**CORONAVIRUS CRISIS (SARS-CoV2)**
**COVID19** (The disease that is caused by SARS-CoV2)

# Data Analysis
# Data Assessment
# Review

**June 9th, 2020.**

Final Text

## Why this report and who?

We are a group of diverse persons, with critical and positive thinking, sharing the need of accurate information and quality data. We are still believers in maths, science, chemistry, evidence-based medicine, public good and humanism, and we value and respect everyone.

The key motivation for us was to assess the situation while avoiding posturing positions.

We conceived this work as a multi-layered communication. One can read part or the whole of it, one can browse some general audience text or go deeper into technical notes and addenda. It is a bit like a hypertext where parts are related and cross-referenced. It is our intent to build this communication like an Open Source effort that may be used as a core repository for future information and contributions. It was written in English to facilitate communication. It does not want to teach anything, just equip the readers with some key information and references that they can control by themselves and generate some healthy questions.

**Our goal is to use this work as a call to action.**
**We have a set of propositions in the 2 last chapters. We feel that a global problem requires a global response, but that some actions are both urgent and evident.**

About the authors (* who can be reached upon request):

- Prof dr. Martin ZIZI *- MD-PhD, Molecular Biophysicist, former Medical Chief Scientific Officer and Chair of the Bioethical Committee of the Belgian Dept. of Defense. He was involved in the Military Applications of Telemedicine. He was also a former UN Bioweapon Inspector, served as advisor to the Belgian Government in Biological And Toxin Weapons Convention Treaty in Geneva, and was an active scientist involved in Operational Epidemiology, Germs and Bacteriophages, and in cancer metabolism. He studied *in-vitro* molecular evolution using molecular random chemistry, and used technologies he invented for peptide drug design or fight against germs. He was an advisor for various Ministries in Belgium, led the creation of the Belgian VA (Veteran Administration) and other Health-related structures. He was involved with many others in the resolution of various Public Health crises (9/11, Radars, Depleted Uranium, GSM radiation…), led expert panels for the Courts in various countries. Througout his career, he wrote and obtained numerous patents across various fields. He currently leads a blue-sky startup in California merging physics, neurosciences and mobile technology.

- Dr. Giuseppe TRITTO * – a well-known surgeon and uro-andrologist, specialized in reconstructive surgery of genital organs, transgender reassignment surgery and microsurgery of male infertility. He was Chairman on Surgical Andrology in Saint-Louis Hospital in Paris until 2006 and Chief of Dept. of Urology in San Carlo Hospital in Rome-Italy for the IDI (Vatican) Project on Urology, Male Ageing and Rehabilitation during the Great Year of Jubilee declared by Pope John Paul II in 2000 in celebration of the new millennium. He is Visiting Professor in Microtechnologies for Microsurgery in Aston University, Birmingham,UK; a Visiting Professor in Nanotechnologies in Brunel University, London, UK, a Visiting Professor and a Chair of NanoMedicine in Amity University, New Delhi, India. He is Member of the Laboratory of Bio-Ethics, directed by prof. Christian Herve in Paris. Giuseppe Tritto is also Executive President of the World Academy of Biomedical Sciences and Technologies, founded under the aegis of UNESCO in 1997. He introduced the new concept of Human Health Medicine under UNESCO/UN umbrella, through the three congresses on Men's, Women's, Children Health Medicine (2004-2006), promoting Human Nutrition, Social Determinants of Human Reproduction, Medicine of Ageing, Gender Medicine and Personalized Medicine and introducing new fields in Innovation Technologies for Health as Bio-nanotechnologies, Pico-technologies and TeleMedicine through Space Technologies. In 2007 He founded with prof. Giulio Tarro, (virologist, fellow of Sabin, who isolated the syncytial virus (RSV) in the epidemics in Naples in 1979) the international Platform on the VirusSphere. In 2013 He founded with prof. Sujoy Guha in India the new Scientific Field of Pico Medicine in Amity University.

- Dr Kaarle Parikka * – PhD. Universite Bretagne (France, 2013). Microbiologist specialized in bacterial viruses. He obtained his PhD studying microbial communities of extreme environments and then worked on the use of viruses as natural born enemies of bacterial pathogens in a clinical setting. After his post-doc, he led the 'Lab de Recherches Microbiologiques' in the Belgian Defense Medical Center.

- Dr. Andreas Hieke * - M.S. Physics, Ph.D. Physical Chemistry- has over 20 years experience both in US elite academic institutions an the high-tech industrial R&D sector. He is member of the scientific review committee of the NSTI World Innovation Conference. He used his wide expertise to build an advanced technology to enhance the analysis and sequencing of proteins and successfully demonstrated it at Stanford University, School of Medicine.
  Dr. Hieke is a prolific inventor and author of 27 patents and/or applications covering numerical methods, data analysis, algorithms, scientific instruments, physical and biochemical analytical techniques and instruments, ionization of biological macromolecules, methods of obtaining medically usable biomarkers and advanced molecular diagnostics. Dr. Andreas Hieke is also founder and manager of a Silicon Valley based company Themis Scientific, LLC, providing expert advisory support related to R&D strategy and IP creation & evaluation to C-level executives of US- and European high-tech companies, as well as to inventors, investors, and lawyers. Dr Hieke independently controlled and reviewed an earlier draft of this report, before contributing as an author to it.

- Dr. P. Fransen * - MD, Neurosurgeon. - consultant neurosurgeon in IM2S Clinique Orthopédique de Monaco and CHIREC Delta hospital Brussels, former Head of the Department of Neurosurgery at the CHIREC - Parc Léopold Clinic. Dr Fransen is also Chairman of the Brussels Spine Center, past Board member for the Belgian Society for Neurosurgery, former President of the Belgian Neurosurgical Spine Society, International Fellow of the American Association of Neurological Surgeons, member of the Société de Neurochirurgie de Langue Française. He has published over 40 papers in indexed peer-reviewed journals, presented over 100 presentations and lectures in international meeting as well as surgeon's trainings. Dr. Fransen was both a reviewer and a contributor.

- Some contributors were journalists and professionals in Belgium and France. They provided general information, comments and reviewed the text for a general audience.
  - Mr. F. Poncelet – Master in Journalism and in Political Sciences. Mr. Poncelet is a specialist with 30 years of experience in in-depth questions related to Security and Management of Information.
  - Mr. A. Breithof – is a web developer and graphist, and an avid reader. He has an in-depth long experience about confined spaces and human response to it because of his work aboard cruise ships.
  - Mr. L. M. (journalist, name witheld).
  - Mr. O. Younes – PhD – Prof. at the Center for Entrepreneurship and Innovation at HEC (Paris – France). Dr. Younes is also a visting professor at UC. Berleley (USA) and at Dauphine (France), and a Mentor at Singularity University. He is the Founding CEO of EXPEN, a Tech Investment Bank. He was an early reader and gave valuable advice.

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- Some contributors were MD's, nurses, and friends across 4 countries sharing their experiences, hopes, and facts on the ground. Some had fears and felt powerless, some even had fear to be cited in this work. Some MD's have read the text and, while agreeing with its core messages, have declined to be involved for personal reasons. We are much indebted to all of them. We are sad that they had to go through such experiences – while being constrained by guidelines they knew were at times not always adapted. Our deepest thanks and appreciation go to their work and courage.

# This is NOT Ebola – Why are we treating it and acting like it is? Pleading for a reasonable and data-driven way out.

*This pandemic crisis originated in China. It is intriguing that the Concept of "crisis" in the Chinese language and the Chinese word for "crisis" (simplified Chinese: 危机; traditional Chinese: 危機) are referred in Western culture with the symbolic of Yin and Yang and interpreted as the double face of "danger" and "opportunity" respectively. While the original meaning of wēijī is "danger at a point of junction" it is fundamentally the description of the point of bifurcation that can evolve towards chaos, which means an unpredictable chain of events.*

*In crisis situations, there is always an initial fog… with too many loops*
*- one has nearly no time to think amid an overflow of bad information and useless noise.*
*- oftentimes the first casualty is common sense.*
*- there is a need for candor to generate adhesion.*

Some of us were involved in various such crises. Some of us regularly advised authorities in various countries… Some of us lived the period of the Cold War, the fall of the berlin wall, various wars…

What did we learn?

- We had to balance – to manage all those white powder envelopes – supposedly with Anthrax – and potential terror attacks with no risk to the public and minimal disturbances to society.

- Authorities are fragile and easily abused at such times. We had to resist all those phone calls and mails of business developers trying to make a quick sale (mostly out-of scope) and – when sales were declined – resist political pressure to buy the useless items anyway. For this we needed to build trust across government.

- No One has all the knowledge - We needed to go OUT of the classical public health expertise, and add psychologists, environmental biologists, military, toxicologists and physicists, anyone willing to contribute… While learning is local, knowledge is global.

- We needed trust from both the authorities and the public. This trust is essential to reach the balance between Governance and Public Well Being. As we will dicuss further, Public health cannot be separated from Social needs.

- We needed clear and candid communication. No one will be blamed for not knowing something.

**How to gain and consolidate trust? Be critical, Avoid noise, and Communicate.**

**Content:**

# EXECUTIVE SUMMARY

Negating a problem – like some did – is a mistake, however making it worse is equally wrong. In Public Health, decisions are complex and must always rely on knowledge, be balanced, and find the optimum common good. The middle road seems to be lost.

This work is not an opinion. It is NOT a scientific paper aiming at teaching virology; it is an integrated analysis of a situation based on a **wide basis of peer-reviewed quality information** and aims to trigger critical thinking. In this executive summary we focus only on a few points from the report – the ones we felt were the most salient, other points are discussed further.

1. The actual correct mortality rate of the SARS-2 virus, the agent for COVID19 (the disease name) – that is including the persons who are positive without being sickened by the complications - is between 0.4% and 0.2% on average. This was independently obtained in 5 different US counties, and 5 different countries and used standard practices for doing so. This value is remarkably identical regardless of the various sampling methods that were used and is much lower (between 10X and 50X) that what is reported daily all over the world.

2. Spreading incorrectly measured mortality rates created deep dysfunctions, that magnified the problems, like hampering the correct functioning of health care, making people afraid to come and see doctors timely, and truly creating **a mass sociogenic disease**.

3. Even with such a low mortality rate comparable or even lower than some flu *(see Fig. 3 in Wong et al – in Note 9, p.34 of this report)*, the SARS-2 virus is a problem. It is fast, virulent and gives to some who are infected very serious complications. Contrary to what is published so far, none of what has been reported in scientific publications is new, as most of it was seen and was published in numerous papers going back to the period 2003-2013 (i.e. studies and reports involving SARS-1 and MERS).

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4. If the virus is not that dangerous, then why are we seeing those fatalities ?
    a. Those fatalities are mostly due to the fact that the virus acts very rapidly following a relatively long silent phase of incubation.
    b. It leads to 2 types of severe complications:
        i. either bacterial surinfection and bacterial sepsis,
        ii. or ARDS (Acute Respiratory Distress Syndrome) and viral sepsis that may lead to various numerous symptoms linked to any organ (this explains all the various '*new*' reports about SARS-2.
        iii. such late stage situations are not specific of SARS-2 as various numerous other viruses do the exact same. The problem with SARS-2 seems to be its speed.
    c. Both those complications should ideally be treated very early by a functioning first line of care, even prior they develop, with antibiotics and other existing medications (like the recently reported remdesevir or even amantadine, or other blockers). This would avoid overburdening the Intensive care units (ICUs').
    d. This problem seems further complicated by the fact that the primary line of care essentially stopped functioning, bringing the people self-isolating into those dire complications and thus towards ICU's.
    e. Part of the reported deaths are also likely not directly due to SARS-2 but to people not having been treated for another problem.

5. **Correct epidemiology** - based on standard methods and serological tests – is the most urgent priority and is essential to devise valuable and effective policies.
**This was and still is the most urgent <u>starting</u> point.** Because this defines everything else. After 6 months, the fact that those <u>basic stats</u> have not even been done systematically and are not available is <u>both appaling and troublesome</u>. Trying to solve questions about long term immunity, or collective immunity, about how long we are contagious, and those media-driven questions will remain irrelevant as long as we do not even know the minimal **<u>true</u>** risk.

# RESUME ANALYTIQUE

Nier un problème - comme certains l'ont fait - est une erreur, mais l'aggraver et créer la panique est tout aussi grave. Dans le domaine de la santé publique, la prise de décision est un processus complexe et doit toujours reposer sur les connaissances acquises. Cette prise de décision doit être mesurée et viser le bien commun. Cependant, le juste équilibre semble aujourd'hui avoir disparu.

Ce travail n'est pas une tribune libre. Il ne s'agit pas NON PLUS d'un article scientifique visant à enseigner la virologie. Ce document est une analyse intégrée, **basée sur un large spectre d'informations de qualité,** dont le but est de susciter une pensée critique sur la situation de l'épidémie du SARS-CoV2. Dans ce résumé analytique, nous nous concentrerons uniquement sur quelques points-clés de notre rapport, ceux qui nous paraissent les plus marquants.

1. Lorsqu'on prend en compte les personnes asymptomatiques, le taux correct et réel de mortalité du virus du SARS-CoV-2, l'agent responsable du COVID19 (qui est le terme utilisé pour la maladie), se situe en moyenne entre 0,4% et 0,2%. Ces chiffres ont été obtenus de manière indépendante en analysant cinq différents comtés américains ainsi que cinq différents pays, tout en ayant recours à des pratiques standards. Les chiffres sont remarquablement identiques, quelles que soient les différentes méthodes d'échantillonnage utilisées. Notons qu'ils sont également très nettement inférieurs - entre 10 à 50 fois plus faibles - que ceux quotidiennement rapportés partout dans le monde.

2. La diffusion de taux de mortalité mesurés de façon erronée a provoqué de profonds dysfonctionnements, ce qui a amplifié les problèmes posés, par exemple en entravant le bon fonctionnement des soins de santé, en générant au sein de la population la peur d'aller consulter - à temps - un médecin et en créant ainsi réellement une **maladie sociogénétique de masse**.

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3. Cependant, même avec un taux de mortalité relativement faible, comparable ou même inférieur à celui de certaines grippes (voir Fig. 3 dans Wong et al., dans la note 9, p. 34 de ce rapport), le virus du SRAS-CoV-2 demeure une menace. Il est rapide et virulent, et provoque chez certaines personnes infectées des complications très sévères. Toutefois, et contrairement à ce qui a été publié jusqu'à présent, rien de ce qui est aujourd'hui rapporté dans les publications scientifiques n'est réellement une nouveauté. En effet, la plupart de ces éléments ont d'ores et déjà été publiés dans de nombreux articles scientifiques remontant à la période 2003-2013 (par exemple, dans les études et rapports relatifs au SRAS-CoV-1 et au MERS).

