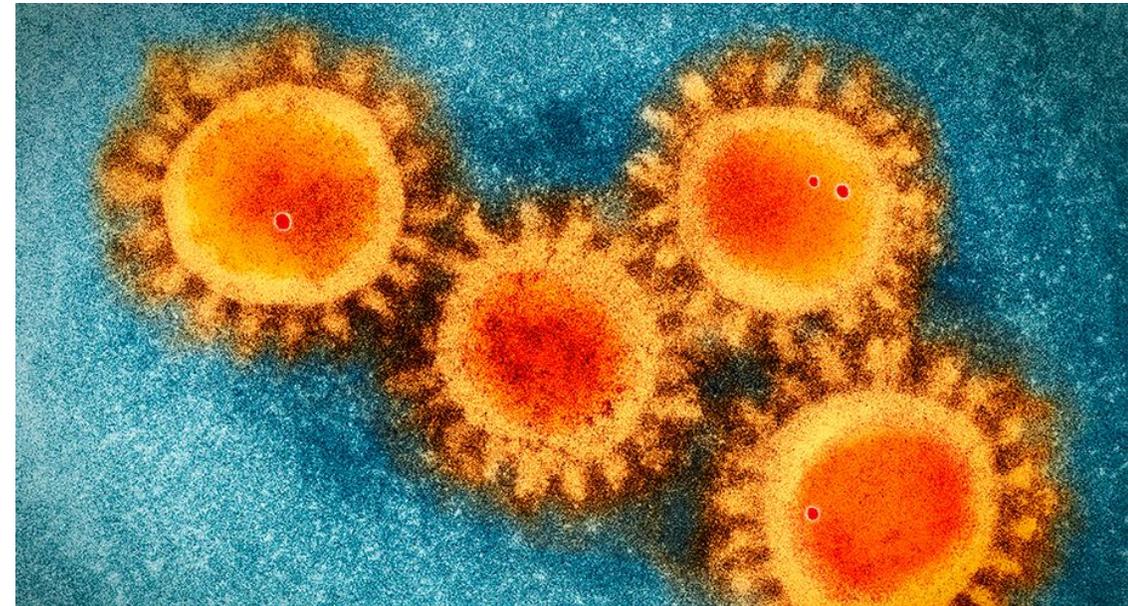


# Covid 19

## views from an integrative physicians perspective



Dr Tim Ewer  
Dr Christabelle Yeoh  
Dr Sandeep Gupta

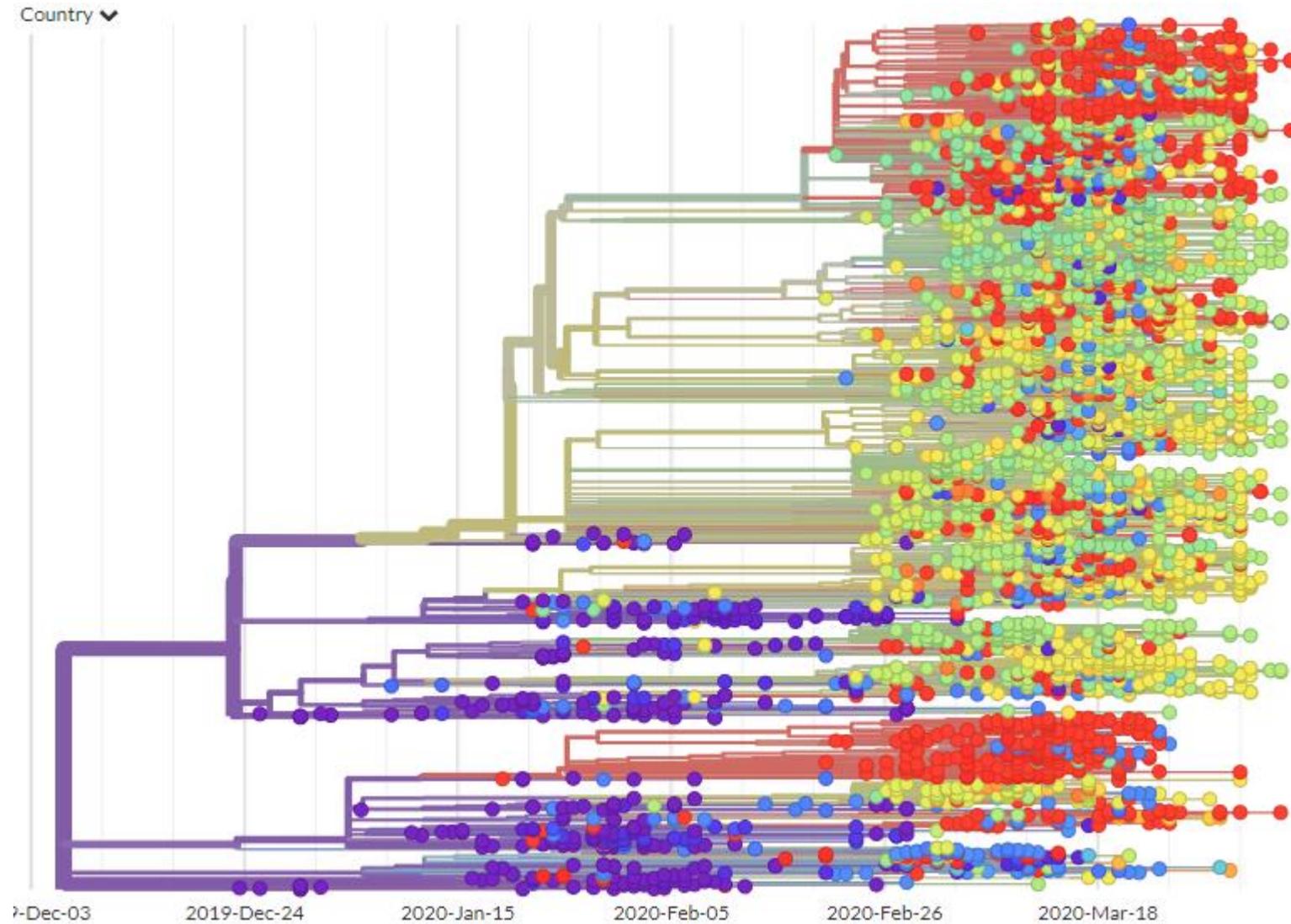
# Important caveats

- Important to follow Ministry of Health guidelines on prevention, containment and treatment of COVID-19
- We are not a virologists or infectious disease physicians
- There is very little high quality research on treatment for COVID-19
- We may extrapolate from studies on other corona virus outbreaks and related research, as well as scientific opinions
- Please do not interpret this discussion as recommendations for treatment
- It is important to get appropriate medical help if unwell

# Genomic epidemiology of novel coronavirus



# Phylogeny



# Sunlight destroys virus quickly

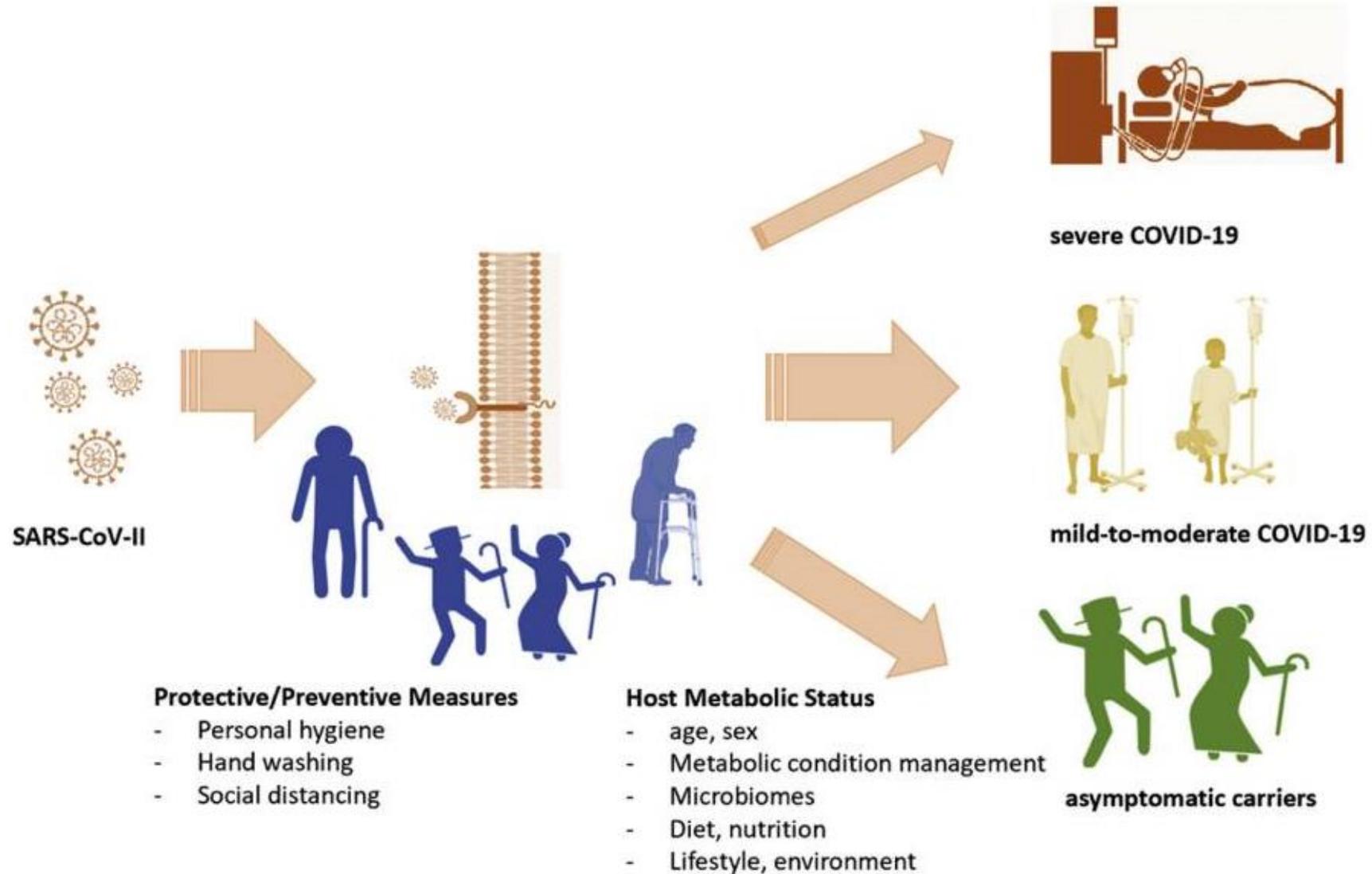
- Preliminary results from National Biodefense Analysis and Countermeasures Center experiments show
  - coronavirus does not survive long in high temperatures and high humidity, and is quickly destroyed by sunlight
  - outdoor daytime environments are lower risk for transmission
  - whereas, areas with low humidity, such as airplane cabins, may require additional care to minimize risk of transmission

