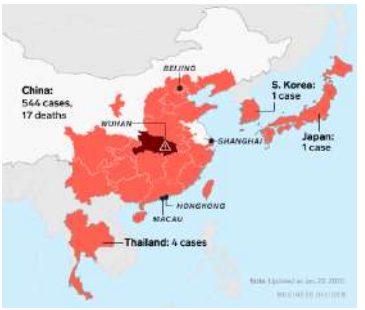
Understanding of COVID-19 based on current evidence

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

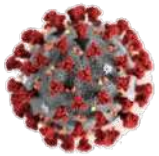
- ✓ Introduction
- ✓ Sources of SARS-CoV-2
- ✓ Epidemiology
- ✓ Etiology & Pathogenesis
- ✓ Symptoms, & Diagnosis
- ✓ The case of infants & children
- ✓ The case of mother & fetus
- ✓ The case of Italy
- ✓ Treatment
- ✓ Prevention
- ✓ Conclusions

The sequence of the events



- Since December 2019, there has been a series of unexplained cases of pneumonia reported in Wuhan, China.

- On 12 January 2020, the WHO named this new virus as the 2019 novel coronavirus (2019-nCoV).



- On 30 January 2020, WHO announced the 2019-nCoV epidemic a public health emergency of international concern.

- On 11 February 2020, the WHO formally named the disease triggered by 2019-nCoV as coronavirus disease 2019 (COVID-19).

- On the same day, the coronavirus study group of the International Committee on Taxonomy of Viruses named 2019-nCoV as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

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•On 12 J… as…

•O… epidemic a pu…

On 23 February 2020, there were 77 041 confirmed cases of SARS-CoV-2 infection in China. The number of infections has exceeded that of the SARS outbreak in China in 2002

severe acute respiratory syndrome

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As of 8 pm, 31 January 2020, > 20 pediatric cases have been reported in China, with an age of onset ranging from 112 days to 17 years.

•O
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Coronavirus: COVID-19 Is Now Officially a Pandemic, WHO says March 11, 2020 12:30 PM Eastern Time Zone

L'Eastern Standard Time è il fuso orario della costa orientale degli Stati Uniti d'America e del Canada

World Health Organization

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The sequence of the events

il 30 gennaio arriva la notizia dei primi due casi accertati anche in Italia:
si tratta di due turisti cinesi che sono stati ricoverati in isolamento all'ospedale Spallanzani.
L'Italia, annuncia il premier Conte, ha deciso di chiudere il traffico aereo da e per la Cina

The sequence of the events

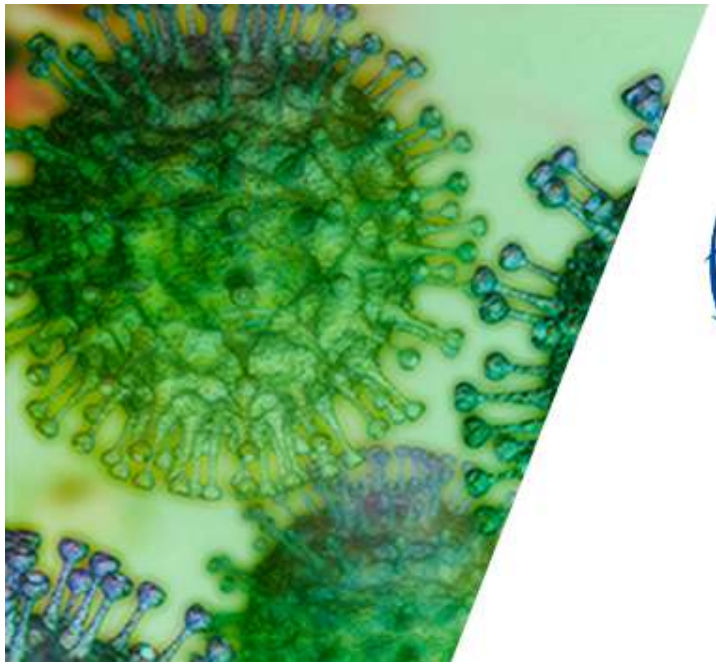
Tra il 21 e il 22 febbraio si registrano i primi contagi in Italia legati al Covid19.
L'emergenza investe anche il nostro Paese dove si registrano centinaia di casi positivi con i focolai maggiori nel Lodigiano e in Veneto. Si susseguono le riunioni fra il premier Conte, la Protezione civile e i ministri competenti. Il Cdm nella serata tra il 22 e il 23 febbraio vara un decreto per contrastare la trasmissione del Coronavirus

MARCH 20, 2020
COVID-19: Global death toll nears 10,000

According to the European Centre for Disease Prevention and Control (ECDC), since 31 December 2019 and as of 20 March 2020, 242 488 cases of COVID-19 have been reported, including 9 885 deaths.

The deaths have been reported from

- Italy (3 407),
- China (3 254),
- Iran (1 284),
- Spain (767),
- France (372),
- United States (150),
- United Kingdom (144),
- South Korea (100),
- Netherlands (76),
- Germany (43),
- Japan (33),
- Switzerland (33),



ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

QUOTIDIANO.NET
Coronavirus Italia, bollettino del 24 marzo.
Altri 743 morti.
Contadi, frena la crescita

- I casi totali sono 69,176, complessivamente 6,820 vittime (9.86%).
- Lombardia, 402 decessi in 24 ore.
- Emilia Romagna altri 719 casi, 93 nuovi morti.
- Bergamo, 1,800 trentenni con polmonite da coronavirus.
- In Italia possibili più contagi di quelli registrati

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Sources of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

- the early COVID-19 cases were related to the **Huanan seafood market**, and the possibility of human-to-human transmissions could not be ruled out.


- the SARS-CoV-2 is a chimeric virus between a **bat coronavirus** *and* **a coronavirus of unknown origin.**

- **snakes** are the most likely **wildlife repository** for the SARS-CoV-2.

- *the research by Benvenuto et al* showed that the SARS-CoV-2 was only closely related to the coronavirus isolated from Chinese **chrysanthemum-headed bats** in 2015.

Benvenuto D, The 2019-new coronavirus epidemic: evidence for virus evolution. J Med Virol. 2020. (Unit of Clinical Laboratory Science, University Campus Bio-Medico of Rome, Rome, Italy).


- their research supported the theory that **the transmission chain started from bats to humans.**

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> the current evidence strongly supports that the SARS-CoV-2 was derived from bats, although the **intermediate hosts of SARS-CoV-2 remain to be determined.**
> *Sun P, Understanding of COVID-19 based on current evidence. J Med Virol. 2020;10.1002*

evolution.

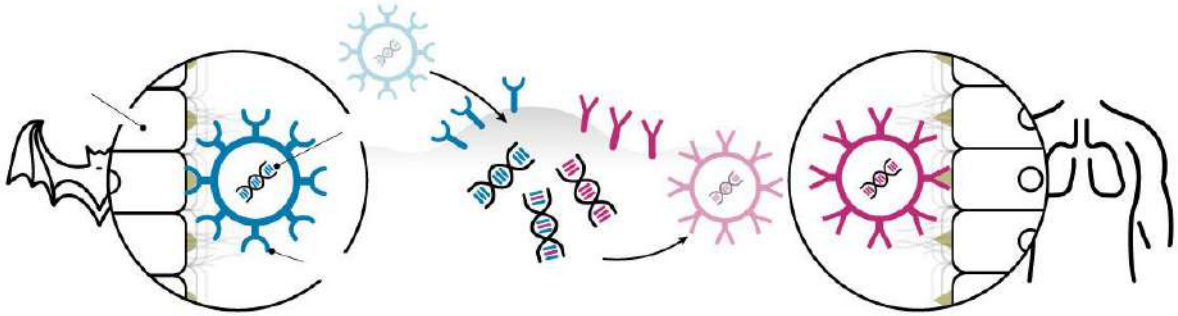

- their research supported the theory that the transmission chain started from bats to humans.

1

Proteins on the outer shell of the virus allow it to latch onto cells in the host's respiratory tract. The proteins' shapes are determined by the virus's genes

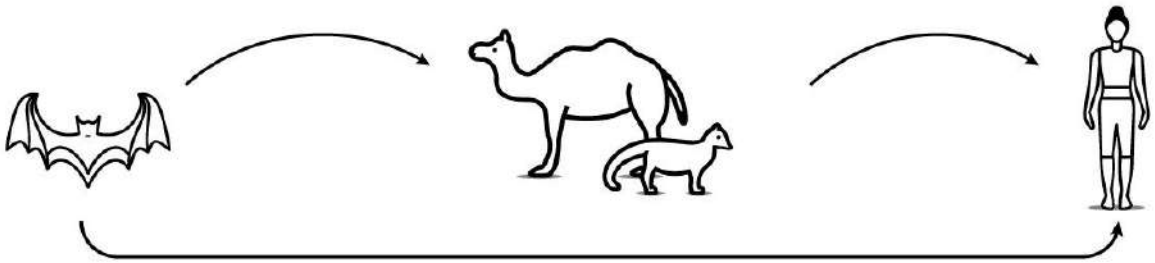
2

To infect new hosts, the virus's genes undergo mutations that alter its surface proteins, allowing them to latch onto the cells of new species.



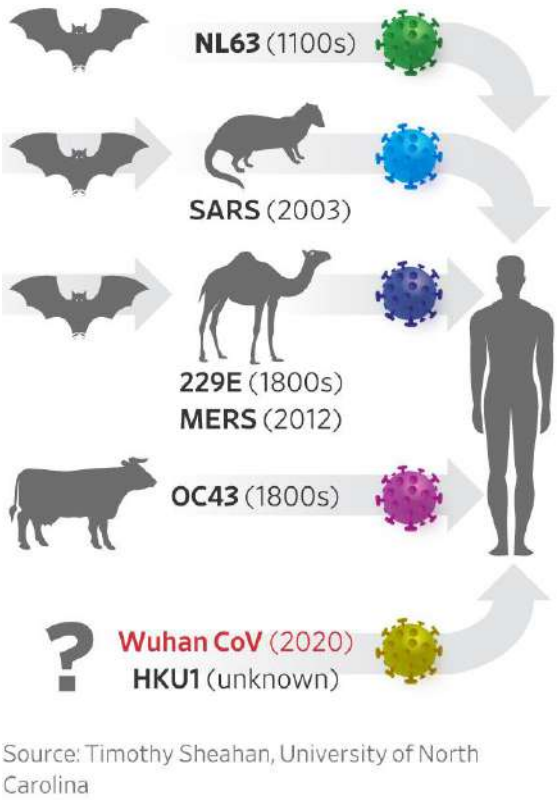
3

In the case of SARS, the virus jumped from bats to civet cats (zibetti / lontra) before gaining the ability to infect humans. In the case of MERS, camels served as the intermediate host.



4

Coronaviruses can also jump directly to humans, without mutating or passing through an intermediate species.



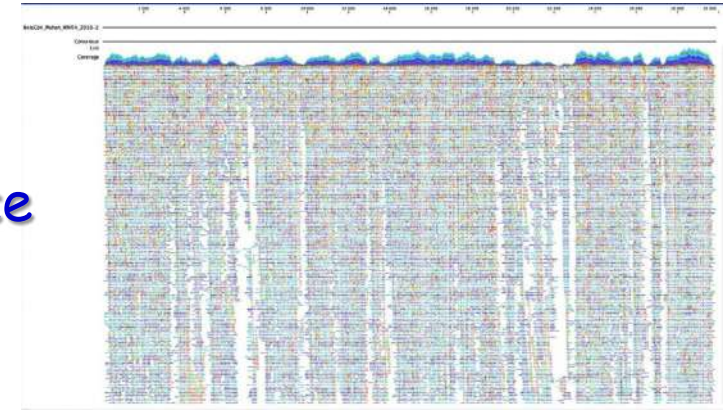
5

Researchers have found the novel coronavirus likely originated in bats, but haven't pinpointed the source of transmission to humans.

COVID-19 coronavirus epidemic has a natural origin

published today in the journal Nature Medicine Date:March 17, 2020

Source: Scripps Research Institute - La Jolla (California)

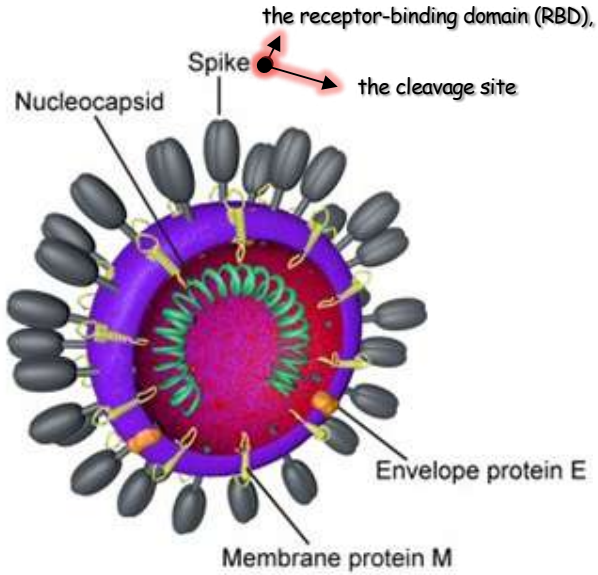


Summary:

•An analysis of public **genome sequence data** from SARS-CoV-2 and related viruses found **no evidence that the virus was made in a laboratory or otherwise engineered.**

•The scientists analyzed the genetic template for **spike proteins**, armatures on the outside of the virus that it uses to grab and penetrate the outer walls of human and animal cells.

•More specifically, they focused on 2 important features of the spike protein: **the receptor-binding domain (RBD)**, a kind of grappling hook that grips onto host cells, and **the cleavage site**, a molecular can opener that allows the virus to crack open and enter host cells.



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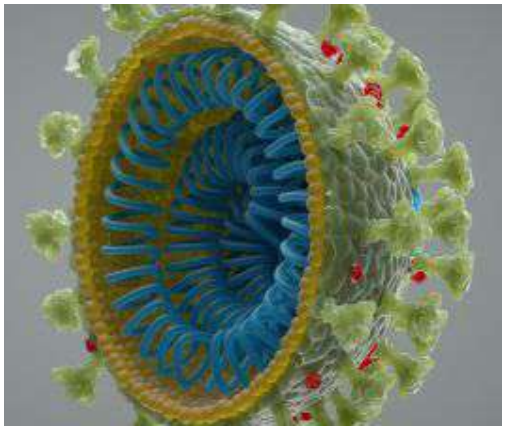

•This evidence for natural evolution was supported by data on SARS-CoV-2's backbone (spina dorsale) -- its overall molecular structure.

•If someone were seeking to engineer a new coronavirus as a pathogen, they would have constructed it from the backbone of a virus known to cause illness.

•But the scientists found that the SARS-CoV-2 backbone differed substantially from those of already known coronaviruses and mostly resembled related viruses found in bats and pangolins.

Il pangolino cinese
è un mammifero
dell'ordine dei Pholidota

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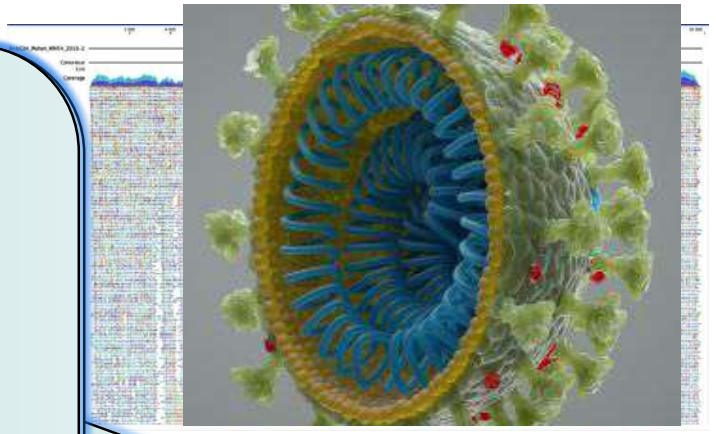
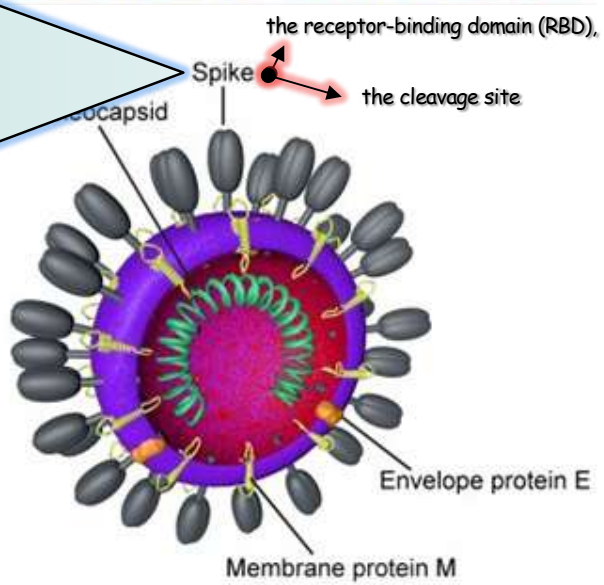
"These two features of the virus,
the mutations in the RBD portion of the spike protein and its distinct backbone,
rules out laboratory manipulation
as a potential origin for SARS-CoV-2".





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Possible origins of the virus

•Based on their genomic sequencing analysis, Andersen and his collaborators concluded that the most likely origins for SARS-CoV-2 followed one of two possible scenarios.

•*In one scenario,* the virus evolved to its current pathogenic state through natural selection in a non-human host and then jumped to humans.

•This is how previous coronavirus outbreaks have emerged, with humans contracting the virus after direct exposure to civets (zibetti) (SARS) and camels (MERS).

•The researchers proposed bats as the most likely reservoir for SARS-CoV-2 as it is very similar to a bat coronavirus.
There are no documented cases of direct bat-human transmission, however, suggesting that an intermediate host was likely involved between bats and humans.

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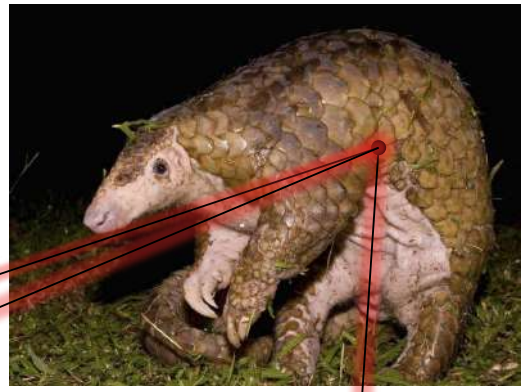
Possible origins of the virus

- *In the other proposed scenario*, a non-pathogenic version of the virus jumped from an animal host into humans and then evolved to its current pathogenic state within the human population.



- For instance, some coronaviruses from pangolins, armadillo-like mammals found in Asia and Africa, have a receptor-binding domain (RBD) structure very similar to that of SARS-CoV-2.

- A coronavirus from a pangolin could possibly have been transmitted to a human, either directly or through an intermediary host such as civets (zibetti) or ferrets (furetti).

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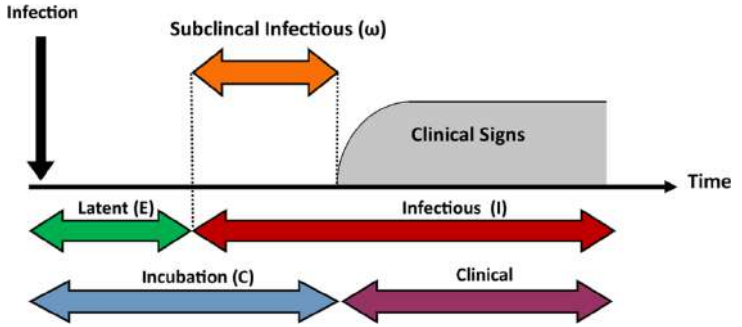
Epidemiological characteristics of COVID-19

Infection sources

- The main sources of the infection are patients infected by 2019-nCoV with or without clinical symptoms.
- Patients in the incubation period may also have potency to transmit the virus.



Transmission route

- The novel virus is spread through respiratory droplets when patients cough, talk loudly or sneeze.

- Close contact is also a source of transmission (e.g., contact with the mouth, nose or eye conjunctiva through contaminated hand).

- Transmission through mother–infant vertically or breast milk seems not to occur.

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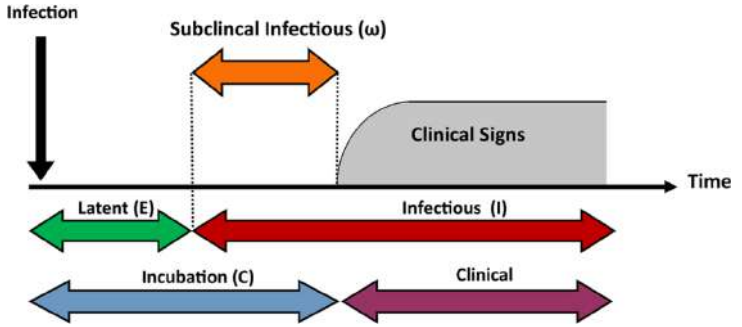
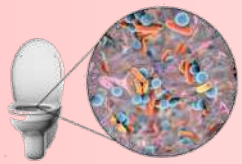


Transmission route

- T

Early GI Symptoms in COVID-19 May Indicate Fecal Transmission



Fecal-oral transmission may be part of the COVID-19 clinical picture, according to two reports published in *Gastroenterology*.

The researchers find that RNA and proteins from SARS-CoV-2, the viral cause of COVID-19, are shed in feces early in infection and persist after respiratory symptoms abate.

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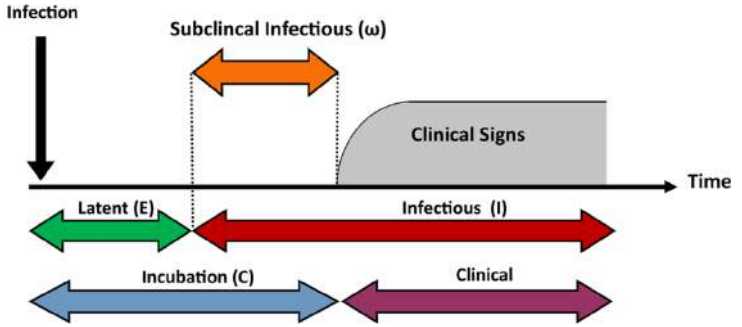


Transmission route

- T

FRIDAY, March 13, 2020 (HealthDay News)

How long can the coronavirus survive in the air and on certain surfaces like plastics?

Coronavirus can live in the air for up to 3 hours,
up to 4 hours on copper, up to 24 hours on cardboard and
up to 2 or 3 days on plastic and stainless steel.

Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1

van Doremalen N, March 17, 2020 DOI: 10.1056/NEJMc2004973

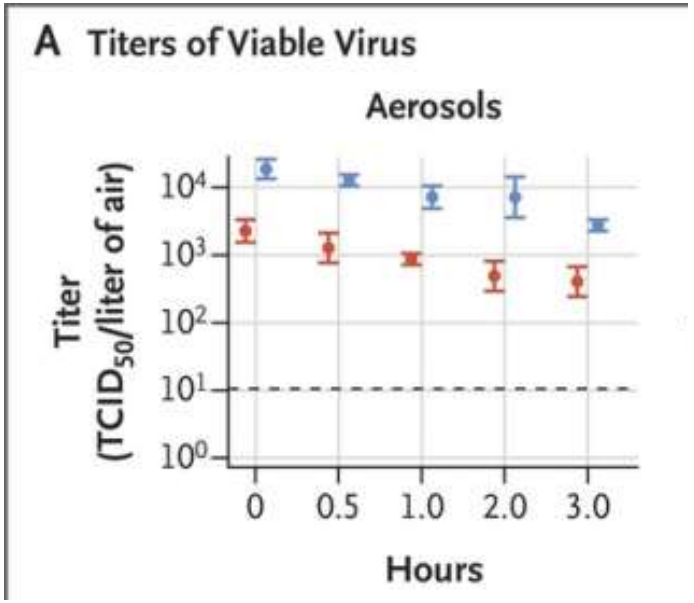
✓aerosol and and on various surfaces stability of SARS-CoV-2 and compared it with SARS-CoV-1, the most closely related human coronavirus.

✓5 environmental conditions:
- aerosols,
- plastic,
- stainless steel,
- copper, and
- cardboard.

✓tissue-culture infectious dose [$TCID_{50}$]

SARS-CoV-2 remained viable in aerosols throughout the duration of our experiment (3 hours), with a reduction in infectious titer from $10^{3.5}$ to $10^{2.7}$ $TCID_{50}$ per liter of air.

This reduction was similar to that observed with SARS-CoV-1, from $10^{4.3}$ to $10^{3.5}$ $TCID_{50}$ per milliliter



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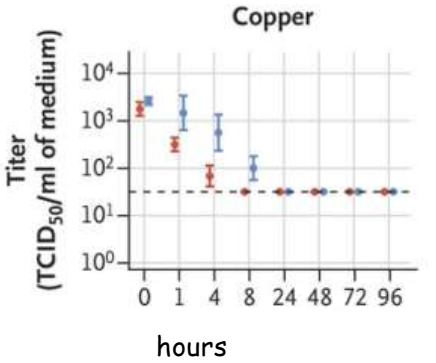
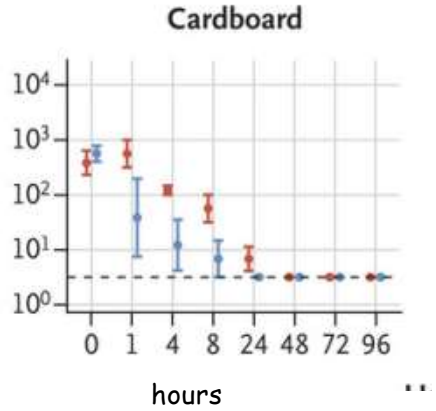
❑On copper,
no viable SARS-CoV-2
was measured after 4 hours
and
no viable SARS-CoV-1
was measured after 8 hours.



❑On cardboard,
no viable SARS-CoV-2
was measured after 24 hours
and
no viable SARS-CoV-1
was measured after 8 hours



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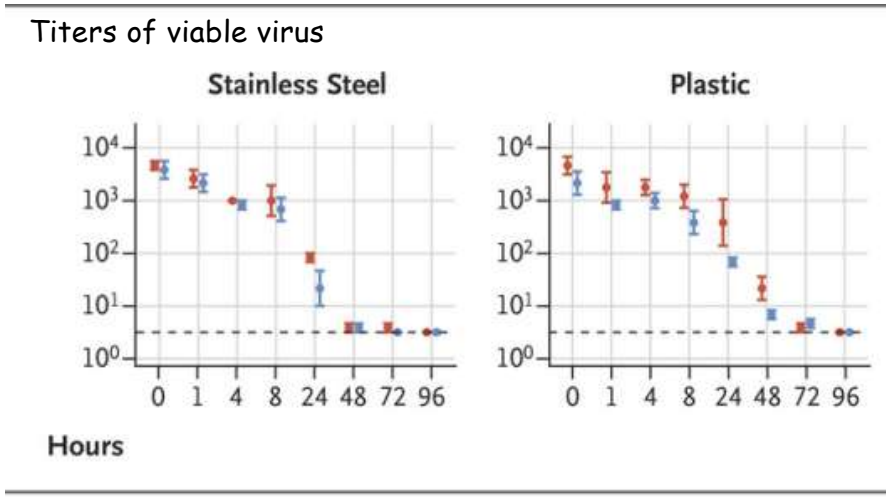
- aerosols,
- plastic,
- stainless steel,
- copper, and
- cardboard.

✓tissue-culture infectious dose [$TCID_{50}$]

SARS-CoV-2 was more stable on plastic and stainless steel than on copper and cardboard, and viable virus was **detected up to 72 hours after application to these surfaces**,

although the virus titer was greatly reduced (from $10^{3.7}$ to $10^{0.6}$ $TCID_{50}$ per milliliter of medium after 72 hours on plastic and from $10^{3.7}$ to $10^{0.6}$ $TCID_{50}$ per milliliter after 48 hours on stainless steel).



SARS-CoV-1

Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1

van Doremalen N, March 17, 2020 DOI: 10.1056/NEJMc2004973

- We found that the stability of SARS-CoV-2 was similar to that of SARS-CoV-1 under the experimental circumstances tested.

- This indicates that differences in the epidemiologic characteristics of these viruses probably arise from other factors, including:
  - high viral loads in the upper respiratory tract and
  - the potential for persons infected with SARS-CoV-2 to shed and transmit the virus while asymptomatic.

- Our results indicate that aerosol and fomite* transmission of SARS-CoV-2 is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces up to days (depending on the inoculum shed).

*transmission of infectious diseases by objects.

Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents.

Kampf G, J Hosp Infect. 2020;104(3):246-251.

✓persistence of human and veterinary coronaviruses on inanimate surfaces

✓inactivation strategies with biocidal agents used for chemical disinfection, e.g. in healthcare facilities.

✓22 studies

❑Severe Acute Respiratory Syndrome (SARS) coronavirus,
Middle East Respiratory Syndrome (MERS) coronavirus or
endemic human coronaviruses (HCoV)
can persist on inanimate surfaces like metal, glass or plastic for up to 9 days,

but

❑can be efficiently inactivated by surface disinfection procedures with

- 62-71% ethanol,
- 0.5% hydrogen peroxide (acqua ossigenata) or
- 0.1% sodium hypochlorite within 1 minute.

Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents.

Kampf G, J Hosp Infect. 2020;104(3):246-251.

Other biocidal agents such as 0.05-0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective.

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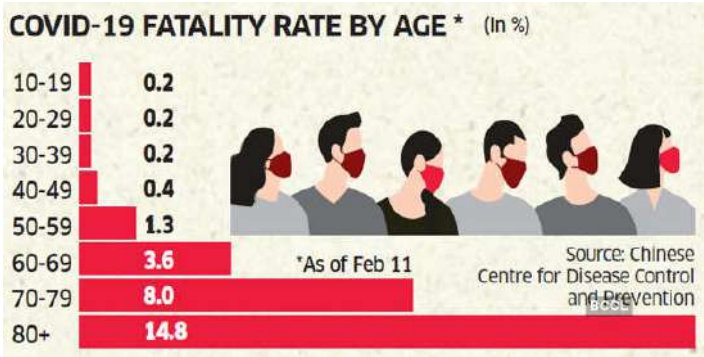
Epidemiological characteristics of COVID-19

- from January 10 to 24, 2020, the number of people diagnosed with the SARS-CoV-2 infection in China increased by 31.4 times (in 2 weeks).

- on 23 February 2020 (1 month later), the number of people diagnosed with COVID-19 in China was 1879 times of that on 10 January 2020.

- They estimated the case fatality rate of COVID-19 to be 2.84% based on their patient pool.



- the ratio of male to female deaths was 3.25:1,
- the median age of death was 75 years,
- the median time from the first symptom to death was 14 days,
- the median time from early symptoms to death in people aged 70 or older (11.5 days) was shorter than that in people under 70 years old (20 days).

Wang W, Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J Med Virol. 2020.

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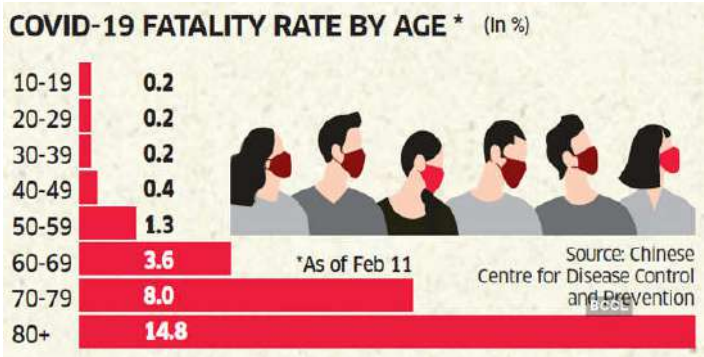
- on 23 February 2020 (1 month later), the number of people diagnosed with COVID-19 in China was 1879 times of that on 10 January 2020.

Females, generally, mount more robust immune responses to viral challenges than males, which can result in more efficient virus clearance in relation to female hormones.



- the ratio of male to female deaths was 3.25:1,
- the median age of death was 75 years,
- the median time from the first symptom to death was 14 days,
- the median time from early symptoms to death in people aged 70 or older (11.5 days) was shorter than that in people under 70 years old (20 days).

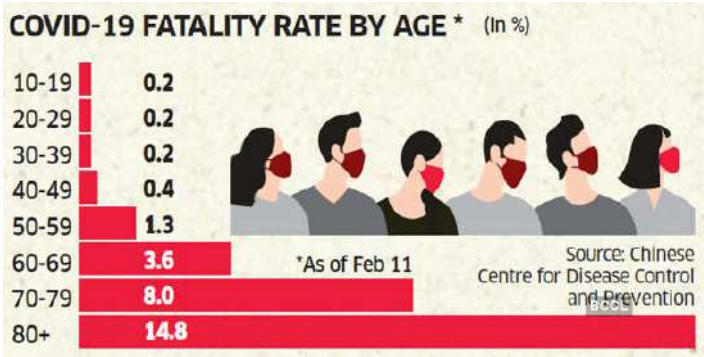
Wang W, Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J Med Virol. 2020.

Epidemiological characteristics of COVID-19

- from January 10 to 24, 2020, the number of people diagnosed with the SARS-CoV-2 infection in China increased by 31.4 times (in 2 weeks).

- on 23 February 2020 (1 month later), the number of people diagnosed with COVID-19 in China was 1879 times of that on 10 January 2020.

These findings suggest the disease may progress faster in the elderly than in the young.



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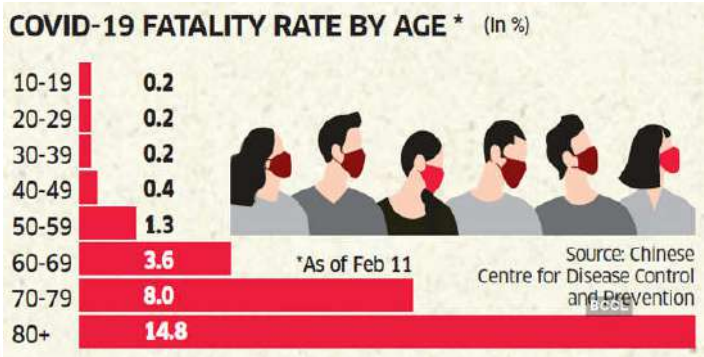

The fatality rate is higher (15%) in patients with underlying diseases, including diabetes, hypertension, and cardiovascular disease.

*Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;**395**:497-506*

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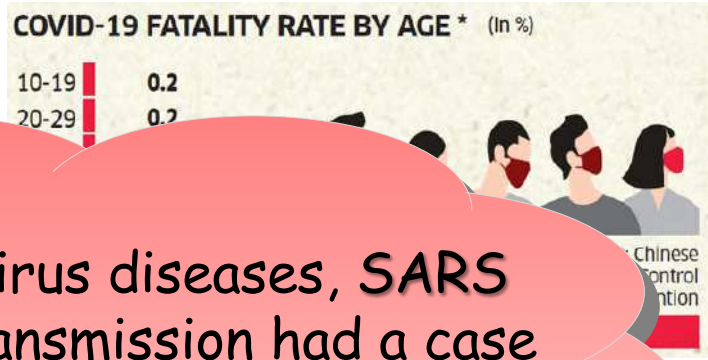

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Wang W, Upda (2019-nCoV) in Wuhan, China. J Med Virol. 2020.

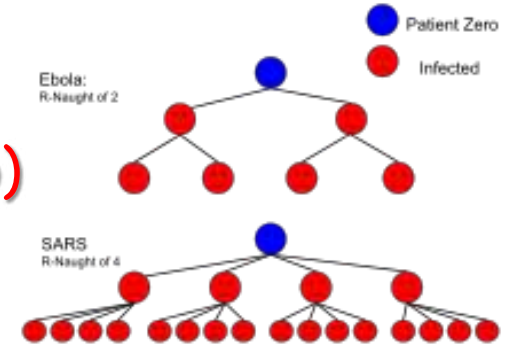
the other two major zoonotic coronavirus diseases, SARS and MERS which caused widespread transmission had a case fatality rates of 9.6% and 35%, respectively.

Hui DS, The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health–the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264-266.

Epidemiological characteristics of COVID-19

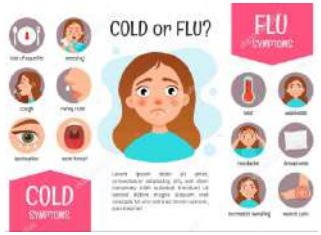
In the study of Li Q, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020:NEJMoa2001316.

- the median age of 425 patients infected with SARS-CoV-2 was 59 years, of which 56% were males,
- the average incubation period was 5.2 days, (ranges 2 - 14 days).
- almost half of the adult patients were 60 years old or older.
- In the early stages, the number of infected patients doubled every 7.4 days.
- The transmission rate of individual infected patients (Ro) ranges between **2.2** and 3.77 in different studies, with the 2.2 more in line with the current situation.



Different epidemiological characteristics between COVID-19 and SARS-CoV.

- COVID-19 replicates efficiently in the upper respiratory tract and appears to cause less abrupt onset of symptoms than SARS, similar to conventional human coronaviruses that are a major cause of common colds in the winter season.



- Infected individuals produce a large quantity of virus in the upper respiratory tract during a prodrome period, are mobile, and carry on usual activities, contributing to the spread of infection.

- By contrast, transmission of SARS-CoV did not readily occur during the prodromal period when those infected were mildly ill, and most transmission is thought to have occurred when infected individuals presented with severe illness, thus possibly making it easier to contain the outbreaks SARS-CoV caused, unlike the current outbreaks with COVID-19.

- *Heymann DL, Shindo N; WHO Scientific and Technical Advisory Group for Infectious Hazards. COVID-19: what is next for public health?. Lancet. 2020;395(10224):542-545.*

COVID-19 spreading from person to person

- Presently COVID-19 seems to spread from person to person by the same mechanism as other common cold or influenza viruses—ie,
  - face to face contact
  - with a sneeze or cough,
    or from
  - contact with secretions of people who are infected.

  - faecal–oral transmission
    was found to occur during the SARS outbreak
    and recently determined also in COVID-19

Ong SWX, Tan YK, Chia PY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient JAMA. 2020;10.1001/jama.2020.3227.

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  - contact with secretions
  - faecal–oral transmission was found to occur during and recently determined a

➢Covid19 was found in:
- air outlet fans,
- toilet sites (toilet bowl, sink, and door handle),

➢Postcleaning samples were negative, suggesting that current decontamination measures are sufficient.

Ong SWX, Tan YK, Chia PY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient JAMA. 2020;10.1001/jama.2020.3227.

Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding.

Xu, Y., Nat Med (2020). https://doi.org/10.1038/s41591-020-0817-4

- We report epidemiological and clinical investigations on 10 pediatric SARS-CoV-2 infection cases confirmed by realtime reverse transcription PCR assay of SARS-CoV-2 RNA.

- **Symptoms in these cases were nonspecific** and no children required respiratory support or intensive care.

Nearly Asymptomatic Children

- **Chest X-rays lacked definite signs of pneumonia**, a defining feature of the infection in adult cases.

- Notably, 8 children persistently tested positive on rectal swabs even after nasopharyngeal testing was negative, raising the possibility of fecal–oral transmission.

Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding.

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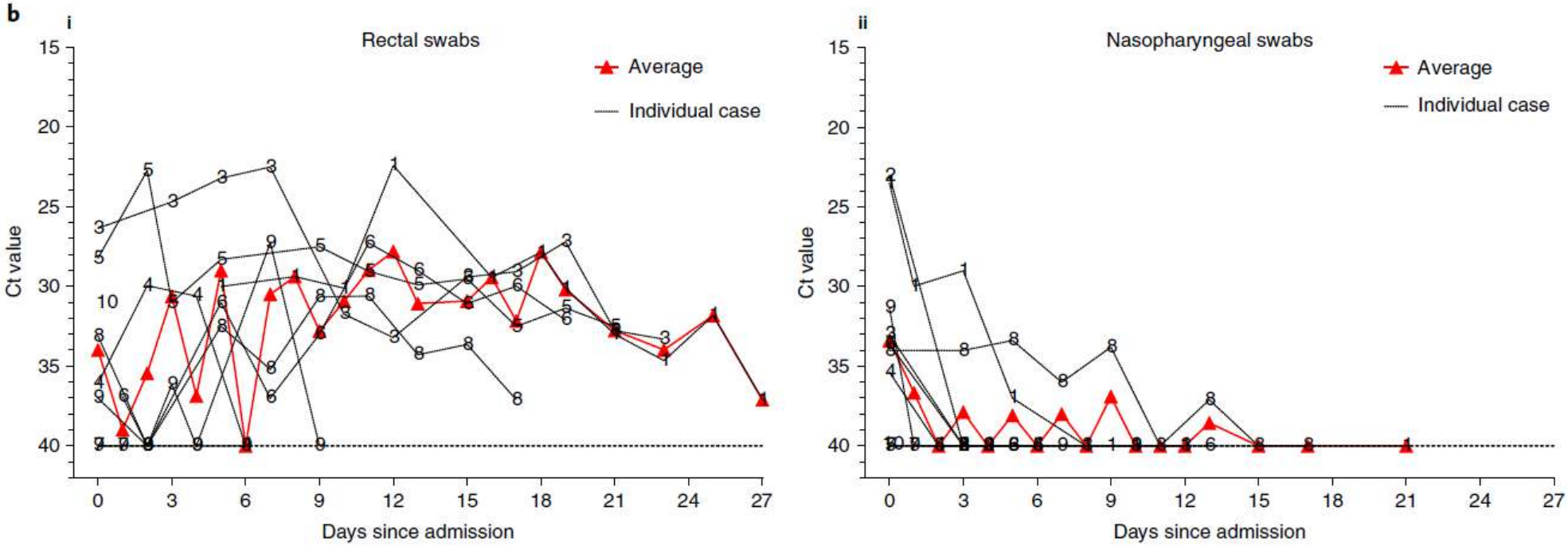
Chronological changes in cycle threshold (Ct) values of the serial rectal and nasopharyngeal swab tests to approximately indicate viral.
Ct values of *Orf1ab and N genes using real-time RT-PCR after hospital admission.*



Viral RNA measurements suggest that viral shedding from the digestive system might be greater and last longer than that from the respiratory tract

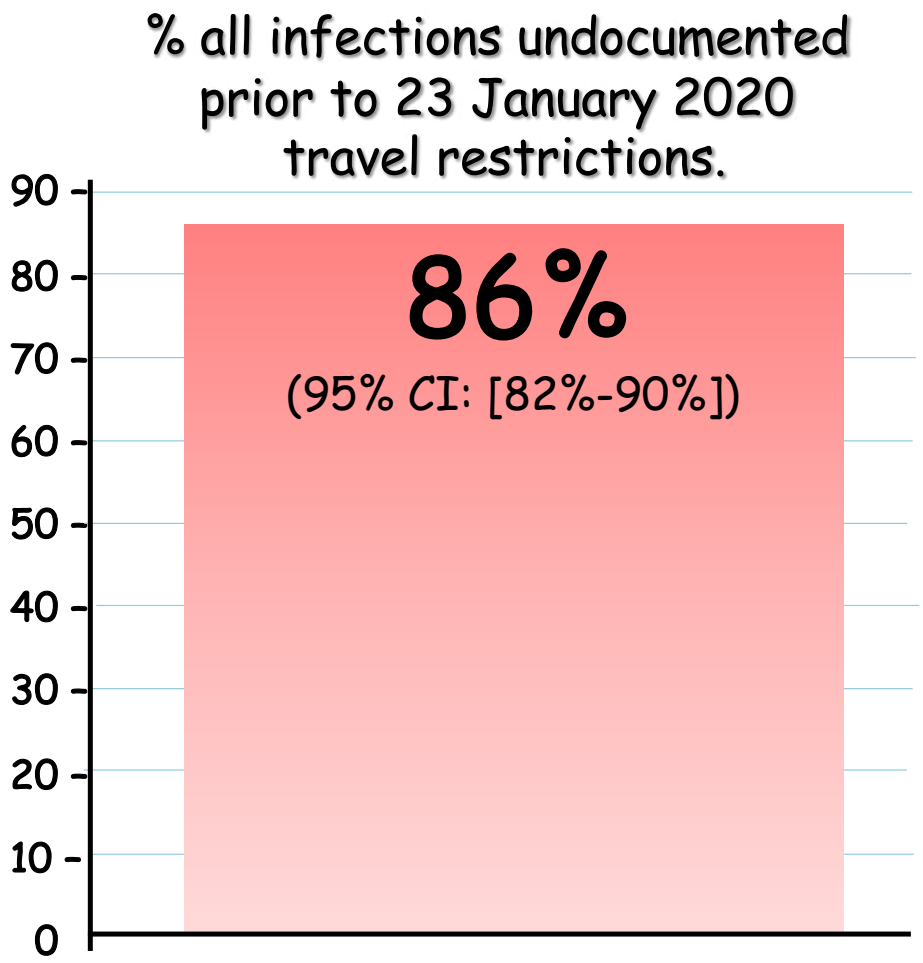
Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2).

Li R, Science. 2020;eabb3221

✓reported infection within China, in conjunction with mobility data,

✓a networked dynamic metapopulation model and Bayesian inference,

✓to infer critical epidemiological characteristics associated with SARS-CoV2,



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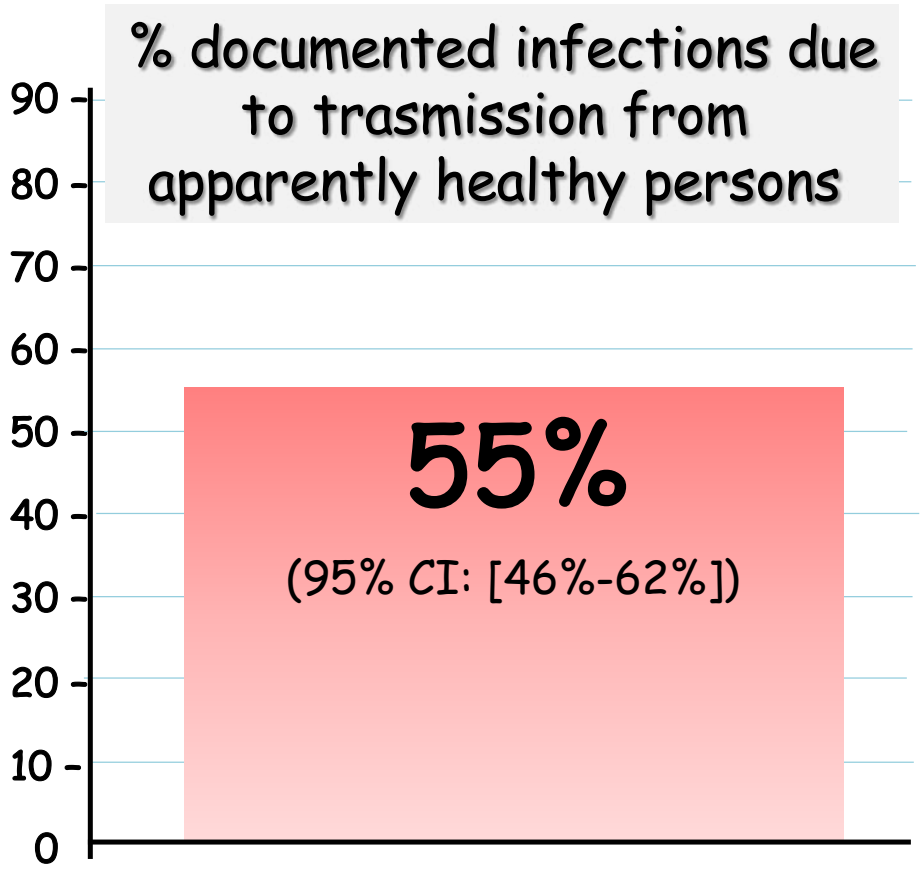

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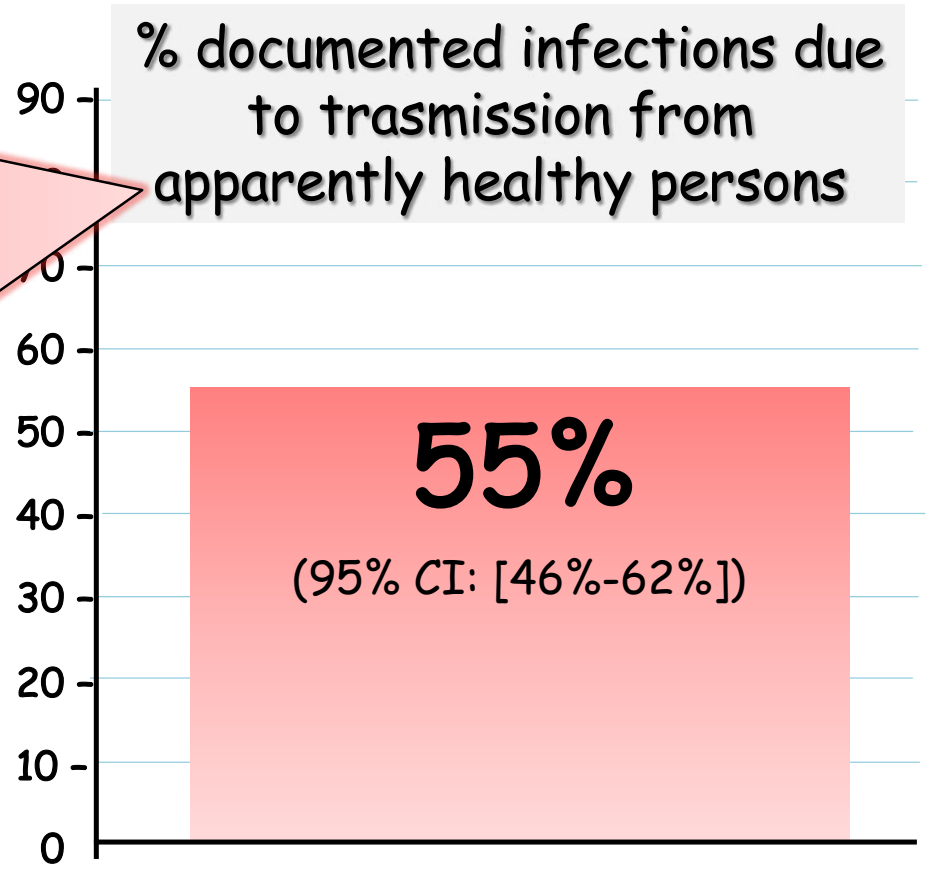
Li R, Science. 2020;eabb3221

due to their greater numbers, undocumented infections were the infection source for **79%** of documented cases.



