Understanding SARS-CoV-2 (COVID-19)

SAMRC Health Systems Research Unit

31 March 2020

Dr Nobubelo Ngandu

OVERVIEW

1. What are coronaviruses
2. The phylogenetics of SARS-CoV-2
3. Life cycle and disease progression
4. Infectiousness and herd immunity
5. Immune response
6. Therapeutic strategies under development
7. Vaccine approaches under development

1. What are coronaviruses?

Coronaviridae family has a wide host and disease range, first identified mid-1960s.

Commonly cause respiratory/gastrointestinal/systemic infections in animals. E.g. cats dogs, cows, pigs, birds.

Four CoVs cause mild common cold in humans (CoV-OC43, CoV-229E, CoV-NL63, CoV-HKU1)

- Antibodies found in 30% of children & up-to 80% of adults

Three CoV human pandemics: SARS-Cov (Severe Acute Respiratory Syndrome), MERS-Cov (Middle East Resp Syndrome), SARS-Cov-2 (2019-2020)

SARS-Cov (2002-2003)

- Started in Southern China (winter) and spread to 37 countries
- Killed 774/8096 identified cases
- Case fatality rate of 9.6
- Eradicated in January 2004
- South Africa had 1 case, 62yr old male, died

MERS-Cov (2012)

- Started in Saudi Arabia & spread to South Korea
- Killed 858/2494 lab-confirmed cases
- Sporadic outbreaks have followed in different countries and years.

SOURCES: Smith (Soc Sc Med 2006(63)), https://www.who.int/csr/sars/country/table2004_04_21/en/, Lee et al (J Theo Biol 2016(408), Yip (Virol 2016), Zaki 2012, Zumla 2015)

SARS-CoV-2 & COVID-19

A contagious respiratory disease that was first detected in China (at a market in Wuhan, Hubei Province) in December 2019

Temporarily named The 2019 novel (new) coronavirus (2019-nCoV)

After phylogenetic and homology assessment –International Committee of Taxonomy of Viruses named it SARS-CoV-2

The disease is named COVID-19.

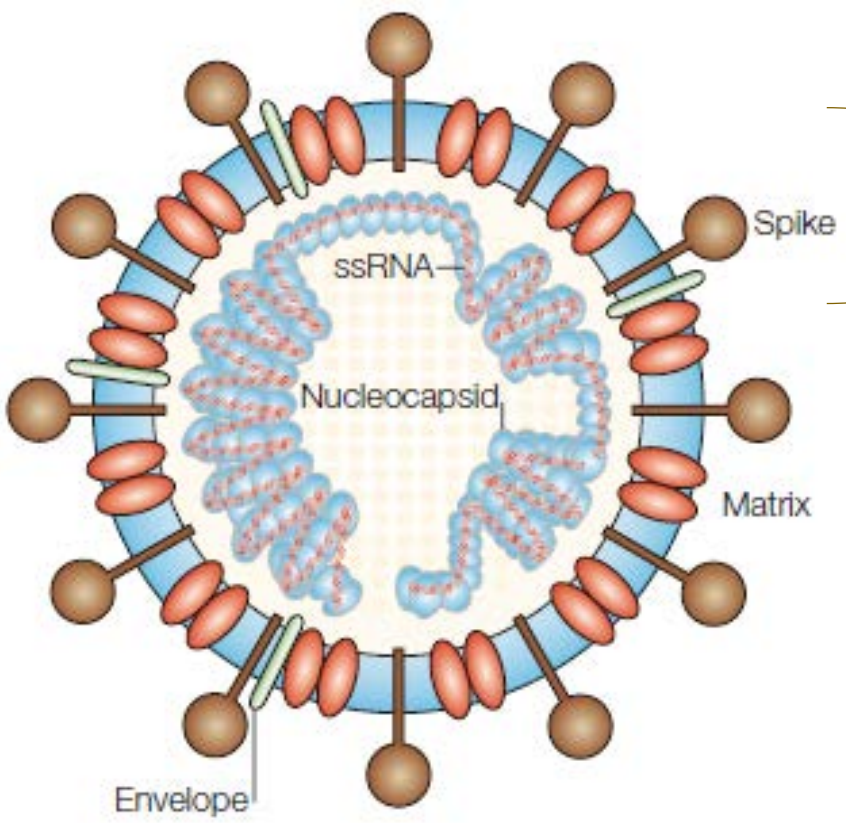
Spread through respiratory droplets

Causes flu-like symptoms.

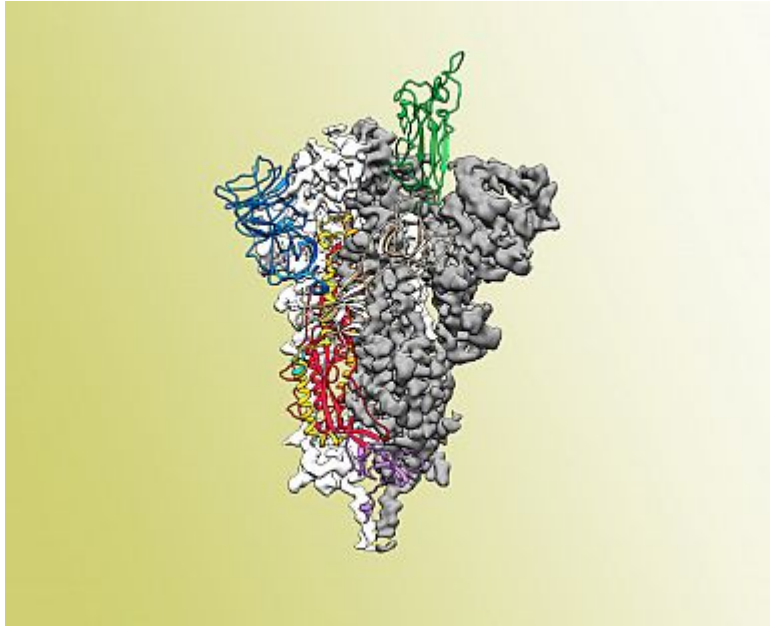
Some patients — particularly the elderly and those with underlying chronic health conditions/immunosuppressed —>> develop a severe form of pneumonia, can lead to death

SOURCES: Huang et al (Lancet2020)

Structure & size



Spike structural protein contains the receptor domain for binding to the host cell receptor (angiotensin-converting enzyme 2, ACE2 in human cells)



Atomic-level structure of the SARS-CoV-2 spike protein. The receptor binding domain, is colored green. *UT Austin, McLellan Lab*

