Why is Covid-19 so scaring?

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The prediction of the next 'Big-One' pandemic event has always been the real question. Is Covid-19 the first virus so scaring? Most of the past pandemics are of viral origin. The latest was Human Immunodeficiency Virus (HIV), which killed 30 million people. Each year one billion people will get infected by influenza virus. In the last 100 years, there have been four major pandemics of influenza in 1918 (Spanish flue), 1956, 1976 and 2009 (swine Flue). The Spanish flu killed more people than the First World War. The arrival of a new pandemic was just time! Covid-19 is a dangerous disease caused by SARS-CoV-2 virus. The virus spreads very quickly from person to person and there is no cure and no vaccine. It first appeared in China and then spread in the rest of the world. What you should know about it to discriminate among real treats and fake news?

What is a virus?

A virus is an extremely small microorganism that invades other living things (as your body) to replicate (make copies of itself) and survives only inside another living organism. It is a parasite! Imagine the virus is a spyware and the human cell is a computer. If the spyware succeeds in entering your computer (there is no antivirus/antispyware), it will use everything in it to make a number of copies of itself. It will destroy your computer and then every single spyware-copy will invade a new computer and the cycle will start again and again … the entire network (your body) will turn into an enormous virus factory and will get damaged if you do not know how to block it. You will be sick!

Why viruses are parasites and hijack the copying machinery of the infected cells? Cell replication is a normal process of our body, and it is controlled by an instruction leaflet (genome) written in the DNA or RNA. The viral genome is simplified and viruses lack the genes that allow them to replicate the way cells do. Why is that? Simply, because viruses are very small (15-300 nm when round-shaped; one nanometer is 10^{-6} millimeter) and have space just for a limited genome, just enough to make the virus efficient in getting into and controlling host cells.

Apart from the genome, viruses are made of proteins. The protein that envelops the viral genome is called capsid; often there is an additional layer called envelope formed by proteins and lipids. On the outer face of the envelope there are bumps/hooks with different molecular structures for each type of virus (Gelderblom, 1996). These spikes play key roles to undisclose why certain infections become a serious problem, others a tragic problem and others appear intermittently or vanish without doing harm:

- they act as keys that open specific padlocks on the membrane of the target cell and allow the virus to attach to the host cell like an airplane stuck to the airport fingers after landing (the interaction with receptors); this interaction is key to discriminate the host: a virus causing infections in birds is unlikely to cause illness in humans, because their lungs are covered with different types of receptors. The shape of the spikes determines also the type of cells (nerves, digestive, respiratory, etc.) that are infected, therefore the type of disease they can cause;
- the spikes mediate penetration, which determines disease severity (how bad the disease is), and affect the speed of the virus spread from one individual to another.

Where does a new virus come from? What is Zoonoses?

A zoonoses is an infectious disease caused by bacteria, viruses, or other parasites that can spread from animals (reservoir) to humans through air or bites and saliva. Transmission can also take place via an intermediate species (vector), which carries the disease pathogen without getting infected. Many diseases started out as zoonotic such as Ebola and HIV. Most strains of influenza that infect humans are human diseases, but occasionally some strains of bird flu and swine flu recombine with flu

human strains (zoonoses) and trigger pandemics.

Zoonoses are new, unrecognized diseases with increased virulence in humans lacking immunity; the key circumstances contributing to the appearance of new zoonotic pathogens in humans is an increased contact between humans and wild animals that might induce a spillover "species jump". Moreover, the environmental impact of agriculture, that promotes deforestation, changing wildlife habitat, and the increased land use has determined an increase of zoonotic spillover in the last 50 year.

A spillover takes place when a reservoir population with a high pathogen prevalenceencounters a novel host population. Some spillover events might end in the adaptation of the microbe to humans, who became a new reservoir; keep in mind that most of the pathogens exclusive of humans, were likely transmitted by animals sometime in the past.

When a spillover takes place the virus enters a new host,the mutual tolerance is broken and new relationships are to be established: the virus may turn into a harmless passenger, a moderate nuisance or a biblical plague. It depends!! (Figure 1A)

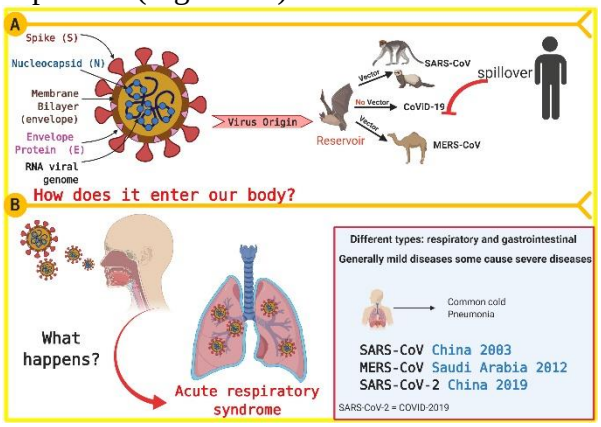

Figure 1 (A) virus structure, its origin and impact on humans. (B) Effects of the virus in our body and different classification

What is Covid-19?

