COVID-19: UNCOVERING INDIVIDUALITY

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ABSTRACT

SARS-Cov-2 is a virus easily transmitted by air and fomites causing acute severe respiratory syndrome. Severity in some cases requires hospitalization and complex expensive intensive care treatments. Its rampant contagious led to a a fearful pandemic affecting the whole world with millions of infected humans and almost half a million deaths in a few months in the beginning of 2020 (until June 17, 2020). SARS-Cov2 is likely to have been spilled over from natural sylvatic cycles in bats from China.

Our purpose is to comment on the human individual immune inflammatory responses to the infection of SARS-Cov2 and the reflections of these individual immunoinflammatory profiles on patterns of the severity of the disease, time for therapeutical intervention, pathogenesis, candidate drugs and indicative comparative drug prices for covid-19.

Efficient treatment for covid-19 may require: 1) early disease detection, 2) a combination of drugs being used for 3) targeting the virus replication cycle and 4) specific/ individualized drug treatment for given immunoinflammatory human profile responses in a 5) timely manner.

Specific serum immuno-markers of covid-19 affected individuals at onset, in the follow-up, and in the resolution of the immunoinflammatory storm during the course of the disease may lead to individualized therapeutics with better outcomes.

Covid-19 is unlikely to be the last emergent human disease with fast pandemic potencial. To gather knowledge on the human host profiles and immunoinflamatory responses is an opportunity that could pave the way to faster, more efficient strategies to tackle upcoming diseases.

KEYWORDS: Immunoinflammation, covid-19, immunoprofiles

INTRODUCTION

We are all different. We are 7 billion of humans with differently arranged DNA material. Upon an incredible variety contained in 3 billion DNA base pairs, the way we live, work, eat, exercise and even, our mental health add variation to our epigenetics.

Even though this is an established fact, when we talk about pathogen invasion and emerging diseases we tend to disregard our immense human genetics and epigenetic variation. In fact, these variations lead to different host immune responses to pathogen infection and to the way human populations and cohorts are impacted.

In the beginning of the 1960's John Murray Last, an Australian doctor, while working as a postgraduate in the London Hospital, UK, observed what he called 'subclinical diseases' and created the strong metaphorical image of 'disease as iceberg' observing that only a fraction of patients show symptoms in a given exposed population (Last 1963[1]) (Figure 1). Last observed these subclinical undetected forms either for acute or chronic diseases such as urinary infections, tuberculosis and for diabetes and rheumatoid arthritis, among others, stating that the 'Disease known to the general practitioner represents only the tip of the iceberg'. In the tip visible part of the iceberg, a few individuals present medium to severe symptoms while for some individuals, in fact the majority of the affected population, mild or no symptoms prevail.

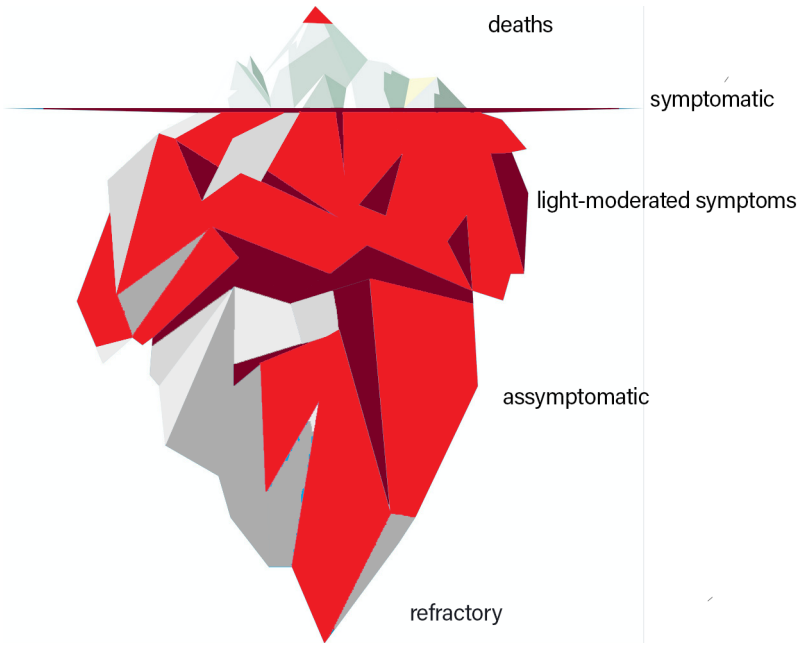

Figure 1. The iceberg. Covid-19 infections in a given exposed population. Some individuals, in fact the majority of the population, present mild symptoms or are asymptomatic. Very few have medium to severe symptoms. Source: The Authors, after Last, 1963.