4. Si le virus n'est pas aussi dangereux que l'image qui lui est attribuée, alors pourquoi sommes-nous touchés par autant de décès ?

    a. Ces décès sont principalement dus au fait que le virus agit très rapidement après une relativement longe phase d'incubation silencieuse.
    b. Cela conduit à deux types de complications sévères :
        i. soit à une surinfection bactérienne et à une septicémie bactérienne,
        ii. soit au SDRA (syndrome de détresse respiratoire aiguë) et à une septicémie virale qui peuvent entraîner de nombreux et différents symptômes liés à chaque organe (ce qui expliquerait tous les différents "nouveaux" rapports concernant le SRAS-CoV-2)
        iii. de telles complications en stade terminal ne sont toutefois pas spécifiques au SRAS-CoV-2 car de nombreux autres virus provoquent exactement la même chose. Le problème spécifique du SRAS-CoV-2 semble être sa vitesse.
    c. Ces deux types de complications devraient idéalement être traités à des stades très précoces, par une première ligne de soins de santé efficace et fonctionnelle, même avant qu'ils ne se développent, avec des antibiotiques ainsi que d'autres médicaments déjà existants (comme le *Remdesevir* qui a récemment fait l'objet d'un rapport ou même

l'*Amantadine ou d'autres bloqueurs*). Cela permettrait d'éviter la surcharge des Unités de soins intensifs (USI).

d. Ce problème semble avoir encore été amplifié par le fait que la première ligne de soins de santé ait substantiellement cessé de fonctionner, amenant les gens à se retrouver isolés avec ces complications désastreuses, qui les conduisaient ensuite vers les unités de soins intensifs.
e. Aussi, une partie des décès signalés ne sont probablement pas directement dus au SRAS-CoV-2 mais bien au fait que ces personnes n'ont pas été traitées pour un autre problème.

5. Une **épidémiologie correcte** - basée sur des méthodes standards et sur des tests sérologiques - est la priorité la plus urgente et elle est essentielle pour élaborer des décisions politiques utiles et efficaces. **Cela a toujours été et reste le point de départ le plus urgent**. Parce que cela définit tout le reste. Après 6 mois, il est épouvantable et perturbant de constater que ces statistiques de base n'ont même pas été effectuées systématiquement et qu'elles ne sont toujours pas disponibles. Tenter de répondre à des questions comme celles de l'immunité à long terme, ou de l'immunité collective, de la durée pendant laquelle nous sommes contagieux et à toutes ces questions véhiculées par les médias demeurera sans aucune pertinence tant que nous ne connaîtrons même pas le véritable risque minimal.

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# Part 1 - Foreword

Think openly one moment about our situation.

A virus, for which 95% of the infected will not be in danger, a virus that is AIRBORNE, is being tackled using measures ONLY adequate for **true direct** killers (Ebola, Plague, Cholera...). Then because of non-existent data about the healthy carriers, we created a useless sense of panic into the world population. This virus - which is really a common cold virus - is however **more dangerous** because it brings some infected people faster into severe complications. In addition because of the same fear of not risking the hospitals and the medical facilities, medical care to persons NOT having complications nearly stopped and nearly all of the infected come to medical facilities when it is already **too late** with those complications and, this situation CLOGS the ICU's of most countries.

Sounds familiar? In Belgium, one 22 year-old died from a heart condition because he was sent home, as he had obviously no fever, and no virus. A brain scan to see a possible risk of a brain bleeding was cancelled for another youngster. In Italy, infected people were left to die on stretchers without antibiotics perfusion for their pneumonia, hence making the false statistics even worse looking. Elsewhere a surgery needed to prevent leg paralysis in an otherwise healthy elderly man was reported *sine die*… Planned vital surgeries everywhere did not happen, people do not dare to come in the Emergency Room out of fear, cancer patient therapies were put on hold... Those are real situations and it would be easy to collect 100's of them from all over the world.

We are in this global frantic and dysfunctional situation. After this first phase, where things fell into place, would it not be time to plan ahead and re-visit some decisions based on facts this time? Is it normal that fear will end killing more than the actual problem?

Certainly not… and alas it obviously has become the case.

Is it normal that people start to flame at each other across the Internet, and that the rare voices of reasons are drowned by noise, insults and threats? Is it normal that the whole planet follows a Chinese Model which was based on wrong data, poor infrastructure and sanitation and, political massaging more than on real public health? An airborne virus has NO borders, and does not need people or airplane trips to circle the planet – birds and animals suffice. Do we ask their visas to wild geese? And unless a deceased person coughs on the caretaker, his/her body does not pose wild risks that cannot be easily mitigated.

*Authorities did what they could, based on a misleading set of information and wrong models. We have to thank them for that, even if it was chaotic.*
*Now it is time for a reasoned landing, time for evidence vs. models.*

**This is a short summary of an extensive and referenced analysis of the situation.**

**This is for general public audiences and aims to present a complicated situation in simple terms.**

**This communication (references and comments) is also aimed at authorities, political and/or medical.**

**It is not pretending to know/solve everything, but aimed at forcing a much-needed open and fast re-assessment of the situation before chaos breeding chaos, situations of conflict and TRUE problems may arise.**

PART 2.

**Summary**
**Elements of Communication for a broader public.**

This part is not aimed at arguing the science, but at building trust.

We can hear and read too many opinions.
What is written here are NOT opinions at all, the statements of this summary are all based on hard facts. This was written with vulgarization for the general public in mind. It is meant to elevate the average citizen knowledge by giving them some info that they can check for references if they would desire. When dealing with health issues, we feel that citizens have to be seen as adults and not treated like children unable to understand the underlying problems.

This part covers 7 main questions. Those are answered as simply as possible.

The evidence supporting the general public statements are contained in a series of 9 technical notes in the Part 3 via numbers for example *[See Note xx]*. Those direct links between facts and the more basic communication may help the reader to further his/her understanding.

In those 9 in-depth Notes, all the scientific, technical and medical elements available are listed, reviewed, discussed and referenced. Those can be controlled by anyone. Nearly ALL of the references are from peer-reviewed high quality publications and some high-end broader reviews. As much as possible, newspaper articles were avoided.

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Part of the problem with this crisis is either a lack of accurate communication, or contradictory communication, or communication by conflicted persons – all of which led to a deep mistrust in the public, and may have made the situation much worse than it needed to be.

The aim of this part is essentially to convey in simple terms for the widest possible audience all of the science and all of the data, because the public needs to understand in order to trust.

What seems obvious is that we all painted ourselves into a corner.

We need a better way out than doing the same thing and expecting some different results.

Note:
The type of *Info-demiology* (Information filled with pseudo-epidemiology) that the average public was exposed to since January 20, was exactly what led to misguided decisions. “Essential data” were aired regardless of their true importance. We feel that a free press has to educate. It is *now* evident that the selection of “essential data and epidemiological models” without hard questions can create misuse and abuse of information, without critical concerns and debates. We give here below some useful keywords for the interested reader, we feel that some public interest actions are needed to avoid a repeat.

- **Institutional Communication Media**
- **Freedom of Media communications and verified Contents**
- **Patient Education Information**
  In 1994 The Patient Education Institute at the University of Iowa in Iowa City, founded by Moe Ajam embarked on the development of an interactive multimedia system to be used at the Point-of -Care to educate patients and to document patient education X-Plain tutorials and modules) (https://pubmed.ncbi.nlm.nih.gov/11497310/ ) (Pr. James Goldberg and G Tritto in Paris promoted the design of Patient Education Information as a general approach to people. Now WABT (Paris) is developing with “ Le centre MOBILE AVICENNE de l’UNESCO” on line-courses on transmissible Infectious diseases in Africa, Central Asia and Mediterranean.

**1. The virus does NOT kill directly, it is not Ebola. Why are we treating it like it is?**

The common cold group of viruses – like the flu one - is quite numerous [See Note 1], and they adapt fast (mutate) so that they can escape classical vaccinations easily [See Note 2 & 5]. However some of them like the SARS, MERS and possibly many others to be discovered, are a bit more dangerous as they can go fast and give more complications like bacterial pneumonias [Note 3] and ARDS (Acute Respiratory Distress Syndrome) [See Note 4]. We say that those viruses are thus more "virulent". However they are absolutely not like Ebola, or other deadly fevers, and they are not like the bacterial plagues or the highly contagious and very deadly infectious diseases of the recent past [See Note 3, 4 and 9]. And yes, good sanitation is always needed as for any infectious disease (sanitation is quite bad in rural or suburban China for ex.). It is not the virus that killed but the **course** of the disease (in this case the severe bacterial pneumonia or viral sepsis).

**2. Wrong statistics led nearly all (but not all) countries to misguided decisions.**

Public health is difficult to manage but it needs accurate information for the authorities to make sensible decisions. When one collects only death data from coughing people, without knowing anything else, does ANY of those so-called death rates make sense? It does NOT! In such malpractice, we could even measure 100% of fatalities if we were to choose to [See Note 9]. Why did that happen will be explained below (see tests). Some real statistics came from South Korea early on, but were dismissed [See Note 9], some other came later out of Germany, US, Iceland but was doubted [Note 9], a key paper was published in the Wall Street Journal highlighting the reality of the problem, without being able to lead us out of the wrong spiral. In short, except at a few places, no one really measured the infected people who were not coming to hospitals, the infected people who came but had NO complications deserving Intensive or Critical care, and the ones who just had a fever or a flu. Conclusion: fatalities are much more lower than the world press has been busy airing 24/7. How much? Probably between 10 and 50 times less! [See Note 9]. And yes, the flu kills more [See Note 9]!
Would we have taken the same decisions if such analysis had been done early on?

**3. Complications from the virus may in some cases bring us to ICU and in the danger zone – but they can be avoided and this is part of the way out of this crisis.**

Such viruses can be very dangerous of course. We all know about the elderly, the infants, the persons with some compromised health (having COPD, Asthma, Smokers, Chemotherapy, Immunotherapy, surgery, patients already in ICU…) [See Note 3 and 4]. At risk we also have some patients with hypertension (too high blood pressure) and diabetes, and also probably some persons who have genetic predispositions for it. With each passing year, those viruses may be fatal to some of those people [See note 3, 4 and 9].

Those fatalities should always be as minimal as possible or even non-existent, but for this we do not need fear-based hospital entrances like in bad movies, we need just plain good medical practices. Triage is fine as long as medical priorities remain priorities, and FAST patient treatment in community is needed [See Note 3]. Upon faster treatment, patients will not need to be hospitalized and clog ICUs. [See Note 4].

Usually this type of virus creates 2 major complications in a minority of the infected persons (remember near 95% of the persons will never have those complications): bacterial infections that come on top of the virus because our lungs have more secretions [See Note 3], and strong

difficulties of breathing linked to the obstruction of our airways by those secretions that lead to many secondary problems seen in different (non-SARS) viruses in fact [See note 4].

1 in 7 of hospitalized patients were infected by bacteria and among those patients fatality was 50%. So the situation is clear [See Note 3 for details]. In general – with other viruses - Doctors usually have a few days (8-10) before seeing those complications, in the case of this SARS-2 virus, one has 2-3 days. So early blind antibiotherapy is warranted.

When a bacterial pneumonia comes, the patient needs antibiotics. When ARDS comes the patient needs antibiotics and either oxygen or respiratory help (with respirators).

Why is this virus creating more complications and becoming a logistics problem?
It acts faster than the other viruses of its category, it goes deeper [See Note 4]. It has some surface that makes it “stickier” to the airways and allows the virus to penetrate airway and lung cells more easily [Note 4]. Also old molecules like amantadine, … may be effective at decreasing the stickiness hence making the viral infection less risky for both the concerned persons and the medical personnel [Note 4].

4. **Why vaccines are needed but will be slow and most likely never as good on their own as natural immunization of the population?**

Vaccines are powerful tools against viruses and bacteria. They are however only effective when those viruses and bacteria do not change fast (mutations). In such case their efficacy can be quite low. An example is the yearly flu vaccine that needs upgrades (modifications) twice a year and still is only 50% effective. But this low efficacy is good enough to decrease the speed and the reach at which the flu virus spreads [See Note 5].

A vaccine made by the industry is like having a very strong key to close a door. The natural vaccination of the population is more like having millions of different keys protecting the same door because each of us will develop antibodies against some <u>different</u> parts of the virus [see Note 5]. When a virus changes (mutates) [See Note 2], then it can evade the vaccine (the single keylock) but can NEVER evade the millions of personal keys. This is called “herd immunity” and is - <u>in those cases where germs change easily and fast</u> - more powerful than actual vaccines. Vaccines take time to be made and tested. It will be at best 12 months before available. But remember this is a member of the common cold family, if a vaccine against those types of viruses was easy it would have been made decades ago. So waiting sheltered while waiting for the vaccine is not a good option as we share this virus with other animals [See Note 7]. There the cure may indeed become worse than the disease. (See below social-distancing and sheltering).

**5. But people are dying - Will leaving the population exposed lead to many fatalities?**
Not necessarily if planned, if we focus on the treatment of the complications **early** and do not wait that a pneumonia needs to be ventilated. By focusing the care on the persons with compromised conditions, the elderly, and the infants, we avoid the dangerous complications (like in Sweden [see Note 9]). By not doing this, we are creating the logistic crisis at the hospitals by having given up the community care giving, and by not taking into account the specific speed of this virus.

**6. The SARS Virus like all/most respiratory viruses is airborne, and animals can be reservoirs. Role of Surfaces, droplets.**

A virus is so infinitely small and weights nearly nothing; hence it is always on the move through the air, a bit like particles of dust. We breathe 1000's of them in and out of our lungs at any given time. The majority of those viruses are harmless to us, and the viruses that can cause us harm, do not always successfully infect us (it takes many virus particles to succeed into bringing us into sickness) [See Note 6], or do infect us only mildly. Only in 10-15 % of the cases [See Note 3, 8 & 9], the infected persons will have a major illness, and only a fraction of those will need to be treated for the complications [See Note 9].

Droplets from infected coughing do contain the viruses [See Note 6], and those droplets indeed fall on the ground and surfaces in less than 6 feet. However lots of droplets remain in the air also, and the virus can survive inside them for 3 hours [See Note 6].

This family of viruses - like the flu - can easily go from one type of animal to the other, or from animals to humans and back [See Note 7]. Remember that bird and swine flus are common. In some cases the animals may be carriers where the virus stays alive without making them sick, in some cases the animals themselves can be sick [See Note 7].

Also this virus was reported to have originated from a live animal market in rural China. Bats, rodents can be reservoirs, but we should not be surprised that civets, rodents, birds or livestock could be hosts [See Note 7].
What do you think will happen when we, humans, get out of our "shelters" again? We will keep exchanging those viruses with animals.

Final Text

**7. Isolation, social distancing and quarantines can be both very good and very bad.**

If a killer virus like Ebola had hit us, ALL of what was decided and implemented would make sense. However when dealing with a virus that is NOT a direct life threat but only an indirect one, after the initial surprise, some proportionate response should be put in place. Isolation and social distancing should not be large scale, nor systematic, but **targeted**.

When infected and coughing - as we all do or should do – we should isolate ourselves, and not go to work to avoid spreading. Given the fact that this virus can bring the complications very fast, remaining isolated with a fever and chills may lead to a worsening of the situation and bacterial infections. The same is valid for those of us who have a pre-existing condition, or are at risk. Isolation in such cases, will inevitably lead to catastrophes.

So community care is essential, as most of the infected persons, if taken up early with appropriate care will not need Intensive care and/or respirators. Leaving people quarantined (like in cruise ships or in large facilities) is downright bad preventive medicine, and can worsen the situation. Having dedicated parts of medical facilities, to test and treat is needed, but treating the patients with the protective gear only seen in *end-of-the-world* movies leads to insane situations. This heavy gear generates huge fears and hampers **everything**: doctors stop thinking, military-style triage replaces medicine, diagnostic are NOT properly done, treatments are being denied even to patients infected with the viruses. Triage is to make choices about 2 patients based on their respective chances of survival and choosing. But given the wrong public health statistics, given the fact that most patients will never be at risk, it has NO place nor use in our actual

situation. It is not the role of the authority to decide what procedures may MD's do or not, as some countries have proposed for specialized medicine.
Isolation of large populations – while waiting on a possibly effective vaccine against this group of viruses – is NOT a sustainable solution; it is not even a solution.