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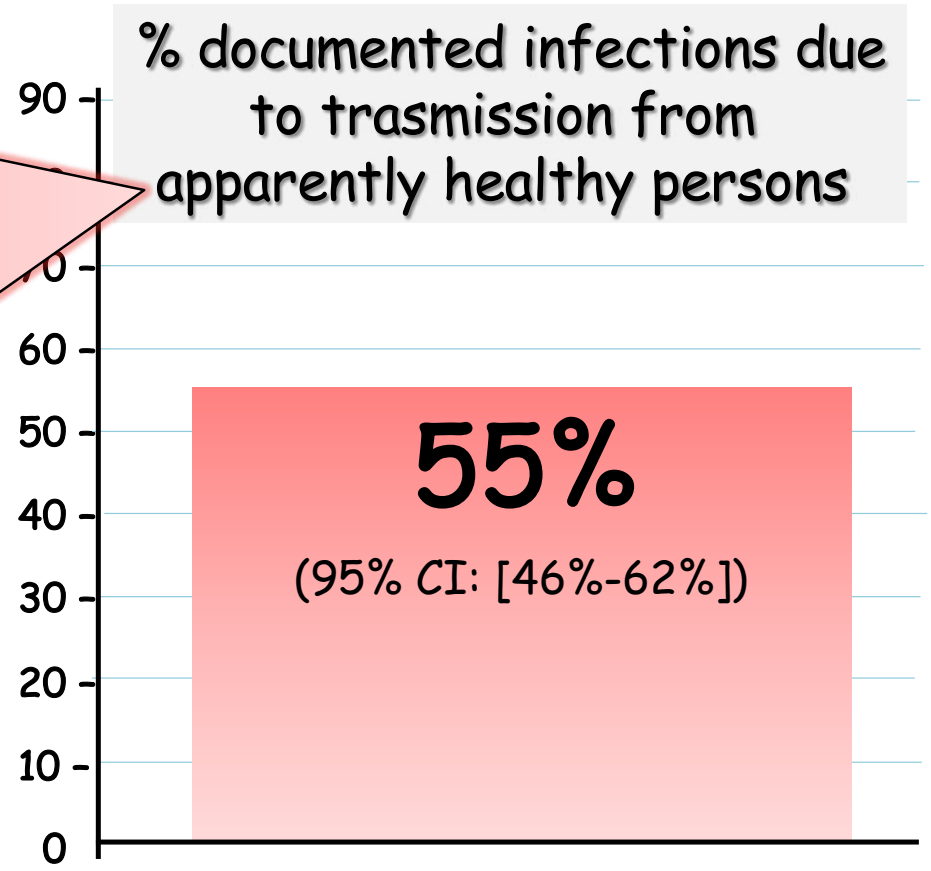
Li R, Science. 2020;eabb3221

These findings explain the **rapid geographic spread of SARS-CoV2** and indicate containment of this virus will be particularly challenging.

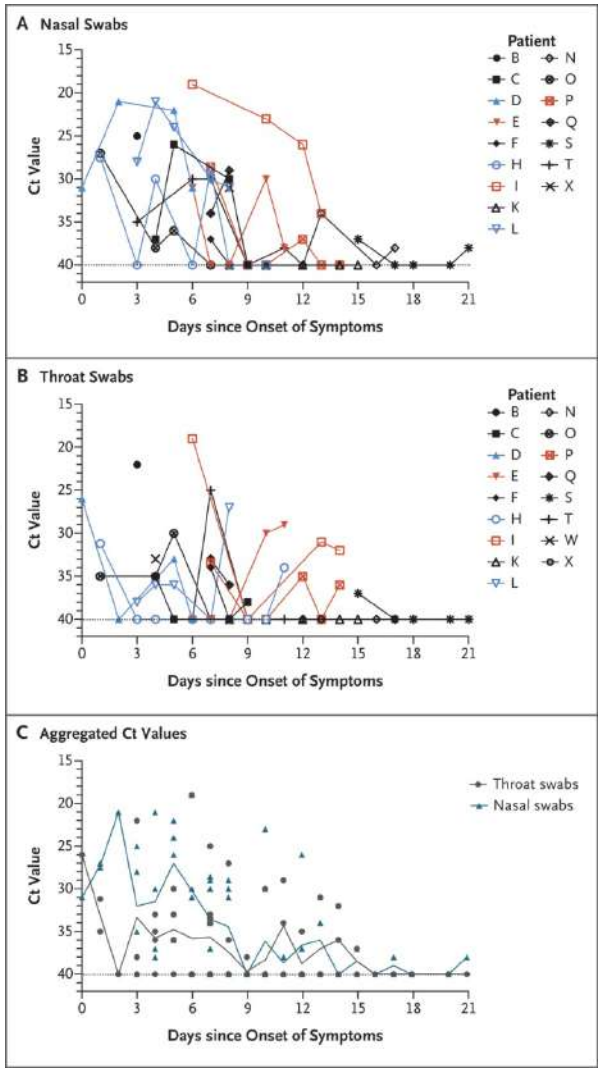


SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.

Lirong Zou, N Engl J Med 2020; 382:1177-1179

✓ARS-CoV-2 viral loads in upper respiratory specimens obtained from 18 patients including 4 patients with secondary infections (1 of whom never had symptoms) within two family clusters

➢Higher viral loads (inversely related to Ct value) were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat.



Viral Load Detected in Nasal and Throat Swabs Obtained from Patients Infected with SARS-CoV-2.

Patients with cases who had severe illness (Patients E, I, and P) are labeled in red, patients with cases who had mild-to-moderate illness are labeled in black, and patients with secondary cases by close contacts (Patients D, H, and L) are labeled in blue.

SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.

Lirong Zou, N Engl J Med 2020; 382:1177-1179

- Transmission of SARS-CoV occurred mainly after days of illness and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset when patients were symptomatic.

- Our analysis suggests that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza and appears different from that seen in patients infected with SARS-CoV where disease was transmitted only by patients with symptoms.

- In Covid-19 the viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients.

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- Case detection and isolation may require strategies different from those required for the control of SARS-CoV

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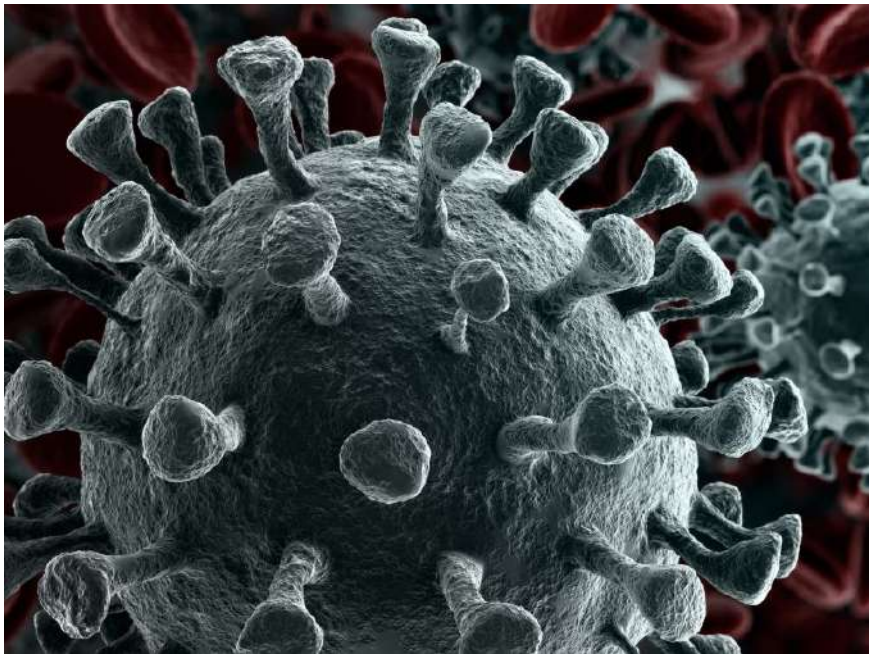
Why Is Coronavirus Spreading Rapidly?

Undetected cases may be driving coronavirus spread, study finds.



- About 86% of COVID-19 cases in China were milder and went undetected during the two-week ramp-up of the epidemic in January, prior to the country imposing travel restriction.

- These undocumented cases of infection are "about half as infectious per person as a documented case who has more severe symptoms and may be shedding more.

- However, "because there are many more of these undocumented cases, it's the undocumented infections that are driving the spread and growth of the outbreak.

Chinazzi M, The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak Science. 2020;eaba9757.

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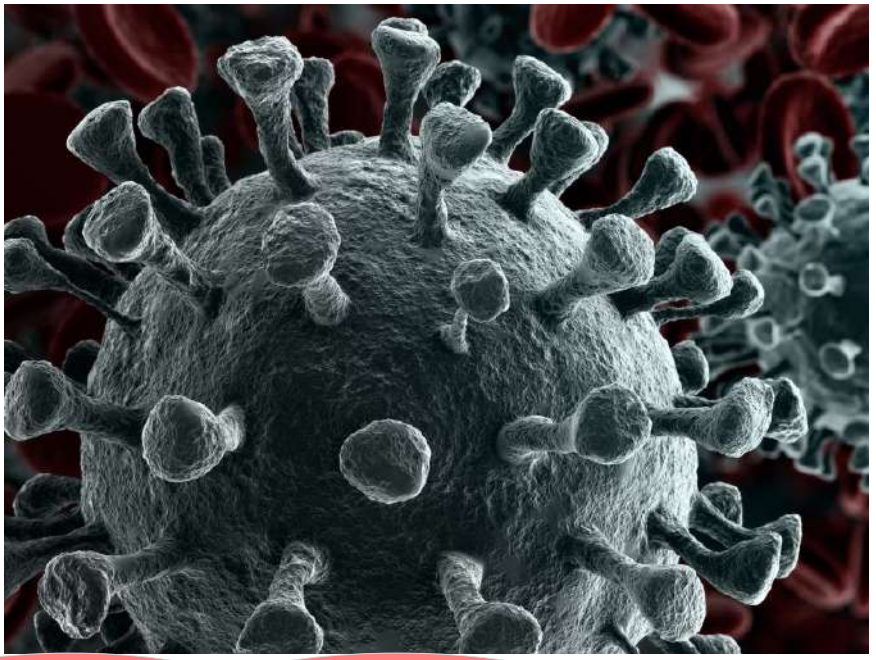

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a significant amount of the coronavirus' spread is fueled by "silent transmission."

Chinazzi M, The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak Science. 2020;eaba9757.

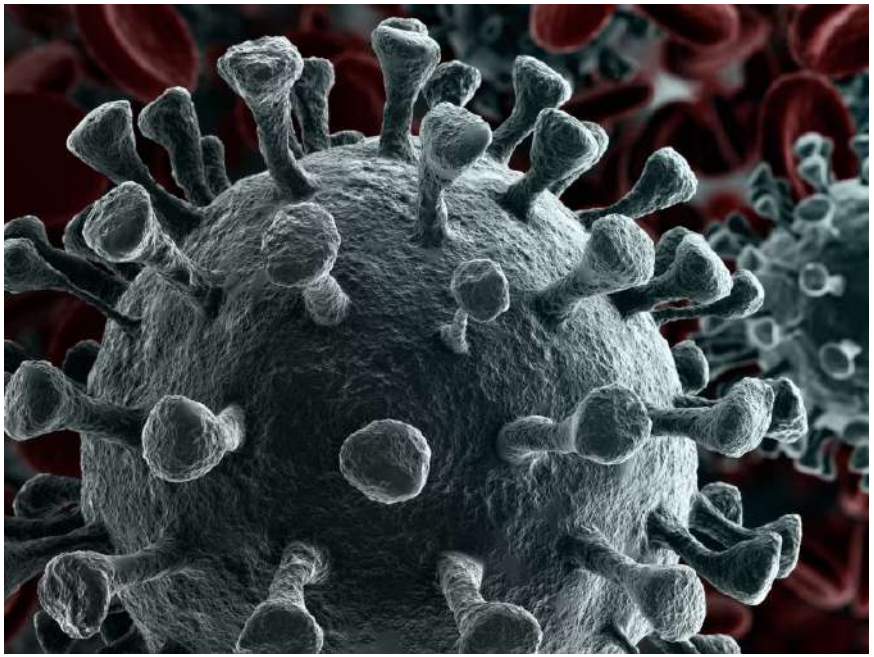
Why Is Coronavirus Spreading Rapidly?

Undetected cases may be driving coronavirus spread, study finds.

"If somebody is experiencing
mild symptoms
we're still going to go about our day."

"We'll still send the kids to school.

We'll still go to work. If we have a little bit of a headache or slight fever, we might take some ibuprofen and still go out shopping and whatnot."



Mobile phone data have shown that it's that sort of continued contact with people that allows the silent transmission of many respiratory viruses."

Rao ASRS, Vazquez JA. Identification of COVID-19 Can be Quicker through Artificial Intelligence framework using a Mobile Phone-Based Survey in the Populations when Cities/Towns Are Under Quarantine. Infect Control Hosp Epidemiol. 2020; Mar 3: 1–18.

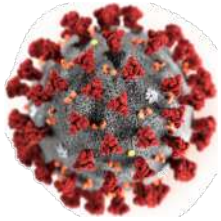
Understanding of COVID-19 based on current evidence

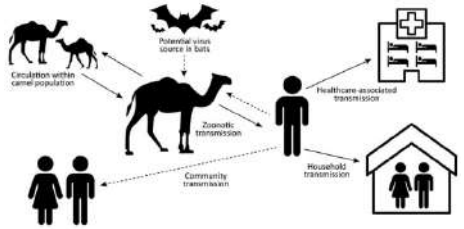
Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

- ✓ Introduction
- ✓ Sources of SARS-CoV-2
- ✓ Epidemiology
- ✓ Etiology & Pathogenesis
- ✓ Symptoms, & Diagnosis
- ✓ The case of infants & children
- ✓ The case of mother & fetus
- ✓ The case of Italy
- ✓ Treatment
- ✓ Prevention
- ✓ Conclusions

Etiology

- 2019-nCoV is a novel human coronavirus in addition to coronavirus
  - 229E,
  - NL63,
  - OC43,
  - HKU1,





  - Middle East respiratory syndrome-related coronavirus (MERSr-CoV) and
  - severe acute respiratory syndrome-related coronavirus (SARS-CoV).

- 2019-nCoV is enveloped single-stranded plus stranded RNA virus with a diameter of 60–140 nm, spherical or elliptical in shape and pleomorphic.

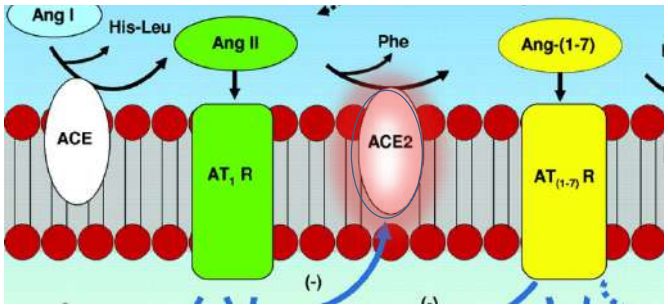
nm =nanometro = un miliardesimo di metro, pari ad un milionesimo di millimetro

- It has been reported that the consistency of whole genome-wide nucleotide sequences of 2019-nCoV with SARS-like coronavirus in bats (bat-SL-CoVZC45) (bat-SL-CoVZC45) ranges from 78 to 89%.

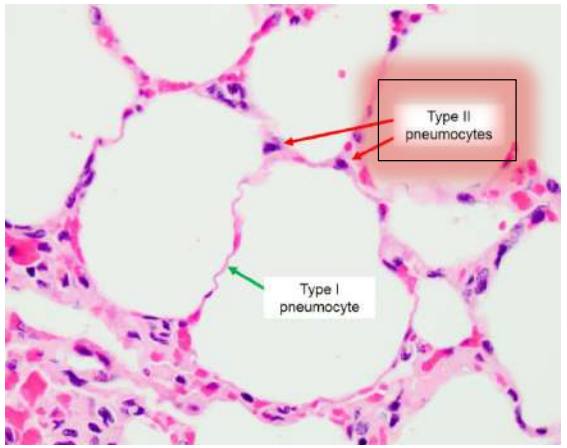
Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

Mechanism of COVID-19

ACE = enzima di conversione dell'angiotensina



➢ *Zhao et al* found that
•angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2.
Zhao Y, Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. bioRxiv. 2020.



•In the normal human lung, ACE2 is expressed on type I and II alveolar epithelial cells.

•Among them, 83% of the type II alveolar cells have ACE2 expression.

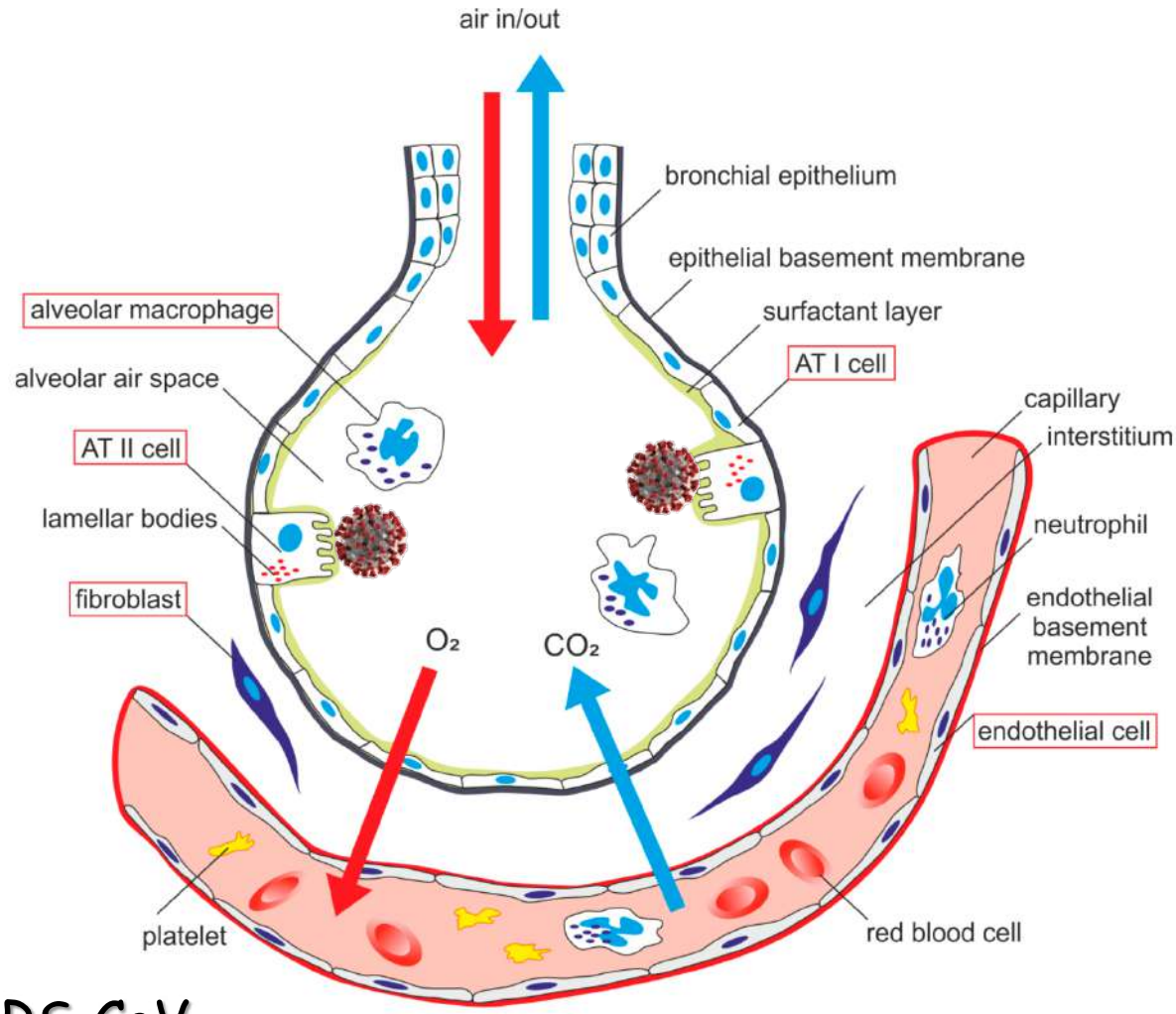
•Men had a higher ACE2 level in their alveolar cells than women.

•Asians have a higher level of ACE2 expression in their alveolar cells than the White and African American populations.

Mechanism of COVID-19

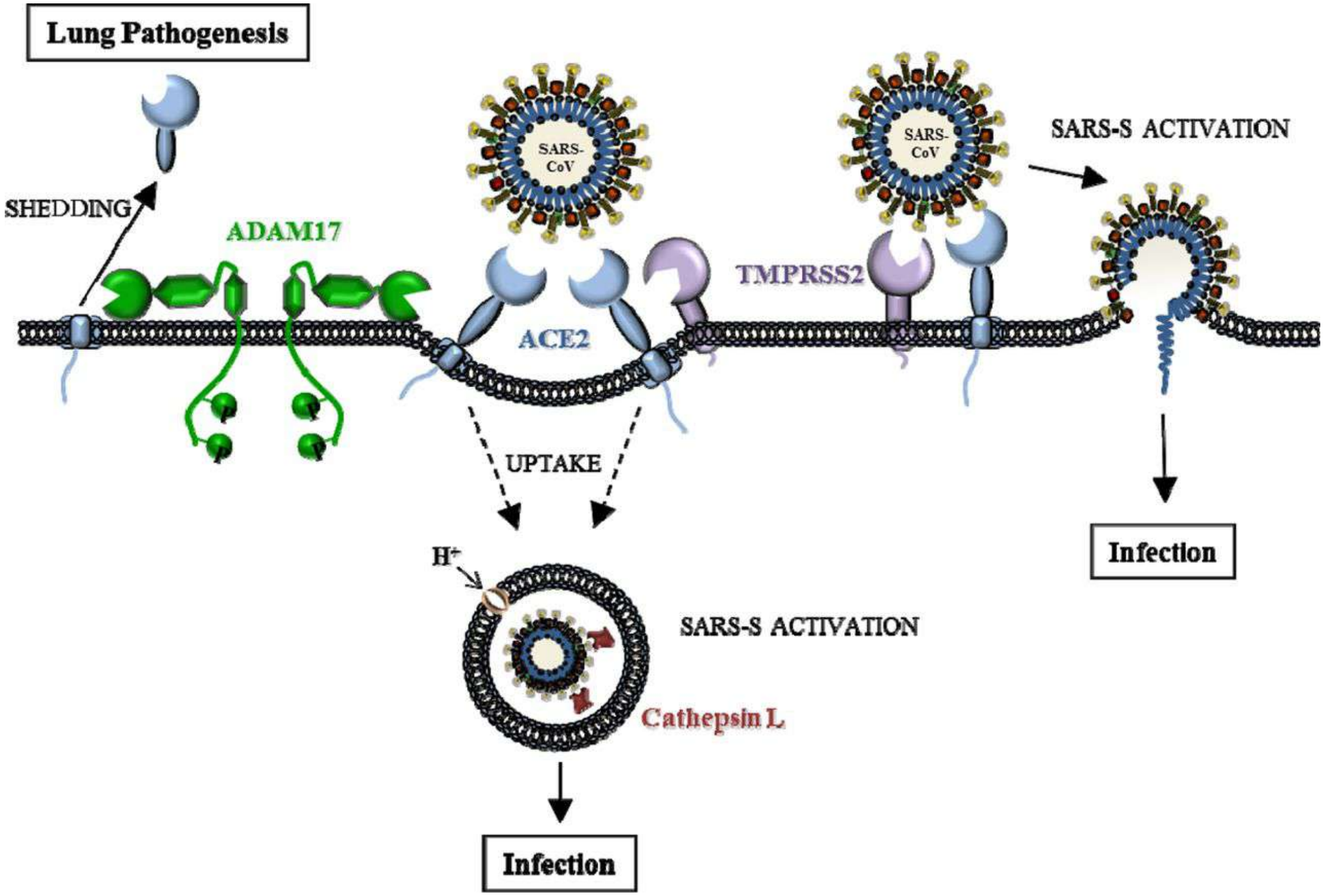
•The binding of SARS-CoV-2 on ACE2 causes an elevated expression of ACE2, which can lead to damages on alveolar cells.

•Damages to alveolar cells can, in turn, trigger a series of systemic reactions and even death.



➢ *Wrapp et al* found that the receptor-binding ability of SARS-CoV-2 is 10 to 20 times stronger than that of SARS-CoV.

Wrapp D, Cryo-EM structure of the SARS-CoV-2 spike in the prefusion conformation. medRxiv. 2020.


Lung Pathogenesis
SHEDDING
ADAM17
SARS-CoV
ACE2
UPTAKE
H+
SARS-S ACTIVATION
Cathepsin L
Infection
SARS-CoV
TMPRSS2
SARS-S ACTIVATION
Infection

COVID-19: consider cytokine storm syndromes and immunosuppression

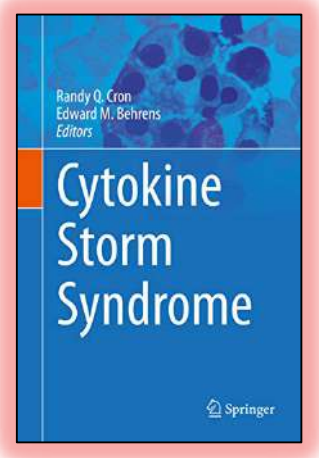
Mehta P, Lancet. 2020;S0140-6736(20)30628-0.

- As of March 12, 2020, coronavirus disease 2019 (**COVID-19**) has been confirmed in 125 048 people worldwide, carrying a **mortality of ≈ 3.7%**, compared with a mortality rate of < 1% from influenza.

- There is an urgent need for effective treatment.

- Current focus has been on the development of novel therapeutics, including **antivirals and vaccines**.

- Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome.



COVID-19: consider cytokine storm syndromes and immunosuppression

Mehta P, Lancet. 2020;S0140-6736(20)30628-0.

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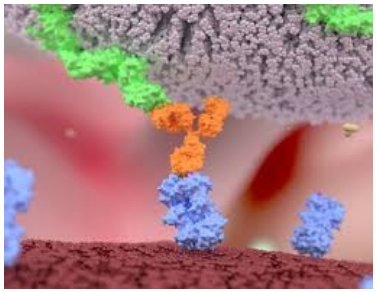
We recommend identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality.

- Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome.

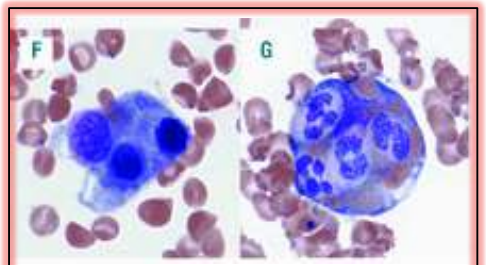


COVID-19: consider cytokine storm syndromes and immunosuppression

Mehta P, Lancet. 2020;S0140-6736(20)30628-0.

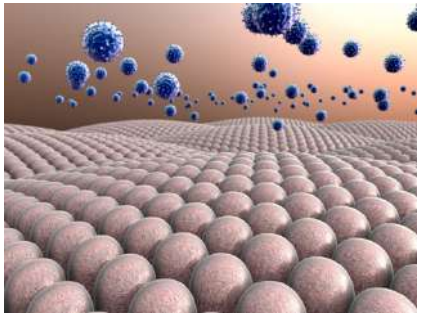
- Respiratory failure from **acute respiratory distress syndrome** (ARDS) is the leading cause of mortality in patients with COVID-19.

- **Secondary haemophagocytic lymphohistiocytosis** (sHLH) is an under-recognised, hyperinflammatory syndrome characterised by a **fulminant and fatal hypercytokinaemia with multiorgan failure.**



the presence of multiple nucleated cells within the cytoplasm of a single HPC (F and G) is highly predictive of the diagnosis of HLH.

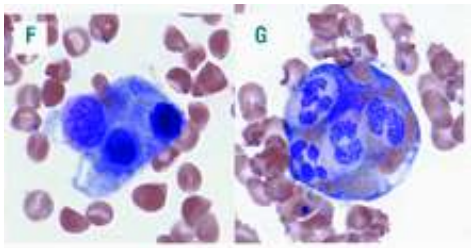
- In adults, sHLH is **most commonly triggered by viral infections** and occurs in 3·7–4·3% of sepsis cases.



COVID-19: consider cytokine storm syndromes and immunosuppression

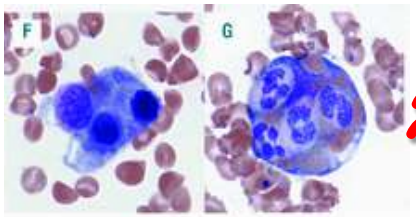
Mehta P, Lancet. 2020;S0140-6736(20)30628-0.

- Cardinal features of sHLH include:
  - unremitting fever,
  - cytopenias, and
  - hyperferritinaemia;
  - pulmonary involvement (including ARDS) occurs in ≈ 50% of patients.



- Secondary haemophagocytic lymphohistiocytosis (sHLH) ≈ Covid-19

- A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterised by increased:
  - IL-2, IL-7,
  - granulocyte-colony stimulating factor,
  - interferon-γ inducible protein 10,
  - monocyte chemoattractant protein 1,
  - macrophage inflammatory protein 1-α, and
  - tumour necrosis factor-α.



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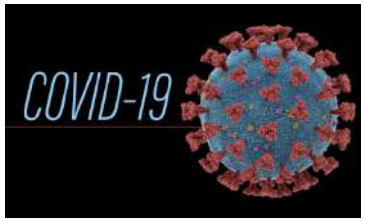

COVID-19: consider cytokine storm syndromes and immunosuppression

Mehta P, Lancet. 2020;S0140-6736(20)30628-0.

- **Predictors of fatality** from a recent retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China, included

  - **elevated ferritin** (mean 1297·6 ng/ml in non-survivors *vs* 614·0 ng/ml in survivors; *p<0·001*)

  and

  - **elevated IL-6** (*p<0·0001*),

suggesting that mortality might be due to virally driven hyperinflammation.

Ruan Q, Clinical predictors of mortality due to COVID-19 based on an analysis of data of150 patients from Wuhan, China. Intensive Care Med 2020; published online March 3.DOI:10.1007/s00134-020-05991-x.

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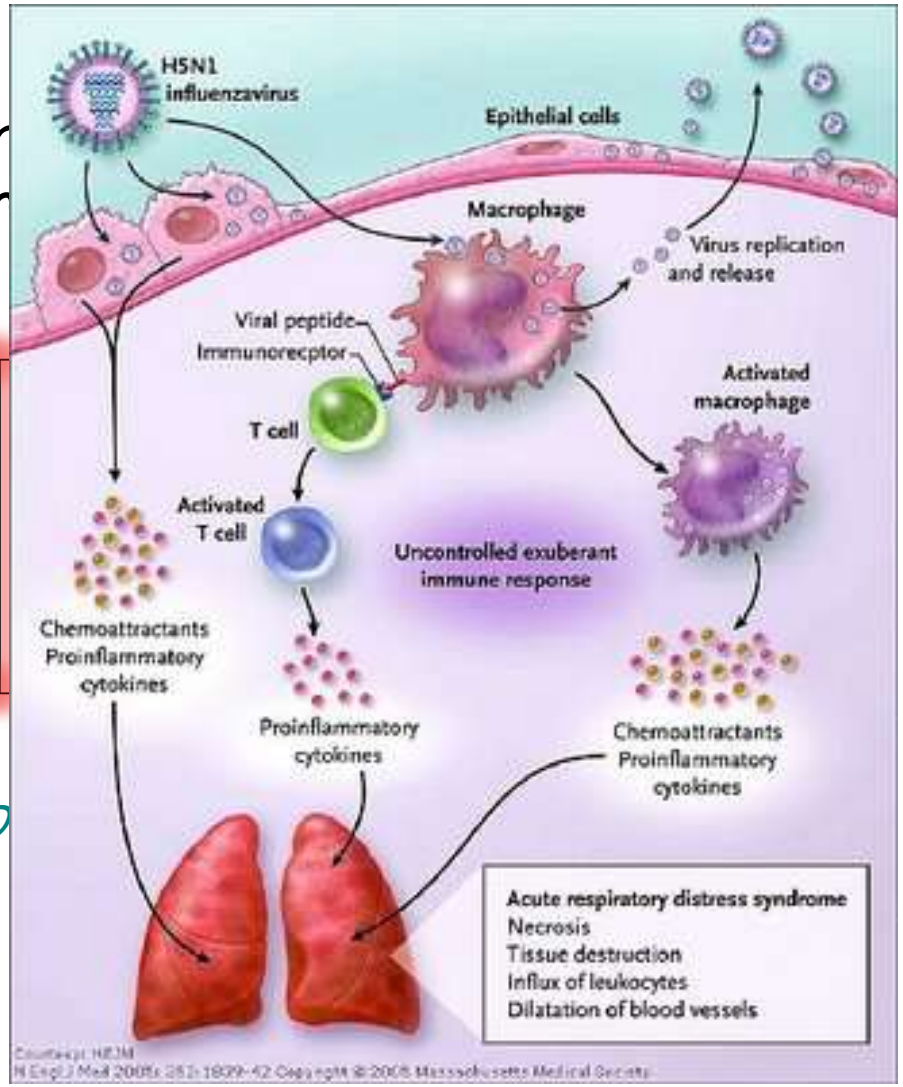


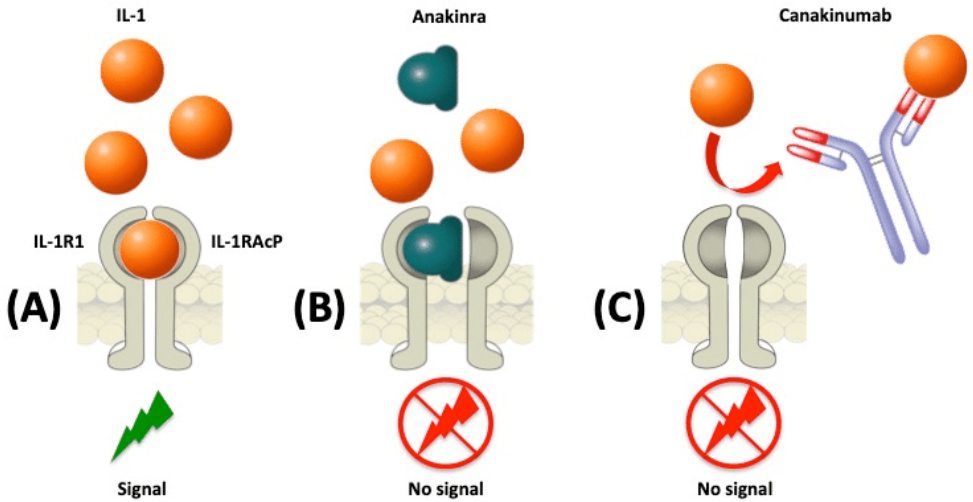
COVID-19: consider cytokine storm syndromes and immunosuppression

Mehta P, Lancet. 2020;S0140-6736(20)30628-0.

- As during previous pandemics (SARS and MERS), corticosteroids are not routinely recommended and might exacerbate COVID-19-associated lung injury.

- However, in hyperinflammation, immunosuppression is likely to be beneficial.

- Re-analysis of data from a phase 3 randomised controlled trial of IL-1 blockade (anakinra*) in sepsis, showed significant survival benefit in patients with hyperinflammation, without increased adverse events.



*Anakinra è un farmaco usato per trattare l'artrite reumatoide e altre gravi patologie infiammatorie quali le sindromi periodiche associate alla criopirina

Shakoory B, Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase iii trial. Crit Care Med 2016; 44: 275-81.

COVID-19: consider cytokine storm syndromes and immunosuppression

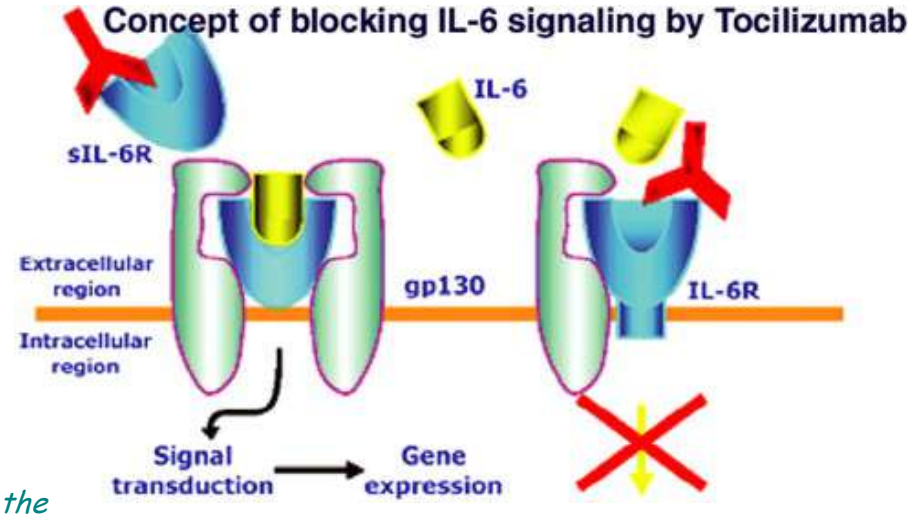
Mehta P, Lancet. 2020;S0140-6736(20)30628-0.

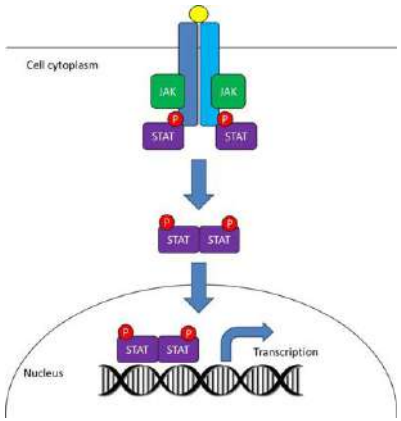
- A multicentre, randomised controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in patients with COVID-19 pneumonia and elevated IL-6 in China (ChiCTR2000029765).

Chinese Clinical Trial Registry. A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). Feb 13, 2020. http://www.chictr.org.cn/showprojen.aspx?proj=49409

- Janus kinase (JAK) inhibition could affect both inflammation and cellular viral entry in COVID-19.

Richardson P, Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020;395:e30-31.





COVID-19: consider cytokine storm syndromes and immunosuppression

Mehta P, Lancet. 2020;S0140-6736(20)30628-0.

- All patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends (eg, increasing ferritin, decreasing platelet counts, or erythrocyte sedimentation rate) and the hyper inflammation score (Hscore) (table) to identify the subgroup of patients for whom immunosuppression could improve mortality.

- Therapeutic options include:
  - steroids,
  - intravenous immunoglobulin,
  - selective cytokine blockade (eg, anakinra or tocilizumab) and
  - JAK inhibition.

	Number of points
Temperature	
<38·4°C	0
38·4–39·4°C	33
>39·4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1·5 mmol/L	0
1·5–4·0 mmol/L	44
>4·0 mmol/L	64
Fibrinogen (g/L)	
>2·5 g/L	0
≤2·5 g/L	30
Ferritin ng/ml	
<2000 ng/ml	0
2000–6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

COVID-19: consider cytokine storm syndromes and immunosuppression

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Yes	18

The Hscore generates a probability for the presence of secondary HLH.

HScores > 169 are 93% sensitive and 86% specific for HLH.

haemophagocytic lymphohistiocytosis

Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH.

HScores can be calculated using an online HScore calculator.

Fardet L, Development and validation of the HScore,a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 2014; 66: 2613–20.

HLH=haemophagocytic lymphohistiocytosis.

*Defined as either haemoglobin concentration of 9·2 g/dL or less (≤5·71 mmol/L), a white blood cell count of 5000 white blood cells per mm^3 or less, or platelet count of 110 000 platelets per mm^3 or less, or all of these criteria combined.

†HIV positive or receiving longterm immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

Understanding of COVID-19 based on current evidence

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

- ✓ Introduction
- ✓ Sources of SARS-CoV-2
- ✓ Epidemiology
- ✓ Etiology & Pathogenesis
- ✓ Symptoms, & Diagnosis
- ✓ The case of infants & children
- ✓ The case of mother & fetus
- ✓ The case of Italy
- ✓ Treatment
- ✓ Prevention
- ✓ Conclusions

Diagnostic criteria

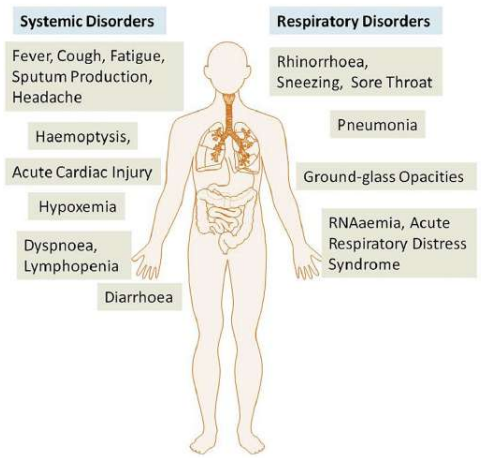
Suspected cases

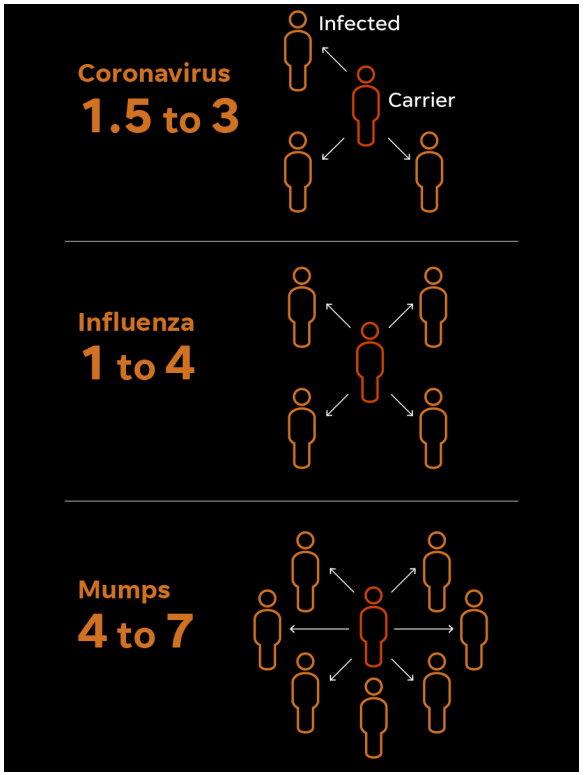
Patients should be suspected of 2019-nCoV infection who if they meet:

- any one of the criteria in the epidemiological history

and

- any two of the criteria in clinical manifestations.





Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr. 2020;10.1007/s12519-020-00345-5.

Diagnostic criteria

Epidemiological history

1. Children with a travel or residence history in Wuhan City and neighboring areas, or other areas with persistent local transmission within 14 days prior to disease onset.
2. Children with a history of contacting patients with fever or respiratory symptoms who have a travel or residence history in Wuhan City and neighboring areas, or in other areas with persistent local transmission within 14 days prior to disease onset.
3. Children with a history of contacting confirmed or suspected cases infected with 2019-nCoV within 14 days prior to disease onset.
4. Children who are related with a cluster outbreak: in addition to this patient, there are other patients with fever or respiratory symptoms, including suspected or confirmed cases infected with 2019-nCoV.
5. Newborns delivered by suspected or confirmed 2019-nCoV-infected mothers.

Diagnostic criteria

Clinical presentations

1. Fever, fatigue, dry cough; some pediatric patients may have no fever.
2. Patients with chest imaging findings;
3. In the early phase of the disease, white blood cell counts are normal or decreased, or with decreased lymphocyte count.

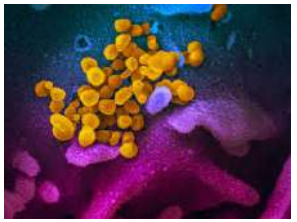
Confirmed cases

Suspected cases who meet any one of the following criteria:

1.Throat swab, sputum, stool, or blood samples tested positive for 2019-nCoV nucleic acid using RT-PCR;

2.Genetic sequencing of throat swab, sputum, stool, or blood samples being highly homologous with the known 2019-nCoV;

3.2019-nCoV granules being isolated by culture from throat swab, sputum, stool, or blood samples.



yellow granules is virus

Symptoms and clinical diagnosis of COVID-19

➢ *Huang et al* found that

*Huang C, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;**395**:497-506.*

- **98% of the patients had fevers**, of which 78% had a temperature higher than 38°C.
- **76%** of the patients had **coughs**,
- **55%** of patients had **dyspnea**,
- **44%** of patients experienced **fatigue and muscle pain**,
- 28% had expectoration,
- 8% had headaches,
- 5% hemoptysis, and
- 3% diarrhea.

