

The ACE2 Receptor - Factor of Morbidity and Mortality in COVID-19 Epidemic

D Popov*

CPET Unit, Clinique La Pinède, Perpignan, France

***Corresponding Author:** D Popov, CPET Unit, Clinique La Pinède, Perpignan, France.

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‘Crossing the species barrier - one small step to man, one giant leap to mankind’ Mark Klempner and Daniel Shapiro (NEJM 2004).

Recent events, such as the reports of cases of avian influenza and monkeypox in humans and the outbreak of severe acute respiratory syndrome (SARS), bring this distinction into sharp focus. Many infectious diseases cross the species barrier.

Many virus infections across species barriers are dead ends for the viruses, as no transmissions to further individuals occur, but sometimes a virus adapts to enable transmission from host to host. A virus may have to undergo one or more adaptations in order for it to:

- Replicate in the new host;
- Evade immune responses of the new host;
- Transmit to other individuals of the new host.

That crossing is not the focus of interest here, it’s obvious that is the case. The question is related to the host - is it any difference in the host receptors and binding sites of the causing pathogen, and is any predisposition linked to gene polymorphism [2,3,9] in different geographic regions and populations?

Human coronaviruses (HCoVs) were first described in the 1960s for patients with the common cold. Since then, more HCoVs have been discovered, including those that cause severe acute respiratory syndrome (SARS 2003) and Middle East respiratory syndrome (MERS 2012), two pathogens that, upon infection, can cause fatal respiratory disease in humans. It was recently discovered that dromedary camels in Saudi Arabia harbor three different HCoV species, including a dominant MERS HCoV lineage that was responsible for the outbreaks in the Middle East and South Korea during 2015. In this review we aim to compare and contrast the different HCoVs with regard to epidemiology and pathogenesis, in addition to the virus evolution and binding in the host, events which have, on occasion, resulted in outbreaks amongst humans.

Coronaviruses (CoVs), of the family Coronaviridae, are enveloped viruses with a single-strand, positive-sense RNA genome approximately 26 - 32 kilobases in size, which is the largest known genome for an RNA virus. The term ‘coronavirus’ refers to the appearance of CoV virions when observed under electron microscopy, in which spike projections from the virus membrane give the semblance of a crown, or corona in Latin. All coronaviruses share similarities in the organization and expression of their genome, in which 16 nonstructural proteins (nsp1 through nsp16), encoded by open reading frame (ORF) 1a/b at the 50 end, are followed by the structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N), which are encoded by other ORFs at the 30 end. CoVs are separated into four genera based on phylogeny: alpha-CoV (group 1), beta-CoV (group 2), gamma-CoV (group 3) and delta-CoV (group 4) (<http://ictvonline.org/proposals/2008.085-122 V.v4.Coronaviridae>). Within the beta-CoV genus, four lineages (A, B, C and D) are recognized. Distinct from other beta-CoV lineages, lineage A viruses also encode a smaller protein called hemagglutinin esterase (HE), which is functionally similar to the S protein [1].

On the face of it SARS is a respiratory tract disease, but in many patients the infection spread to other parts of the body. Diarrhoea developed in some patients and the virus was shed in the faeces and urine for several weeks [6]. Actually, The SARS 2003 is eradicated and

the novel 2019 CoV is named COVID-19 [14]. The World Health Organization declared severe acute respiratory syndrome contained on 5 July 2003. The outbreak at 2012 of MERS is unhappily not eradicated thus far.

The causative agent was found to be a new coronavirus. The natural reservoir for the SARS coronavirus has been found - Horseshoe bats and transmitted to humans by civets, but coronaviruses with very similar genome sequences were isolated from animals sold in markets in the region of China where the first SARS cases appeared. In some parts of its range Asian palm civets are hunted for bush meat and the pet trade. In southern China it is extensively hunted and trapped. Antibodies to these viruses were found in many workers in the markets, but none of the workers had any history of SARS. A similar virus has also been isolated from several bat species. It is likely that coronaviruses have repeatedly crossed into humans from other mammalian species, but in the majority of cases the virus has lacked the ability for efficient human-to-human transmission. It would seem that the SARS coronavirus evolved from a rare virus that had this ability [10,11].