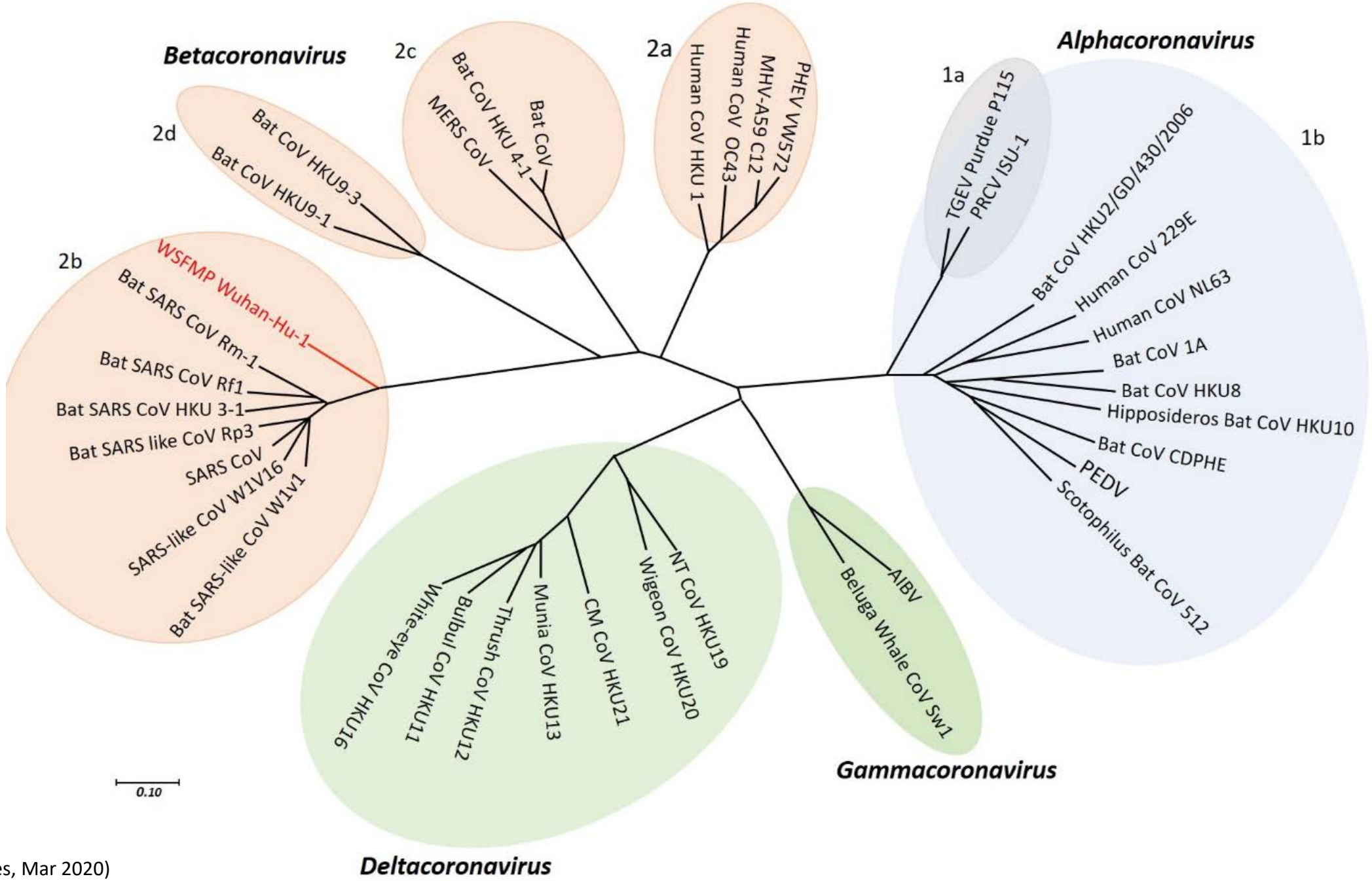
Largest RNA viruses, 28-30kb genome, +ssRNA

Low mutation and recombination rates

SOURCES: Perlman & Dandekar (Nature Reviews-Immunology 2005(5)), McLellan Lab (Science 2020),), Hoffmann (Cell 2020)

1. What are coronaviruses?
2. **The phylogenetics of SARS-CoV-2**
3. Life cycle and disease progression
4. Infectiousness and herd immunity
5. Immune response
6. Therapeutic strategies under development
7. Vaccine approaches under development

Overview of Coronaviridae family phylogeny



SOURCES: Shereen et al(J Adv Res, Mar 2020)

Phylogeny of Betacoronaviruses

SARS-CoV-2 samples taken from:

- 8 patients who visited Huanin market
- 1 lived at nearby hotel
-throat swabs
-bronchoalveolar lavage fluids

SARS-CoV-2 to belongs to:

- Same lineage as SARS-CoV but different lineage from MERS-CoV & other common cold CoVs

- Different clade from SARS-Cov

- Same clade as 2 bat CoVs

SOURCES: Lu et al (The Lancet, Feb 2020(395))