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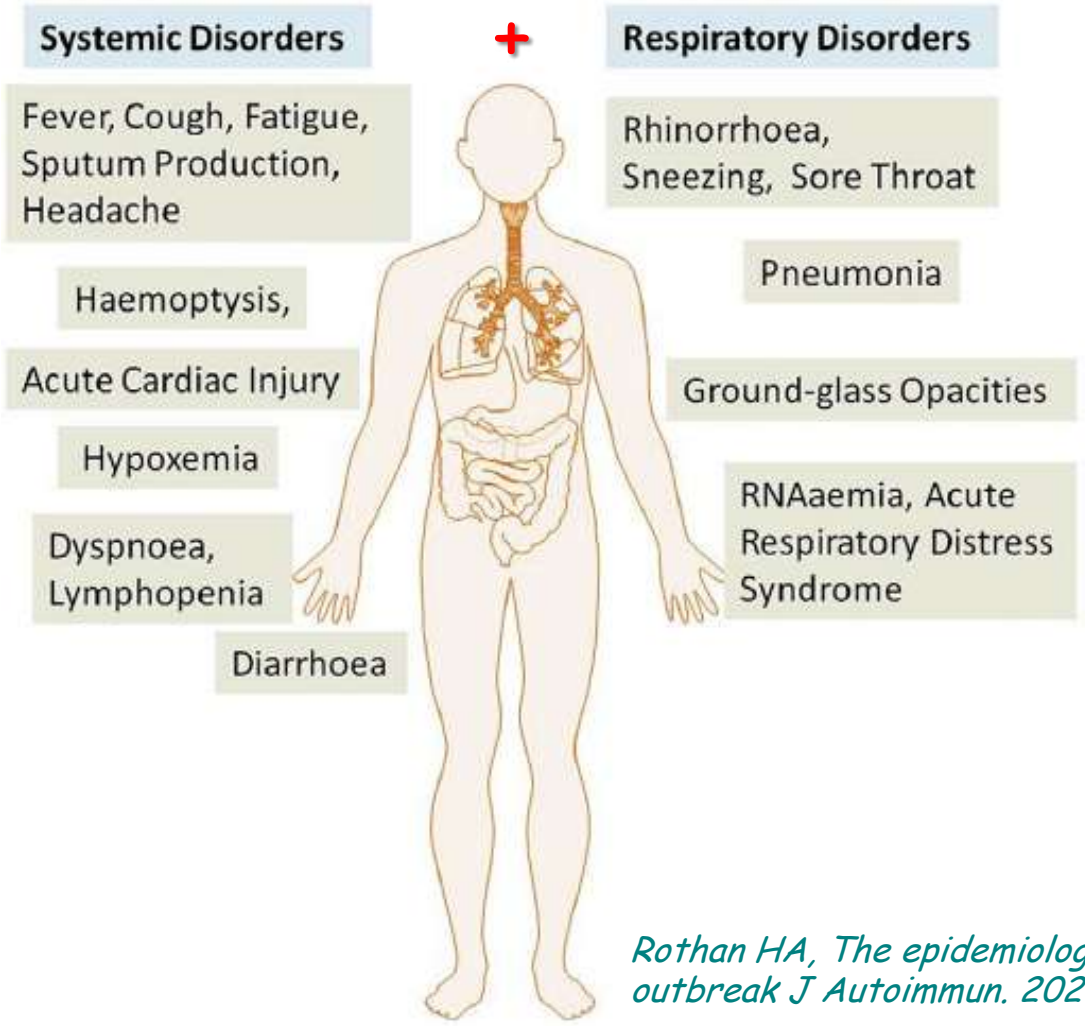
fevers

and

coughs

are the most common symptoms

Symptoms and clinical diagnosis of COVID-19



The systemic and respiratory disorders caused by COVID-19 infection.

Whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhoea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress.

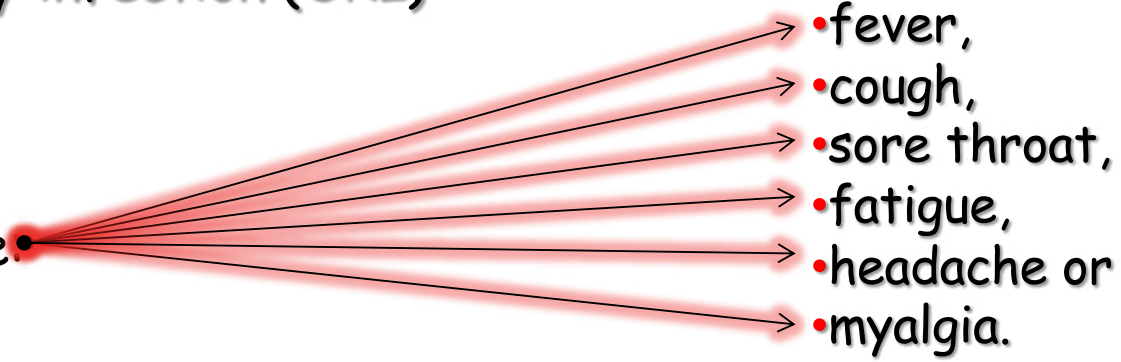
Therefore, it is important to test faecal and urine samples to exclude a potential alternative route of transmission, specifically through health care workers, patients etc

Rothan HA, The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak J Autoimmun. 2020;102433. doi:10.1016/j.jaut.2020.102433

Clinical classifications of the severity of the disease

Mild type (almost all children)

- This type of patient includes those with:
  - asymptomatic infection,
  - upper respiratory infection (URI) and
  - mild pneumonia.



- Some patients show pneumonia signs on chest imaging.
  - These patients do not have any of the severe or critical symptoms and complications described below.

Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

Clinical classifications of the severity of the disease

Severe pneumonia

Disease progresses to meet any of the following conditions:

1. Increased respiration rate: **RR ≥ 70/min (≤ 1 year), RR ≥ 50/min (> 1 year).**

2. **Hypoxia: $SpO_2 \leq 93\%$** (< 90% in premature infants) or nasal flaring, suprasternal, intercostal and subcostal retractions, grunting and cyanosis, apnea, etc.

3. Blood gas analysis: **$PaO_2 < 60$ mmHg, $PaCO_2 > 50$ mmHg.**

4. **Consciousness alterations:** restlessness, lethargy, coma, convulsion, etc.

5. **Poor feeding**, bad appetite, and even dehydration.

Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

Clinical classifications of the severity of the disease

Severe pneumonia

Disease progra

1. Increas

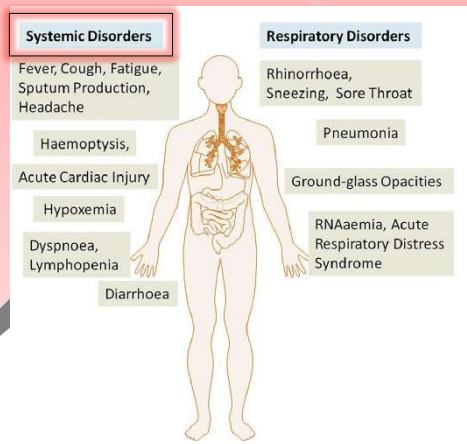
2. I
in

3. Bl

4. Co

5. Poor feeding, b

6. Other manifestations:
- **coagulation disorders** (prolonged prothrombin time and elevated level of D-dimer),
- **myocardial damage** (increased level of myocardial enzyme, electrocardiogram ST-T changes, cardiomegaly and cardiac insufficiency in severe cases),
- **gastrointestinal dysfunction**,
- **raised level of liver enzyme** and
- **rhabdomyolysis**.



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Clinical classifications of the severity of the disease

Critical cases

Disease progresses rapidly along with organ failure with any of the following conditions:

1. *Respiratory failure which requires mechanical ventilation* Patients present with acute respiratory distress syndrome (ARDS) and are featured by refractory hypoxemia, which cannot be alleviated by conventional oxygen therapy, such as nasal catheter or mask oxygen supplement.

2. *Septic shock* In addition to severe pulmonary infection, 2019-nCoV can cause damage and dysfunction of other organs. When dysfunction of extrapulmonary system such as circulation, blood and digestive system occurs, the possibility of sepsis and septic shock should be considered and the mortality rate increases significantly.

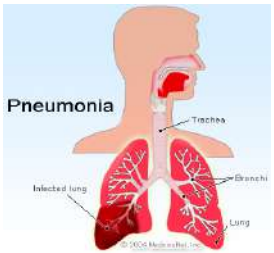
3. Accompanied by other organ failure that needs ICU monitoring and treatment.

Clinical course of COVID19 infection

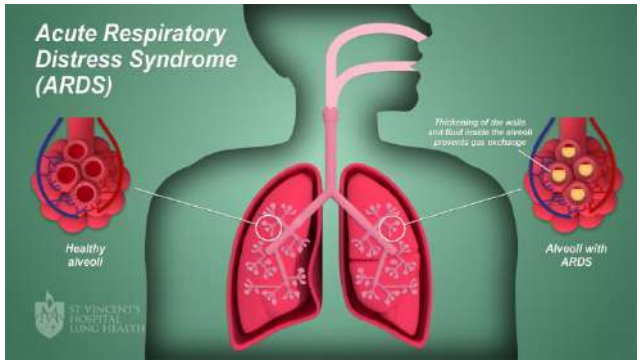
- There seem to be 3 major patterns of the clinical course of infection:

1. mild illness with upper respiratory tract presenting symptoms;

2. non-life-threatening pneumonia; and



3. severe pneumonia with acute respiratory distress syndrome (ARDS) that begins with mild symptoms for 7–8 days and then progresses to rapid deterioration and ARDS requiring advanced life support



Heymann DL, Shindo N; WHO Scientific and Technical Advisory Group for Infectious Hazards. COVID-19: what is next for public health?. Lancet. 2020;395(10224):542-545.

Symptoms evolution of COVID-19

The incubation period ranges from 2 to 14 days, most often rangs from 3 to 7 days

fever (37 to 38°C) and had coughs accompanied by chest discomfort.

Gradual resolution of symptoms

coughs and chest discomfort aggravation in 3-4 days

respiratory distress 7 days after the onset of symptoms and worsening within the next 2 days.

Zhu N, A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-733.

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coughs and chest discomfort aggravation in 3-4 days

respiratory distress 7 days after the onset of symptoms and worsening within the next 2 days.

The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days

Zhu N, A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-733.

Laboratory diagnosis of COVID-19

➢Huang et al found that

*Huang C, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;**395**:497-506.*

- Laboratory tests found that
  - 25% of infected patients had **leukopenia** and
  - 63% had **lymphocytopenia**
  - 37% had **elevated leves of aspartate aminotransferase** (AST/GOT)

  - ***C-reactive protein (CRP)*** normal or increased.

  - ***Procalcitonin (PCT)*** normal in most cases.

The level of PCT>0.5 ng/mL indicates the co-infection with bacteria.

  - ***Others***

Elevation of **liver enzymes, muscle enzymes**
(Creatine kinase (CK), lactate dehydrogenase (LDH)) and **myoglobin**,
and increased level of **D-dimer** might be seen in severe cases.

Zhi-Min Chen, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World Journal of Pediatrics. 2020 in press

Laboratory diagnosis of COVID-19

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- Laboratory tests found that
  - 25% of infected patients had **leukopenia** and
  - 63% had **lymphocytopenia**
  - 37% had **elevated leves of aspartate aminotransferase** (AST/GOT)

- **Myocarditis** was diagnosed in **12%** of the patients, and the level of **hypersensitive troponin I was significantly increased** in these patients.

- ***Others***

Elevation of **liver enzymes, muscle enzymes** (Creatine kinase (CK), lactate dehydrogenase (LDH)) and **myoglobin**, and increased level of **D-dimer** might be seen in severe cases.

Zhi-Min Chen, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World Journal of Pediatrics. 2020 in press

Chest X-ray CT scan diagnosis of COVID-19

➢ ***Chest X-ray examination***

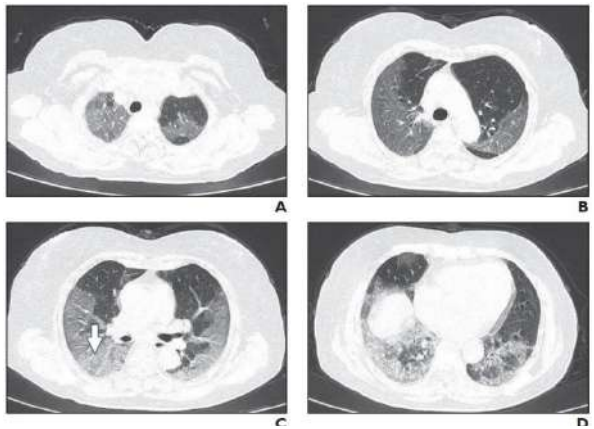
•In the early stage of pneumonia cases, chest images show **multiple small patchy** (irregolari) **shadows and interstitial changes,** **remarkable in the lung periphery**.

•Severe cases can further develop to **bilateral multiple ground-glass opacity**, infiltrating shadows, and **pulmonary consolidation**, with **infrequent pleural effusion.**

Chan JF, A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020.

➢ **Abnormalities** in **chest computed tomography** (CT) images were found in **100% of adult** patients.

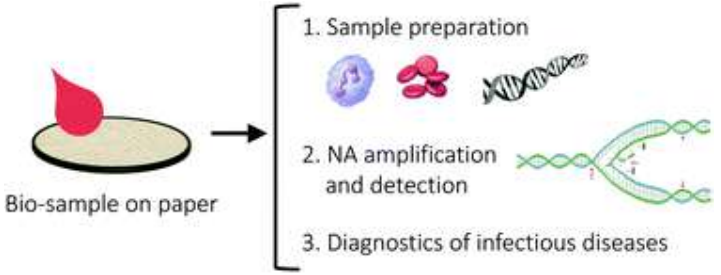
•**Grinding glass-like and consolidation areas** were found in 98% of the infected patients' bilateral lungs. **Pneumonia** is always present in patients with severe COVID-19



Laboratory diagnosis of COVID-19

Laboratory diagnosis of COVID-19

Etiologic detection

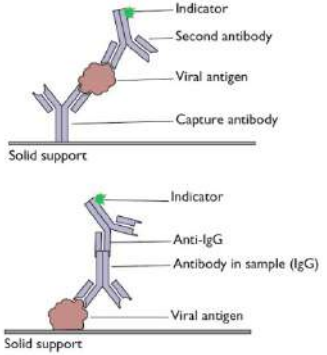


- Nucleic acid testing is the main method of laboratory diagnosis.

- 2019-nCoV nucleic acid can be detected by RT-PCR or by viral gene sequencing of nose-throat swabs, sputum, stool or blood samples.

- *Other methods* 2019-nCoV particles can be isolated from human respiratory epithelial cells through virus culture, but this experiment cannot be carried out in general laboratories.

- Virus antigen or serological antibody testing kits are recently became available at present.



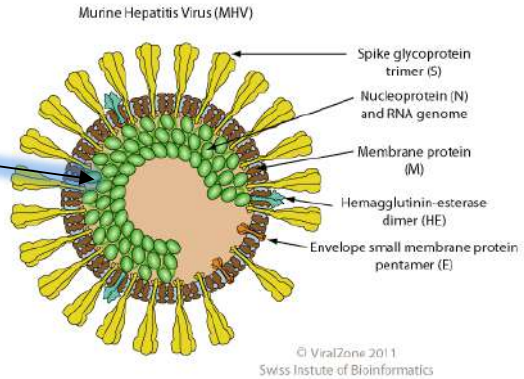
Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

Serological Evidence of Bat SARS-Related Coronavirus Infection in Humans, China.

Wang N, Virol Sin. 2018;33(1):104-107

- Polyclonal antibodies against each of the six nucleocapsid proteins (NPs) were prepared in rabbits.

- The Rp3 NP was chosen to develop a SARSr-CoV specific ELISA for serosurveillance.

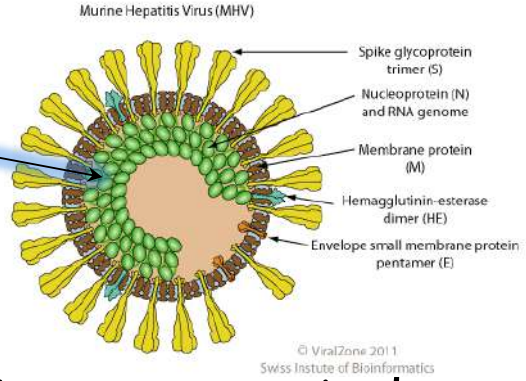


- Micro-titer plates were coated with 100 ng/well of recombinant Rp3 NP and incubated with human sera in duplicates at a dilution of 1:20, followed by detection with HRP labeled goat anti-human IgG antibodies (Proteintech, Wuhan, China) at a dilution of 1:20,000.

Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes.

Zhang W, Emerg Microbes Infect. 2020;9(1):386-389.

In-house anti-SARSr-CoV IgG and IgM ELISA kits were developed using SARSr-CoV **Rp3 nucleocapsid protein** as antigen, which shared above 90% amino acid identity to all SARSr-CoVs.



For IgG test, MaxiSorp Nunc-immuno 96 well ELISA plates were coated (100 ng/well) overnight with recombinant NP.

Human sera were used at 1:20 dilution for 1 h at 37°C.

An anti-Human IgG-HRP conjugated monoclonal antibody (Kyab Biotech Co., Ltd, Wuhan, China) was used at a dilution of 1:40,000.

The optical density (OD) value (450–630) was calculated.

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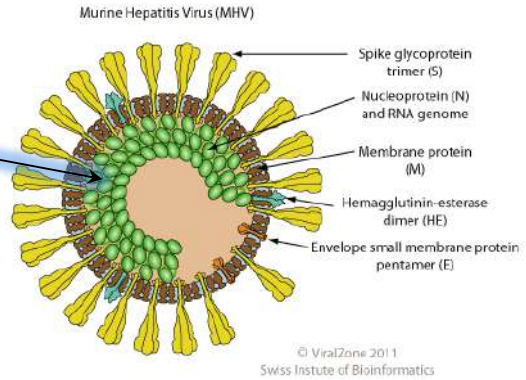


For IgM test, MaxiSorp Nunc-immuno 96 wellELISA plates were coated (500 ng/well) overnight with anti-human IgM (μ chain).

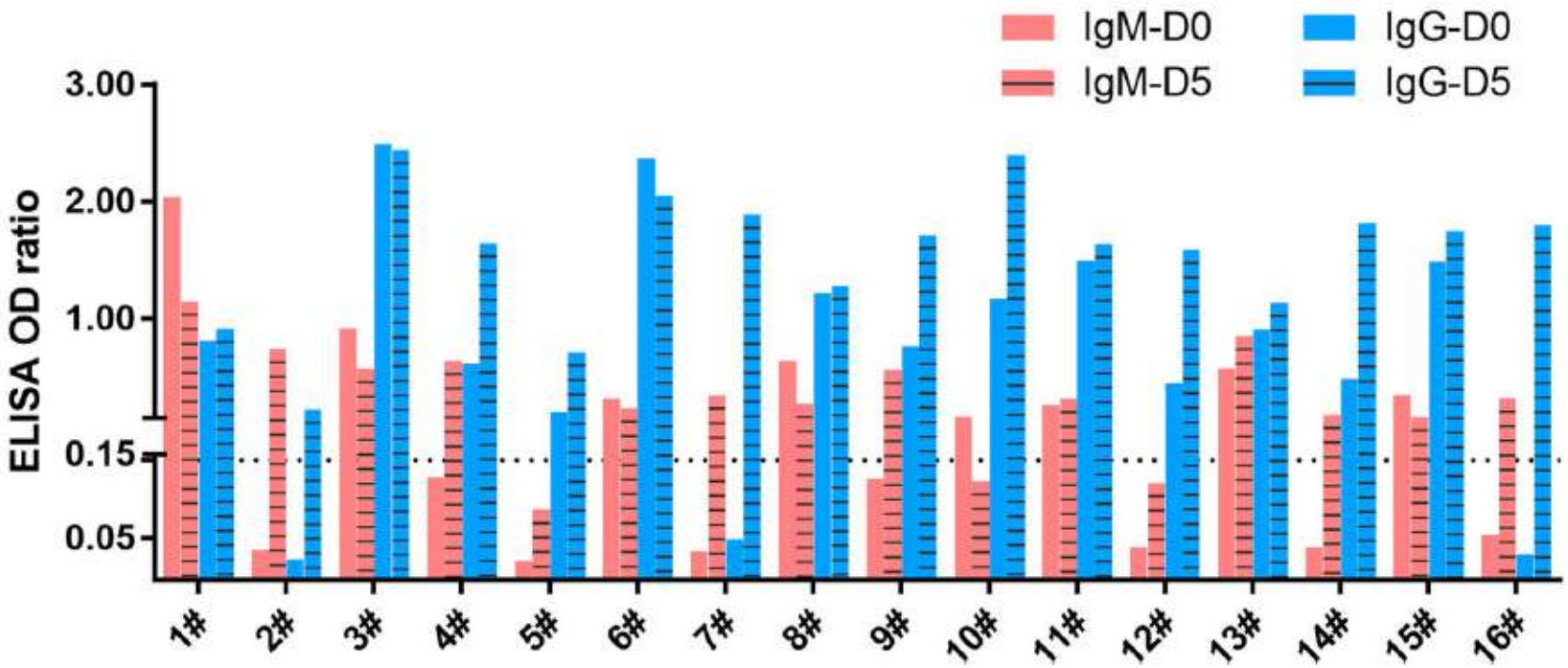
Human sera were used at 1:100 dilution for 40 min at 37°C, followed by anti-Rp3 NP-HRP conjugated (Kyab Biotech Co., Ltd, Wuhan, China) at a dilution of 1:4000.

The OD value (450–630) was calculated.

Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes.

Zhang W, Emerg Microbes Infect. 2020;9(1):386-389.

On day 5, an increase of viral antibodies can be seen in nearly all 16 patients, which was normally considered as a transition from earlier to later period of infection (Figure 1). IgM positive rate increased from 50% (8/16) to 81% (13/16), whereas IgG positive rate increased from 81% (13/16) to 100% (16/16).



Serological detection of 2019-nCoV in 16 patients.

Dashed line indicates cutoff, which was determined based on data from healthy controls.

Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes.

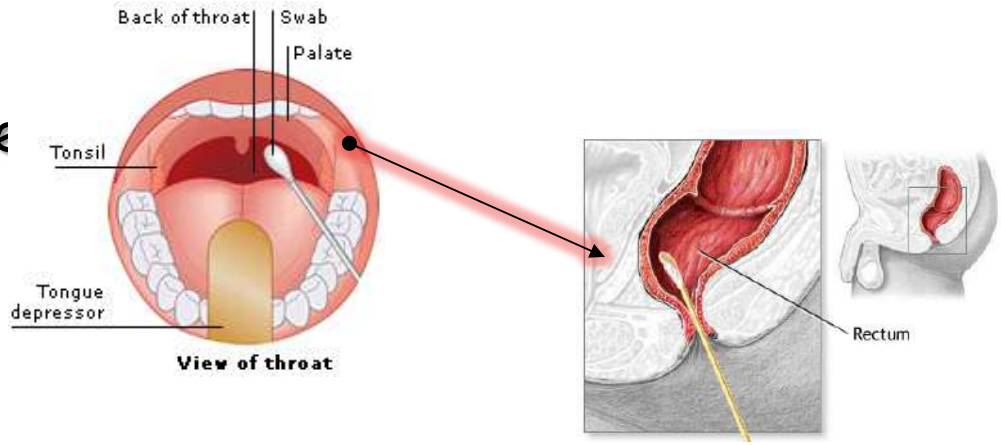
Zhang W, Emerg Microbes Infect. 2020;9(1):386-389.

- We show that the current strategy for the detection of viral RNA in oral swabs used for 2019-nCoV diagnosis is not perfect.
- The virus may be present in anal swabs or blood of patients when oral swabs detection negative.
- None of the patients with viremia blood had positive swabs.
- These patients would likely be considered as 2019-nCoV negative through routine surveillance, and thus pose a threat to other people.
- In contrast, we found viral antibodies in near all patients, indicating serology should be considered for 2019-nCoV epidemiology.

Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes.

Zhang W, Emerg Microbes Infect. 2020;9(1):386-389.

- A possible **shift from oral positive** during early infection to anal swab positive during late infection can be observed.



- This observation implied that **we cannot discharge a patient purely based on oral swabs negative**, who may still shed the virus by oral-fecal route.

- Above all, we strongly suggest **using viral IgM and IgG serological test to confirm an infection**, considering the unreliable results from oral swabs detection.

Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis *Li Z, J Med Virol. 2020;10.1002/jmv.25727.*

- Although the virus (SARS-Cov-2) nucleic acid RT-PCR test has become the standard method for diagnosis of SARS-CoV-2 infection, these real-time PCR test kits have many limitations.

- In addition, high false negative rates were reported.

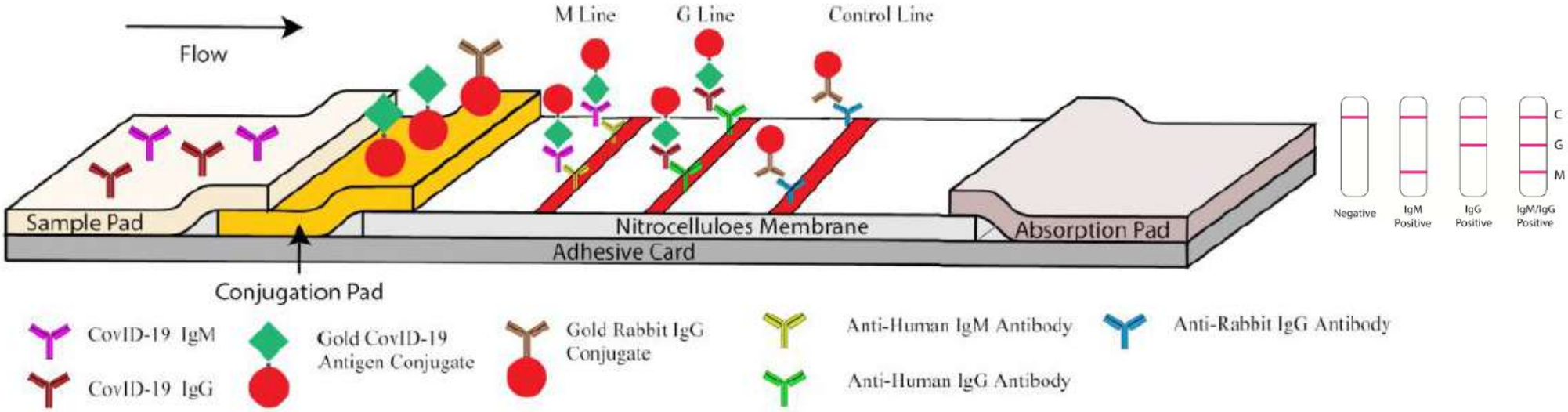
- There is an urgent need for an accurate and rapid test method to quickly identify large number of infected patients and asymptomatic carriers to prevent virus transmission and assure timely treatment of patients.

- We have developed a rapid and simple point-of-care lateral flow immunoassay which can detect IgM and IgG antibodies simultaneously against SARS-CoV-2 virus in human blood within 15 minutes
which can detect patients at different infection stages.

Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis

Li Z, J Med Virol. 2020;10.1002/jmv.25727.

Figure 1: Schematic illustration of rapid SARS-CoV-2 IgM-IgG combined antibody test. A: Schematic diagram of the detection device; B: An illustration of different testing results, C means control line, G means IgG line, M means IgM line.



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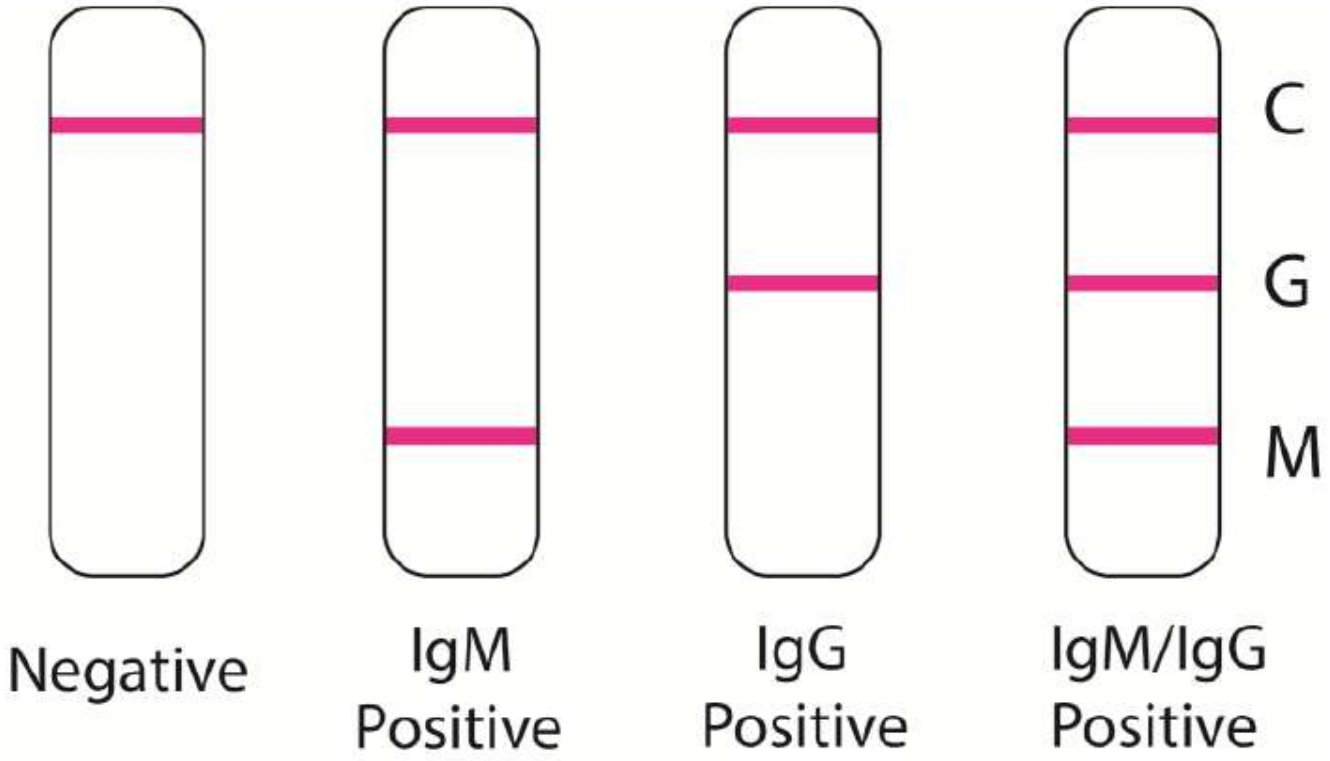
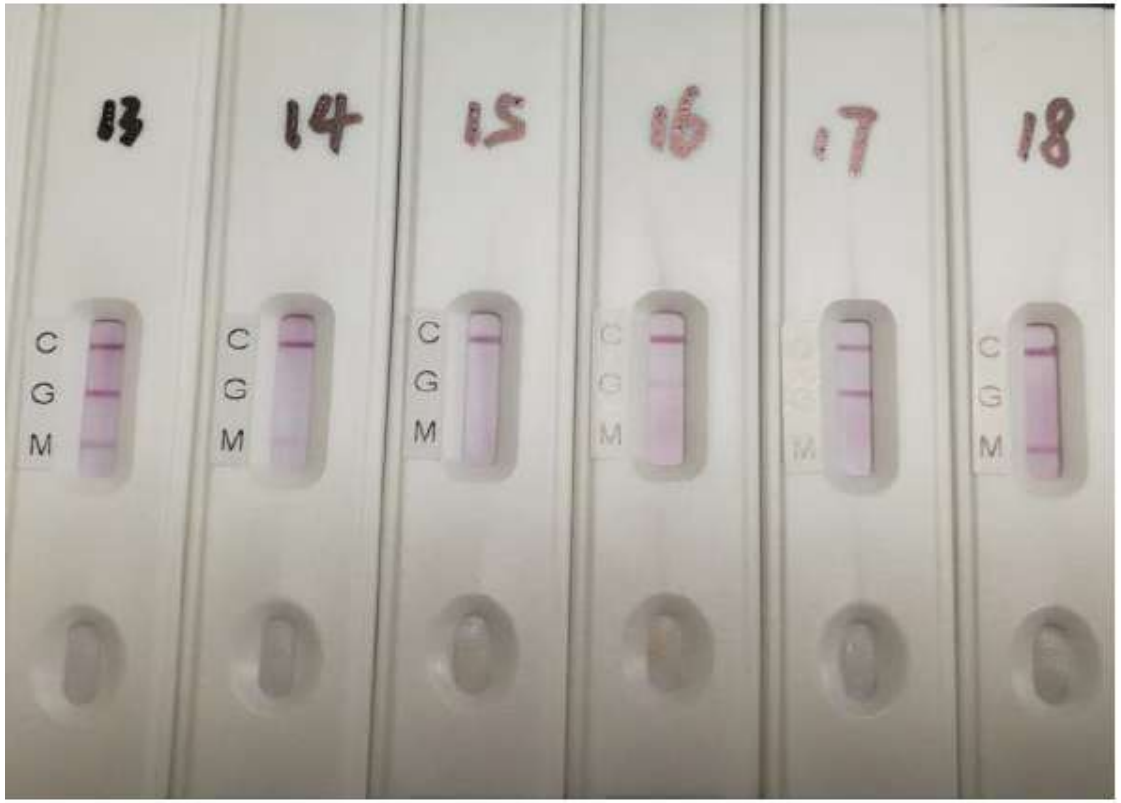


Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis *Li Z, J Med Virol. 2020;10.1002/jmv.25727.*

Figure 2: Representative photo for different patient blood testing results.



#13) Both IgM and IgG positive,

#14) IgM weak positive,

#15) Both IgM and IgG negative,

#16) IgG weak positive,

#17) IgG positive,

#18) IgM positive.

Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis *Li Z, J Med Virol. 2020;10.1002/jmv.25727.*

✓sensitivity and specificity of this test measured using blood samples collected from 397 PCR confirmed COVID-19 patients

and

✓128 negative patients at 8 different clinical sites.

The overall testing

❑**sensitivity** (% sick people who are correctly identified as having the condition) **was 88.66%**

false negative rate = 11.34

and

❑**specificity** (% healthy people who are correctly identified as not having the condition) **was 90.63%**

false positive rate = 9.37

Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis *Li Z, J Med Virol. 2020;10.1002/jmv.25727.*

Conclusion

- We developed a rapid **SARS-CoV-2 IgG-IgM combined antibody test** using lateral flow immune assay techniques.

- **It takes less than 15 minutes to generate results** and determine whether there is recent SARS-CoV-2 infection **with fingerstick blood.**

- **It is easy to use, and no additional equipment is required.**

- Results from this study demonstrated that this test is **sensitive and specific.**

- This rapid test has great potential benefit for the fast screening of SARS-CoV-2 infections,

Understanding of COVID-19 based on current evidence

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

- ✓ Introduction
- ✓ Sources of SARS-CoV-2
- ✓ Epidemiology
- ✓ Etiology & Pathogenesis
- ✓ Symptoms, & Diagnosis
- ✓ The case of infants & children
- ✓ The case of mother & fetus
- ✓ The case of Italy
- ✓ Treatment
- ✓ Prevention
- ✓ Conclusions

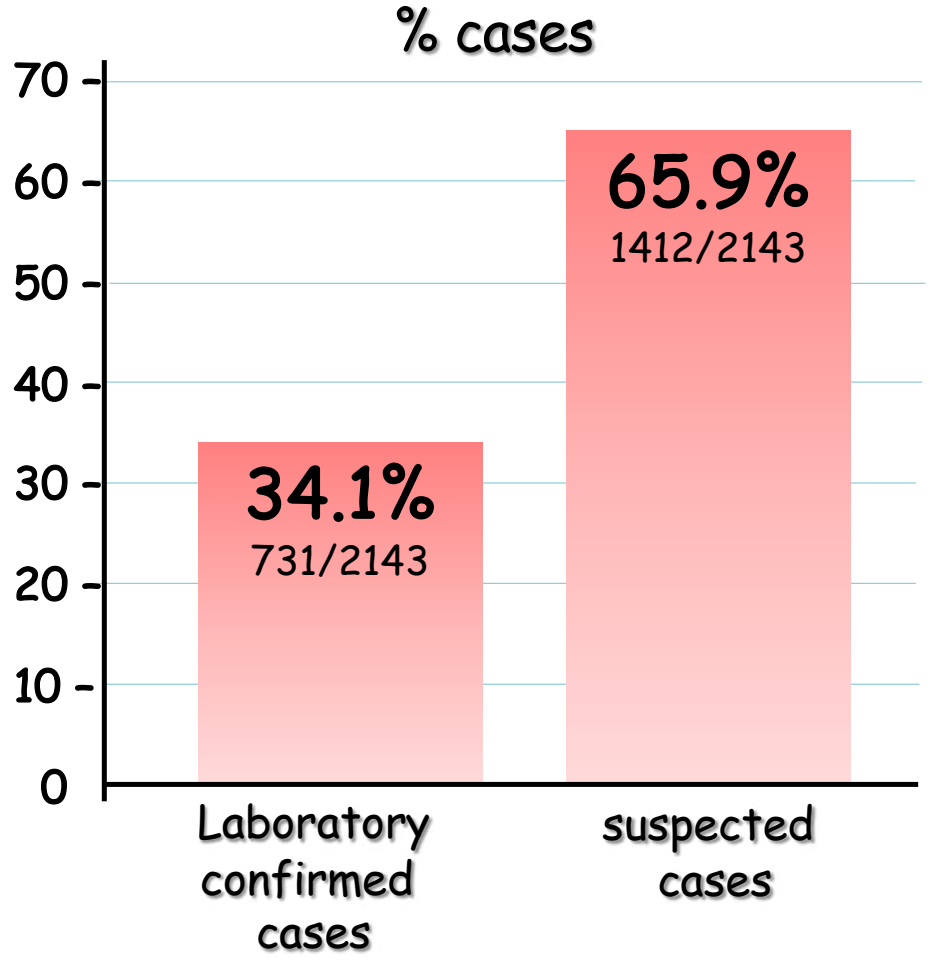
Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China

Dong Y, Pediatrics. 2020;e20200702.

✓Nationwide case series of 2143 pediatric patients with COVID-19 reported to the Chinese Center for Disease Control and Prevention from January 16 to February 8, 2020

Confirmed cases:

1. Nasal and pharyngeal swab specimens or blood samples tested positive for 2019-nCoV nucleic acid using real-time reverse-transcriptase polymerase-chain-reaction (RT PCR) assay;
2. Genetic sequencing of respiratory tract or blood samples is highly homologous with 2019 nCoV.



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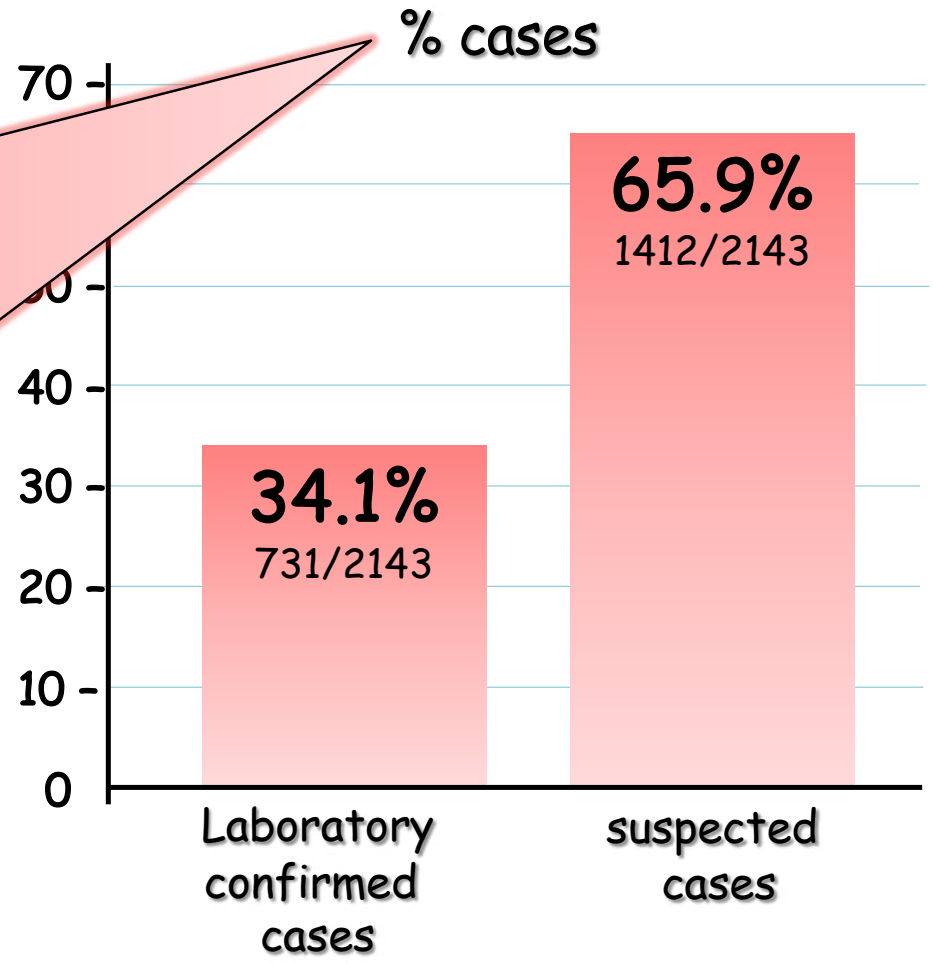
Dong Y, Pediatrics. 2020;e20200702.

The median age of all patients was 7 years (interquartile range: 2-13),

and

1213 cases (56.6%) were boys.



Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China

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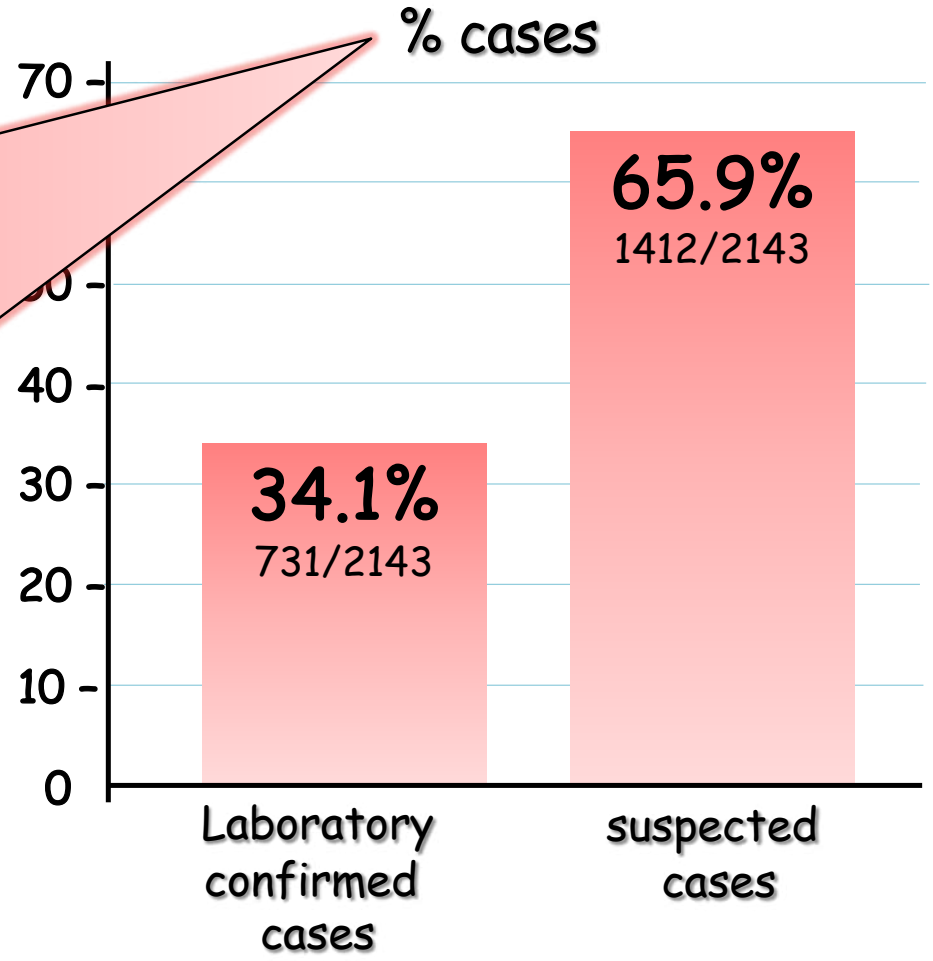
94% of all patients were asymptomatic, mild, or moderate cases.

The median time from illness onset to diagnoses was 2 days (range: 0 to 42 days).



Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China

Dong Y, Pediatrics. 2020;e20200702.

1. Asymptomatic infection: without any clinical symptoms and signs and the chest imaging is normal, while the 2019-nCoV nucleic acid test is in a positive period.

2. Mild: symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Physical examination shows congestion of the pharynx and no auscultory abnormalities. Some cases may have no fever, or have only digestive symptoms such as nausea, vomiting, abdominal pain and diarrhea.

3. Moderate: with pneumonia, frequent fever and cough, mostly dry cough, followed by productive cough , some may have wheezing, but no obvious hypoxemia such as shortness of breath, and lungs can hear sputum or dry snoring and / or wet snoring. Some cases may have no clinical signs and symptoms, but chest CT shows lung lesions, which are subclinical.

4. Severe: Early respiratory symptoms such as fever and cough, may be accompanied by gastrointestinal symptoms such as diarrhea. The disease usually progresses around 1 week, and dyspnea occurs, with central cyanosis. Oxygen saturation is less than 92%, with other hypoxia manifestations.

5. Critical: Children can quickly progress to acute respiratory distress syndrome (ARDS) or respiratory failure, and may also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury. Organ dysfunction can be life threatening.

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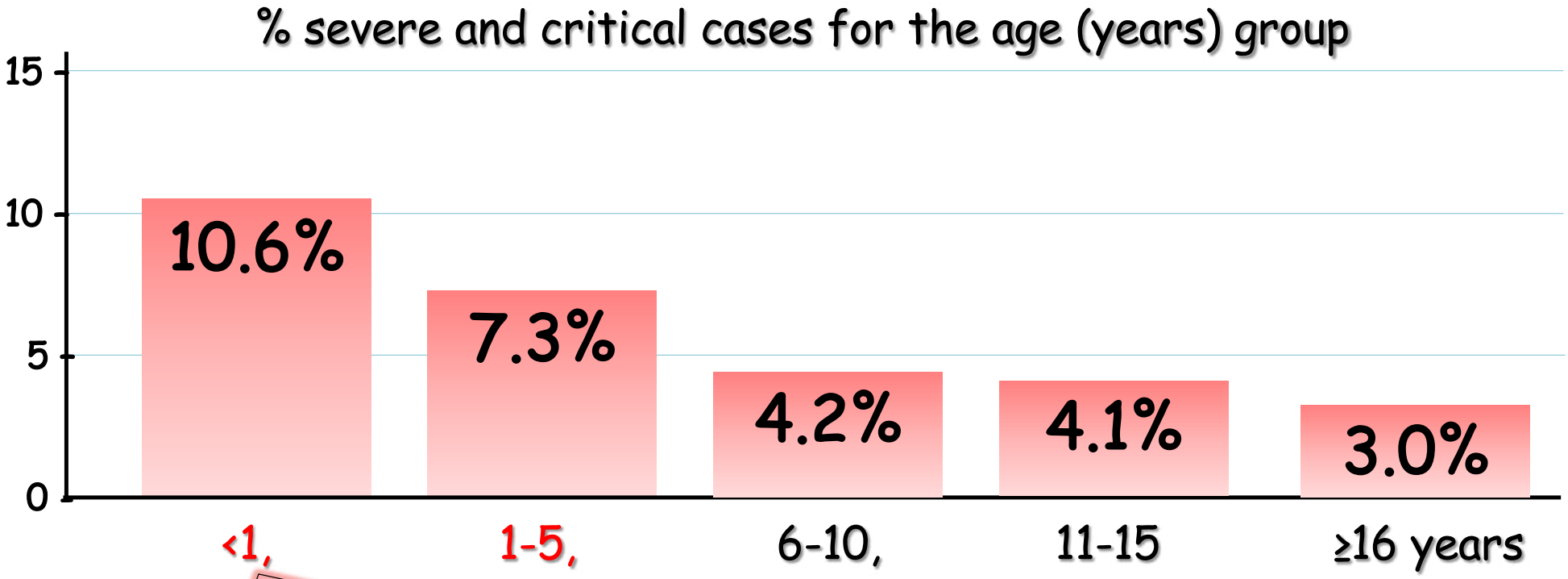
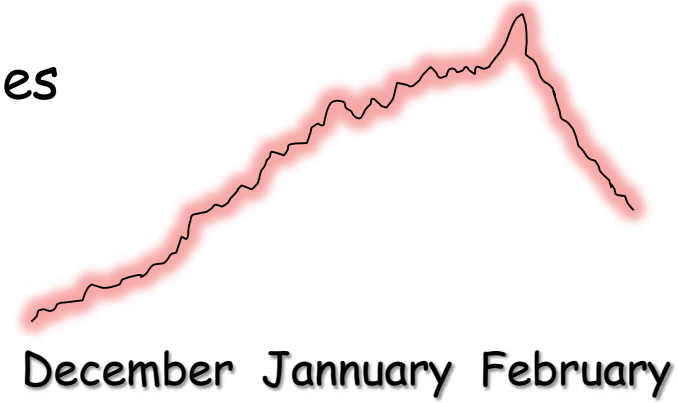


severity of illness by age reveals that young children, particularly infants, were vulnerable to 2019-nCoV infection.

Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China

Dong Y, Pediatrics. 2020;e20200702.

- Temporal distribution of children's COVID-19 cases shows that, **in the early stage of the epidemic** (i.e., between Dec., 2019 and early Feb., 2020), **there was a trend of the rapid increase of disease onset.**



- Since early **February 2020, the number** of children's COVID-19 cases **has been declining.**

➢ It indicates that the disease **control measures implemented by the government were effective**, and it is likely that this epidemic will continue to decline, and finally stop in the near future unless sustained human-to-human transmissions occur.

Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China

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Conclusions

- Children at all ages were sensitive to COVID-19, and there was no significant gender difference.

- Clinical manifestations of children's COVID-19 cases were less severe than those of adults' patients. However, young children, particularly infants, were vulnerable to 2019-nCoV infection.

- The distribution of children's COVID-19 cases varied with time and space, and most of the cases concentrated in Wuhan and surrounding areas.

- There is a strong evidence for human-to-human transmission as children were unlikely to visit the Huanan Seafood Wholesale Market where the early adult patients were reported to obtain 2019-nCoV

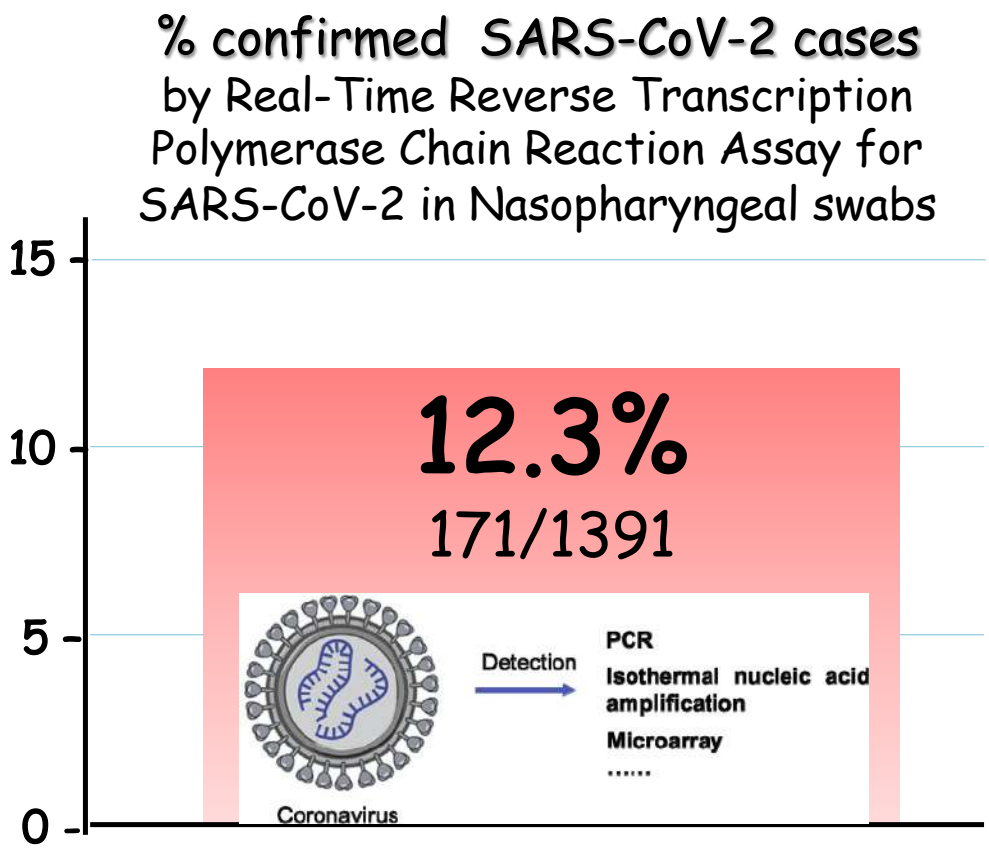
SARS-CoV-2 Infection in Children .

Lu X, N Engl J Med. 2020;10.1056/NEJMc2005073.

✓A recent review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that less than 1% of the cases were in children < 10 years of age.

Wu Z, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020 February24

✓1391 children infected with SARS-CoV-2 and treated at the Wuhan Children's Hospital



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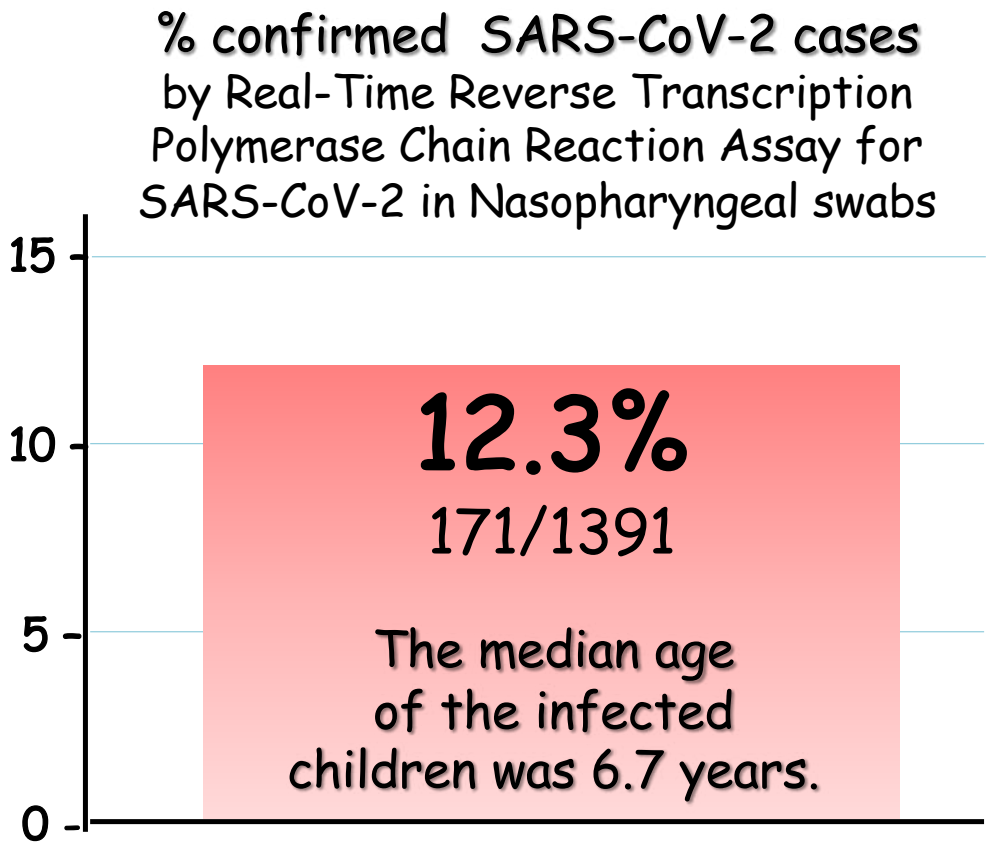

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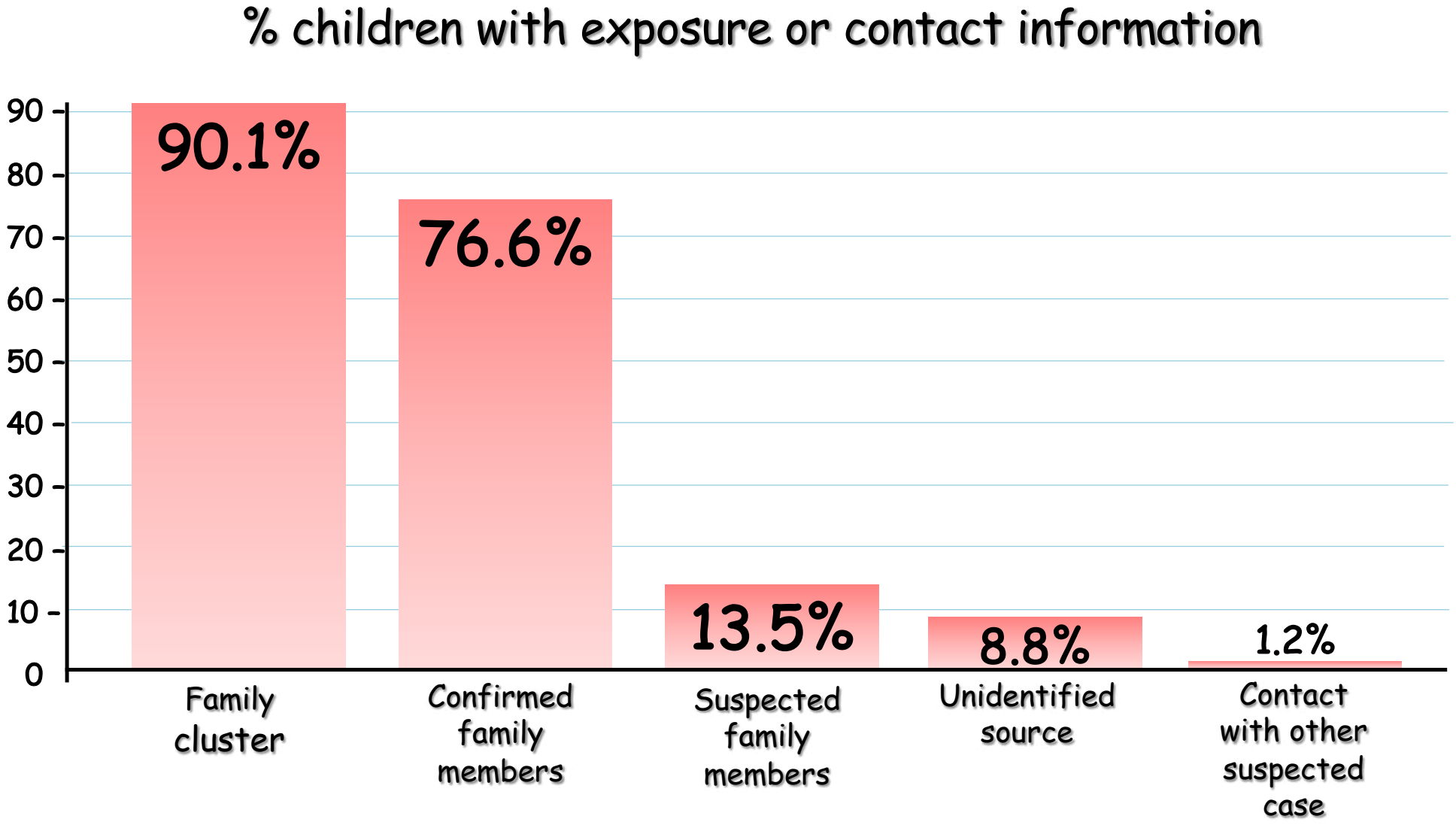

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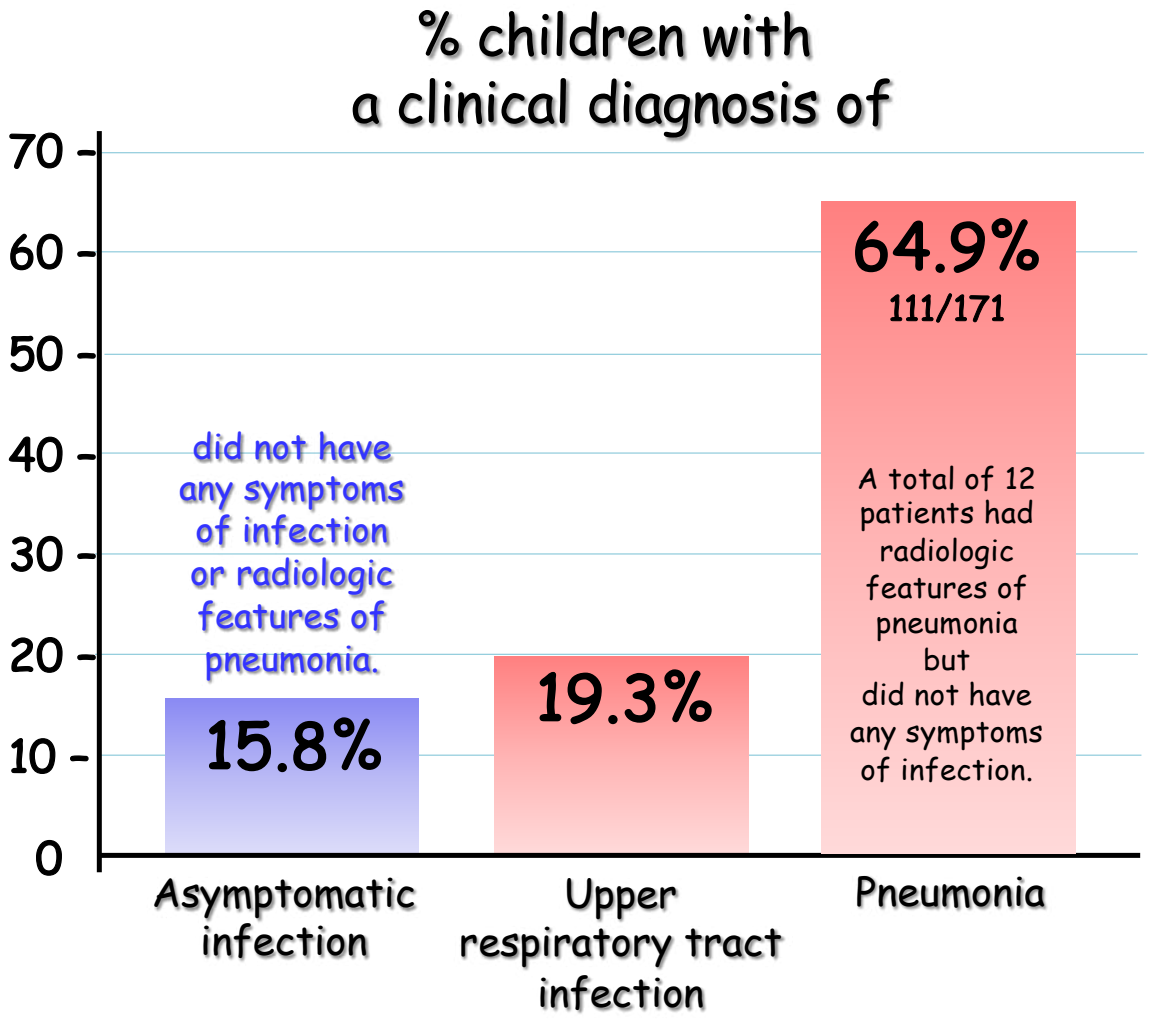

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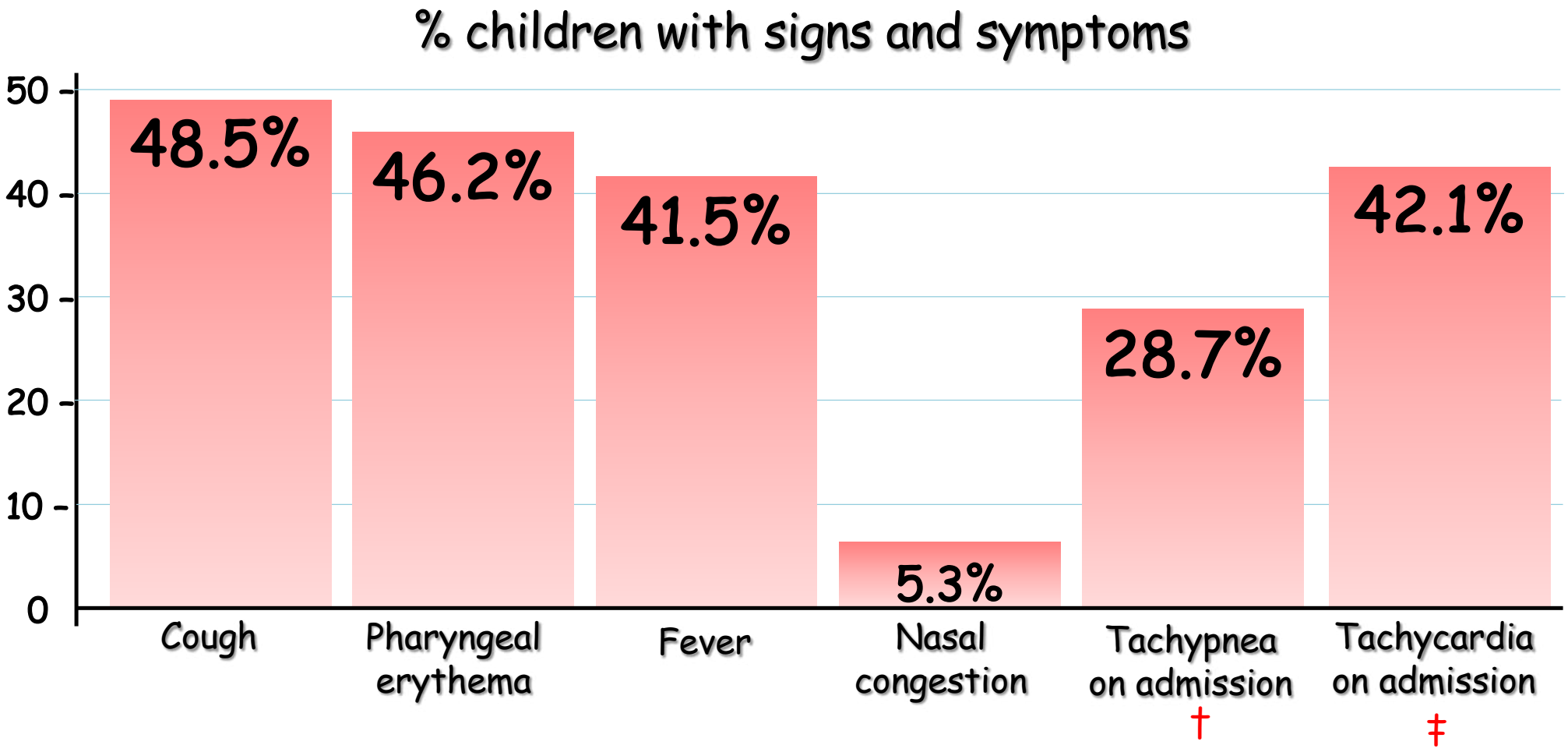

Oxygen saturation <92% during period of hospitalization was observed in only 2.3%

SARS-CoV-2 Infection in Children .

Lu X, N Engl J Med. 2020;10.1056/NEJMc2005073.

† **The normal ranges of respiratory rate** (in breaths per minute) were as follows:
40 to 60 for newborns,
30 to 40 for children younger than 1 year of age,
25 to 30 for those 1 to 3 years of age,
20 to 25 for those 4 to 7 years of age,
18 to 20 for those 8 to 14 years of age, and
12 to 20 for those older than 14 years of age.
Tachypnea refers to a respiratory rate higher than the upper limit of the normal range according to age.

‡ **The normal ranges of pulse rate** (in beats per minute) were as follows:
120 to 140 for newborns,
110 to 130 for children younger than 1 year of age,
100 to 120 for those 1 to 3 years of age,
80 to 100 for those 4 to 7 years of age,
70 to 90 for those 8 to 14 years of age, and
60 to 70 for those older than 14 years of age.
Tachycardia refers to a pulse rate higher than the upper limit of the normal range according to age.

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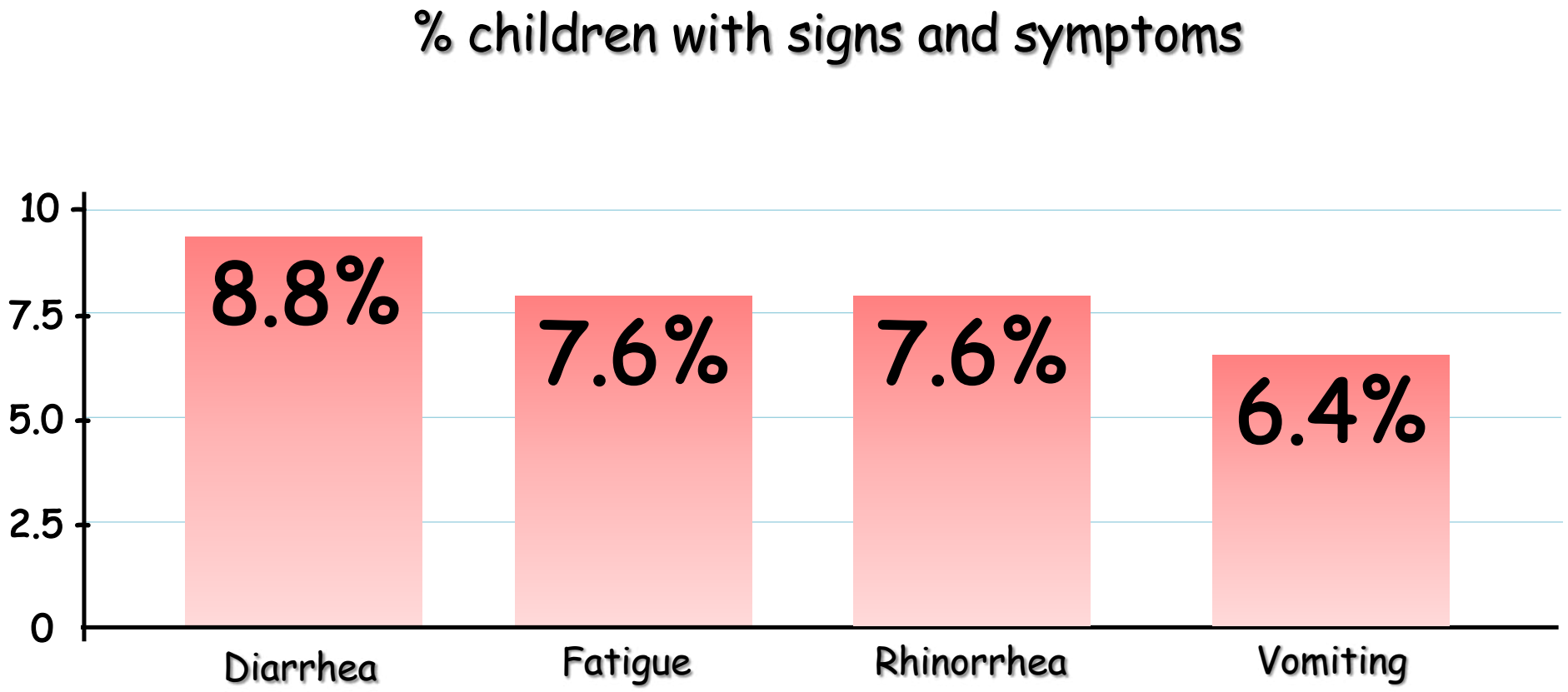

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Other Clinical & Radiologic Findings of 171 Children with SARS-CoV-2 Infection.*

Characteristic	Value
Median duration of fever (range) — days	3 (1–16)
Highest temperature during hospitalization — no. (%)	no. (%)
<37.5°C	100 (58.5)
37.5–38.0°C	16 (9.4)
38.1–39.0°C	39 (22.8)
>39.0°C	16 (9.4)
Abnormalities on computed tomography of the chest — no. (%)	
Ground-glass opacity	56 (32.7)
Local patchy shadowing	32 (18.7)
Bilateral patchy shadowing	21 (12.3)
Interstitial abnormalities	2 (1.2)

* Percentages may not total 100 because of rounding.

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Interstitial abnormalities	2 (1.2)

Lymphopenia (lymphocyte count, $<1.2\times10^9$ per liter) was present in 6 patients (3.5%).

SARS-CoV-2 Infection in Children .

Lu X, N Engl J Med. 2020;10.1056/NEJMc2005073.

- During the course of hospitalization, 3 patients required intensive care support and invasive mechanical ventilation; all had coexisting conditions (hydronephrosis, leukemia [for which the patient was receiving maintenance chemotherapy], and intussusception).

- A 10-month-old child with intussusception had multiorgan failure and died 4 weeks after admission.

- As of March 8, 2020, a total of 21 patients were in stable condition in the general wards, and 149 have been discharged from the hospital.

SARS-CoV-2 Infection in Children .

Lu X, N Engl J Med. 2020;10.1056/NEJMc2005073.

- In contrast with infected adults, most infected children appear to have a milder clinical course.

- Asymptomatic infections were not uncommon.

- Determination of the transmission potential of these asymptomatic patients is important for guiding the development of measures to control the ongoing pandemic.

Children are less susceptible to COVID-19

- Available reports to date show that **COVID-19 seems to be uncommon in children.**

- C. Huang, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 395 (2020), pp. 497-506.
- Q. Li, Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med (2020), 10.1056/NEJMoa2001316
- W.C. Ko, Remdesivir for SARS-CoV-2 pneumonia Int J Antimicrob Agents (2020)

- Recent data reported from the Chinese Centers for Diseases Control and Prevention indicated that **among the 44,672 confirmed cases of COVID-19** as of February 11, 2020,

  - **416 (0.9%) were aged 0–10 years** and
  - **549 (1.2%) aged 10–19 years.**

The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020. CCDC weekly 2020;2. Zhonghua Liu Xing Bing Xue Za Zhi vol. 41 (2020), pp. 145-151 [in Chinese]

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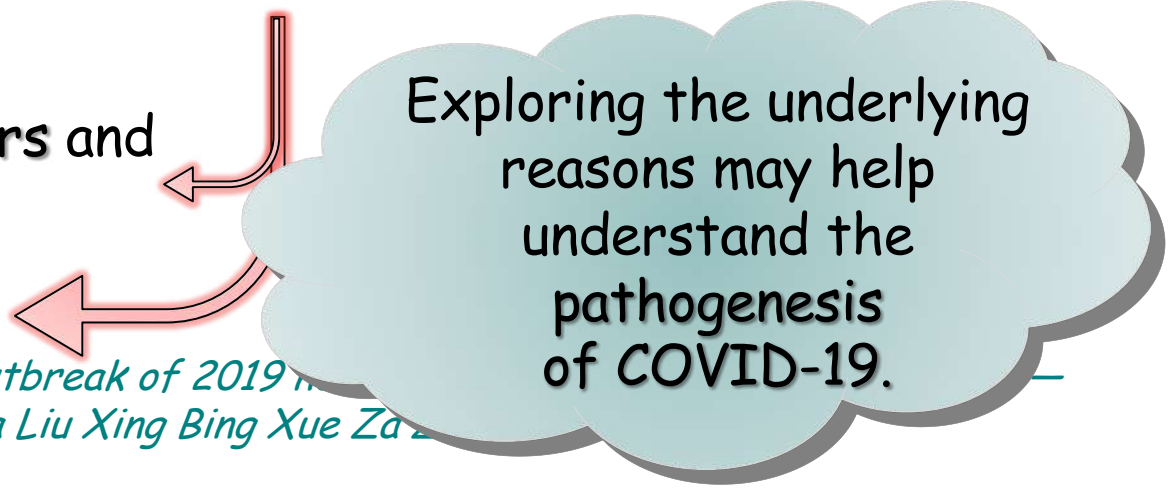

The epidemiological characteristics of an outbreak of 2019 n… China, 2020. CCDC weekly 2020;2. Zhonghua Liu Xing Bing Xue Za Z… vol. 41 (2020), pp. 145-151 [in Chinese]

Children are less susceptible to COVID-19

- There are many possible reasons for reduced susceptibility (to disease not to infection) because children have:

1) fewer outdoor activities and

2) undertake less international travel,

} making them less likely to contract the virus,

3) a more modulated innate immune response (more vitamin D?),

4) healthier respiratory tracts, and

} they have not been exposed to as much cigarette smoke and air pollution as adults

5) fewer underlying disorders.

Lee PI, Are children less susceptible to COVID-19? J Microbiol Immunol Infect. 2020;S1684-1182(20)30039-6.

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A more vigorous and disregulated immune response in adults may be associated with the acute respiratory distress syndrome.

4) healthier respiratory trac… and

} they have not been exposed to as much …ette smoke and air pollution as adults

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Lee PI, Are children less susceptible … 1182(20)30039-6.

Children are less susceptible to COVID-19

- A difference in the distribution, maturation, and functioning of viral receptors is frequently mentioned as a possible reason of the age-related difference in incidence.

- The SARS virus, SARS-CoV-2, and human coronavirus-NL63 (HCoV-NL63) all use the angiotensin-converting enzyme-2 (ACE2) as the cell receptor in humans.

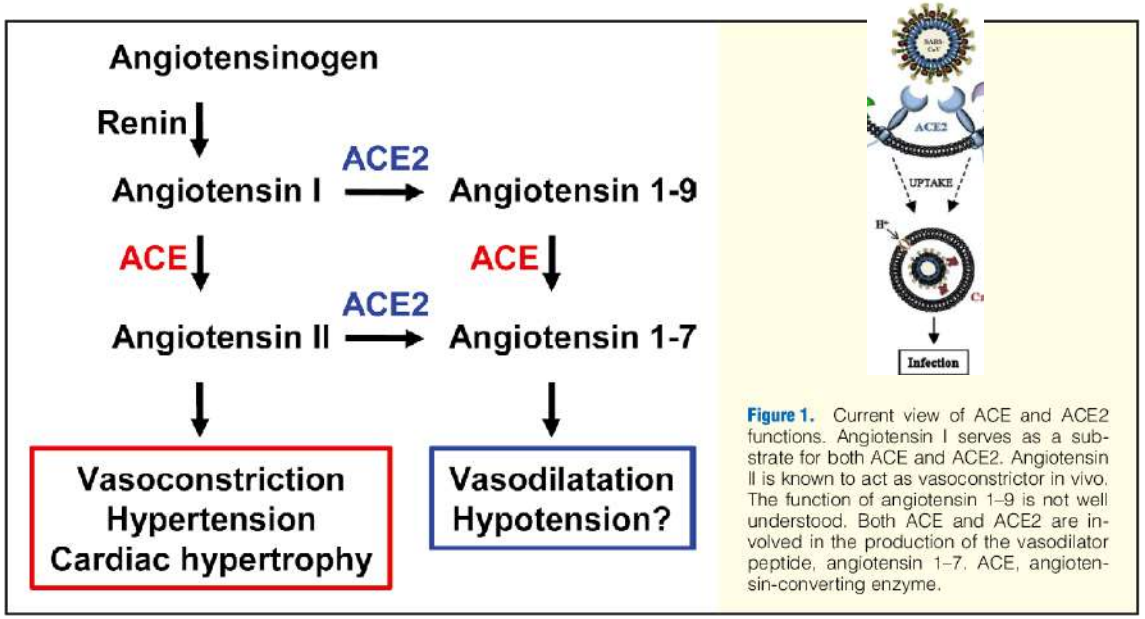

Figure 1. Current view of ACE and ACE2 functions. Angiotensin I serves as a substrate for both ACE and ACE2. Angiotensin II is known to act as vasoconstrictor in vivo. The function of angiotensin 1–9 is not well understood. Both ACE and ACE2 are involved in the production of the vasodilator peptide, angiotensin 1–7. ACE, angiotensin-converting enzyme.

- Previous studies demonstrated that HCoV-NL63 infection is more common in adults than in children.

S.H. Huang, Epidemiology of human coronavirus NL63 infection among hospitalized patients with pneumonia in Taiwan. J Microbiol Immunol Infect, 50 (2017), pp. 763-770.

Children are less susceptible to COVID-19

But ACE2 expression in rat lung has been found to dramatically decrease with age. *X. Xie, Life Sci, 78 (2006), pp. 2166-2171*

This finding may not be consistent with
a relatively low susceptibility of children to COVID-19.

However, studies show that ACE2 is involved
in protective mechanisms of the lung.

- It may protect against severe lung injury induced by respiratory virus infection in an experimental mouse model and in pediatric patients.

- ACE2 also protects against severe acute lung injury that can be triggered by sepsis, acid aspiration, SARS, and lethal avian influenza A H5N1 virus infection. *H. Gu, Sci Rep, 6 (2016), p. 19840.*

Children are less susceptible to COVID-19

- Furtermore, several infectious diseases are well known to be less severe in children:

  - Paralytic polio occurred in approximately 1 in 1000 infections among infants, in contrast to approximately 1 in 100 infections among adolescents.

  - As compared with young children, teenagers and adults tend to have symptomatic rubella more frequently and have systemic manifestations.

Lee PI, Are children less susceptible to COVID-19? [published online ahead of print, 2020 Feb 25]. J Microbiol Immunol Infect. 2020;S1684-1182(20)30039-6. doi:10.1016/j.jmii.2020.02.011

➢ Thus far, no deaths have been reported in the paediatric age group.

Understanding of COVID-19 based on current evidence

Attilio Boner
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- ✓ Introduction
- ✓ Sources of SARS-CoV-2
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- ✓ Symptoms, & Diagnosis
- ✓ The case of infants & children
- ✓ The case of mother & fetus
- ✓ The case of Italy
- ✓ Treatment
- ✓ Prevention
- ✓ Conclusions

Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia.

Zhu H, Transl Pediatr. 2020;9(1):51-60.

✓clinical features and outcomes of 10 neonates (including 2 twins) born to 9 mothers with confirmed 2019-nCoV infection in 5 hospitals from January 20 to February 5, 2020 retrospectively analyzed.

➢Among these 9 pregnant women with confirmed 2019-nCoV infection:

❑**onset of clinical symptoms** occurred:
- before delivery in 4 cases,
- on the day of delivery in 2 cases, and
- after delivery in 3 cases.

❑In most cases, **fever and a cough** were the first symptoms experienced, and 1 patient also had diarrhea.

Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia.

Zhu H, Transl Pediatr. 2020;9(1):51-60.

✓clinical features and outcomes of 10 neonates (including 2 twins) born to 9 mothers with confirmed 2019-nCoV infection in 5 hospitals from January 20 to February 5, 2020 retrospectively analyzed.

➢Of the newborns born to these mothers,

- 8 were male and 2 were female;
- 4 were full-term infants and
- **6 were born premature (60%);**
- 2 were small-for-gestational-age (SGA) infants and
- 1 was a large-for-gestational-age (LGA) infant;
- there were 8 singletons and 2 twins.

Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia.

Zhu H, Transl Pediatr. 2020;9(1):51-60.

✓clinical features and outcomes of 10 neonates (including 2 twins) born to 9 mothers with confirmed 2019-nCoV infection in 5 hospitals from January 20 to February 5, 2020 retrospectively analyzed.

*The PCIS has 10 items. The full score is 100.
The scores of approximately 100 = non-serious condition
approximately 80 = serious condition
approximately 70 = extremely serious patients' condition.

- Of the neonates,

❑6 had a Pediatric Critical Illness Score (PCIS)* score < 90.(moderate/serious condition)

❑the first symptom in the neonates was:

- shortness of breath (n=6),
- fever (n=2),
- thrombocytopenia accompanied by
- abnormal liver function (n=2),
- rapid heart rate (n=1),
- vomiting (n=1), and
- pneumothorax (n=1).

Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia.

Zhu H, Transl Pediatr. 2020;9(1):51-60.

✓clinical features and outcomes of 10 neonates (including 2 twins) born to 9 mothers with confirmed 2019-nCoV infection in 5 hospitals from January 20 to February 5, 2020 retrospectively analyzed.

- 5 neonates have been cured and discharged,
- 1 has died, and
- 4 neonates remained in hospital in a stable condition

❑Pharyngeal swab specimens were collected from 9 of the 10 neonates 1 to 9 days after birth for nucleic acid amplification tests for 2019-nCoV, all of which showed negative results.

Detection

PCR
Isothermal nucleic acid amplification
Microarray
.....

Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia.

Zhu H, Transl Pediatr. 2020;9(1):51-60.

Conclusions:

- Perinatal 2019-nCoV infection may have adverse effects on newborns, causing problems such as:
  - fetal distress,
  - premature labor,
  - respiratory distress,
  - thrombocytopenia accompanied by abnormal liver function, and
  - even death.

- However, vertical transmission of 2019-nCoV is yet to be confirmed.

Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records.

Chen H, Lancet. 2020;395(10226):809-815.

✓9 pregnant women with laboratory-confirmed COVID-19 pneumonia

✓Evidence of intrauterine vertical transmission by testing for the presence of SARS-CoV-2 in amniotic fluid, cord blood, and neonatal throat swab samples.

✓Breastmilk samples tested after the first lactation.

❑7 patients presented with a fever.

❑Other symptoms, included:
- cough (in 4 of 9 patients),
- myalgia (in 3),
- sore throat (in 2), and
- malaise (in 2).

❑None of the patients developed severe COVID-19 pneumonia or died

❑All nine patients had a caesarean section in their third trimester.

Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records.

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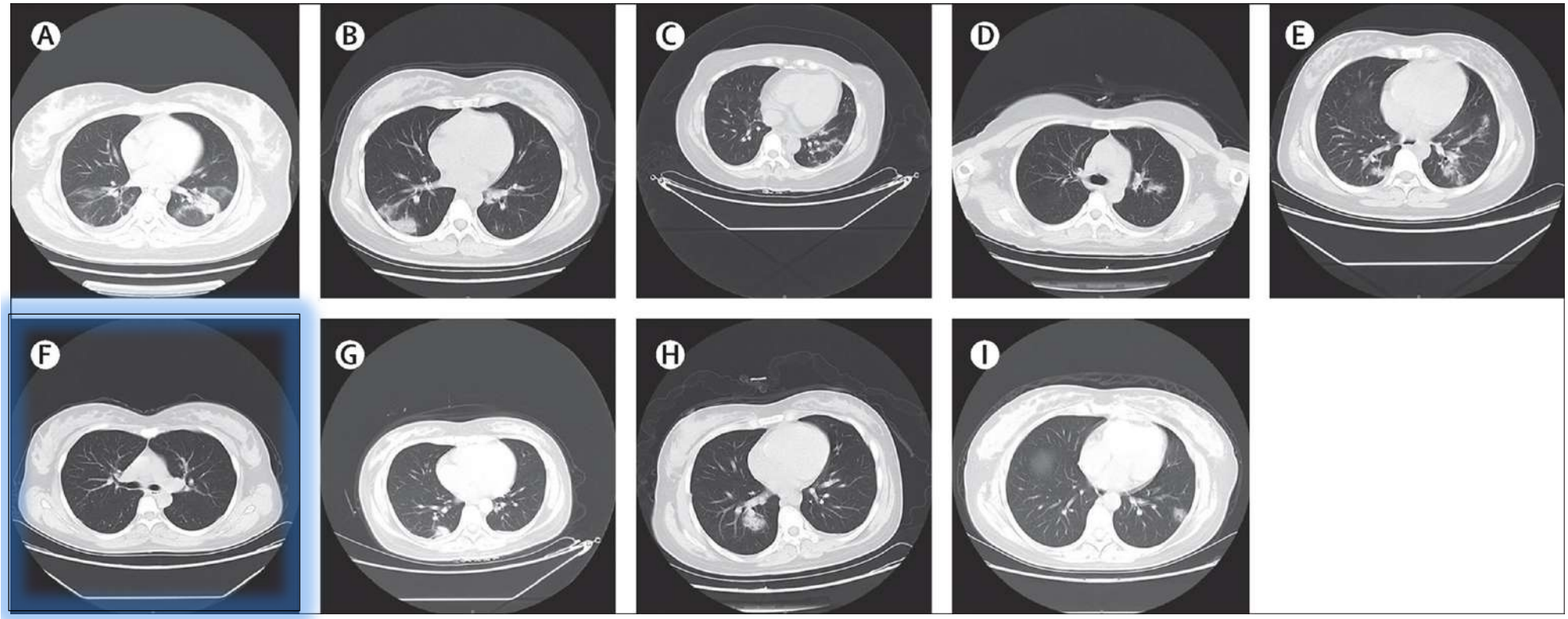
All 9 patients had a chest CT scan.

8 patients showed typical findings of chest CT images—multiple patchy ground-glass shadows in lungs



(A) Patient 1: left-sided patchy consolidation and multiple bilateral ground-glass opacities. (B) Patient 2: subpleural patchy consolidation in the right lung and slightly infiltrated shadows around left bronchus. (C) Patient 3: bilateral multiple ground-glass opacities, prominent on the left. (D) Patient 4: left-sided patchy ground-glass opacity. (E) Patient 5: multiple ground-glass opacities bilaterally. (F) Patient 6: bilateral clear lung fields with no obvious ground-glass opacities. (G) Patient 7: right-sided subpleural patchy consolidation. (H) Patient 8: multiple bilateral ground-glass opacities, prominent on the right. (I) Patient 9: multiple bilateral ground-glass opacities.

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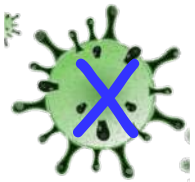
✓Evidence of intrauterine vertical transmission by testing for the presence of SARS-CoV-2 in amniotic fluid, cord blood, and neonatal throat swab samples.

✓Breastmilk samples tested after the first lactation.

❑No neonatal asphyxia was observed in newborn babies.

❑All nine livebirths had a 1-min Apgar score of 8-9 and a 5-min Apgar score of 9-10.

❑Amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples all tested negative for the virus.



Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records.

Chen H, Lancet. 2020;395(10226):809-815.

- Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia, because they are at an immunosuppressive state, and physiological adaptive changes during pregnancy (eg, diaphragm elevation, increased oxygen consumption, and oedema of respiratory tract mucosa) can render them intolerant to hypoxia.

- For example, the 1918 influenza pandemic caused a mortality rate of 2·6% in the overall population, but 37% among pregnant women.

- Pregnant women were reported to be at an increased risk of complications from the pandemic H1N1 2009 influenza virus infection, and were more than 4 times more likely to be admitted to hospital than the general population (relative risk 4·3 [95% CI 2·3–7·8]).

Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records.

Chen H, Lancet. 2020;395(10226):809-815.

- Around 50% of pregnant women who developed SARS in 2002-2003 were admitted to the intensive care unit,

- Around 33% of pregnant women with SARS required mechanical ventilation, and the mortality rate was as high as 25% for these women.

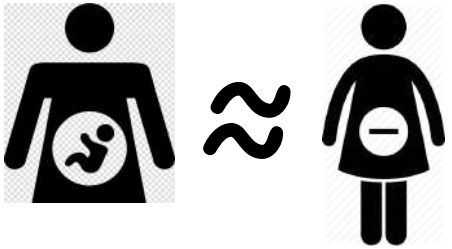
- Considering that SARS-CoV-2 has up to 85% sequence similarity with SARS, although none of our 9 patients developed severe pneumonia or died of COVID-19 infection, we should be alert to the possibility that the disease course and prognosis of COVID-19 pneumonia could follow the same trend as SARS in pregnant women.

Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records.

Chen H, Lancet. 2020;395(10226):809-815.

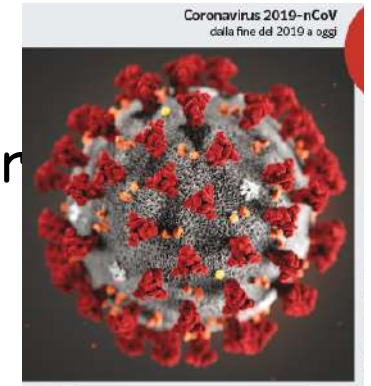
Interpretation:

- The clinical characteristics of COVID-19 pneumonia in pregnant women were similar to those reported for non-pregnant adult patients who developed COVID-19 pneumonia.



- Findings from this small group of cases suggest that there is currently no evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy and no evidence of increased susceptibility of pregnant women.

What are the risks of COVID-19 infection in pregnant women?. *Qiao J. Lancet. 2020;395(10226):760–762.*



- Homology modelling has revealed that SARS-CoV-2 has a similar receptor-binding domain structure to that of SARS-CoV-1, which suggests that COVID-19 infection might have a similar pathogenesis to SARS-CoV-1 infection.

- Thus, the risk of vertical transmission of COVID-19 might be as low as that of SARS-CoV-1.

- The present study by Chen and colleagues did not find any evidence of the presence of SARS-CoV-2 viral particles in the products of conception or in neonates, in accordance with the findings of a previous study on SARS-CoV-1.

SF Wong, Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome Am J Obstet Gynecol, 191 (2004), pp. 292-297.

What are the risks of COVID-19 infection in pregnant women?. *Qiao J. Lancet. 2020;395(10226):760-762.*

- Two neonatal cases of COVID-19 infection have been confirmed so far, with one case confirmed at 17 days after birth and having a close contact history with two confirmed cases (the baby's mother and maternity matron) and the other case confirmed at 36 h after birth and for whom the possibility of close contact history cannot be excluded.

National Health Commission of the People's Republic of China Transcript of Press Conference on Feb 7, 2020
http://www.nhc.gov.cn/xcs/s3574/202002/5bc099fc9144445297e8776838e57ddc.shtml,

- However, no reliable evidence is as yet available to support the possibility of vertical transmission of COVID-19 infection from the mother to the baby.

What are the risks of COVID-19 infection in pregnant women?. *Qiao J. Lancet. 2020;395(10226):760–762.*

- Previous studies have shown that SARS during pregnancy is associated with a high incidence of adverse maternal and neonatal complications, such as spontaneous miscarriage, preterm delivery, intrauterine growth restriction, application of endotracheal intubation, admission to the intensive care unit, renal failure, and disseminated intravascular coagulopathy.
  - *SF Wong, Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol, 191 (2004), pp. 292-297.*
  - *CM Lam, A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. BJOG, 111 (2004), pp. 771-774.*

- However, pregnant women with COVID-19 infection in the present study had fewer adverse maternal and neonatal complications and outcomes than would be anticipated for those with SARS-CoV-1 infection, the findings are mostly consistent with the clinical analysis done by Zhu and colleagues of ten neonates born to mothers with COVID-19 pneumonia.

H Zhu, Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia Transl Pediatr (2020).

What are the risks of COVID-19 infection in pregnant women?. *Qiao J. Lancet. 2020;395(10226):760–762.*

- Nonetheless, pregnant women and newborn babies should be considered key at-risk populations in strategies focusing on prevention and management of COVID-19 infection.

The National Health Commission of China proposed strengthening health counselling, screening, and follow-ups for pregnant women, reinforcing visit time and procedures in obstetric clinics and units with specialised infection control preparations and protective clothing,
and emphasised that

- neonates of pregnant women with suspected or confirmed COVID-19 infection should be isolated in a designated unit for at least 14 days after birth and
- should not be breastfed, to avoid close contact with the mother while she has suspected or confirmed COVID-19 infection.