# Air conditioning appears to spread coronavirus— but opening windows could stop it

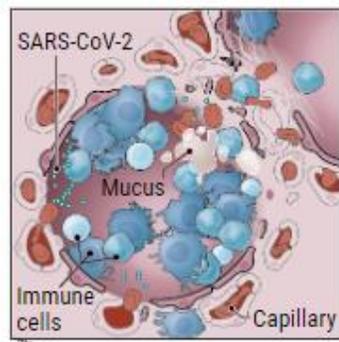
- Experts in health, the built environment and microbiology at the University of Oregon and the University of California, Davis, made recommendations by reviewing existing studies including SARS-CoV-2
- "For most buildings, the easiest way to deliver outside air directly across the building envelope is to open a window"



# Individual risk management strategies



# How does coronavirus kill?



## 1 Lungs

A cross section shows immune cells crowding an inflamed alveolus, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fevers rise, and it takes more and more effort to breathe.

## 2 Liver

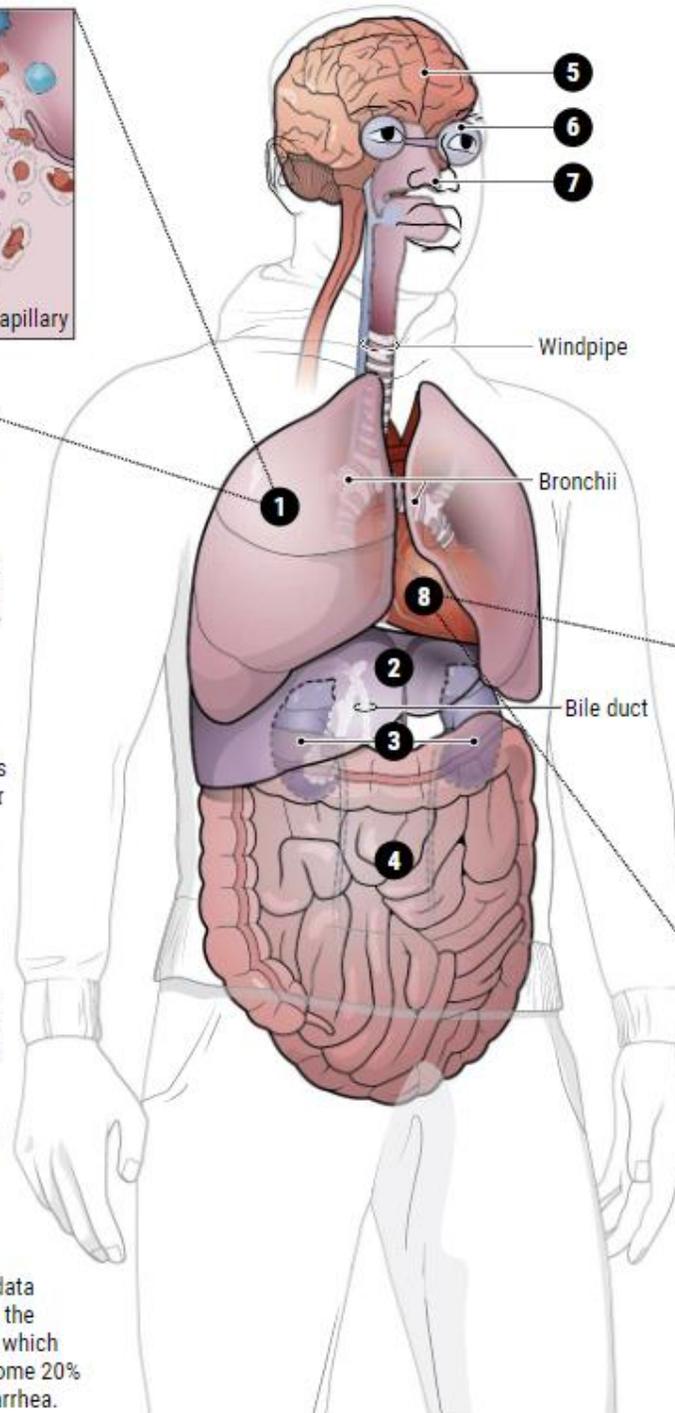
Up to half of hospitalized patients have enzyme levels that signal a struggling liver. An immune system in overdrive and drugs given to fight the virus may be causing the damage.

## 3 Kidneys

Kidney damage is common in severe cases and makes death more likely. The virus may attack the kidneys directly, or kidney failure may be part of whole-body events like plummeting blood pressure.

## 4 Intestines

Patient reports and biopsy data suggest the virus can infect the lower gastrointestinal tract, which is rich in ACE2 receptors. Some 20% or more of patients have diarrhea.



## 5 Brain

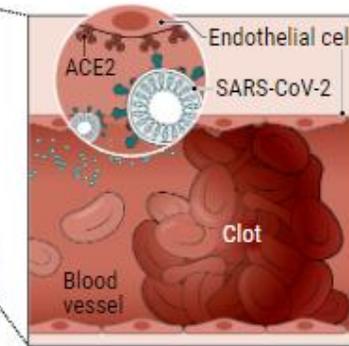
Some COVID-19 patients have strokes, seizures, mental confusion, and brain inflammation. Doctors are trying to understand which are directly caused by the virus.

## 6 Eyes

Conjunctivitis, inflammation of the membrane that lines the front of the eye and inner eyelid, is more common in the sickest patients.

## 7 Nose

Some patients lose their sense of smell. Scientists speculate that the virus may move up the nose's nerve endings and damage cells.



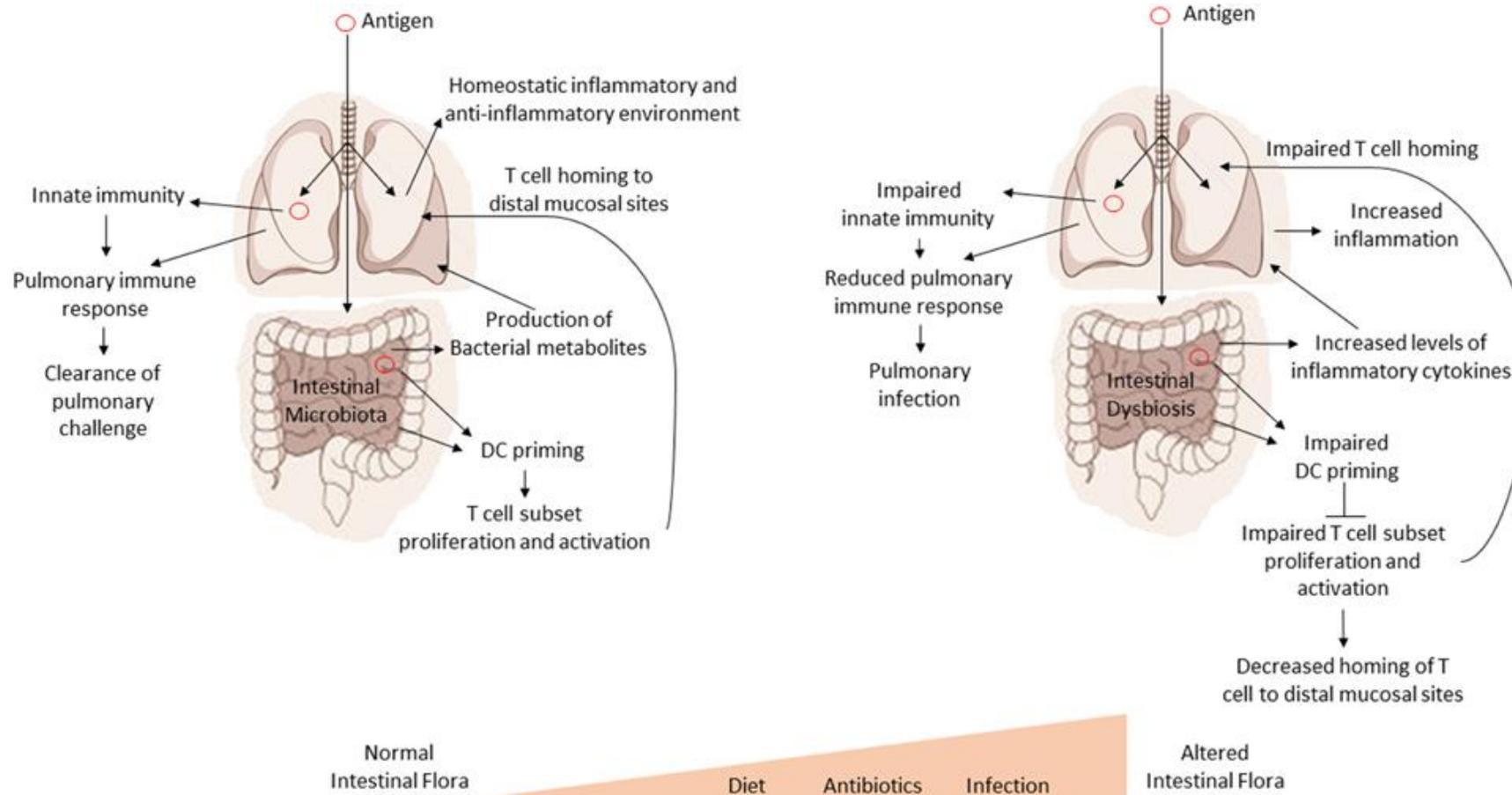
## 8 Heart and blood vessels

The virus (green) enters cells, likely including those lining blood vessels, by binding to ACE2 receptors on the cell surface. Infection can also promote blood clots, heart attacks, and cardiac inflammation.

