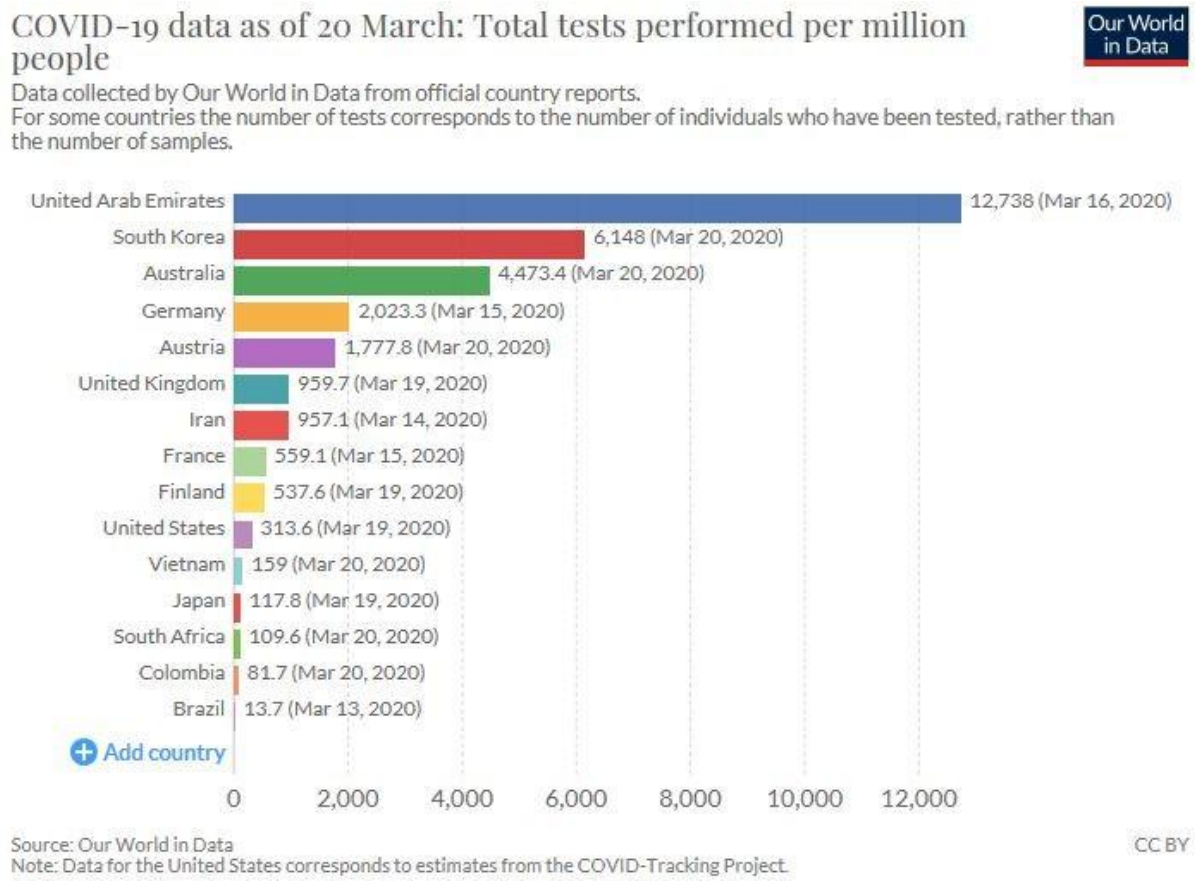
President Macron announced new testing capacities (up to 29'000 tests /day ?) which will be reserved for elders in EHPAD (long stay for elders), and for Health Care Professionals. This decision sounds reasonable.

Massification of testing? Are you fu… kidding me?

Some people, among them, politicians are now saying we should copy the protocols in South Korea, Singapore, Hong-Kong based (in their understanding) on massive testing of

their population and targeted confinement. In their eyes, massive testing might be one solution to alleviate the massive confinement of the population and the Acute Distress Economy Syndrome that is caused by this (maybe Episode 3 will focus on this).

How massive is a massive testing. Let me explain to you basic figures about "Massive testing". If we have a look to the number of tests per capital, we clearly see that even the country who does the highest number of tests, is very far from testing its whole population has it roughly tests 1.3% of its whole population. (Yes this is what massive means for politics).



