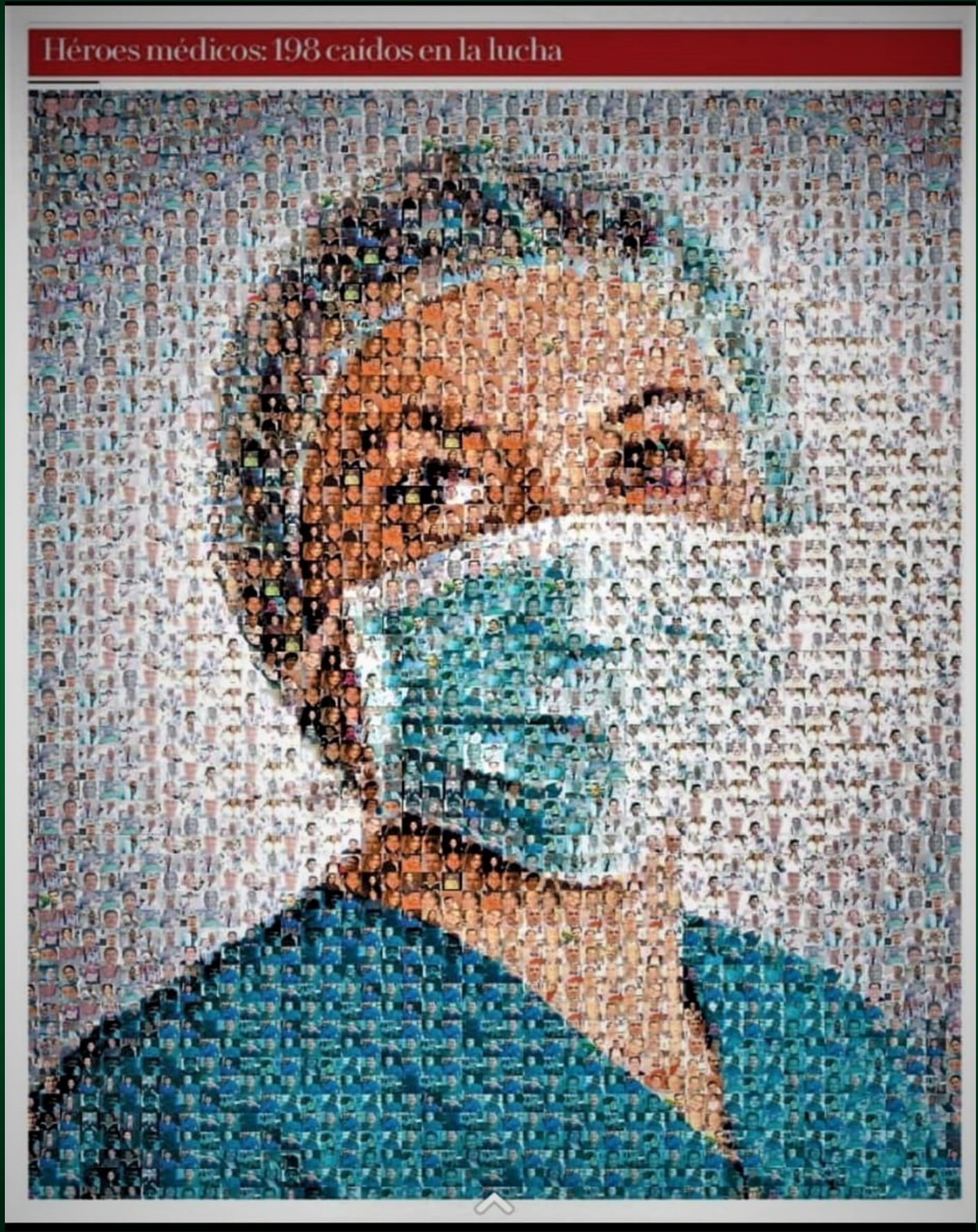
Kuwait Pharmacy Bulletin

DRUG INFORMATION FOR THE HEALTH PROFESSIONAL



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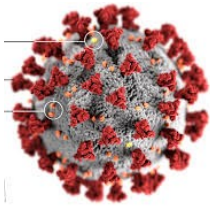
Treatment strategies for COVID-19 -a fast shifting landscape



The coronavirus disease 2019 (COVID-19) originating in Wuhan China, has spread rapidly to all parts of the world in just 8 months, with a devastation not seen since the '*Spanish flu*' of 1917, At the time of writing, it has infected in excess of 30 million people with near to 1,000,000 recorded deaths (3% mortality rate); increasing daily. Currently, clinical management of COVID-19 relies mainly on supportive care, particularly in the form of assisted ventilation for severely ill patients (CDC, 2020a; Pascarella et al., 2020). This review will focus on the most widely publicised drug treatments currently being trialled or under development by Pharma (big and small) in collaboration with universities and research institutes across many countries. Fig 1 shows several re-purposed drugs in clinical trials and their possible therapeutic targets at different stages of the viral life cycle. More are being added to this list.

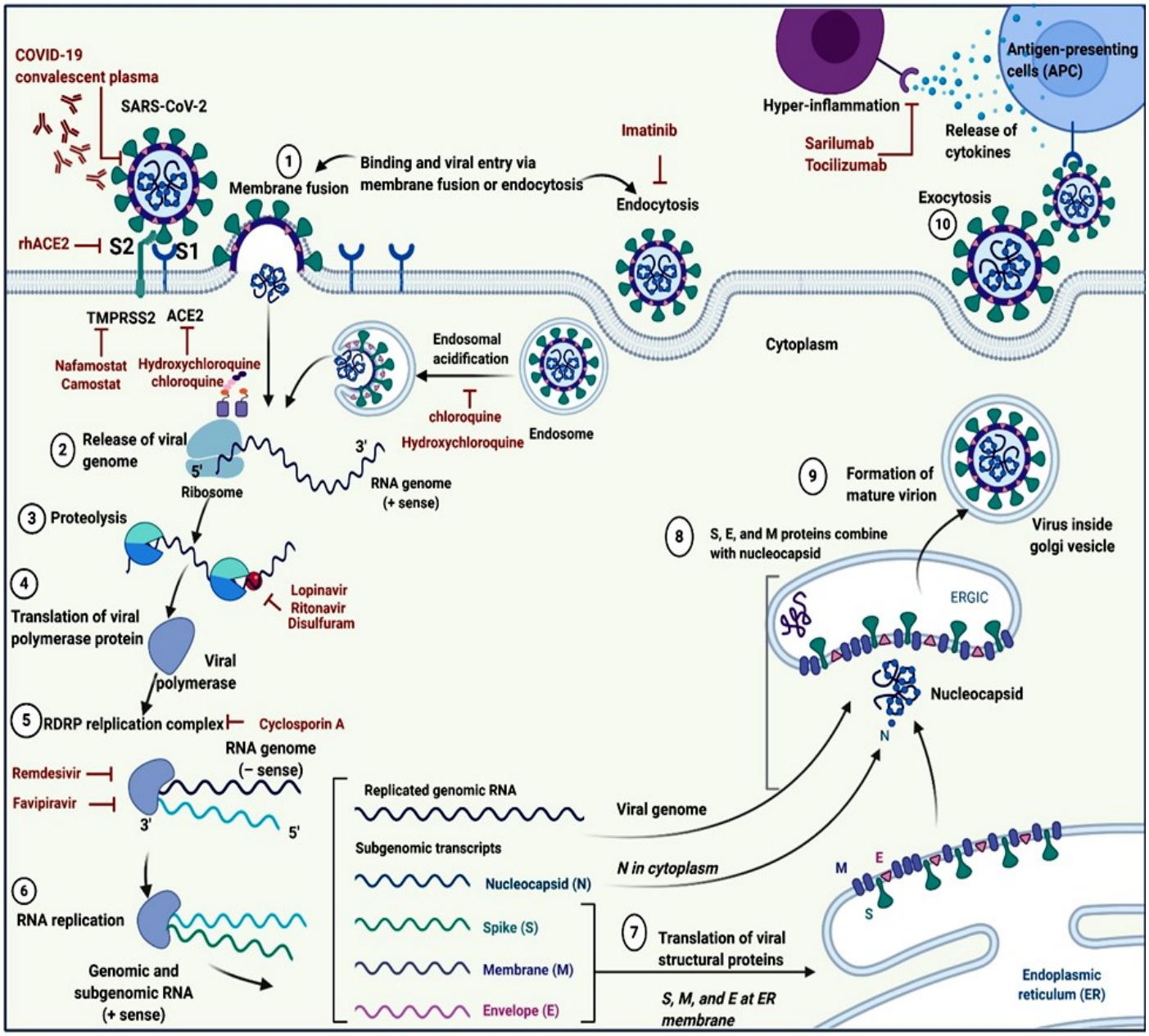


Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) lifecycle and targets of some re-purposed drugs for COVID-19 treatment. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; RdRp, RNA-dependent RNA polymerase; rhACE2, recombinant human ACE2; TMPRSS2, transmembrane protease serine type 2 (courtesy Esraa Aly)

Various clinical guidelines have been issued for management of patients with confirmed COVID-19 including those from the U.S. Center for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) (*CDC, 2020b; NIH, 2020a*).

Individuals can be classified as asymptomatic, or having mild, moderate, severe, or critical illness depending on the presence or absence of symptoms, as well as their severity.

Asymptomatic patients should self-isolate or move to isolation centres depending on national guidelines. And if they develop symptoms, they should contact their healthcare provider.

Patients with mild symptoms can be managed at home or in ambulatory or isolation centres, where they should maintain adequate hydration and nutrition and get necessary treatment for symptoms such as fever, sore throat, or cough (*Pascarella et al., 2020*). However, high risk patients (e.g. the elderly and those with cardiovascular and respiratory diseases) might need to be monitored closely in hospital.

The NIH recommends use of remdesivir and corticosteroids (including dexamethasone) for specific COVID-19 patients with severe or critical illness. For those with moderate, severe or critical illness the NIH advises clinicians to refer to the "Antiviral Therapy and Immune-Based Therapy sections of the guidelines" to review the available clinical data regarding investigational drugs being evaluated for treatment of this disease (*NIH, 2020a*). Table 1 is a list of some of these investigational drugs; these include agents with potential antiviral activity, immunomodulators and immune-based therapy, antithrombotic/anticoagulation drugs.