In Guangdong Province markets, the virus was isolated from palm civets, a meat- and fruit-eating mammal with a cat-like appearance that was sold for meat. SARS-CoV was also isolated from civet meat (*Paradoxurus hermaphroditus*) from a restaurant that employed a worker that had contracted SARS. Although the palm civets were the most likely source of SARS-CoV in this outbreak, much higher rates of SARS-CoV were found in palm civets from local markets as compared to palm civets (*Paguma larvata*) on distant farms. This suggested that the palm civets themselves may have contracted SARS-CoV from another animal source while in the market. The virus has also been identified in horseshoe bats, the likely natural reservoir of this zoonosis [11].

The CoV 2019 outbreak was not brought under control by quarantine measures, and there had been over 65000 cases with nearly 1500 deaths until now. The SARS-CoV 2019 is known as COVID-19, for distinction from the as yet eradicated and contained 2003 SARS-CoV.

SARS-CoV (betacoronavirus, lineage B) - Patients infected with SARS-CoV initially present with fever, myalgia, headache, malaise, and chills, followed by a nonproductive cough, dyspnea, and respiratory distress generally 5 to 7 days later, which may result in death (<https://www.who.int/csr/sars/en/WHOconsensus.pdf>). Other notable features in some cases include infection of the gastrointestinal tract, liver, kidney, and brain. Diffuse alveolar damage, epithelial cell proliferation, and an increase in macrophages is seen in SARS-CoV infection of the lung. Lymphopenia, hemophagocytosis in the lung, in addition to white-pulp atrophy of the spleen observed in SARS patients, are similar to fatal H5N1 influenza virus infections [7]. Evidence for the presence of this virus includes identification in bronchoalveolar-lavage fluid in three patients by whole-genome sequencing, direct RT- real time PCR, and culture. The illness likely to have been caused by this COVID-19 was named "novel coronavirus-infected pneumonia" (NCIP) [11]. A massive intrapulmonary right-to left shunt occurs with organizing pneumonia and crazy paving CT pattern, typically needing MV, prone position or ECMO, despite all, with eventually fatal outcome [13].

A carboxypeptidase, ACE2, cleaves one amino acid from the carboxyl terminal to convert AngII to Ang(1-7). ACE2 may also convert Ang I to Ang(1-9), which is then converted to Ang(1-7) by ACE, neprilysin, and endopeptidases (Santos, 2014). ACE2 contains a single catalytic domain that is 42% identical to the two catalytic domains of ACE. Ang II is the preferred substrate for ACE2, with 400-fold higher affinity than Ang I.

Angiotensin-converting enzyme 2 is not inhibited by the standard ACE inhibitors and has no effect on bradykinin. Reduced expression or deletion of ACE2 is associated with hypertension, defects in cardiac contractility, and elevated levels of Ang II. Inhibition of AT1 receptors by ARBs increases the expression of ACE2. Overexpression of the ACE2 gene decreases blood pressure and prevents Ang II-induced cardiac hypertrophy in hypertensive rats [2,3,8].

ACE2 is protective against diabetic nephropathy through the Ang(1-7)/Mas receptor pathway Ang(1-9), which is generated from Ang I by ACE2, may also have vasodilating and protective effects by activating AT2 receptors In addition, ACE2 metabolizes Apelin peptides, serves as a receptor for the SARS CoV and COVID-19, and has been reported to interact with and regulate amino acid transporters (Figure 1).

Severe high mortality rates are thought to be caused by a lung receptor in 16% of Chinese who are absent in European and African populations - 0% - namely - SARS-CoV binds to ACE2 receptor in lungs, highly expressed in Asians. Left on the graph below figure 2 [2,8].