[source]

So, this is not massive tests.. it is statistical sampling at the utmost. While sampling works well for political polls... they do not for pandemic containment... not at all.

Why such "massive test" should do a difference? Such a sampling approach works well also for epidemics because these are statistics about the pandemic. Especially, the more you test your population, and the more your "Case Fatality Rate" (number of validated COVID-19 deaths/number of validated diagnosed cases) converges towards the actual "Mortality Rate". With appropriate sampling you might be able to estimate the actual mortality rate out of the CFR you measure. New calculations made in Wuhan now estimate the mortality rate to be around 1.4% while some previous estimates were

between 2 to 3.4%, and while the first CFR estimation was around 15% (on the 41-people cohort) [**source**].

Are massive tests the root cause of the better pandemic management in south east Asia and middle-east? As you can see above, for the best in class, United Arab Emirates, there are 12'738 people tested per million people. **Another way to say it, is there are 987,262 people who are NOT tested**. Yes... No, comment: Massive testing is not the root cause of a better pandemic management.

Not convinced yet? Let us do some simple maths on french figures.

- If we assume that the Case Fatality Rates (CFR) of South Korea and Germany are close to the actual mortality rate of COVID19 and let us be cautious and chose a 1% CFR. (Last figure for Hubei Region was around 1.4%) [**source**]
- Tonight (25th march 2020), we learnt that alas that there were 1'331 COVID19-related deaths in France, and roughly 25'000 people diagnosed through RT-PCR (5,32% CFR).
- Now if we apply a conservative 1% CFR, 1'331 dead people turn into 133'000 probably contaminated people.
- Let's assume we decide to do massive tests, really massive, unprecedented massification of tests to be the best in class on the Earth.. We are going to test not 1%, not 2%, not 3% but 10% of our population.
- Let's even assume that we are lucky, and that we do not randomly test 67 millions of french people (among which 133'000 are probably COVID19), but we only test people among these 133'000 probably contaminated people. Once again, under these highly favorable testing conditions.. **we still leave 120'000 contaminated and contaminating people un-tested**.

Do you really count of test "massification" to deconfine people ? I don't ! Issue with pathogens is it is binary... you cannot do something in between, because only once missed case is able to restart the pandemic. **So forget about test massification to enable a targeted confinement, especially in the acceleration phase**.

Targeted confinement based on test massification is just an utopia, or rather, it will lead to a dystopic nightmare for Health Care Professionals and people.

Test massification announcement is just a political tool (for some politicians who relates it to target confinement) to decrease people anxiety.

Massive confinement is the only solution now to decrease R(0)

Despite false hope related to test massification, despite the Acute Distress Economy Syndrome, despite the fact that massive confinement might cause a daily stress leading to Post Traumatic Stress Disorders…

Strict confinement is the unique working solution at that stage of the pandemic. **It should even have been decided earlier for more impact**, with the creation of a safe european zone within the Schengen area with a sanitary exclusion zone in which people would have been confined, and borders closed simultaneously + quarantine for travelers stuck in the airport. The harm to the economy would have been bigger but limited in time. And such a protocol would have provide a faster resolution of the pandemic (especially if coordinated worldwide), than the mild decisions ("et en même temps" ..French private joke) that let the pandemic silently thrive.

So once again, be a "hero", "Stay home, save lives". And disinfect your clothes, shoes, surfaces within your home, wash you hands like a surgeon… Consider your home as an Operating Room… with a lovely bleach scent in the air.. so relaxing ! (my favorite perfume nowadays). And whenever you have to go out, do enforce the barrier gestures. **As I keep telling my children, this is not a game, take it very seriously.**

So if not massive testing, why the pandemic seems to be better managed in South East Asia?

These countries were hit frontally by SARS in 2003, with high mortality rate, and high fear facing an unknown outbreak. Their institution decided to take (bold and strong action) so "it will never happen again "… not the pandemic outbreak, it is likely to happen again and again… But they decided that the will never again feel that desperate being helpless feeling.. Just watching people die.

Institutions puts in place efficient plans, strategic stocks/inventories of medical devices (**who said masks ???**), alerting and communication systems, to face the stress of a pandemic with appropriate strategies to manage it.