In December 2019, 27 pneumonia cases of unknown origin happened in Wuhan, China. Most patients had been in a seafood wholesale market in Wuhan. Patients developed severe acute respiratory infection symptoms, and some of them died. The virus was quickly characterized as a novel human coronavirus, now called SARS-CoV-2 (Covid-19). By the end of March 2020, Covid-19 spread to all continents and lead to WHO's declaration of a Public Health Pandemic Emergency. Covid-19 belongs to a large family of viruses called Coronaviruses, most of which cause mild infections such as the common cold, but some such as Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) cause severe and potential fatal respiratory tract infections (Dong et al.). (Figure 1B)

Sequence analyses proved that Covid-19 is closely related to bat coronaviruses. A bat coronavirus might have jumped into a civet or some other mammal, and from there to humans. Initial confirmed cases of Covid-19 were related with Wuhan seafood and live animal markets. It is important to note that, bats were not sold in the Wuhan market; thus, animals that served as the transmission vehicle remain to be identified. Given these circumstances, although only in theory, until no animal source will be been identified spillover events may continue to occur.

Do you remember the last time you were sick? You may have experienced pain or fever a few times in your life, due to different infections. Covid-19 is a particularly bad infection, which may cause high fever, bad cough, red and itchy eyes. If you are lucky, the symptoms go away after about 10 days. Covid-19 can spread through coughs, sneezes, and saliva from other people who are sick. Once in your body, the infection might attack lungs and lead to death.

What do we know about Covid-19? Coronaviruses are the largest family of positive-strand RNA viruses with an approximate diameter of 125 nm. Covid-19 structural characteristics are similar to common coronavirus with an enveloped, single, positive-stranded RNA genome that encodes four major viral proteins:

- spike (S) protein, in charge of receptor-binding and viral entry into host cells, and is therefore a major therapeutic target.
- envelope (E), and membrane (M) proteins, responsible of viral assembly
- nucleocapsid (N) protein, necessary for RNA synthesis

What does our body do to defend?

Luckily, your body can count on a private security service called the immune system, which protects it from external treats. Most of the symptoms of flu are necessary but uncomfortable side effects of the body fighting the virus. The immune system can be trained by vaccines to recognize pathogens. The immune system searches the body day and night to locate any invader, such as infectious viruses or bacteria. Each microorganism uses different means to infect you, and therefore the immune system security needs specific training to recognize and arrest them. When your immune system encounters a microorganism, it generates antibodies, proteins able to precisely bind to the microorganism.

The idea of a vaccine is to train the immune system with a weakened versions or pieces, produced in the labs, of the microorganisms that are not capable of making the person sick. Thus, vaccination is a training for the immune system to recognize and arrest the real virus, if you ever come into contact with it, and produces antibodies that hopefully will be present in your blood for the rest of your life and protect you from getting sick.

I am well. Why do I still need to stay at home?

People travel all over the world and get in contact with many viruses. If a vaccine exists and if you are vaccinated against it, then you cannot get sick. This is the case of measles that is normally rare in western countries but still common in many developing countries.

Being vaccinated therefore actually reaches two objectives:

- it protects you from becoming sick,
- it prevents you from spreading the disease.

The number of infected people can be significantly reduced if the majority of people who may be in contact with a specific virus are protected , and hopefully the virus will eventually die out completely. This is what is known as 'herd protection'. When enough people have been given a vaccine, the disease will no longer spread and we can contain outbreaks avoiding that many people become sick. (Figure2)

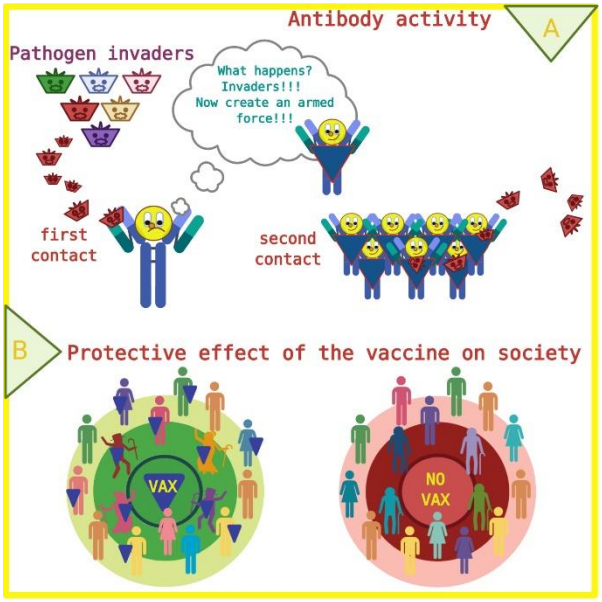

Figure 2 A) How immunity works. B) Different effects on the population with and without vaccine