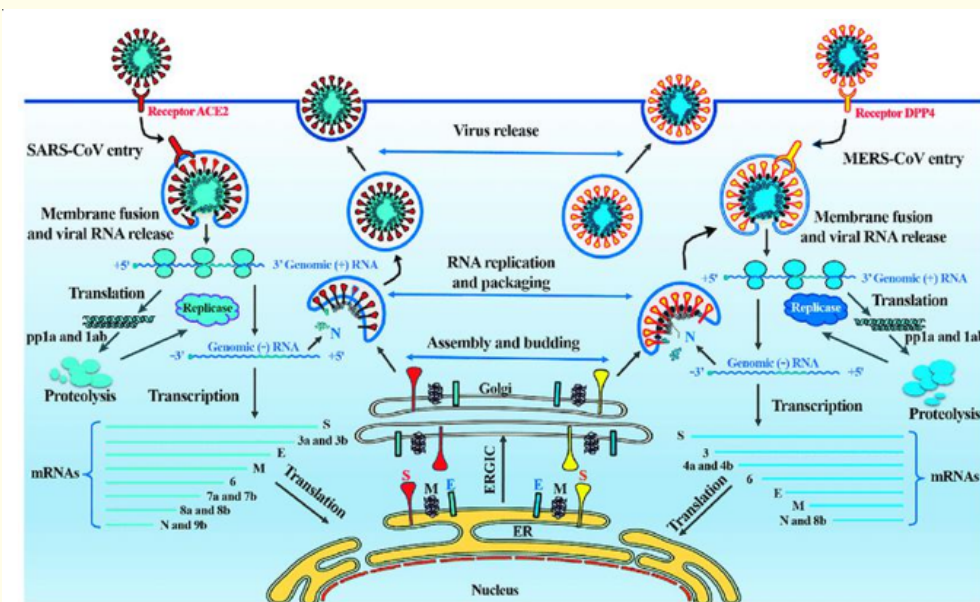


Figure 1: Source [16].

Phylogenetic analysis and homology modelling of the receptor-binding domain of the 2019-nCoV, SARS-CoV, and MERS-CoV(A) (Figure 2).

The star highlights 2019-nCoV and the question marks means that the receptor used by the viruses remains unknown. Structural comparison of the receptor-binding domain of SARS-CoV (B), 2019-nCoV (C), and MERS-CoV (D) binding to their own receptors. Core subdomains are magenta, and the external subdomains of SARS-CoV, 2019-nCoV, and MERS CoV are orange, dark blue and green, respectively. Variable residues between SARS-CoV and 2019-nCoV in the receptor-binding site are highlighted as sticks [2,3].

Just for comparison, MERS-CoV binds to Dipeptidyl peptidase-4 (DPP4), also known as adenosine deaminase complexing protein 2 or CD26. It is also found on the surface of cells in the airways and kidneys.

It is unlikely for now that, if the hypothesis is confirmed, the coronavirus will turn into a severe pandemic outside China and the Far East. There will be no worldwide pandemic. However, 16% of Chinese are seriously affected. ACE2, angiotensin converting enzyme 2 plays a major role in the spread of the infection, with the virus binding to ACE2 receptors in the lung.

There have been conflicting studies as to which population, what expression of ACE2 is present. 16% of Chinese have a polymorphism [3,9] especially well expressed in SE China, which both Europeans and Africans do not have, and makes them susceptible to several categories of respiratory and cardiac diseases [8]. In Europe, the prevalence is zero.

Worldwide Polymorphism Distribution: China, Europe, Africa: None of Europeans have this polymorphism (dangerous version - in brown and green on the graph in the link below). For precision, the ers6632677 polymorphism also makes its carriers susceptible to some respiratory and heart disease (Figure 2 and 3-SNPedia).

The virus is likely to attack “successfully” mainly people with this polymorphism, and others will not become infected and become ill more easily. Lastly, the mistake is true - Europeans are significantly less threatened by the coronavirus than the Chinese, with the most threatened being people from Southeast China, where the mutation is most common. distribution schedules are from: <https://www.snpedia.com/index.php/Rs6632677>.