Final Text

PART 3.

## EXPLANATORY NOTES AND REFERENCES



Final Text

## Note 1. Common Cold and Influenza (Flu).

This type of virus targets our lungs and bronchi. Usually they remain in what we call the upper respiratory tract, but in some cases they can go deeper and become more dangerous. Some viruses attack other organs.

**Their benign form of disease** is known to us all, and is characterized by a runny and stuffy nose, sneezing, cough and a sore throat. Often we loose the sense of smell and taste. That Covid19 can alter the sense of smell is thus NOT unexpected and, cannot be used, as 'proof' that it does what other members of its family do not do. The viruses enter some of the cells in our airways and, then reproduce themselves – after 10 of thousands of new viruses are made - the infected cell explodes, and all those new viruses with the cell broken pieces are expelled either by **normal breathing** or by **coughing**. This coughing can be dry or can be 'wet' (droplets of mucus). The secretions may be clear or colored (this is the sign of an additional bacterial infection).

The flu (i.e. influenza) is also a disease of the respiratory system with very similar symptoms to the common cold, but that typically also includes fever, muscle and body aches, fatigue and chills.

Viruses cause both the common cold and the flu. The influenza viruses belong to a *single* family (the *Orthomyxoviridae*), the common cold can actually be caused by *numerous* viruses belonging to *different* families. Here their names with our apologies:

- Rhinoviruses, Enteroviruses (*Picornaviridae*)
- Respiratory Syncytial Virus (aka. RSV and Human parainfluenza viruses (*Paramyxoviridae*)
- Adenoviruses (*Adenoviridae*)
- Human Metapneumoviruses (*Pneumoviridae*)
- and the (now infamous) Human Coronaviruses (*Coronaviridae*). There are 7 known Human coronaviruses (4 benign, MERS, SARS1, SARS2 (CoVID19)), and probably more to come.

Final Text

**Sometimes the disease is not benign.** Some viruses may be more aggressive (virulent) than others, some may find their way deeper in the bronchi. When this happens, we start to see what we call complications. Two main complications for those viruses are the sur-infection by bacteria and what we call ARDS (Acute Respiratory Distress Syndrome) and finally Multiple Organ Failures. **For COVID19, like the flu, complications come in 10-30 % of the infected persons [see Ref #1 in Note 3].**

During the bacterial sur-infection, often it is the strepto (as the one in strep throat) that comes in. The bacteria come easily and frequently inside a person with such viral infections because the destroyed lung cells and the extra mucus offer them a good "home", an ideal medium to grow. While antibiotics cannot fight viruses, antibiotics are **essential** to fight those secondary infections.

What happens during ARDS, is that the virus being more aggressive and going deeper in the bronchi, generates more damage, more debris, more fluid and hence all this can 'plug' the airways. This blocks the oxygen going into some parts of the lungs, and the fluids hinder the blood oxygenation. Oftentimes, bacteria take advantage of this situation too. In this case we need either oxygen or respiratory assistance BUT also antibiotics, and sedatives [as it is near impossible to use a respirator on a patient who is not sedated, his lungs will fight the machine!!!]

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- **Centers for Disease Control and Prevention at *https://www.cdc.gov***

## Note 2. These viruses mutate very frequently

We all know that flu and cold viruses mutate frequently. The vaccine against the flu has to be "done" twice a year to be up-to-date. For the common cold group of viruses, in more than 60 years we never succeeded at making an effective vaccine. Because they modify themselves (they mutate) very frequently. They mutate even faster than the famous HIV, for which after 30 years of hard research, we only start to test and see the possibility for an effective vaccination.

A recent study (PNAS) analyzing only the latest version of the virus from 160 Covid19 patients already saw 3 major viral groups, and 101 different genetic sequences. All this divergence occurred in patients ONLY and in a few months. Another study (from Johns Hopkins) reports a mutation rate of around 1/1000 RNA bases/yr, this would mean for a 30kbase genome, around 30 variants per year.

While it is likely that scientist can find some sequences in the virus that could be more stable and thus candidates for a vaccine (see Shang ref. below), announcing the vaccine, as the 'way' out of this pandemic is absolute mis-information. And actually some mutations may even attenuate the virus, and make it less dangerous, some other mutations may make it spread faster.

A vaccine development may take close to 1 year, and then what? Injections 3 times a year, and having ALL the side effects if we were to rush testing? Dr. A. Fauci (Former Head of Infectious Diseases at the NIH, Bethesda, USA) did mention both a possible but very optimistic timeline.

A world renown authority (Dr. Nabarro, Prof. of Global Health at Imperial College, London, UK) explained in 2 interviews what ALL biologists and virologists know: that we should not let the population assume that vaccination is the solution, and that one can stay safely inside waiting for a near-impossible vaccination. [Quote] *"You don't necessarily develop a vaccine that is safe and effective against every virus. Some viruses are very, very difficult when it comes to vaccine development - so for the foreseeable future, we are going to have to find ways to go about our lives with this virus as a constant threat". "That means isolating those who show signs of the disease and also their contacts. Older people will have to be protected. In addition hospital capacity for dealing with cases will have to be ensured. That is going to be the new normal for us all."* [End quote]

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It is important to note that in both cases these persons have no conflict of interest. The bill/cost for a 'salvation' vaccine will likely reach between $ 1-2 B. It is obvious that the industry and the vaccine experts will call for the need to develop a new vaccine. And it is **both** needed and the right thing to do. However when one reads a recent high profile publication in Nature/NPJ vaccine, some possible genetic sequences are potential candidates for a vaccine (good), but the paper very honestly also lists in Table 1, all the possible pitfalls (not so good). And the list does not include the fact that the virus will ADAPT to the new situation with the vaccine, by mutating and escaping it. **Interestingly those authors mention pneumonia as the cause of their call** (even in the title itself!)

In the same manner, explaining that we could eradicate this virus – this means wiping out the virus FOREVER from the planet - is not correct, even not possible. We could eradicate the Poxvirus totally from our planet, and we are nearing the full eradication of the Poliovirus, only because we – humans – are the only hosts/victims of those 2. But when a virus can choose between species like most members of this family (that can go between humans, bats, pangolins, rodents… but also cats, tigers, dogs…), eradication is just IMPOSSIBLE. We would have to vaccinate all humans, all other animal hosts or animal reservoirs.

References:


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- Prof. Nabarro's analysis can be found here: *https://www.theguardian.com/world/2020/apr/18/dont-bet-on-vaccine-to-protect-us-from-covid-19-says-world-health-expert*
- **The outbreak of SARS-CoV-2 pneumonia *calls for viral vaccines.*** *Shang et al. pj Vaccines (2020)5:18 ; https://doi.org/10.1038/s41541-020-0170-0*
- Dr. A. Fauci – numerous press conferences at the White House (USA)
- **Center for Health Security**–Johns Hopkis Bloomberg School of Public Health–SARS-CoV2 Genetics, April 2020.

## Note 3. The bacteria are very frequently taking advantage of viral infections. Treating at the community level may avoid infected patients flooding the ICU's?

For the majority (more than 80%) of Covid19 infected persons, their flu-like symptoms will be mild, and they will recover in a few days. For some the symptoms will be more painful. It is estimated that 10-30% of the infected will develop a secondary bacterial infection. Half of those (which means 5-15% of the total infected) will die from a bacteria if not treated well (see Reference 1 from Antibiotic Research below).

Unless a person is in severe bad health, nearly no one dies DIRECTLY from the virus, but many may die from its complications. The major complication is a bacterial infection on top of the virus. This was ALREADY reported in Wuhan (Zhou et al. Lancet). 50% of the patients who died, died of a secondary infection. [Quote] *Sepsis was the most frequently observed complication, followed by respiratory failure, ARDS, heart failure, and septic shock (table 2). Half of non-survivors experienced a secondary infection, and ventilator-associated pneumonia occurred in ten (31%) of 32 patients requiring invasive mechanical ventilation. The frequency of complications were higher in non-survivors than survivors (table 2).* A lot of those are related to bacterial pneumonia and sepsis (bacterial septicemia ie. blood invasion by bacteria) – Once the situation reaches ICU level, then further complications like cardiac or kidney damages and further lung tissue damage (Destruction of pulmonary alveolae) may happen. We have early reports that increased levels of Troponin 1 could indicate the patients at risk of cardiac worsening.

Numerous studies report frequent co-infections or secondary infections with this virus:

- A French paper by Bleibtreu in 2018, analyzing a cohort of 93 patients (74 were pilgrims from Mecca) that were supposed to be infected with MERS-CoV (Middle East Corona Virus) showed that 24% had a bacterial infection (Streptococcus pneumonia, Legionella pneumonia). EARLY and EMPIRICAL treatment with 1 or 2 antibiotics saved everyone except 2 persons! (Empirical means : blind, without antibiogram).
- A Canadian study (by Zahariadis et al.) evidenced that during SARS (SARS-CoV1) epidemy, co-infection with bacteria like Chlamydophyla pneumoniae and/or Mycoplasma pneumoniae was present in half the cases (40%). Patients were positive for those infections even when the genetic test for those bacteria were negative. [Fully expected as those bacteria remains mostly **inside** cells and barely reach the blood].
- Same rates are found (30%) in Community acquired pneumonia, infections with multiple germs. (Libermann et al., as 1 example, many reports exist). 30% multiple infections in children, etc…
- In another study, such co-infections can also be triggered by the corticotherapy used to treat the respiratory distress – 3 cases out of 20 in a case-controled study in Toronto (Hwang et al.).
- In a more general study about SARS-CoV, Gu et al. reported again that one finds various bacteria in the lungs (Aspergillus, Pseudomonas, Streptococcus, Staphylococcus…)

The situation was the same in the different mortal Flu pandemics of 1918, 1957, and 1968, where it was shown that MOST deaths were caused by the bacterial secondary infections. During the pandemic of 2009 (caused by H1N1), between 4 and 20% of the cases had secondary bacterial infections, and this was the main cause for the severe cases (deaths and ICU's). It was calculated that between 30% and 55% of the deaths were caused by secondary bacterial pneumonia (Morris et al. - See also 5 refs about the Flu below).

Treating early – and blindly – with antibiotics could really make a difference (20-30 % of the cases). Choosing NOT to treat empirically to avoid bacterial resistances, waiting that bacteria is confirmed misses the 'intracellular' not traceable bacteria, and is a bit like trying to read the license plate of the truck that comes running you over. We could treat ALL or use some criteria (see additional note at the bottom of the references below). Such strategy was successfully implemented in some places like the HUG (Hôpital Universitaire de Genève) in Switzerland (see additional note and ref)

Using OLD molecules (like Penicillin, Amoxycillin, Vibramycin, Bactrim,…) can save lives while at the same time avoids increasing antibiotic resistance risks (see again Ref. 1 below). An added advantage

would be to catch and treat patients when they are still in relative good shape, instead of seeing them at the complicated stage in the ICU (better outcomes, less costs, no panic).

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**Additional Information for the specialists – Who to treat? :**

1. There is a huge misconception about the clinical definition of the virus, as written earlier, the SARS-2 virus can easily and quickly cause pneumonia. So in the early stage, it is a bit like the flu, and very quickly it goes deeper in the lungs [See Note 4].
2. This difference between early and late stages - the early stage with symptoms similar to a flu, and the florid phase of pneumonia - is one of the reason that the group of Dr. Raoult in Marseille developed the low-dosage lung CT scan method to detect the pneumonia signs even if the symptoms were scanty, for a differential diagnostics with the seasonal flu. In other world this would allow to make the difference between that patients who may be receiving early and empirical antibiotics and those for whom one could wait. Maybe some lung sonography would have its place here.
3. As of mid-March 20, the Infectious Diseases unit of the HUG Geneva had issued regular guidelines for broad antibiotic use, and even Remdesevir (which back then was not fully approved) 2 notes **« Prise en charge d'un patient infecté par le SARS-CoV-2 »** et **« Strategies Therapeutiques SARS-Cov2 »** by Dr Vetter et al. (see next page – fig in French).
4. It is also worth noting that 4 coronaviruses show a well-known seasonal pattern in humans, (see Monto et al in April 2020 here below). So it will be most likely a seasonal recurrrence and it is too early to know.


- **Coronavirus Occurrence and Transmission Over 8 Years in the HIVE Cohort of Households in Michigan.** Monto et al. *The Journal of Infectious Diseases*, jiaa161, *https://doi.org/10.1093/infdis/jiaa161*

Examples of guidelines in HUG (CH).

First line, severe pneumonia is mentioned. [Translated Quote] *The new coronavirus SARS-CoV2 may give rise to severe pneumonia* [End quote]. This is the core of the situation as these pneumonia are either very rapidly leading to bacterial deep lung infections or sepsis, or even worse to a generalized viral infection termed viral sepsis. Second exhibit shows a clear flow chart for EARLY treatment.

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|---|---|---|
| **Rédacteurs :** P Vetter, DL Vu, A Calmy, C Samer, T Agoritsas | **Approuvé par :** L Kaiser, M Schibler, MC Zanella Terrier Groupe Guidelines COVID | |
| **Stratégies thérapeutiques SARS-CoV-2** | | |

**1. Introduction**

Le nouveau coronavirus SARS-CoV-2 peut entraîner des pneumonies sévères.

Il n'existe pas de traitement spécifique qui soit validé, et la prise en charge repose sur les soins symptomatiques et les soins de support (mesures de réanimation), avec administration d'oxygène, traitement des surinfections bactériennes, des complications parfois graves telles que myocardites ou ARDS, avec prise en charge dans une unité de soins intensifs au besoin.

Certains traitements expérimentaux actifs sur les coronavirus pourraient avoir une activité sur le SARS-CoV-2, mais très peu de données cliniques sont actuellement disponibles. Plus de 80 essais cliniques randomisés sont en cours, la plupart en Chine, dont les résultats à cette date ne sont pas encore publics. Ce document a pour but de les revoir et de fournir des recommandations basées sur les évidences cliniques.


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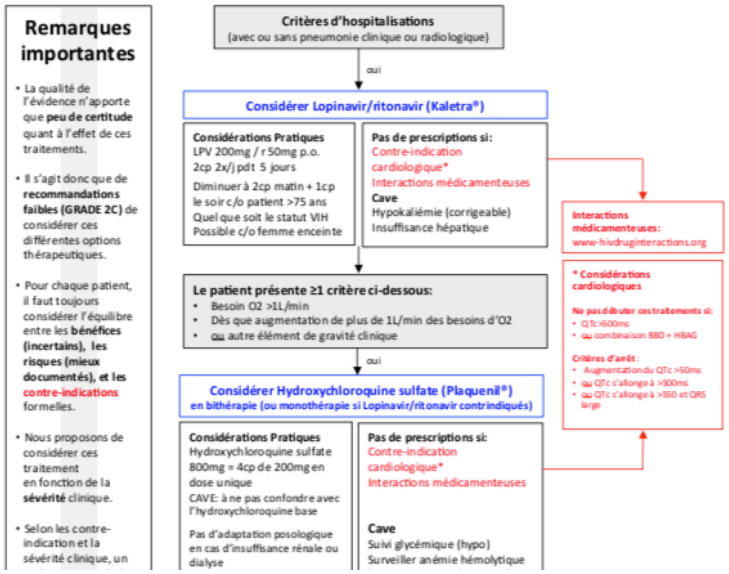
| **Stratégies thérapeutiques SARS-CoV-2** | | |

**NOTE 4 - Another complication is ARDS - leading to a *rapid* degradation and multiple organ failure (MOF). The cardiovascular, coagulation, neurological, and the other symptoms are linked to a *FAST* viral spread (viral sepsis). None of it is surprising, we have known this for years.**
**Treating at community level BEFORE may avoid infected patients flooding the ICU's?**

While most patients will not develop any severe complications, some persons once they start to develop a deeper pneumonia, also develop **classical** complications seen with many other pulmonary viruses SARS-Cov2. The evolution of SARS is not new; its symptoms through the body have been studied in detail and can be found in excellent reviews (Gu et al. 2007). It starts by targeting the lung cells, then later goes deeper inside the bronchi, then penetrate in the blood and goes inside the cells in the blood vessels, the intestine, the kidney, and the brain. Lots of respiratory viruses do that actually – SARS just goes faster there. In some ways it resembles the RSV known in children. When the lungs are damaged, patients suffer what is called ARDS (Acute Respiratory Distress Syndrome). That is when they need respiratory assistance.