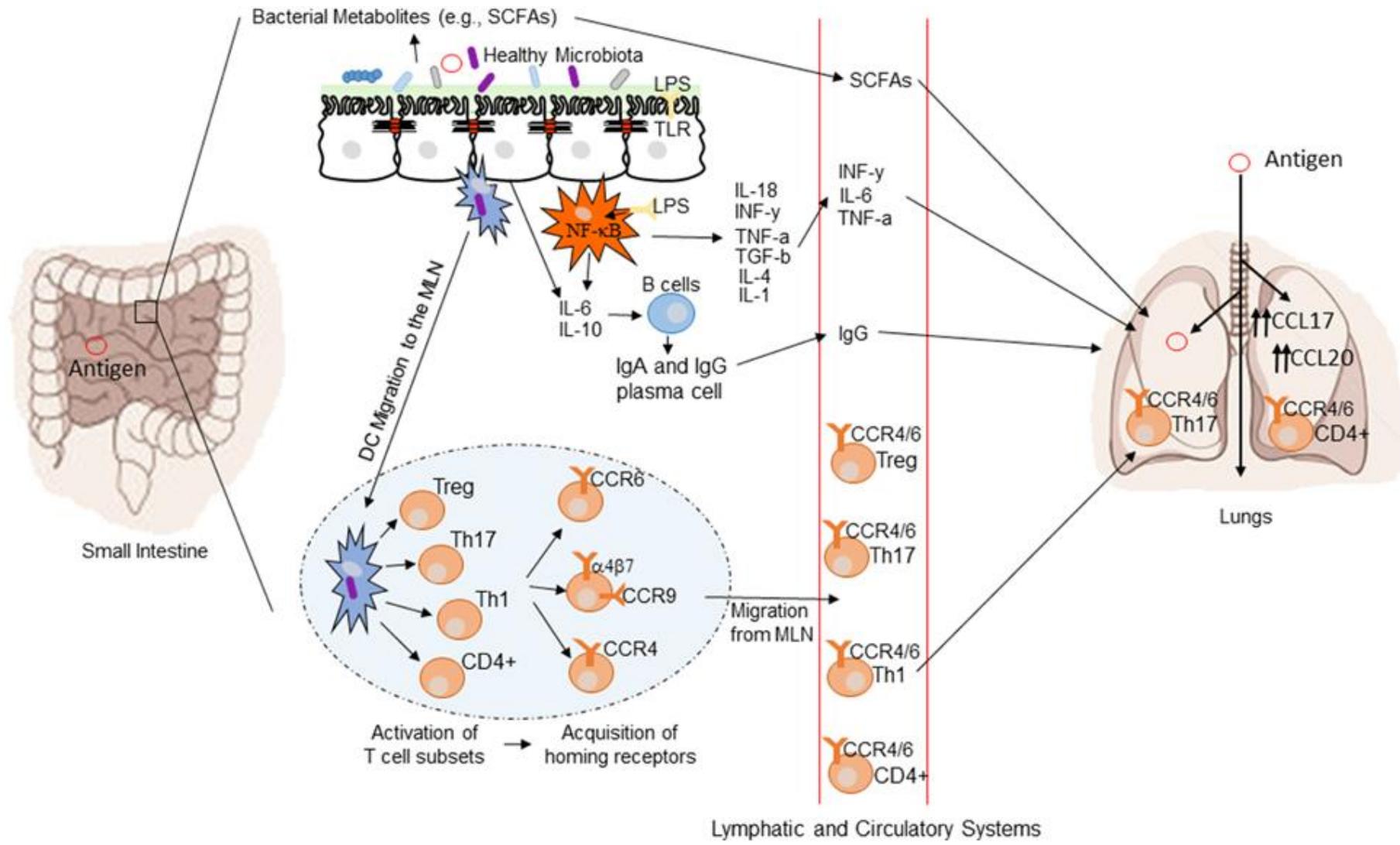
# Changes in the elderly

- high pro-inflammatory immune responses and low adaptive immune responses
- clinical or subclinical micronutrient deficiency is common in older adults
- respiratory tract microbiota influences immune response and affected by age
- respiratory viral infections disrupt the host-microbiota interactions and create the intestinal dysbiosis with the post-viral immune responses, that contribute to pneumonia development by the secondary bacterial infection

# Effects of the GI Microbiota on Pulmonary Health



# Gut-lung axis



## CURRENT METHODS FOR TARGETING THE INTESTINAL MICROBIAL FOR TREATMENT OF RESPIRATORY DISEASES

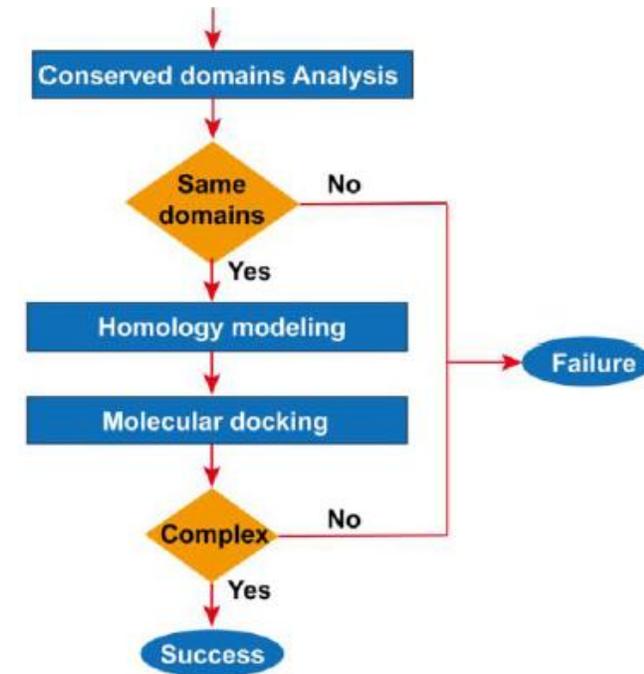
- Probiotics (Commonly used probiotics)
    - *Lactobacillus gasseri*
    - *Lactobacillus rhamnosus*
    - *Lactobacillus casei*
    - *Lactobacillus acidophilus*
    - *Bifidobacterium lactis*
    - *Lactobacillus delbrueckii subsp. Bulgaricus*
    - *Streptococcus thermophiles*
    - *Bifidobacterium bifidum*
    - *Bifidobacterium breve*
  - Oral vaccines against Respiratory Pathogens
    - *Mycobacterium* spp.
    - *Francisella tularensis*
    - *Brucella melitensis*
    - *Mycobacterium tuberculosis*
  - Probiotic coupled vaccines (Probiotics commonly used as adjuvants)
    - *Lactococcus lactis*
    - *Lactobacillus rhamnosus*
    - *Bifidobacterium animalis*
    - *Lactobacillus paracasei*
- Enhanced phagocytosis level during normal conditions
  - Suppressed levels of phagocytosis during allergic conditions
  - Enhance the production of antigen-specific IgG and IgA antibodies
  - Suppressed the proliferation of mononuclear cells during inflammation
  - Reduced burden of pathogens in the lung
  - Prevents dissemination to the blood
  - Increased  $INF\gamma$ , IL-6, IL-4, TNF- $\alpha$  and IL-10 levels in BAL
  - Increased natural killer cell activity
  - Increased levels of serum antibodies
  - Increased production of IL-2 and  $INF\gamma$  from splenocytes
  - Increased levels of antigen-specific antibodies in BAL fluid
  - Enhanced proliferation of antigen-specific  $INF\gamma$  producing cells
  - Significant reduction in pathogen burden in the lung following infection
  - Increased antigen-specific IgM, IgG (IgG1 and IgG2), and IgA antibodies
  - Serum, BAL, and intestinal lavage fluids.
  - Stimulation of both Th1 and Th2 responses
  - Increased production of both  $INF\gamma$  and IL-4.
  - Induces a cross-protective immunity to multiple serotypes
  - Can be enhanced by a prime-boost vaccination strategy

# How COVID-19 Affects the Brain

- review of 214 hospitalized patients
  - CNS (24.8%) - hypogeusia (5.6%) and hyposmia (5.1%)
  - PNS (8.9%)
  - skeletal muscle symptoms (10.7%)
  - dizziness (16.8%)
  - headache (13.1%)
  - ischaemic stroke in 5% of another series and 1 encephalopathy
  - with smell and taste loss, more than 10 times more likely to have COVID-19
- SARS-CoV-2 might enter nervous system via ACE2 receptor, which is present in glial cells, neurons, skeletal muscle, and other organs
- still unclear whether these symptoms result from direct injury or possibly causing immune-mediated neural injury