Table 1. Medications and therapies under clinical evaluation for treatment of COVID-19

Anti-viral agents	Immunomodulators	Other agents
Baloxavir	Anakinra	Angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs)
Baricitinib*	Azithromycin* (in combination with hydroxychloroquine)	Ascorbic acid*
Camostat	COVID-19 convalescent plasma and SARS-CoV-2 immune globulins*	Anticoagulants (low molecular weight heparin unfractionated heparin [UFH]
Chloroquine phosphate*	Colchicine	Epoprostenol (inhaled)
Favipiravir	Corticosteroids (general)	Famotidine
HIV protease inhibitors (lopinavir/ritonavir, darunavir/ cobicistat)	Cyclosporine	HMG-CoA reductase inhibitors (statins)
Hydroxychloroquine*	Interferon-alfa*	Niclosamide
Ivermectin	Interferon-beta*	Nitazoxanide
Nafomostat	Methylprednisolone	Nitric oxide (inhaled)*
Neuraminidase inhibitors	Non-SARS-CoV-2 specific	Tissue plasminogen activator
Remdesivir	Ruxolitinib, Sarilumab	Vitamin D*
Umifenovir	Siltuximab, Sirolimus	

**** both anti-viral and immunomodulatory*** ***(****from NIH, 2020a; ASHP, 2020; Clinicaltrials.gov****)***

Most patients with moderate and severe symptoms will require hospitalisation, further clinical examination, imaging, and laboratory tests. Antibiotics can be administered if bacterial pneumonia is highly suspected and de-escalated or stopped when there is no evidence of bacterial infection (*NIH, 2020a*).

Patients with severe symptoms or critical illness need oxygen therapy, using nasal cannula or high-flow oxygen, and should be placed in airborne infection isolation rooms (AIIRs), if available, as they will undergo aerosol-generating procedures.

The management of patients with critical illness with COVID-19 is mainly centred on taking care of or preventing the most common complications of severe COVID-19 such as "pneumonia, hypoxemic respiratory failure/acute respiratory distress syndrome (ARDS), sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalisation, including secondary bacterial infections, thrombo-embolism, gastrointestinal bleeding, and critical illness polyneuropathy myopathy" (*CDC, 2020b*).

Agents with potential antiviral activity

Drugs targeting the SARS-CoV-2 S protein

The SARS-Cov-2 S protein binds to angiotensin-converting enzyme 2 (ACE2), enabling the virus to enter the host cells. Another protein called transmembrane protease serine type 2 (TMPRSS2), which is expressed on host cells, is needed for priming/activation of the S protein for the virus to enter the cell (*Hoffmann et al., 2020a*). See Fig 2.

A soluble recombinant human ACE2 (rhACE2) has undergone phase 1/2 clinical trials in healthy volunteers and in patients with acute respiratory distress syndrome (ARDS) and was well tolerated (*Khan et al., 2017*). A pilot trial of rhACE2 in patients with severe COVID-19 (NCT04287686) was rapidly initiated

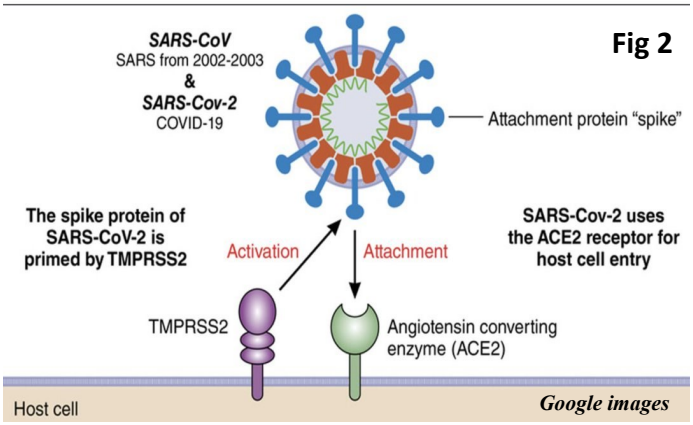


Fig 2

in February 2020 (*Zhang et al., 2020a*). This study was however (for undisclosed reasons) stopped early, before enrolling its first participant.

Camostat mesylate, an inhibitor of TMPRSS2, has been reported to partially inhibit SARS-CoV-2 from entering cells (*Hoffmann et al., 2020a*). Re-purposing camostat mesylate, which is already approved in Japan for the treatment of chronic pancreatitis, to treat COVID-19 has been proposed and several clinical trials are underway to evaluate its impact- alone (NCT04321096 and NCT04353284) or in combination with hydroxychloroquine (NCT04338906 and NCT04355052). Another TMPRSS2 inhibitor, nafamostat, which is available in some countries as an anti-coagulant in special groups of patients, has been reported to inhibit SARS-CoV-2 entry into host cell with a higher efficiency than camostat mesylate (Hoffmann et al., 2020b). A clinical trial (NCT04352400) has been registered to study the effect of nafamostat in COVID-19 patients.

Chloroquine and hydroxychloroquine

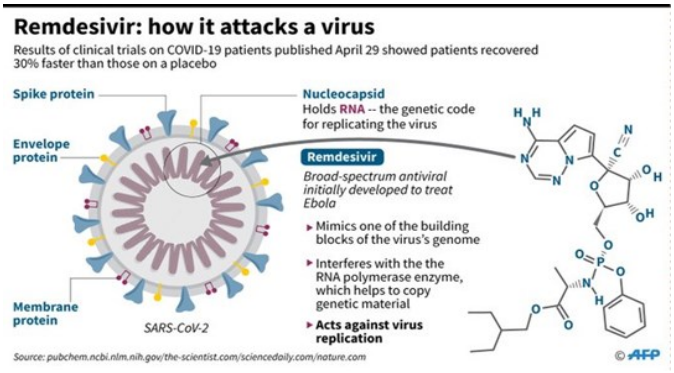
Chloroquine and its derivative hydroxychloroquine are anti-malarial drugs, which are also used for the treatment of amoebiasis, chronic Q fever, porphyria cutanea tarda and autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus (*ASHP, 2020; Gautam and Aulakh, 2020; Pascarella et al., 2020*). Hydroxychloroquine has a favourable toxicity profile compared to chloroquine.

Their antiviral activity seems to rely on interfering with the terminal glycosylation of ACE2, and also on increasing the endosomal pH, inhibiting fusion between the virus and the host cell membrane (*Pascarella et al., 2020*).

Both have immunomodulatory activity, which can be beneficial in the case of COVID-19.

In various studies, hydroxychloroquine is used in the treatment of COVID-19 either alone or in combination with azithromycin. On 25th May 2020, WHO announced a "temporary pause on the hydroxychloroquine arm within the Solidarity Trial while the safety data is reviewed by the Data Safety Monitoring Board". The temporary pause was initiated after data from an observational study showing increased risk of mortality and ventricular arrhythmias in hospitalised COVID-19 patients treated with chloroquine or hydroxychloroquine alone or with a macrolide (*Mehra et al., 2020*). However, an open letter published by James Watson supported by 146 scientists and physicians, raised concerns about the integrity of the methods and data published in this article (*Watson, 2020*). Afterwards, Lancet retracted the article by Mehra and colleagues upon request of three of its authors because they could no longer vouch for the "veracity of the primary data sources" (*Mehra et al., 2020b*). This shows the impact publications can have on real life decisions. On the other hand, it also shows the contribution of good readers who scrutinize what they read and thus also positively shape the science and real-life decisions as well.

Remdesivir



Remdesivir was developed by Gilead Sciences for treating hepatitis C and failed but was later re-purposed for treating Ebola virus disease and is now being re-purposed for COVID-19. Remdesivir was given an Emergency Use Authorization (EUA) on the 1st of May 2020 by the U.S. FDA (2020) and received conditional approval for use in Singapore on 10th June 2020, and various degrees of approval in other countries.

Remdesivir (formerly GS-5734) is a pro-drug metabolically converted inside cells to a nucleotide analogue that inhibits SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) causing premature termination of RNA transcription, thus blocking formation of the genome necessary to produce new virions (Figure 1; *Huang et al., 2020; Kotwani and Ghandra, 2020*). Data from clinical studies show that remdesivir is one of the most promising drugs for the treatment of COVID-19 and is the first reported to have efficacy in an extensive and rigorous multinational phase 3 clinical trial (*Beigel, 2020*).

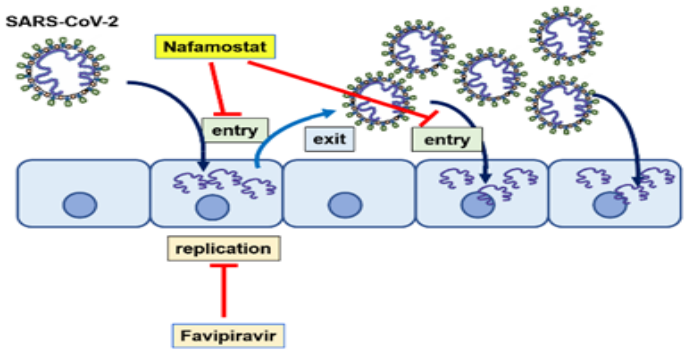
Preliminary analysis of data from a clinical trial (*ClinicalTrials*.gov number, NCT04280705) involving more than 1,000 patients carried out in 60 sites and 13 sub-sites in various countries showed that remdesivir treatment shortens the median time to recovery and may have provided a survival benefit compared to a placebo group (ASHP*, 2020; Beigel et al., 2020*). However, the high mortality even in the remdesivir group suggests that the drug on its own is insufficient, thus might need to be used in combination with other drugs. Data obtained from a cohort of hospitalised patients who received remdesivir on compassionate grounds show that there was clinical improvement in 36/53 patients (68%). The authors opine that the ongoing randomised, placebo-controlled trials of remdesivir therapy are required to measure efficacy of the drug (*Grein et al., 2020*).

