

MMed and DCH Lectures

Covid-19 update: where are we in 2021: vaccines and variants

February 1st, 2021

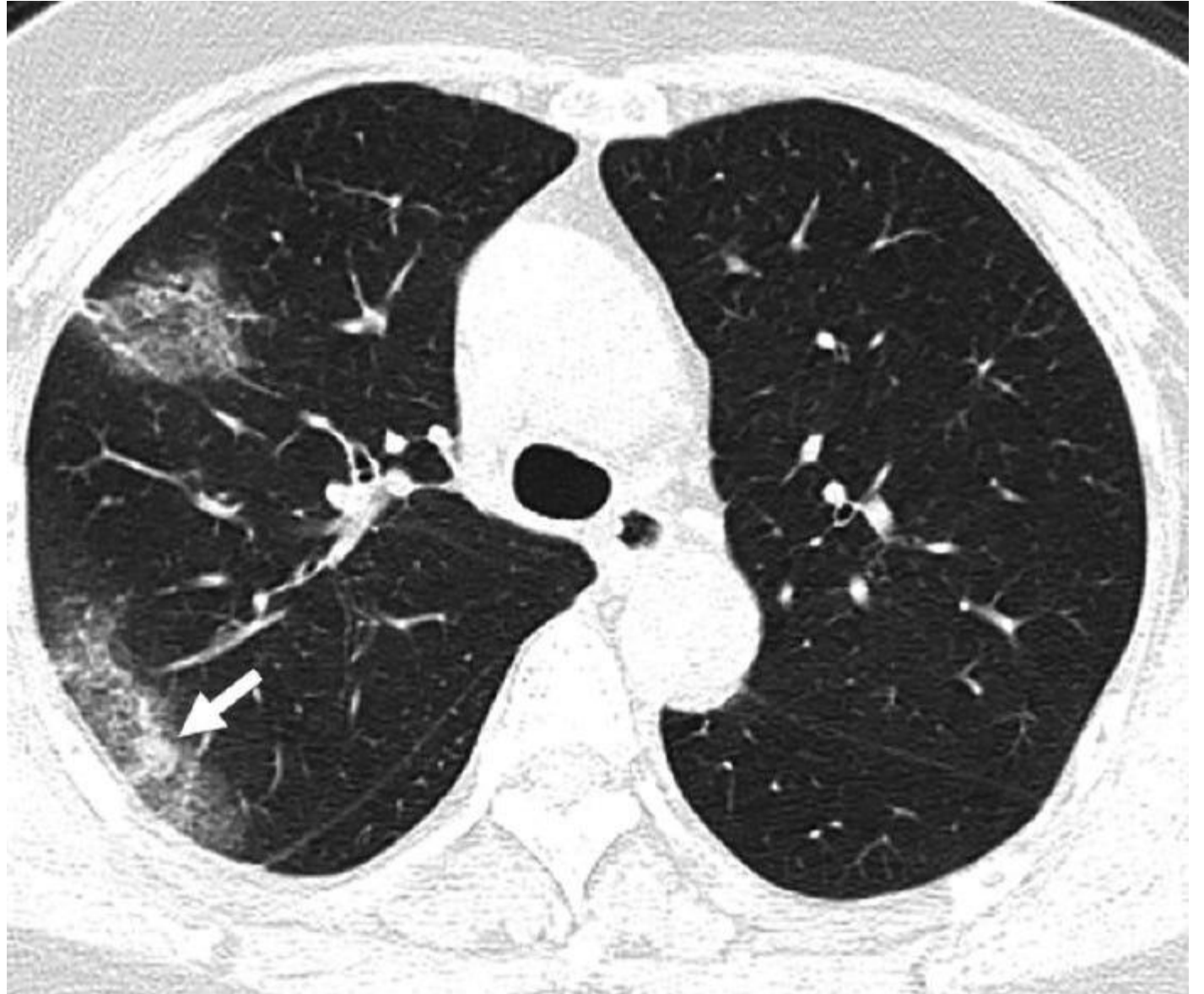
Prof Trevor Duke

Aims of today's session

- Recap on Covid-19 in 2020
- Where are we in 2021?
- Covid-19 vaccines
- New genetic variants and their implications

January 2020

- Day 0-4: Ground glass opacities on CT (peripheral)
- Days 5-10: progression into more lobes
- 11-13: clinically most severe
- 14+ resolution and clinical improvement