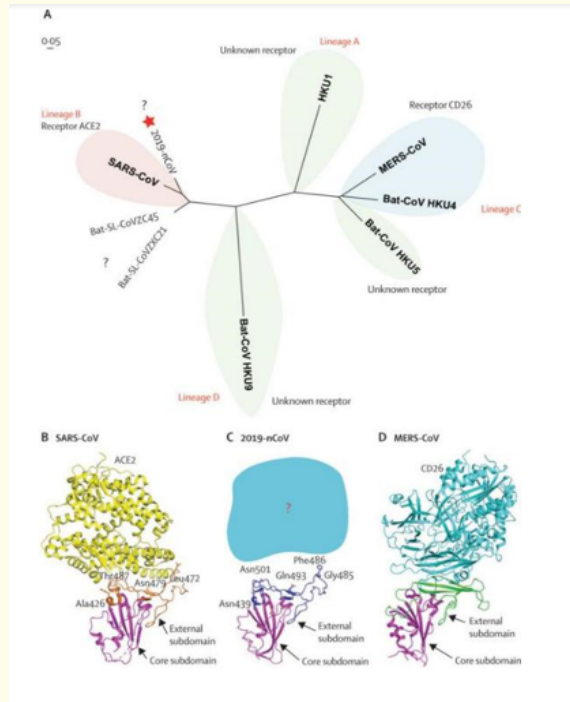


Figure 2: Source [1].

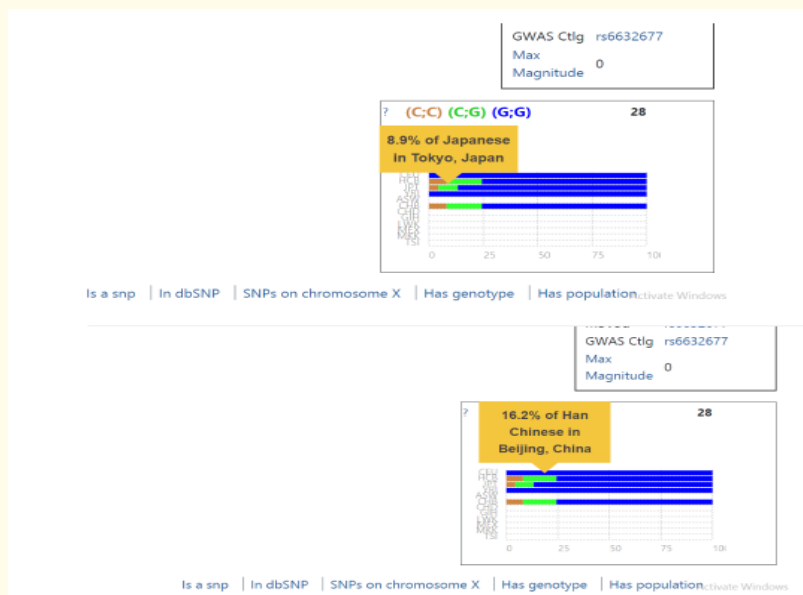


Figure 3

A worldwide pandemic is unlikely. The ACE2 systems of Chinese and Europeans are different. It does not mean that Europeans are protected by the virus - they are not. just makes a pandemic in Europe like the one in Wuhan, significantly less likely.

The receptor-binding domain of betacoronaviruses, which directly engages the receptor, is commonly located in the C-terminal domain of S1, as in SARS-CoV29 for lineage B, and MERS-CoV30, 31 and BatCoV HKU4,32 for lineage C. Through phylogenetic analysis of the receptor-binding domain of four different lineages of betacoronaviruses, is found that, although 2019-nCoV, from now on COVID-19, was closer to bat-SL-CoVZC45 and bat-SL-CoVZXC21 at the whole-genome level, the receptor-binding domain of 2019-nCoV fell within lineage B and was closer to that of SARS-CoV.

This analysis suggested that, like other betacoronaviruses, the receptor-binding domain was composed of a core and an external subdomain. Notably, the external subdomain of the 2019-nCoV receptor-binding domain was more similar to that of SARS-CoV. This result suggests that 2019-nCoV also use angiotensin-converting enzyme 2 (ACE2) as a cell receptor which expression is far more frequent in SE Asia. However, is also observed that several key residues responsible for the binding of the SARS-CoV receptor-binding domain to the ACE2 receptor were variable in the 2019-nCoV receptor-binding domain (including Asn439, Asn501, Gln493, 485 and Phe486; 2019-nCoV numbering).