Favipiravir

Favipiravir (Avigan®, Favilavir) is an anti-viral drug developed by Fujifilm Toyama Chemical and licensed in Japan and China for the treatment of influenza (*ASHP, 2020; Kotwani and Ghandra, 2020; Lu et al., 2020*). It is a guanine analogue that inhibits SARS-CoV-2 RdRp, causing premature termination of RNA transcription, thus, blocking RNA replication (Figure 1; *Kotwani and Ghandra, 2020; Lu et al., 2020*). Similar to remdesivir, it inhibits the formation of the genome and production of new virions.

Preliminary results from a small, open-label, non-randomised clinical study conducted in China (ChiCTR2000029600), show that COVID-19 patients treated with favipiravir had a shorter viral clearance time and significant improvement in chest imaging compared with the control group that received lopinavir/ritonavir, both groups received interferon (IFN)-α by aerosol inhalation (*Cai et al., 2020).*

Immunomodulators and Immune-based therapy



Nafamostat, an existing safe drug, may inhibit entry of SARS-CoV-2 by targeting TMPRSS2. Favipiravir inhibits proliferation of SARS-CoV-2 in host cells.

Corticosteroids

Corticosteroid drugs are mainly used to reduce inflammation and suppress the immune system. They have many side effects that are mainly dependent on their mechanism of action including immunosuppression, which can make some patients susceptible to infections, hypertension, hyperglycaemia, glaucoma etc., thus their use is tailored to the least possible dose and duration of treatment.

There has been concern that corticosteroids could increase the risk of severe COVID-19 symptoms and delay viral clearance (*Russell et al., 2020*). However, because of their anti-inflammatory and immunosuppressive activities it is thought that corticosteroids might be useful to reduce the severe symptoms and mortality of COVID-19 due to hyper-inflammation and hyper-activity of the immune system (*Shang et al., 2020*).

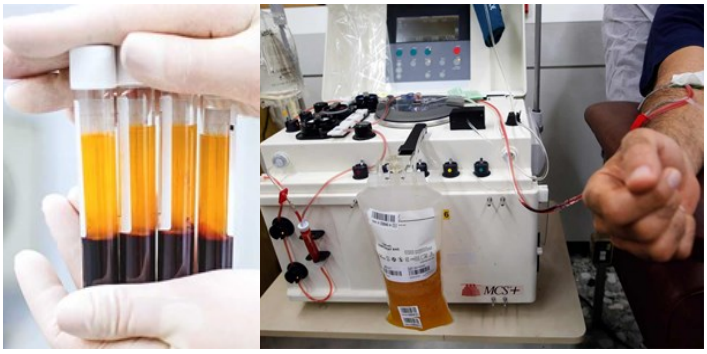
As of 1st July 2020, there were 45 or more clinical trials registered on Clinicaltrials.gov to study the effects of various corticosteroids such as dexamethasone (NCT04381936; NCT04445506; NCT04347980; NCT04325061; NCT04395105), prednisone (e.g. NCT04451174; NCT04344288), methylprednisolone (e.g. NCT04374071; NCT04263402) and inhaled budesonide (e.g. NCT04361474; NCT04416399) on COVID-19.

One study showed that an early short course of methylprednisolone in hospitalised patients with moderate to severe COVID-19 resulted in reduced time spent in hospitals and improved clinical outcomes compared to standard care (*Fadel et al., 2020*).

Preliminary results from a phase II/III randomised, controlled trial being conducted in the UK by Oxford University, RECOVERY (Randomised Evaluation of COVID-19 Therapy) clinical trial (NCT04381936), showed that dexamethasone reduced death in hospitalised COVID-19 patients that needed respiratory assistance (Horby et al., 2020). The findings of this study were good news because dexamethasone was the first drug shown to reduce death in COVID-19 patients, also with the advantage of being widely available and cheap. After the publication of the RECOVERY findings there was a surge in the demand for dexamethasone (*Mahase, 2020a*).

The results of these studies show that when properly used, corticosteroids can improve clinical outcomes and reduce mortality of COVID-19 patients. The results of ongoing clinical studies will shed more light on the effects of corticosteroids in COVID-19 patients.

COVID-19 convalescent plasma



COVID-19 convalescent plasma, obtained from patients who have recovered from COVID-19, has been in the news since the FDA issued an EUA on the 23rd of August 2020. It contains SARS-CoV-2 antibodies that can neutralise the virus. A non-peer reviewed preprint publication of results from a clinical trial (NCT04338360) reported that transfusion of COVID-19 convalescent plasma with high antibody levels significantly reduced 7- and 30-day mortality compared to convalescent plasma with low antibody levels (*Joyner et al., 2020*). The FDA has been criticised for issuing the EUA without enough evidence to support its efficacy (*Mahase, 2020b*). However, there are more than 100 clinical trials with COVID-19 convalescent plasma registered on Clinicaltrials.gov.

Interferons

Interferons (IFNs) are cytokines with immunomodulatory and anti-viral activities. There are various clinical trials currently evaluating IFN-beta together with other anti-virals for the treatment of COVID-19 (ASHP, 2020; NCT04315948; NCT04492475; NCT04324463; NCT04343768; NCT04385095). On 20 July 2020, Synairgen plc announced results from its clinical trial of an inhaled formulation of interferon beta (SNG001) in hospitalised COVID-19 patients. Administration of SNG001 lowered the risk of developing severe disease and increased the likelihood of patient recovery compared to placebo. However, experts are cautious about the data and await fully published results and a bigger trial (*Sciencemediacentre, 2020*).

Other agents targeting other pathogenetic mechanisms of COVID-19

Vitamins

Vitamins are naturally occurring organic molecules that the body does not produce (or produce in insufficient amounts) but needed for its normal function. These have to be obtained from the diet.

Deficiency or low concentrations of vitamin D in the plasma have been associated with increased COVID-19 morbidity, severe symptoms, and mortality (*Panagiotou et al., 2020*). There are some publications reporting that

vitamin D supplementation can reduce the risk of COVID-19 (*Ilie et al., 2020; Tan et a., 2020*). However, some of these studies have not been peer reviewed and are on pre-print websites such as *medrxiv.org, researchsquare.com and preprints.org*.

On the 29th of June the UK's National Institute for Health and Care Excellence (NICE) published a rapid evidence summary with an advisory statement which reads "There is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19" (*NICE, 2020*). However, one of the criticisms of the NICE rapid evidence summary is that it did not include evidence from many studies that are on pre-print websites as they are not yet peer reviewed (*Torjesen, 2020*).

Vitamin C (ascorbic acid) has antioxidant, anti-microbial and immune-modulatory properties, especially in high concentrations (*Liu et al., 2020*). It has been shown to block production of inflammatory cytokines (*Carr and Maggini, 2017*). Through its anti-oxidative activity, it might protect the host/patient lungs and cells against infection-induced oxidative stress and damage (*ASHP 2020*).

In clinical trials conducted on patients with bacterial -induced sepsis and acute respiratory distress syndrome (ARDS), high dose of intravenous vitamin C was found to be safe and have varying degrees of efficacy in reducing length of stay in the intensive care unit, duration of mechanical ventilation and mortality (*Liu et al., 2020*). There is no data on the effectiveness of vitamin C in the prevention or treatment of COVID-19, however there are various clinical trials being conducted to find answers to that issue (*Clinicaltrials.gov*).

Up to now there is insufficient data to formulate guidelines to recommend vitamins for the prevention or treatment of COVID-19.

Zinc

Zinc is an essential mineral, present in some foods and also taken in some dietary supplements, that is constantly needed for maintenance of steady state because the body has no specialized zinc storage system (*NIH, 2020b*).

Zinc deficiency has been linked to increased risk of respiratory tract infections and zinc supplementation has been reported to reduce the frequency, duration, and severity of the common cold, caused by coronaviruses (*Wessels et al., 2020*).

Zinc supplementation has documented antioxidant and anti-inflammatory activities (*ASHP, 2020; Gautam and Aulakh, 2020*). Zinc has anti-viral activities and has been reported to enhance the anti-viral activity of chloroquine, which is an ionophore, and could directly inhibit the RNA-dependent RNA polymerase of the virus (*Wessels et al., 2020*).

As of 27th August 2020, there are 24 clinical trials registered on Clinicaltrials.gov to study the effects of zinc, alone or in combination with other supplements such as vitamins or with drugs such as hydroxychloroquine, on COVID-19. However, data on the effect of zinc supplementation on prevention or treatment of COVID-19 is still pending.

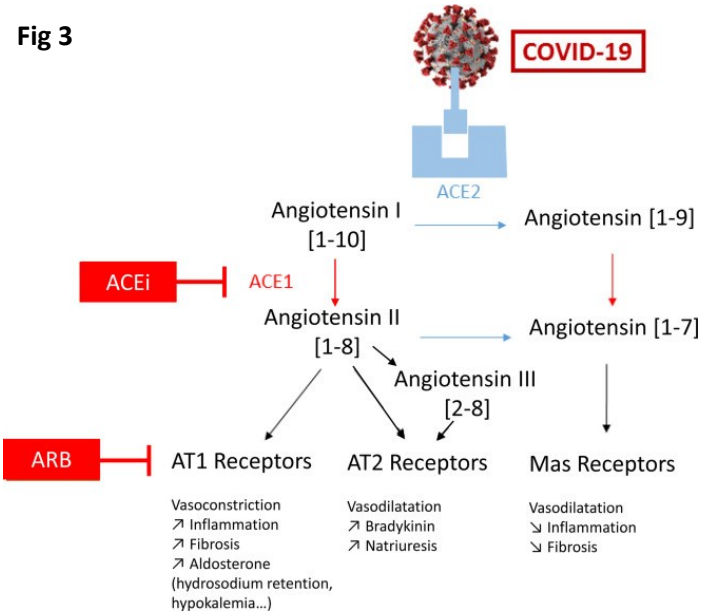
Drugs that modulate the activity of the renin-angiotensin system (RAS)

There is dysregulation of the renin-angiotensin system (RAS) in COVID-19 patients, including elevated levels of angiotensin II (Ang II), which has been associated with hypertension and lung damage (*Meng et al., 2020*).

Drugs that modulate the RAS such as ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are used in the treatment of hypertension and heart failure. The use of ACEIs decrease the formation of Ang II, whilst ARBs block the binding of Ang II to its receptor angiotensin II type 1 receptor (AT1R) (Fig 3).

Results from recent studies show that ACEIs/ARBs have beneficial effect in COVID-19 patients with hypertension

Fig 3



(*Meng et al., 2020; Zhang et al., 2020b*).