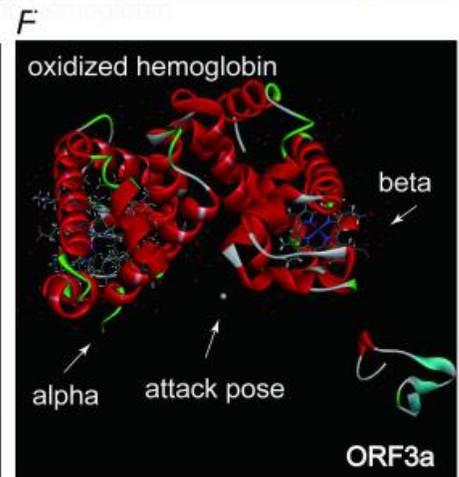
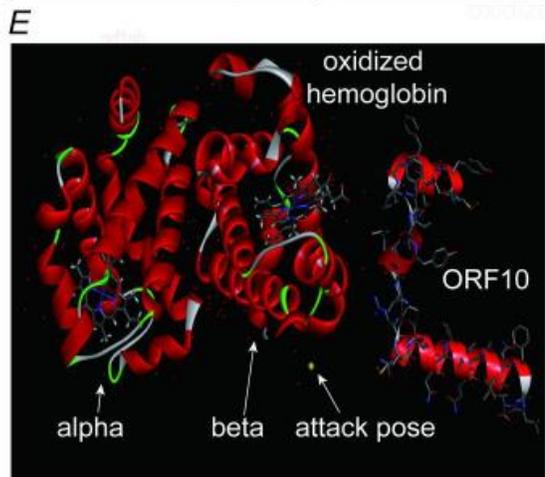
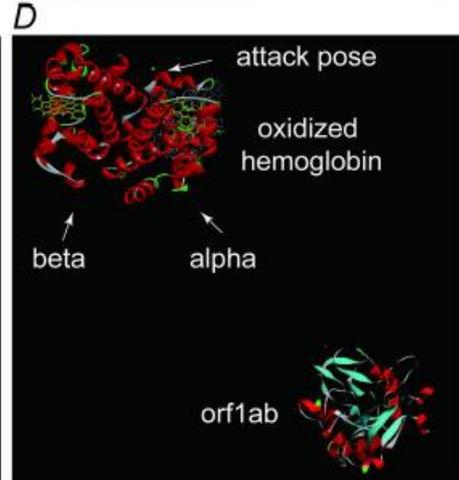
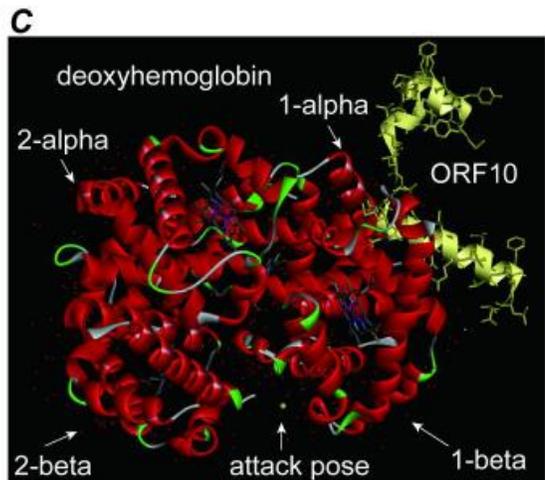
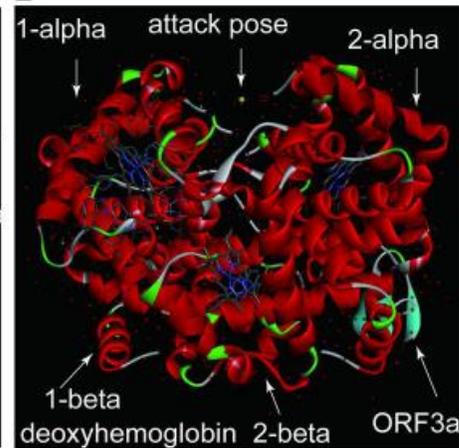
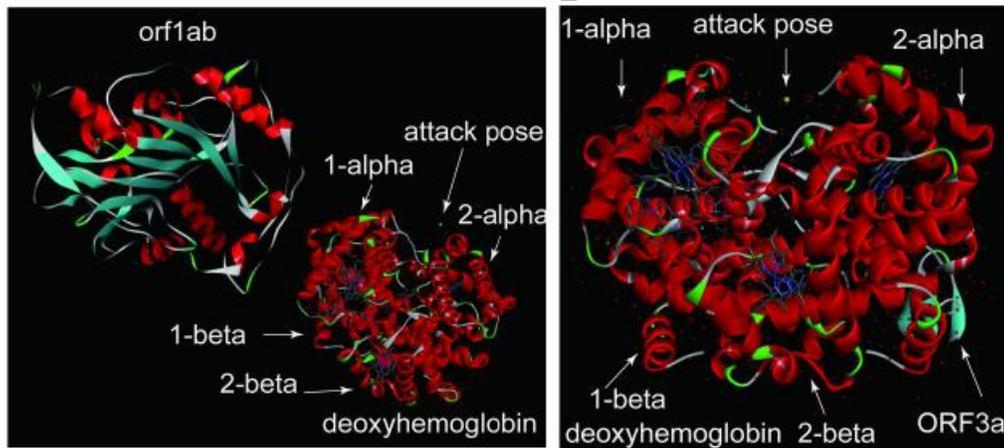
# COVID-19 attacks 1-beta chain of hemoglobin and captures porphyrin to inhibit human heme metabolism

- domain analysis and homology modeling
- ORF8 and surface glycoprotein could bind to the porphyrin
- orf1ab, ORF10, and ORF3a proteins could coordinate attack on the 1-beta chain of hemoglobin to dissociate the iron to form the porphyrin
- will cause less and less hemoglobin available to carry oxygen
- chloroquine could prevent orf1ab, ORF3a, and ORF10 attack



# Viral non-structural protein attack hemoglobin

- **A.** orf1ab attacks the deoxyhemoglobin
- **B.** ORF3a attacks the deoxyhemoglobin
- **C.** ORF10 attacks the deoxyhemoglobin
- **D.** orf1ab attacks the oxidized hemoglobin
- **E.** ORF10 attacks the oxidized hemoglobin
- **F.** ORF3a attacks the oxidized hemoglobin



# Flawed methods in study

- Randy J Read, Department of Haematology, University of Cambridge
- no experimental evidence is provided to support any of conclusions
- computational results do not hold up or provide support for hypotheses
- when interpreted correctly, there is no evidence for these shared functional domains

# What's in the (shortened) pipeline

- **Remdesivir**

- originally used for Ebola virus and other highly contagious diseases
- works to prevent human cells from infection with SARS-CoV-2
- clinical trials in China, USA and Europe
- University of Chicago Medicine open trial of 125 participants, 113 with severe disease - only two patients died, and the rest have been discharged

- **Chloroquine and hydroxychloroquine**

- confounds ability of SARS-CoV-2 virus to enter and replicate in human cells
- clinical trials of these agents for both pre- and post-exposure prophylaxis
- FDA has issued an Emergency Use Authorization in adults and adolescents

# “No Hydroxychloroquine Benefit in Small, Randomized COVID-19 Trial”

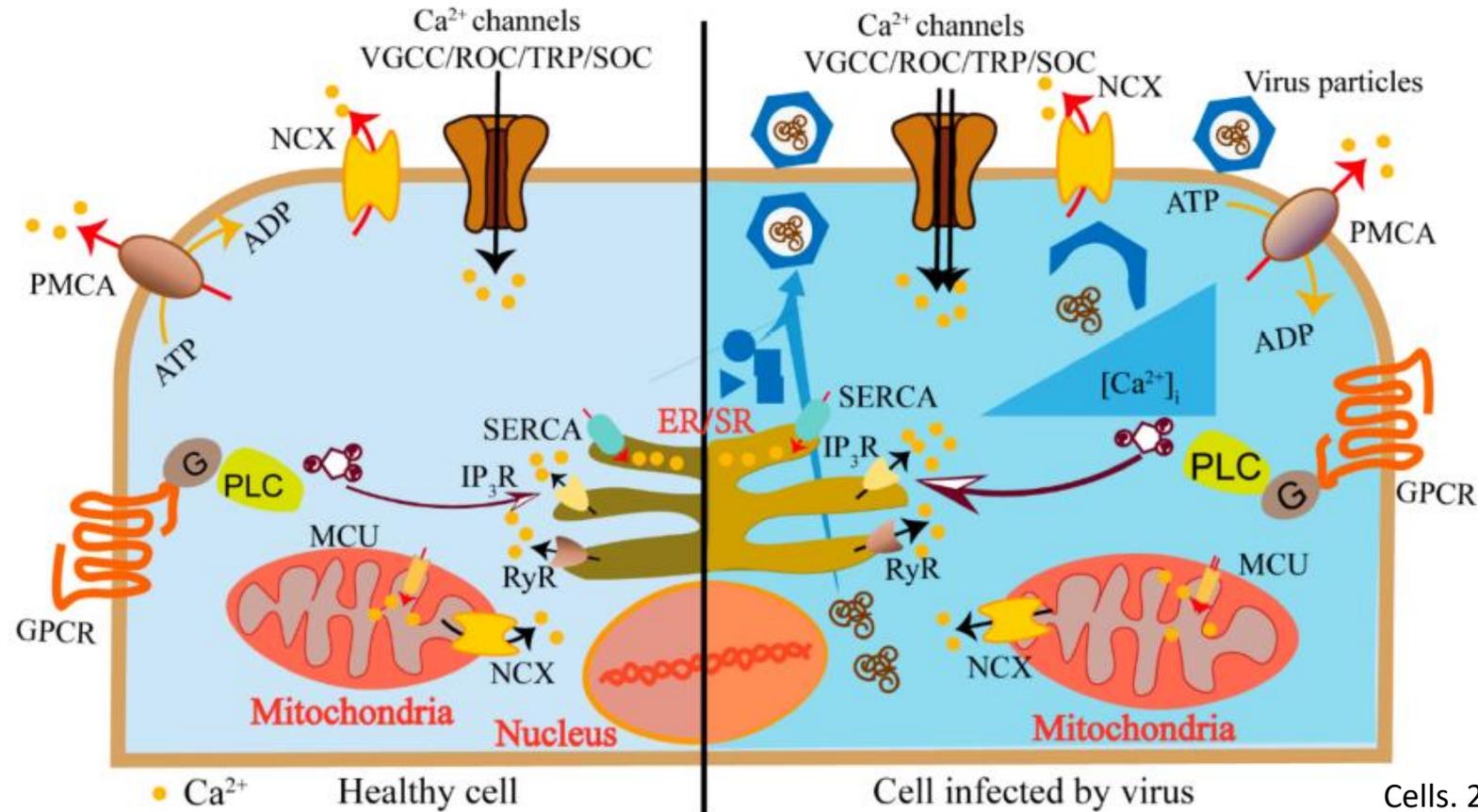
- RCT of 150 adult patients hospitalized for COVID-19
- loading dose of 1, 200 mg daily 3/7 followed by 800 mg daily (2 or 3 weeks for mild/moderate or severe patients, respectively)
- no difference in 28-day negative conversion rate of SARS-CoV-2
- significant efficacy of HCQ on alleviating symptoms after adjusting for the confounding effects of antiviral agents
- significantly greater reduction of CRP
- adverse events were found in 8.8% of SOC and 30% of HCQ (2 serious)
- (Australian doctors face a \$13,000 fine if prescribe HCQ for COVID-19)