There are seven coronaviruses known to infect people. Four of them-229E, NL63, OC43, and HKU1-typically cause a cold and only rarely result in death. The other three-MERS-CoV, SARS-CoV, and the new SARS-CoV-2, COVID-19-have varying degrees of lethality. In the 2003 SARS outbreak, 10 percent of infected people died. The the virus binds to the ACE-2 receptor on human cells in order to gain entry. This receptor is present in ciliated epithelial cells in the upper and lower airway, as well as in type II pneumocytes, which reside in the alveoli in the lower airway and produce lung-lubricating proteins. The type II pneumocytes are very important for lung function, so this is part of why the lower respiratory disease can be so severe.

In figure 4 [19] are shown the data of variant distribution and AFs may contribute to the further investigations of ACE2, including its roles in acute lung injury and lung function [12]. The East Asian populations have much higher AFs in the eQTL variants associated with higher ACE2 expression in tissues (Figure 1c), which may suggest different susceptibility or response to 2019-nCoV/SARS-CoV-2 from different populations under the similar conditions.

Schematics of 32 coding variants in ACE2 identified in the ChinaMAP and 1KGP databases. Yellow stars indicate the nonsense variants; dots indicate the missense variants. The number of samples with hotspot variants was marked. b The distribution of hotspot missense mutations of ACE2 in different populations. The colors indicate different populations. c The distribution and the allele frequencies of representative eQTL variants for ACE2 in different populations. Pie charts depict the allele frequencies of an intron variant of ACE2 (rs4646127) in the world. Orange color denotes the frequency of alteration allele, and blue color denotes the reference allele. The allele frequencies of 15 eQTLs for ACE2 gene are shown in tables. The color gradient from blue to red indicates the increasing of allele frequencies. The allele frequencies of INDEL variant rs200781818 were annotated by the gnomAD database. EAS, East Asian; EUR, European; AFR, African; SAS, South Asian; AMR, Ad Mixed American.

The best way to combat coronaviruses staying on common surfaces, such as glass, metal, and plastic, is by cleaning them with a solution that's 62 percent to 72 percent ethanol, 0.5 percent hydrogen peroxide, or 0.1 percent sodium hypochlorite within one minute of contamination.

In February 2020 the nature of the 2019-nCoV outbreak is still slowly coming into focus but it appears to be acting more like bad pandemic influenza (efficient spread, overall lower mortality) than like SARS (less efficient spread, overall higher mortality [12]. The former type of spread especially outside Asia, the latter mostly in SE regions of the Asian continent.