COVID-19 patients with hypertension receiving an ACEI/ARB had lower rates of severe COVID-19 symptoms and lower peak viral load during hospitalisation compared to those who were receiving other anti-hypertensive drugs.

There was also a trend toward lower levels of the cytokine IL-6 in peripheral blood of patients from the ACEI/ARB group compared to the non-ACEI/ARB group. In a retrospective study, Zhang et al (2020b) found that the use of ACEI/ARB by COVID-19 patients with

hypertension who were hospitalised was associated with lower risk of mortality compared to the use of other anti-hypertensive drugs.

Therefore, the results of these studies suggest that ACEIs/ARBs used by hypertensive patients most likely protect them from the detrimental effects of COVID-19 and thus have a better clinical outcome than patients who use other anti-hypertensive drugs.

There are ongoing interventional clinical trials to evaluate effects of an ARB losartan (NCT04312009) and an ACEI ramipril (NCT04366050) on patients with COVID-19 who require hospitalisation.

Non-steroidal anti-Inflammatory drugs (NSAIDs): friend or foe?

Non-steroidal anti-inflammatory drugs (NSAIDs) are some of the most prescribed and consumed medications for the management of pain and inflammation, thus the probability that people would be taking NSAIDs and have SARS-CoV-2 infection is extremely high.

There have been reports that the use of NSAIDS is associated with worse outcomes or increased risk of complications in patients with respiratory tract infections, including those caused by viruses (*Voiriot et al., 2019*).

With regards to COVID-19, there has been concern that NSAIDs and corticosteroids could aggravate its symptoms (*Russell et al., 2020*). Some publications suggest that NSAIDs, such as ibuprofen, can increase the levels of ACE2, which is a receptor for SARS-CoV-2 and consequently could facilitate the infection and worsening of symptoms in COVID-19 patients.

Because of those concerns, WHO carried out a rapid systematic review on NSAIDs and viral respiratory infections including COVID-19; published on their website in April (*WHO, 2020a*) concluding that at that time there was no evidence of "severe adverse events, acute health care utilisation, long-term survival, or quality of life in patients with COVID-19, as a result of the use of NSAIDs". In answer to the question "Could ibuprofen worsen disease for people with COVID19?" they released a message on Twitter on 19th April 2020 stating that "based on currently available information, WHO does not recommend against the use of ibuprofen" (*WHO, 2020b*). In May 2020, the European Medicines Agency (EMA) also issued a statement that currently there was no scientific evidence linking ibuprofen and worsening of COVID-19 and thus patients who are on NSAIDs for chronic diseases had no reason to stop taking them (*EMA 2020*).

A retrospective study by *Rinott et al (2020)* found that the use of ibuprofen for relief of symptoms such as fever in COVID-19 patients did not have a difference in terms of clinical outcomes (such as need for respiratory support or mortality) compared to paracetamol or not taking any antipyretics.

There are various clinical trials registered on *Clinicaltrials.gov* to study the effects of NSAIDS on COVID-19: designed to evaluate either the possible detrimental effects of NSAIDs or to find possible beneficial effects of NSAIDs.

For example, on one hand, one study (NCT04383899) intends to determine effects of ibuprofen on COVID-19, taking into consideration the suggestion previously put forward by various groups that patients taking ibuprofen might be at a higher risk of developing more severe cases of respiratory tract infections including COVID-19.

On the other hand, another study (NCT04325633) intends to study the possible beneficial effects of adding a different NSAID naproxen to hospitalised COVID-19 patients already on standard care. Naproxen has anti-inflammatory activities and inhibits viral nucleoprotein binding to RNA and consequently inhibits viral transcription/replication (*Zheng et al., 2019*). Although aspirin (acetylsalicylic acid) is a NSAID, most of the registered studies are using doses lower than those used to relieve pain and fever, and thus evaluating its possible beneficial effects in COVID-19 patients as an anti-platelet agent (NCT04410328; NCT04343001; NCT04365309; NCT04324463; NCT04368377; NCT04333407).

Hopefully, the results from these studies will shed more light on whether NSAIDS are friend or foe in patients with COVID-19.

Anticoagulants: low molecular weight heparin [LMWH], un-fractionated heparin [UFH]

Critically ill patients with COVID-19 develop coagulopathy. In one study, anti-coagulant therapy with heparin (mainly low m.wt) was found to be associated with better prognosis in severe COVID-19 patients with sepsis -induced coagulopathy (SIC) or elevated D-dimer in the plasma (*Tang et al, 2020*). Treatment with heparin significantly reduced the 28-day mortality compared to those who did not use heparin, in patients with SIC scores ≥ 4 or D-dimer > 6-fold the upper limit of normal. A recent systematic review of COVID-19 treatment trials found that heparin benefited patients with severe COVID-19 (*Siordia et al., 2020*). More studies are needed to ascertain the role of heparin in COVID-19 patients.

Conclusions

Amongst the drugs discussed in this article, remdesivir and dexamethasone have been shown to improve the outcome of hospitalised COVID-19 patients i.e. shorten the time to recovery (allow patients to be discharged from hospital earlier) and reduce mortality, respectively

and are recommended by several organisations for the treatment of specific groups of hospitalised COVID-19 patients. The ongoing clinical trials will shed more light on the usefulness of other drugs for the prevention or treatment of COVID-19.

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Willias Masocha,
Faculty of Pharmacy,
Kuwait University

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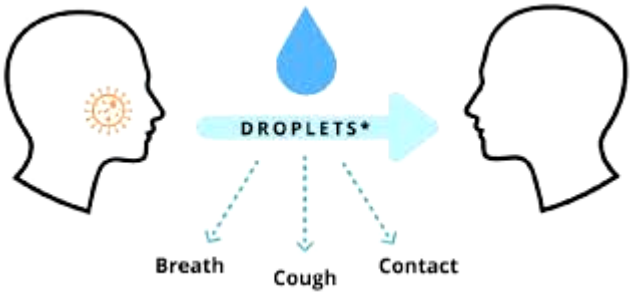
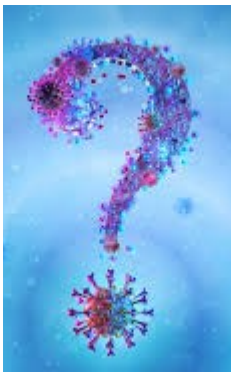


TEST YOUR KNOWLEDGE

Answers on back page



1. What does "vid" in "covid-19" mean?
a) 'vi' for 'virus,' and 'd' for diversity
b) 'vi' for 'virulence,' and 'd' for dormant
c) virulence
d) 'vi' for 'virus,' and 'd' for disease
e) video

2. A person with no symptoms of covid-19 is not a risk to others
a) True
b) False

3. A commonest symptom of covid-19 is
a) Vomiting
b) Stomach cramps
c) Cough
d) Chest pain
e) Difficulty in swallowing

4. Which of the following is a host receptor of covid-19 for cell entry?
a) ACE 2
b) NMDA
c) nAChR
d) 5-HT3
e) P2X

5. The incubation period of covid -19 is estimated to be between:
a) 1 to 21 days
b) 1 to 30 days
c) 1 to 3 days
d) 1 to 14 days
e) 1 to 40 days

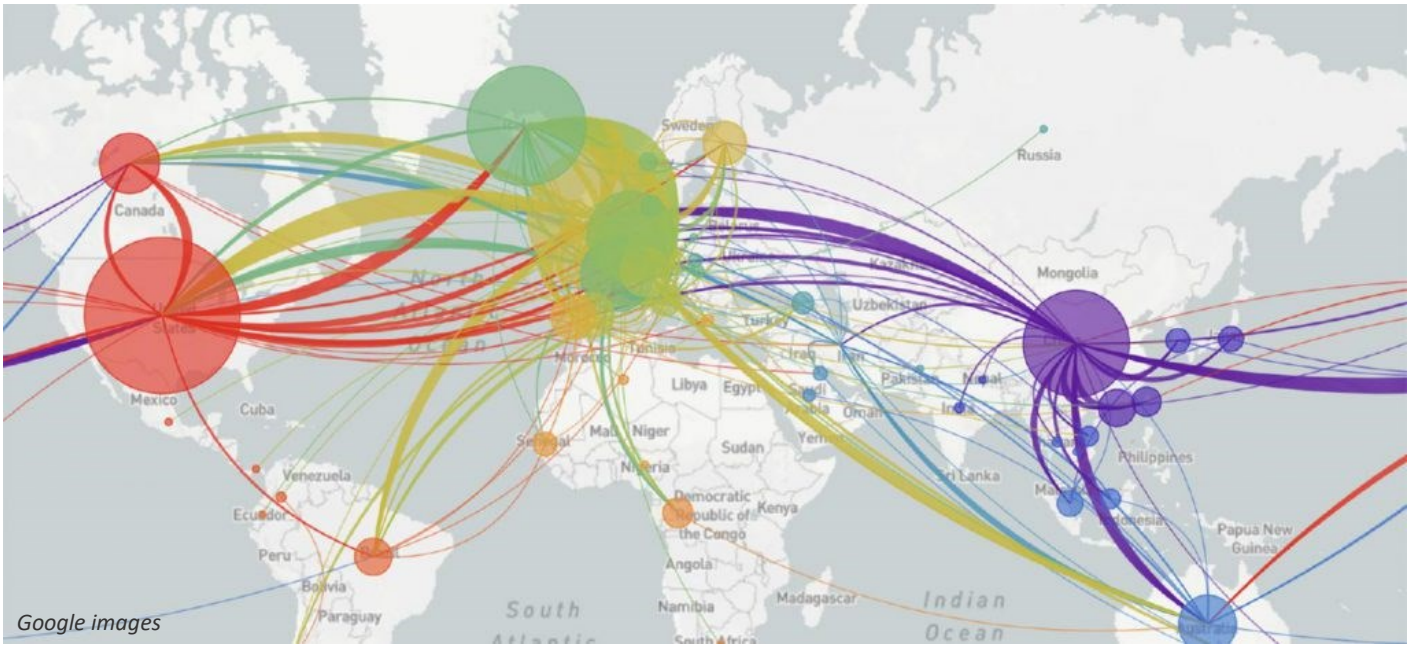
6. Which of the following are associated with prolonged viral shedding associated with covid-19?
a) Male sex
b) Older age
c) Comorbid hypertension,
d) Severe illness on admission
e) All of the above

7. Which of the following is used by covid-19 for S protein priming and fusion of viral and host cell membranes?
a) TMPRSS2
b) k-casein
c) trypsin
d) pepsin
e) carboxypeptidase B

8. According to NIH clinical classification, which of the following is a feature of critical illness of covid-19?
a) Respiratory frequency >30 breaths per min
b) SpO_2 ≤93% on room air at sea level
c) PaO_2/FiO_2 <300
d) Septic shock
e) Lung infiltrates >50%

9. Which is a prodrug for which FDA issued emergency use authorisation for treatment of covid-19 in hospitalised patients with severe disease?
a) Abacavir
b) Acyclovir
c) Remdesivir
d) Tenofovir
e) Lamivudine

COVID-19: Genetic network analysis provides 'snapshot' of pandemic origins



By analysing the first 160 complete virus genomes to be sequenced from human patients, using genetic network techniques, researchers from Cambridge, UK, and Germany have mapped some of the original spread of the new coronavirus through its mutations, which creates different viral lineages, and reconstructed the early "evolutionary paths" of COVID-19 in humans as infection spread from Wuhan out to Europe and North America.