# Hydroxychloroquine Mechanism of Action

- Immune modulatory effects
- Alkalinizes vacuolar & lysosomal pH
  - It is alkaline
  - Inhibits protozoal food vacuole functioning
  - Inhibits endocytosis, liposomal fusion and function
- Is a zinc ionophore
  - Allows influx of zinc into cells and lysosomes
- Binds to sialic acid

- **Colchicine**
  - usefulness in mitigating the cytokine storm and overproduction of immune cells
- **Sarilumab and Tocilizumab**
  - interleukin (IL)-6 inhibitors
  - possible ability to calm the cytokine storm
- **Losartan**
  - blocks the ACE2 receptor, to which SARS-CoV-2 binds
  - however, could actually induce the body to make more ACE2
  - RCT's ongoing re preventing multi-organ failure in patients hospitalized
- **EIDD-2801**
  - investigational agent introducing genetic mutations into coronavirus' RNA
  - damaged mutations accumulate and render the virus unable to infect
  - preclinical studies - effective against strains of influenza, RSV & chikungunya
- **Plasma-derived therapy**
  - FDA currently expediting use for seriously ill patients

# Calcium Channels in Viral Infections



- Calcium channel blocker amlodipine besylate is associated with reduced case fatality rate of COVID-19 patients with hypertension

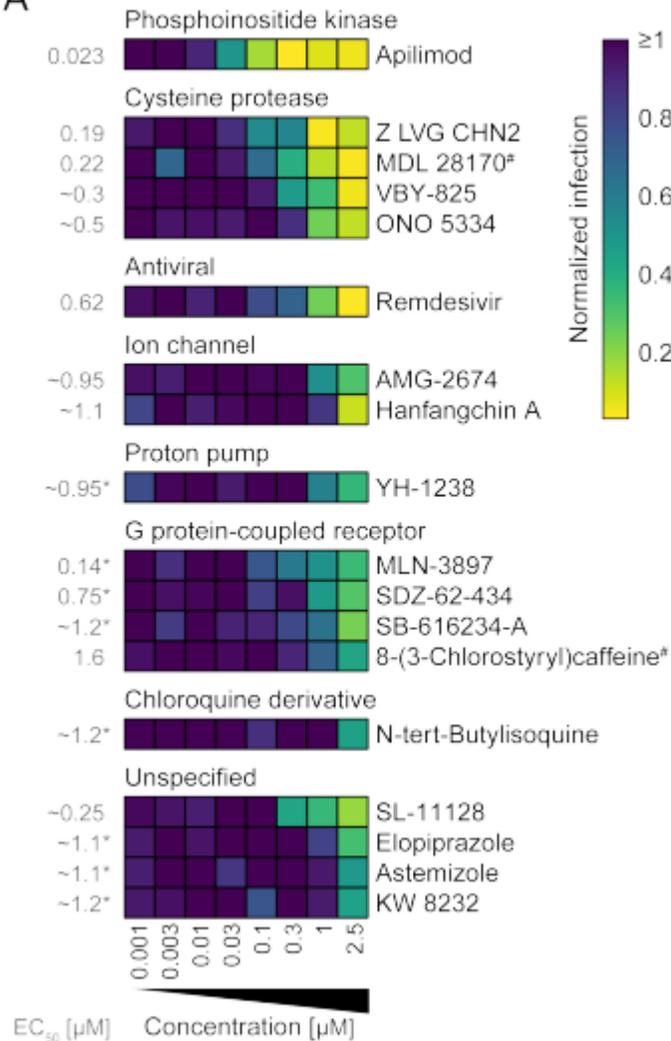
# Metronidazole - a Potential Novel Addition

<b>COVID-19</b>	<b>Metronidazole</b>
↑ IL8 (5)	↓ IL8 (10-13)
↑ IL6 (6, 8)	↓ IL6 (10-15)
↑ IL1B (5)	↓ IL1B (10-15)
↑ TNF $\alpha$ (5)	↓ TNF $\alpha$ (11-13, 15-17)
↑ CRP (6)	↓ CRP (11, 12)
↑ IL12 (21)	↓ IL12 (11, 13, 14)
↑ IFN $\gamma$ (5)	↓ IFN $\gamma$ (11, 14, 16)
↑ Neutrophils (5, 6)	↓ Neutrophils (11, 17, 18)
↓ Lymphocytes (5, 6, 8)	↑ Lymphocytes (11, 17), lymphoproliferative proper- ties (11, 19)

CRP: C-reactive protein; IFN: interferon; IL: interleukin;  
TNF: tumor necrosis factor.

# Large-scale Drug Repositioning Survey for SARS-CoV-2 Antivirals

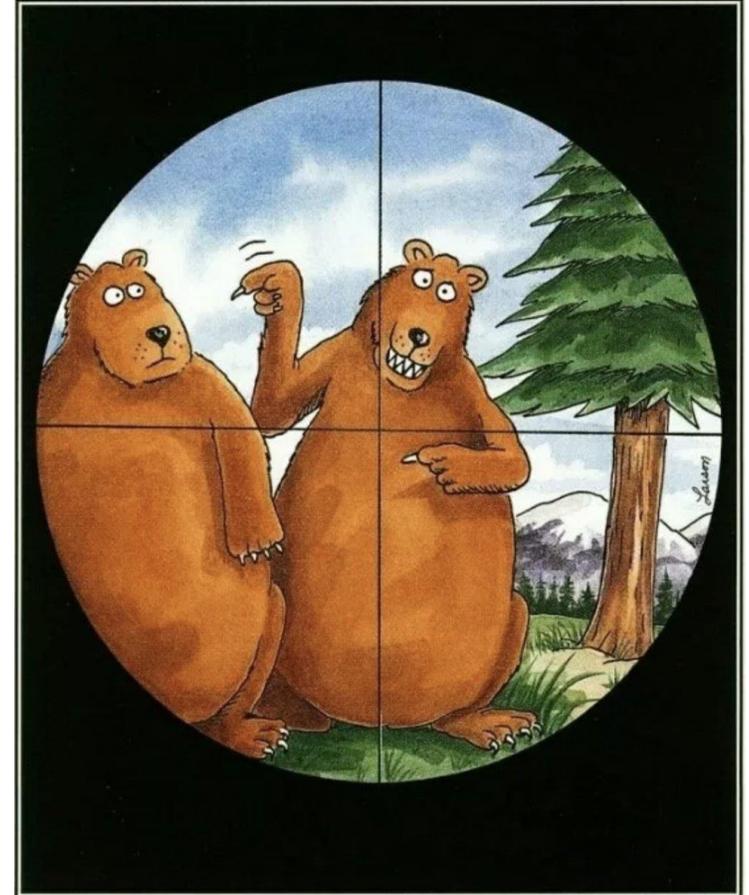
A



- Reviewed 12,000 clinical-stage small molecules
- 30 known drugs that inhibit viral replication
- 6 likely to be commensurate with therapeutic doses in patients
- PIKfyve kinase inhibitor Apilimod, cysteine protease inhibitors MDL-28170, Z LVG CHN2, VBY-825, and ONO 5334, and the CCR1 antagonist MLN-3897

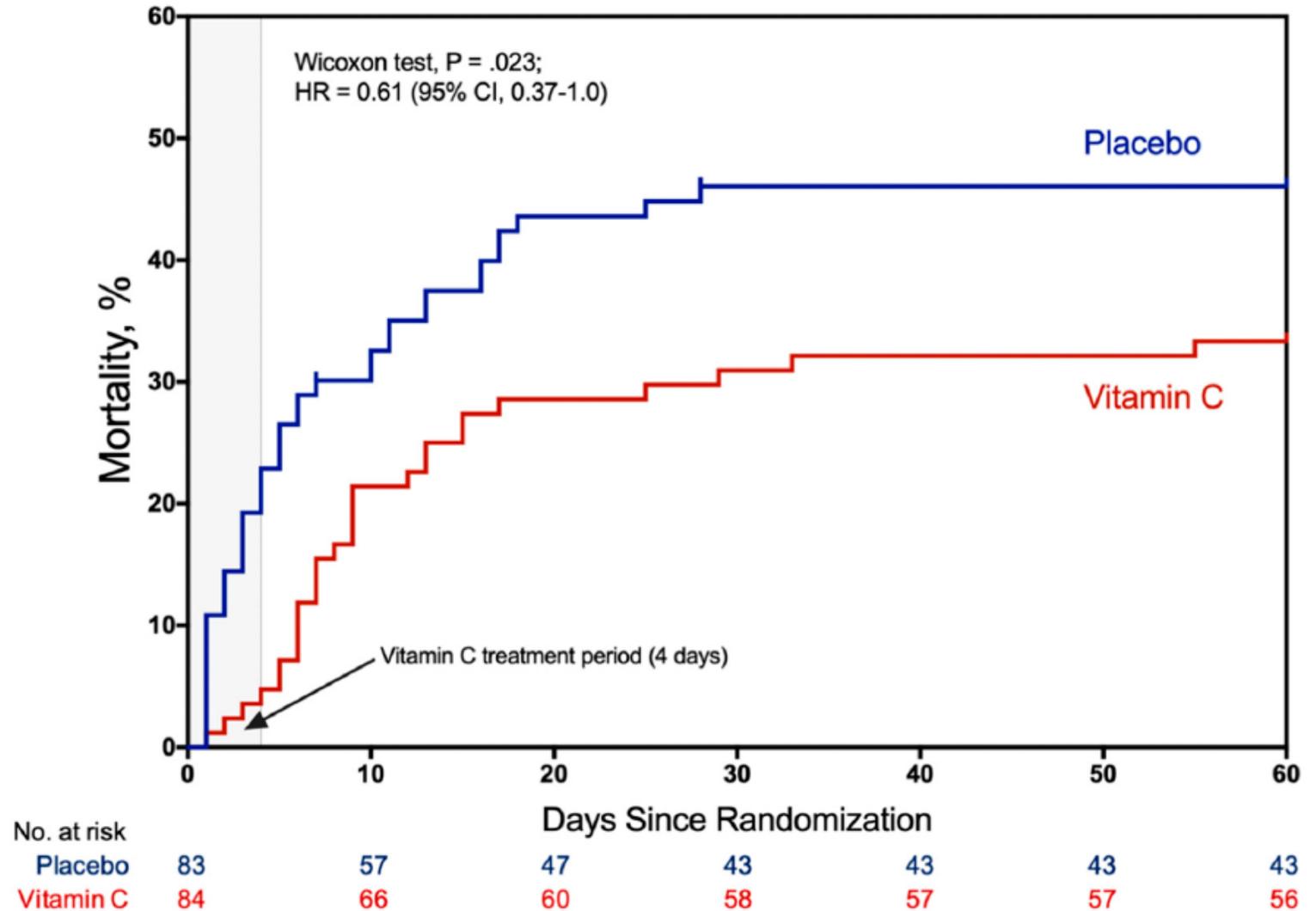
# Following slides may be more contentious