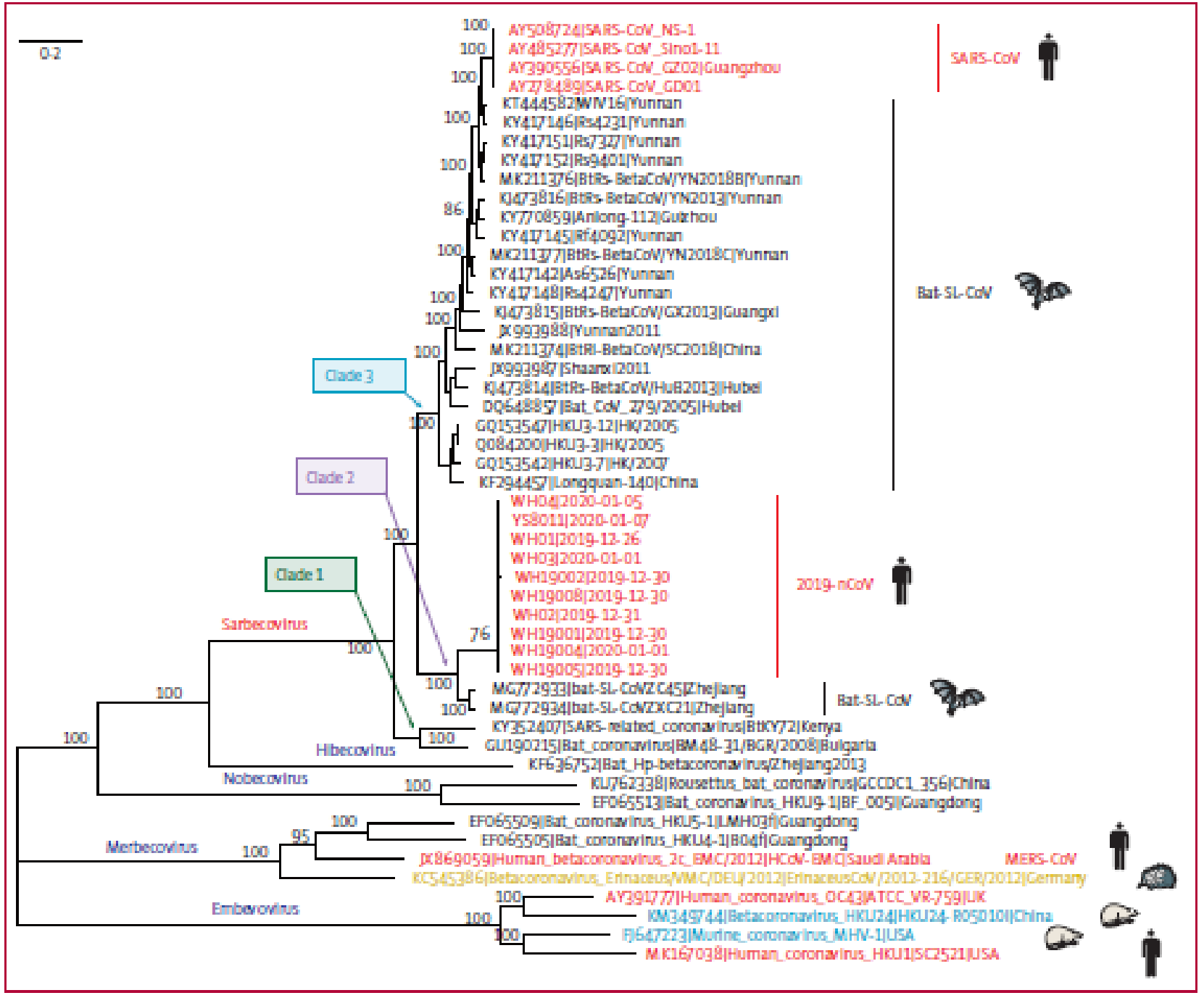
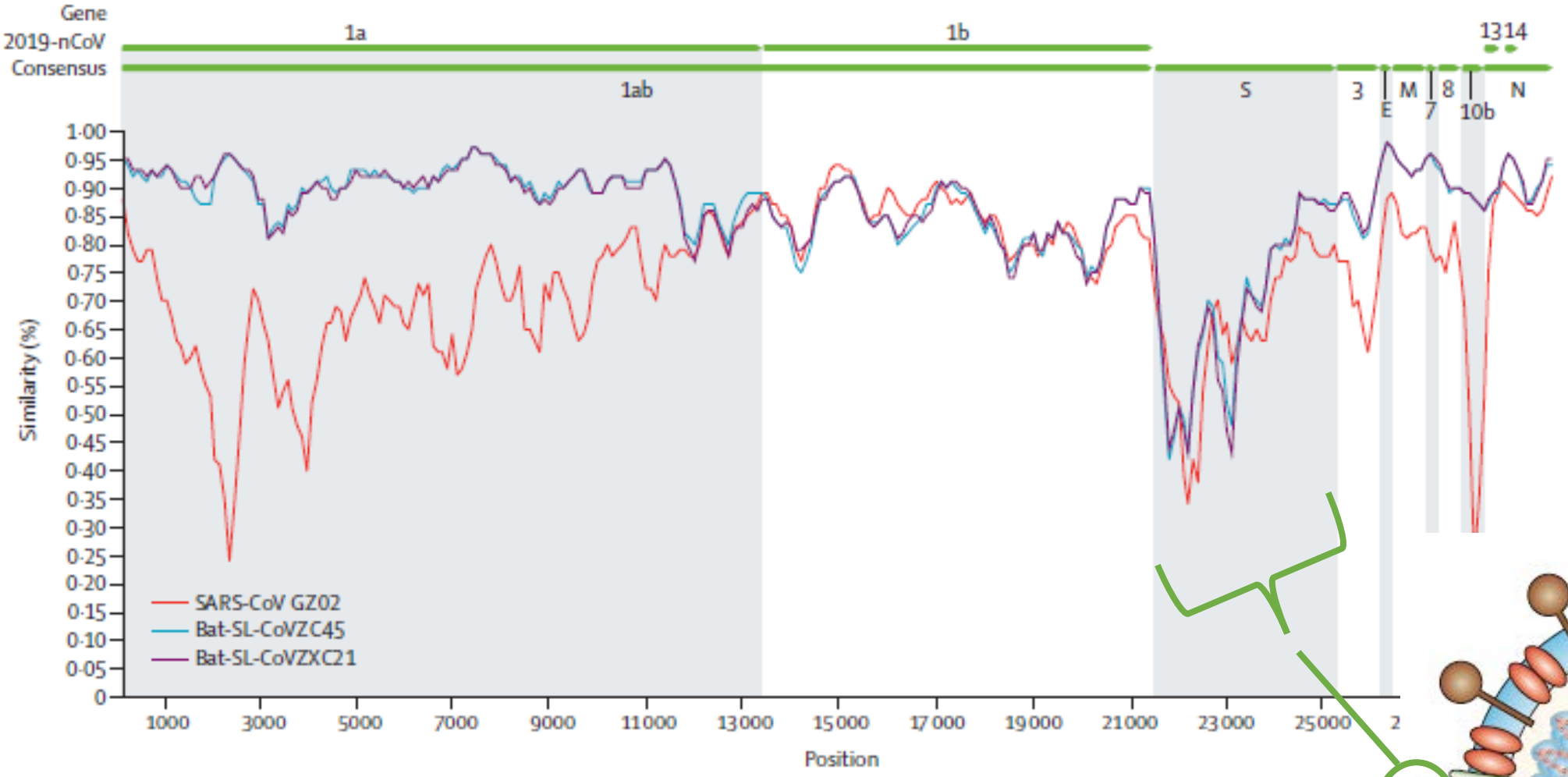
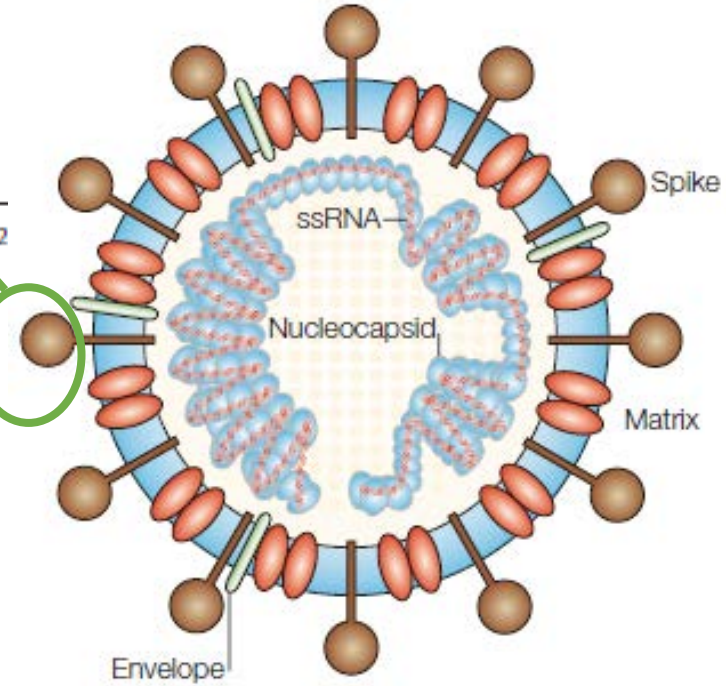


Figure 3: Phylogenetic analysis of full-length genomes of 2019-nCoV and representative viruses of the genus Betacoronavirus