As there are too many rapid mutations to neatly trace a COVID-19 family tree, they used a mathematical network algorithm to visualise all the plausible trees simultaneously.

These techniques are mostly known for mapping the movements of prehistoric human populations through DNA, and may be the first time they have been used to trace the infection routes of a coronavirus like COVID-19.

The team used data from virus genomes sampled from across the world between 24 December 2019 and 4 March 2020. They identified three distinct "variants" of COVID-19, consisting of clusters of closely related lineages, which they labeled 'A', 'B' and 'C'.

They found that the closest type of COVID-19 to the one discovered in bats -- type 'A', the "original human virus genome" - was present in Wuhan, but surprisingly was not the city's predominant virus type.

Mutated versions of 'A' were seen in Americans reported to have lived in Wuhan, and a large number of A-type viruses were found in patients from the US and Australia.

Wuhan's major virus type, 'B', was prevalent in patients from across East Asia. However, the variant didn't travel much beyond the region without further mutations, implying a "founder event" in Wuhan, or "resistance" against this type of COVID-19 outside East Asia.

The 'C' variant is the major European type, found in early patients from France, Italy, Sweden and England. It is absent from the study's Chinese mainland sample, but seen in Singapore, Hong Kong and South Korea.

Their analysis also suggests that one of the earliest introductions of the virus into Italy came via the first documented German infection on January 27, and that another early Italian infection route was related to a "Singapore cluster."

Importantly, the researchers say that their genetic networking techniques accurately traced established infection routes: the mutations and viral lineages joined the dots between known cases.

As such, they argue that these "phylogenetic" methods could be applied to the very latest coronavirus genome sequencing to help predict future global hot spots of disease transmission and surge.

"Phylogenetic network analysis has the potential to help identify undocumented COVID-19 infection sources, which can then be quarantined to contain further spread of the disease worldwide.

The findings are published in *PNAS* and the software used in the study, as well as classifications for over 1,000 coronavirus genomes and counting, is available free at http://www.fluxus-technology.com.

both bats and pangolins, is described as "the root of the outbreak" by researchers. Type 'B' is derived from 'A', separated by two mutations, then 'C' is in turn a "daughter" of 'B'.

Researchers say the localisation of the 'B' variant to East Asia could result from a "founder effect": a genetic bottleneck that occurs when, in the case of a virus, a new type is established from a small, isolated group of infections.

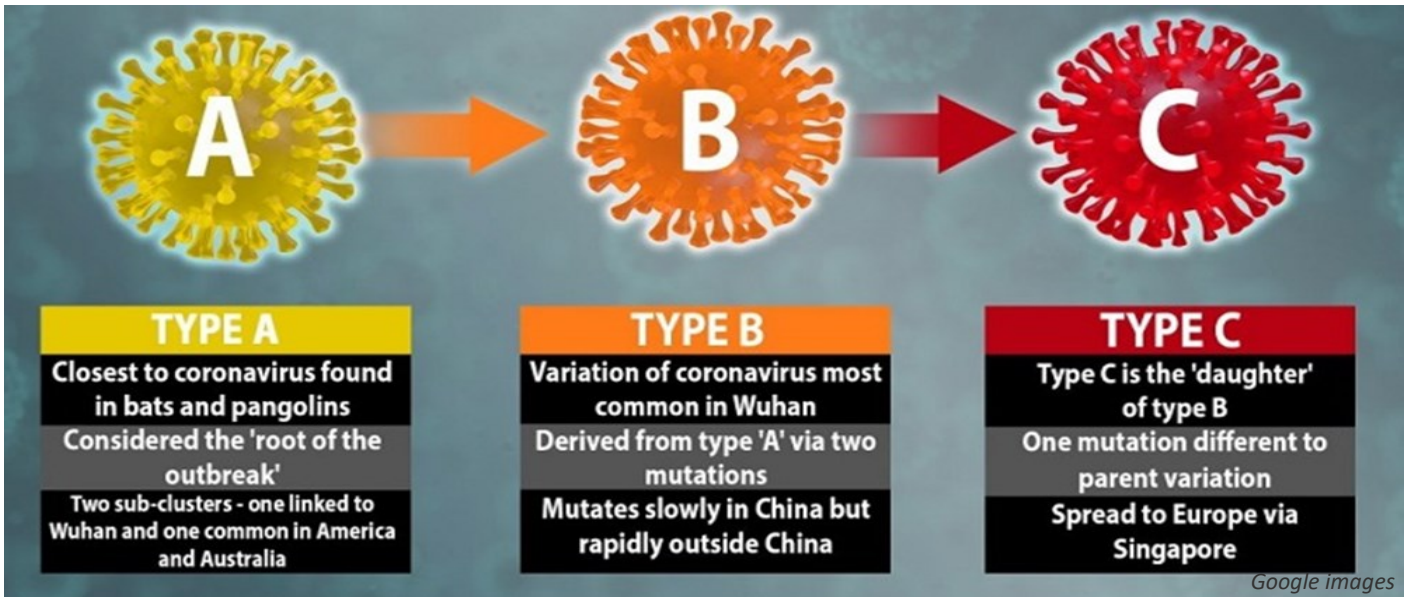
They argue that there is another explanation worth considering. "The Wuhan B-type virus could be immunologically or environmentally adapted to a large section of the East Asian population. It may need to mutate to overcome resistance outside East Asia. We seem to see a slower mutation rate in East Asia than elsewhere, in this initial phase."

They add: "The viral network we have detailed is a snapshot of the early stages of an epidemic, before the evolutionary paths of COVID-19 become obscured by vast numbers of mutations. It's like catching an incipient supernova in the act."

Since this study was conducted, the research team has extended its analysis to 1,001 viral genomes. They believe that the first infection spread among humans of COVID-19 occurred between mid-September and early December.

The phylogenetic network methods used, allowing the visualisation of hundreds of evolutionary trees simultaneously in one simple graph, were pioneered in New Zealand in 1979, then developed by other German mathematicians in the 1990s.

Source
https://healthcare-in-europe.com/en/news/genetic-network-analysis-provides-snapshot-of-pandemic-origins.html



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Covid 19: Blood clotting mechanism identified

A recent study published in *Circulation* suggests a possible mechanism for elevated presence of blood clots in COVID-19 patients. This may help clinicians develop more effective treatments for COVID-19.

The sudden emergence and rapid global spread of the new coronavirus have meant clinical responses have focused on supporting those with severe infections, supplemented with emergency societal interventions, such as widespread social distancing, to reduce infection rates. Because SARS-CoV-2 is a new virus, previous treatments developed for similar strains will not necessarily work. Instead, possible therapies need to be identified in theory, tested and, once safe, implemented in the real world.

However, this all takes time. SARS-CoV-2 is mainly a danger because for some patients, particularly those with certain underlying health conditions, compromised immune systems, or who are later in life, a type of severe acute respiratory syndrome can develop, similar to pneumonia.

COVID-19 and coagulation

COVID-19 makes a person's lungs inflamed. If this inflammation is severe, inflammatory material can collect in the bottom of the lungs. This can make it

difficult to gain enough oxygen into the blood, and cause organs to shut down, potentially leading to death. However, in addition to this pneumonia-like reaction, clinicians have also noticed that patients with COVID-19 can develop organ damage in a way not directly linked to a lack of oxygen in the blood. This is particularly common in the kidneys and heart. There is some evidence that a problem with blood coagulation causes this organ damage. Coagulation is the process where a person's blood thickens. It is crucial in stopping a person from bleeding if they get a cut. However, if a person's blood coagulates too much or too little, they can have serious issues: too little, and they can develop internal or external bleeding, as seen in hemophilia. Too much and they could develop blood clots that can cause a stroke or heart attack. The authors of the recent study note that COVID-19 may increase coagulation in some people's blood, which consequently causes organ damage as blood vessels become blocked. However, it is not yet clear how or why this occurs, which impedes the development of effective treatments.

Neutrophils and platelets

In the study, the researchers studied 62 patients, including autopsies on five of whom had died. Of these individuals, 38 had confirmed COVID-19. After conducting multidimensional flow cytometry, a way of measuring the presence of particular cells in a fluid, and comparing these results to the control groups, the researchers identified a significant number of neutrophils and platelets in the subjects. Neutrophils are a type of immune cell that combat pathogens entering the body, such as the SARS-CoV-2 virus, while platelets are a type of blood cell necessary for coagulation. The researchers found that these two cells seemed to react to and activate one another, resulting in excessive coagulation, blockage of blood vessels, and serious damage to nearby tissue. Furthermore, when activated, the neutrophils exude web-like structures designed to help them trap bacteria, but experts believe they exacerbate the blocking of blood vessels. These findings contribute to a better understanding of the pathophysiology that underlie disease progression in COVID-19. The study also identifies immunothrombosis as a promising target for the prevention and treatment of lung failure and thrombotic complications that arise in cases of COVID-19.