For covid-19, caused by the number 2 coronavirus - SARS-CoV2, the number of severe cases seem to follow the iceberg model of disease (Fig. 1) (Table I). Even though testing and notifications are believed to confirm only a fraction of the coronavirus infections actually happening, 0.001 to ~ 1% of cases in the total population could still be confirmed using fast immunochromatographic tests for antibodies and polymerase chain reaction-PCR antigen testing (Table I). These numbers will be considered by us as a proxy of individuals having moderate to severe symptoms, seeking testing in hospitals and health care units and being statistically registered. Testing studies in 120 cities in Brazil corresponding to 32.7% of the total Brazilian population, or 68.6 million individuals have shown average percentages of 3% of infected individuals sometimes completely assymptomatic (EPICOVID19 -Universidade de Pelotas, data of 11 June 2020[2]). These numbers are highly variable showing different realities for different Brazilian cities. In some capitals tests showed IgM positive for covid-19 raging from 0.5% in most cities of the

Southern Brazilian States to 25% in Boa Vista, Roraima in the Northern Region (EPICOVID19 -Universidade de Pelotas, data of 11 June 2020).

Table I. Percentages of confirmed cases and deaths per country by covid-19 in descending order of % deaths. Data of 15 June 2020.

Country	confirmed cases	% confirmed cases who have died	deaths	deaths per million people	cases per million people	Population	% of confirmed cases in the total population	% of deaths in the total population
Belgium	60100	16.07	9661	845	5185.7	11589623	0.52	0.0834
UK	297342	14.05	41783	631	4493.0	67886011	0.44	0.0615
Spain	243928	11.12	27136	585	5262.0	46754778	0.52	0.0580
Italy	236989	14.49	34345	579	3992.0	60461826	0.39	0.0568
France	194153	15.15	29410	453	2988.0	65273511	0.30	0.0451
USA	2094058	5.53	115732	357	6454.0	331002651	0.63	0.0350
Canada	100404	8.18	8218	224	2741.0	37742154	0.27	0.0218
Brazil	867624	4.99	43332	207	4146.0	212559417	0.41	0.0204
Peru	229736	2.91	6688	208	7142.0	32971854	0.70	0.0203
Chile	174293	1.91	3323	184	9654.0	19116201	0.91	0.0174
Mexico	146837	11.67	17141	133	1138.9	128932753	0.11	0.0133
Iran	187427	4.71	8837	109	2309.0	83992949	0.22	0.0105
Germany	187518	4.69	8801	107	2238.1	83783942	0.22	0.0105
Turkey	178239	2.70	4807	57.0	2113.4	84339067	0.21	0.0057
Russia	528267	1.31	6938	47.5	3669.0	145934462	0.36	0.0048
Saudi Arabia	127541	0.76	972	27.9	3872.0	34813871	0.37	0.0028
South Africa	70038	2.11	1480	25.0	1180.9	59308690	0.12	0.0025
Pakistan	144478	1.89	2729	12.4	654.1	220892340	0.07	0.0012
Bangladesh	87520	1.34	1171	7.1	531.4	164689383	0.05	0.0007
India	320922	2.87	9195	6.7	232.6	1380004385	0.02	0.0007
China	84335	5.50	4638	3.2	58.6	1439323776	0.01	0.0003

Sources: https://informationisbeautiful.net/visualizations/covid-19-coronavirus-infographic-datapack/; https://coronavirus.jhu.edu/map.html; https://www.worldometers.info/world-population/population-by-country/ accessed 15 June 2020.