National Health Commission of the People's Republic of ChinaNotice on strengthening maternal disease treatment and safe midwifery during the prevention and control of new coronavirus pneumonia
http://www.nhc.gov.cn/xcs/zhengcwj/202002/4f80657b346e4d6ba76e2cfc3888c630.shtml,

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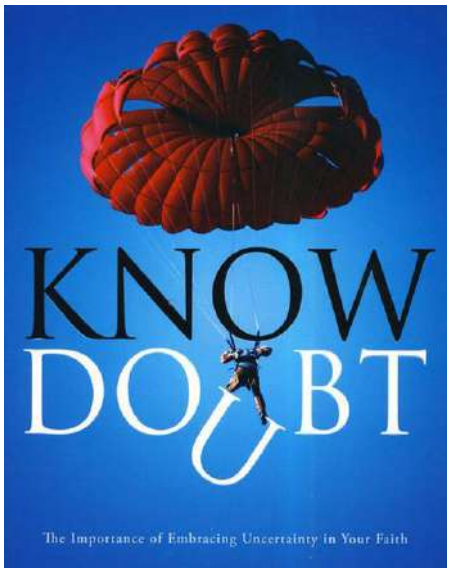

Newborn tests positive for COVID-19 in London
By Jeanna Bryner - Live Science Editor-in-Chief

Doctors don't know if the virus passed to the baby in the womb, or some time during or after delivery.

A newborn in London has tested positive for the novel coronavirus SARS-CoV-2, just minutes after being born to a mother who was also infected with the virus, according to news reports.

Days prior to giving birth, the woman was admitted to a hospital for symptoms of pneumonia, finding out she had tested positive for the virus that causes COVID-19 only after her baby was born at North Middlesex hospital in Enfield, in north London, The Guardian reported.

Coronavirus disease (COVID-19) and neonate: What neonatologist need to know.

Lu Q, J Med Virol. 2020;10.1002/jmv.25740. doi:10.1002/jmv.25740

TRANSMISSION

- Maternal-infant vertical transmission is doubtful— there have been no documented neonates of intrauterine vertical transmission occurring with SARS and MERS.

- At least 230 COVID-19 cases in children (≤18 years) have been reported in China.

- The SARS-CoV-2 rapid spread in children suggests that it has a strong transmission capacity in the special population (neonate, children).

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CLINICAL PRESENTATION OF COVID-19

- The incubation periods of COVID-19 were 1 to 14 days, with a mean of 5.2 days

- 97.5% of those who develop symptoms will do so within 10.5 days (95% CI: 7.3-15.3) of infection.

- SARS-CoV-2 infection can range from asymptomatic infection to severe respiratory distress in neonates and children.

- However, respiratory distress occurs in children with underlying conditions.

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CLINICAL PRESENTATION OF COVID-19

- The most common clinical symptoms of COVID-19 included fever, fatigue, and dry cough.

- A few patients showed upper respiratory symptoms such as nasal obstruction, nasal discharge, and sore throat.

- Gastrointestinal symptoms such as abdominal discomfort, vomiting, abdominal pain, and diarrhea may also occur.

- SARS-CoV-2 can be mixed to different pathogen including mycoplasma pneumonia, influenza A, influenza B, RSV, and EB virus.

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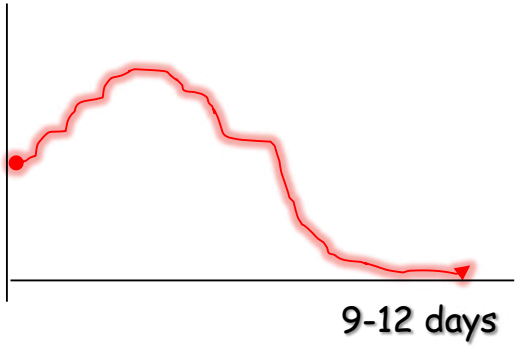
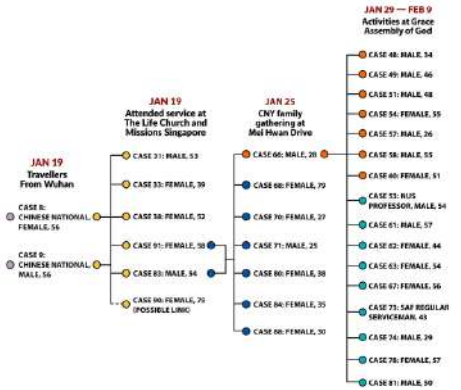
CLINICAL PRESENTATION OF COVID-19

- The clearance time of SARS-CoV-2 nucleic acid from nasopharyngeal swab was recorded in 3 children:
  9 days in two patients,
  12 days in one patient.



- Thus far, no deaths have been reported in the children which are similar to SARS.

- Few newborns have been diagnosed up to date who mainly belonged to family cluster cases.



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DIAGNOSIS

- The diagnosis of COVID-19 is based on comprehensive **contact history** and precise laboratory tests.

- Current diagnostic tools were the **nucleic acid or virus gene tests**.

- Samples included nasopharyngeal swab, sputum, secretion of the lower respiratory tract, blood, and feces.

- The **nasopharyngeal swab** is the most common specimens, however, its **detection positive rate is less than 50%.**

- Repeated detection is necessary for improving the positive rate.

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DIAGNOSIS

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- Sam
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The positive rate of **bronchoalveolar lavage** fluid was high, but it is not suitable for most of the patients due to increased risk of cross-infection

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INFECTION CONTROL AND TREATMENT

designed to filter 95% of airborne particles

- Neonatologist must wear protective equipment (including hats, goggles, protective suits, gloves, N95 masks, etc) to resuscitate neonates delivered by confirmed and/or suspected COVID-19 puerperant.

- If the puerperant is positive for SARS-CoV-2, the neonate must be isolated, then detected SARS-CoV-2.

- Early identification and early isolation are imperative for COVID-19 control.

- COVID-19 neonates should be placed in negative pressure rooms or in rooms in which room exhaust is filtered through high-efficiency particulate air filters with reference to MERS management.

- No visiting is allowed for neonates of COVID-19.

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Treatment mainly depends on adult patients' clinical experience due to few cases in children.

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INFECTION CONTROL AND TREATMENT

- Symptomatic and supportive treatment is the mainstay of therapy for patients of SARS-CoV-2 infection including the supply of oxygen, the maintenance of water-electrolyte, and acid-base balance.

- The supplement of water and electrolyte should be appropriate, so as to avoid aggravating the pulmonary edema and reduced oxygenation.

The Society of Pediatrics, Chinese Medical Association, The Editorial Board, Chinese Journal of Pediatrics. Recommendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition). Chin J Pediatr. 2020;58(3):169-174.

- For newborns with severe acute respiratory distress syndrome, high-dose pulmonary surfactant, inhaled nitric oxide, high-frequency oscillatory ventilation, and extracorporeal membrane lung may be useful.

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  so as to av ... **ion.**
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- **For** ...
  high-dose pulmon ... **ide, high-frequency oscillatory ventilation, and extracorporeal membrane lung** may be useful.

Moreover, **convalescent sera from SARS-CoV-2-recovered patients may be useful for SARS-CoV-2 infection**, because of a significant reduction in the mortality following convalescent sera from SARS-recovered patients treatment.

Understanding of COVID-19 based on current evidence

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

- ✓ Introduction
- ✓ Sources of SARS-CoV-2
- ✓ Epidemiology
- ✓ Etiology & Pathogenesis
- ✓ Symptoms, & Diagnosis
- ✓ The case of infants & children
- ✓ The case of mother & fetus
- ✓ The case of Italy
- ✓ Treatment
- ✓ Prevention
- ✓ Conclusions

The possible Latitude Effects

interview to Human Virology Scientists

By Dennis Thompson *HealthDay Reporter*, March 19, 2020

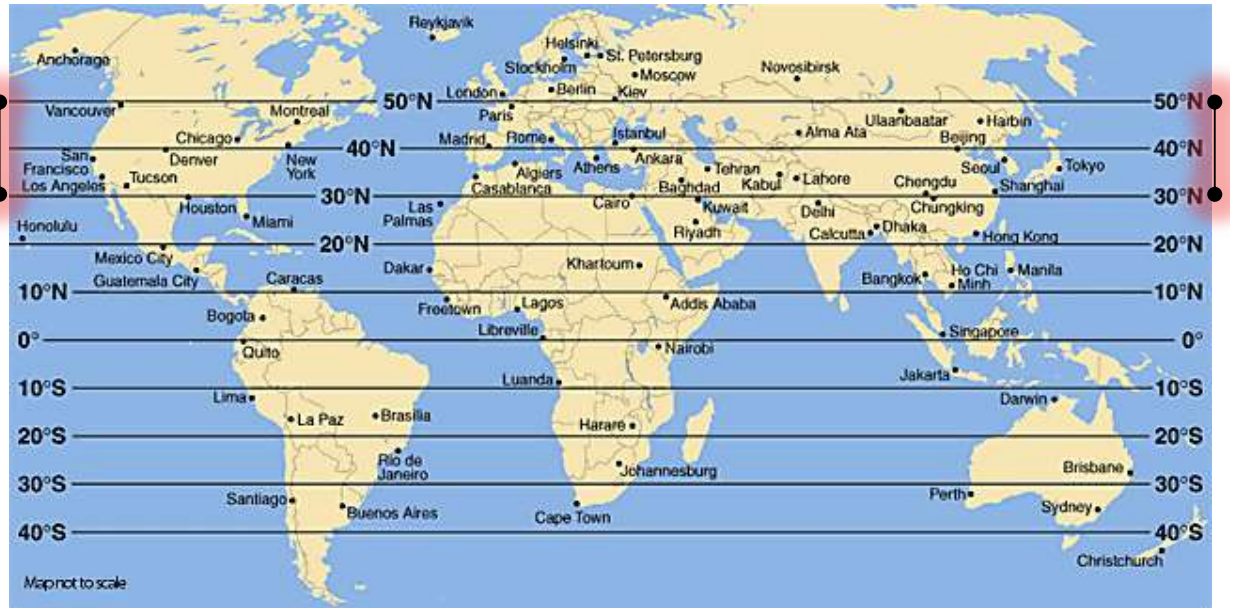
Prof Mohammad Sajadi Institute of Human Virology at the University of Maryland School of Medicine, in Baltimore

- The novel coronavirus appears to arise with major outbreaks occurring mainly in regions that match **a specific set of climate conditions.**

- All areas experiencing significant outbreaks of COVID-19 fall within a **northern corridor** that has an **average temperature of 5° to 11° degrees Celsius** and an **average humidity of 47% to 79%.**

Temperature, humidity, and latitude analysis to predict potential spread and seasonality for COVID-19

- These affected regions -- China, South Korea, Japan, Iran, Northern Italy, New York, Seattle and Northern California -- all fall within a band **between 30 to 50 degrees Northern latitude.**



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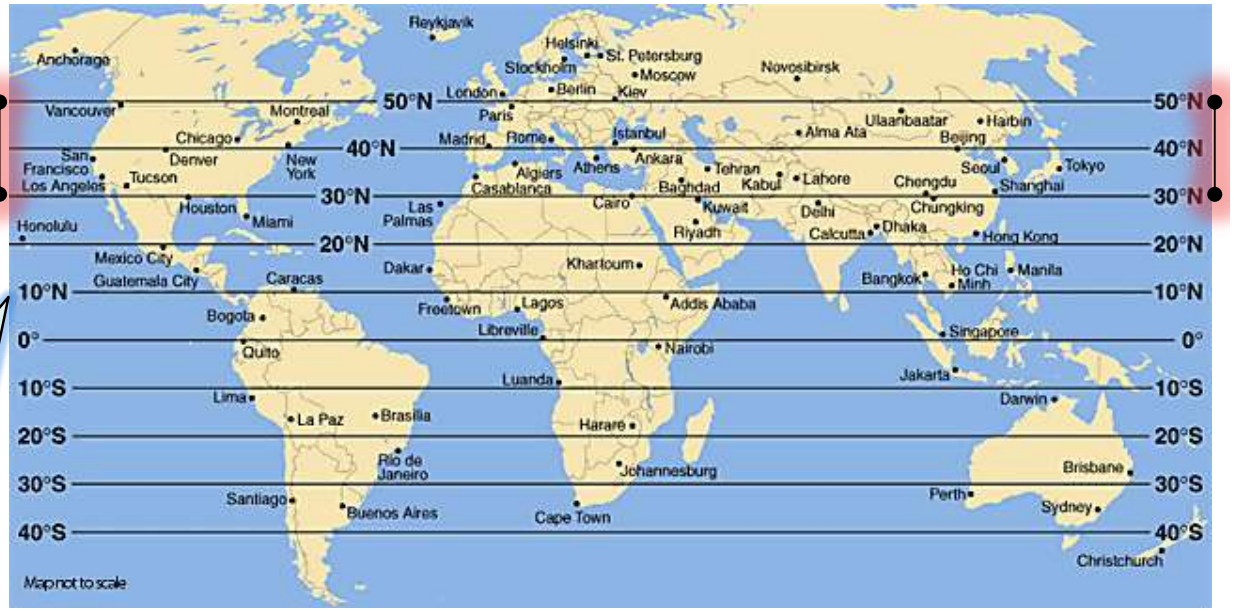
Temperature, humidity, and latitude analysis to predict potential spread and seasonality for COVID-19

There's been a lack of significant spread of COVID-19 into countries farther South



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- "To us, this suggests temperature and also low absolute and specific humidity could hold a key role in transmission."

- "Putting all this together, we think the distribution of significant community outbreaks along restricted latitude, temperature and humidity are consistent with the behavior of a seasonal respiratory virus,"

- This doesn't mean that COVID-19 infection rates can be expected to fall with the coming of summer, however.

- Infectious disease experts note that the novel coronavirus has proven particularly infectious, given that humans have no established immunity against it.

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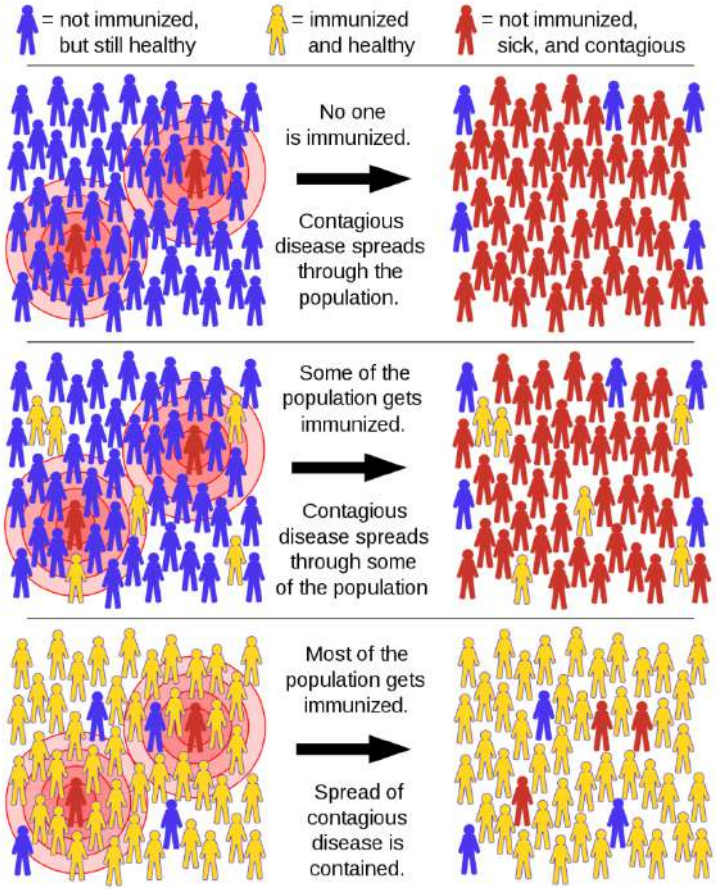
Dr. Elizabeth Halloran, professor of biostatistics at the University of Washington School of Public Health

- The coronavirus has an estimated **transmission rate ≥ 2.5**, said Elizabeth Halloran, a professor of biostatistics at the University of Washington School of Public Health, in Seattle.

- That means every 2 people infected with the virus will likely spread it to a total 5 more people.

- **A virus stops being contagious when its transmission rate drops below 1,** meaning that a person infected with it is not likely to spread it to another human being.



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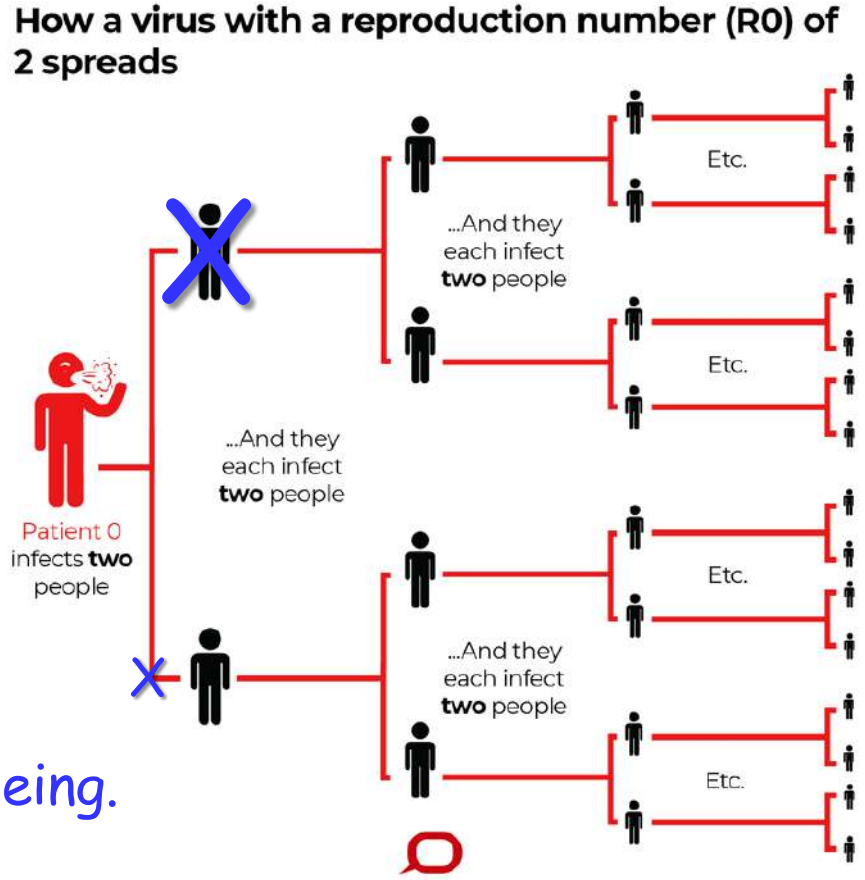

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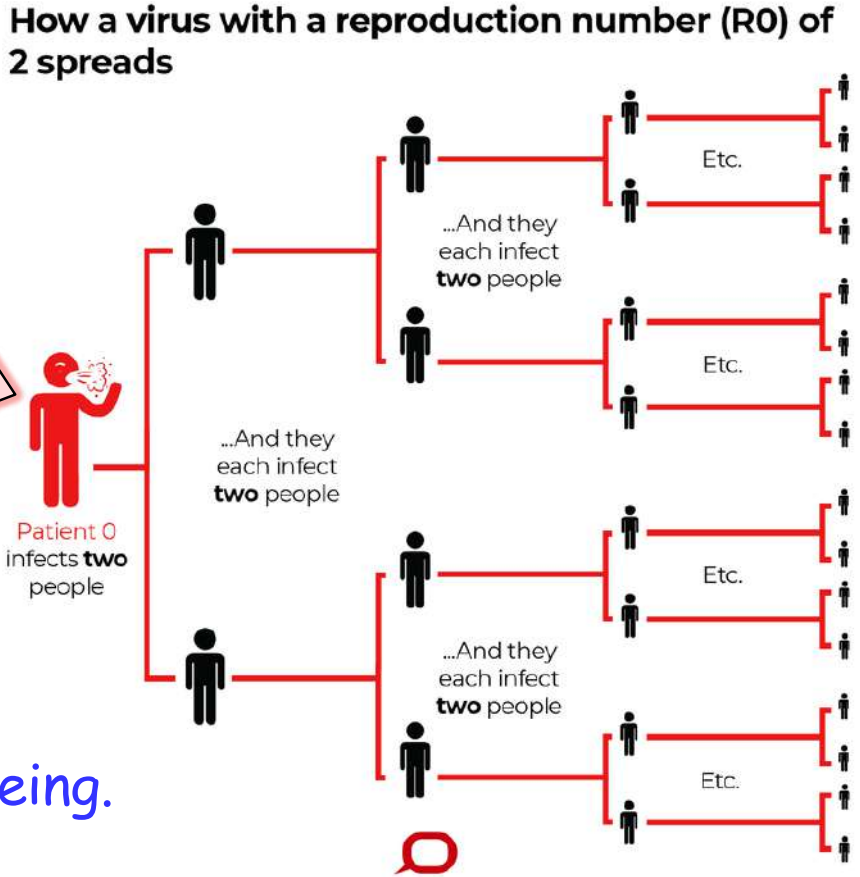
"It's going to be difficult, even if it does go down somewhat seasonally in the summer, to bring that down necessarily below 1," Halloran said. *"We're looking at a very contagious infection."*



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interview to Human Virology Scientists

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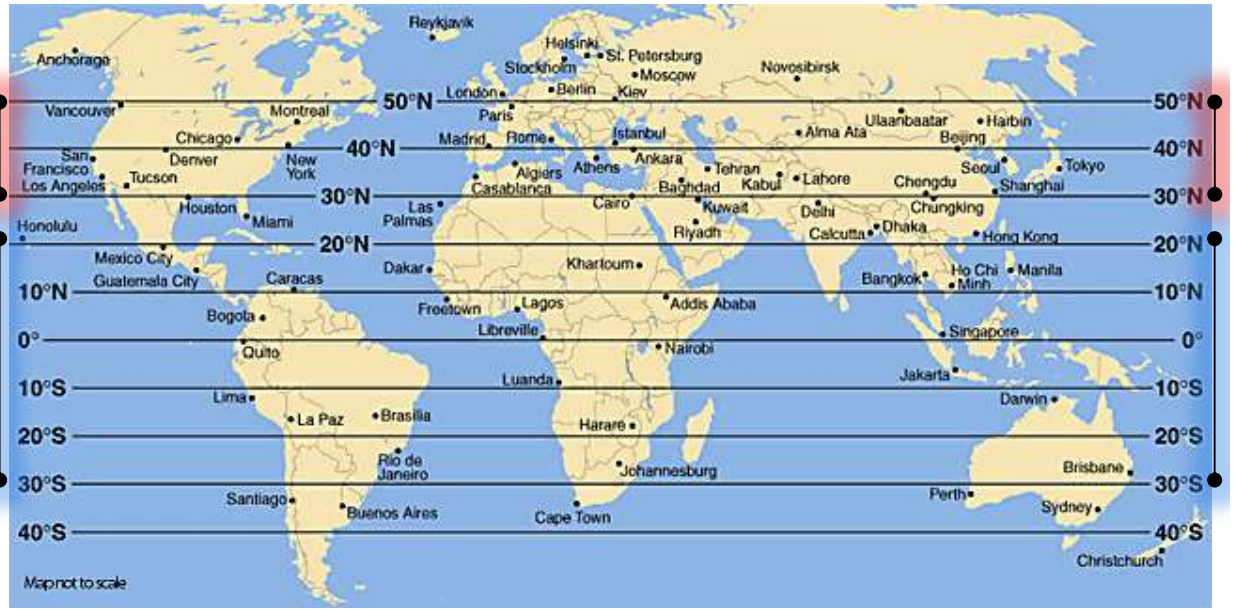
The investigators found that in cities where the coronavirus is spreading within a community -- **Wuhan, Milan and Tokyo – temperatures did not drop below the freezing mark.**

Lab studies also showed that a temperature of 4°C and a humidity level of 20% to 80% is most conducive to the virus' survival.

"Based on what we have documented so far, it appears that the virus has a harder time spreading between people in warmer, tropical climates," *Sajadi said.*



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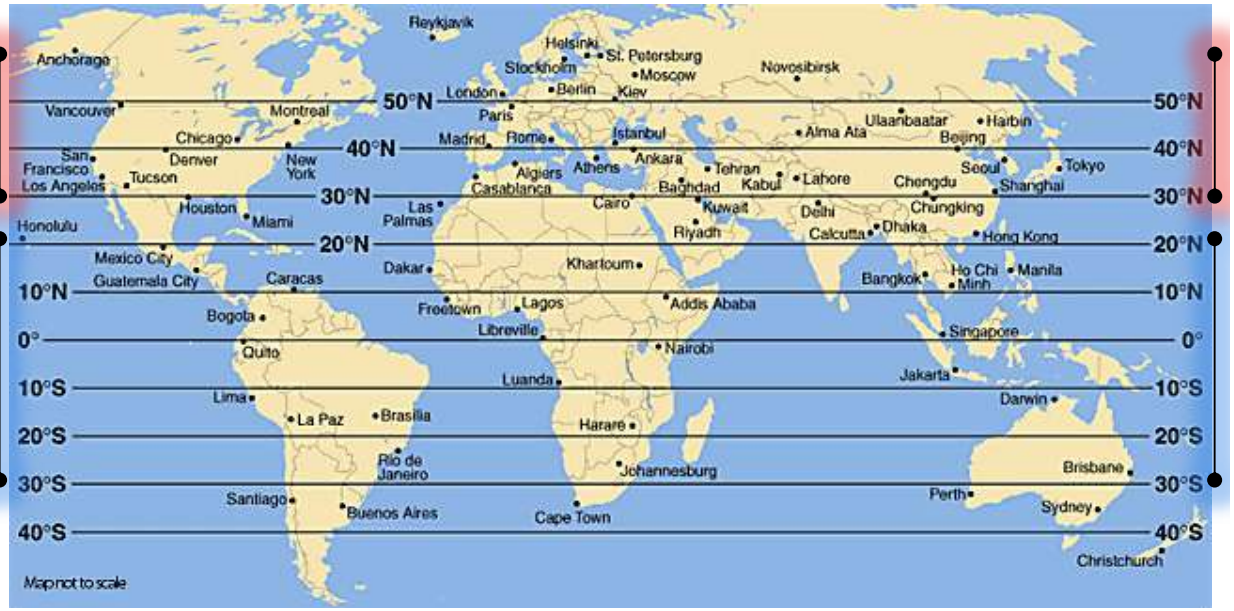
Lab studies also showed that a temperature of 4°C and a humidity level of 20% to 80% is most conducive to the virus' survival.

But Sajadi and his colleagues warned that risk of community spread could increase in more northern areas like the Mid-Atlantic states and New England as spring blooms.



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By Dennis Thompson *HealthDay Reporter*, March 19, 2020

Dr. Martin Hirsch, professor of infectious diseases and immunology at the Harvard T.H. Chan School of Public Health, in Boston, and Editor-in-Chief of J Infect Diseases

- No one's really sure why season is a factor in the spread of viruses like influenza and coronavirus.

- It's not been established whether viruses can't survive in warmer weat.

- Further, each virus responds to weather in its own way,

noted Dr. Martin Hirsch, a professor of infectious diseases and immunology at the Harvard T.H. Chan School of Public Health, in Boston.

- "SARS [severe acute respiratory syndrome] appeared in winter and was gone by June.

- Others like MERS [Middle East respiratory syndrome] certainly persist on the Arabian peninsula, however, which is pretty hot," Hirsch noted.

The possible Latitude Effects

interview to Human Virology Scientists

By Dennis Thompson *HealthDay Reporter*, March 19, 2020

Nicholas DeFelice, assistant professor of environmental medicine and public health the Icahn School of Medicine at Mount Sinai in New York City

- "Environmental conditions are one of many things that play a role within disease transmission as it is," .

- "If people are susceptible, the virus can still transmit even under less-than-ideal circumstances."

- "Also, keep in mind that being in a low-risk area does not necessarily mean that a significant outbreak will not happen there,"

- "Public health measures may play the strongest predictive role in determining whether this virus spreads widely in the U.S.".

- "That is why implementation of social distancing is just as crucial in Miami as it is in New York, despite the differences in temperature."

Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line

Rosenbaum L, M.D. March 18, 2020 DOI: 10.1056/NEJMp2005492

- A few weeks ago, Dr. D., a middle-aged chief of cardiology at one of the biggest hospitals in northern Italy, developed a fever.
- Fearing he might have Covid-19, he sought confirmatory testing but was told there weren't enough tests available for those who hadn't had demonstrated exposure to an infected person.

- He was therefore advised to stay home until the fever resolved.
- He returned to work 6 days later, but 5 days after that, a mild fever recurred, and soon he developed a cough.

- He again quarantined himself in the basement of his home so as not to expose his family.

- With half his hospital's 1000 beds occupied by patients with Covid-19, Dr. D., who finally received a positive test result on March 10, knows he's fortunate.

Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line

Rosenbaum L, M.D. March 18, 2020 DOI: 10.1056/NEJMp2005492

- About 60 to 90 patients with symptoms suggestive of Covid-19 were presenting to his hospital's emergency department daily.

- Noninvasive ventilation was attempted in as many as possible, but the rapidity of respiratory deterioration in the most severely affected patients, including some young ones, was striking and often unforeseeable.

- "You have no predictive bible to help you," Dr. D. told me.

- This uncertainty only heightened the agony of the impossible decisions doctors were facing.

- "We have to decide who can go forward," he said.

Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line

Rosenbaum L, M.D. March 18, 2020 DOI: 10.1056/NEJMp2005492

- Dr. L., a staff doctor at a different hospital, had received a hospital memo forbidding press interviews so as to avoid causing further public alarm.

- Yet, as he emphasized, minimizing the gravity of the situation was having lethal consequences.

- "The citizens won't accept the restrictions," he said, "unless you tell them the truth."

- That truth is rather grim.

- Though Italy's health system is highly regarded and has 3.2 hospital beds per 1000 people (as compared with 2.8 in the United States), it has been impossible to meet the needs of so many critically ill patients simultaneously.

Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line

Rosenbaum L, M.D. March 18, 2020 DOI: 10.1056/NEJMp2005492

- "The infection is everywhere in the hospital," Dr. D. told me. "Although you wear protective gear and do the best you can, you cannot control it."

- The challenge, he suggested, had less to do with caring for patients with Covid-19–related critical illness, in whose rooms clinicians are shielded in protective gear, than with caregivers' many other daily activities: touching computers, riding elevators, seeing outpatients, eating lunch.

- Mandatory quarantine of infected workers, even those with mild illness, seems critical to infection control.

- But not all caregivers are equally vulnerable to severe illness, and workforce shortages will have to be managed somehow.

Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line

Rosenbaum L, M.D. March 18, 2020 DOI: 10.1056/NEJMp2005492

- One junior attending, Dr. S., told me that at his hospital **young physicians were on the front lines**, signing up for extra shifts and working **outside their specialties**.

- Nevertheless, he describes an eagerness (impazienza) among his senior colleagues to step up (intensificare). **"You can see the fear in their eyes,"** he said, **"but they want to help."**

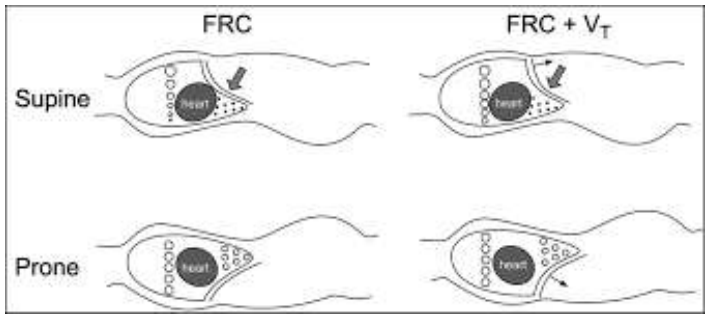
- Though Lombardy's richly resourced health care system has expanded critical care capacity as much as possible, **there simply were not enough ventilators for all patients who needed them.**

- "There is no way to find an exception," Dr. L. told me. **"We have to decide who must die and whom we shall keep alive."**

Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line

Rosenbaum L, M.D. March 18, 2020 DOI: 10.1056/NEJMp2005492

•Contributing to the resource scarcity is the prolonged intubation many of these patients require as they recover from pneumonia — often 15 to 20 days of mechanical ventilation, with several hours spent in the prone position and then, typically, a very slow weaning.



•In the midst of the outbreak's peak in northern Italy, as physicians struggled to wean patients off ventilators while others developed severe respiratory decompensation, hospitals had to lower the age cutoff — from 80 to 75 at one hospital, for instance.

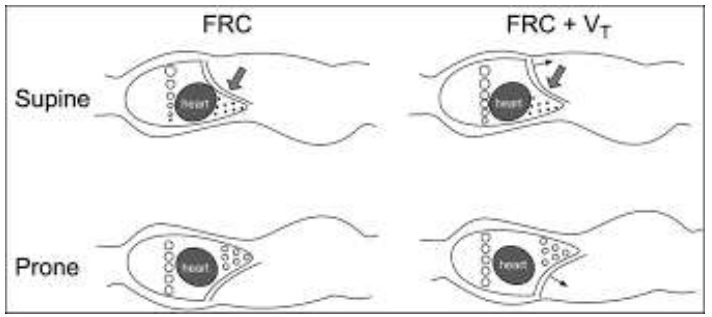
Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line

Rosenbaum L, M.D. March 18, 2020 DOI: 10.1056/NEJMp2005492

Dr. D. told me his hospital was also considering,

- the number of comorbidities,
- the severity of respiratory failure and probability of surviving prolonged intubation,

- aiming to dedicate its limited resources to those who both stand to benefit most and have the highest chance of surviving.



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Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line

Rosenbaum L, M.D. March 18, 2020 DOI: 10.1056/NEJMp2005492

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— from 80 to 75 at one hospital,

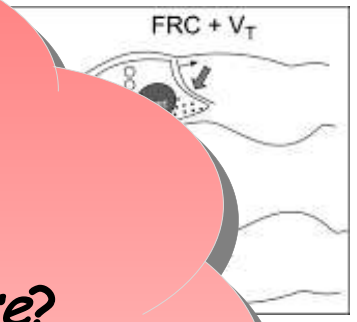
•Furthermore any physiscian should ask himself:

Am I a part of the cure, or am I part of the disease?

Keeping Coronavirus Out When a Doctor Comes Home

Rose C, M.D. March 18, 2020 DOI: 10.1056/NEJMp2004768

•41% of the Covid-19 cases in Wuhan resulted from hospital-related transmission.



Task force COVID-19 del Dipartimento Malattie Infettive e Servizio di Informatica, Istituto Superiore di Sanità. Epidemia COVID-19,

Aggiornamento nazionale: 23 marzo 2020

- I primi casi sintomatici risalgano alla fine di gennaio, con un andamento in crescita del numero di casi fino al 12 marzo 2020 .

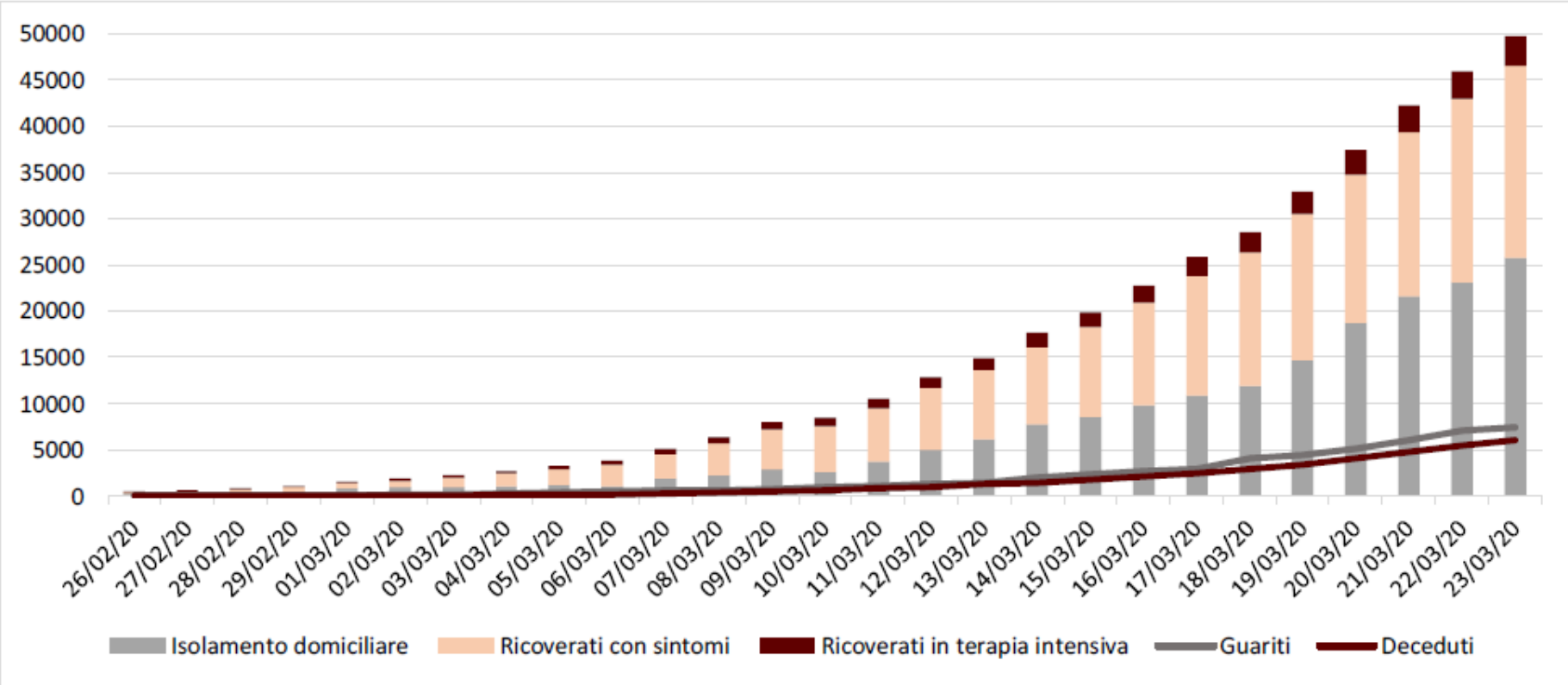
- L'indagine epidemiologica suggerisce che la trasmissione dell'infezione sia avvenuta in Italia per tutti i casi, ad eccezione dei primi tre casi segnalati dalla regione Lazio che si sono verosimilmente infettati in Cina.

- Attualmente lo stato clinico è disponibile solo per 17.798 casi, di cui
  - 1.063 (6,0%) asintomatici,
  - 1.900 (10,7%) pauci-sintomatici,
  - 2.940 (16,5%) con sintomi per cui non viene specificato il livello di gravità,
  - 7.316 (41,1%) con sintomi lievi,
  - 3.761 (21,1%) con sintomi severi tali da richiedere ospedalizzazione,
  - 818 (4,6%) con quadro clinico di gravità che richiede ricovero in Terapia Intensiva.

Task force COVID-19 del Dipartimento Malattie Infettive e Servizio di Informatica, Istituto Superiore di Sanità. Epidemia COVID-19,

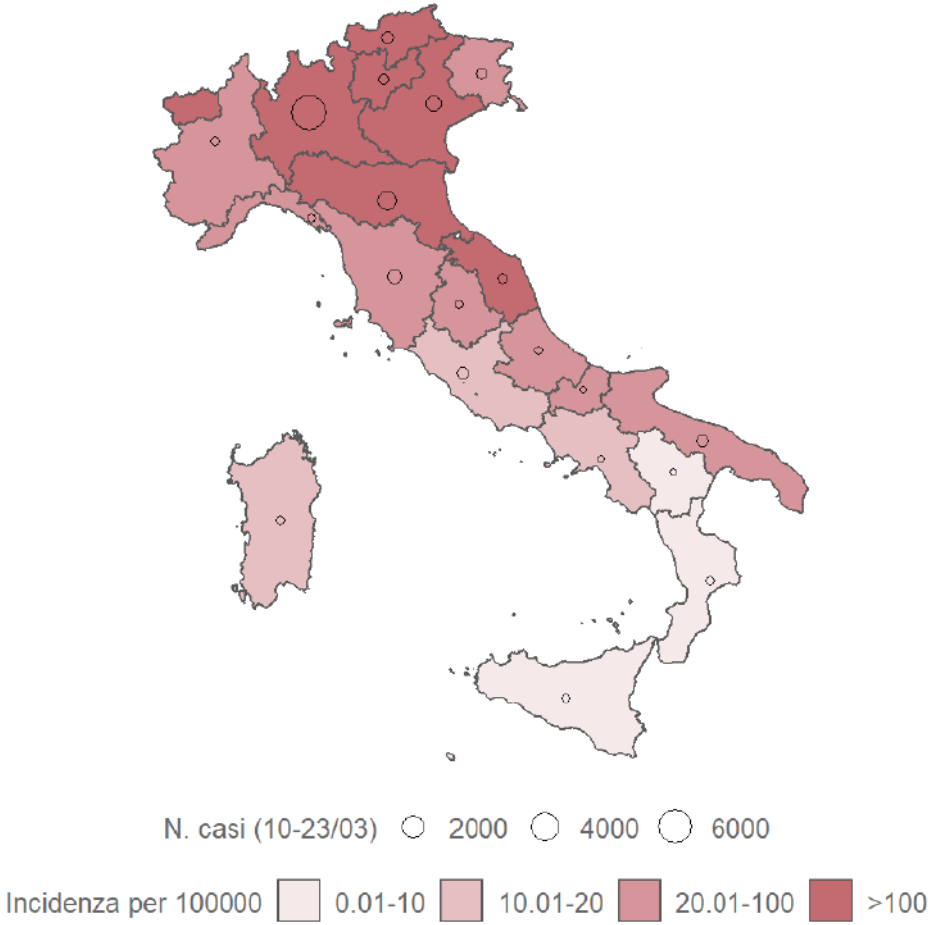
Aggiornamento nazionale: 23 marzo 2020

Numero Di Casi Cumulativo Di Covid-19 Diagnosticati Dai Laboratori Di Riferimento Regionale, Per Stato Di Ricovero/Isolamento ed Esito (N=63.927) Al 23/03/2020



Task force COVID-19 del Dipartimento Malattie Infettive e Servizio di Informatica, Istituto Superiore di Sanità. Epidemia COVID-19,

Aggiornamento nazionale: 23 marzo 2020



Incidenza (Per 100.000 Abitanti)
dei Casi di Covid-19 Diagnosticati dai Laboratori di Riferimento Regionale (N=57.989)
e
Numero di Casi Segnalati con Insorgenza Sintomi negli ultimi 14 Giorni (N=10.886),
per Regione

Task force COVID-19 del Dipartimento Malattie Infettive e Servizio di Informatica, Istituto Superiore di Sanità. Epidemia COVID-19,

Aggiornamento nazionale: 23 marzo 2020

TABELLA 3- DISTRIBUZIONE DEI CASI CON ETÀ <18 ANNI DIAGNOSTICATI DAI LABORATORI DI RIFERIMENTO REGIONALE, PER FASCIA DI ETÀ (N=597)

Classe di età (anni)	N. casi	%	Femmine	Maschi	% Femmine	% Maschi
0-1	178	29.8	73	103	41.5	58.5
2-6	81	13.6	39	42	48.1	51.9
7-17	338	56.6	157	180	46.6	53.4
≤17 anni	597		269	325	45.3	54.7

TABELLA 4- DISTRIBUZIONE DEI CASI CON ETÀ <18 ANNI DIAGNOSTICATI DAI LABORATORI DI RIFERIMENTO REGIONALE, PER FASCIA DI ETÀ (N=446)

Classe di età (anni)	N. casi a domicilio	N. casi ospedalizzati	% ospedalizzati per classe di età	% ospedalizzati (su totale)
0-1	113	24	17.5	49.0
2-6	57	8	12.3	16.3
7-17	227	17	7.0	34.7
≤17 anni	397	49	11.0	

NOTA: NESSUN CASO RISULTA IN TERAPIA INTENSIVA

Task force COVID-19 del Dipartimento Malattie Infettive e Servizio di Informatica, Istituto Superiore di Sanità. Epidemia COVID-19,

Aggiornamento nazionale: 23 marzo 2020

TABELLA 5. DISTRIBUZIONE DEI CASI, DECEDUTI E LETALITÀ IN OPERATORI SANITARI

Classe d'età (anni)	Casi [n (%)]	Deceduti [n (%)]	Letalità (%)
18-29	371 (7.2%)	0 (0%)	0%
30-39	864 (16.8%)	0 (0%)	0%
40-49	1491 (28.9%)	1 (12.5%)	0.10%
50-59	1767 (34.3%)	5 (62.5%)	0.30%
60-70	661 (12.8%)	2 (25%)	0.30%
Totale	5154 (100%)	8 (100%)	0.20%

NOTA: LA TABELLA NON INCLUDE I CASI CON ETÀ NON NOTA

Doctor News 27 marzo
Covid, cresce la lista dei morti.
37 medici morti a ieri, 18 di famiglia

Understanding of COVID-19 based on current evidence

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

- ✓ Introduction
- ✓ Sources of SARS-CoV-2
- ✓ Epidemiology
- ✓ Etiology & Pathogenesis
- ✓ Symptoms, & Diagnosis
- ✓ The case of infants & children
- ✓ The case of mother & fetus
- ✓ The case of Italy
- ✓ Treatment
- ✓ Prevention
- ✓ Conclusions

Management principles

The 4 principles of

"early identification",

"early isolation",

"early diagnosis", and

"early treatment".

should be emphasized

Treatment of COVID-19

- no COVID-19 vaccine has been successfully developed until now.

- at present, the treatments of patients with SARS-CoV-2 infection are mainly symptomatic treatments.

- the most common complications in patients with 2019-nCoV infection are:
  - **acute respiratory distress syndrome**,

  followed by:
  - **anemia**,
  - **acute heart injuries**, and
  - **secondary infections**.

- Therefore, **empirical antibiotics**, **antiviral therapy** (oseltamivir, **remdesivir**), and **systemic corticosteroids** were often used for treatments.

Holshue ML,. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020:NEJMoa2001191.
Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

Treatment of COVID-19

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- the most common complications in patients with 2019-nCoV infection are:
  - **acute respiratory distress syndrome**,

followed by

In mild cases broad-spectrum antibiotics and corticosteroids should not be used.

- Therefore, **empirical antibiotics**, **antiviral therapy** (oseltamivir, **remdesivir**), and **systemic corticosteroids** were often used for treatments.

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Treatment of COVID-19

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- at present, the treatments of patients with SARS-CoV-2 infection are mainly symptomatic treatments.

Antibiotics application
- Irrational use of antibiotics should be avoided.
- Bacteriological monitoring should be strengthened.
- If there is evidence of secondary bacterial infection, appropriate antibiotics should be used timely.

- Therefore, **empirical antibiotics**, **antiviral therapy** (oseltamivir, **remdesivir**), and **systemic corticosteroids** were often used for treatments.

Holshue ML,. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020:NEJMoa2001191.
Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

Treatment of COVID-19

Systemic corticosteroids should be considered in the following situations:
1. With rapidly deteriorating chest imaging and occurence of ARDS.
2. With obvious toxic symptoms, encephalitis or encephalopathy, hemophagocytic syndrome and other serious complications.
3. With septic shock.
4. With obvious wheezing symptoms.

Intravenous methylprednisolone (1–2 mg/kg/day) is recommended for 3–5 days, but not for long-term use

- Therefore, empirical antibiotics, antiviral therapy (oseltamivir, remdesivir), and systemic corticosteroids were often used for treatments.

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Treatment of COVID-19

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Severe and critical case
Antibiotics, corticosteroids, bronchoalveolar lavage, mechanical ventilation, and other more invasive intervention, such as blood purification and extracorporeal membrane oxygenation (EMCO) should be applied cautiously.

- Therefore, **empirical antibiotics**, **antiviral therapy** (oseltamivir, **remdesivir**), and **systemic corticosteroids** were often used for treatments.

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- at present, the treatments of patients with SARS-CoV-2 infection are mainly symptomatic tr

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Patients with intractable hypoxemia are given invasive mechanical ventilation.

- Therefore, empi py (oseltamivir, remdesivir), and systemic corticosteroids were often used for treatments.

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  - se[illegible]

viral infections can increase the risk of pulmonary fibrosis.

Sheng G, Chen P, Wei Y, et al. Viral infection increases the risk of idiopathic pulmonary fibrosis: a meta-analysis. Chest. 2020 in press

- Therefore, empi[illegible]py (oseltamivir, remdesivir), and **systemic corticosteroids** were often used for treatments.