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Tests for corona virus

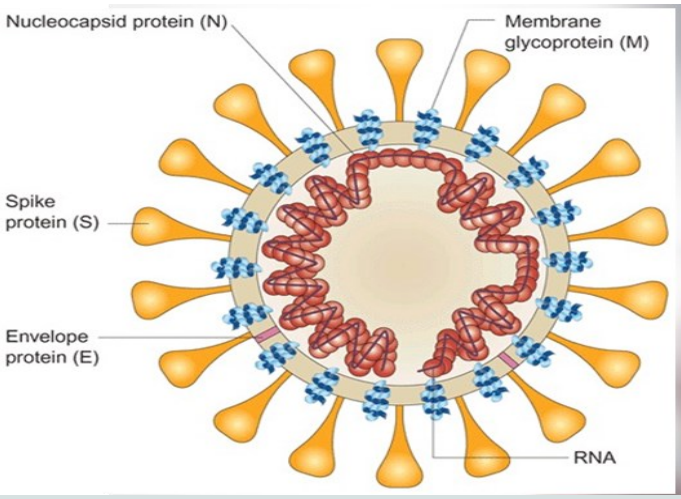
The perspective of the general public is usually that a "medical test" is simple, routine, accurate and definitive, and provides a certain predictable outcome for the patient. The scientific reality is much more complex.

In practice the reliability of a biological measurement is subject to a multitude of factors including:

- The sample: source, quantity, method and time of sampling, handling of sample, time of storage prior to analysis, storage conditions
- The expertise and understanding of the person doing the test; is it a specialised lab, a general lab or a physician 'point of care' site where the operator may be less skilled
- Use of the correct and validated instrumentation, and accurate performance with appropriate controls (negative and positive)
- Method of detection of the target
- Specificity of the test; to what degree does it measure only the intended target and nothingelse
- Sensitivity of the test; what is the limit of detection-how many target molecules are needed and what level is biologically significant (we probably harbour low levels of many microorganisms that could potentially cause diseases but do not)

Ideally we would want 100% specificity and 100% sensitivity which in practice is difficult to achieve, and the test should be fast, relatively cheap and reproducible.

The biggest issue is ***false negatives***; this can be due to bad or inadequate sample, poor sample processing or technical problem in the assay - and ***false positives***; this issue can be resolved with controls.



The tests for this corona virus are

* **Detection of the RNA viral genome using quantitative RTPCR amplification which takes several hours (or isothermal NA amplification which is easier and quicker but maybe less reliable)**
* **Detection of antigen to determine the presence of viral protein**
* **Serology test to detect IgM and/or IgG antibodies indicative of a viral infection by ELISA chemiluminescent or neutralisation assays**

These tests do not measure the same thing and do not provide the same information

- **The PCR and antigen tests detect directly the presence of the viral genome/protein (inferring presence of virus) in the specific sample taken *at that time*. It does not indicate whether there is infectious virus. This is a DIAGNOSTIC test.**
- **The serology test indirectly indicates the presence of the virus due to an immune response whether the virus is still present or not. Serology testing does not detect the presence of the virus, it detects the antibodies that are, or were, produced by the body in fighting the disease. It can identify people who were infected but have recovered.**

The timing of the tests will also affect the result, so it is complicated

It was initially believed that this corona virus affected only the lungs and therefore most of the focus was on methods to alleviate pulmonary symptoms - mainly oxygen supply through ventilators in extreme cases medications to suppress unwanted effects of over-active immune response (with anti-inflammatory agents), and anti-viral agents to destroy the cause, with emphasis on aerosolised inhaled products

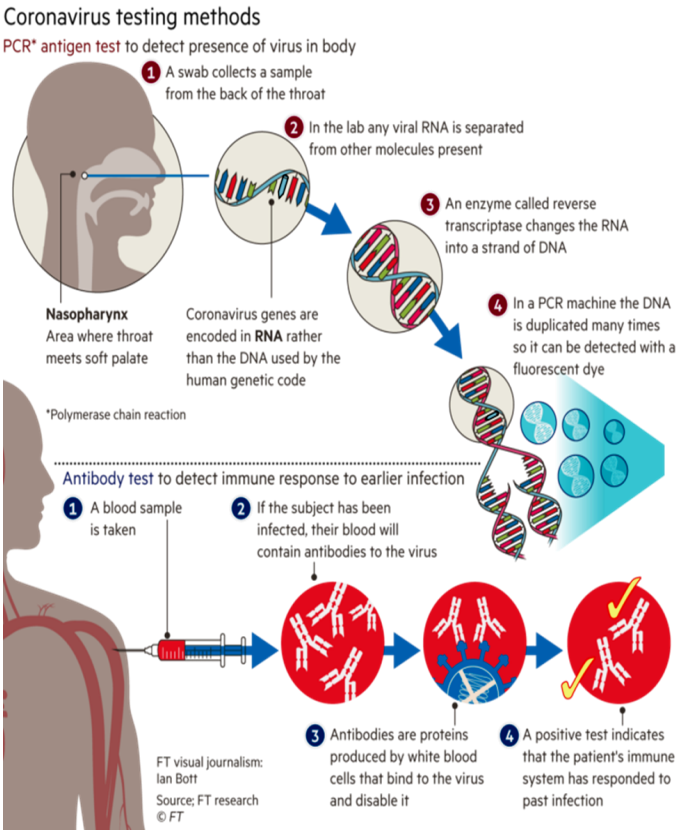
The test samples also reflect the above scenario so they are -nasopharyngeal swab, sputum (coughed up material), throat swabs, deep airway material collected via suction catheter or saliva- and blood for the anti-body test (can also be used for the PCR test)

But now it is realised that this virus can spread to other parts of the body wherever there are suitable receptors for its attachment

Thus systemic testing (blood/stool) and treatment is needed in addition to the immediate acute problem of lung resuscitation in patients with serious symptoms. For those with mild or no symptoms, the virus concentration in the lungs may not be sufficiently high to detect (sensitivity of test) but may be present in other parts of the body where there are receptors for the virus. So the source of the sample can give different result outcomes.

The situation with testing has been complicated by the use of different samples, ways of collecting them and different test kits developed by several companies as this is not only a medical issue but also a hugely lucrative commercial enterprise giving rise to vested interests. After the viral sequence was made available to public databases by the Chinese in January, many biotech companies have been frantically designing their own PCR primers and selling kits for PCR detection.

Whilst, in the correct setting, PCR analyses are robust,



https://blogs.deloitte.co.uk/health/2020/04/covid-19-testing-how-it-works-and-why-we-need-it-urgently.html

reliable and accurate, it is impossible to know how well they are performed in the multitude of centres that have been hastily adapted or set up for mass screening throughout the world. It is quite likely that there is a substantial margin for error in the reported numbers of positive cases.

The usual QC procedure is for the same samples to be distributed from a coordinating centre and analysed by several different laboratories using similar and/or different procedures to determine the consistency of the data in and between each participating site. The urgency during these last 6 months has probably not allowed this to be done in any rigorous manner, although the Who has been trying to organise and validate testing methods worldwide.

Abbott has developed ID NOW instrument/procedure as the fastest and simple method for SARS-CoV-2 detection in a clinical sample from nasal, nasopharyngeal and throat swabs, yielding results in just 5-15 min. It has received the Emergency Use Authorisation (EUA) for authorised laboratories and hospital point-of care settings. This allows companies to forgo normally stringent regulations meant to test the standards and accuracies of new technologies. It is based on Reverse Transcription Loop-mediated Isothermal Amplification (LAMP) using DNA polymerase from Bacillus stearothermophilus and therefore faster than conventional 2/3 step PCR amplification. Because of the complexity of the primer design (targeting several regions of the viral genome) this new method is currently most suitable for dedicated diagnostic purposes. However, despite Abbott's claims of 91% accuracy, other investigators report much higher rates of *false negatives*, so it remains to be seen how successful it will be.

Competitors for Abbott's machine are the Xpert Xpress from Cepheid, Accula by Messa Biotech and Cue Covid-19 Test by Cue Health Inc which deliver results in 25-30 min.

In early August, Sorrento signed a licensing agreement with Columbia University for a saliva-based test that takes 30 min and can be performed in a wide variety of settings, such as airports and sporting events, as well as for at-home testing.

On 15th August, Yale School of Public Health said the FDA had granted its saliva-based diagnostic test (SalivaDirect), emergency use authorisation, with an estimated cost of $10 per sample, but this still requires to be done in a laboratory.

Another issue that should be mentioned is the occurrence of mutations in the viral genome, which is a common occurrence encountered in many viruses, (has been a particular problem in HIV diagnostics), which critically hinders the development of PCR primers and also has a bearing on the production of vaccines. There may be different mutated forms around the world so PCR tests need to have primers to well conserved regions, otherwise this may be another source of false positive results.

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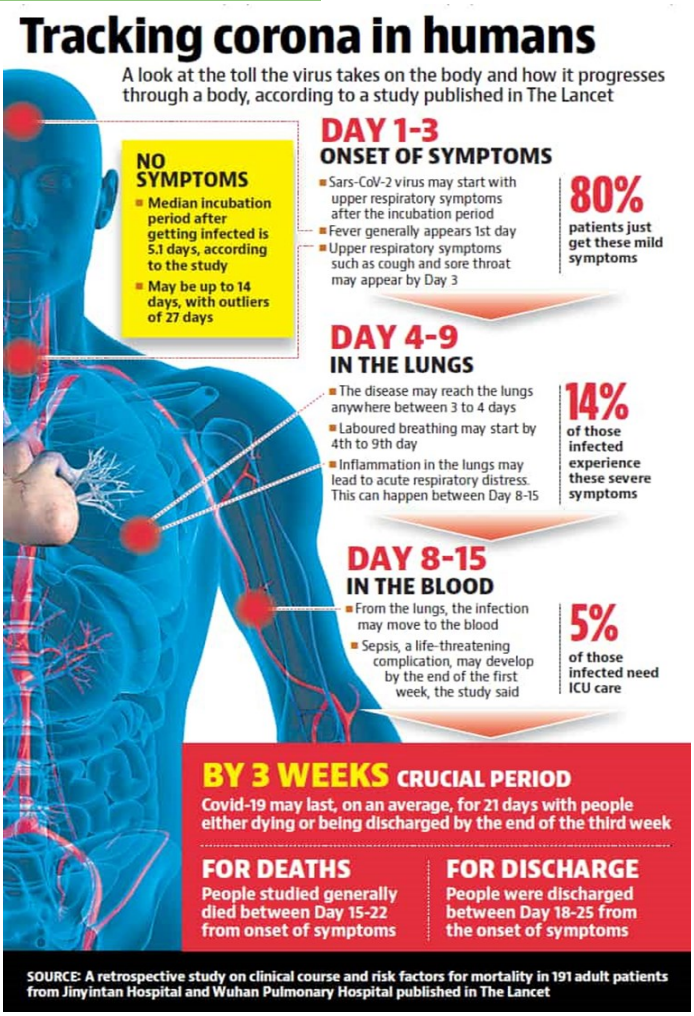
How vaccines work– and herd immunity

The basic mechanism by which vaccines work is simple: they create immunity in an individual by introducing a weakened or killed form of the pathogen that make us ill- such as bacteria or viruses- or its toxins or one of its surface proteins. The vaccine induces acquired immunity so that when your body encounters the real disease-causing agent it is ready to mount a defense.