These numbers look small. Nonetheless, they are still of concern and challenge even for the most prepared health systems, since covid-19 is a fast spreading contagious acute respiratory syndrome which requires complex treatment involving intensive care units, ventilators and other special equipment, high use of disposable consumables and highly skilled personnel, all ready at once. Some patients require intensive care for weeks and approximately 1 to 16% of those symptomatic individuals will not recover (Table I).

Individual immune responses. When we look retrospectively to a new emerging pathogen such as the severe acute respiratory syndrome by SARS-CoV2, individual exacerbated immunoinflamatory responses in attempt to overcome the pathogen invasion seem to be linked to the symptomatic full blown covid-19 disease[3]. These responses are not only likely to vary on individual fashion but also during covid-19 time progression and are linked to disease outcomes.

Comorbidities and risk groups alone can not by itself explain covid-19 clinic presentation segmentation in a given population, from mild to severe. Although the elderly, hypertensive, diabetic, obese, immunosupressed and chronically ill are majorly at risk, as for any infection, some healthy individuals in the population seem to be more susceptible to develop covid-19 severe cases. These severe covid-19 cases are usually linked with clinics presentation of a 'cytokine storm'.

Out of control. Unregulated immune-inflammation is a central pathological process in several infectious diseases such as haemorrhagic dengue (Sierra et al 2010[4]) and severe malaria (Penha-Gonçalves 2019[5]).

The term 'cytokine storm' was first used in 1993 on a paper on graft-versus-host disease (Ferrara et al 1993[6]). Cytokine storm phenomenon was applied for the avian H5N1 influenza virus, cytomegalovirus, Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis, group A streptococcus, variola virus and for the previous severe acute respiratory syndrome coronavirus (SARS-CoV) (reviewed in Tisoncik et al 2012). Cytokine storm was revived for covid-19 since its striking immune-inflammatories cellular and molecular processes seem to be strongly linked with death outcomes (Fig. 2).

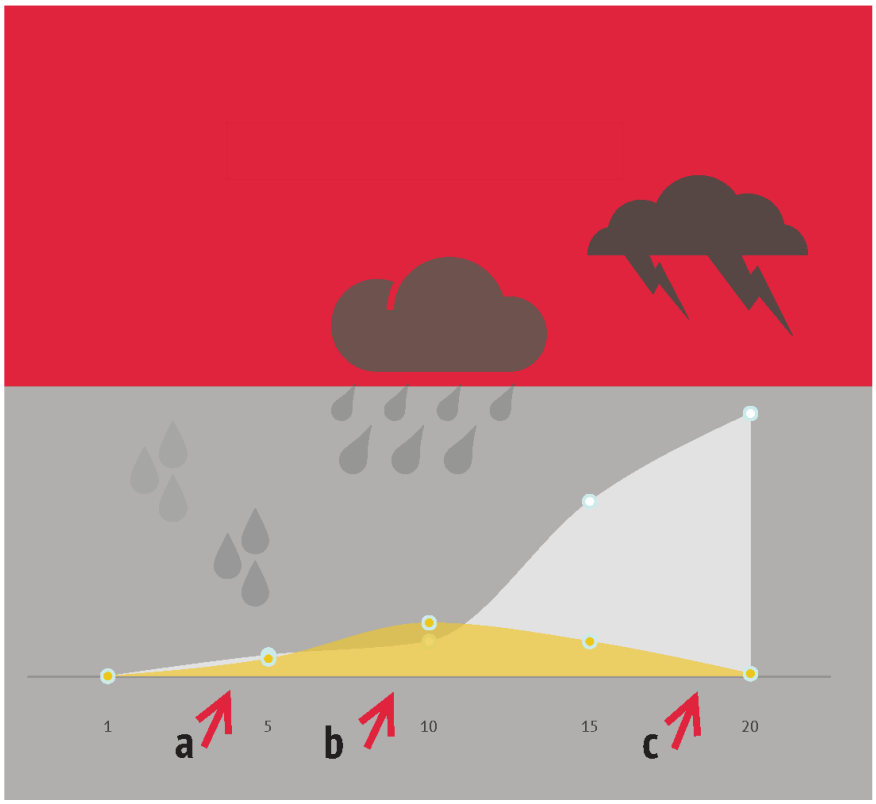

Figure 2. The covid-19 storm. The x axis is time in days and the y axis is the amount of immuno-inflamatory response by the host, normal in yellow and abnormal in light gray. Red arrows represent possible times for drug intervention: a) early (possibly using antivirals), b) symptomatic (probably using anti-inflammatory drugs) and c) storm (probably using MAbs and corticoids). Source: The Authors.