**Why is the SARS-2 virus more dangerous than others? *Speed, speed and speed.***

- First the rapidity of this process compared to the other viruses.
  In short, primary care givers do not have much time between the onset of a complication and the rapid degradation - if left untreated.
- Another danger is that the virus is 'stickier' than others (This helps getting it inside our cells)
- And an even more hidden danger is in the capacity of the virus to fuse the cells (see also Gu 2007) that it infects with each other, thus making giant distorted cellular blobs (plugs in the airways) and triggering a strong and inadapted immune response (a process called cytopathy). This happens in the majority of SARS patients with complications (Gu et al. 2007). In a lower number of patients with complications, the little lung structures where blood is being oxygenated (the alveolae) are physically breached and plasma and blood cells make the oxygenation impossible – even with respirators.

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We will see below that none of those 3 dangerous features are specific to this type of virus, as many viruses fuse the cells (a process called "syncytial formation" and leading to super large cells called "syncytia"). The list includes Reoviruses, RSV, HIV, Dengue and many others… The same goes for the 'stickiness', it is linked to some special genetic sequences called PDZ (PDZ binding motifs). They are present in many viruses, including HIV and they just make those viruses stick more to cell membranes and their receptors, helping them getting INSIDE the cells.
**What is striking in SARS is its speed to complications in 2-3 days once they start in the minority of the cases.**

[Rem: A known French politician, P. Devedjian died in 2-3 days while being clinically stable and being an in-patient for just observation. At NO time he was put under therapy as he went from totally stable with fever and positive testing to the ICU]
[Rem: Prof Montagnier in France recently claimed that the coronavirus was a bioweapon because it contained genetic sequences present in HIV- sorry to mention that he should know better, those sequences are NORMAL in many viruses!]

In COVID19, the virus binds to the cells in the lung via a receptor (ACE2) (Gu et al. 2007). [A molecular receptor is like the mooring of a ship, it is a tight anchoring or binding]. This receptor is present in high concentrations in deep lung cells but also present in the blood vessels. It also explains why some people with heart diseases, hypertension, diabetes, are more susceptible to complications. Other receptors [anchors, cathepsin D being one] are also needed, but this is beyond the point of this note.

What is truly disturbing in the situation we are living now is ***the total disconnect with what was/is already known about the SARS of 2003, and the narrative of SARS in 2019.*** While there may be some subtle difference (between SARS 1 and 2), the mechanisms of action are fully similar. This should have helped clarify the situation, and it seems that it did NOT. A problem in this whole crisis is linked to scientific publications. Although a lot is already known, quite numerous authors get quick papers published as 'hypothesis' or as 'viral sepsis hypothesis'. While being incremental is a good scientific quality, it does

not help educate the authorities and the public during crisis – there is no need to re-invent the wheel just to fill in the gaps. It is obvious from all the clinical data that when a case becomes severe, and when the integrity of the air-blood barrier (the little alveolae in the lungs) is destroyed, oxygen does not help anymore, and this results in a vicious circle (see Gu et al 2007, but also in Li et al. in The Lancet 2020, and in Ling Lin 2020). In those rare patients with complications, after 6-7 days, the virus enters the blood and targets many systems (multiple organs failure situation) - this is NOT a hypothesis but a fact! Thus proposing more research (see 2 quotes right below) to be able to help with the understanding of how the virus kills – while a sound scientific proposal – is not a good message to authorities and the general public. ***Preventing the known complications known since 2003-2007 before they arise is key, and it is actually do-able by treating as early as possible.***

[Rem: Quote 1 "More immune-related research is needed to help us understand the pathogenesis, guide the treatment of the disease, and improve the prognosis". Quote 2 "Future basic science research is needed to explore whether SARS-CoV-2 directly attacks vascular endothelial cells, and to examine the effect of SARS-CoV-2 on coagulation and virus dissemination." ]

[Rem: When dealing with a fast-paced complex research effort, the press in search of a story but without the scientific training will report any new factoid as equally important and create the noise that prevent rational decisions and may even paralyze the health care workers and the MD's].

**Coagulation troubles.**

About the coagulation troubles, they are known since 2007, they come in LATE stages (when it is probably too late even), and it is both hyper- and hypo-coagulation at the same time. We can thus have strokes, blood clots, or blood not coagulating enough, but also micro-strokes in capillaries requiring even amputations (see Zhu Xu-You in 2010). Those are very complex situations, but they are NOT specific of the SARS – the cytomegalovirus (see Delbos et al. 2007) and the Herpes virus can do it too (see Gorek et al. 2007). Likewise it is known that the flu can do it in late stages of severe pneumonia (Yang et al. 2016). It is also known that this complex situation (called DIC – Disseminated Intravascular Coagulation) arises often in severe viral infections when they lead to septic shock, and is associated with high mortality rates around 50% (in Seki et al. 2013). Recent reports confirm that the coagulation troubles in SARS 2 like in SARS 1 may also lead **to permanent cardiovascular problems** – this makes the use of cardiac medications like chloroquine and its derivatives but also Statins (anti-cholesterol drugs used too frequently amongst the elderly) delicate as they may not be good to use for every patient during late stages.

So abnormal clotting is of course highly dangerous but *normal* once the disease becomes severe – (see Ref. Med page Today for a vulgarized perspective, and Giannis et al. 2020 for a more in-depth description) - like it is again the case with many other viruses. These severe coagulation problems occur in1 in 6 hospitalized patients (16% in Giannis et al, note: hospitalized COVID patients represent a minority of all the infected persons). But clinicians know this… and they know how to handle severe troubles of the coagulation, and they know how to treat patients. They should be allowed to work in peace, without non-contributing noise, or comments about *never seen before* coagulation troubles. Unfortunately, this expected complication of viral diseases was seemingly overlooked.

Coming back to the speed of SARS – which is the main cause of the ICU's being overwhelmed –

- It starts with very high and rapid viral multiplication in some patients (10-15%). This was already reported in 2004 for SARS1 and MERS (see CM Chu et al. in CMAJ. 2004) where it was seen that SARS gave higher viral loads. This meant more virus reproduction per unit time and volume and it was a bad sign (bad prognosis). This happens in the most severe cases, and not for the lighter cases. Same situation for MERS (see Oh et al, NEJM in 2016). See also Channapanavar in 2017, for a review about SARS more specifically.
  ***More viruses means FASTER disease (speed again !)***
- The more dangerous coronaviruses (like CoV1 and CoV2) infect the lungs at a deeper levels, this means where our airways have smaller diameters and thus can be more easily clogged. And this deeper infection with more cloggings leads to an abnormal immune response and then to Multiples Organ Failure (Channappavar et al. 2017).

**Why are those viruses "stickier"?** *(data from humans, animals and cell models)*

Apologies to all scientists for such a non-scientific term, but it is better understood by the non-biologists. A lot of viruses have some genetic sequences that makes their envelope a bit stickier – those are referred to as PDZ-binding motifs - this means that the protein of the envelope may interact and bind itself to numerous other proteins it can meet and can stick to the exterior of the cells it tries to enter (hence the term sticky!).

Those genetic sequences are not unique to this family of viruses but make them more effective at infection and entry inside our lung cells. This happens in humans and was proven in animals (see Jimenez-Guarden et al. 2014). In animal models, when such PDZ domains were removed, the virus became much more mild. **It is then understood that such domains are also targets for future medications.** This is also explained in an excellent review of the factors influencing the severity of the SARS family of viruses (see Fung et al. 2019).

Besides being sticky, this envelope protein is also essential for the virus entering our cells, and for the formation of the syncytia already mentioned. This protein is called a VIROPORIN because it forms holes in the membrane of the cell that is attacked (it actually forms what we call ion channels in biological jargon and - because of that - can also influence and control various processes in the cell).

These viroporins exist in many different viruses (see Chung et al. in 2015, also Farag et al. 2020) – like the RSV or the flu for example – and they are ALWAYS associated with the severity of the pneumonia and its side effects. They have many roles:

- Define the severity of the inflammation and of the immune responses (see Farag et al. 2020).
- They are also helping forming the plugs inside the bronchi (syncitya) (see Fung et al. in 2019).
- This viroporin type is important for the aggressive or for the benign character of the infection (viral fitness) (see Nieto-Torres et al PLOS One in 2014 & Farag et al. in 2020).
- In short those viroporins are essential for many aspects of the lifecycle of the SARS viruses (Schoeman et al 2019) and this was proved in cell models infected by the virus also (Li et al. 2020).

The viroporins are essential for many aspects that make those viruses fast and aggressive in some patients. **Medications that can block the viroporins are thus important to prevent the severe complications of ARDS.** (Alsaadi et al. 2019)

From the flu, we know that blocking its viroporin with AMANTADINE (a very old EMA and FDA approved medication) offers a relative preventive protection in humans. This is why amantadine was used and is still being used to protect both - in a preventive and curative manner - the medical personnel during flu pandemics. It costs nothing compared to Tamiflu. Amantadine has been shown in 1992 to block the pore of the viroporin (blocking the ion channel activity of this protein called M2 in the flu). More recent work has shown that amantadine may also interfere with the Viroporin of the SARS virus (Torres 2007). While this is not done *in vivo*, given the fact that amantadine is risk-free and has been widely used in the past, it would be worth considering it as prevention like in the flu. At least for the medical community.

This is a good example that it is possible to revisit the molecules that we have in our inventory to find specific and/or relatively specific therapeutic strategies against the virus. Designing NOVEL products makes commercial sense and should be encouraged, but NOT at the cost of existing knowledge that makes Public Health sense.

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## Note 5. Why natural immunity and vaccines work together – Many locks vs. Single lock. Industry will always be slower than live biology.

Everyone knows and understands that vaccines can block viruses and prevent many infectious diseases. They help the immune system, which is our biggest protecting organ. There are different ways of fighting viruses with our immune system: vaccination, monoclonal antibody therapy, natural immunity (also called 'Herd immunity').

Vaccination is an efficient tool for *preventing* viral diseases. It is based on using viral components, stripped of their infectious power (e.g. parts of viral particles, damaged viruses, etc.), in order to stimulate an immune response, which will remain in its memory. At later times (even years later) when coming in contact with the actual disease-causing virus, our immune system already has at its disposal (in its memory) tailor-made antibodies to fight it. This is called *active immunity* and works in a lock-key principle: our immune system recognizes some part of the invading disease-causing particle as a lock (called an *antigen*) and then creates a key (called an *antibody*) to block it. The key closes the lock (they fit together) and nothing else can happen.

When the industry produces a vaccine, it imitates the natural process: i. a stable part of the virus is chosen to avoid that mutations make the vaccine ineffective too quickly, ii. a product is made that once injected will trigger the immune system and its memory. iii. to control a pandemic, at least half the population has to be vaccinated. Some vaccines are more successful than others, as the viruses that do not mutate are easier to fight. Virus that mutate can escape their vaccine quite easily (we call this Darwinian selection), the flu and the SARS-CoV2 are in this category.
One can include different antigens in the vaccine to make it polyclonal (poly = multiple, clonal = copy), to increase the chances of not losing efficacy.

But this takes time, lots of time. The cycle of the industrial production of vaccines is quite slow; one needs to find the good target (the good antigen/lock), then develop the good key, then test for safety and efficacy. And if the virus escapes, we will have to re-do it all over again.

[Note: A possible faster way to develop vaccines is based on RNA technology – but it is not yet widespread].

The natural immunization is the same, but happens inside our bodies, is "always on" at all times, and repeats itself naturally whenever needed. It takes ONLY a few weeks to become immunized.

But in dealing with pandemic, the natural immunization has an enormous advantage. Because of the diversity of individuals, both the recognized part of the viral particle as well as the key that will be generated will be different among a population. Natural immunization will generate millions/billions of different keys by having each of us generating a different key. It is hence a system based on *polyclonal* (poly=multiple; clonal=copy) antibodies.

Having millions (or billions) of solutions/keys to lock and block the virus, makes it very hard for any virus to be effective, and makes the infection of additional persons very difficult thus protect the whole population. If the virus evolves, NO Problem, many people will spontaneously develop in their bodies some immunity, protecting the group.

Passive immunity*,* on the other hand, is injecting *ready-made* antibodies, produced in laboratories. This is a single ready-made key able to fit a specific lock. This is the principle of monoclonal (mono = single; clone = copy) antibody therapy (aka. serotherapy). This explains why the serum of the infected people who already healed can be used to treat and protect the newly infected people. However this does not work for all the viruses – for SARS we still do not know.

There are a few reasons why efficient and durable vaccines are hard to obtain for respiratory viral infections:

- There are several different viruses that can cause a common cold (*Simancas-Racines et al., 2013*). Getting vaccinated against a specific one will protect against that virus only. Since there are a myriad of viruses that are responsable for the common cold, being protected against specific virus will not prevent getting a cold.
- Sometimes, more than one virus is active at the same time, so that a patient gets infected by 2 different viruses in the lungs. This has been shown to be the case with Covid19.
- All living organisms mutate (= change). Viruses can evolve particularly fast. Furthermore, some viruses tend to mutate recognizable parts of themselves faster than others, just to escape the natural immunity or the vaccine immunity. This is particularly the case for the viruses that cause the common cold and the seasonal flu (*Keilman, 2019; Webster and Govorkova 2014; Simancas-Racines et al., 2013*).
- For SARS-CoV2, the reported mutation rates are likely to generate **30 different variants** per year [see Note 2].

Therefore, therapies based on monoclonal antibodies (whether monoclonal antibody therapy or vaccines based on specific parts of viruses) become *obsolete* as viruses mutate and become resistant (*Berry, 2018*). In the case of the seasonal flu, vaccines have to be updated regularly in order to counter new viral strains, a time-consuming and costly process whose efficiency ranges between 10-60% and that easily leads to stockpiles of unused batches (*Erbelding et al., 2018; Soema et al., 2015*).

**As viruses mutate, all "older" versions of viruses will still be killed by our immune system, but newer versions will be able to circumvent our protection and consequently a natural polyclonal-based strategy presents advantages.**

A natural polyclonal protection is *herd immunity* (or *protection*), where a group of individuals exposed to a virus, in which each individual will construct a different personal key to block an individually recognized lock that will then prevent viral transmission and slow an epidemic on a population scale. This mass immunization can also be achieved by mass vaccination, but in the latter case, herd protection depends on the type of vaccine (in which case the vaccine has to achieve solid immunization). Herd immunity has an important role in preventing epidemics and disease elimination or eradication (*Rachid et al., 2012; Smith 2019*). When a vaccine is not that effective, herd immunity becomes a social need.

We all immunize ourselves hundred of times a day against many things, without any side effects, our industry cannot do the same as fast. Even if it will have to play an essential role against many diseases.