Overall genome similarity

- 87.5% similarity to Bats
- 79% similarity to SARS-Cov

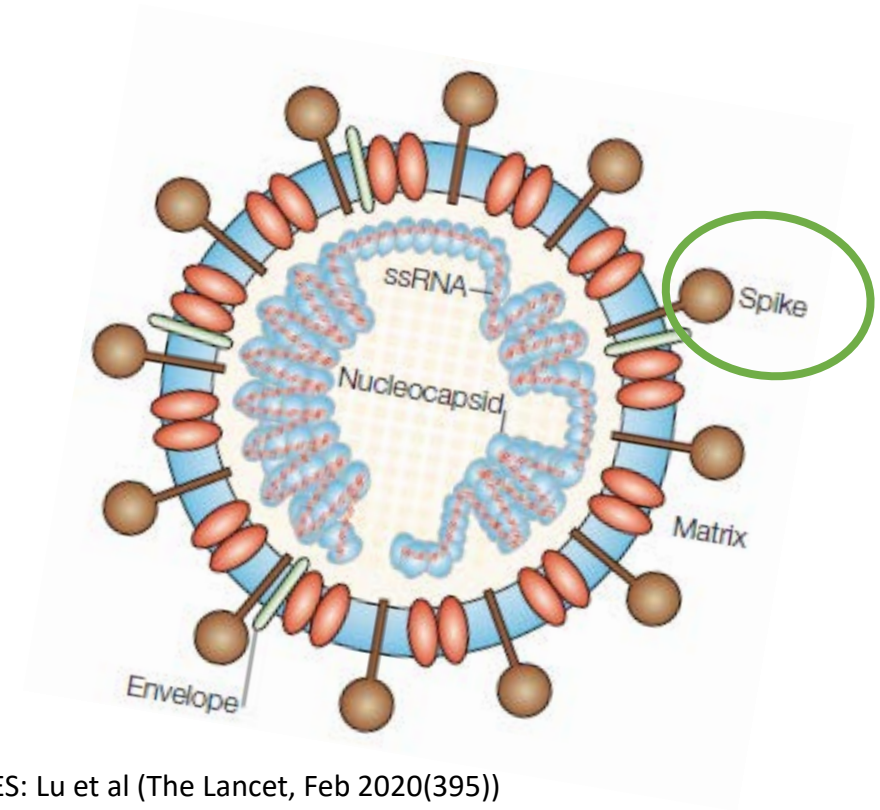


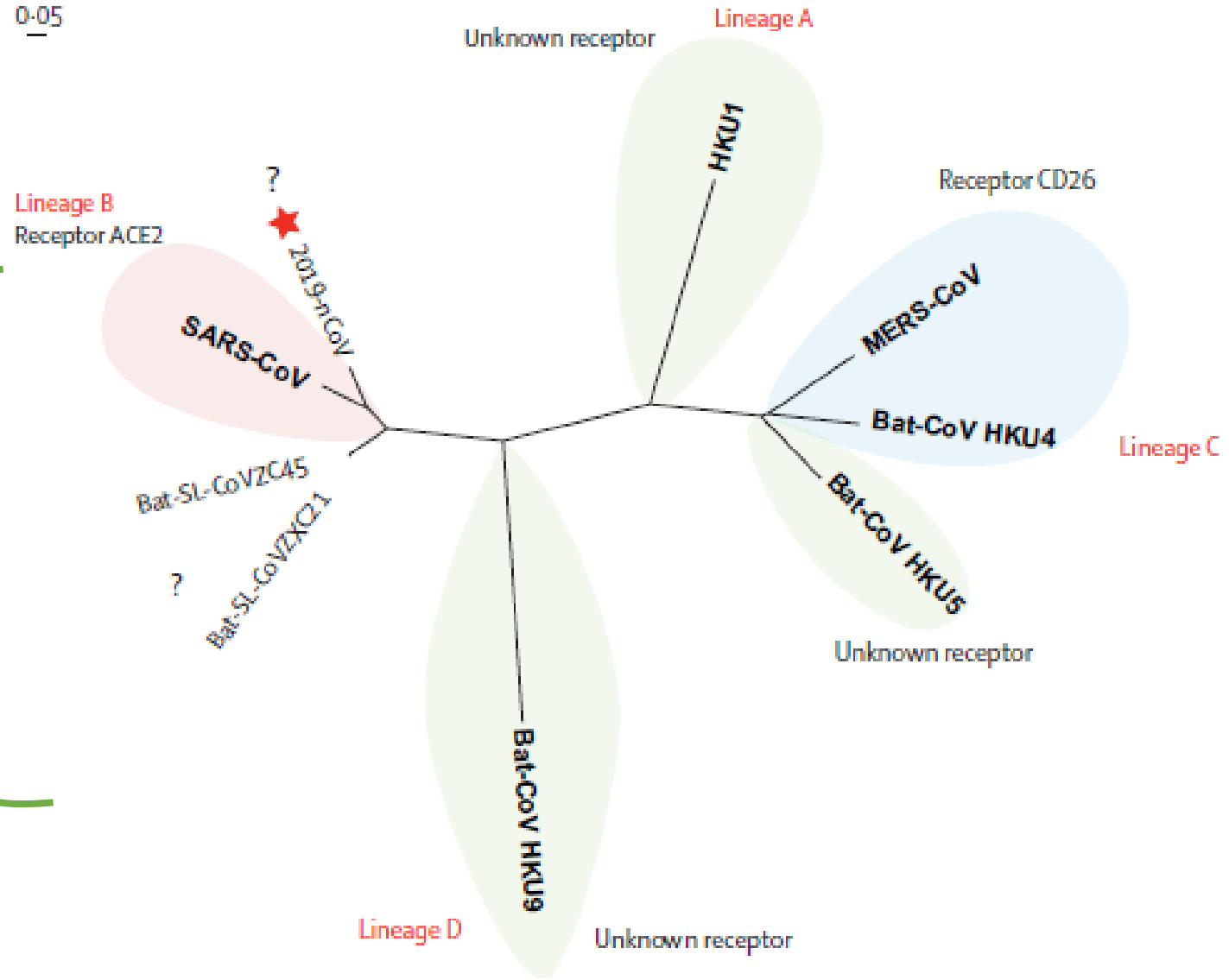
The receptor binding domain of betacoronaviruses is on the spike protein

SOURCES: Lu et al (The Lancet, Feb 2020(395))

Homology of 3-dimensional structure of the receptor binding domain

- Higher homology with SARS-CoV (only 5 amino acid differences)
- SARS-CoV-2 likely uses the same human cell receptor (ACE2) to infect cells
- Hence WHO named 2019-nCoV to SARS-Cov-2





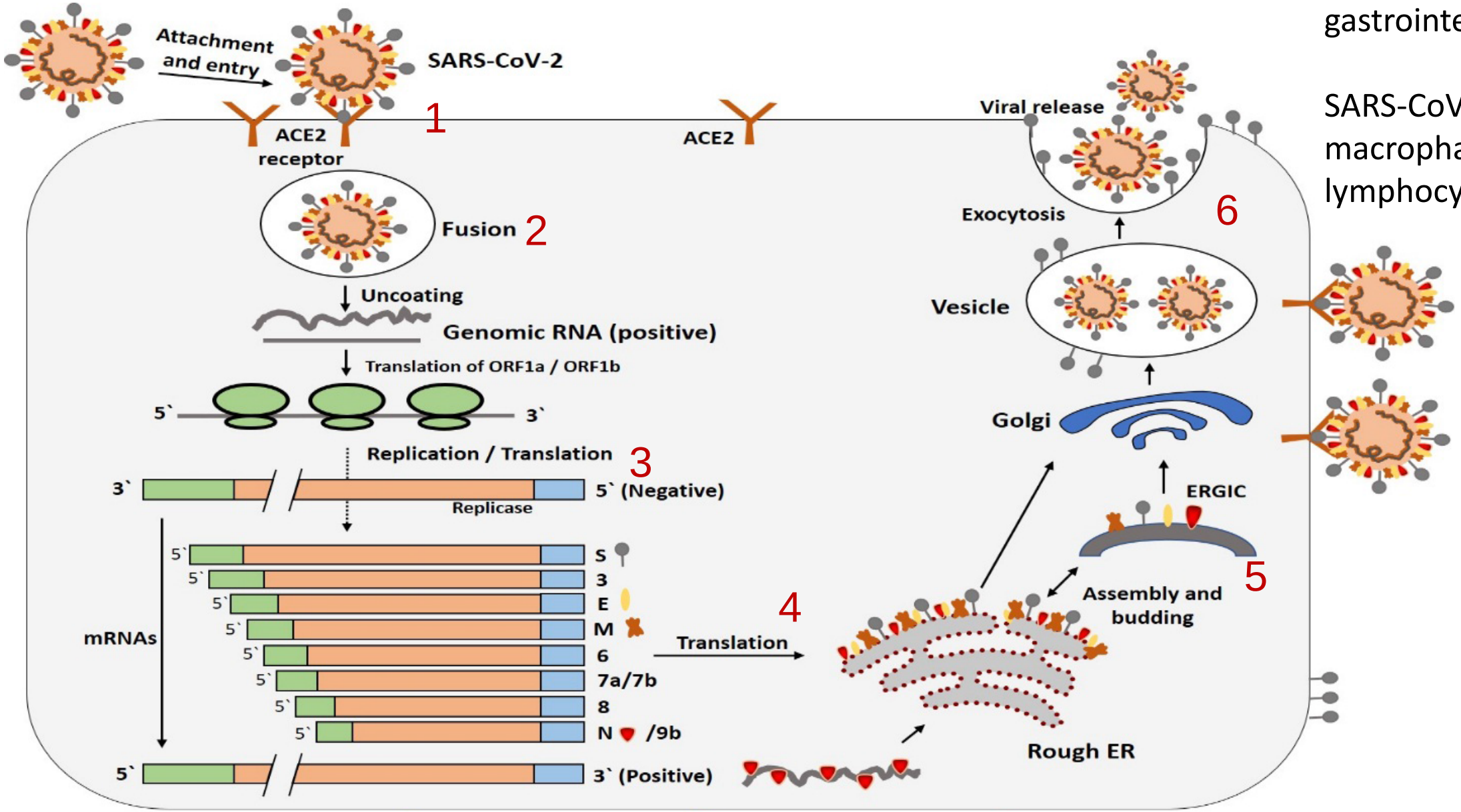
SOURCES: Lu et al (The Lancet, Feb 2020(395))

1. What are coronaviruses?
2. The phylogenetics of SARS-CoV-2
3. **Lifecycle and disease progression**
4. Infectiousness and herd immunity
5. Immune response
6. Therapeutic strategies under development
7. Vaccine approaches under development

Life-cycle of SARS-CoV-2 in host cells

ACE2 receptor found in the lungs & gastrointestinal tract.