Immunoinflammatory profiles. We would expect that genetics, immune and inflammatory profiles of each infected individual play a role in the outcome for covid-19 but we have just started gathering knowledge to have the tools to separate these individuals in groups and take this knowledge to the clinics. These profiles are not static in time and ought to be dependent on the genetics and epigenetics of the individuals.

We therefore would like to suggest at least three major human immunoprofile groups for covid-19 which can be applied to other cytokine storm prone-diseases: 1) individuals who will probably not develop a cytokine storm, 2) those who potentially will make a storm and 3) those will most likely will make a storm. These 3 major groups could be separated based on: i) the ratio nucleocytes/ monocytes (Tay et al 2020), ii) interleucin-6 - IL-6 levels and iii) immunoinflamatory factors such as tumor necrosis factor (TNF-a), interferon gamma (IFN-c) and tumor grow factor beta (TGF-b) and other interleukins such as IL-10, IL-2, IL-4 and IL-5 (Sierra et al 2010, Tay et al 2020). Better laboratory indicators of factors present in the blood serum will most likely help to better outcome predictions using fast practical approaches.

If we could know more about the specific immune and inflammatory responses of each individual we would be in a better position to understand risk groups. Genetic and epigenetic factors are not only important for infectious pathogens such as bacteria and viruses but also for several degenerative conditions, from endometriosis (Bellelis et al 2019[7], Garcia-Goméz et al 2020[8]) to senility (Hu et al 2019[9]).

Hence, the categorization of human immunoinflammatory profiles would also allow for better therapeutics.

Possible suitable times for drug intervention in covid-19 are represented by red arrows in Figure 2: a) early (probably using antivirals), b) symptomatic (probably using anti-inflammatory drugs) and c) storm (probably using MAbs and corticoids) (Fig.2).

Possible drugs for covid-19. As an emerging disease, there are no drugs tested for covid-19. Time and money are required in order for a drug, or a vaccine, to reach shelves's pharmacies and hospitals. In fact, from 5-10 years in tests from drug discovery in the laboratory to 3 phases of clinical research in animal and human populations of increasing sizes is required. With such complex from bench to bed pathways, a single drug costs from tens to hundreds of millions of dollars to be available to the society. Often, treatment for a disease, even if it exists, cannot be applied until it is authorized, registered and regulated. For a deadly highly contagious disease as covid-19, the repositioning of drugs is the emergency strategy indicated in the integrated management of the pandemic.

The first drugs that come to mind are antivirals, because covid-19 is caused by a virus. Directly linked cell destruction and tissue damage is likely to be linked to the virus pathogenesis mechanisms. However, we must ask ourselves if the human host response is the cause for the major burden to the infected organism in covid-19. Due to the urgency, repositioning of drugs have been proposed as a viable way to tackle covid-19. All these drugs are already on the market and safely used to treat other diseases. Some anti-inflammatory drugs have also been used to experimentally treat covid-19.

Knowledge of inflammation pathways and triggers provide opportunities for therapeutic targets.

Tackle inflammation as well as viral infection would better manage homeostasis in the moderate to high immunoinflammatory profile group likely to present a heavier illness.

Among the many pathological mechanisms studied and reviewed to date in covid-19 are: 1) direct attack of the viral particle on the lung tissue with cell destruction at the exit after replication (Tang & Kang 2020[10]); 2) dissociation of the hemoglobin structure producing iron and porphyrin (Wenzhong & Hualan 2020[11]); 3) uncontrolled/ exacerbated inflammatory responses (Fig.3) which may cause a series of blood related pathologies such as ischemia, tissue destruction of organs like heart, brain, kidneys and lungs (Dhama et al 2020[12]).