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## Note 6. Those viruses are airborne. Human-human contacts are ONLY part of transmission – focusing on this misses many points. Are surfaces relevant?

Of course, with highly deadly viruses, it is logical to avoid transmission, and many viruses actually do need personal contacts to infect, one can think about STD (Herpes, HIV, even some but not all hepatitis…), think about hemorrhagic fevers (Ebola, Lhassa, Marburg, Yellow fever…).
**But many other viruses do not need personal contacts only.**

Viruses may kill fast and in great numbers and then cannot infect many, or they can infect many very fast and then they are not the worst 'killers'.

This does NOT mean that SARS-CoV2 and the disease we see (COVID19) are benign or not dangerous, **like it was announced by some**. But the viruses we are dealing with here are not effective **direct** killers. Nevertheless they are dangerous and still pose a major public health threat that has to be dealt with. Spreading the opposite view is irresponsible.

All those viruses (cold, flu…) are also AIRBORNE, which means that human-human contacts are the *major* but *only* a part of the problem. Viruses are so small that they weight essentially 'nothing'. They are not only present in cough droplets but also exist as individual particles on their own - in incredibly huge numbers. This means that they do not need humans, airplanes or ships to travel the world. Like dust and small sand particles, they are lifted by winds, and **any** atmospheric disturbance. Viruses can then be carried thousands of kilometers away in the upper atmosphere, before being deposited back onto the Earth's surface. A virus may take only a couple of days to make the trip Sidney-Brussels, no human needed! This is not a hidden secret knowledge; it has been studied for many years, as even vulgarization papers exist. *"Every day, more than 800 million viruses are deposited per square meter above the planetary boundary layer"* to quote an article published in a magazine in January 2018 (Science Daily – 2018) and also see (Reche et al, *ISME Journal* 2018).

Hence when papers in reputable journals like Nature title in bold that experts are disagreeing on this, it does not help (see Nature, Lewis April 2020). Experts cannot disagree on chemistry and biophysics – as this is what the airborne question is about - but can disagree about the **risks**. When the WHO states that there is not sufficient evidence, they emit an opinion, they do not say that viruses do not fly; they try to state that the chances of getting the disease are low. Experts would agree on this, but it is not the same as saying that the virus is NOT airborne. Once airborne however, contact tracings become much less useful (as Sweden logically decided – see Note 9).

This has been widely studied by many scientists and for many viruses even larger than CoV2 like the Flu (See Nikitin et al, *Adv. Virol*). When one person is infected – even without coughing – one shed viral particles by the millions with each breathing cycle (this is called tidal – or normal – respiration). Coughing, sneezing, talking and breathing generate clouds of airborne particles with different sizes between 1 and 50 micrometers, the largest being even in the millimeter range. Large droplets (above or at 10-50 microns) fall and settle on the ground quickly in minutes (like within less than 2 m distance). Small particles (like 10 microns) can stay airborne for hours and can be inhaled deeply by any other persons. **Studies with the flu showed that 99% of exhaled particles were smaller than 5 microns** (Nikitin et al)**. [Remember that the flu is even larger than the Coronaviruses!]**

About the Coronavirus, the WHO (see NPR org ref.) and others (see Wired magazine ref.) tried to educate the public about this. Transmission routes from a person to another happens through direct or indirect contact, droplets (e.g. when sneezing) and through airborne routes (e.g. normal breathing or from the air). This is true for all airborne viruses *including* coronaviruses (with evidence suggesting aerosol transmission and thus infection for the Severe Acute Respiratory Syndrome coronavirus SARS-CoV 1 outbreak of 2003, as well as Middle-East Respiratory Syndrome-associated coronavirus MERS-CoV outbreak of 2012) (*Kutter et al., 2018; Yu et al., 2004; Tellier et al. 2019; Booth et al., 2005*).

Now it is obvious that the doses – that is the number of particles – that one inhales is lower from the air than when being exposed to sneezing and coughing. Depending on the winds, the walls, the layout

of a space, one can get higher or lower concentrations of those airborne viruses, and hence we can breathe the particles but usually without becoming sick. Sometimes we do. Most viruses can infect (*Tellier et al. 2019*), although the chance of getting sick is lower, one gets enough particles to get immunized, as the immune system works best at very low doses. There were early (February 2020) a few reports labeled by the press as "mystery cases" as they showed no trace of contamination by any contact – those were NOT so mysterious, they are part of what is called 'community' infections. Lots of people without having being even sick may have gotten the virus and have already safely immunized themselves (see numerous independent data about this crucial point in the Note 9 Statistics). This airborne element is what convinced Sweden to NOT fight human-human contacts, as it would no longer be useful anymore [See Note 9]. Once the virus is in the air, tracing it via contacts becomes useless.

Relatively little is known of the number of viral particles that are necessary for a major infection. However, evidence shows it depends on the type of virus and various other parameters (environmental…) and can range from as few tens of particles (in the case of a Norwalk virus) to thousands of particles for others (*Teunis et al., 2008; Nikitin et al., 2014*).

It is mostly the environmental biologists who study and understand the ecology and the spread of viruses. In a recent paper (see Morawska et al. 2020), we can read the following:
[quote] "Still Despite the evidence and strong hypotheses, the world appears to be locked in the old way of thinking that only direct contact matters in viral infection spread. It is disconcerting that with all the experience and evidence currently available, when faced with a new viral outbreak of COVID-19, the authorities still fail to acknowledge the airborne pathway of transmission, although many experts in China and other countries have had experience in dealing with SARS". No comments needed…

**Hence, in closed spaces (such as healthcare facilities or a cruise ship for example), airborne infection is a true threat** (*Chughtai et al., 2019; Jones and Brosseau, 2014 and 2015*).

Final Text

Some of the medical procedures that are used in hospitals (intubation, setting up respirators…) are generating very high aerosols concentrations that are sufficient themselves to transmit infections. Endotracheal intubation, in particular, has been shown to result in significant risk of nosocomial SARS infections at least by a factor of 3 (with an odds ratio of 2.8, see Fowler at al.). [Note: "Nosocomial" means originated in hospitals]. Here both medical personnel and the intubated patients (without any SARS virus at first) may be infected as a consequence of those procedures inside the closed air system of the hospital. Another study done in Honk Kong evidenced also that long-range viral airborne transmission was a problem in an ICU (See Xiao et al, role of fomites in PLOS One 2017), others confirmed this problem too (Booth et all, 2005). (Note: Fomites are surfaces that can be contaminated and dangerous)

**What role can various surfaces and materials play in the liveliness of the virus? And can it be a major source of human infections?**

**No one has any valid statistics about people being infected from touching surfaces.**
So everything that has been written and said are opinions, based on a certain common sense. Studies exist for hospitals and in the health care worker community – and there it is obviously relevant.

While this question about surface viability may sound like an adequate question, given the fact that most of the viral particles are airborne, it is not highly relevant outside of the professional settings. Sometimes what *seems* clean is *not* clean and vice versa. For example plastic and metallic surfaces that are visually 'cleaner' are in general less safe than, say, a dirty wooden plank in a butcher shop. This has been shown numerous times by bacteriologists, as wood contains tannic molecules (tannic acids = antiseptics) and has a more complex surface than plastic/metals. (see Nese et al, 1994).

It is known that the flu (both Influenza A and B) can survive for 1-2 days on steel and plastic, but only 8-12 hours on cloths, papers and tissues (Bean et al., J Inf. Dis. 1982). What is very important to note

is that one can get the virus transferred from these surfaces but the virus did not survive more than 5 minutes on the hands. This without ANY disinfectant – our skin protects itself, due to its pH and porosity. So cleaning hands and keeping hands clean surely helps a lot. Soap vs. disinfectant? Alcohol-based hand sanitizers while getting rid of the viruses, do not kill off Noroviruses, and E. coli – soap does.

The aerosols and the surface stability of SARS-CoV2 were studied (see Van Doremalen et al. in NEJMed. 2020). While it is interesting to confirm that cardboard are safe, and copper surfaces are safe too (copper is a known antiseptics), it neglects the consequences of the virus being airborne. As explained microbes – like dust - can in open spaces travel thousands of kilometers (see *Yahya et al., 2019* for a study in the Red Sea region).

A highly relevant question is what role does the surface of medical filters play – as it directly impacts the health care workers (see Chugtai, 2019)? Airborne respiratory viruses may settle on the surface of used masks layers, resulting in contamination. Virus (adenovirus, RSV, flu) could reliably be measured and, shown to lead to self-contamination, especially with longer use (like > 6 hours, Chugtai).

Those facts have serious consequences that have been overlooked:

1. Do we really need to disinfect all the surfaces outside hospitals? Lots if not most SARS Virus particles stay airborne.
2. Why are we making our life harder by wearing masks that will NOT stop viral particles (see Note 8 about mask)?
3. We should indeed protect health care workers, and actually lots of good work have been done for years fighting SARS-CoV1 and have led to very valuable recommendations (see the 4 references from Fowler/Xiao/Booth and Brosseau among many).
   ***The CIDRAP (Brosseau) is a highly educating reference written for a general public.***
4. Why aren't we not putting filters where needed ? In aeration/ventilation/HVAC systems instead of the noses of whole populations? Final Text
5. Never forget that what is useful to protect health care workers may be of very dubious uselfulness to protect the citizenry. Human contacts are a much more important risk for health care workers than for the average person.

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Final Text

## Note 7 – We share those virus families with many animals (wild and domestic) – Is a lockdown useful knowing that the virus will remain around?

Some viruses originate in animals, in which they are not pathogenic (this means they do not make the animals sick). These animals serve as natural evolutionary *reservoirs*. That is a place where the virus can stay… *forever*. For some viruses the animals themselves can be sick, the avian and swine flus being examples. Occasionally, viruses mutate and transmission between species can occur and these viruses become pathogenic. Animals can transmit diseases to humans, crossing the inter-human barrier (this is called *zoonosis*). And then human can also give those viruses back to animals… and so on. This back and forth of viruses between species has been going on even before the rise of humans.
Strange times when the front pages of some newspapers reported **ONE** dog infected in Honk Kong, **ONE** cat sick in Brussels, some 2 tigers sick in a zoo… as if all of this would be surprising (it is not).

In the case of several coronaviruses, bats and rodents have served as reservoirs. Before passing the inter human barrier, they have infected *intermediate* hosts, such as bovines, dromedaries (in the case of MERS-CoV), palm civets (in the case of SARS-CoV1) and probably pangolins in the case of the new SARS-CoV2 (*Ye et al., 2020; Fehr and Perlman, 2016*), which often infect humans on wet markets.

Some studies found that SARS-CoV2 replicates poorly in dogs, pigs, chickens and ducks (Shi et all, *Science* 2020). This does not mean that the virus cannot live inside those animals - it does multiply itself, but does not spread itself easily from one animal to another animal. Some dogs sero-converted – this means that although they were not sick, they hosted the virus and developed antibodies against it. The virus 'survives' waiting for better hosts. It was also shown that ferrets and cats were permissive to infection (Shi et all, *Science* 2020, and Martina et al. Nature 2003) – thus they can be sick. Also it was found experimentally that cats are susceptible to airborne infections.

From 2003 on, genetics indicated that the SARS family of coronaviruses originated from a merging of virus from birds and mammals. Some components of the virus were identical to those found in cats, cows, and mice. Some others were identical to those found in chicken and ducks. And some were obviously mixed – this was the case of the main viral protein (linked to the S gene and though which the virus BINDS to its target cells) (see Stravinides & Guttman , J. Virol 2003). While such "mosaic" combination of genomes is known, this 'merging' hypothesis was not accepted in 2003 - however this showed that if we were to look into birds, we would likely find some of those viruses. This is exactly what was done in 2012 (see Woo et al, 2012), since then it became also known that bats and birds contain various families of coronaviruses. While they are not yet ALL recognized as causing diseases to humans, no sane scientist would bet that it would NOT happen given the mutation rates.

Shall we ask birds to not fly to some countries? SARS like all germs know of no borders!

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**Note 8 – Masks – like initially said are good at blocking droplets, not at catching particles.**

As mentioned in Note 6, the viruses causing respiratory tract infections have diverse transmission routes, including airborne routes. Thus, using masks to prevent getting contaminated or spreading viruses to others appears reasonable.

However, data dealing with respiratory viruses on personal protective equipment (PPE), and on masks more particularly, is surprisingly scarce. Intuitively, any barrier would seem better than none, and two better than one, but as it is the case with gas, the important question is the efficacy of the filter/barrier. As viruses are extremely small (usually 80-100 nanometers), protective barriers have to be nearly "air-tight" to be effective, a bit like the military masks used during WW1.

Studies conducted on the efficacy of masks **all** conclude, that using barriers slow down pathogens. However, efficacy depends on the fabrics, the seal of the mask to the face, as well as the route of viral transmission (e.g. droplets are more blocked than airborne particles) (*Davies et al., 2013; Milton et al., 2013*). Evidence also suggests that mask efficacy declines with usage time and the number of ill people (that is producing viral particles) surrounding the user (*Chughtai et al., 2019*).

Most studies test masks with a certain flow of air, or with particles that are not viruses.
2 studies however stand out by their quality:

One is a careful comparative study about cloth facemasks that was done to evaluate their efficacy against particles of small sizes - below 2.5 microns - because those penetrate deeper in the lungs and are more relevant to public health. It showed that 40 to 85% of the particles passed THROUGH the masks. This was not done on virus particles, it also showed that cloth facemasks were better at filtering LARGE particles than surgical ones. (see Shakya et al, 2017).

The other, one of the most careful study ever performed (Mc Intyre et al, in BMJ) actually randomized during a period of 4 weeks, 1600 health care professionals, in 15 hospitals, with either medical masks, cloth masks, or control, and measured **actual infection rates** (including 17 respiratory viruses like RSV, Flus, SARS, Adeno, Bocaviruses… in their PCR). They found higher rates of infection with cloth masks – those allowed particles penetration in 97% of cases, medical masks only in 44%.

The most efficient masks would seem to be "N95 respirator"- type masks, followed by surgical masks, and the least efficient would be (homemade) cloth masks (*Blachere et al., 2018; Davies et al., 2013*). It should be noted that N95 respirators may not provide necessary protection against pathogens (*Lee et al., 2007; Loeb et al., 2009*) and that flu viruses can pass though surgical masks (*Booth et al., 2013*). Remember that the Flu virus is BIGGER than the Corona. Homemade cloth masks are not recommended and should be used only as a last resort (*Davies et al., 2013)*.

A recent opinion article in the Washington Post recently (April 2, 2020) reminded us “Everyone wore masks during the 1918 Flu pandemic. They were useless.”

All of this is known - the question then becomes: Are “optics” and “social blame” useful in such public health crisis? No one doubts that masks are useful for the infected and the professionals – there are however serious doubts that generalizing facemasks will do anything effective except putting social blame on some people by giving a FALSE perception, and feeding a sense of powerlessness. And accusing some of being ‘criminals’ because they refuse to relinquish ***logic***, ***chemistry*** and ***physics*** may be going way to far! Shouldn’t we do better than Medieval reflexes – this is not the plague?

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**Note 9 – In public health GOOD statistics are always needed to make good decisions.**

***Why do we have a statistical problem during this crisis?***
***Essentially because there is a 100% mortality rate among dead people!***

This is just a provocative way to explain where we had major analytics and then communication flaw: ALL the numbers we could read in the press or hear from official sources were misleading as they ONLY accounted for the very sick. Those were the persons who were infected and were hospitalized in severe conditions, the ICU cases, or even those at late stages of the disease who were admitted in Intensive care while dying (with an already too deep ARDS and its complications).