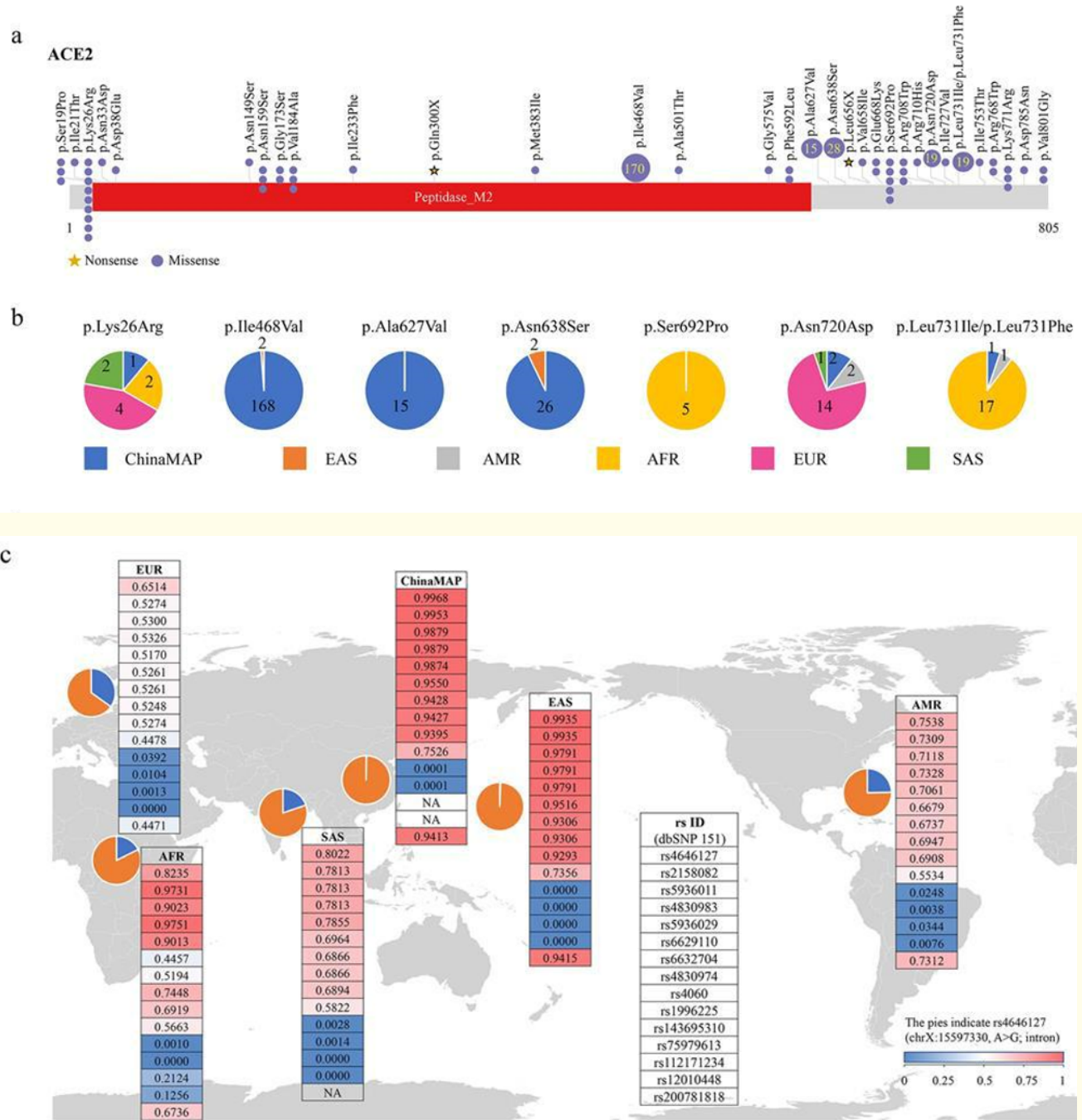


Figure 4: The coding-region variants and eQTL variants for ACE2 in East Asian and other populations [19]. AF – allele frequency.

From: <https://www.nature.com/articles/s41421-020-0147-1> Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations [19].

MERS might be treated with interferon B-1b/ribavirin, and COVID-19 experimentally with remdesivir, Gilead - (or lopinavir/ritonavir - Kaletra, potential second candidate for cure) successful IV application of remdesivir In Toulouse Medical Faculty, Pr Denis Malvy (France). Complete remission with reduced viral lung load and no residual RT-PCR viral traces were obtained. Remdesivir (GS-5734) is a nucleotide prodrug that has broad antiviral activity against viruses from different families in vitro, and therapeutic efficacy in nonhuman primate models of lethal Ebola virus and Nipah virus infection. Studies in human airway epithelial cells showed that remdesivir also inhibits replication of a wide range of coronaviruses, including COVID-19 and MERS-CoV [15]. Chloroquine 500 mg/d for 10 days showed high efficacy against COVID-19 and began its use in certain centers treating RT-PCR confirmed CoV cases.

Two more acronyms enter the stage - R0 and CFR. One quantity scientists use to measure how a disease spreads through a population is the “basic reproduction number,” otherwise known as R0. This number tells us how many people, on average, each infected person will in turn infect. While it doesn’t tell us how deadly an epidemic is, R0 is a measure of how infectious a new disease is and helps guide epidemic control strategies implemented by governments and health organizations.

Another important number for understanding diseases is the “case fatality rate” or CFR: What percentage of people who have a disease die from it? On one extreme, we have rabies, which has a 99 percent fatality rate if untreated. On the other is the common cold, which has a relatively high R0 but is almost never fatal (the exceptions being mostly immunocompromised people). The seasonal flu has a low CFR, but enough people get it every year that the CDC estimates as many as 30,000 Americans may have died from it between October 2019 and February 2020. Influenza type A (H1N1) virus.