Among the drugs tested against covid-19 are: antiviral drugs (favipiravir, remdesivir, lopinavir, ritonavir, ribavirin, oseltamivir), aminoquinolonas (cloroquina and hidroxicloroquina), monoclonal antibodies (sarilumab, tocilizumab, anti-cytokynes such as anti-IL-6), immune-plasma (plasma from recovered patients), plasma with inflammation regulatory factors (PlasmaCord ®), antibiotics (azytromycin), anti-helminthic (nitazoxanide), corticosteroids, immunomodulators (interferon) and other classes of drugs (camostat) (Table II, prices are given comparatively per 100 mg whenever possible).

Table II. Covid-19 repositioning candidate drugs, drug target and usages, country of production and source of Active Pharmaceutical Ingredient-API and price in USD per 100mg for comparison. Source: The Authors.

Drug	Target	Used for	Produced in	Active pharmaceutical ingredient-API-produced in	Price 100 mg in USD
chloroquine phosphate	Blocking viral entry by inhibiting host receptor glycosylation, proteolytic processing, and endosomal acidification. Additional: immunomodulatory effects by inhibition of cytokine production, autophagy and lysosomal host cell activity	Malaria, immunomodulator in autoimmune rheumatological diseases	Brazil, India	India	66
hydroxy-chloroquine sulphate	Same as chloroquine	Same as chloroquine	Brasil, India	India	120
Lopinavir/ ritonavir	Protease 3CL		India		96 e 180
Umifenovir (Arbidol)	Protein S/ ACE2, membrane fusion inhibitor	influenza virus	Russia, China	Russia, China	317
Remdesivir	RNA polymerase inhibitor		India, USA	USA	8500
Oseltamivir	neuraminidase inhibitor	influenza A and B.	India, USA	India, USA	60
Ribavirin	antiviral	HCV, HIVl, and RSV.	USA, India	Italy, USA, India, China, Japan, Korea	60
favipiravir	Antiviral RNA polymerase inhibitor	Influenza	Russia	China, India	150
Sarilumab	Monoclonal antibody-Mab target: anti interleucin-6 (IL-6)	rheumatoid arthritis	France, USA	Germany	Undetermined
Tocilizumab	MAb (Anti-Human IL6R, Humanized Antibody)	rheumatoid arthritis	Switzerland, USA	China	28000 (1mg = 280)
Immune Plasma	Viral particles, viral spicules		Brazil		Undetermined

plasma with inflammation regulatory factors (Plasma Chord R)	Unknown	Inflammatory diseases		Custom, probably mainly local production	Undetermined
Azythromycin	Azithromycin is a macrolide antibiotic useful for the treatment of a number of bacterial infections.		Brazil, Chile, Portugal, Italy and many other countries	Spain, Portugal, India	96
Nitazoxanide	antiprotozoal agent and canine antiviral - possible interference with the pyruvate:ferredoxin oxidoreductase enzyme dependent electron transfer reaction. virus - electively blocking the maturation of the viral hemagglutinin at a stage preceding resistance to endoglycosidase H digestion.	Human antiprotozoal agent, anti-parasitic drug and canine influenza virus, cryptosporidiosis in AIDS. s	China, India, Spain	India,USA, Belgium, Argentina,	288
Corticosteroids (as prednisolone)	down-regulation of immune-active molecules, reductio, of postischemic oxidative stress, perfusion pressure, and transudate formation.	Immunodiseases, exacerbated inflammation, allergies	Brazil, Germany, USA and many other countries	USA, France, Italy, China	10
Interferon (as human, recombinant alpha and beta)	antiviral, antitumor and immunomodulatory activity	Viral, tumors and immunodiseases	USA, Israel, Germany, Cuba, China and may other countries	China, Israel	170 por 100 microgramas
Camostat mesylate	trypsin-like protease inhibitor inhibits generation of TGF-beta by suppressing plasmin activity and reduces the activity of TGF-beta, which blocks in vitro activation of HSCs [1].	Immunodiseases	Japan	Japan, India	140

Note: Major players for APIs are: China, India, Germany, Italy, Spain, Israel, USA (Pharmacompass 2020[13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32]).