- these slides have limited evidence
- or are simply opinions
- or are examples of possibilities which may be proven incorrect
- and do not necessarily reflect my own or AIMA's position



# CITRIS-ALI Randomized Clinical Trial

- 167 patients in ICU
- IVC 50 mg/kg every 6 hours for 96 hours
- Failed to improve organ dysfunction scores or inflammatory markers
- 28-day mortality was 29.8% in the vitamin C group versus 46.3% in the placebo group
- most dramatic reduction in mortality was noted during the period of HDIVC infusion



# IVC RCT in Wuhan

- 140 patients with a placebo control or IVC
- 24g/day for 7 days
- assess requirements for mechanical ventilation and vasopressor drugs, organ failure scores, ICU length of stay and 28-day mortality
- complete the trial by the end of September

Crit Care. 2020; 24: 133

# U.S. Hospitals Use IVs of Vitamin C

- *“If you can administer Vitamin C intravenously starting in the Emergency Room and every 6 hours thereafter, while in the hospital, the mortality rate of this disease and the need for mechanical ventilators will likely be greatly reduced”*
- Dr. Pierre Kory, the Medical Director of the Trauma and Life Support Center and Chief of the Critical Care Service at the University of Wisconsin
- Dr. Marik HAT protocol (IV hydrocortisone, ascorbic acid, thiamine)

<https://www.worldhealth.net/news/3-us-hospitals-use-ivs-vitamin-c-other-low-cost-readily-available-drugs/>

# Are bacteria increasing the virulence of COVID-19?

- Two distinct phases of the virus with initial more typical viral infection symptoms and then more virulently appears in the lungs
- Prevotella species are anaerobic Gram-negative bacteria of the Bacteroidetes extensively present throughout the human body
- linked to inflammatory disorders, periodontitis, RA, IBD
- Th17, IL-8, IL-6 activation – indicator of cytokine storm in COVID-19
- Prevotella is showing up in sequencing data from China + elsewhere
- is COVID-19 a bacteriophage?

# Professor Luc Montagnier

## 2008 Nobel Prize winner for Medicine



- Chinese researchers are said to have used coronaviruses in their work to develop an AIDS vaccine
- HIV DNA fragments are believed to have been found in the SARS-CoV-2 genome
- “With my colleague, bio-mathematician Jean-Claude Perez, we carefully analyzed the description of the genome of this RNA virus”
- “SARS-CoV-2 is a virus that was manipulated and accidentally released from a laboratory in Wuhan, China, in the last quarter of 2019”

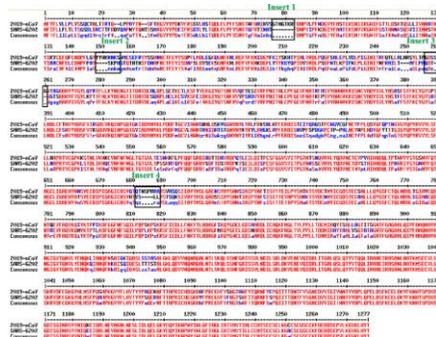
# Wuhan Institute of Virology

- opened in 2018 with the founder of a French bioindustrial firm, Alain Merieux, acting as a consultant in its construction
- largest virus bank in Asia which preserves more than 1,500 strains
- maximum security lab equipped to handle Class 4 pathogens (Ebola, etc)



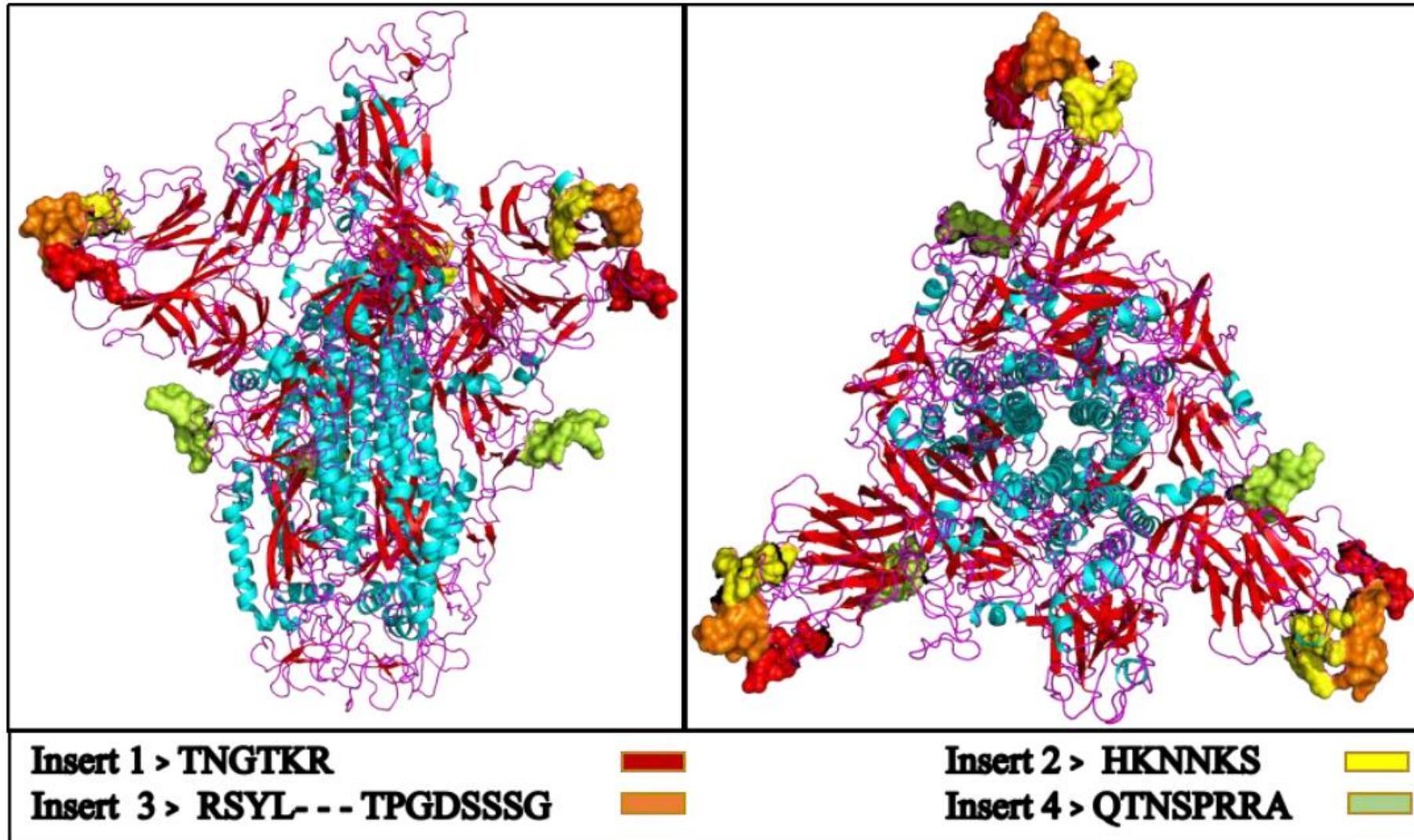
# Uncanny similarity of unique inserts in the 2019-nCoV spike protein to HIV-1 gp120 and Gag

- We found 4 insertions in the spike glycoprotein (S) which are unique to the 2019-nCoV and are not present in other coronaviruses
- Importantly, amino acid residues in all the 4 inserts have identity or similarity to those in the HIV-1 gp120 or HIV-1 Gag
- The finding of 4 unique inserts in the 2019-nCoV, all of which have identity /similarity to amino acid residues in key structural proteins of HIV-1 is unlikely to be fortuitous in nature



bioRxiv preprint doi: <https://doi.org/10.1101/2020.01.30.927871> bioRxiv preprint

# Modelled homo-trimer spike glycoprotein of 2019-nCoV virus



# HIV-1 did not contribute to 2019-nCoV genome

- ...conspiracy theories that the new pathogens are man-made often surface as the source
- lack of the definite origin of 2019-nCoV has led to speculation that 2019-nCoV might be derived from genetic manipulation or even for the purpose of use as a bioweapon
- however, while the 100% match between the insertion 1 and 2 sequences and the HIV sequences were found in 19 entries, the matches between the insertion 3 and 4 sequences and HIV-1 sequences were rather poor (from 42% to 88%)

# Generation of a coronavirus-based multigene AIDS vaccine

- EU project AIDS-COVAC aimed to generate a novel coronavirus-based HIV vaccine vector that would target DCs
- Researchers decided to use human coronavirus vectors as vaccine delivery systems since they possess certain desirable features
- Pre-clinical data are encouraging for the further exploitation of coronavirus vectors

[Clin Dev Immunol.](#) 2006 Jun-Dec;13(2-4):353-60

<https://cordis.europa.eu/article/id/90846-new-approach-to-vaccine-for-aids>

# Influenza vaccination and respiratory virus interference

- Department of Defense personnel during the 2017-2018 influenza season
- compared vaccination status of 2880 people with non-influenza respiratory viruses to 3240 people with pan-negative results
- vaccine derived virus interference was significantly associated with coronavirus
- *this means that influenza vaccine increases the risk of coronavirus infection*

Vaccine. 2020 Jan 10;38(2):350-354.