Numerous voices pointed out that to have a decent estimate of a mortality rate for a pandemic, we needed to have the estimate of the TOTAL numbers of infected (most of whom were actually not very sick or even not sick at all) but were ignored. Some newspapers mentioned this whenever they printed mortality rates – but explaining that their numbers may not be accurate does not tell the general population in which direction those inaccuracies go (over-estimation or under-estimation).

There were a few exceptions to this situation like in South Korea (one of the 1st country that was hit), in Iceland, in some parts of Germany, in Sweden, in some States in the US.

***Besides this HUGE bias problem, some additional decisions were made that led to another cause of inflation and thus to an additional artificial increase in the mortality rates:***

- Decision to include ALL suspected mortality to COVID19 – even when not proven (as requested by Dr Birx, USA). This would lead to overestimates – and it has to be mentioned. However when the medical system is at a near halt, one could reach a point where those deaths represent the patients without viruses that were NOT taken care of. There are numerous reports of community practices, MD's, and even specialists who report that they used to see and treat 50-100 patients a day, and are now down to a few like 3-5 ! What happens to the persons who needed critical care on any given day ?

- Decision to include all excess deaths in the reports – some linked to COVID19, some not linked to it and, some even provoked because the patients without ANY infection were NOT treated at all. This method would be the best one if the medical system was functioning normally. But it is not the case thus mentioning or using *excess death numbers* is wrong, as it compares apples with oranges. Without any testing one cannot use such data.

- Decision to either not test any suspected case, or to reserve testing for the most severe cases – which is totally arbitrary because based on the doctor's impression or experience or - worse - access to tests. What can a doctor or a nurse do in such cases ? They sent patients with mild fever or cough back home, not knowing what their problem really was.

- Decision not to focus as soon as possible on building (or even buying) test capacity (both genetic like PCR and serologic) [South Korea did set up its tests in December 2019]

There are however some good reasons to this situation:

- Tests to estimate the virus presence and numbers (load) in a person are based on genetic sequences (test PCR) and have some failure rates and some mutations will not be caught. Hence a setting up time was needed.
- Tests based on the antibodies present after someone has been exposed to the virus were not widely available. They usually take a few weeks to set up.
  [Note : antibodies stay present in the blood serum after an infection – this is called seroconversion – and is PROOF of an infection, even when the antibodies are no longer effective because the virus may have mutated, even if they have NO virus-blocking activity. They evidence that the virus was once present in this person]

**Old clinical studies from 2003, 2007 and 2013 had the wrong statistics from a Public Health standpoint – but the correct ones form a clinical standpoint. The context of a non-pandemic situation makes this normal.**

When there were not enough cases, the focus was correctly put ONLY on severe cases mortality. As mentioned this is logical, but what is NOT normal is to rely on this during a pandemic, after it is evident that better measurements are needed.

About SARS-1,

- About SARS-1, in August 2003, around 8,096 cases tallied with a mortality rate around 10%, no mention of screening of non-symptomatic contacts (Gu et al. 2007) (Rota et al. 2003) (Drosten et al. 2003)
- Same in Chu (in 2003), 8,000 cases from Nov 2002-Jul 2003 with a mortality rate at 7% (and 17% for a subset) – again no screening.
- Fung et al (in a 2019 review), SARS1 cases are listed as ~8,000 with a mortality rate of 9.6%, and for MERS it was 2,000 cases with a mortality rate around 35%. No Screening.
- MERS cases and mortality confirmed by WHO (site accessed in May 2020) 2494 cases, and 858 case-associated deaths (34.4%) (See WHO recent stats reference)
- The same numbers were reported by Channapavanar in 2017 – SARS-1 : 8400 cases with 9.6% mortality and for MERS : 1936 cases with a mortality of 36%.

About SARS-2, *as of February 2020*, there were 80,000 confirmed cases in China with 2500 deaths showing thus a mortality rate around 3% (Lin et al. 2020). Another report one month later in The Lancet, mentioned *as of March 19th 2020*, 200,000 confirmed cases, 95% of which are mild, ONLY 5% of which have severe lung injury and/or Multiple Organ Failure, leading to a mortality rate of 1.4% (Li et al.). Again those are data selectively obtained from people who went to see doctors or were hospitalized only.

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All this partial information – based on the patients who were either in ICUs thus very sick, or mildly symptomatic – *while correct to the clinicians* - gave us biased public health responses during this 2020 pandemic. From a public health standpoint, this is not an unknown *unknown*; it is a KNOWN unknown to every professional in the field.

Then publishing daily numbers of total deaths – some of which may not even be related to the virus, some of which may have already a dire and mortal condition – without knowing the most important parameter, has no rational explanation and could be considered disingenuous at best.

**There are a lot of asymptomatic cases, or cases with mild symptoms, so the clinical statistics do not tell us anything about the real mortality rates. They should not even be used when communicating to the population.**

In March 2020, Hennegan et al. issued a report from the Centre for evidence-based medicine at Oxford University in the UK to raise this classical question (See Hennagan et al. 2020). They analyzed 21 different reports and studies published since the beginning of the crisis. While a couple of those reports showed around 5-10% of people could be asymptomatic, most of those reports had larger numbers mostly between 20-40% with some at 60 or even 80% being without symptoms. Whatever the real numbers are, as expected in all those a **very large fraction is asymptomatic**.

Usually even when a person is NOT symptomatic, s/he could presumed to be contagious because the virus is there, but reproducing less aggressively, and it can be shed out by the plain respiration (aka. as tidal respiration). One does not need to cough and have droplets to be infective. This may or may not have been mentioned. At the same time, there were reports in the press of “mystery cases’ – that is cases

where NO human-human contact history had happened. Those community-based cases are not mysterious; they reflect the fact that viruses can also be travelling the planet outside the human bodies. (See Note 6 – virus are airborne).

A very recent paper (Li et al. Science, May 2020) did model the spread of undocumented cases, and estimated it at 86%. However their claim that the situation improved AFTER the travel ban is totally unwarranted. It mostly improved documentation of the severe cases, while still missing ALL if not most of the people who were positive without being sick. But such data is actually confirming the importance of non-direct human-human transmission, because such rapid spread started most likely before any travel ban and contact tracing. Such data also support the fact that by focusing on the clinical and most sick cases, most of the actual positive cases were missed.

Japan studied their nationals who were evacuated from Wuhan as soon as they debarked from planes in a very well controlled study, and found that the number of positive cases without symptoms – that is the persons who are infected, contagious and NOT sick – was 30% (see Nishiuara et al. Int. J. of Infectious Diseases. 2020).

An official communication by the Director of the South Korean CDC (center for disease control) reported that more than 20% of the persons being tested were not showing symptoms. South Korea did more testing so far than any other country, and those values fit well within the other reported values, while at the same time consolidating them given the extensive tests that were done (see Korean TV program on 16 March 2020).

Most persons are and will remain without symptoms. However when symptoms start, SARS-2 goes very fast. UC Davis reported a community case where a barely sick person deteriorated in 24 hours. [Quote] "Within 24 hours of admission, her respiratory infection deteriorated to the point where she was intubated and given a series of antibiotics that failed to clear the source of the infection, according to the report" (See news report KCRA).

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**How to obtain the NEEDED numbers: the total number of infected people?**
**And what about the real mortality rate after infection?**

After nearly 5 months, one would/should have started to do this. Testing for sero-conversion, that is the presence of antibodies in the blood. The debate about the immunity from the antibodies or about the overall performance of the test is NOT relevant. EACH and every test done daily in our hospitals always has a few percent of mistakes. This is about identification not about immunity, which is a separate issue. There are 2 ways to obtain such useful information:

- One would be to test the **whole** of the population. This would be quite costly, would bring logistics problems and is time consuming. While costs and logistics are political decisions based on expert advices – **Time** is not! **Time** cannot be, as the virus follows it own tempo, and its speed to infect and generate serious complications if part of our problem.

- A second one would be to do **random** testing in communities or across a country. One can also do this based on demographics. Then one can project those results with some confidence on the WHOLE of the population. This is regularly done in public health estimates, and is not different than some refined political pollings. If done well, this can be quite accurate.

We could learn from some screening that was done during the past MERS outbreak in 2014 in Saudi Arabia. However it was not random, not demographics - 5065 persons were screened but ONLY from suspected patients consulting for a viral disease (virology lab samples) and their contacts and also the Health Care workers. So this is also a bias, but a lesser one. This gave a 2% infection rate. While it is far from perfect, the study included a follow-up for 12 months, and this rate oscillated between 2.6 and 1.6% (Memish et al. 2014). We have to understand that using such 2% value – which does not tell us anything about the true infection rate in the population - would immediately decrease the mortality rate enormously.

(# deaths divided by 2 % of the population which was 30.2 million in 2014 so roughly 858 – assuming that most occurred in SA- divided by 604,000). *This is absolutely not correct of course because of the limitations of the study;* also because those were only a part of the pilgrims analyzed, etc… but would be 0.14%! The gross mortality when looking ONLY at sick people who came inside hospitals is around 36%... see the difference? ***We will use this as an example to understand what follows and which was done using more appropriate and valid samplings.***

- In NY, on the 27th of April, Gov. Cuomo announced the results of SYSTEMATIC mass testing (for antibodies): 24.7 % of NYC residents had already met the virus and had antibodies in their blood (forget about immunity, let's just focus on statistics for now. NYC had a total reported of 172,000 cases that were tested positives (no doubt there), and 13,365 deaths. (data from Google statistics, obtained by searching with 'total deaths COVID NYC' on May 2, 2020). NYC has a total of 8,400,000 inhabitants split in 5 burroughs. If 25% have seroconverted – they represent the total # of infected that is needed, such number increases with time also – this number is 2,100,000. Dividing total # deaths/total # infected = 0.6% (less than 1 %).

- The Chair of Emergency medicine at St Barnabas in the Bronx reported that 43% of the residents of the Bronx had already been positive. The population there is 1.48 million. Using other data from JAMA (Wadhera et al, JAMA 2020) – showing a total so far of 224 deaths (tested positive for the virus)/100,000 habitants in the Bronx, and with 43% per 100,000 habitants being the total of positive cases, gives a mortality rate of 0.5% (224 divided by 43,000). Telling the public that one has twice more chances to be sick and die if one lives in the Bronx vs. Manhattan like some reports did, do not tell us ANYTHING about mortality rate due to the virus – which is the REAL risk to the people.

- An analogous but RANDOM study (random sample of 1,400 persons matching the county's population) done in University of Miami (FL) in Dade county reported that 6% of the population of this county have had the virus (between 4.4% and 8% with 6% as best estimate – 95% confidence interval). This corresponds to 165,000 residents, and is 15X times higher than the officially reported positivity rates (let's remember that those are erroneously taken on the persons who are very sick). The total county population is 2.75 million. Contrary to the official communication from the mayoral office, the obvious conclusion is not about the efficacy of social distancing, but about the mortality rate being divided by 15X! Reported to the total number of deaths reported by the Miami Dade county – which is at the same time 302 (data from Google statistics, obtained by searching with 'total deaths COVID Miami Dade' on May 2, 2020) this gives a mortality rate of 0.2% (2/10 of one percent !) Doing the same maths using the official data of only the cases in hospitals gives 2.6% (302/11,570). The numbers that are given to the public nearly 24/7. The fact that the authorities do not correct their mediatized mortality rates raises questions. Even if such test had a false positive rate in 10% of the cases, that means that one out of 10 tests adds a false count, it will be 12X – so those arguments about test limits fall short. (165,000 minus 10% = 140,000 and 140,000/11,570 = 12.2).

- In Santa Clara County (CA), Stanford University performed a RANDOM serological study (Bendavid et al. MedRxiv April 2020). When projected to the whole county population, the results indicate that between 2.5% and 4.2% of all residents have been infected by the virus. This is between 50 and 80X higher than the results obtained from the ICU and the sick patients and their contacts. Santa Clara county has 1,94 million residents. California population is 35.5 million, between 2-4% makes between 710,000 and 1,400,000 persons. With a total of 2,073 victims (obtained on May 2, 2020 on Google 'total COVID deaths in Santa Clara county'), this gives a crude mortality rate between 0.3% and 0.14%. Same results using the Santa Clara total fatalities at 113. Many criticized the sampling method, claiming that it was biased and collected the more 'concerned and afraid' crowd. Interestingly if it were the case, the differential would be even larger in favor of the Stanford study, as this bias would go in the same direction as the « more sick » bias found in the Emergency rooms.

- Los Angeles county did also a recent study, conducted by researchers from USC, this study was NOT RANDOM but based on a curated database representative of the county population patterns (demographics matching, done by a market research firm). It concluded that 2.8 to 5.5% of the county adult population has been exposed by the coronavirus. That translates to 221,000 to 422,000 residents who have been infected. This puts the rate of infection at 28 to 56 times higher than what was reported so far (see Communication by University of South California). This would decrease the actual death rate by the same factor. Again a quick calculation shows that the more correct mortality rate would be between 0,3% and 0.5% (1209 fatalities for LA county divided by 221,000 or 422,000) (1209 fatalities – see Google Stats on May 2, 2020).

- This shows near identical mortality rates all across the US between 0.2% and 0.5% regardless of the location whenever a randomized or demographics-based sampling and testing was done. In the past few weeks, more than 180 academic centers, hospitals and private manufacturers have notified the U.S. Food and Drug Administration that they intend to create serology tests for COVID-19, according to spokeswoman Stephanie Caccomo. They've been able to jump into the fray because the FDA has relaxed regulations for developing tests as part of its emergency response to the pandemic.

- **The situations and the rates are near identical in other parts of the world:**

- **Iceland**

  Iceland, with a total population of 364,000 inhabitants tamed the pandemic very early and had barely any mortality (10 deaths). No full lockdown, just avoiding large groups gatherings, but proactive actions. Before one mentions that Iceland is an island and this 'easy', it is also worth mentioning that Iceland did early on large scale testing either on the persons at risk (travelers coming back, plus their contacts plus the persons at risk (health care personnel) or at random in their population, or even upon free open invitation in the population also (see Gudbjartsson et al. New England J Medicine, 6 April 2020). In their targeted study, they had to test 9199 persons who had traveled to infected regions, plus their contacts, or the people at risk, and they found out that 13.3 % of those were positive, whether they were sick or NOT. They also did a random testing (sending out invitations to 2283 persons) and found out a positive rate of 0.6%. In their open invitation (not random but open to anyone desiring to be tested), they found a positive rate of 0.8% for the SARS-2 virus.

  From their testing on confirmed and tested sick patients, on can derive a mortality rate for the high risk group of 0.5% (10 deaths/ 1799 confirmed case), data based on the Icelandic government web site (see at *www.government.is* on March 15th 2020).

  From the testing on the general population, if we take 0.8% of the population (number of persons who are infected), we obtain a mortality rate for the infected of 0.3% (0.8% of 364k = ~3,000, 10 divided by 3,000 = 0.3%).

  From the Icelandic data, we also learn that during an in-depth analysis of 4,197 samples, they found 425 positives cases, and those split as 1/3 linked to travel, 1/3 linked to domestic infections, and 1/3 for which NO trace of the source is found. This is important to note as human-human transmission – while the most frequent is NOT the only one (see Note 6 on Airborne).

  **[Note : As kari Stefansson, neuroscientist and Founder of de-Code - the icelandic company that initiated all those tests - said "I couldn't understand how we could calculate out the death rate without knowing the spread of the virus in the community".**
  **This is the core question of this statistical note – it is not so hard to understand, so it must be assumed that in crisis, common sense is the first casualty.]**

- **Germany**.