Vaccines. Currently there are more than 135 clinical trials on SARS-CoV-2. Vaccines demand a long way from lab to society with usually 4 phases: preclinical (with non-human animal testing) and phases I (safety), II (expanded), III (efficacy) to approval (WHO 2020[33], New York Times 2020[34]). These vaccine candidates have different designs to allow humans to produce antibodies against SARS-CoV-2 such as: 'self-amplifying RNA; vectors using chimpanzee adenovirus ChAdOx1, adenovirus Ad26, adeno-associated virus delivering coronavirus gene fragments into cells (gene therapy), vesicular stomatitis viruses; protein-based molecules; whole attenuated viral particles and the repurposed tuberculosis vaccine (WHO 2020, New York Times 2020). Even using fast, combined approaches in an unforeseen fashion, a vaccine for covid-19 will be ready to market only at the end of 2020/ yearly 2021. Billions of doses will have to be manufactured, shipped and available to cover the whole world.

Concluding Thoughts

SARS-CoV-2 is highly contagious, being easily transmitted by air and fomites and some cases' severity require hospitalization and complex expensive intensive care treatments.

Some individuals in the population seem to be more susceptible to covid-19 and risk groups such as the elderly, hypertensive, diabetic, obese and with other comorbidities have been majorly affected by covid-19. It might also be that the genetic, immune and inflammatory profile of each infected individual play a role in the outcome of the covid-19 disease helping to form the iceberg presentation of the disease (Last 2013). If we knew more about the specific immune and inflammatory response of each individual we would be in a better position to talk about risk groups, since these genetic and epigenetic factors are not only important for viruses, but for several degenerative conditions, from endometriosis to senility.

Unregulated inflammation is a central pathological process in several infectious and non-infectious diseases. Knowledge of inflammation pathways provides opportunities for therapeutic targets.

Efficient treatment for covid-19 may require: 1) early detection 2) a combination of drugs being used for 3) targeting the virus replication cycle, for 4) specific/ individualized treatment for specific immunoinflamatory human profiles/ responses in a 5) timely manner.

Specific immuno-markers of covid-19 present in human serum at onset, in the follow-up, and in the resolution of the immunoinflammatory storm may lead us to individualized therapeutics with better outcomes.

Pathogens transmission cycles in nature between non-human hosts, vectors and pathogens often leave these cycles in a phenomenon called spillover, or 'spill out of the cycle', reaching the human host. Several of the recently observed emerging and reemerging diseases such as Zika or yellow fever, have so happened.

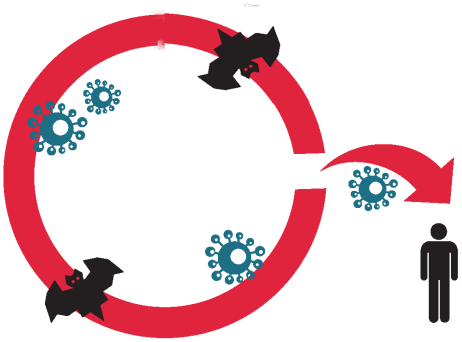

Figure 3. Simplified representation of SARS-CoV-2 spilling over its natural cycle among bats to reach humans. Source: The Authors.

Serious acute respiratory syndromes have recently occurred caused by two other coronaviruses spilled over from sylvatic cycles (Fig.3). The first coronavirus was the SARS-CoV with 8096 infected people and 774 deaths in various countries in Asia, Africa, Europe and America during 2002-2003. The second coronavirus was MERS-CoV (Middle East respiratory syndrome coronavirus) an outbreak in 2012 circumscribed to Southeast Asia and the Middle East. MERS-COV was registered in 26 countries, with 1621 confirmed cases and 584 deaths globally[35] (World Health Organization-WHO, December 7, 2015) where it could probably have again secluded to sylvatic cycles having camels as reservoirs[36].

Besides new emerging diseases, in recent years we have experienced pandemics of reemerging old diseases such as dengue, yellow fever, Zika, chikungunya and even measles for which a vaccine is available.

Covid-19 is unlikely to be the last rampant emergent human disease. To gather knowledge on the human host profiles and immunoinflamatory responses to infectious diseases is an opportunity-to-learn that could lead to faster, more efficient ways to tackle ever challenging human emerging diseases.

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