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Therefore, pulmonary fibrosis may be one of the severe complications after patients recover from 2019-nCoV infections.

- Therefore, empi py (oseltamivir, remdesivir), and systemic corticosteroids were often used for treatments.

Holshue ML,. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020:NEJMoa2001191.

Treatment of COVID-19

Antiviral therapy

- There are no effective antiviral drugs for children at present.

- **Interferon-α2b nebulization** can be applied,
and the recommended usage is as follows:
1.*Interferon-α2b nebulization* 100,000–200,000 IU/kg for mild cases, and 200,000–400,000 IU/kg for severe cases, two times/day for 5–7 days.

- *Lopinavir/litonavir (200 mg/50 mg)* (used for AIDS) **neuraminidase inhibitors**. The recommended doses:
weight 7–15 kg, 12 mg/3 mg/kg;
weight 15–40 kg, 10 mg/2.5 mg/kg;
weight > 40 kg, 400 mg/100 mg as adult each time, twice a day for 1–2 weeks.

- However, the efficacy, treatment course and safety of the above drugs remain to be determined.

Treatment of COVID-19

Antiviral therapy

In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care.
Cao B,. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19 [published online ahead of print, 2020 Mar 18]. N Engl J Med.

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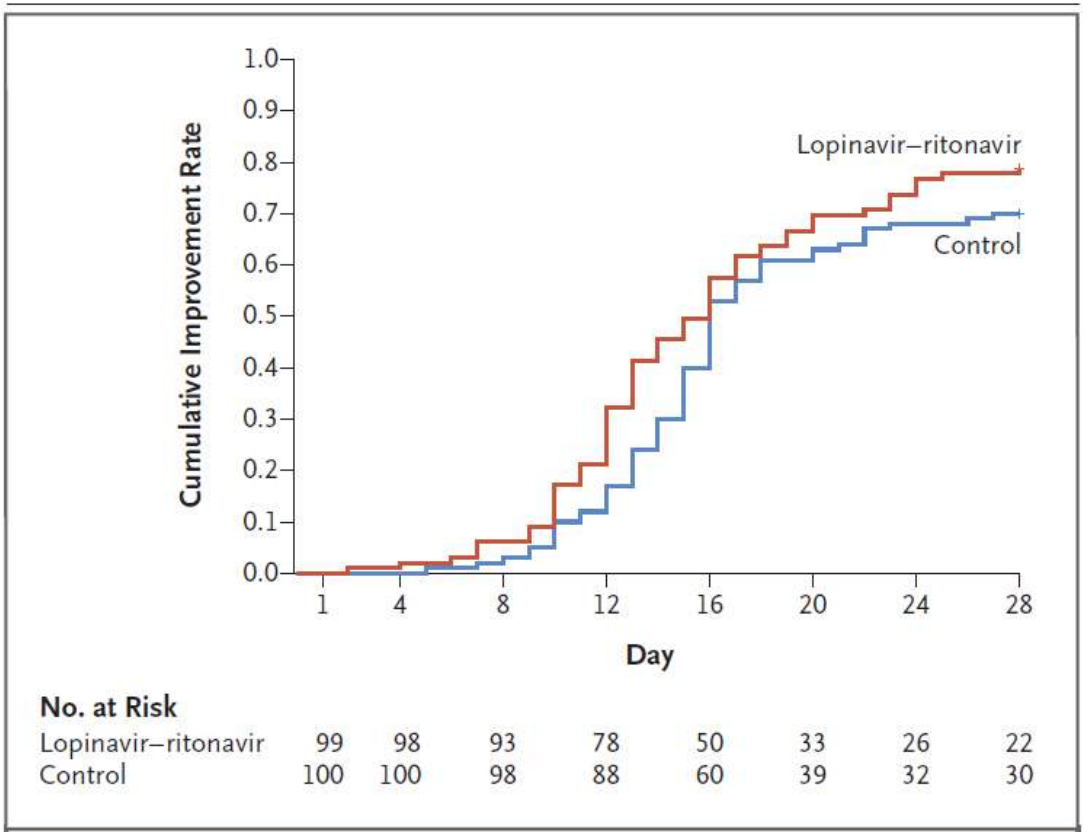
A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19

Cao B, N Engl J Med. 2020;10.1056/NEJMoa2001282.

✓199 adult patients with SARS-CoV-2 infection, and Sao_2 ≤94% in ambient air or a ratio of the partial pressure of oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) < 300 mm Hg.

✓randomly assigned in a 1:1 ratio to receive either lopinavir-ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone.

Time to Clinical Improvement in the Intention-to-Treat Population

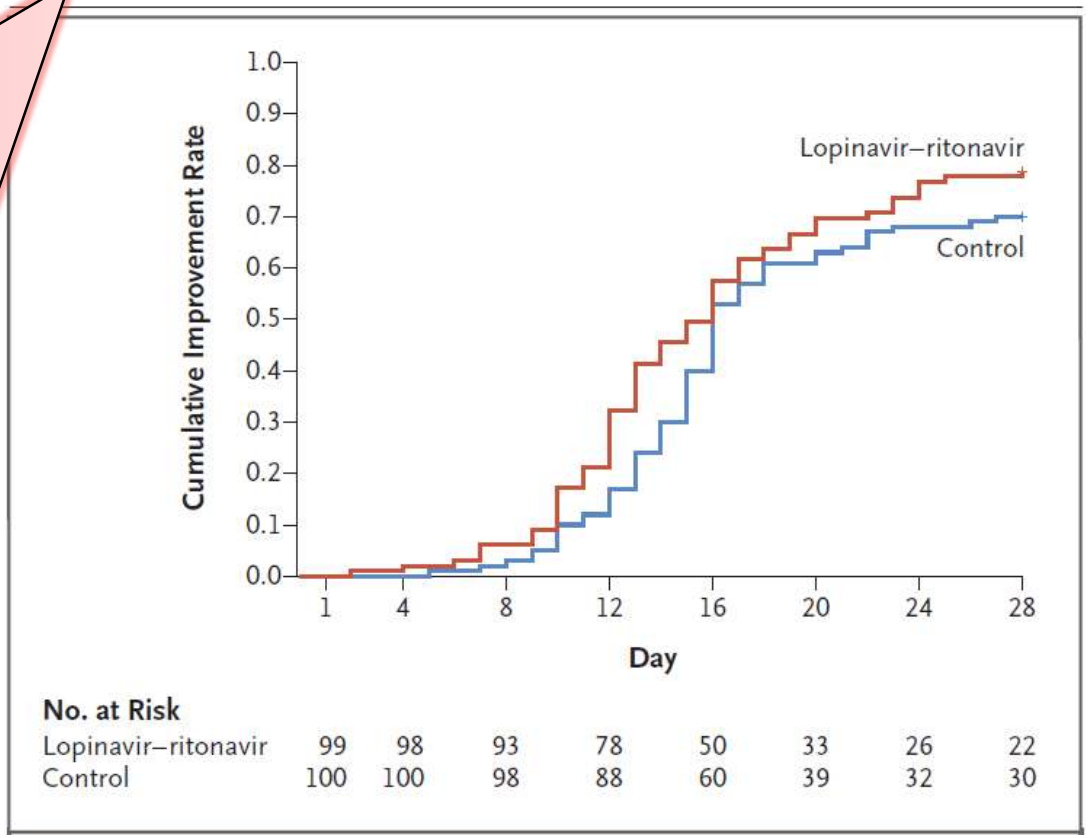


A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19

Cao B, N Engl J Med. 2020;10.1056/NEJMoa2001282.

Treatment with lopinavir-ritonavir was **not associated with a difference from standard care in the time to clinical improvement** (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72).

Time to Clinical Improvement in the Intention-to-Treat Population



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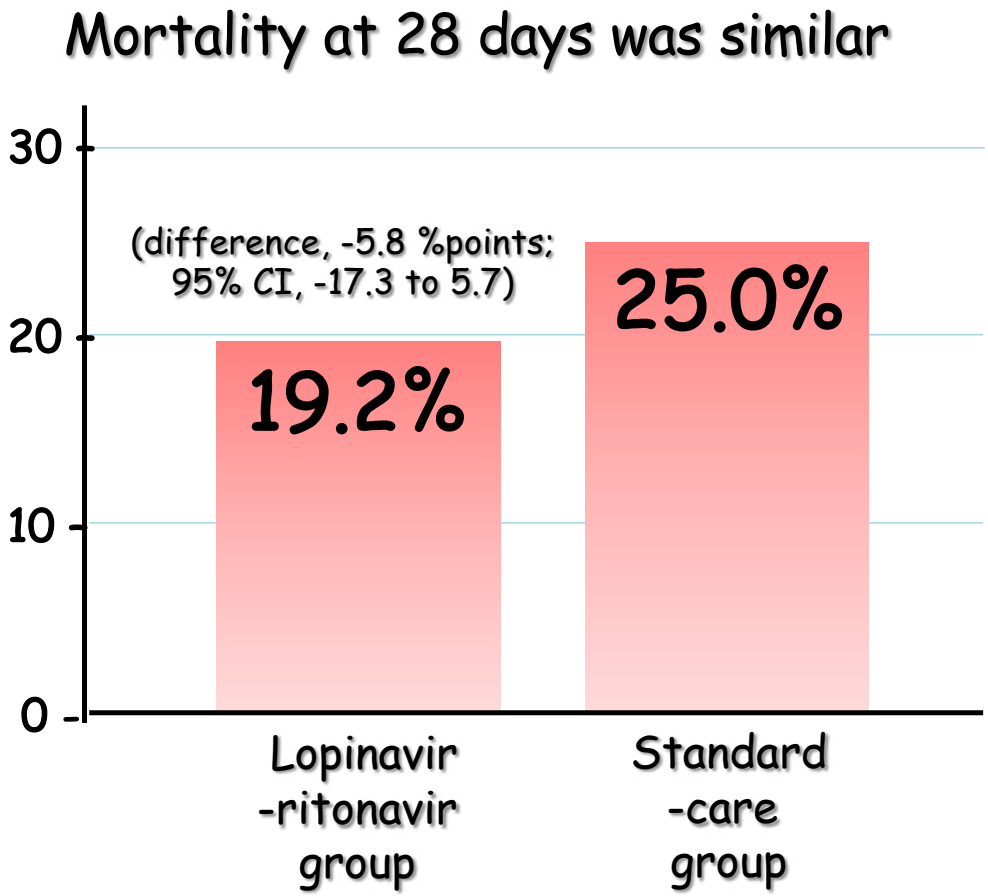


A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19

Cao B, N Engl J Med. 2020;10.1056/NEJMoa2001282.

- The percentages of patients with detectable viral RNA at various time points were similar between active treatment and placebo.

- Gastrointestinal adverse events were more common in the lopinavir-ritonavir group,
but
serious adverse events were more common in the standard-care group.

- Lopinavir-ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.

Treatment of COVID-19

- It has been postulated that, in addition to antiviral interferers and antibiotics,
  - neuraminidase inhibitors,
  - RNA synthesis inhibitors, and
  - Chinese traditional medicine

} could also be used in the treatment of COVID-19.

Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends. 2020.

- Nevertheless, the efficacy of these drugs still needs to be verified by clinical trials.

Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

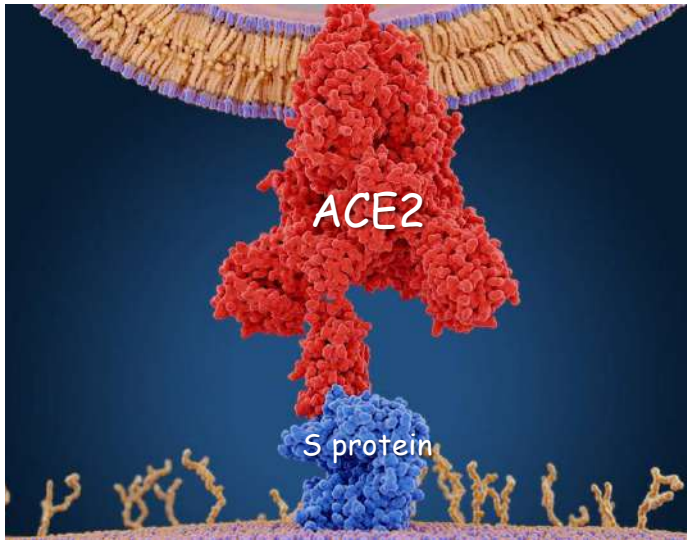
Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Gurwitz D. Drug Dev Res. 2020;10.1002/ddr.21656.*

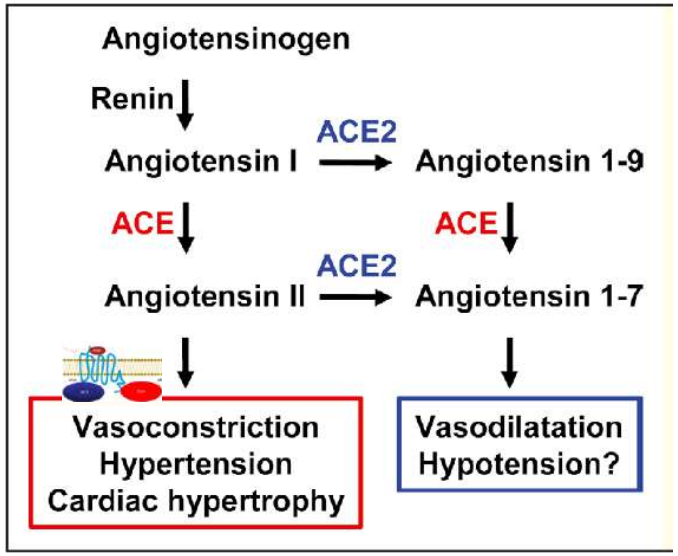
- SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor binding domain for its spike protein.

- Notably, angiotensin-converting enzyme (ACE) and its close homologue ACE2, while both belonging to the ACE family of dipeptidyl carboxydipeptidases, serve two opposing physiological functions.

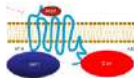
- ACE cleaves angiotensin I to generate angiotensin II which binds to and activates angiotensin II type 1 receptor AT1R to constrict blood vessels, elevating blood pressure.

- By contract, ACE2 inactivates angiotensin II while generating angiotensin 1–7, a heptapeptide having a potent vasodilator function via activation of its Mas receptor and thus serving as a negative regulator of the renin–angiotensin system.





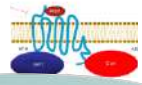
Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Gurwitz D. Drug Dev Res. 2020;10.1002/ddr.21656.*

- The angiotensin II type 1 receptor (**AT1R**),  antagonists losartan and olmesartan, commonly applied for reducing blood pressure in hypertensive patients, were shown to increase cardiac ACE2 expression about three-fold following chronic treatment (28 days) after myocardial infarction induced by coronary artery ligation of rats.

- Losartan was also shown to upregulate renal ACE2 expression in chronically treated rat.

- In agreement with these observations, higher urinary ACE2 levels were observed in hypertensive patients treated with the AT1R antagonist olmesartan.

Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Gurwitz D. Drug Dev Res. 2020;10.1002/ddr.21656.*

•The angiotensin II type 1 receptor (**AT1R**),  antagonists losartan and olmesartan, [illegible] hypertensive patients [illegible] fold for [illegible] by coro[illegible]

Taken together, these observations suggest that chronic AT1R blockade results in ACE2 upregulation in both rats and humans.

•Losartan [illegible] in c[illegible]

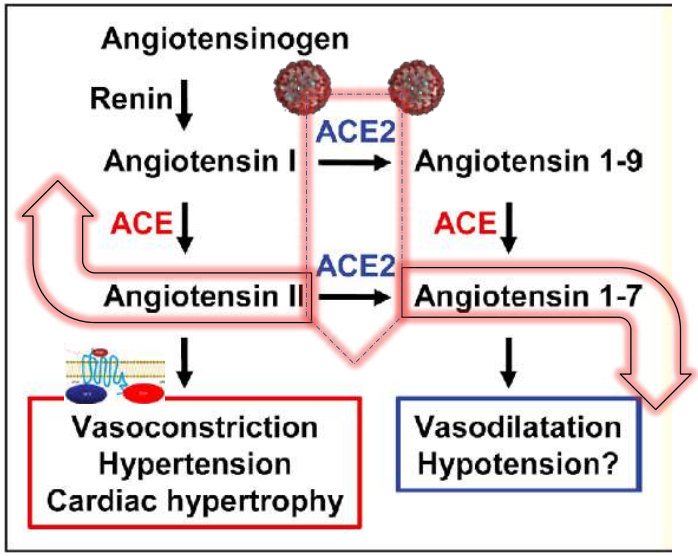
Hence, the suggestion to treat SARS patients with AT1R antagonists for increasing their ACE2 expression seems counter-intuitive.

•In agreement with [illegible] urinary ACE2 levels were observed in hypertensive patients treated with the AT1R antagonist olmesartan.

Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Gurwitz D. Drug Dev Res. 2020;10.1002/ddr.21656.*

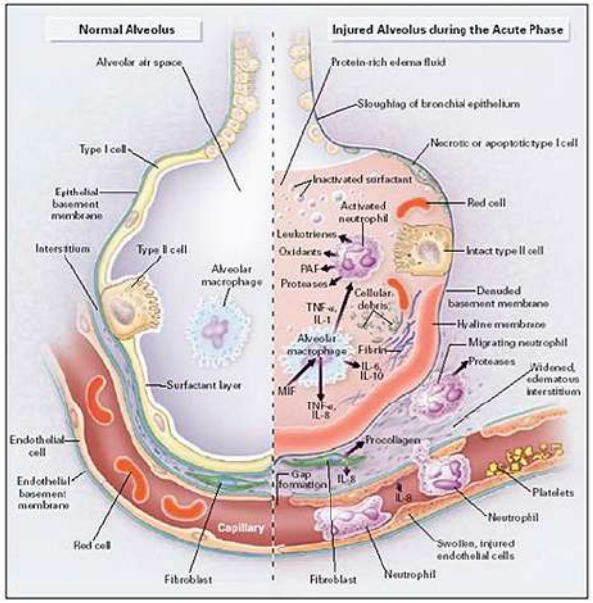
- However, several observations from studies on SARS-CoV, which very likely are relevant also for SARS-CoV-2, seem to suggest otherwise.

- It has been demonstrated that the binding of the coronavirus spike protein to ACE2, its cellular binding site, leads to ACE2 downregulation, which in turn results in excessive production of angiotensin by the related enzyme ACE, while less ACE2 is capable of converting it to the vasodilator heptapeptide angiotensin 1–7.



- This in turn contributes to lung injury, as angiotensin-stimulated AT1R results in increased pulmonary vascular permeability, thereby mediating increased lung pathology

Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Gurwitz D. Drug Dev Res. 2020;10.1002/ddr.21656.*



➢Therefore, higher ACE2 expression following chronically medicating SARS-CoV-2 infected patients with AT1R blockers, while seemingly paradoxical, may protect them against acute lung injury rather than putting them at higher risk to develop SARS.

➢This may be accounted for by two complementary mechanisms:

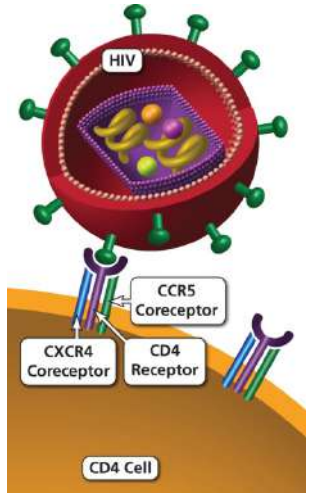
- blocking the excessive angiotensin-mediated AT1R activation caused by the viral infection,

as well as

- upregulating ACE2,

thereby reducing angiotensin production by ACE and increasing the production of the vasodilator angiotensin 1–7.

Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Gurwitz D. Drug Dev Res. 2020;10.1002/ddr.21656.*



- Incidentally, in the context of the human immunodeficiency viruses (HIV), it has been demonstrated that higher expression levels of the HIV binding sites CCR5 and CD4 protect from, rather than increase, HIV virulence.

- It remains to be studied if a comparable mechanism for avoiding superinfection has evolved in coronaviruses; in which case, the suggestion of applying AT1R blockers as SARS therapeutics, even that they upregulate the expression of the ACE2 virus binding site, will not seem paradoxical.

- However, it should be noted that around half of SARS-CoV patients developed hypotension during their hospitalization

Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Gurwitz D. Drug Dev Res. 2020;10.1002/ddr.21656.*

- At time of writing this commentary, no comprehensive information is available on hypotension rates among hospitalized SARS-CoV-2 patients; it is thus premature to estimate what percentage of SARS patients of the currently ongoing epidemic can be safely treated with AT1R blockers without risking exacerbated hypotension.

- The tentative suggestion to apply AT1R antagonists such as losartan and telmisartan as SARS-CoV-2 therapeutics for treating patients prior to the development of acute respiratory syndrome remains unproven until tried.

Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Gurwitz D. Drug Dev Res. 2020;10.1002/ddr.21656.*

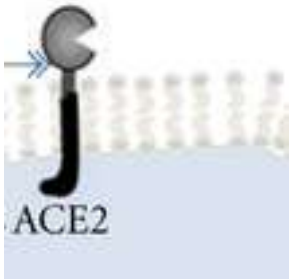
- The most rapid approach for assessing its feasibility is to analyze clinical patient records and apply datamining technologies to determine whether patients who were prescribed with AT1R antagonists prior to their diagnosis (for treating their hypertension, diabetic kidney disease, or other indications) had better disease outcome.

- Moreover, the percentage of people chronically medicated with AT1R blockers in the general population should be compared with the percentage among hospital admissions of SARS-CoV-2 infected patients presenting serious symptoms.

Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?.

Fang L, Lancet Respir Med. 2020;S2213-2600(20)30116-8.

- The most distinctive comorbidities of non-survivors from intensive care unit patients with novel coronavirus disease are those with
  - hypertension ,
  - diabetes mellitus,
  - coronary heart diseases, and
  - cerebrovascular disease.



- SARS-CoV-2 bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.

- The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs).

- Hypertension is also treated with ACE inhibitors and ARBs, which results in an upregulation of ACE2.

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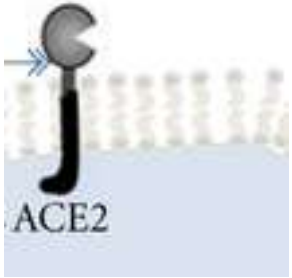
  ang pressed by epithelial c blood vessels.

ACE2 can also be increased by thiazolidinediones, oral antidiabetic drugs and ibuprofen.



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- Consequently, the increased expression of ACE2 would facilitate infection with COVID-19.

- If this hypothesis were to be confirmed, it could lead to a conflict regarding treatment because ACE2 reduces inflammation and has been suggested as a potential new therapy for inflammatory lung diseases.

- A further aspect that should be investigated is the genetic predisposition for an increased risk of SARS-CoV-2 infection, which might be due to ACE2 polymorphisms that have been linked to diabetes mellitus, cerebral stroke, and hypertension, specifically in Asian populations.

- Summarising this information, the sensitivity of an individual might result from a combination of both therapy and ACE2 polymorphism.

18 Marzo 2020

L'EMA fornisce indicazioni sull'uso degli antinfiammatori non steroidei per COVID-19

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Attualmente **non vi sono prove scientifiche** che stabiliscano una correlazione tra l'ibuprofene e il peggioramento del decorso della malattia da COVID-19.

- Nelle informazioni sul prodotto di molti medicinali FANS sono presenti già delle avvertenze che gli effetti degli **anti-infiammatori non steroidei possono mascherare i sintomi di un peggioramento dell'infezione**.

- l'EMA sottolinea la **necessità di condurre tempestivamente studi epidemiologici**, al fine di fornire adeguate evidenze sugli effetti dei FANS sulla prognosi della malattia da COVID-19.

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Gautret P. Inter J Antimicr Agents 17 March 2020 -*

- Early clinical trial conducted in **COVID-19 Chinese patients**, showed that **chloroquine (500 mg twice a day for 10 days.)** had a significant effect, both in terms of clinical outcome and viral clearance, when comparing to controls groups.
Gao J, Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020 Feb 19

- **Hydroxychloroquine** (an analogue of chloroquine) has been demonstrated to have an anti-SARS-CoV activity in vitro.

- Hydroxychloroquine clinical **safety profile is better** than that of chloroquine (during long-term use) and **allows higher daily dose** and has **fewer concerns about drug-drug interactions.**

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- Early clinical [illegible] that chloroqui[illegible] bo[illegible] cont[illegible] *Gao J [illegible] COVID-19 [illegible]*

➢ contraindication to treatment with hydroxychloroquine are
- retinopathy,
- G6PD deficiency and
- QT prolongation

- Hydroxychloroquine (an analogue of chloroquine) has been demonstrated to have an anti-SARS-CoV activity in vitro.

- Hydroxychloroquine clinical safety profile is better than that of chloroquine (during long-term use) and allows higher daily dose and has fewer concerns about drug-drug interactions.

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Gautret P. Inter J Antimicr Agents 17 March 2020 -*

✓COVID-19 patients
(mean age of 45.1 years)

✓200mg x 3 hydroxychloroquine
daily for 10 days

✓Depending on their clinical
presentation, azithromycin
500 mg first day,
250 mg for other 4 days

✓nasopharyngeal swab

➢20 treated cases showed

❑a significant reduction of the viral carriage at D6-post inclusion compared to controls,
and

❑much lower average carrying duration than reported of untreated patients in the literature.

❑Azithromycin added to hydroxychloroquine
was significantly more efficient for virus elimination.

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Gautret P. Inter J Antimicr Agents 17 March 2020 -*

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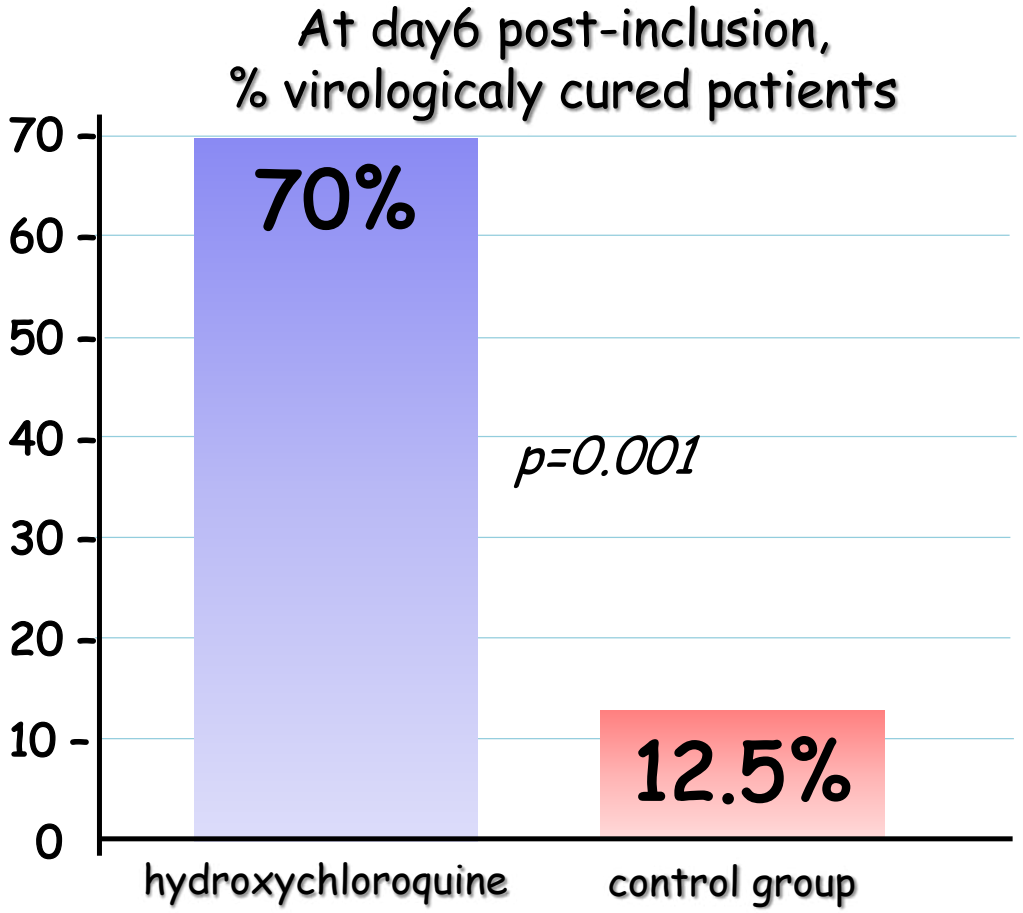
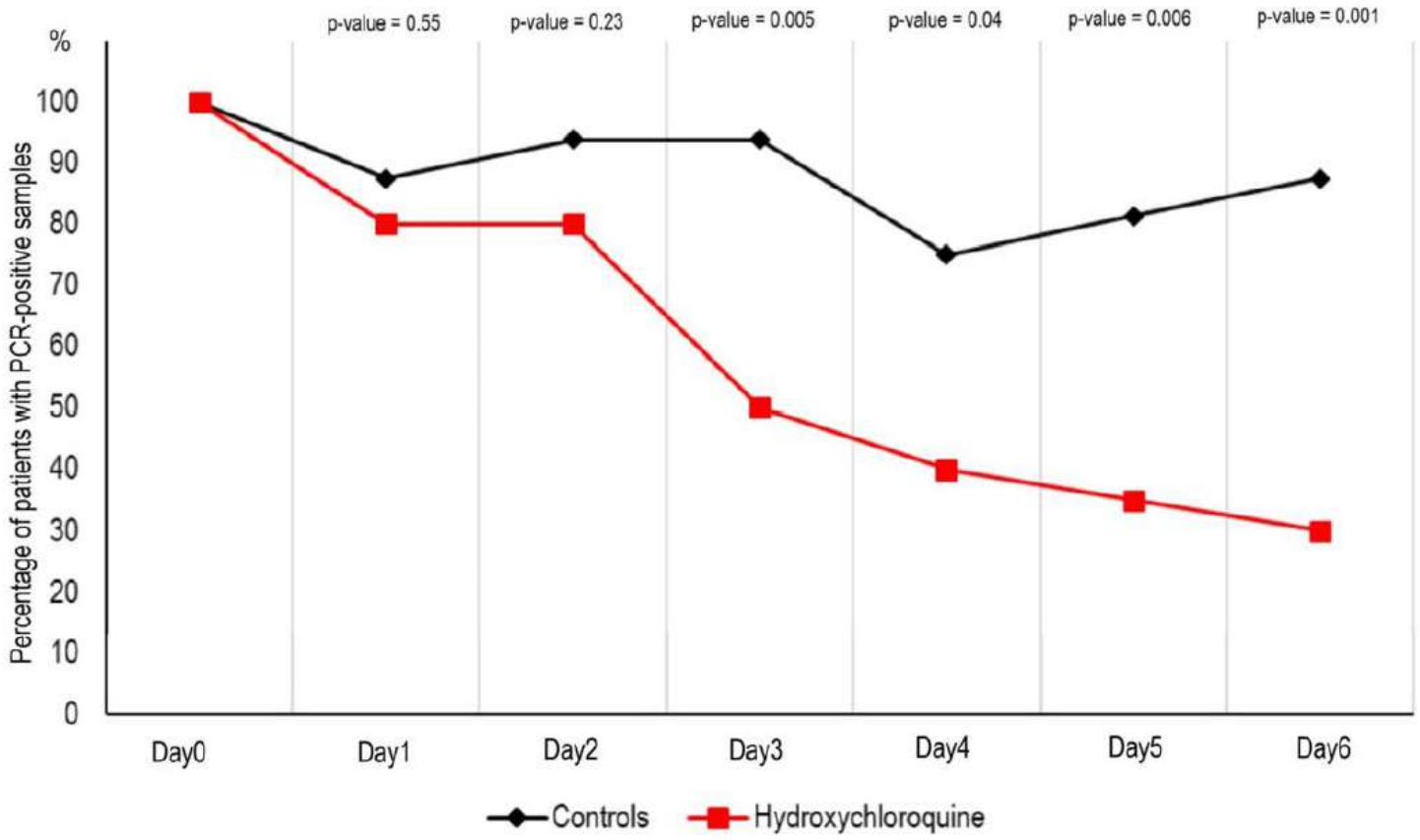


Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Gautret P. Inter J Antimicr Agents 17 March 2020 -*

% patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine and in COVID-19 control patients.



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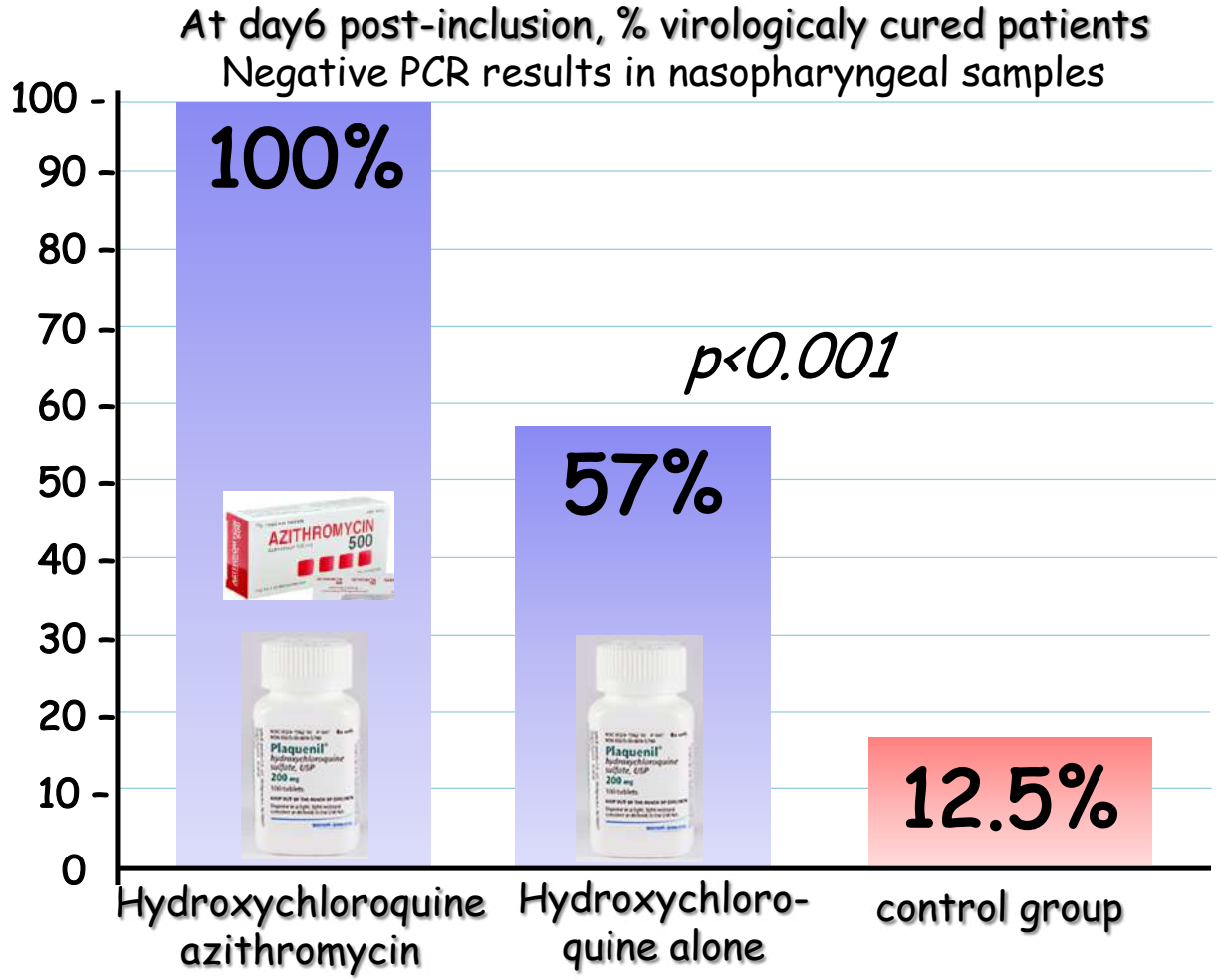
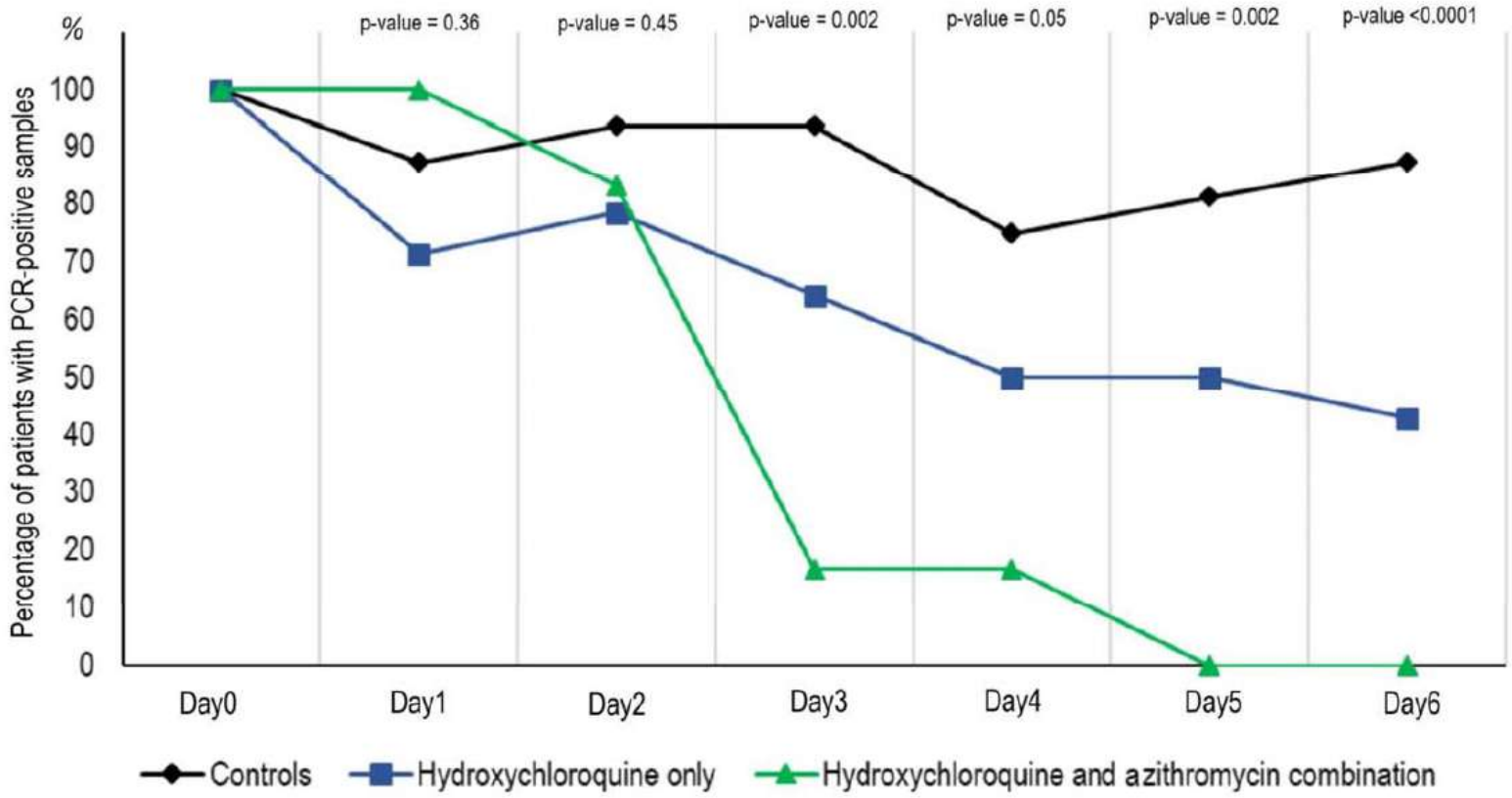


Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Gautret P. Inter J Antimicr Agents 17 March 2020 -*

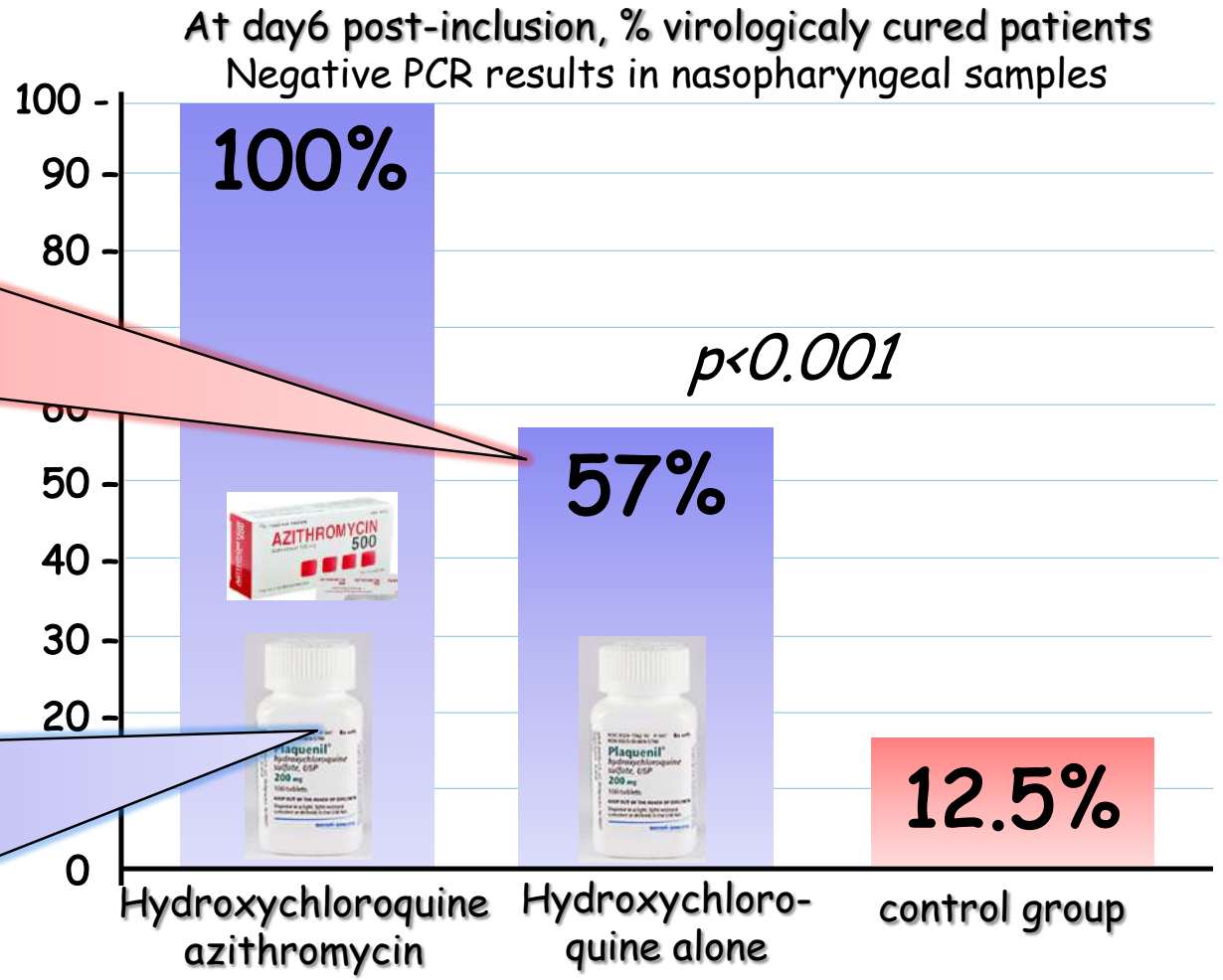
% patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithomycin combination, and in COVID-19 control patients.



Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Gautret P. Inter J Antimicr Agents 17 March 2020 -*

Of note, one patient who was still PCR-positive at day6-post inclusion under hydroxychloroquine treatment only,

received azithromycin in addition to hydroxychloroquine at day8-post inclusion and cured her infection at day-9 post infection.

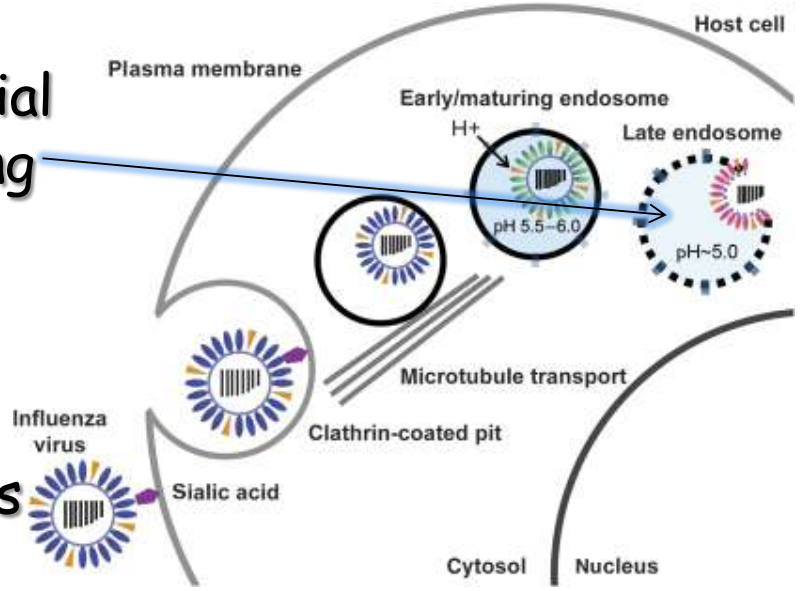


Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Gautret P. Inter J Antimicr Agents 17 March 2020 -*

- These results are of great importance because the mean duration of viral shedding in patients suffering from COVID-19 in China was 20 days (even 37 days for the longest duration).

Zhou F,. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 11.

- Studies revealed that chloroquine has potential broad-spectrum antiviral activities by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV .



- The anti-viral and anti-inflammatory activities of chloroquine may account for its potent efficacy in treating patients with COVID-19 pneumonia.

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Gautret P. Inter J Antimicr Agents 17 March 2020 -*

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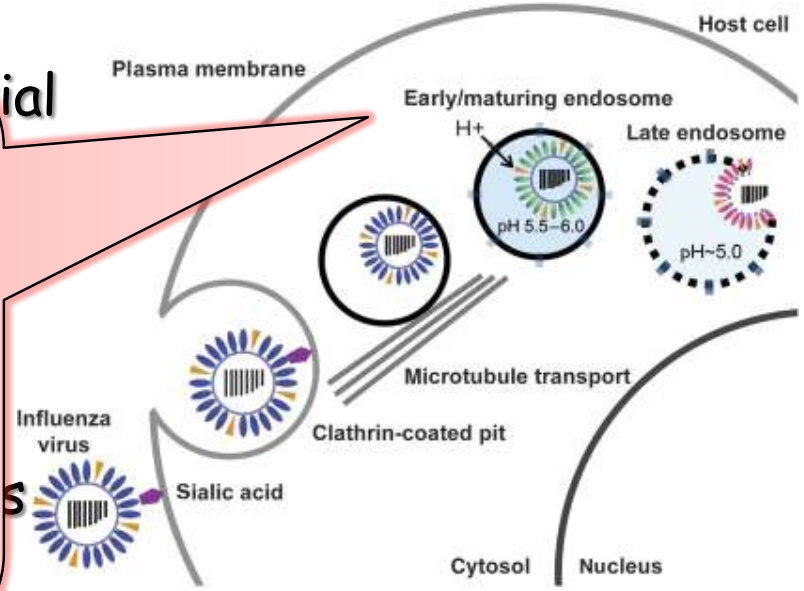
Viral spike protein;
1) binds to the host cell receptor ACE2 and other coreceptors,
2) mediates viral entry into host cells as a type 1 viral fusion protein;
3) require acidification of endosomes for efficient S-mediated viral entry;



pneumonia.