No vaccine and no cure is available for Covid-19, so how to protect the weakest members of our society, who cannot defend themselves and are more likely to become very sick? Effective protections are social distance, cancellation of major events, postponing of sports seasons and Olimpic games, and sending many into self-imposed quarantine and self-isolation.

Rules to be to respected to protect weakest person	
Wash often your hands	
Avoid close contact with people	
Do not touch eyes, nose and mouth with your hands	
Cover your mouth and nose if sneeze or cough	
Stay at home	

Is there any drug already available? Some "old" drugs effective again Covid-19.		
Drug	**Clinical use**	**Activity**
Remendervis (GS-5734)	In clinical trials for EbolaAlso used for SARS-CoV and MERS-CoV in animal models	The drug works by shutting off the virus ability to replicate inside cells.
Lopinavir/Ritonavir (Kaletra)	In clinical trials for HIV	The drug blocks a key enzyme that helps viruses replicate
Tocilizumab	In the clinics for severe rheumatoid arthritis	Reduces the pathogenesis of the inflammation
Favipiravir (Avigan)	Used in Japan since 2014 against new influenza viruses	The drugs blocks an enzyme (RNA polymerase)
Chloroquine	In the clinics for Malaria	Drug's ability to bind both heme and lactate dehydrogenase causes the drug to be toxic primarily to the parasite
Coronavirus sera (passive immunization)	Well established prophylaxis for viral infections	Antibodies from convalescent patients

Are there other strategies? Can we develop new drugs?

Scientist are at work: a valid target is to interfere with the spike proteins on the envelope of the virus (Wrapp et al., 2020). We may block viral entry and thus infection! The S protein mediates fusion of the viral and host cell membranes with subsequent release of the viral genetic material inside the host cell: it is a key target for vaccines, therapeutic antibodies and diagnostics.

There are 3 important steps of viral entry that can be challenged:

1) The S protein has to be cleaved in its S1 and S2 subunits.
2) The S1subunit binds to a host cell receptor. Covid-19 binds very well to angiotensin-converting enzyme 2 (ACE2).
3) The S2 subunit is the one really involved in the fusion process. It is activated after S1 binds to the receptor and contains the so-called fusion peptide, which is the one, in fact performing the fusion of the two membranes. (Figure 3A).

Acting on these steps, it is possible to block the virus activity and scientists are studying the three dimensional structure of spike proteins to guide and develop vaccines or antivirals (Figure 3B).

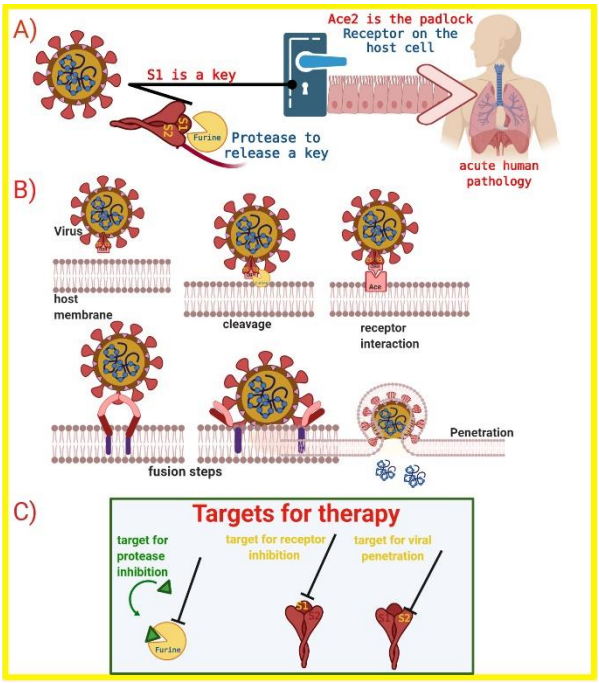

Figure 3 A) Key steps for virus infection B) Receptor interaction and membrane penetration steps C) Some of the therapeutical targets

Conclusion

The study of nature and its phenomena, will provide you the keys of the knowledge, your safest protection!

References

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