SARS-CoV also infects macrophages & lymphocytes



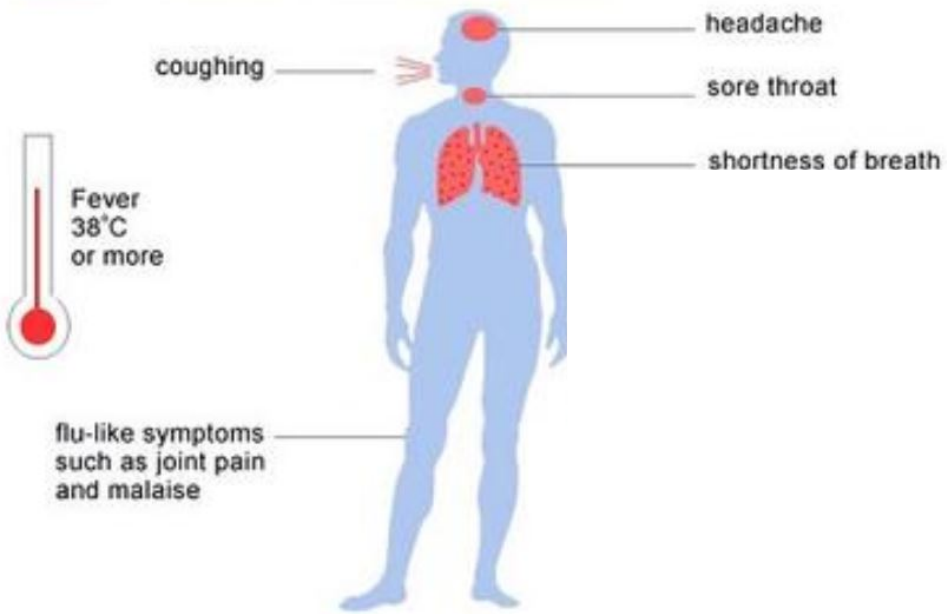
SOURCES: Shereen et al(J Adv Res, Mar 2020), Hoffmann (Cell 2020)

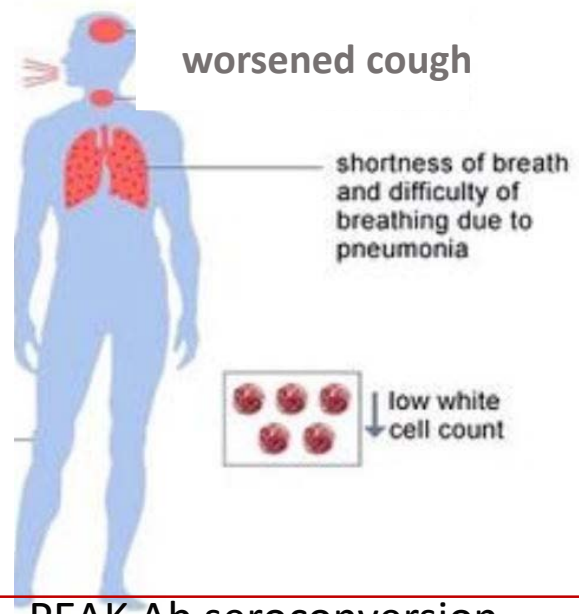
COVID-19 disease progression

LATER DISEASE STAGE

- Severe form of pneumonia
- 20% get hospitalized, ~4% die.
- 50-80% get ill like a bad flu then recover (period??)
- ~30% asymptomatic

INCUBATION PERIOD





PEAK Ab seroconversion

1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-20	21-30	31-40
DAYS POST-INFECTION									

SOURCE: Gostic (2020), Nick Mark, MD (2020), Zhuo et al(medRxiv Mar2020), Mizumoto et al (medRxiv Mar2020)

1. What are coronaviruses?
2. The phylogenetics of SARS-CoV-2
3. Life cycle and disease progression
4. **Infectiousness and herd immunity**
5. Immune response
6. Therapeutic strategies under development
7. Vaccine approaches under development

Population stats

Covidvisualizer.com 30 March 2020	Total cases	Current active	Deaths	Recoveries
World (@3.5 months)	739 385	546 297	35 019 (4.74%)	156 280 (21.2%)
China (@3.5 months)	81 470	2 466	3 304 (4.1%)	75 700 (**92.9%**)
Spain (@1.5 months)	85 195	61 075	7 340 (**8.6%**)	16 780 (19.7%)
South Africa (@1 month)	1 326	1 292	3 (0.22%)	31 (2.3%)

Who is at highest risk of developing severe disease:

- HIV-positive persons with low CD4 count
- Persons with chronic illness e.g., cancer, diabetes, TB, Asthma, lung & kidney diseases
- Smokers and alcoholics
- Elderly (*male gender???*)

Model projections (SA):

1000 cases – 1 April

10 000 cases – 15 April

(***Pearson 2020***)

Huang et al (Lancet2020)

Understanding transmission rate

Infectiousness of a pathogen measured using **basic reproductive number** (***R_0***)

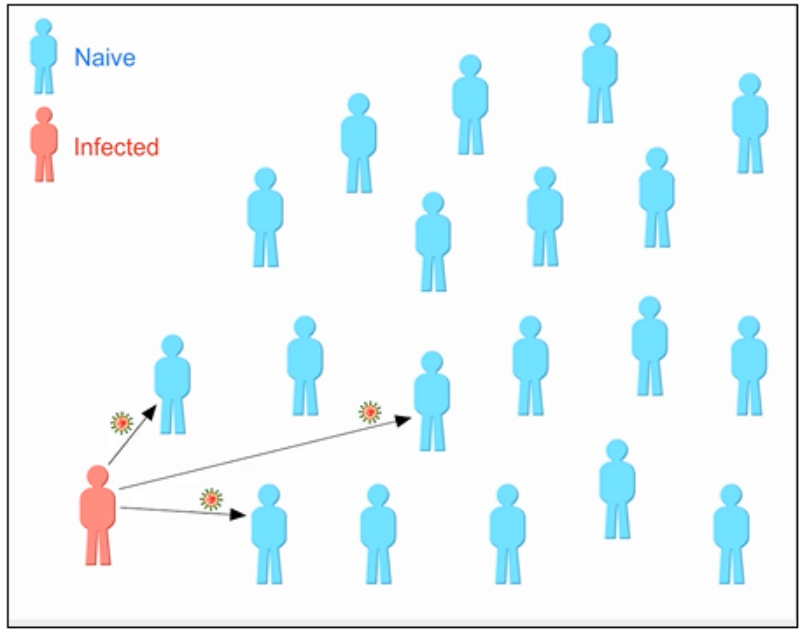
- The average number of individuals one infectious person would infect (over their entire period of infectiousness) if **everyone in the population were susceptible**.
- R_0 >1 :each case infects more than one person before they recover and the epidemic grows;
- R_0 <1: epidemic disappears rapidly

Vaccination affects $R_{(t)}$ and not R_0

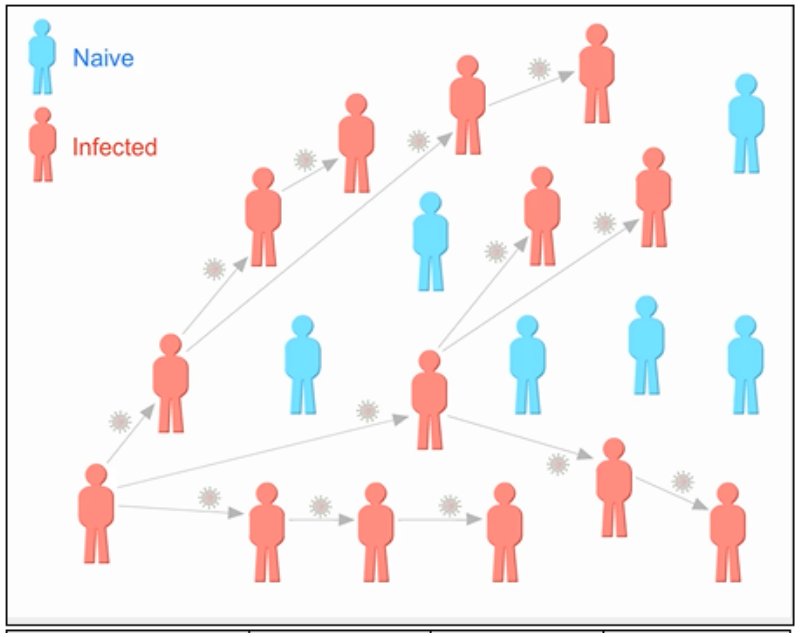
Effective reproductive number ($R_{(t)}$) is R_0 in the presence of herd immunity (*through vaccination or naturally-induced*)