They also have a social distance by design (the do not shake hands, embrace people,..). They have high standards of hygiene, and they are not latin people…Oops sorry for these bias/cliché… they are disciplined **and they have masks !!!** My P3-laboratory inspired home disinfection protocol which I thought was smart and robust, happened to be implemented in every home in South Korea: delimit a sanitary hatch, leave there your shoes and clothes, disinfect them and the floor, and the door, put your clothes in the washing machine, go and have a shower including hair washing (hair, facial hair are pathogen repositories)… and obviously enforce barrier gestures.

To decrease R(0), you need to increase physical distance, but also reduce the viral load in your close environment going beyond the sole barrier gestures, and once again… Do consider your home like an Operating Room… A Sanctuary.

Meanwhile, what should we be doing?

Massification of tests is just a massive joke and addresses a political issue, not a public health issue.

The strategy did not change: we need to decrease R(0) to limit the pressure COVID19 puts on the healthcare system and healthcare professionals (this strategy to be discussed in coming Episode).

Once again, the massive confinement seems to be the sole solution during the acceleration/generalization of the pandemic with appropriate behavioral barrier gestures and beyond.

What can be done during this phase, is to prepare the aftermath, when we shall have to manage **a progressive and secured deconfinement of our population**.

Remember the outbreak timeline in introduction and how the Chinese CDC researcher started with the definition of the clinical presentation of what was named at that time Viral Pneumonia of Unknown Etiology (VPUE). **We should go back to this approach based on a clinical presentation, enriched with all the new symptoms exhibited by COVID10 recently.**

We need to standardize and make globally available to anyone an auto-evaluation questionnaire. This questionnaire will be a kind of auto-anamnesis and will provide a simple score on which therapeutic strategies need to be built.

- Create and standardize an auto-evaluation questionnaire, enriched with all the various clinical presentation COVID19 has exhibited (intestinal symptoms, agosia, anosmia, mild symptoms…) that will provide a "disease likeliness score" and/or a "disease severity estimation".
- This questionnaire main channel should be an inclusive-designed mobile application to decrease the marginal costs of testing while remaining specific, and accurate. But we also need to be inclusive, *i.e.* deploy call centers with human agents to assist people/patients. We could even think about printing the questionnaire and scoring rules in daily newspapers.
- The application would feed also a national database (european even better) of anonimized data on which we could do some advanced data-mining to refine the scoring algorithm, and possibly to be able to identify the weak signs of future deadly complications (for a better clinical surveillance of these specific people and for ICU bed capacity management). Possibly we could temporary be more permissive from a General Data Protection Regulations standpoint. As we might not need to geolocalized sick people in almost realtime like it seems South Korea did. However we could provide a "security score" for specific locations.

- The application would also be the channel to distributed "circulation certificates" to present to the police validating you were cleared to be deconfined.

This mobile application, database, data mining, data intelligence platform could be great assets to carefully and securely manage the deconfinement phase as studies (logically) show that people are far less contaminant if they have being asymptomatic for 48 hours (even it viremia - the quantity of virus circulating in the blood- is not null).

Conclusion

So let's mobilize our collective intelligence, think out of the box, be less compliant with strict regulation as COVID19 pushing us in the coffin corner forces us to take smart risks.

Keep calm, think smart, and build resilient capabilities for the next pandemics based on digital platforms that can autoscale to adapt to the pandemic kinetics.

We need to address the pandemic at its own scale: worldwide

We need to do it with appropriate tools an strategies.

- We've seen that massification of tests was not the solution (because of its costs, and logistics issue).
- We've seen that massive confinement was a working solution, despite it has been misused (delays in application, and not strict enough sometimes).

This crisis will come to an end. Our individual behaviors are key to shorten the crisis, and to avoid to put our health care professional at vital risks.

Meanwhile, we must prepare the aftermaths, and build these necessary tools to manage at the planet level the deconfinement at minimal marginal costs. I think digital platforms can do a lot to have the right level of coordination, and to minimize crisis management costs.

Comments

As I shall write new articles to shed some light on what's going on, do not hesitate to comment is you need to correct what's been shared here or to ask additional questions.

***Do not hesitate to share, if you think such information is worth spreading*.**

In case you miss them: [**Episode1**], [**Episode3**]