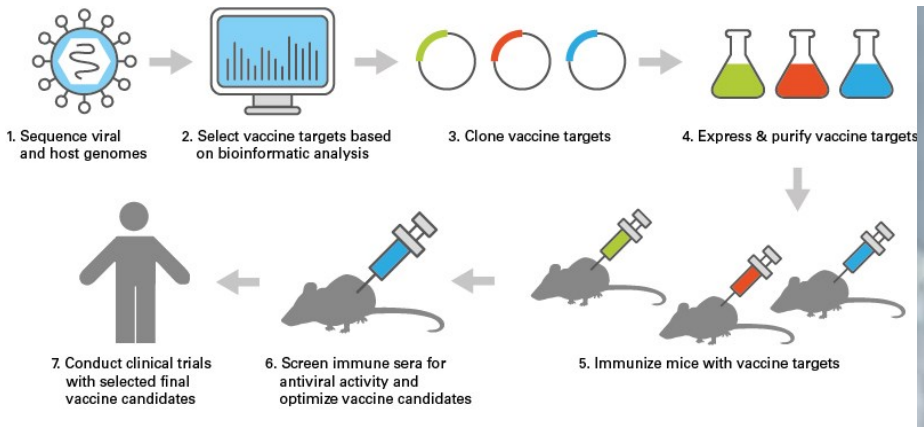
There is a collective social benefit in a high vaccination coverage. For most diseases, the greater the proportion of people who are immunized, the better protected is everyone in the population as the disease transmission can be reduced or stopped. Herd immunity is a community protection that is created when a high percentage of the population is vaccinated, such that it less likely that the infectious disease spreads.

Disease	Transmission	R No.	Herd Immunity Threshold
Measles	Airborne	12–18	92–95%
Pertussis	Airborne droplet	12–17	92–94%
Diphtheria	Saliva	6–7	83–86%
Rubella	Airborne droplet	6–7	83–86%
Smallpox	Airborne droplet	5–7	80–86%
Polio	Fecal-oral route	5–7	80–86%
Mumps	Airborne droplet	4–7	75–86%
SARS	Airborne droplet	2–5	50–80%
Ebola	Bodily fluids	1.5–2.5	33–60%
Influenza	Airborne droplet	1.5–1.8	33–44%



Herd immunity provides a protective barrier, especially also for those who cannot be vaccinated -vulnerable groups such as babies too young to be vaccinated or immune-compromised children who are the first potential victims of low vaccination rates.

When a person is immune to a disease they can act as a barrier to slow down or prevent the transmission of disease to other people. When the number of people in a population that are immune against a disease is reached, such that a disease no longer persists in the population, this is called the herd immunity threshold (HIT). The Table shows the HIT for several diseases. Measles and pertussis are highly contagious airborne diseases and a larger share of people need to be vaccinated to stop the transmission. Because of this, these diseases have the highest HIT rates that need to be reached. For example, two doses of measles vaccination offers 99% protection, while in the absence of immunisation, the lifetime risk of infection is nearly 100%.



Summary of vaccine production www.takarabio.com/products/covid-19-research/vaccine-development

Stages of vaccine development/testing

135

PRECLINICAL: vaccine given to animals (mice to monkeys) to see if it produces an immune response

19

PHASE 1 SAFETY TRIALS: vaccine given to a small number of people to test safety and dosage &confirm it stimulates the immune system

12

PHASE 2 EXPANDED TRIALS: vaccine given to hundreds of people split into groups, such as children and elderly, to see if it acts differently in them. This further tests vaccine's safety & ability to stimulate immune system

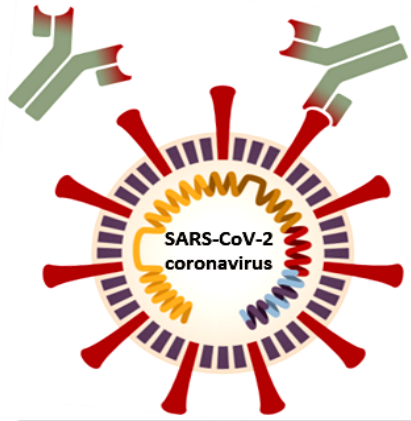
COMBINING PHASES: To accelerate development some vaccines are now in Phase 1/2 combined trials, in which they are tested for the first time on hundreds of people

8

PHASE 3 EFFICACY TRIALS: vaccine given to thousands of people to see how many become infected, compared with volunteers who received placebo. These trials can determine if vaccine protects against the coronavirus- needs to protect at least 50% of vaccinated people to be considered effective. Also should indicate evidence of side effects missed in earlier studies

2

APPROVAL: Regulators review trial results and decide whether to approve the vaccine. During a pandemic, a vaccine may receive emergency use authorisation before getting formal approval. Once licensed, researchers continue to monitor people who receive it to make sure it's safe and effective



Numbers shown are estimated (major) candidate vaccines indicated at each stage as of ***August 19th 2020.***
There could be in excess of 2500 if all are counted around the world, with 580 companies involved.

Who's developing what type of vaccine?

Genetic vaccines	Viral vector vaccines	Protein based vaccines	Whole virus vaccines
Moderna	**CanSinoBio**	Anhui Zhifei	**Wuhan Inst**
Biontech	**Astrazenaca**	Novavax	**Sinopharm**
Zydus	Johnson	Dynavax	**Sinovac**
Curevac	**Gamaleya**	Vaxine	Chinese Academy
Imperial College	Reithera	Medicago	Bharat
Anges	Novartis	CSL	Merck
Arcturus	Vaxart	KBPMedigen	
Inovio		Baylor college	
Genexine		U Pittsburgh	
Abogen		Sanofi	
Sanofi			

***Blue** = phase 3, **red** = early approval*

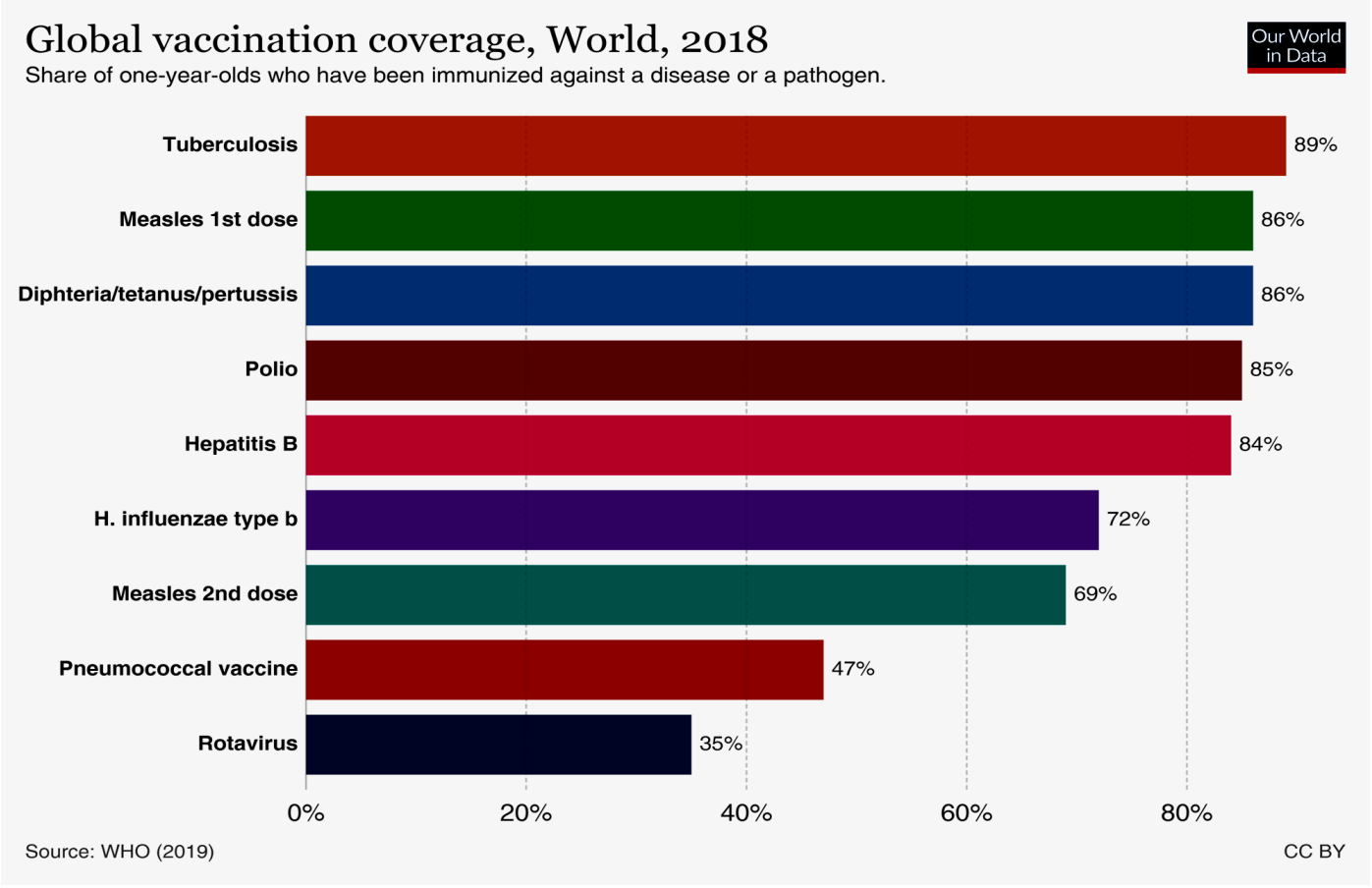
Vaccine Development & Licensing

Although most of the vaccines in use today were developed in the 20th century, evidence exists that the Chinese employed smallpox inoculation (variolation) as early as 1000 CE. It was practiced in Africa and Turkey as well, before it spread to Europe and the Americas. Edward Jenner's innovations in 1796, with use of cowpox material to create immunity to smallpox, quickly made the practice widespread in Europe, eventually leading to the eradication of smallpox. Louis Pasteur's development of vaccines against rabies and anthrax in the late 1800s was followed by anti-toxins and vaccines against diphtheria, tetanus, cholera, plague, typhoid, tuberculosis, and more, through the 1930s.