- Average number of new infections where not everyone is susceptible
- **$R_{(t)}$**= $R_0(S_{(t)}/N_{(t)})$, *where $S_{(t)}/N_{(t)}$ = proportion of susceptible at time (t)*
- **$R_{(t)}$ <1: epidemic disappears and re-infection is prevented**

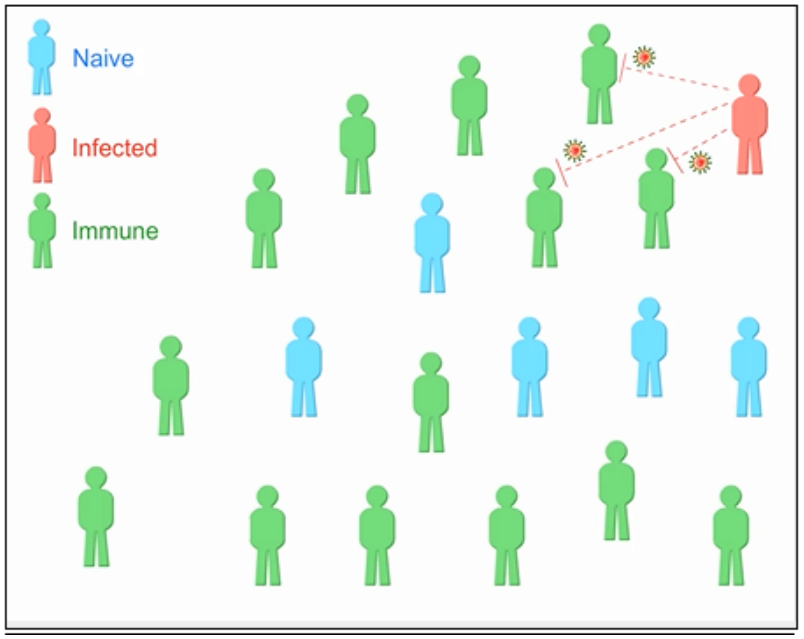
HERD IMMUNITY



- Naïve population
- Completely susceptible



- Nearly everyone exposed gets infected
- $\mathbf{R_0}$



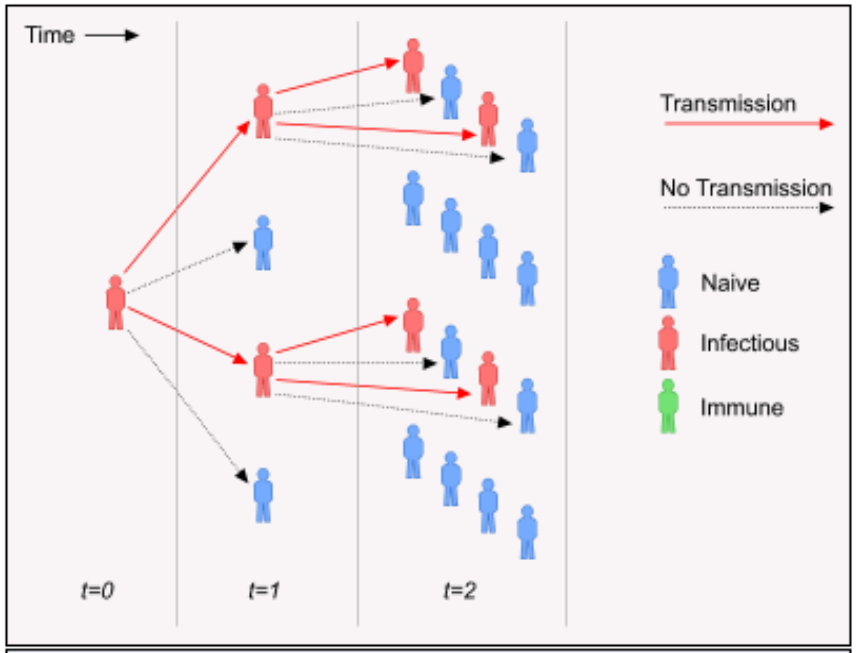
- Development of herd immunity through natural infection
- **Development of long-lived antibodies and/or build up of memory immunity**
- Virus reproduction decreases
- Prevents spread of virus to naïve/susceptible persons
- Prevents re-infection

HERD IMMUNITY ACHIEVED BY human infecting CoV??

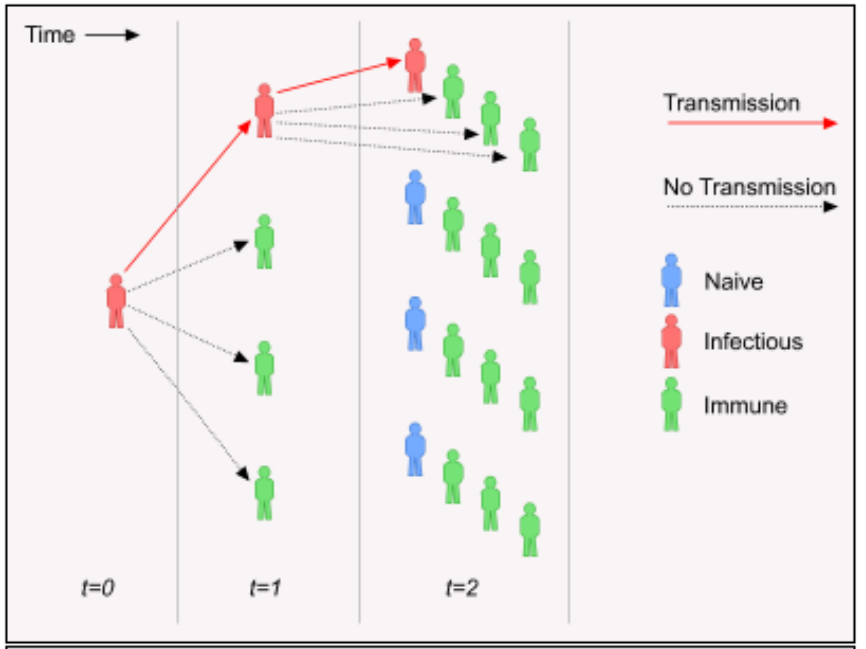
No clear evidence yet!

SOURCE: Gostic (2020),

<u>After vaccination</u>, presence of **herd immunity** monitored by calculating the effective reproductive number $R_{(t)}$



Totally susceptible population, $R_0 = 2$; $R(t) = 2$ (initially).



75% of the population vaccinated, $R_0 = 2$; $R(t) = 0.5$ (initially)