- A randomized placebo-controlled trial in children showed that flu shots increased fivefold the risk of acute respiratory infections caused by a group of non-influenza viruses, including coronaviruses

Clin Infect Dis. 2012 Jun 15; 54(12): 1778–1783

- Cohort sub-analysis of children and adults in the MoSAIC community surveillance study from 2013 to 2016
- there was an increase in non-influenza respiratory pathogens post-influenza vaccination compared to unvaccinated children

Vaccine. 2018 Apr 5;36(15):1958-1964

- Latest Cochrane review of influenza vaccine 2016
- vaccines can reduce the proportion of healthy adults who have influenza and ILI, but their impact is modest
- we are uncertain about the effects of vaccines on working days lost or serious complications of influenza during influenza season

[https://www.cochrane.org/CD001269/ARI\\_vaccines-prevent-influenza-healthy-adults](https://www.cochrane.org/CD001269/ARI_vaccines-prevent-influenza-healthy-adults)

# Coronavirus Cases, March 26, 2020

- **Coronavirus Cases:** 2,482,550 (NZ 1,451 )
- **Currently Infected:** 1,659,592 (NZ 439)
- **New Cases:** 2,047+ (NZ 6)
- **Mild Condition:** 1,602,237
- **Serious or Critical:** 57,355
- **Deaths:** 170,479 (NZ 14)
- **Recovered:** 652,479 (NZ 1,036 )

<https://www.worldometers.info/coronavirus/>

# “No evidence that Covid-19 is causing huge loss of life”

- Professor Michael Levitt, a Nobel laureate and Stanford biophysicist, says there is no clear evidence that Covid-19 is causing massive loss of life
- people who are dying from coronavirus are those who are at risk of death anyway

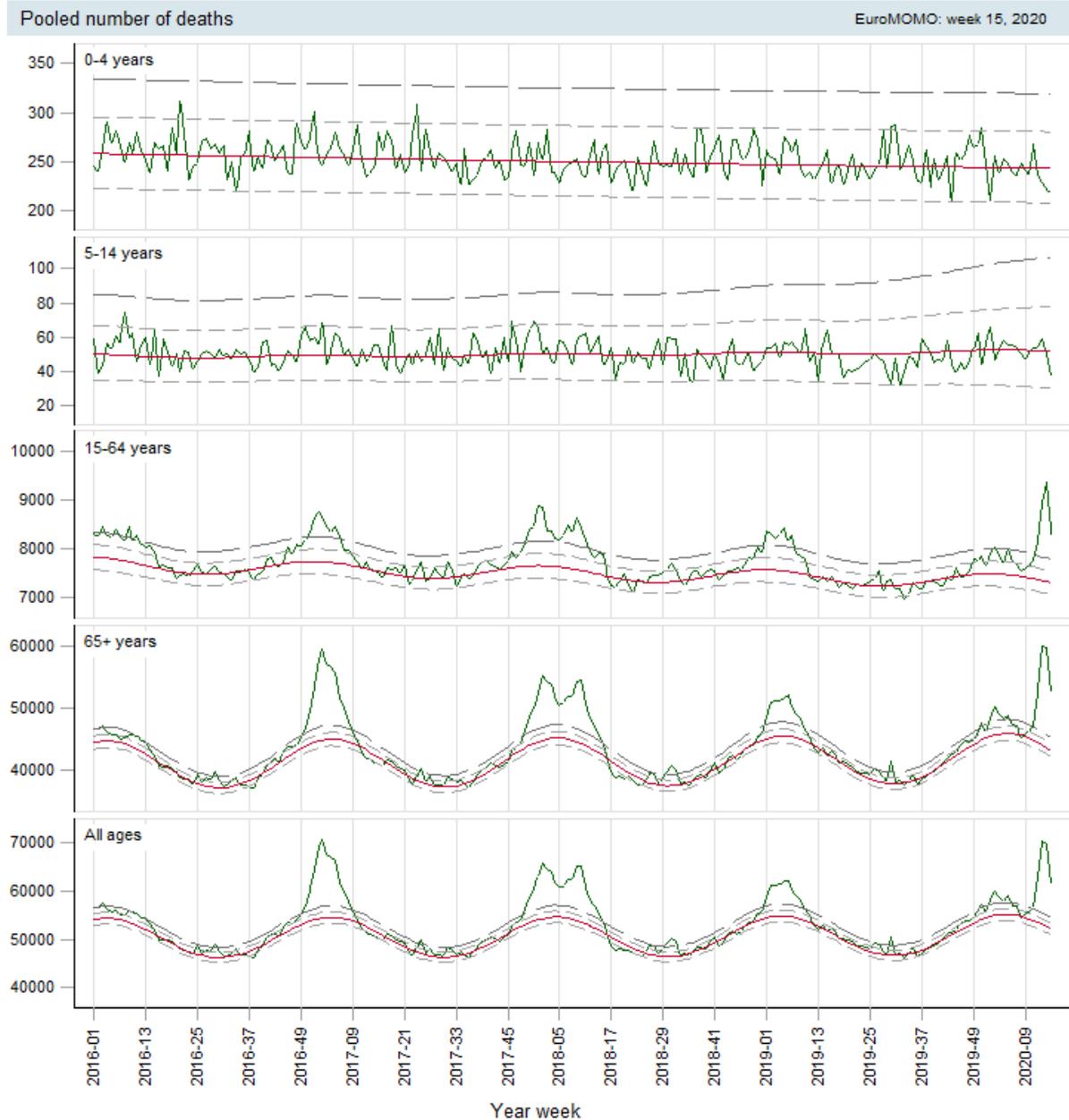


<https://www.rnz.co.nz/national/programmes/sunday/audio/2018743210/no-evidence-that-covid-19-is-causing-huge-loss-of-life>

# SARS-CoV-2: fear versus data

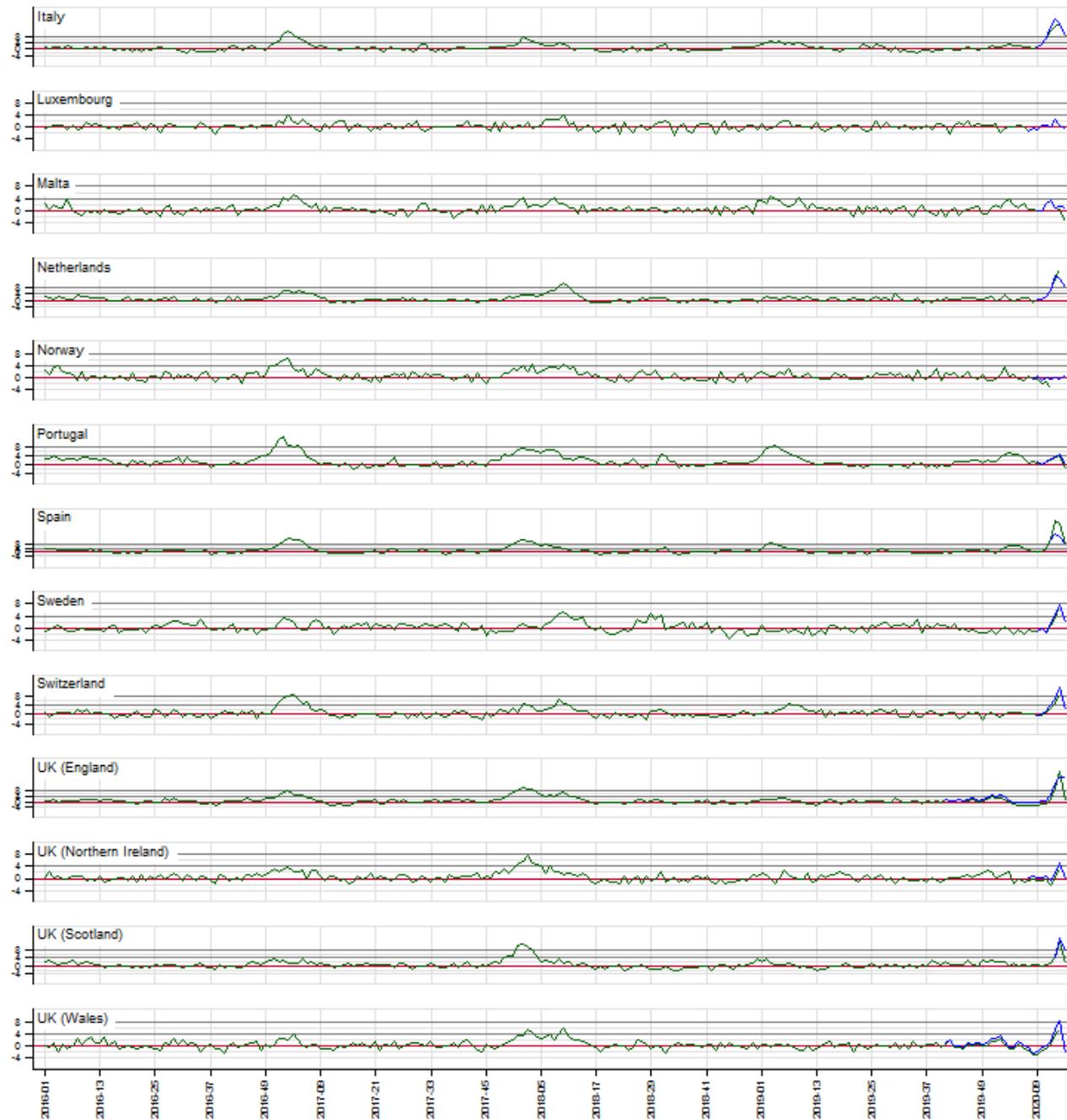
- Four common coronaviruses are in current circulation and cause millions of cases worldwide
- 16 endemic viruses in common circulation in developed countries
  - (adenovirus, bocavirus, cytomegalovirus, enterovirus, influenza A H1N1 virus, influenza A H3N2 virus, influenza B virus, metapneumovirus, parainfluenzae virus 1, parainfluenzae virus 2, parainfluenzae virus 3, parainfluenzae virus 4, parechovirus, picornavirus, rhinovirus, syncytial respiratory virus)
- 2.6 million people die of respiratory infections each year