Similarly, measles is extremely infectious, but rarely fatal (though its spooky effect on the immune system can make victims susceptible to other life-threatening diseases). Smallpox was less infectious with an R0 of 5 to 7, but its CFR of roughly 30 percent made it devastating. Measles, though less serious, has such a high infection rate that it needs a much larger vaccinated population for proper herd immunity; smallpox vaccines achieved herd immunity at much lower rates, and wiped the illness out entirely by 1980.

If R0 is less than 1, the disease will typically die out: Each infected person has a low chance of passing the infection along to even one additional individual. An R0 larger than 1 means each sick person infects at least one other person on average, who then could infect others, until the disease spreads through the population. For instance, a typical seasonal flu strain has an R0 of around 1.2, which means for every five infected people, the disease will spread to six new people on average, who pass it along to others.

Measles is a champion disease in this respect. Its R0 is usually cited between 12 and 18, meaning each person with measles infects between 12 and 18 new people in an unvaccinated population. In the era before widespread vaccination, measles could easily sicken an entire school’s worth of children.

On January 23, the World Health Organization met to discuss whether the virus constitutes a global public health emergency (not yet, they concluded). Their scientists presented data that showed an R0 of 1.4 to 2.5.

This report from Imperial College London on January 25 estimates an R0 of 2.6 [17].

A worldwide pandemic is unlikely, hoping that isn’t solely a bold conjecture. The ACE2 systems of Chinese and Europeans are different. It does not mean that Europeans are protected by the virus - they are not. Just makes a pandemic in Europe like the one in Wuhan, significantly less likely. Thus, the ACE2 receptor might be the Coronavirus disease 2019 (COVID-19) epidemic’s high-impact factor, which modify the R0 and CFR for the Chinese population. For the rest, the epidemic is of mostly of fear, without any ground for the moment.

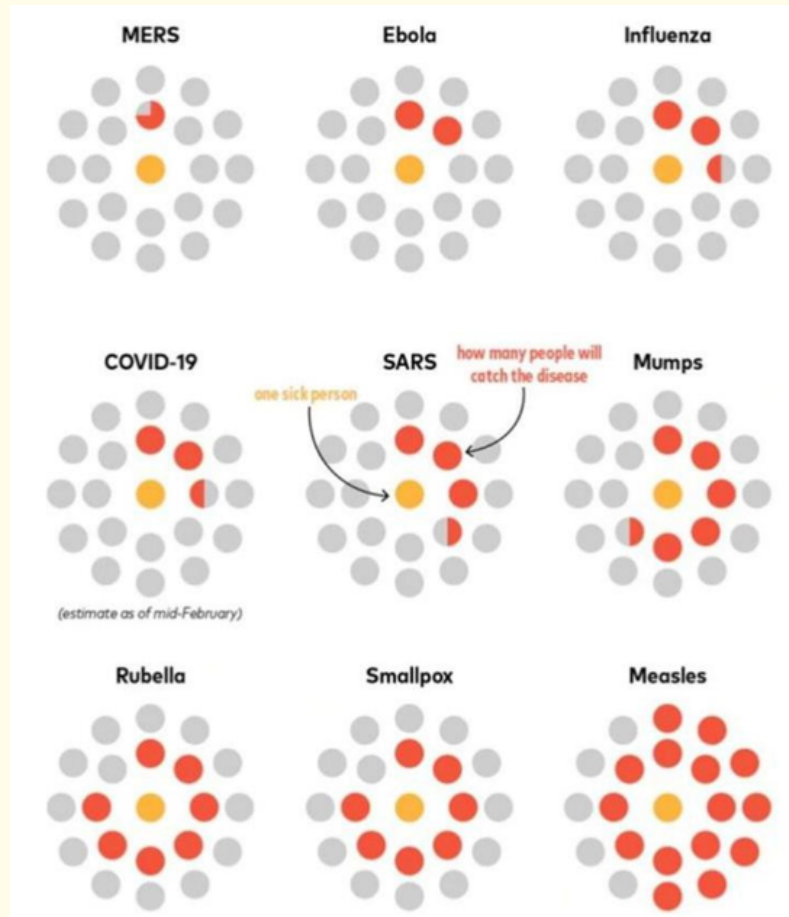


Figure 5: R0 illustrated.

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