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Gautret P. Inter J Antimicr Agents 17 March 2020 -*

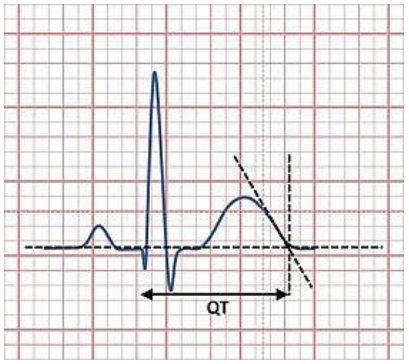
➢ **Azithromycin** has been shown to be active *in vitro* against Zika and Ebola viruses

- *Retallack H, Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proc Natl Acad Sci U S A. 2016 Dec 13;113(50):14408-14413.*
- *Madrid PB, Evaluation of Ebola Virus Inhibitors for Drug Repurposing. ACS Infect Dis. 2015 Jul10;1(7):317-26.*
- *Bosseboeuf E, Azithromycin inhibits the replication of Zika virus. J Antivirals Antiretrovirals. 2018 10(1):6-11.*

➢ and to **prevent severe respiratory tract infections** when administrated to patients suffering viral infection.

- *Bacharier LB, Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: A randomized clinical trial. JAMA. 2015 Nov 17;314(19):2034-2044.*

➢ Potential risk of severe **QT prolongation** induced by the association of the two drugs has not been established yet but should be considered.



Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Dong L, Drug Discov Ther. 2020;14(1):58-60.*

Table 1. Antivirals included in the Guidelines (version 6) for treatment of COVID-19

Drug	Dosage	Method of administration	Duration of treatment
IFN-α	5 million U or equivalent dose each time, 2 times/day	Vapor inhalation	No more than 10 days
Lopinavir/ritonavir	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day	Oral	No more than 10 days
Ribavirin	500 mg each time, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir	Intravenous infusion	No more than 10 days
Chloroquine phosphate	500 mg (300 mg for chloroquine) each time, 2 times/day	Oral	No more than 10 days
Arbidol	200 mg each time, 3 times/day	Oral	No more than 10 days

Arbidol is an antiviral that can be used to treat influenza virus.

A study has revealed that arbidol can effectively inhibit SARS-CoV-2 infection at a concentration of 10-30 μM *in vitro.*

Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Dong L, Drug Discov Ther. 2020;14(1):58-60.*

- Besides the drugs above that have been included in the Guidelines, favipiravir (Avigan®) is a drug that warrants attention.

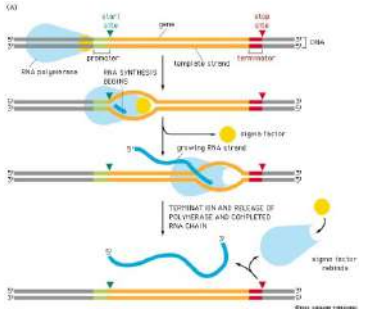
- Favipiravir was approved for treatment of novel influenza on February 15, 2020 in China.

- This drug is currently undergoing clinic trials in treating COVID-19.

- Favipiravir is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor.

- In addition to its anti-influenza virus activity, favipiravir is capable of blocking the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses.

- Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, thus inhibiting RNA polymerase activity.



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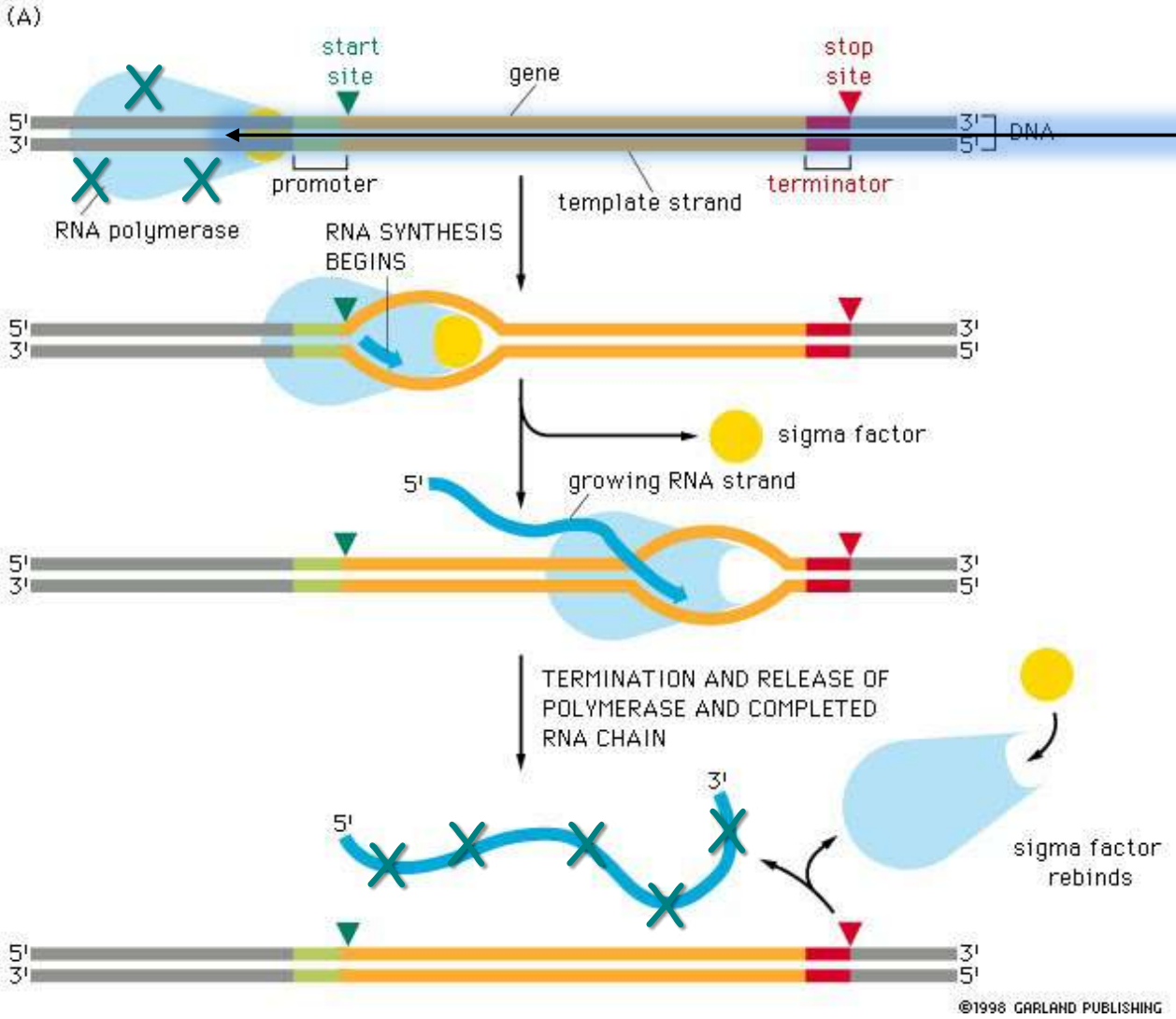


Therefore, favipiravir may have potential antiviral action on SARS-CoV-2, which is a RNA virus.

Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Dong L, Drug Discov Ther. 2020;14(1):58-60.*

- On February 14, a clinical trial on favipiravir (Avigan®) for the treatment of COVID-19 initiated by the Clinical Medical Research Center of the National Infectious Diseases and the Third People's Hospital of Shenzhen achieved promising results.

- The preliminary results from a total of 80 patients (including the experimental group and the control group) indicated that favipiravir had more potent antiviral action than that of lopinavir/ritonavir.

- No significant adverse reactions were noted in the favipiravir treatment group, and it had significantly fewer adverse effects than the lopinavir/ritonavir group.

News. *http://www.szdsyy.com/News/0a6c1e58-e3d0-4cd1- 867a-d5524bc59cd6.html (accessed February 22, 2020). (in Chinese).*

Potential interventions for novel coronavirus in China: A systematic review. *Zhang L, J Med Virol. 2020;in press*

In the absence of a specific treatment for this novel virus, there is an urgent need to find an alternative solution to prevent and control the replication and spread of the virus.
We have done an online search on PubMed and Web of Science with the keywords of SARS, MERS, and coronaviruses.
We summarize and propose therapeutic options available for the treatment of this novel coronaviruses.

- Vitamin A is also called "anti-infective" vitamin and many of the body's defenses against infection depend on an adequate supply.

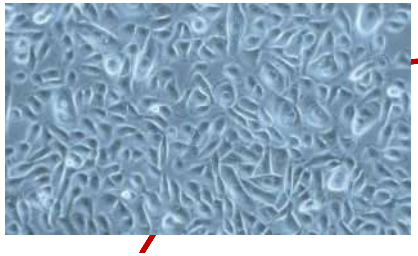
- As shortage of B vitamins may weaken host immune response, they should be supplemented to the virus-infected patients to enhance their immune system.

- Vitamin C also supports immune functions and protects against infection caused by a coronavirus.

- The decreased vitamin D status in calves had been reported to cause the infection of bovine coronavirus. Therefore, vitamin D could work as another therapeutic option for the treatment of this novel virus.

Pulmonary activation of vitamin D_3 and preventive effect against interstitial pneumonia.

Tsujino I, J Clin Biochem Nutr. 2019;65(3):245-251.



bleomycin

human pulmonary fibroblast cell lines (HPFCs)

a mouse model of bleomycin-induced pulmonary fibrosis

expression of inflammatory cytokines and fibrosis markers

expression of fibrosis markers and symptoms

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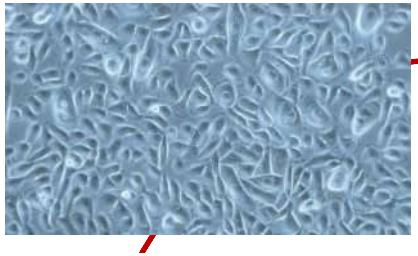

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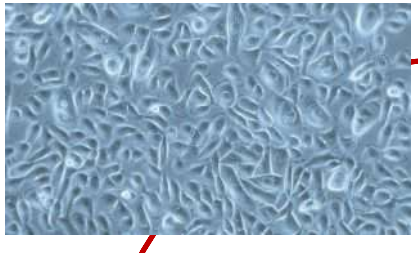

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expression of
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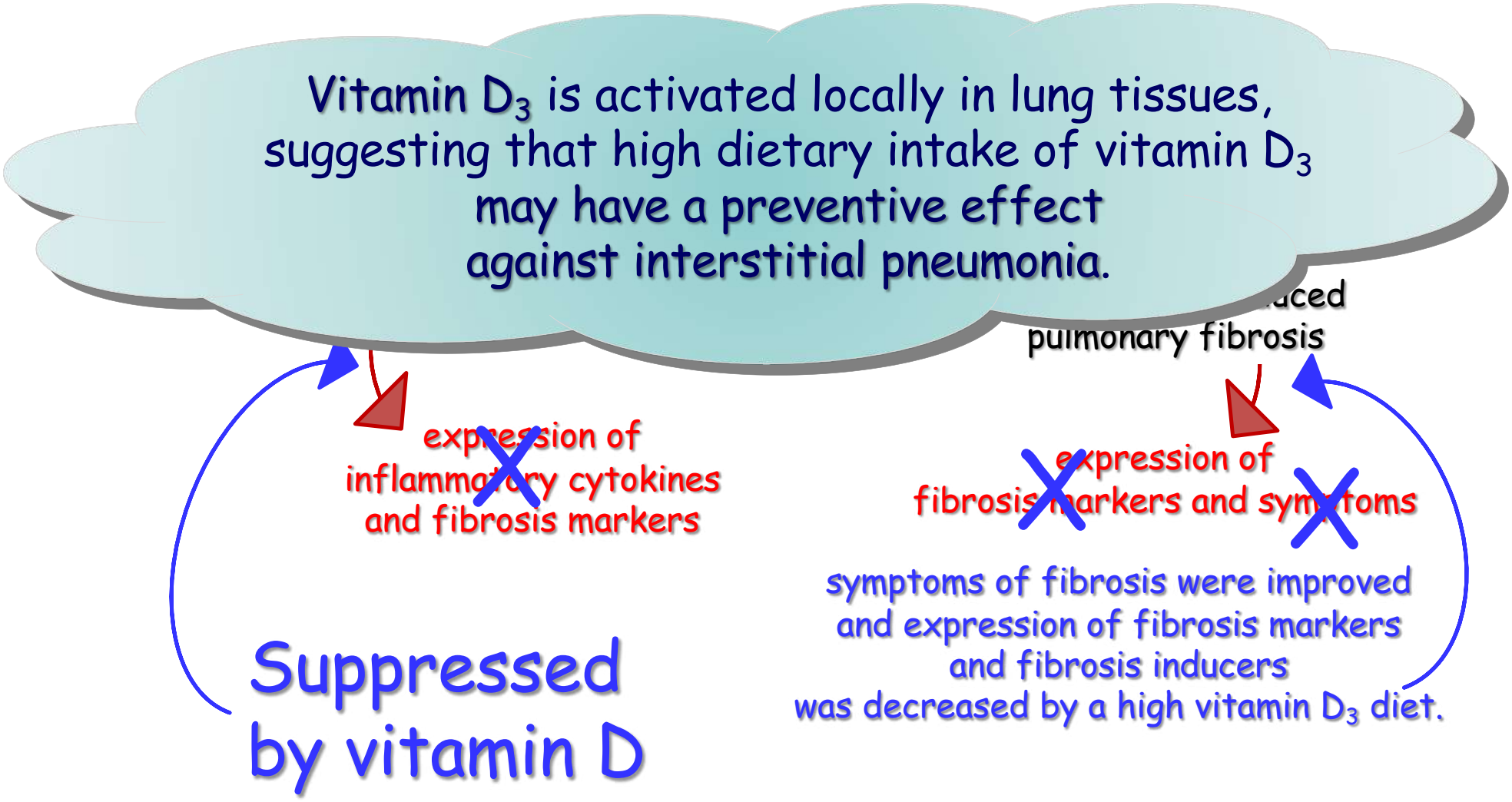
Suppressed
by vitamin D

symptoms of fibrosis were improved
and expression of fibrosis markers
and fibrosis inducers
was decreased by a high vitamin D_3 diet.

Pulmonary activation of vitamin D_3 and preventive effect against interstitial pneumonia.

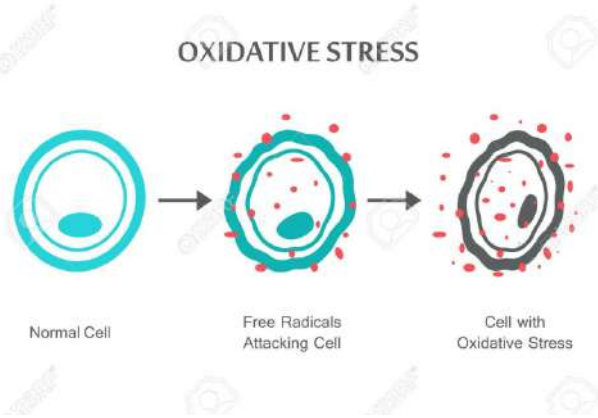
Tsujino I, J Clin Biochem Nutr. 2019;65(3):245-251.



Potential interventions for novel coronavirus in China: A systematic review. *Zhang L, J Med Virol. 2020;in press*

- The decreased vitamin E and D status in calves also caused the infection of bovine coronavirus.

- Vitamin E plays an important role in reducing oxidative stress through binding to free radicals as an antioxidant.



- Vitamin E deficiency had been reported to intensify the myocardial injury of coxsackievirus B3 (a kind of RNA viruses) infection in mice and increased the virulence of coxsackievirus B3 in mice due to vitamin E or selenium deficiency.

- Protectin D1, the omega-3 PUFA-derived lipid mediator, could markedly attenuate influenza virus replication via RNA export machinery

Potential interventions for novel coronavirus in China: A systematic review. *Zhang L, J Med Virol. 2020;in press*

Dietary selenium deficiency that causes oxidative stress in the host can alter a viral genome so that a normally benign or mildly pathogenic virus can become highly virulent in the deficient host under oxidative stress.

Selenium deficiency could not only increase the pathology of an influenza virus infection but also drive changes in genome, permitting an avirulent virus to acquire virulence due to genetic mutation.

Zinc is a dietary trace mineral and is important for the maintenance and development of immune cells of both the innate and adaptive immune system.

Zinc deficiency results in dysfunction of both humoral and cell-mediated immunity and increases susceptibility to infectious diseases.

Potential interventions for novel coronavirus in China: A systematic review. *Zhang L, J Med Virol. 2020;in press*

Immunoenhancers

- Interferon-α is produced very quickly as part of the innate immune response to virus infection. IFN-α inhibits the replication of animal and human coronaviruses.

- Cyclophilin A, the non-immunosuppressive derivatives of cyclosporine A, might bind to nucleocapsid protein (NP) of SARS-CoV, inhibiting virus particle assembly and release, and might serve as broad-range coronavirus inhibitors applicable against the emerging novel virus-like COVID-19.

Potential interventions for novel coronavirus in China: A systematic review. *Zhang L, J Med Virol. 2020;in press*

Chinese medicine

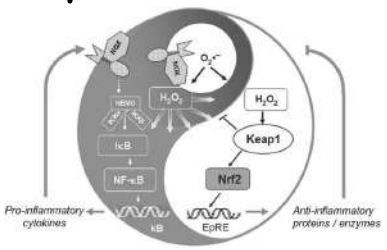
•Glycyrrhizin, an active component of liquorice roots, and Baicalin, another Chinese herb, could inhibit the replication of SARS-associated virus in vitro.

•Flavonoids such as quercetin 3-β-d-glucoside are coronaviral protease inhibitors potentially useful.

•Resveratrol, a phytoestrogen from grape seeds and red wine, had been reported to be a potent anti-MERS agent in vitro.

•Curcumin is a phytochemical isolated from Curcuma longa. It is widely used in Asia and has many therapeutic properties, including antioxidant, **anti-viral**, anti-bacterial, anti-mutagenic, anti-amyloidogenic and anti-inflammatory.

•Sulforaphane might have an anti-viral activity by Nrf2 activation.



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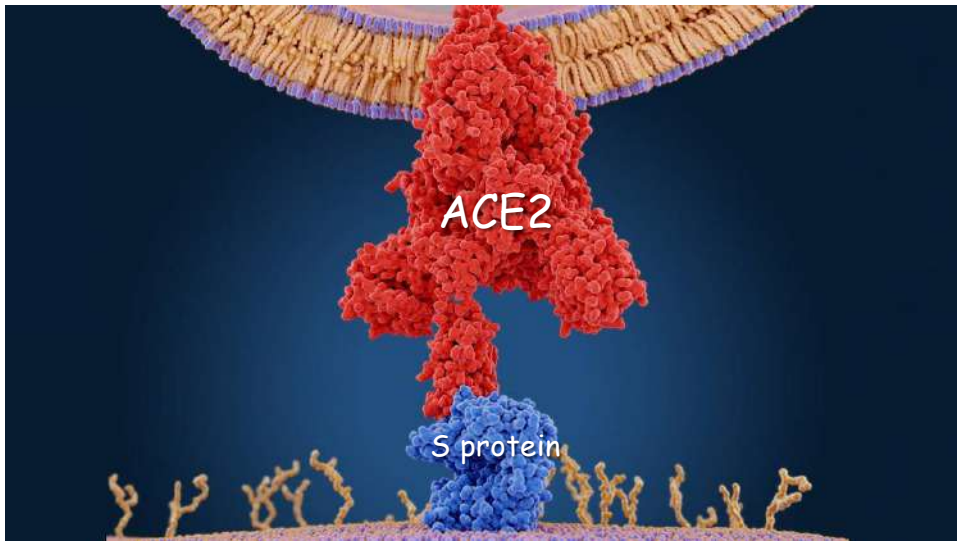

•**Chloroquine** , a well-known antimalarial drug, was also found to be a potent inhibitor of SARS coronavirus infection through **interfering with ACE2**, one of cell surface binding sites for **S protein of SARS-CoV**.

•**Emodin**, an anthraquinone compound derived from genus *Rheum* and *Polygonum,* and **promazine,** an anti-psychotic drug, might be able to inhibit SARS-CoV infectivity through blocking the interaction of S protein and **ACE2**.

Discharge from hospital criteria

Children with:

- body temperature back to normal for at least 3 days,

- significant improvement in respiratory symptoms, and

- completion of two consecutive negative tests of respiratory pathogenic nucleic acid (sampling interval of at least 1 day) can be discharged.

- If necessary, home isolation for 14 days is suggested after discharge.

Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

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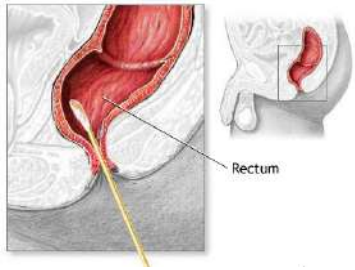
- significant improvement in respiratory symptoms, and
- completion of two consecutive negative tests of respiratory pathogenic nucleic acid (sampling interval of at least 1 day)

can be discharged.

Better to perform also a



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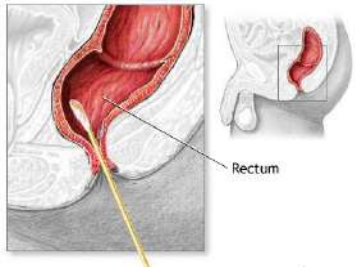

And give patients Optimal hygiene Instructions

- If necessary, home isolation for 14 days is suggested after discharge.

Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

Understanding of COVID-19 based on current evidence

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

- ✓ Introduction
- ✓ Sources of SARS-CoV-2
- ✓ Epidemiology
- ✓ Etiology & Pathogenesis
- ✓ Symptoms, & Diagnosis
- ✓ The case of infants & children
- ✓ The case of mother & fetus
- ✓ The case of Italy
- ✓ Treatment
- ✓ Prevention
- ✓ Conclusions

Prevention of COVID-19

- In the absence of effective treatments, the best way to deal with the SARS-CoV-2 epidemic is to control the sources of infection.

- Strategies include:

1) early diagnoses,
2) reporting,
3) isolation, and
4) supportive treatments;
5) timely release of epidemic information; and
6) maintenance of social orders.

Guan W, Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv. 2020.

Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

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1) early diagnoses,
2) reporting,
3) isolation, and
4) supportive treatments;
5) timely release of epidemic information; and
6) maintenance of social orders.

Medical isolation
•Suspected case should be isolated in a single room, while
•confirmed cases can be arranged in the same room.

Guan W, Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv. 2020.

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Prevention of COVID-19

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•Strategies include:

1) early diagnoses,
2) reporting,
3) isolation, and
4) supportive treatments;
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6) maintenance of social orders.

General treatments
The general strategies include bed rest and supportive treatments; ensuring sufficient calorie and water intake; maintaining water electrolyte balance and homeostasis, and strengthening psychotherapy for elder children when necessary.

Guan W, Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv. 2020.

Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

Prevention of COVID-19

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•Strategies include:

1) early diagnoses,
2) reporting,
3) isolation, and
4) supportive treatments;
5) timely release of epidemic information; and
6) maintenance of social orders.

Assessment
During the course of treatment, pay close attention to the changes in children's conditions, regularly monitor vital signs, SpO_2, etc., and identify the severe and critical cases as early as possible.

Guan W, Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv. 2020.

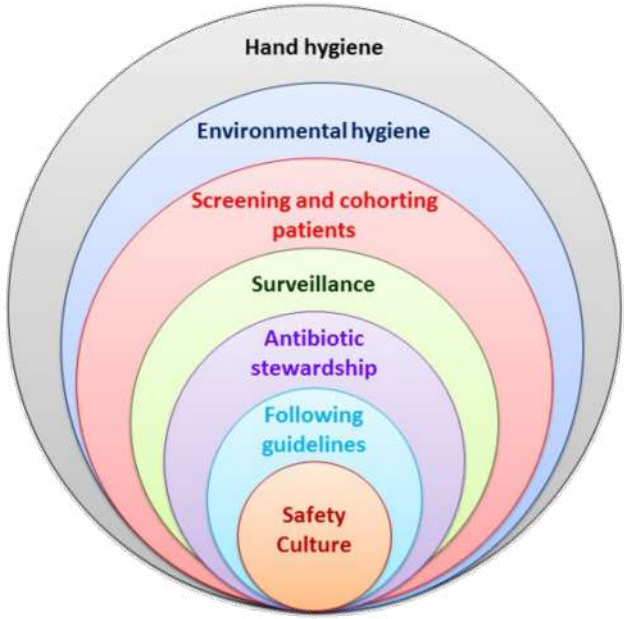
Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

Infection control in hospital

Strict implementation of standard prevention

Medical personnel are supposed to have:

1. good personal protection,
2. hand hygiene,
3. ward management,
4. environmental ventilation,
5. object surface cleaning and disinfection,
6. medical waste management and



7. other hospital infection control work, based on the standard prevention protocol, to minimize nosocomial infection.

Infection control in hospital

Personal protective equipment

1. All medical personnel are required to wear surgical masks during medical activities.

2. Pre-check triage: wearing medical overalls, caps, and surgical masks.

3. **Fever clinic, respiratory clinic, emergency department, infectious diseases department, and isolation ward:** equipped with medical overalls, caps, disposable isolation clothing, surgical masks, and goggles (occhiali) or face shield for daily medical activities and ward rounds; fit with goggles or face shield is stressed when collecting respiratory samples; using latex gloves in addition when contacting with blood, body fluid, secreta, or excreta; wearing surgical masks, goggles or face shield, latex gloves, medical protective clothing (disposable impermeable isolation clothing can be added), and respiratory hood when necessary, to prevent aerosol or splash during operations of endotracheal intubation, bronchoscopy, airway nursing, and sputum suction.

Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line

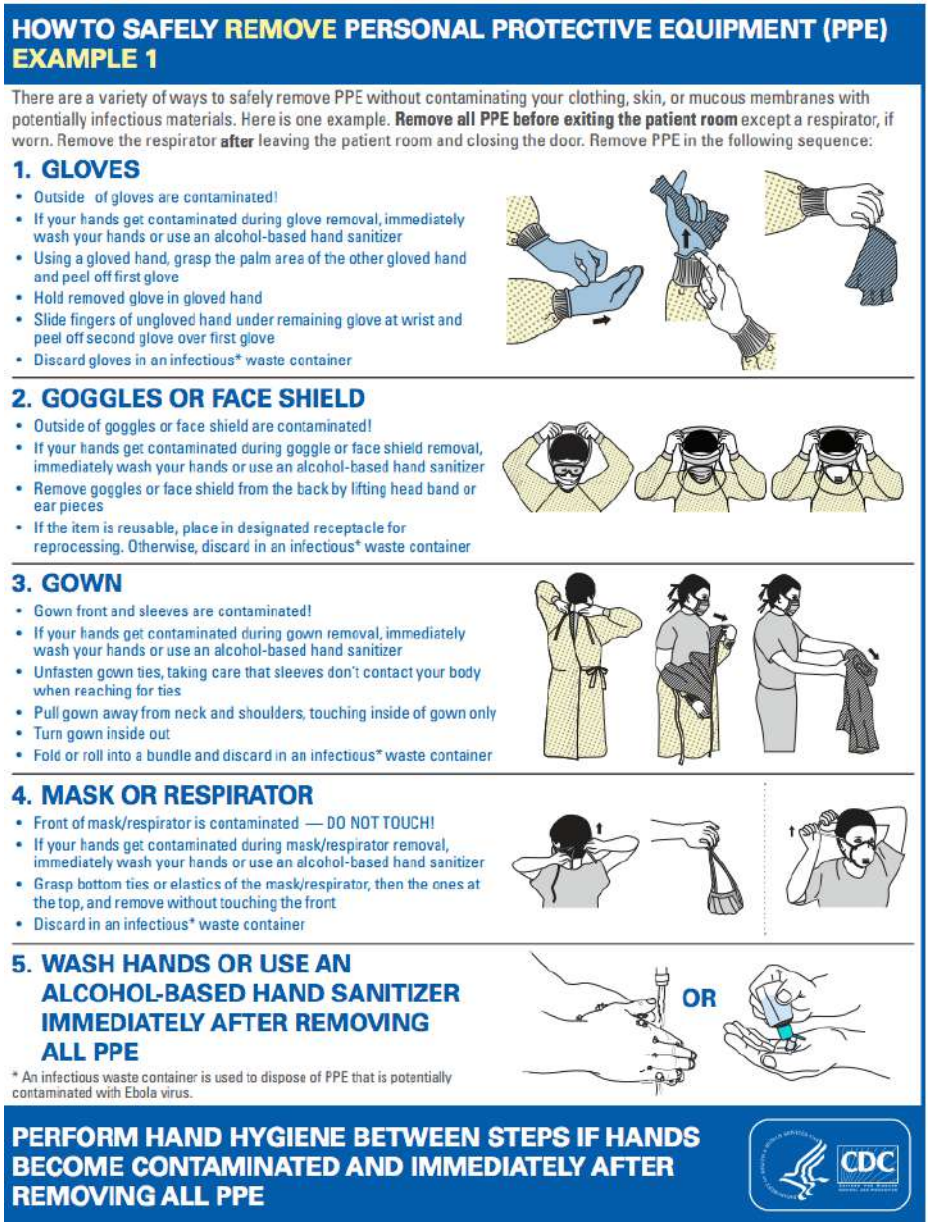
Infection control in hospital

Personal protective equipment

4. Medical personnel should wear and remove personal protective equipment in strict accordance with the on–off procedure, rather than leaving ward with the contaminated equipment, so as to avoid cross-contamination in different zones.

5. Patients and their accompanying family members are required to wear surgical masks.

Chen ZM, Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus World J Pediatr. 2020;on-line



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In Italia
la percentuale degli
operatori sanitari
infetti è
l'8,3% dei casi totali,
il doppio rispetto
al numero rilevato
nell'emergenza cinese.

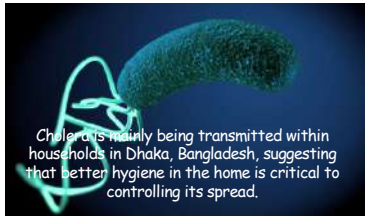
Fondazione Gimbe
18 marzo 2020

Protecting health-care workers from subclinical coronavirus infection.

Chang D, Lancet Respir Med 2020;8(3):e13-e13.

- According to recent guidelines from the China National Health Commission, pneumonia caused by COVID-19 was included as a Group B infectious disease, which is in the same category as other infectious viruses such as severe acute respiratory syndrome (SARS) and highly pathogenic avian influenza (HPAI).

- However, current guidelines suggest ensuring protective measures for all health-care workers similar to those indicated for Group A infections —a category reserved for highly infectious pathogens, such as cholera and plague.



- Recent evidence suggests that even someone who is non-symptomatic can spread COVID-19 with high efficiency, and conventional measures of protection, such as face masks, provide insufficient protection.

Protecting health-care workers from subclinical coronavirus infection.

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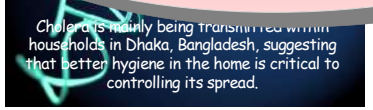
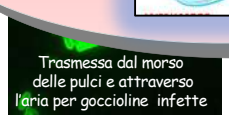
•According to recent guidelines from the China National Health Commission, pneumonia caused by COVID-19 was included as a Group B infectious disease, which is in the same category as other infectious viruses such as severe acute respiratory syn… avian influenza (…

•How… hea… —a … chole… and plague.

Patients can also shed high amounts of the virus and infect others even after recovery from the acute illness and they should wear a surgical mask





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Protecting health-care workers from subclinical coronavirus infection.

Chang D, Lancet Respir Med 2020;8(3):e13-e13.

- These findings warrant aggressive measures (such as **N95 masks**, **goggles**, and **protective gowns**) to ensure the safety of healthcare workers during this COVID-19 outbreak, as well as future outbreaks, **especially in the initial stages where limited information about the transmission and infective potency of the virus is available.**

- Health-care workers face an elevated risk of exposure to infectious diseases, including the COVID-19.

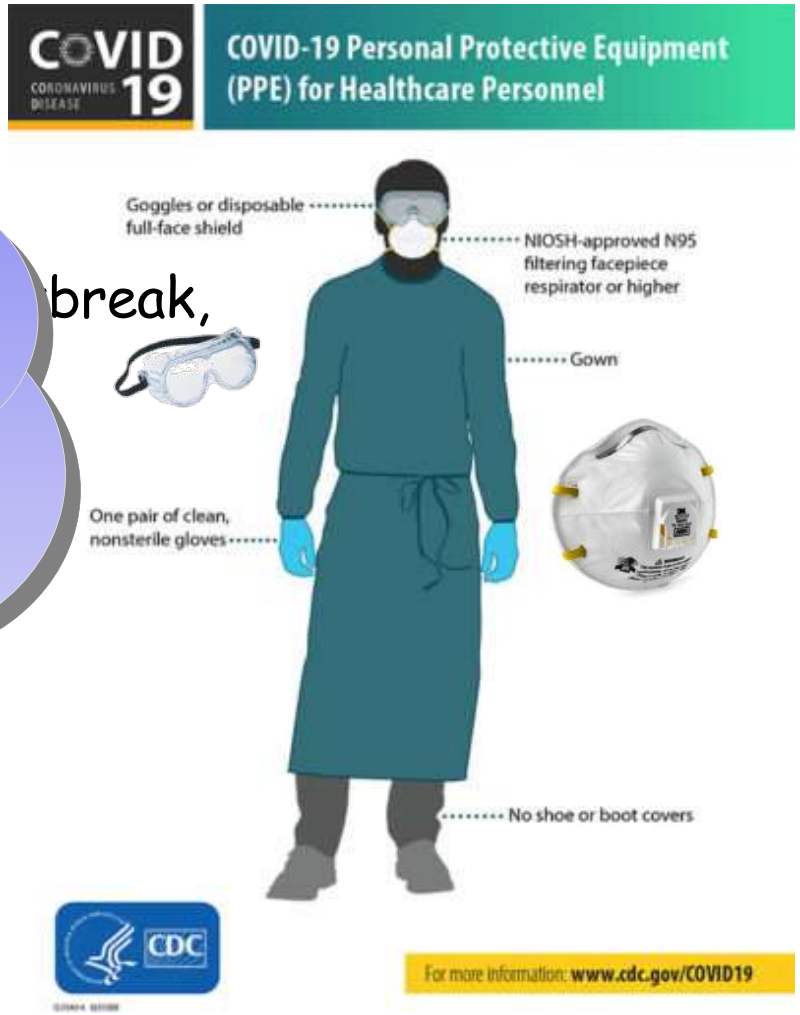
Protecting health-care workers from subclinical coronavirus infection.

Chang D, Lancet Respir Med 2020;8(3):e13-e13.

- These findings warrant aggr[illegible]ures (such as N95 mask[illegible] protecti[illegible] of heal[illegible] break, as wel[illegible] es[illegible] lim[illegible] and [illegible]

It is imperative to ensure
the safety of healthcare workers
not only to safeguard
continuous patient care
but also to ensure
they do not transmit the virus.

- Health-c[illegible] risk of exposu[illegible] seases, including the COVID-19.



Vademecum utilizzo mascherine:

Come sfruttare al meglio le mascherine sul nostro territorio.

- 

FFP3 (con valvola di esalazione) OSPEDALI Reparti Terapia Intensiva, (perché sono a contatto con pazienti certamente contagiati).

- FFP2 (con valvola di esalazione) SOCCORRITORI (perché sono a contatto con persone e/o pazienti potenzialmente contagiati).

FFP2 (SENZA valvola) FORZE DELL'ORDINE solo in caso di emergenza ed ausilio a Soccorritori (perché devono essere protetti ma non rischiare di contagiarsi tra di loro)

- FFP2 (SENZA valvola) MEDICI di famiglia e GUARDIE MEDICHE.

Tra le mascherine ffp1, ffp2, ffp3, quali sono le differenze?

In generale, maggiore è la classe, maggiore è la potenza filtrante della mascherina

Vademecum utilizzo mascherine:

Come sfruttare al meglio le mascherine sul nostro territorio.

- 

-

In alternativa con valvola (ma ricordiamo che la valvola è di aiuto a chi è costretto ad utilizzarla a LUNGO TEMPO in presenza di PAZIENTE POTENZIALMENTE MALATO);
i medici potranno abbinare la mascherina chirurgica sopra alla MASCHERINA FFP2 con valvola per limitare la diffusione della loro esalazione dalla valvola.

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- 

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Vademecum utilizzo mascherine:

Come sfruttare al meglio le mascherine sul nostro territorio.

MASCHERINE CHIRURGICHE o FATTE IN CASA,

devono usarle:

- tutta la POPOLAZIONE CIRCOLANTE,
- tutte le PERSONE CHE LAVORANO o SONO COSTRETTE A LAVORARE,
- le FORZE dell'ORDINE,
- gli uffici aperti al pubblico,
- gli addetti alla vendita di alimentari ed, in ogni caso,
- tutte le persone o lavoratori in circolazione

(si ricorda alla POPOLAZIONE che è MEGLIO RESTARE CASA).

Per gli addetti all'ospedale, infermieri e/o gli stessi medici, quando non in reparto si potrebbe consigliare di usare le chirurgiche (oppure se disponibili le FFP2 o FFP3 ma senza valvola o con aggiunta della MASCHERINA chirurgica davanti alla VALVOLA) per limitare al massimo la DIFFUSIONE del contagio.

Vademecum utilizzo mascherine:

Come sfruttare al meglio le mascherine sul nostro territorio.

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ATTENZIONE:

CHI NON DEVE utilizzare le FFP2 ed FFP3 con valvola

NO!

E' importante sapere che:
Dalla VALVOLA della Mascherina fuoriescono le esalazioni
(che equivale a DIFFONDERE il possibile contagio, è come non averle) quindi:

-**Assolutamente sconsigliate per la popolazione,** ci contamineremmo uno con l'altro.

-Sconsigliate anche per:

- **Forze dell'Ordine** che sono costrette ad un contatto ravvicinato tra colleghi, si contaminerebbero l'uno con l'altro.
- **Reparti di alimentari** o banchi del fresco.
- **Uffici aperti al pubblico**, si contaminerebbero uno con l'altro tra colleghi.

Vademecum utilizzo mascherine:

Come sfruttare al meglio le mascherine sul nostro territorio.

CHI DEVE avere le FFP2 ed FFP3 CON valvola:

SI !

-Ospedali Reparti TERAPIA INTENSIVA ed INFETTOLOGIA
-I SOCCORRITORI 118, CROCE VERDE, CROCE ROSSA, **o assimilati.**
(Queste categorie si presume che avranno contatti con persone o pazienti CERTAMENTE CONTAGIATI) devono fare sforzi e/o devono tenerle per lungo tempo.

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CHI DEVE avere le FFP2 ed FFP3 SENZA valvola:

-Le FORZE DELL'ORDINE da usare solo ed esclusivamente per interventi di emergenza o interventi in assistenza ai soccorritori,
in abbinamento ad OCCHIALI E GUANTI MONOUSO.

Vademecum utilizzo mascherine:

Come sfruttare al meglio le mascherine sul nostro territorio.

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IN SINTESI:

-La **CITTADINANZA NON** deve usare le MASCHERINE CON VALVOLA perché possono diffondere il contagio.

NO!

-**Gli ADDETTI alla vendita** NON devono usare le MASCHERINE CON VALVOLA perché possono diffondere il contagio.

NO!

-QUESTE PERSONE devono usare mascherine SENZA VALVOLA o CHIRURGICHE **o fatte in casa con tessuti pesanti che assorbano l'esalazione ed umidità trattenendola e non rilasciandola.**


SI !

Filter capacity of different types of Respirators

N95 (95%) = FFP2 (94%)

N100 (99.97%) = FFP3 (99.95%)

Respirator standard	Filter capacity(removes x% of all particles that are 0.3 microns in diameter or larger
FFP1	80%
FFP2	94%
N95	95%
FFP3	99.95%
N100	99.97%

Are N95/N100 actually better than FFP2/FFP3?

Whilst the specifications for the NIOSH (N95/N100) are marginally higher than FFP, that doesn't mean the respirators are any better.

N95 Respirators vs Medical Masks for Preventing Influenza Among Health Care Personnel – A Randomized Clinical Trial – Lewis J. Radonovich Jr, MD et al. – JAMA –Sept 2019

Can Surgical Masks Filter the Corona virus?

- Surgical masks are primarily designed to protect vulnerable patients from medical professionals.

- Stopping the wearer from spreading their germs when coughing/sneezing/speaking.

- So they're designed to protect patients, not to protect the wearer.

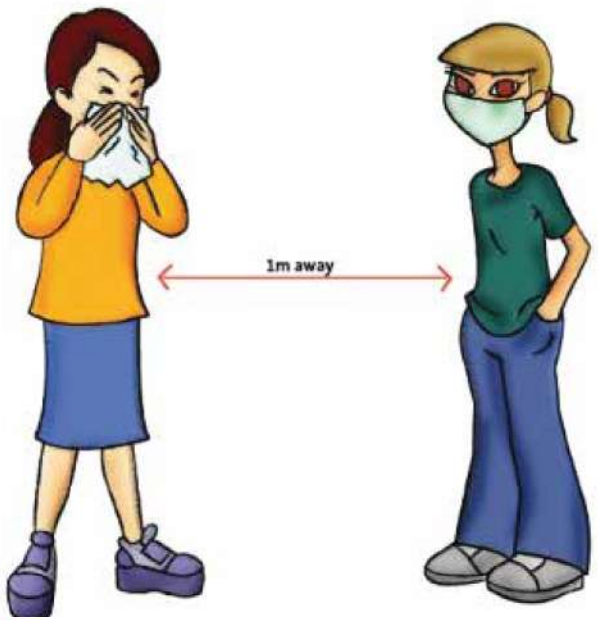
- There isn't currently research available on the efficacy of surgical masks (or even respirators), for protecting wearers against the corona virus.

Less Protection

More Protection

WHAT CAN YOU DO TO REDUCE RISK?

Social Distancing



SANITIZE YOUR PHONE

- Avoid handshakes, hugs and kisses
- Avoid holding on railings of steps
- May use pens for switching on lights in common areas, lift buttons
- Use gloves

Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19)

Interim guidance
27 February 2020

World Health Organization

The most effective preventive measures in the community include:

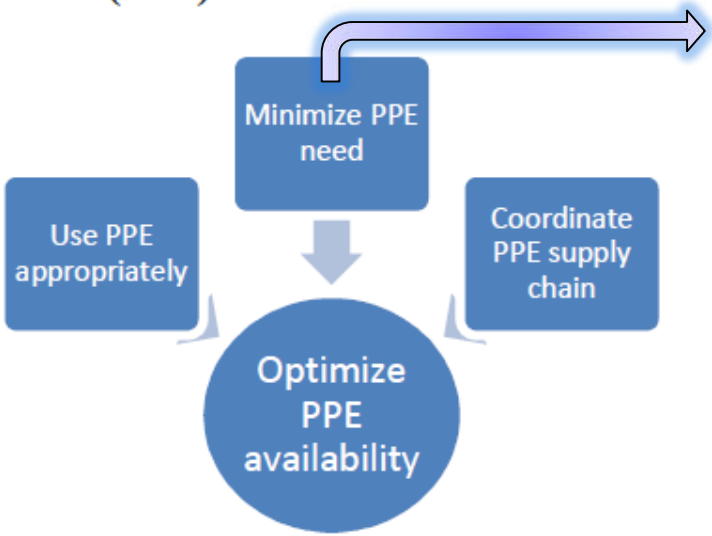
- performing **hand hygiene** frequently with an alcohol-based hand rub if your hands are not visibly dirty or with soap and water if hands are dirty;
- **avoiding touching** your **eyes, nose and mouth**; *ON AVERAGE, PEOPLE TOUCH THEIR FACES 23 TIMES AN HOUR*
- practicing respiratory **hygiene by coughing or sneezing** into a bent elbow or tissue and then immediately disposing of the tissue;
- **wearing a medical mask if you have respiratory symptoms** and performing hand hygiene after disposing of the mask;
- maintaining **social distance (a minimum of 1 m)** from individuals with respiratory symptoms.

Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19)

Interim guidance
27 February 2020

World Health Organization

Fig. 1. Strategies to optimize the availability of personal protective equipment (PPE)



- telemedicine to evaluate suspected cases of COVID-19 disease.
- physical barriers (glass or plastic windows) in areas setting where patients will first present, such as triage areas, the registration desk at the emergency department or at the pharmacy window where medication is collected.
- Restrict healthcare workers from entering the rooms of COVID-19 patients if they are not involved in direct care.
- visitors will not be allowed.

Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19)

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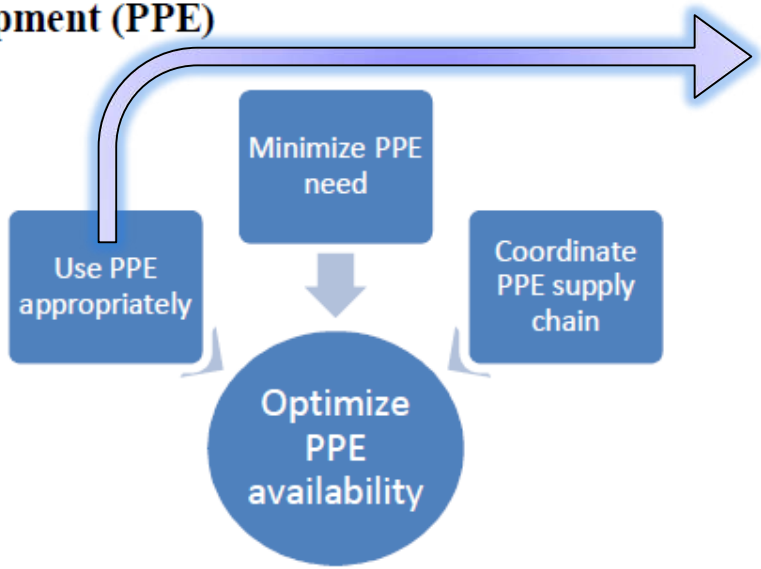

- The type of PPE used when caring for COVID-19 patients will vary according to the setting and type of personnel and activity.

- for aerosol-generating procedures
(e.g., tracheal intubation, non-invasive ventilation, tracheostomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy)
healthcare workers should use respirators (N95, FFP2 or equivalent standard), eye protection, gloves and gowns; aprons should also be used if gowns are not fluid resistant.

Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19)

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27 February 2020

World Health Organization

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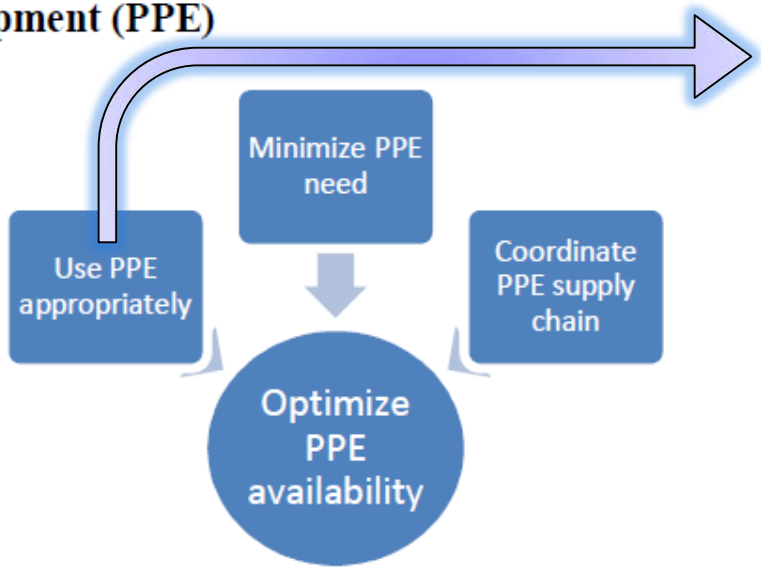

- wearing the same respirator while caring for multiple patients who have the same diagnosis without removing it.
- however, using one respirator for > 4 hours can lead to discomfort.
- for asymptomatic individuals, wearing a mask of any type is not recommended. Wearing medical masks when they are not indicated may cause unnecessary cost and a procurement burden and create a false sense of security that can lead to the neglect of other essential preventive measures.

Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19)

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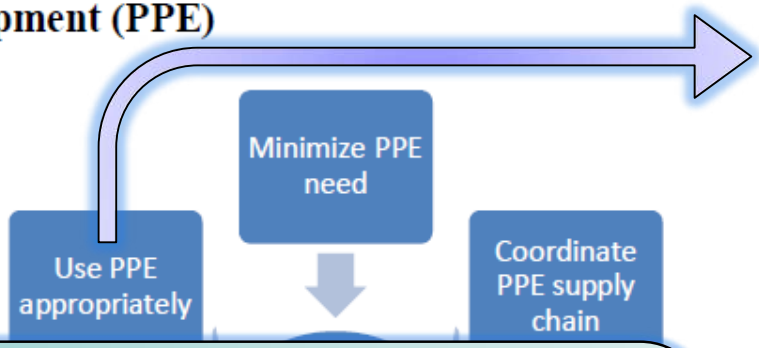

If masks are used, best practices should be followed on how to wear, remove, and dispose of them and on hand hygiene action after removal.

Interim guidance 29 January 2020

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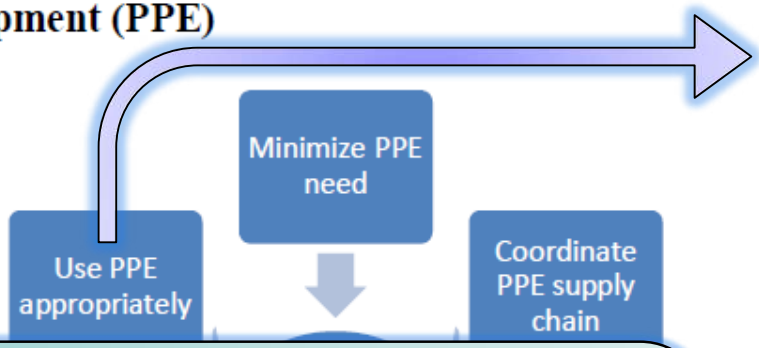

- wear a medical mask and seek medical care if experiencing fever, cough and difficulty breathing, as soon as possible;

Interim guidance 29 January 2020

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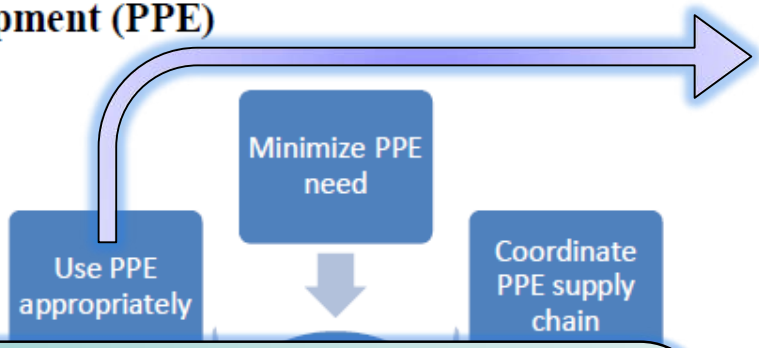
Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19)

Interim guidance
27 February 2020

World Health Organization

Fig. 1. Strategies to optimize the availability of personal protective equipment (PPE)



-wear a medical mask if you want to protect other people just in case you might be coronavirus (+) or when you ask for a medical consultation in order to protect physicians and nurses, just in case.

Attilio Boner personal opinion

- wearing the same respirator while caring for multiple patients who have the same diagnosis without removing it.
- however, using one respirator for > 4 hours can lead to discomfort.
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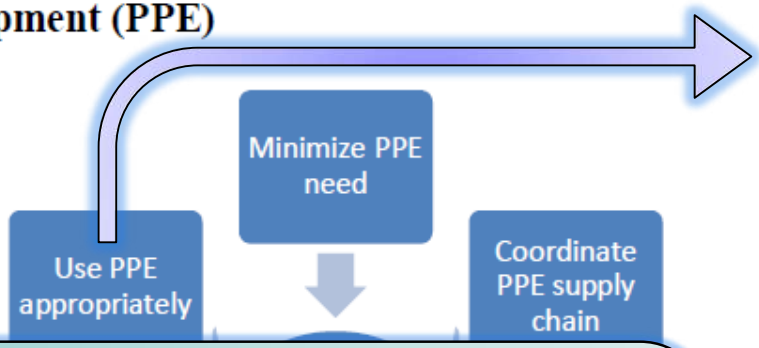

-At this regard also home made mask may have some efficacy and may be better than nothing if they are made with material that retain moisture and further have the advantage of being washable and reusable.
-Attilio Boner personal opinion

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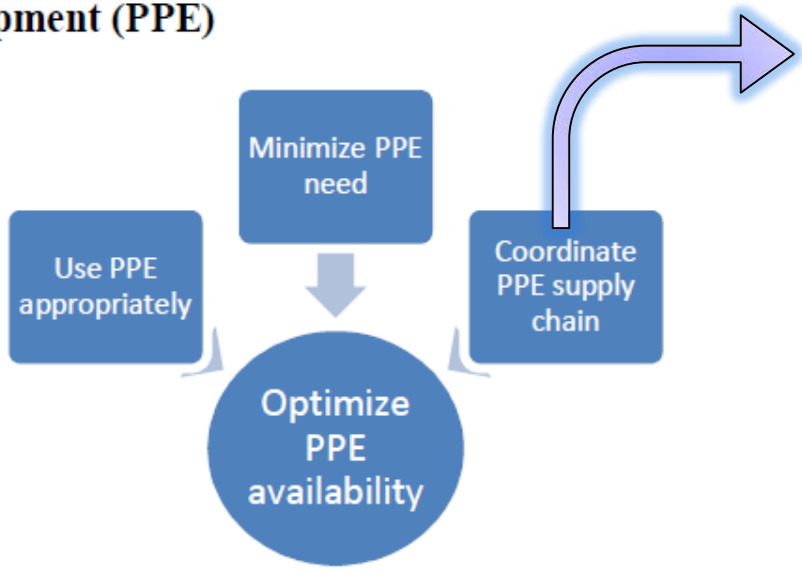

- using PPE **forecasts** (previsioni) that are based on rational quantification models
- **monitoring and controlling PPE requests from countries** and large responders;
- promoting the use of a **centralized request management**
- **monitoring the end-to-end distribution** of PPE

Infection control in hospital

Additional notes

1. Channels for medical personnel and patients in the isolation ward should be separated and equipped with medical personnel channel buffer zone (zona cuscinetto).

2. Wearing gloves cannot replace hand hygiene.

3. Perform strict visiting regulations for pediatric patients admitted in isolation, and ask visitors to have personal protection according to relevant regulations when necessary.

4. Optimize medical procedures to reduce the frequency of medical personnel's contact with patients.

5. Attention should be paid to the strict elimination and disinfection of the patient's secretions and excretions.

Prevention of COVID-19

- For individuals, protective measures, including

1) improving personal hygiene,
2) wearing medical masks,
3) adequate rest, and
4) keeping rooms well ventilated,

} can effectively prevent SARS-CoV-2 infection spread.

- *Guan W, Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv. 2020.*
- *Sun P, Understanding of COVID-19 based on current evidence [published online ahead of print, 2020 Feb 25]. J Med Virol. 2020;10.1002/jmv.25722.*

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As the pandemic has developed, a fact has become apparent: there is a serious dearth of emergency medical supplies, and especially an extreme shortage of personal protective equipment such as masks.

•If you are healthy, you only need to wear a mask if you are taking care of a person with suspected 2019-nCoV infection.

•Wear a mask if you are coughing or sneezing.

•Masks are effective only when used in combination with frequent hand-cleaning with alcohol-based hand rub or soap and water.

•If you wear a mask, then you must know how to use it and dispose of it properly.

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•Before putting on a mask, clean hands with alcohol-based hand rub or soap and water.

•Cover mouth and nose with mask and make sure there are no gaps between your face and the mask.

•Avoid touching the mask while using it; if you do, clean your hands with alcohol-based hand rub or soap and water.

•Replace the mask with a new one as soon as it is damp and do not re-use single-use masks.

•To remove the mask: remove it from behind (do not touch the front of mask); discard immediately in a closed bin; clean hands with alcohol-based hand rub or soap and water.

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See:

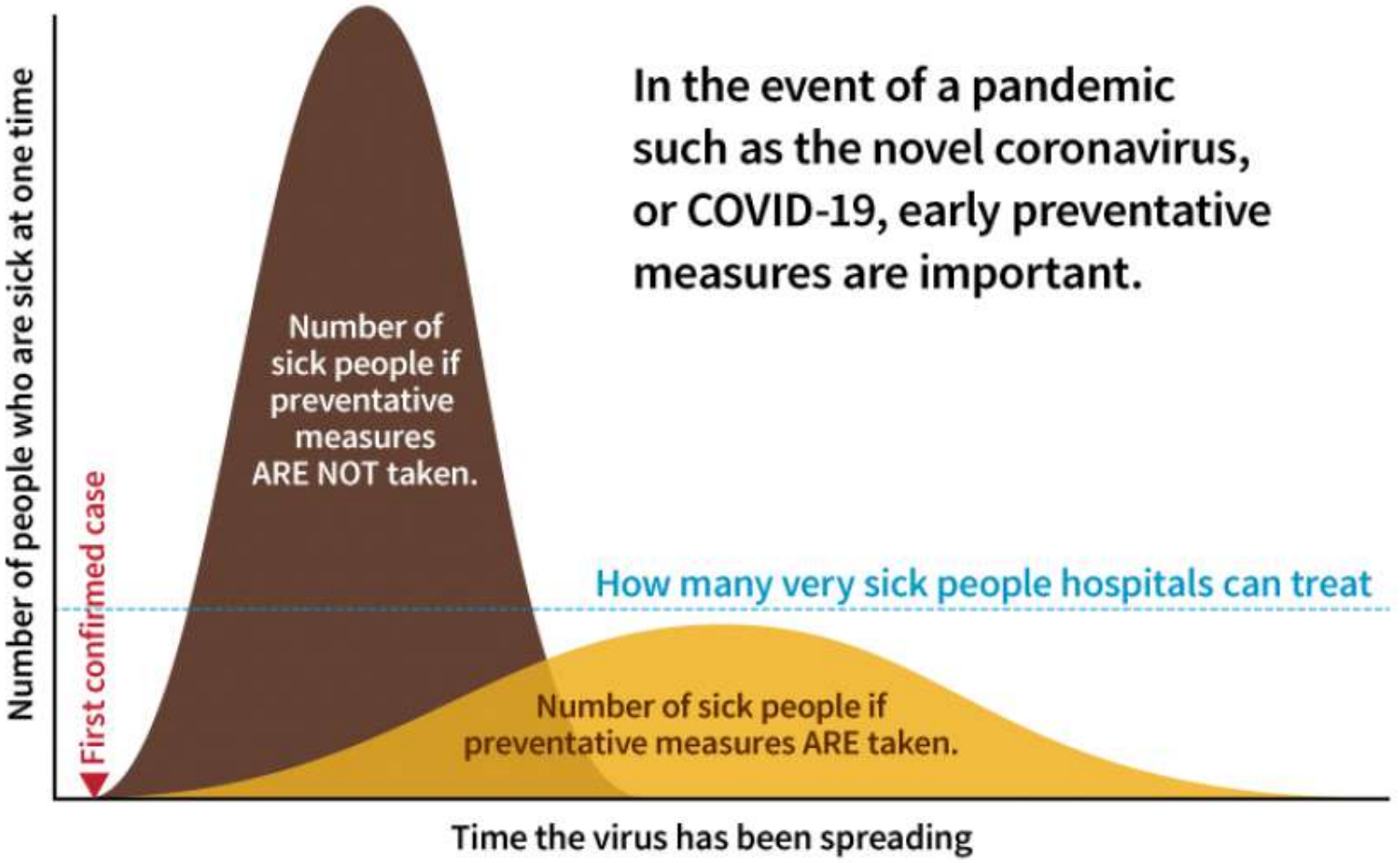
Coronavirus disease (COVID-19) advice for the public: When and how to use masks

World Health Organization

WESTERN MICHIGAN UNIVERSITY

WMU

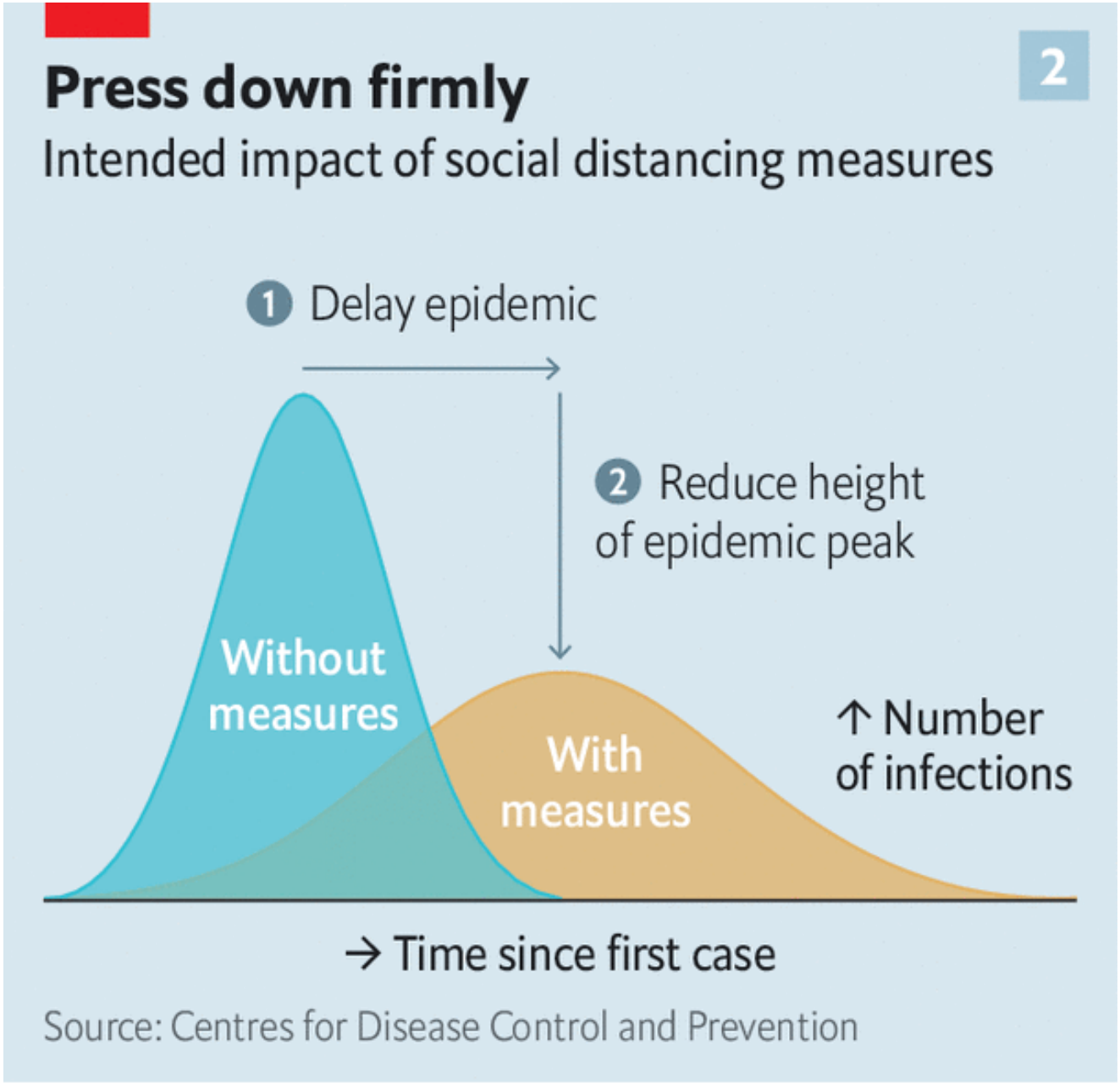
WHY WMU IS SUSPENDING IN-PERSON EDUCATION



In the event of a pandemic such as the novel coronavirus, or COVID-19, early preventative measures are important.

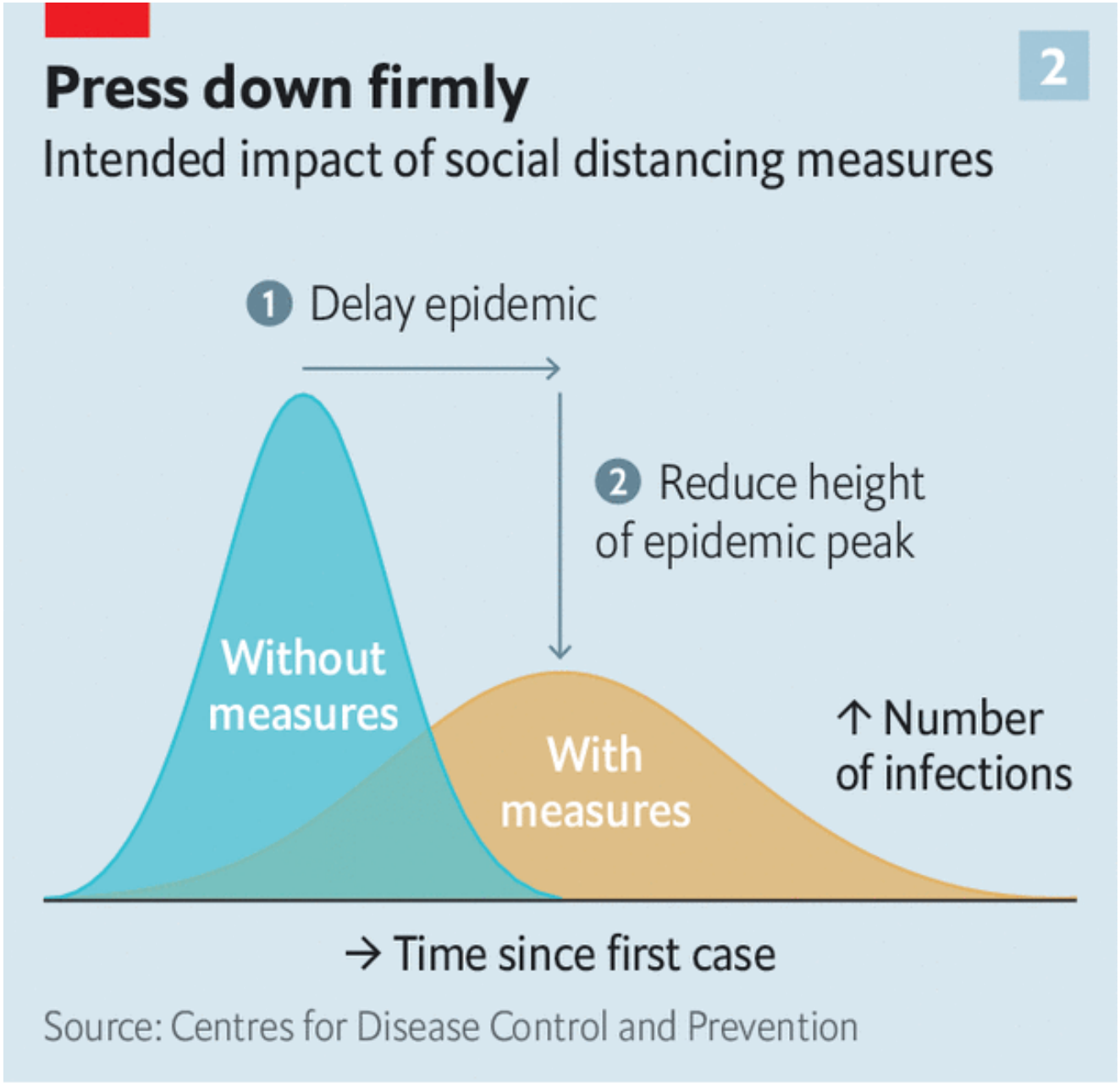
Distance education reduces concentrations of large numbers of people to slow the spread of the disease.

Adapted from the CDC and the University of Michigan.
https://www.cdc.gov/mmwr/volumes/66/rr/rr6601a1.htm?s_cid=rr6601a1_w#F1_down



The Economist Feb 27th 2020

- The course of an epidemic is shaped by a variable called the reproductive rate, or *R*.
- It represents, in effect, the number of further cases each new case will give rise to.
- If *R* is high, the number of newly infected people climbs quickly to a peak before, for want of new people to infect, starting to fall back again.
- If *R* is low the curve rises and falls more slowly, never reaching the same heights.
- With sars-cov-2 now spread around the world, the aim of public-health policy, whether at the city, national or global scale, is to flatten the curve, spreading the infections out over time.
- This has two benefits.
First, it is easier for health-care systems to deal with the disease if the people infected do not all turn up at the same time. Better treatment means fewer deaths; more time allows treatments to be improved.
Second, the total number of infections throughout the course of the epidemic can be lower.



The Economist Feb 27th 2020

Restate a casa!

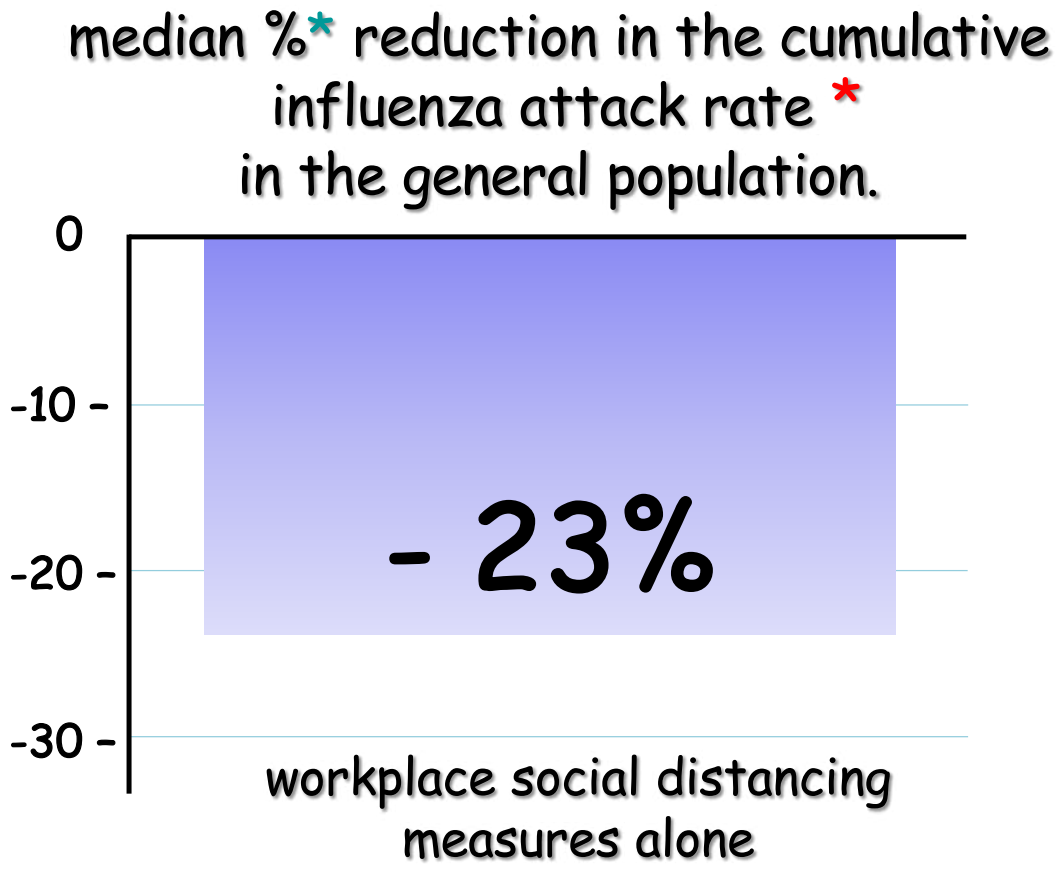
Effectiveness of workplace social distancing measures in reducing influenza transmission: a systematic review.

Ahmed F, BMC Public Health. 2018;18(1):518. Published 2018 Apr 18.

✓15 studies, representing
- 12 modeling and
- 3 epidemiological,

* Percentage reduction = ((Attack rate in the absence of intervention – Attack rate with intervention) / Attack rate in the absence of intervention) × 100

* clinical attack rate is calculated by dividing the estimated number of influenza cases by the total number of participants



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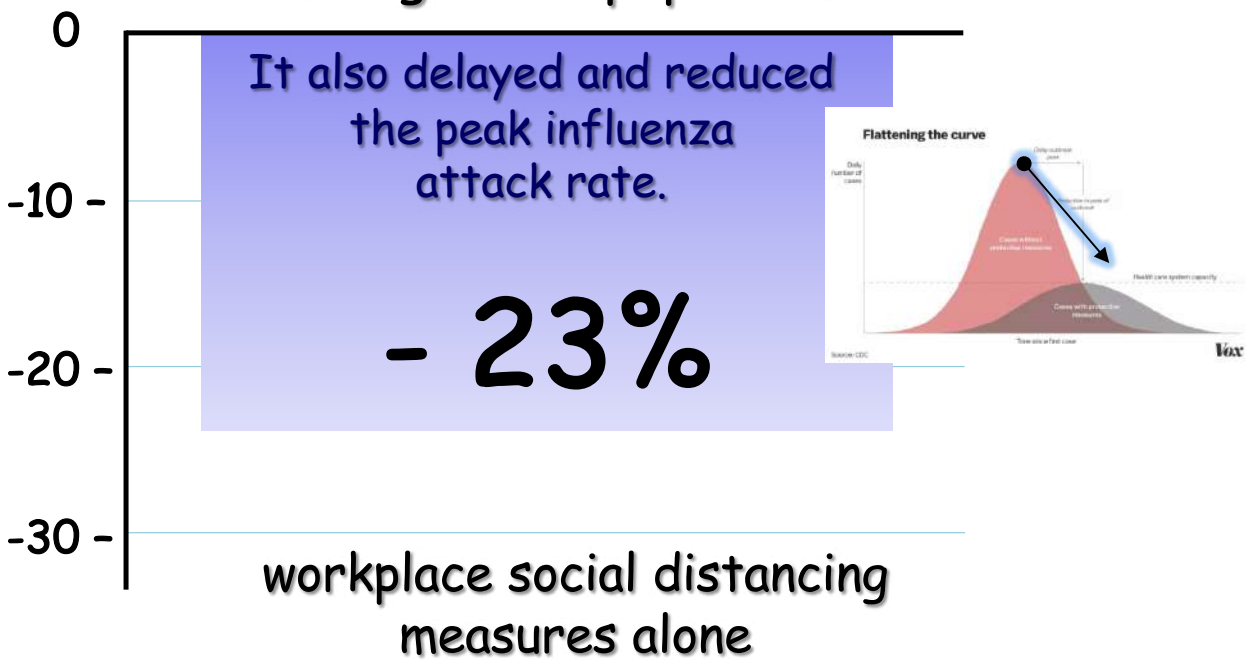
median %* reduction in the cumulative influenza attack rate *
in the general population.



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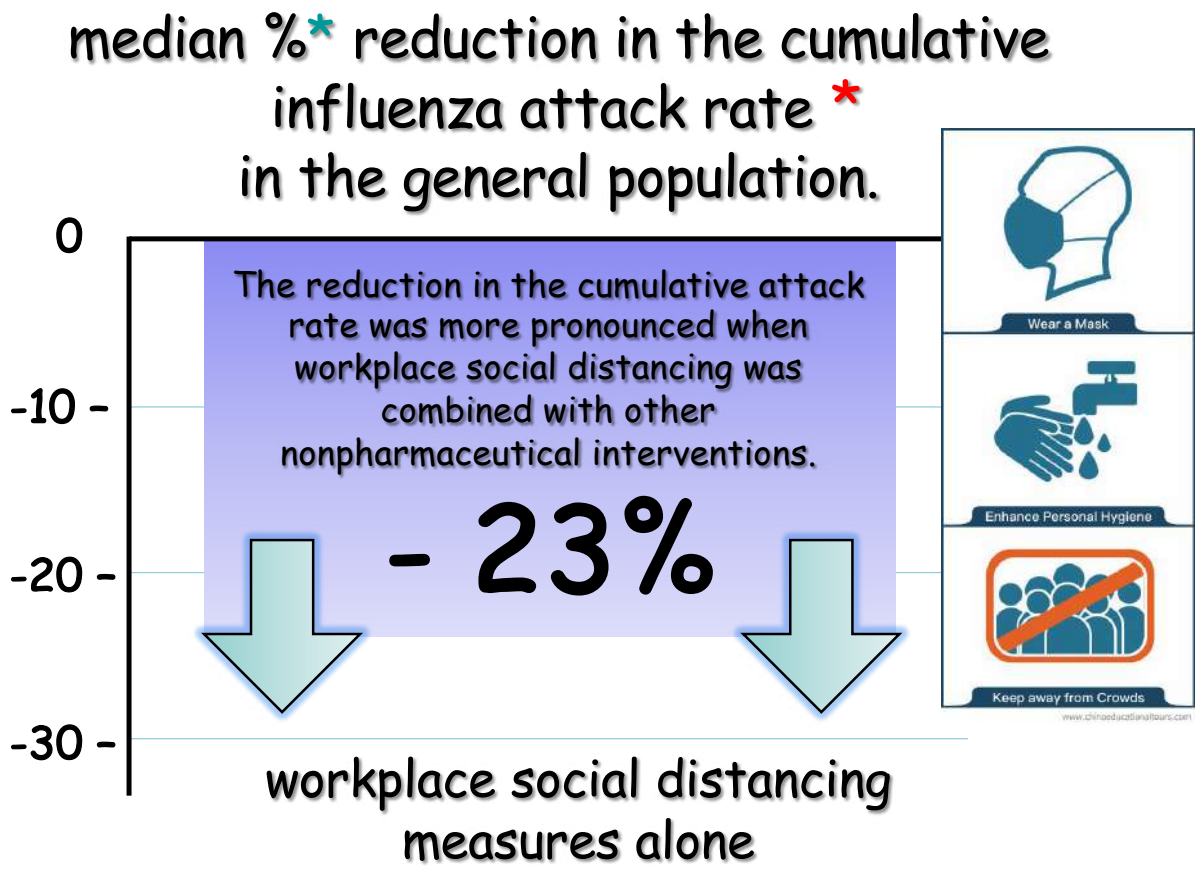

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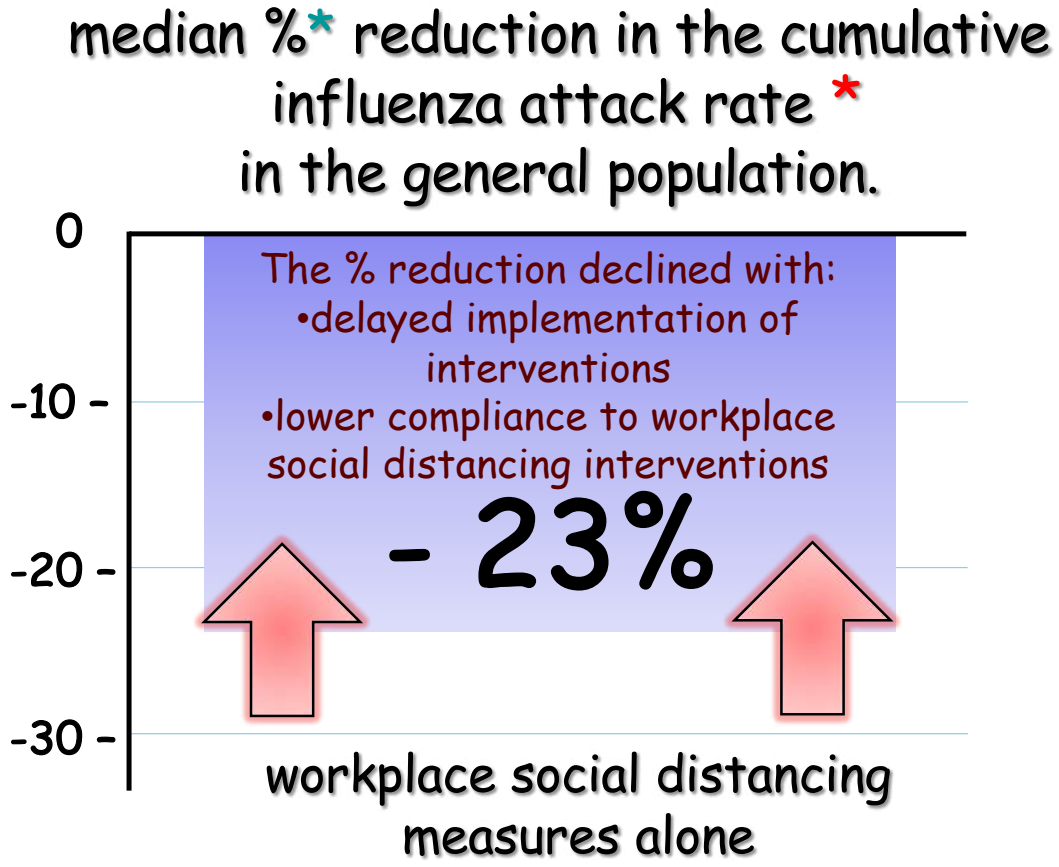
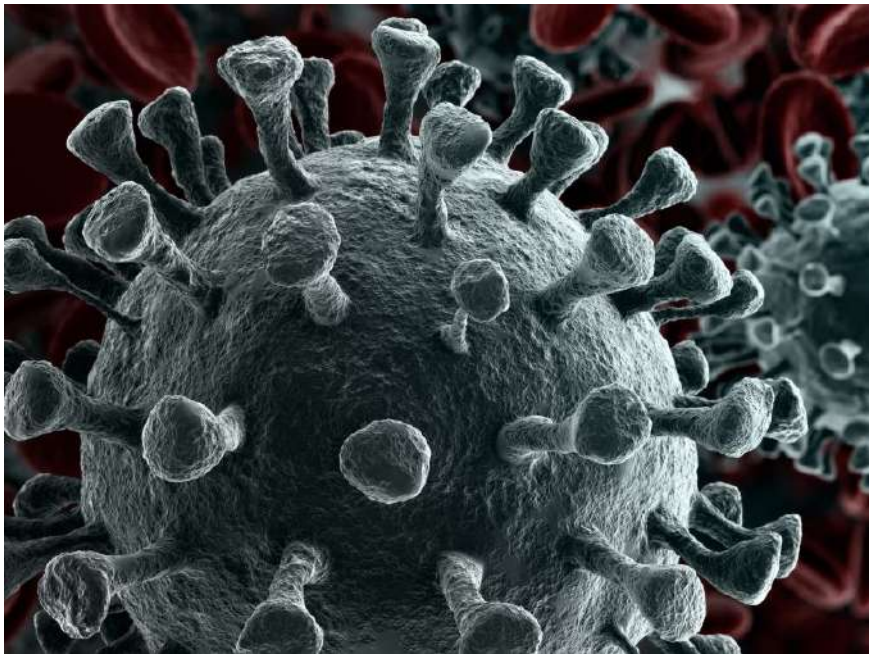


Why Is Coronavirus Spreading Rapidly?

Undetected cases may be driving coronavirus spread, study finds.



- About 86% of COVID-19 cases in China were milder and went undetected during the two-week ramp-up of the epidemic in January, prior to the country imposing travel restriction.

- These undocumented cases of infection are "about half as infectious per person as a documented case who has more severe symptoms and may be shedding more.

- However, "because there are many more of these undocumented cases, it's the undocumented infections that are driving the spread and growth of the outbreak.

Chinazzi M, The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak Science. 2020;eaba9757.

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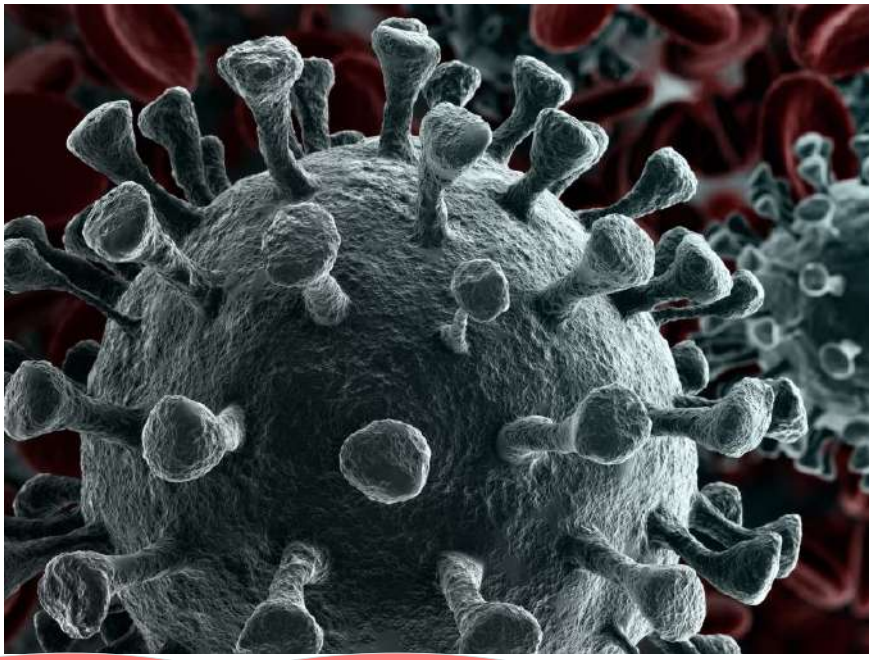

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a significant amount of the coronavirus' spread is fueled by "silent transmission."

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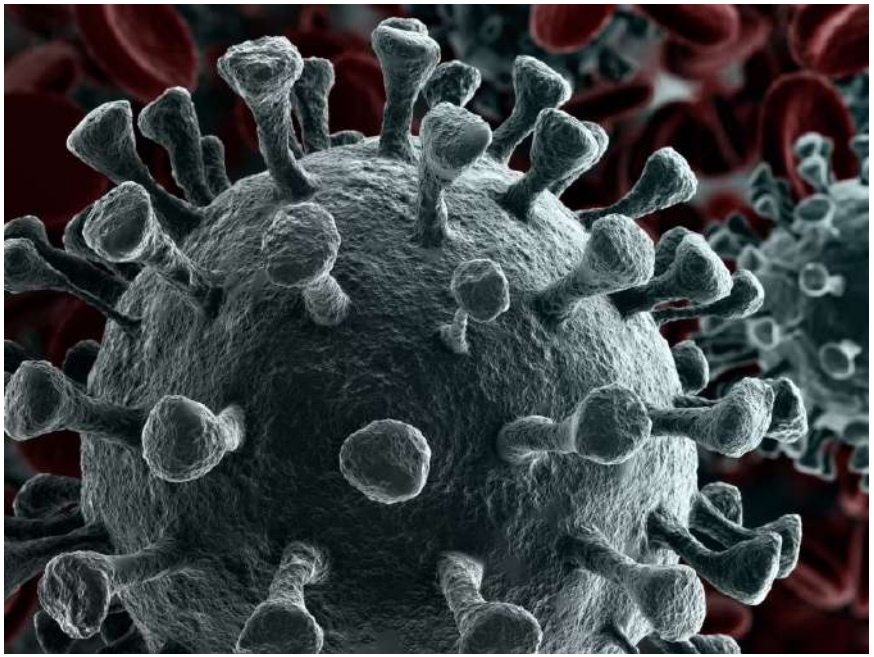
Why Is Coronavirus Spreading Rapidly?

Undetected cases may be driving coronavirus spread, study finds.

"If somebody is experiencing
mild symptoms
we're still going to go about our day."

"We'll still send the kids to school.

We'll still go to work. If we have a little bit of a headache or slight fever, we might take some ibuprofen and still go out shopping and whatnot."



Mobile phone data have shown that it's that sort of continued contact with people that allows the silent transmission of many respiratory viruses."

Rao ASRS, Vazquez JA. Identification of COVID-19 Can be Quicker through Artificial Intelligence framework using a Mobile Phone-Based Survey in the Populations when Cities/Towns Are Under Quarantine. Infect Control Hosp Epidemiol. 2020; Mar 3: 1–18.

Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts

Hellewell J, Lancet Glob Health. 2020;S2214-109X(20)30074-7.

$$\begin{cases} \frac{dI}{dt} = \frac{\alpha_I}{1+\left(\frac{R}{R_{50}}\right)^{\mu_R}} + \frac{\alpha_A}{1+\left(\frac{A}{A_{50}}\right)^{\mu_A}} \cdot e^{\beta \cdot \omega c} - \delta \cdot I & (1.1) \\ \frac{dR}{dt} = \frac{\alpha_R}{1+\left(\frac{I^F}{I_{50}}\right)^{\mu_I}} - \delta \cdot R & (1.2) \\ I^F = \frac{I}{1+\left(\frac{IPTG}{IPTG_{50}}\right)^2} & (1.3) \end{cases}$$

✓mathematical model to assess if isolation and contact tracing are able to control onwards transmission from imported cases of COVID-19.

✓scenarios that varied in:
- the number of initial cases,
- the basic reproduction number (R_0),
- the delay from symptom onset to isolation,
- the probability that contacts were traced,
- the proportion of transmission that occurred before symptom onset, and
- the proportion of subclinical infections

❑To control the majority of outbreaks,

- for R_0 of 2·5 more than 70% of contacts had to be traced,

and

- for an R_0 of 3·5 more than 90% of contacts had to be traced.

Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts

Hellewell J, Lancet Glob Health. 2020;S2214-109X(20)30074-7.

- In most scenarios, highly effective contact tracing and case isolation

is enough to control a new outbreak of COVID-19 within 3 months.

- The probability of control decreases with:

1) long delays from symptom onset to isolation,

2) fewer cases ascertained by contact tracing, and

3) increasing transmission before symptoms.

Understanding of COVID-19 based on current evidence

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

- ✓ Introduction
- ✓ Sources of SARS-CoV-2
- ✓ Epidemiology
- ✓ Etiology & Pathogenesis
- ✓ Symptoms, & Diagnosis
- ✓ The case of infants & children
- ✓ The case of mother & fetus
- ✓ The case of Italy
- ✓ Treatment
- ✓ Prevention
- ✓ Conclusions

We are the most diseased species on earth

- Human beings are almost certainly the most diseased species on earth.

- By one accounting, there are at least 1400 human pathogens, including bacteria, fungi, prions, protozoa, viruses, and worms, and of these, 100-150 appear capable of causing human epidemics.

- To understand modern human disease prevalence, we have only to look to the most basic principles of epidemiology.

- A simplified version is that diffuse or small host populations (our preagricultural hunter–gathers) cannot sustain an acutely infectious agent, meaning one in which infection is followed by clearance and long-term immunity or death.

The Imperative to Vaccinate. Hedrick SM. J Pediatr. 2018 Oct;201:259-263.

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Small or low-density populations can only sustain (mantenere) a certain type of infectious agent, one that persists, usually for the life of the host: herpes viruses, mycobacterium tuberculosis, intestinal protozoa, worms, and fleas (pulci).

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Our Paleolithic ancestors were not disease-free, but they almost certainly did not experience periodic and devastating epidemics.

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- Conversely, large populations that live at high density, such as modern human beings, can sustain a much greater diversity of infectious agents, including those that the immune system is able to clear.

- Transmission from person to person is rapid enough and continuous, such that there is little selective pressure for persistence.

- Large and dense urban populations can maintain acutely infectious agents indefinitely due to a constant source of newly susceptible hosts.

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This is the answer to why we are the most diseased species on earth.

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Dalla spagnola al coronavirus, la lezione delle emergenze: nessuno è lontano. Il Sole 24 ore 9/03/2020

Siamo all'inizio di un periodo lungo e complicato.

La strada è mettersi a disposizione, facendosi carico di problemi e difficoltà altrui.

Gerusalemme


Niagara


Dubai


New York


Sarajevo


Parigi

after we should
not be the same

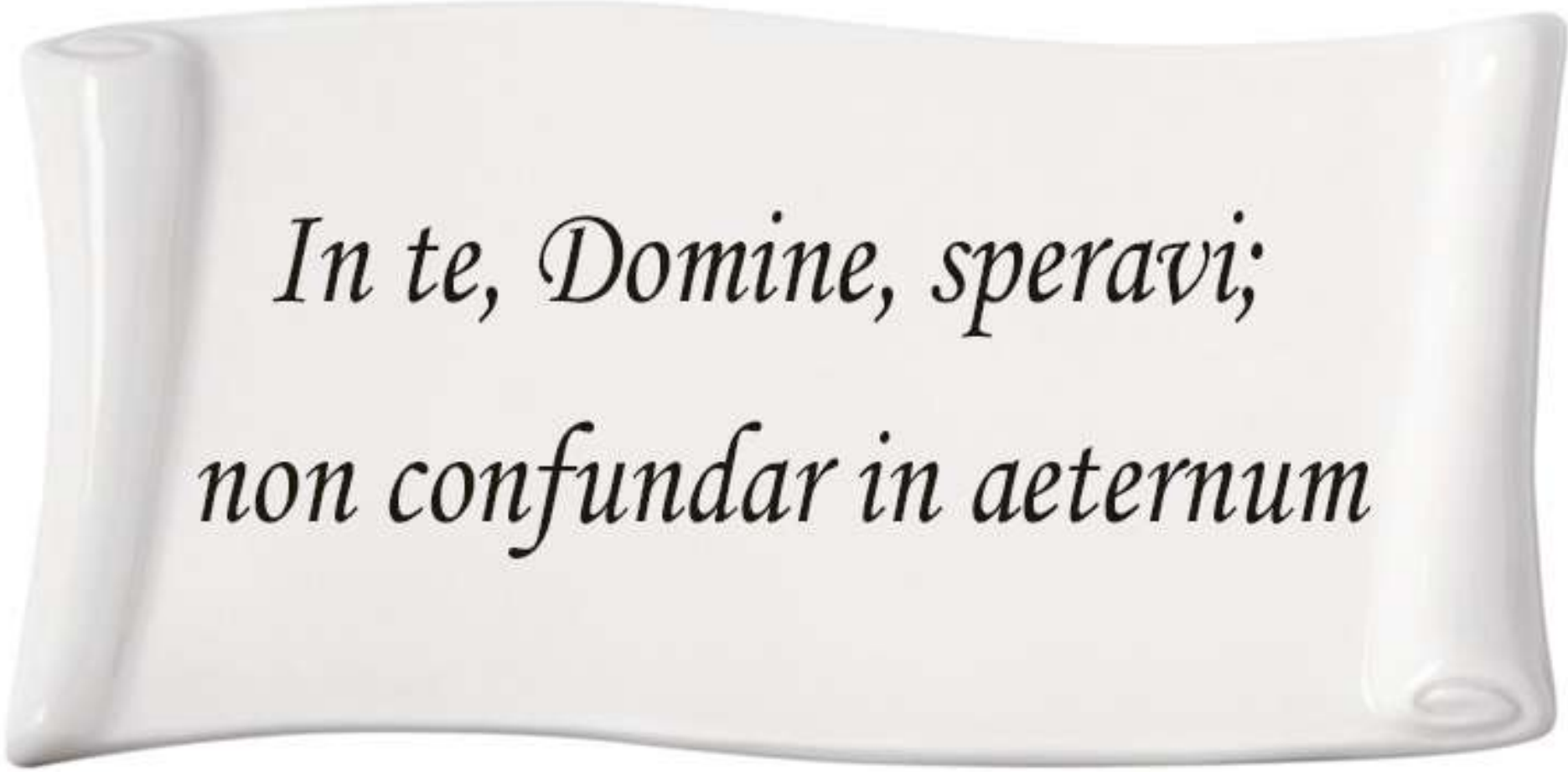

Palestina


Bosnia


KEEP
CALM
AND
no
panic


THINK
BEFORE
YOU ACT


Knowledge
Competence
Skill
Attitude



Riferimento bibliografico: mia nonna Carmela che è passata attraverso altre due simili epidemie la Spagnola (1918–1919) e l'Asiatica (1957-1958)