  The situation is interesting, Germany has more people than France, more cases than most countries in the EU and still has lower death rates. As of end of March, 31,000 positive cases had been reported for 149 deaths and a mortality reate of 0,5%. (See Vox report, March 27, 2020 – by

a well respected journalist, now working for NPR). All of this with a population which is older than most countries. This is the mortality rate based on clinical hospitalizations. This is to be compared with Italy where mortality is at 10% and the US where it is at 1.4-2%.

One of the most careful study was done in a German community of 12,000 people [Gangelt, GE] by the University of Bonn (see Streek et al.). This was a random sampling study – done in accordance of the WHO standards and combining both genetic testing (is the virus there in the person ?) and antibody testing (has the person been reacting to the infection ?) . The results showed that the infection rate in persons who were not sick and thus not seen by doctors was close to 20%. This gave a mortality rate of 0.28 %.

[The study is a good read for MD's and Health professionals]

A respected program on ZDF (Hamburg), presented the interview of an authority in pathology who performed autopsies on ALL 50 victims tested postive for COVID19 at that time. The result was that ALL those patients had some major other intertwined cause of death. SARS-2 was a co-factor like the Flu would be in the same cases (see Interview of Hamburg pathologist Prof. Klaus Püschel).

- **South Korea**.

South Korea has a population of 51 million, and was the first country hit following China. As early as January, when no one paid attention after the first case, SK started to develop and mass produce reliable and controlled testing kits. By mid-february, they could churn out 1,000 of kits per day. By March 5th, they had tested 145,000 people, more than most other countries combined. At that moment, people on social media were openly doubting and dismissive of what the South Koreans were doing. They somehow learned the lessons from the earlier MERS pandemics, and the fact that the former governement was impeached the year before created a political culture of accountability. [This may have played a role in the professionalism of the SK authorities].

**To spare hospitals from being overrun with patients**, as they were in 2015, Korean officials opened 600 testing centers and pioneered the use of drive-through testing stations to reduce face-to-face contact indoors. Inspired by drive-through counters at fast-food restaurants, these pop-up centers offered patients 10-minute tests without forcing them to leave their cars. (see D. Thompson in The Atlantic, May 2020).

On May 6th 2020, with a total of 255 deaths to date for a total of 10,806 cases, the press and some authorities report a mortality rate of 2.4 % - but with 51 million inhabitants and their reported 20% value for asymptomatic carriers (ie. 10,200,000 cases), the real mortality rate due to the infection is 0.003% (255/10,200,000). This extremely low number is real, and is likely the result of BOTH the real low mortality of the SARS-2 itself, combined with an extraordinary effective health care system, which is NOT clogged, and likely by intervening always as soon as the first symptom sets in, treats patients early enough to avoids the ICU. So combining FAST responses, systematic testing are keys.

There is however something unexplained. Why all authorities and the press still mentions the 2% mortality rate when they know it is magnitudes lower ? This will warrant quite an explanation !

- **Sweden**.

The case of Sweden is very interesting. The country did not do any lockdown, started early by testing the high risk and the sick patient, then stopped and radically modified its strategy to focus ALL resources on the more fragile and the more at risk. The country is regularly blamed when pictures of happy diners are shown at cafe's terraces.

People and authorities all over the world criticized what they label as « Sweden Laxist policy that brings everyone at risk » (see Interview of Anders Tegnell in Nature, 21 April 2020). Their death rate – as reported by the press - is the highest in Scandinavia (2,941 deaths for 23,918 cases on May 6th 2020), which would be above 12%. However their Chief epidemiologist does not come across like some crazy advisor. The Swedes promoted and counted on personal responsibility and common civic sense. 22 renown swedish scientists openly published a letter criticizing the policy.

Then the Swedes were attacked about lack of mass testings,. But when comparative data are shown, the story looks different. Sweden did as of March 17th 2020, 1,412 tests per 1,000,000 inhabitants. This is higher than Danemark (1,314/Million), than the UK, and than the US (125.4/Million at the same time). In fact, the official policy of the country is focusing its tests for coronavirus on people with a role that is essential to society, such as police, firemen and those who work in care homes for the elderly (see Article in Brussels Times for a critical comment about this). Authorities have shifted their focus away from testing all possible cases, and instead on protecting the most vulnerable groups. People with severe respiratory symptoms or who belong to a risk group will still be tested (see Fact Check article in TheLocalSE).

What is very interesting is that Sweden made this change following the first signs of community infection (cases that could not be linked to overseas travel or previously confirmed cases). This meant that contact tracing would no longer be as effective, since not all cases were accounted for. **This is VERY logical,** once human-human contacts are no longer thought to be the only way to get infected, tracking, identifying them, and building ANY health policy around those human contacts is poorly effective. It is hence logical to best prioritise resources, that the Swedish Public Health Agency shifted its focus on the most seriously ill or at risk people.

Logic aside what can we learn from the Swedish statistics ? As written above, the calculated (wrong) mortality rate is at 12%. But we know from numerous sources that the number of infected persons in the general population is quite high and could vary between 10-30% on average. With a population of 10.23 M inhabitants, Swede would thus count 1,023,000 positive cases (mostly asymptomatic) if we used the very conservative value of 10%. This would translate in a mortality rate of 0.28% - which would compare well with all the values reported so far. It would even be lower at 30%. This is a fair assesment, see here 2 additional interesting articles describing the situation of the asymptomatic infected (see Asymptomatic Coronavirus up to 30% at DW Science, and Bloomberg News 22 March 2020).

Although being attacked, the Chief Epidemiologist is far from being wrong, he just proposed logical measures based on sound Epidemiology, while the rest of the world worked on a set on inaccurate assumptions. The harsh criticism of Sweden highlights that very fact!

- ***France.***
  *Applying the same reasoning, when France reports that 5% of its population has been contaminated and uses this as a proof that it is far from collective immunity, they forgot to mention that their actual infected death rate falls at 0.8% !*

That the **same values** (for correct mortality rates when calculated as they should) can be obtained with so many different locations, methods, cultural behaviors, and policies, attest of the solidity of those very low mortality rates. Mortality rates on the order of 0.2% – 0.4 % for SARS-2 are real, with some extremes at 0.6%.

**How do those rates compare with the seasonal flu and with the pandemic flu?**
**The seasonal flu – based on total tested cases has comparable and even mostly higher mortality rates. All viruses – once they give pneumonia can give high mortality rates (5% and more)**

Quite a lot of **good faith** but misleading information is published based on the **wrong** comparisons. An example is an article in LiveSciences on April 30, 2020 (Reitner, LIfeSCi). This article, very well explained and documented, highlights the flu seasonal mortality rate based on press reports at 0.1%. Then a rate for Covid19 of 6% is mentioned - based on confirmed cases – but only from sick and symptomatic patients. The paper recognizes that problem and mentions that Researchers from Columbia University recently estimated that only 1 in 12 cases of COVID-19 in the U.S. are documented, which they said would translate to an infection fatality rate of about 0.6%. But still concludes – contrary to the available scientific evidence that this would be 6 times higher that the rate for the flu. However it is worth to note that this Coronavirus mortality rate would be consistent with the data obtained from random/large testing. The problem as we will see later is in the estimates that this journalist used for the mortality of the flu.

An in-depth mortality study of the **yearly** flu in the US, reviewed that each year the flu kills between 10,000 and 40,000 people, 60-90 % of those deaths occur above age 65. It is important to note that between half and ¾ of those fatalities are due to pneumonia (see ref. 1-5 in Maletic Neuzil et al. JAMA 1999).

In 2013, a huge review of many studies performed all over the world about the H1N1 virus of 2009, was published (Wong et al. Epidemiology 2009). Assessing strict quality criteria, the authors narrowed the analysis down to 50 large-scale studies. Even so they could report marked differences in mortality rates – that were due to methodological differences. The spread of the mortality rates was between 10 and 10,000 deaths per 100,000 cases. ***Their figure 3 is important***, it clearly shows for all to see that the lower estimates that are usually reported for the flu are linked to studies that used reported 'infection' data or 'symptomatic cases' without even being sure if it was the flu or not. But when the studies used REAL cases based on testing for confirmed cases, the mortality rate per 100,000 cases were on average around and even way above 1000.

This would correspond to a mortality rate of at least 1% and higher for the flu. This would be **above** what SARS-Cov2 shows when the analysis is again based on infected cases conformed by positive tests.

**Figure 3 from Wong et al.**
Look below on the open blue circles [10 of those are even between 1,000 (1% mortality) and 10,000 (10% mortality!)]. The green and red points – who everyone always mention on the news - are only so low because they are not counting the positive cases of the flu, but the ones that doctors suspect to be the flu, of the ones who are reporting symptoms that may even be linked to other things than the flu. Hence with so much more cases (flus plus others) the actual flu-related mortality becomes apparently lower. The only correct values are the ones in blue, obtained from studies where testing was done to be sure that the infection was well the flu – in in those studies, the figure makes it clear that between 2009 and 2013 the flu REAL mortality was between 1% and 10% in some places. Arrows to scale, added to compare: Flu (blue arrow) between 1 and 3% (thus between 1,000 and 3,000/100,000), SARS-2 at 0.3% (300/100,000), and SARS-2 in South Korea at 0.03% (lowest estimate, ~ 30/100,000)

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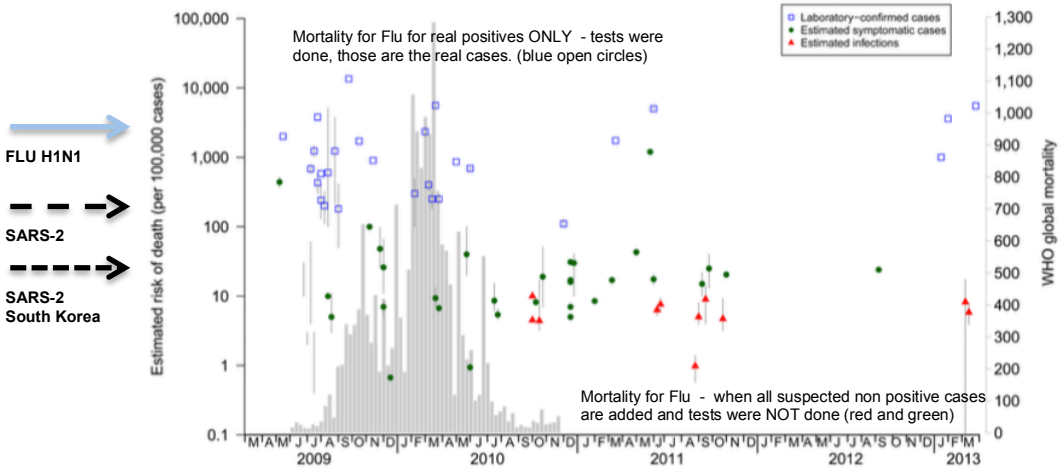


**Figure 3.**
Estimated risk of death by eventual publication dates of the studies included in the review (points with 95% CI) compared with the histogram of confirmed H1N1pdm09 deaths reported to the World Health Organization (underlying histogram).

In 2020, in a compilation about the mortality and morbidity of the pneumonia given by many different viruses, Z. Mosenifar reported that the seasonal flu gave 40,000 excess deaths per year (See

Medscape). The pandemics of 2009 had substantial mortality rates for all. Especially when infected patients have pneumonia, the avian flu (H5N1) has a 59% (!) mortality rate for patients with pneumonia. For the RSV (respiratory syncytial virus) for example, the overall mortality rate is between 0.5-1.7% - thus comparable with the available estimates for the coronavirus. If viral pneumonia came in, this mortality increases up to 5% of the patients with the pneumonia. The situation was identical for ALL the viruses, once they give pneumonia by going deeper in the lungs, the mortality rates are always high.

In conclusion, it is quite striking that good statistical epidemiological practices were not followed.

Is it useful to manage pandemics with some political contest between countries to have or show the lowest infection rates, or the lowest mortality rates (even if wrongly computed)? Is it useful when opinions – not data – are so widespread and shared? If – by doing the right testing right away (random sampling for example) - we had known that the overall mortality rates were so low, would the authorities have decided a lockdown? What are the consequences of stopping ALL Society – part of health care included – for the REAL excess deaths by the virus and by ALL the pathologies and emergencies that went untreated? What was due to the virus, and what was self-inflicted by our behavior?

What about the people who – thinking they were doing the right thing to protect others - spent a few days degrading, then went asleep one evening, with a starting deep pneumonia, only to wake up in need of an ICU? What if this did not even protect anyone?

Now that it is finally understood that testing is the best way to manage this pandemics, it would be a even greater mistake to reserve serological testing ONLY to people at risk or to the sick in the name of "being more efficient". This is the surest way to never get at the reality of what has happened.

***Disclaimer:***
***This note about the need for correct statistics aims at empower rational thinking. It is not meant to attack anyone. It is not perfect, nor does it need to be. Its main use is to educate authorities, medical colleagues, health care workers, and any interested reader.***

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Part 4 –
What To do Locally Then? A series of “martyr” proposals.

It is not the purpose of this paper to tell experts and authorities what to do, we simply want to highlight a few viable and less hysterical paths to be assessed and discussed at their level with the appropriate authorities. So why not think or debate the merits of the following:

1. **Testing to obtain and publish the correct mortality data.**
    a. It is obvious that tests are needed, both molecular (PCR) and serological (antibodies). But the serological testing value is mostly in risk assessment and mortality rates, not in controlling a permanent state of immunity, which we know may never happen due to this type of virus.This does not mean that blocking antibodies will not be found and be usable later.
    b. Also such testing should NOT be reserved to the suspected cases, but done according to what was always done (adding random samples). Testing a whole population would not be logistically easy and would take too much time, and would essentially give the same answers as random sampling only at a higher price.
    **c.** It is the rightful priority of most governments, and economic protectionism should ideally not play any role, as tests can be bought – after the appropriate validation of course.

2. **Primary caregivers**
    a. They should be allowed to fulfill their normal tasks/jobs in a normal way – as they know how to handle most viruses and flu pandemic.
    b. Trying to micro-control the tasks they may or NOT may do – as some countries have planned - would just hamper their services further, and will likely increase the crisis not solve it. The **first** line is where the coronavirus can be tamed/ beaten – once in the ICU it is a bit too late.
    c. All the ‘moonsuits’ are obviously not very useful, nor very practical, and not needed according to the statistics – so why keep them ? – masks and gloves with all the appropriate Good Medical Practices they are trained to follow would be suffficient. Do we think doctors dare to use their stethoscopes on patients they think are lethally contagious ? How many non-diagnosed cases are just being sent home ? There may be a place for an accredited continuous medical education program for GP’s in Infectious diseases.

3. **Establish protocols.**
    a. <u>No one</u> in active in Medicine or Public Health needs this note to establish those medical protocols and guidelines. It is however our hope that the information we gave and discussed within this note may be useful to trigger their further thinking.
    b. Treat Early with blind/empirical antibiotics then collect the swab (do not try to read the license plate of the truck that runs you over) – time to adapt antibiotics later.
        i. And antibiotic resistance should not be a huge worry if we were to use OLD molecules.
        ii. This could protect against the frequent pneumonia and bacterial sepsis and avoid ICU trips
        iii. However disinfecting everything all the time with antibiotic soaps will likely create antibiotic resistances.
    c. Treat the ARDS <u>preventively</u> – Remdesevir (recently tested with success), why not Amantadine ?
        i. Preventing cell fusion decreases the immune response and the lung destructions – giving the medications once at the ICU is again a bit late.
        ii. Once alveolaes are filled with blood, the situation is unstable, any organ may suffer, and respirators are less useful – this happens in all end-stage viral sepsis (and is not SARS – specific).
        iii. Assess Chloroquine or other medications in a correct way (**early**, not late when it will likely not do anything any more – and not with ‘cardiac’ patients ).
        iv. Treating ARDS early could protect against the risk of viral sepsis and avoid ICU trips.