# Deaths in Europe 2016-2020



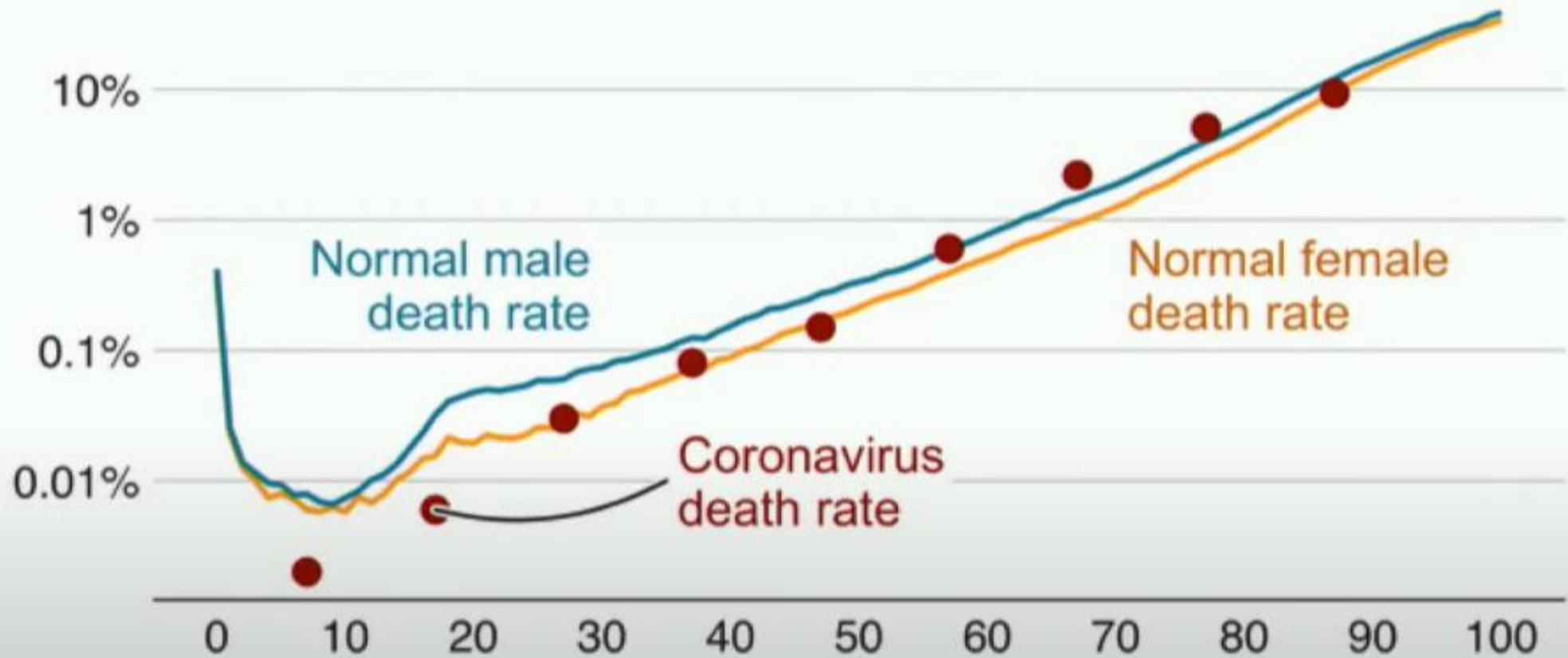
<https://www.euromomo.eu/>

— Stratified baseline — Delay-adjusted number of deaths  
- - - Normal range (+- 2 z-scores) - - - Substantial increase (4 z-scores)



These slides have limited evidence, or are simply opinions, or are examples of possibilities which may be proven incorrect and do not necessarily reflect my own or AIMA's position

# Risk of dying each year by age (GB)



Log scale used to see differences in rates at younger ages

Source: Prof. Sir David Spiegelhalter, ONS, Imperial College London



# Sweden Nearing Herd Immunity to Virus

- "we have reached a plateau [in new cases] and we're already seeing the effect of herd immunity,"
- 20% of the population in Stockholm, the location of most of the country's 15,000 confirmed cases, is already immune to the coronavirus
- "we're seeing a slow decline in cases, in spite of sampling (testing for the coronavirus) more and more" - chief epidemiologist, Dr. Anders Tegnell of Sweden's Public Health Agency



A background image of a waterfall with white water cascading over rocks. The text is overlaid on this image.

**NOT an overreaction**

New Zealand (4.8 Million)

Ireland (4.9 Million)

*First reported cases:*

NZ 28th March

Ireland 29th March

**As at 18th April 2020**

NZ 1094 confirmed cases

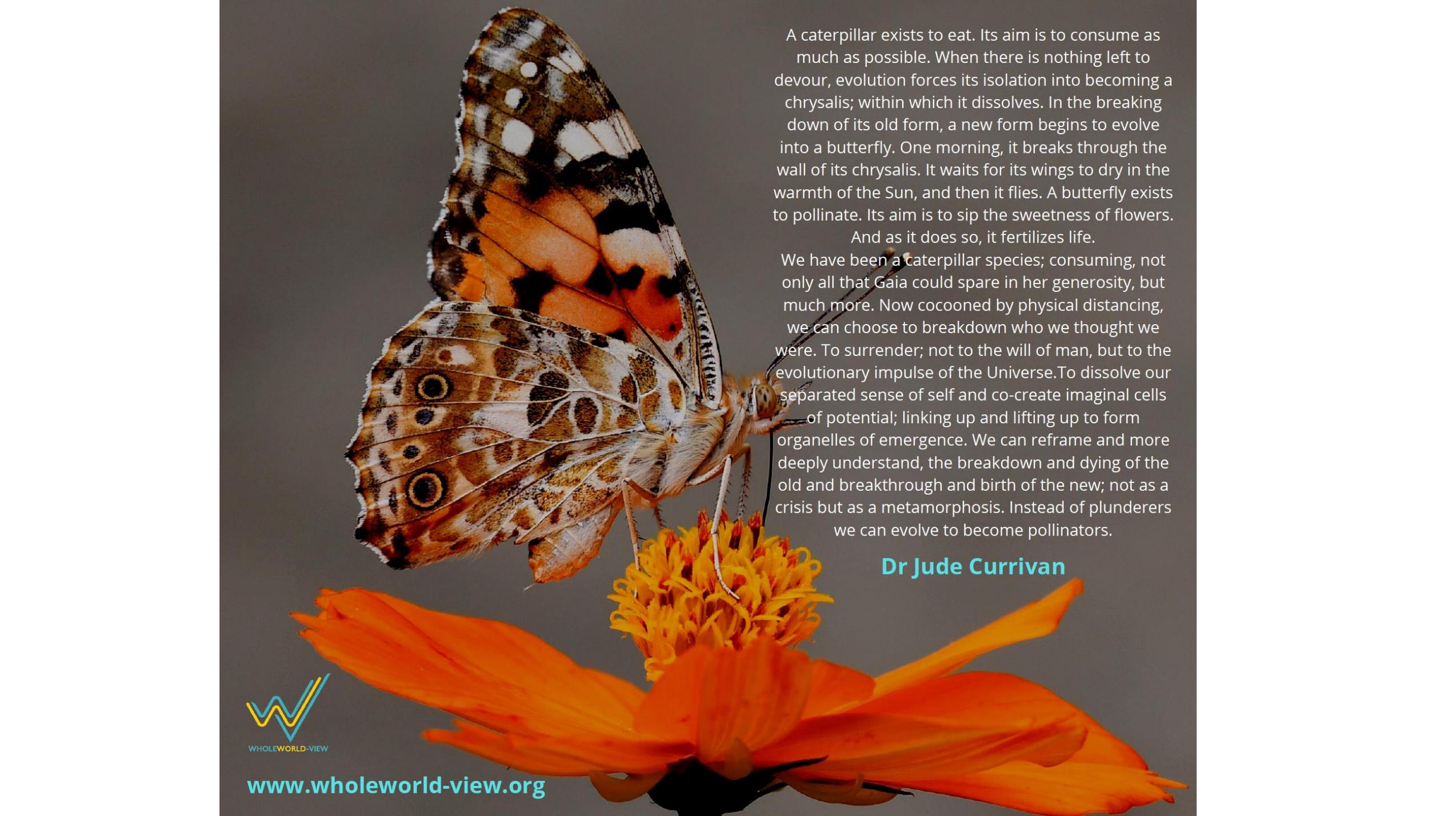
11 Deaths

Ireland 14,758 confirmed cases

571 Deaths

**NOT a political game**

**Do it right New Zealand!**

A detailed photograph of a butterfly with intricate orange, black, and white patterns on its wings, perched on a vibrant yellow flower. The background is a soft, out-of-focus grey.

A caterpillar exists to eat. Its aim is to consume as much as possible. When there is nothing left to devour, evolution forces its isolation into becoming a chrysalis; within which it dissolves. In the breaking down of its old form, a new form begins to evolve into a butterfly. One morning, it breaks through the wall of its chrysalis. It waits for its wings to dry in the warmth of the Sun, and then it flies. A butterfly exists to pollinate. Its aim is to sip the sweetness of flowers.

And as it does so, it fertilizes life.

We have been a caterpillar species; consuming, not only all that Gaia could spare in her generosity, but much more. Now cocooned by physical distancing, we can choose to breakdown who we thought we were. To surrender; not to the will of man, but to the evolutionary impulse of the Universe. To dissolve our separated sense of self and co-create imaginal cells of potential; linking up and lifting up to form organelles of emergence. We can reframe and more deeply understand, the breakdown and dying of the old and breakthrough and birth of the new; not as a crisis but as a metamorphosis. Instead of plunderers we can evolve to become pollinators.

**Dr Jude Currivan**



[www.wholeworld-view.org](http://www.wholeworld-view.org)