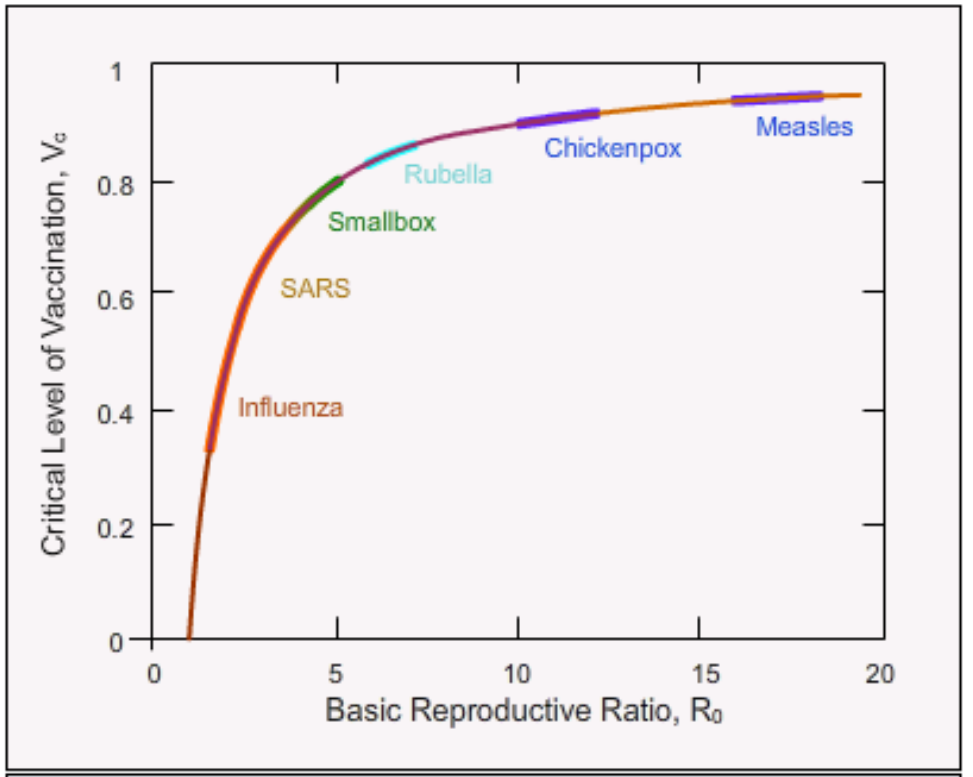
Critical vaccination threshold

Critical vaccination threshold is the proportion of the population that needs to have immunity (induced by vaccination) to prevent an epidemic occurring

Critical vaccination threshold = $1-1/R_0$

Highly infectious pathogen= high R_0 = high critical vaccination threshold

- **$R_{(0)}$** for SARS-CoV-2 = 1.5-4 (similar to influenza)
- Attack rate = 30-40%



The graph shows the relationship between the critical level of vaccination needed to eradicate infection and the basic reproductive ratio, R_0. Superimposed on this curve are parameter estimates for six well-known infectious diseases, ranging from influenza (low R_0) to measles (high R_0)

"Herd Immunity" is Epidemiological Neoliberalism

ON MARCH 19, 2020 / BY ISABELFREY

While most European countries are preparing for lock-downs to stop the spread of the coronavirus, a few countries are opting for a different strategy: herd immunity. Instead of testing as many people as possible and implementing measures to increase social distancing, they want to purposefully let the virus spread among people who are at low risk, so that a large part of the population becomes immune. This approach was first proposed by UK's prime minister Boris Johnson, who refused to implement social distancing measures until a few days ago. While the UK has officially distanced itself from this strategy, the Netherlands and Sweden continue to hold on to this approach, despite harsh criticism by the WHO.

Does infection with SARS-CoV-2 induce herd immunity??

NO, *for now!*

These countries argue that building herd immunity is the only long-term strategy for dealing with the virus, since the epidemic can no longer be contained and could always resurge again. Instead of putting the entire country under lockdown, only at-risk populations should be put into quarantine while the epidemic keeps spreading. However, countless epidemiologists and virologists have criticized the strategy for being risky, unscientific and likely to result in a high death toll. A recently published report by the Imperial College London, which led to the change in UK government policy, estimated the strategy to result in 250,000 deaths in the UK. Since it is not possible to effectively isolate at-risk populations, especially when the virus keeps spreading, the health care system is likely to become overwhelmed and at risk of completely collapsing.

SOURCE: https://thequarantimes.wordpress.com/2020/03/19/herd-immunity-is-epidemiological-neoliberalism/

So how do we flatten the curve without any herd immunity for COVID-19?

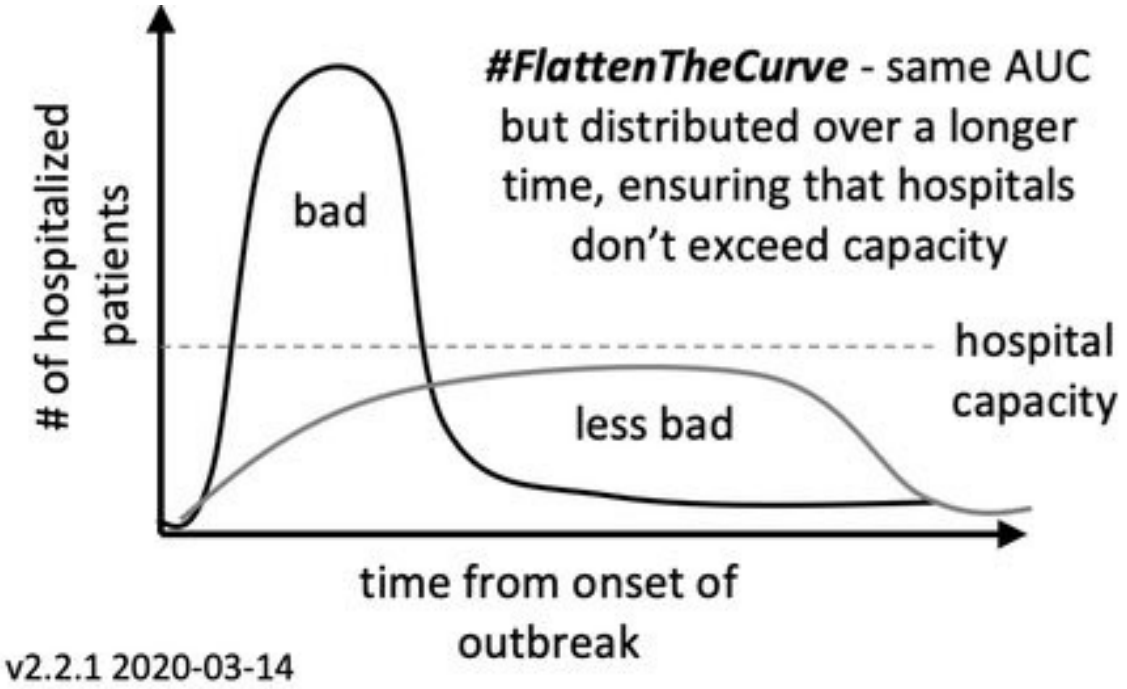
Obey the non-therapeutic & preventative initiatives

Reduce number of infections and hence number of severe cases per unit time

Increase screening coverage to identify cases for early management

Maintain manageable hospital burden

Eventually stop the spread



SOURCE: Nick Mark, MD/Seattle

1. What are coronaviruses?
2. The phylogenetics of SARS-CoV-2
3. Life cycle and disease progression
4. Infectiousness and herd immunity
5. **Immune response**
6. Therapeutic strategies under development
7. Vaccine approaches under development

Evidence of antibody (Ab) immune responses against COVID-19

Data from 173 SARS-CoV-2 patients in China

% of patients who developed antibodies (sero-conversion) over time:

	Median time for seroconversion	Day 7 sero-conversion rate	Day 15 sero-conversion rate
	(in days)		
Ab	11	<40%	100%
IgM	12		94.3%
IgG	14		79.8%

Patients who do not develop severe disease have an earlier onset of Ab peak ~~7 days

Higher sensitivity for total Ab detection.

Higher Ab titer -> worsening clinical disease but decrease of viral RNA load

IgG detection not ideal for serological diagnosis during early disease stage

SOURCES: Zhao et al(medRxiv, Mar 2020), Thevarajan et al (Nature 2020)

Concerns and considerations about immune responses

Why has no successful vaccine been developed since the SARS-CoV outbreak in 2002/3?

Infection with CoVs in humans mainly causes lung pathology

Also associated with immunopathology (immune system becomes destructive rather than protective to the host)

SARS-CoV induced immune hypersensitivity leading to overproduction of monocytes (& a 'cytokine storm') -> attacking not only infected lung cells but also healthy lung cells.