4. **Hospitals and Infra**
    a. Many people are knowledgeable in Public Health, Clinical safety, … use their opinions and skills.
    b. Obviously this crisis begs for an organization able to separate infected patients from others – this need did not start last fall.
        i. This may require investments instead of budgetary restrictions.

ii. There is NO need to centralize all infected patients, as most problems are likely to be with airborne pathogens, shuttling patients around is not the best move.
iii. There are in each country many MD's and others specialized in catastrophic medicine to help taylor the adequate plans.

c. In crisis, the normal functionning of Health care has to be preventively protected. So **all** clinicians need to be able to function normally. In a perverse way, focusing on protecting ICU's clogged those ICU's !
d. Likewise for all institutions of Public Health – they need to be re-inforced and inter-connected.

5. **Strategic reserves.**
   a. Keep a strategic reserve of a few items -no one needs this note to know it would be the right thing to do, hence our apologies.
   b. Antibiotics – Rolling stocks kept by the manufacturers to avoid peremption and undue logistics.
      i. The producers of 2-3 key molecules are paid to keep for example 5-10 Million doses for 2 months in a buffer storage prior selling to their markets
      ii. First box in – first box out principle – this keeps the stock forever 'fresh', and could justify a markup of a few percent on the list price.
      iii. Those boxes are to be deliverable on request.
      iv. Doing so would never perturbate any regular medication approvision
   c. Same with critical anti-viral drugs
   d. Masks, gloves,… – no comment, a few months worth of supplies, same principle : rolling stocks
   e. Respirators. To be assessed.
   f. This list far from exhaustive… Anything that we learned and was needed…

6. **Avoid conflicted commercial decisions.**
   a. In major crises, this is one of the most **recurrent** and vexing problem…
   b. List is known… no need to lecture colleagues and authorities here.
   c. What about a social Tracking App ? Probably the worst « good » idea !
      i. As soon as those viruses are airborne, as it happened, this is most likely useless
      ii. This results mosly from subtle antidemocratic and commercial constituencies pressures.
      iii. For the few sick, why not… but never for a whole population, as one cannot IMPOSE that each citizen should carry his/her phone at all times.

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7. **There must be numerous topics that were not covered here… the aim was to provoke critical thinking, not to lecture…**

8. **A few moments of levity…**
   a. Every crisis has its flip side… people re-discovered their family, their time, re-evaluated priorities… too much useless destruction and losses but it was self-inflicted.
   b. We are only passengers on this planet, germs existed before us and will outlive us as a species, so there is here the chance for a moment of humility as humans **cannot** control Nature, no matter how hard they may try.
   c. Using Public Health concerns as a reason to close borders is possibly the most misguided policy ever, as germs and wild life does not know of any borders – so cooperation is warranted, instead of having an inter-nations contest about who has the lowest mortality rate !
   *d.* Recently the King of Jordan, Abdullah, wrote an Op-Ed in the Washington Post, titled : "It's time to return to globalization. But this time let's do it right." He may be onto something very deep both from human and from economical perspectives, WE all have to unite the planet, we have so many problems that are beyond the reach of individual nations… we should get out of this by gong up, not down…
   *Ref: https://www.washingtonpost.com/opinions/global-opinions/its-time-to-return-to-globalization-but-this-time-lets-do-it-right/2020/04/27/b5e8b442-88b4-11ea-8ac1-bfb250876b7a_story.html*

9. **And a not so stupid question… Now that the first phase is over, and that authorities are debating the re-opening of society, wouldn't it be a good time to stop the attacks and start looking very favorably at what Sweden did ? No need to be afraid if we have a functioning first medical line, and if we focus of the persons who are the most at risk. Real mortality rate is the same in Sweden as everywhere.**

**Let us all remember that there is no place to blame, not for competition between States, just avoid both extreme positions, which are both equally invalid.**

Part 5 – What to do medium/long term globally AFTER the Pandemics?

## Rebuilding Strategies for Public Health and Health Care after Pandemics in General.

Public Health is based on trust. Making any problem worse ends up as bad as denying it. We hope by this factual report to help any interested reader to educate further and to be able to recover some of this needed trust. As it is often the case the true path lies in the middle.

What have we been hearing so far?

- Many people, decision-makers, institutional speakers have compared the crisis as a war (against the invisible enemy) with war consequences and war-like decisions,
- Others national and international players have attempted to minimize the event and its social impacts in terms of deaths and social freedom restrictions, as a temporary virulent flu that would become an attenuated seasonal flu.

None of these models today seems to fit a critical analysis of the epidemics that is beginning to evaporate in some countries and yet continues in other ones as in Brazil, Russia for example. The SARS-2 virus does not kill as much as a pandemic flu but – by its speed of action and side-effects does not behave like a flu.

If we were to follow a "war model" followed by a post-war rebuilding period, we would need to enter a very complex transition phase back to a "peace and prosperity for all" Model. Because borders are closed, economies are destroyed, hunger and violence may arise, a lot would need to be rebuild. To get out of this corner will include a security component, a political component, a social component and an economic component.
If we were to follow the second model and ignore the dynamics of what happened and is still happening, hoping to surf on this and forget it, we will be closing our eyes on the fundamental insufficiencies of the governance revealed by this event, and on the consequences and political responsibilities that have impaired all at once: - the freedoms and the rights of citizens, - the trusting relationship between doctors and their patients, - the responsible use of media-communications (i.e. the right to be informed with as less disinformation as possible) and have generated such a heavy socio-economical impact on all.

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None of this ought to happen, if we were to recognize:
- the actual magnitude of the problem with correct statistics and testing
- that we could have done better by taking a hard look at where we failed.

By humbly accepting this, we also make it possible to build up and prevent that such event happens ever again. Germs have been on the planet before us, and will be there after us, we just have to have sound structures and reflexes in place.

We need first to define the problem correctly: this is a Health Population Problem (HPP) and a Health Shock (HS). An epidemics starts with an infectious agent - known or unknown -, has a time-line scale, starts in a given place and progressively propagates along numerous routes of transmission (human, animals, air, water, cargo…). A HPP epidemics can be a Health Shock (HS) phenomenon, with small or large impacts on the number of people involved and on the fatalities.

Such Public Health shock obviously impacts the relationship between Health and Wealth. Ideally we should integrate the concepts of Health – Welfare – Wealthfare.

It is not because we have large scientific and technological platforms, and that we think biotechnology may lead the way (with vaccines for example) that we are prepared to deal with such Health Shock event.

In physically connected societies with extremely highly mobile persons, goods and services, Containment Measures are *a non-sense*. Especially after the initial phase of epidemics has ended and after the virus is *airborne*. They could be justified ONLY if there were no-ready to-go structures and processes for on-the-ground inter-operability in the epidemics. We would understand that in regions like rural China for example where the infrastructures are not yet adequate. However most of the strong economies that had to crash had the resources, they had the know-how, they had their platforms for preventive and predictive medicine. All those elements were present but somehow they were not utilized, or were ignored, or were mis-used with wrong decision-making process.

Obviously we need solutions adapted to the socio-economical models implemented in the real world.
This means **specific** models for Large Developing Countries with accelerated growth (like China, India, Brazil…), for Smaller Countries with accelerated growth (like South Korea, some African countries…), for slow growth countries (like EU, US, Japan…), or for poor and under-developed countries. Even failed states have to be taken into account.

While the local solutions will be adapted, some ESSENTIALS are common and have to be put in place regardless of the country. We can only suggest an inventory that will certainly be incomplete:

- Having functional structures with inventories of infrastructures and resources. If resources for prevention and reserves are NOT there, it would be a priority to build them up. Regular training would be a must.
- Obtaining and exchanging accurate information as early as possible. This is crucial.
- Germs know of no boundaries and wildlife is still the norm of our planet. **So meteorologists and environmental biologist and others are relevant.**
- How to protect the Hospital infrastructure? By re-strengthening the First line. Was stopping or blocking the first line of caregivers, as it happened everywhere, the smartest way to "flatten the curve"? It is truly the wrong way of doing this, as then everyone ends up in the ICU's.
- Health is a social science, hence social determinants – NOT just miscalculated death rates - are keys to evaluate the impacts of such Health shocks. We need to agree on Common Health Metrics. Those must include accurate statistics, and social, socio-economic metrics. It is being reported for example that domestic violence skyrocketed during confinement, that children were having troubles, that depression and anger augmented…
- If tracing and protection have to be done, those actions are to be specifically focused on the people at risk and the fragilized, or the elderly and the retirement communities. THOSE should be the protected – tracking whole populations is essentially killing democracy and useless.
- Likewise presenting Health care workers as heroes is nice but does not solve anything. They should be helped, protected, funded, hospitals should have procedures, materials, and buildings should have adequate filters in HVAC. Their clinical expertise should be allowed, NOT controlled, in times of crises guidelines for example restricting antibiotics prescriptions are mostly counterproductive.

Basically we have to remain focused on what an epidemic represents: it is a Health Shock with impact on the populations. It is not about politics, but about global threats requiring global answers.

**We feel that Preventative and Predictive Medicine, based on Social Determinants of Health and Health Metrics of a Society, is the basic Key to design, develop and implement Solutions at the Point-of-Care.**

## Part 6. Various Thoughts to Reflect and Explore Further.

As we wrote, we are just trying to educate, we present apologies to the reader for being so long, for the interested readers we would like to generate additional thoughts.

**Notes about Medical information.**

*Info-demiology* truly made this public health crisis worse. The quality of information is not equal to the quantity of this information, and this is an obvious problem. How can we do better?
As germs have no borders, we need an effective chain of transmission of **quality** information.

We see 3 happening at levels:

- The Global Chain of Transmission ….e.g. from China through WHO to Countries Governments
- The Right of International Intervention to evaluate the casualties in the place of epidemics
- The Institutional Public Communication: there were great discrepancies among the western countries, relative to Representativity, Methodology and Open debate.

For example, in some countries, the communication was made political (we can think about the US, France, Belgium,…) with direct outputs towards the public. In some others, it was political but with an open technical approach (like Germany, Switzerland, South-Korea…). In some others it was political but very direct and very candid (New Zealand for example). In others it was not political but mostly technical without real decision power (Italy being an example). While those differences reflect *in fine* a country's governance and the way their Health care systems function, the decisions should always be **integrative.** The debate about the masks (yes?-no?-maybe?-but for who?) being a prime example. The initial advices to reserve them for Health care professionals was sound and based on the accumulated years of practice, but fear and optics pushed it way too far, in the end even altering official web sites and negating years of physical chemistry doing so.

Final Text

**About vaccines.**

It may be surprising to some but the future of the "expansion" of human immunity may not be represented by vaccines, but by the implementation of the advanced Human Genomics, as we are just at the first generation of CRISPR/cas Technologies), with some support from Synthetic Biology. In the mean time it is announced for June 4 in London: "*The UK government hosts Gavi's third donor pledging conference to mobilize at least **US$ 7.4 billion** in additional resources to protect the next generation with vaccines, reduce disease inequality and create a healthier, safer and more prosperous world".* This may raise a parallel between the vaccine industry and the financial industry mutualizing ALL risks while keeping revenues private.

At some point, maybe we should consider to stop playing by the germs and viruses playbook: a germ > a vaccine >a mutation > a new vaccine… etc… This is not a sustainable solution. Vaccinate all the time against everything? Really? So exploring the power of genomics and stem cells, and immunity directly may be worth considering too. This would be cutting edge research worth funding.

**Airborne Viruses and Pollution levels.**

While there is no debate that viruses circulate through the atmosphere, there is debate about the effects of those free viral particles. It may be worth using modelization; it may be worth considering the level of urban pollution while tackling this question. Decreasing general pollution levels, will likely be better than having everyone walking with masks like in some sci-fi movies, and will likely mitigate airborne diseases. There seems to be an increase not only in pulmonary pathologies but also in pathologies linked to imbalances between the man and the environment.

**About the Disease itself.**

Quite a lot of the fatalities were suffering of other ailments. Of course they should not be used as excuses for inaction but the truth of the matter is that those co-morbidity factors were not completely evaluated, as well as the companion medications and the life-style conditions of minorities or special populations clusters with pathological traits. Worse they were used either added to inflate statistics or subtracted to deflate them.
Maybe worth pondering and studying correctly.

Another problem, that is truly un-expected, is the slow rate of recovery of some severe patients who survived the ICU, with semi-permanent impairments at the pulmonary or neuro-muscular and cardio-vascular levels. There seems to be no specific rehabilitative protocol that is effective. Could this be the result of having survived a very late stage general sepsis, which usually never happens *en masse*?
There is need for some solid research there, and possibly a place for stem cells regenerative medicine?

**About a COVID No fault mechanism for good faith actors/victims.**

The current COVID 19 crisis has created a situation that will generate many hurdles not only for the economic activity to start again, but also for the medical care to recover and to start working at its former level. There will be a huge need to heal in a broadest sense.

Many doctors, hospital directors and other actors of the medical sector live in fear of being confronted with litigation or medico-legal issues in relation with the COVID crisis, whether for having lost a patient because of the disease, or for being accused of delayed treatment. Also, medical treatments having been debated so much in the media, everyone ended up with an opinion on which treatment should be given or not, it is easy to see that claims could be numerous (eg. chloroquine vs. no chloroquine, etc…)

As we are writing these lines, it is also evident that there is a second epidemic of delayed care, with an unusually high number of patients that are appearing in emergency wards, with increasingly severe conditions. These are and will be the real second wave of COVID, and these patients - treated with delay - may not fully recover from their conditions. For that too, patients and lawyers may want compensation, either from medical care actors or even from political leaders.

Finally, the socio-genic fear of contagion may cause a lot of problems to business owners who do no want to risk being accused for spreading infection or – worse – causing the death of one of their customers or employees. They are likely to prefer staying closed thus feeding the economical abysmal loop in which most countries are falling. Disinfecting all surfaces all the times will only generate more real antibiotic resistance and will not erase fears.

For these reasons, the idea of some No-Fault Insurance Mechanism ought to be considered regarding businesses, which return to normal operations. Such concept, taking into consideration that everyone facing an unprecedented situation, did the best they could to limit the damage to all, would mitigate the social and societal damages. While the precise modalities (financing? catastrophe insurance funds…?) ought to be defined, this may ease the political de-confinement, would enable everyone (health care professionals, business owners…) to go back to work with some peace of mind, and would reduce the economic crisis to come.

A reasoned approach to this new phase is needed to help to heal Society, by sharing means instead of spreading blame. When Society as a whole dysfunctions, who is to blame for ‘viral crimes’?
This COVID no-fault should be implemented as soon as possible in order to maximize its efficacy.

Of course, there will be many other facts and areas where – if we are candid enough – we may learn from.

Of course this report and analysis is far from perfect, and far from exhaustive.

We hope to have brought forward a data-based general information, free from political optics, with call for simple and fast actions, and the seed of some deeper prospective thinking for everyone.

We can change the world but only one brain at a time… our own!

**A society with too few independent thinkers is vulnerable to control by disturbed and opportunistic leaders. A society, which wants to create and maintain a free and democratic social system, must create responsible independence of thought among its young.**

Final Text

*John Dewey (1859-1952).*