In the mid 20th century advances in DNA/protein manipulation and microbiological technologies for growing viruses in the laboratory led to rapid discoveries and innovations, including the creation of vaccines for polio. Researchers targeted other common childhood diseases such as measles, mumps, and rubella, and vaccines for these diseases have greatly reduced the global burden of infectious disease. Innovative techniques now drive vaccine research, with recombinant DNA technology and new delivery techniques leading scientists in new directions. Disease targets have expanded, and some vaccine research is even beginning to focus on non-infectious conditions such as addiction and allergies.

Milestone timelines

1936 Max Theiler Develops Yellow Fever Vaccine
1944 Vaccine for Japanese Encephalitis
1955 Polio Vaccine Results Announced
1960 Sabin's Polio Vaccine Licensed
1968 Vaccine for Hong Kong Influenza Pandemic
1969 Rubella Vaccine Licensed
1971 Measles, Mumps, Rubella Vaccine Licensed
1974 Meningococcal PolysaccharideVaccine Licensed
1976 Swine Influenza Vaccine
1981 Hepatitis B: First Subunit Viral Vaccine in U.S.
1986 Hepatitis B: Recombinant Vaccine Licensed
1987 Conjugate Hib Vaccine Licensed
1995 Hepatitis A: Vaccine Licensed
1995 Chickenpox Vaccine Licensed
2006 Rotavirus: Vaccine Recommended
2008 Rotavirus: Another Vaccine Licensed
2014 Group B Meningococcal Vaccine Approved



Surge in infectious disease deaths due to interruptions by COVID-19

Experts around the world expect the COVID-19 pandemic to have a significant impact on society. This includes not only the illness and deaths caused by the disease itself but also the economic consequences of global lockdowns and disruptions to essential services.

Indications are that the pandemic's knock-on effects are likely to be most severe in low and middle-income countries, where health systems are less robust and economic reserves are more limited.

Particular concern is for countries with high burden of infectious diseases such as HIV and tuberculosis (TB), which depend on sustaining regular, large-scale programmes of control and treatment.

A recent modeling study published in Lancet Global Health draws attention to the knock-on effect that COVID-19 disruptions to health services could have on increased HIV, tuberculosis and malaria deaths in low- and middle-income countries. They estimate that these fatalities could increase over the next 5 years and, in the worst-case scenario, occur on a similar scale to the direct impact of the COVID-19 pandemic.

The model

The researchers based the study on a model that assumes a reproduction number of 3 for SARS-CoV-2. The reproduction number (R_0) indicates the average number of new people who will contract the virus from one person who has been infected.

Using R_0 as a starting point, they modeled the impact of four different policy scenarios for COVID-19:

- taking no action
- mitigation, leading to a potential 45% reduction in R_0 for 6 months
- suppression-lift, leading to a potential 75% reduction in R_0 for 2 months
- suppression, leading to a potential 75% reduction in R_0 lasting for 1 year

They then used models of transmission for HIV, TB and malaria to estimate the impact of the COVID-19 policy scenarios on these diseases. Potential impacts included COVID-19 interventions limiting routine programme activities, and COVID-19 cases overwhelming the health system.

Disruption to health services

The results showed that disruption to health services caused by COVID-19 could increase the number of deaths from HIV by 10%, from tuberculosis by 20% and from malaria by 36% over the next 5 years. The impact varied according to disruption to activities and success of interventions in reducing COVID-19 transmission.

The model predicted that the most significant impact for HIV would be interruptions to the supply of anti-retroviral treatment due to the high demand on the healthcare system. To combat this, the researchers suggest giving people multiple prescriptions at a time or delivering them to their homes. They indicated that disruptions to diagnosis and treatment were likely to have the most significant impact on TB cases.

The model also predicted that interruptions to the delivery of mosquito nets could be devastating in terms of the number of malaria cases. Planned net campaigns usually take place every 3 years, and without this, malaria deaths could increase by 36% over the next 5 years.

Deaths can still be prevented

The researchers say that the disruptions caused by COVID-19 could, in the worst-case scenario, lead to a loss of life years (the expected number of years a person might have lived had they not died of a particular cause) on a similar scale to the direct impact of the pandemic itself.

However, there is still time to reduce the death toll. The researchers say that authorities and other organisations must maintain critical services, such as providing anti-retroviral treatments for HIV and insecticide-treated nets for malaria.

There are some important limitations to note about this modeling study. The authors say the scenarios they modeled are not "exhaustive" and do not account for the impact of long-term global changes, such as an economic recession, which presumably could make things even worse.

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Coronavirus Disease 2019 (COVID-19) Situation Report

Data as reported by national authorities by 23:00 local time 18th of November 2020

Situation Report No. 180 - State of Kuwait
19th of November, 2020

World Health Organization
WHO Office - Riyadh

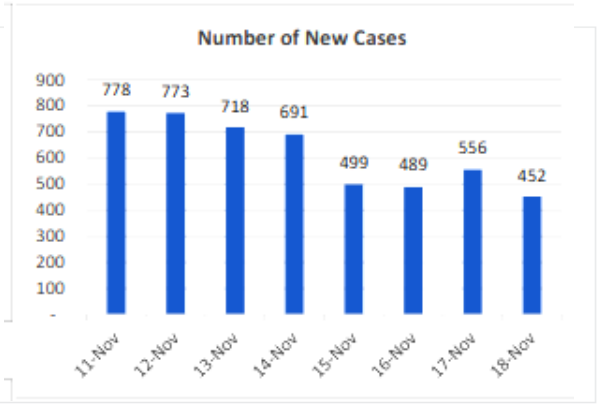
	Global		Eastern Mediterranean Region	
	COVID-19 Cases	COVID-19 Deaths	COVID-19 Cases	COVID-19 Deaths
Total	55,326,907	1,333,742	3,649,052	92,651
New	536,224	9,220	37,381	857

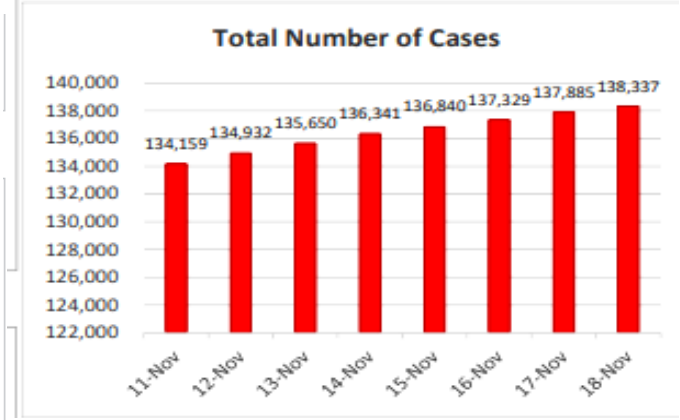
State of Kuwait

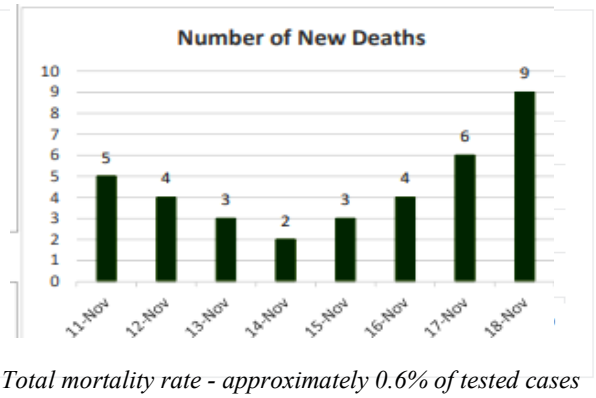
	Confirmed Cases	Recovered Cases	Deaths	Active Cases	Critical Cases	PCR Tests
Total	138,337	129,839	857	7,641	105	1,029,227
New	452	798	9	-	-	6,068

HIGHLIGHTS

- Several economists reject the return of the lockdown stressing that another lockdown will negatively impact Kuwait's economy, particularly small and medium enterprises.
- The Ministry of Health has formed teams tasked to provide psychological support for those affected by corona pandemic.
- Today, the cabinet will review the list of 32 banned countries.
- WHO publishes public health considerations while resuming international travel, see link.
- WHO and UNICEF provide advice on the use of masks for children in the community in the context of COVID-19, see link.
- WHO: Interim guidance on considerations for quarantine of contacts of COVID-19 cases with updates on ventilation and on the care of children in quarantine; see link.







Total mortality rate - approximately 0.6% of tested cases

Latest update can be seen at **http://www.emro.who.int/kuwait/information-resources/covid-19-situation-reports.html**

Answers to: Test your knowledge

Correct answers: 1-D; 2-B; 3-C; 4-A; 5-D; 6-E; 7-A; 8-D; 9-C

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***Executive Editor*: Yunus Luqmani. *Assistant Editors*: Leyla Hasan Sharaf, Samuel Koshy**

Editorial Office: Faculty of Pharmacy, Health Sciences Centre, Kuwait University, PO Box 24923 Safat, 13110 Kuwait, Fax:25342087; email: Yunus.Luqmani@ku.edu.kw http://www.hsc.edu.kw/FOP/KPB_magazine.aspx
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