- Inactivated whole virus vaccine (preclinical – ferrets & NHP), protective signal
- Protein-like particles (mice), protective signal
- Challenge with SARS-CoV led to immunopathology

Exposure to natural pathogen (e.g., during an outbreak) and hence activation of memory immunity (induced by vaccination) should not induce immune hypersensitivity

SOURCES: Perlman & Dandekar (Nature Reviews-Immunology 2005(5)), Tseng et al (PLoS ONE 2012)

1. What are coronaviruses?
2. The phylogenetics of SARS-CoV-2
3. Life cycle and disease progression
4. Infectiousness and herd immunity
5. Immune response
6. **Therapeutic strategies under development**
7. Vaccine approaches under development

Screening & Diagnostics

Screening for symptoms – mainly cough & fever temperature(scanner depends on onset of symptoms)

Diagnostics:

- Laboratory diagnostics use real time PCR to detect viral RNA
- Throat and nasopharyngeal swabs
- Lower viral load in upper respiratory tract concern for false-negatives
- Expensive and time-consuming
- Strategy for improved and rapid diagnosis needed
- **Strong evidence for serological Ab testing accumulating (detectable mostly after 7 days post infection)**

SOURCES: Zhao et al(medRxiv, Mar 2020)

Current treatment

NO therapeutic or vaccine strategy has been developed to date against any of the 3 human pandemic coronaviruses

Symptom management is current approach for COVID-19. e.g. use of antiretrovirals such as HIV drug Kaletra, metal (e.g. zinc)-containing formulations

Therapeutic strategies under investigation

Drug	strategy
Chloroquine	**Blocks viral entry into endosome**
Remdesivir	**Block RNA dependent polymerase**
Lopinavir/ritonavir	Protease inhibitors
Tocilizumab	Block IL-6
Corticosteroids	Reduce inflammation
Other broad- spectrum antivirals previously used for SARS-CoV and MERS	

Remdesivir alone or in combination with chloroquine or interferon beta significantly blocked the SARS-CoV-2 replication in patients who recovered

Drug against Nsp15 (initially for SAR-CoV) promising to be effective against COVID-19
Clinicaltrials.org

Hydroxychloroquine for COVID-19 treatments in Phase 3 clinical trial

Neutralizing antibodies
monoclonal antibody (CR3022) also a potential candidate for therapeutic or prevention use

SOURCES: Shereen et al(J Adv Res, Mar 2020); Colson et al., 2020; Gao et al., 2020; clinicaltrials.org

1. What are coronaviruses?
2. The phylogenetics of SARS-CoV-2
3. Life cycle and disease progression
4. Infectiousness and herd immunity
5. Immune response
6. Therapeutic strategies under development
7. **Vaccine approaches under development**

Pre-clinical vaccine studies

MOST APPROACHIES INFER FROM SARS-CoV vaccine studies

- Both viruses use the Human ACE2 receptor, but SARS-CoV-2 has 10-20x higher affinity
- mice & hamster models used in SARS-CoV are being used
- Inactivated/live-vectored vaccine candidate reduced viral infection
- Recombinant protein vaccine candidate – induced protective antibodies

INO-4800-DNA nearly close to clinical studies

Inactivated candidate being developed by Chinese CDC

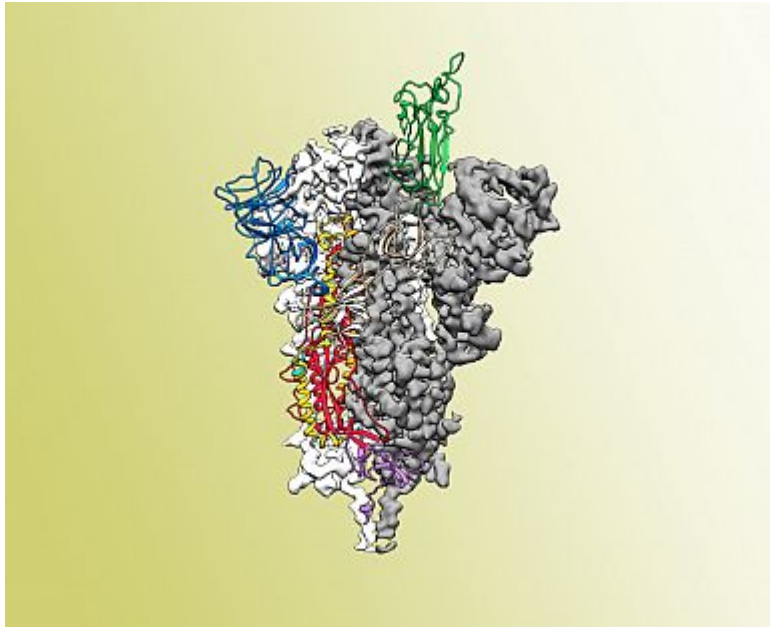
3 other candidates being developed by pharmaceuticals (Stermirna Therapeutics, Geo Vax-Bravo Vax, White Clover Biopharmaceuticals

Other companies such as Johnson & Johnson, VIDO-InterVac, GeoVax-BravoVax, Clover Biopharmaceuticals investigating different strategies

SOURCES: Shereen et al(J Adv Res, Mar 2020)

Potential Neutralizing antibody vaccine candidate

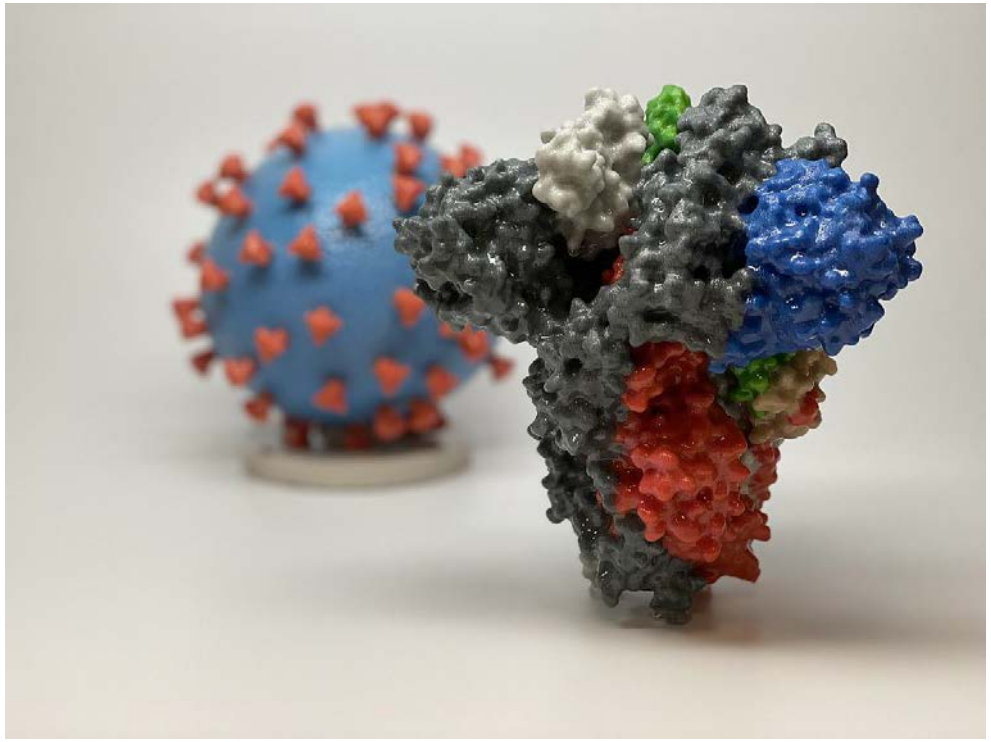
- Spike protein of SARS-CoV-2
- nAb for SARS-Cov(2002) could not bind to the recent protein
- Isolate and test Ab from persons with COVID-19



Atomic-level structure of the SARS-CoV-2 spike protein. The receptor binding domain, is colored green. *UT Austin, McLellan Lab*

Clinical vaccine studies

- mRNA-1273 Phase-I trial for SARS-CoV-2 started (US-NIAID)
- To enroll 45 adults (18-55 years old)
- 2 im doses (4 weeks apart)
- 3 arms for different doses
- Largest dose delayed



Monitored over 6 weeks for:

- Safety
- Induction of immune response

SOURCES: https://clinicaltrials.gov/ct2/show/NCT04283461?term=mrna-1273&draw=2&rank=1

DISCLAIMER: *DUE TO RAPID PRODUCTION OF NEW INFORMATION ON SARS-CoV-2/COVID-19, SOME OF THE INFORMATION PRESENTED HERE MIGHT BE OUTDATED AT THE TIME OF THIS PRESENTATION*

Nobubelo.Ngandu@mrc.ac.za