February 7th 2020: 30,877 cases

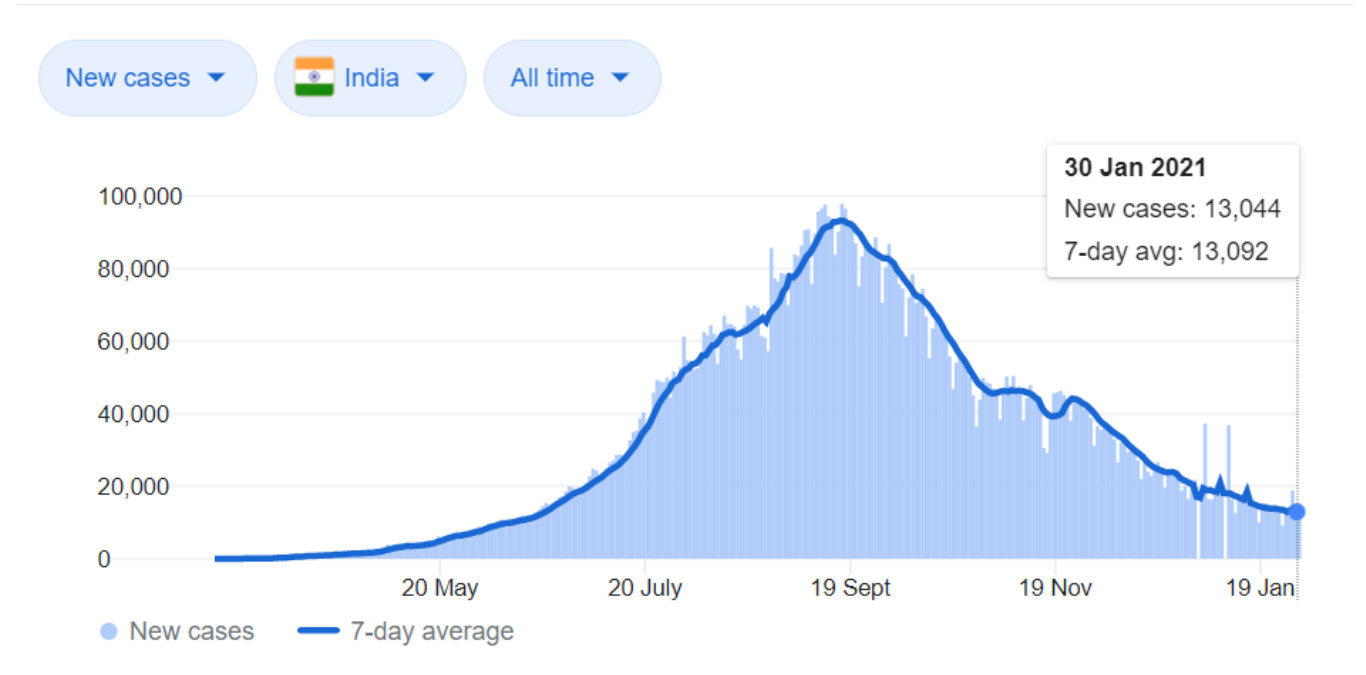
Now:

- 103 million cases
- 2.2 million deaths
- Currently 25 million cases
- Per day now: 500,000-600,000 cases per day, 15,000 deaths



India

- Peak of 96,000 cases per day in September
- Now 13,000 cases per day
- 4 strict lockdowns
- Now >1 million vaccinated (but decline came with public health measures)



Covid-19 cases that are children ≤ 18 years

- United States: 2%
- China: 2.2%
- Italy: 1.2%
- Spain: 0.8%
- Brazil: 2.1%
- Ecuador: 4.1%
- Texas: 11%
- Melbourne: 10%

Wu Z, McGoogan JM. *Characteristics of and Important Lessons From the Coronavirus Disease 2019 Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention*. JAMA

Livingston E, Bucher K. *Coronavirus Disease 2019 (COVID-19) in Italy*. JAMA

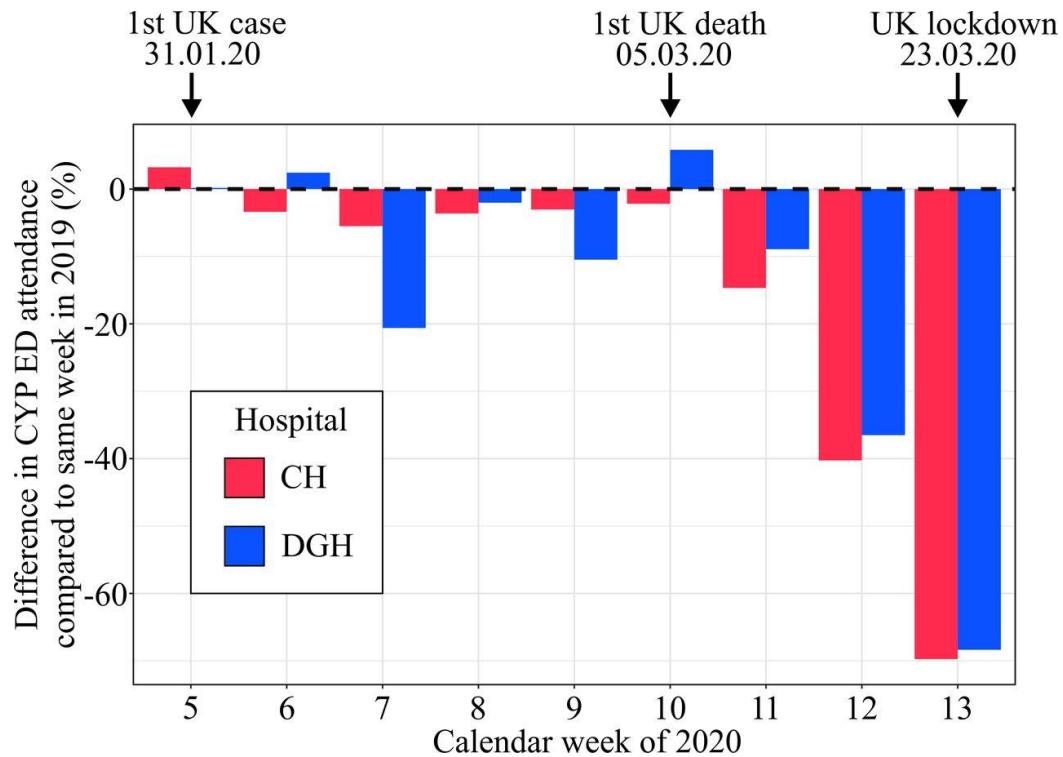
CDC COVID-19 Response Team. *Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020*. MMWR Morbidity and Mortality Weekly Report. ePub: 6 April 2020.

Tagarro A, Epalza C, Santos M, et al. *Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain*. JAMA Pediatr

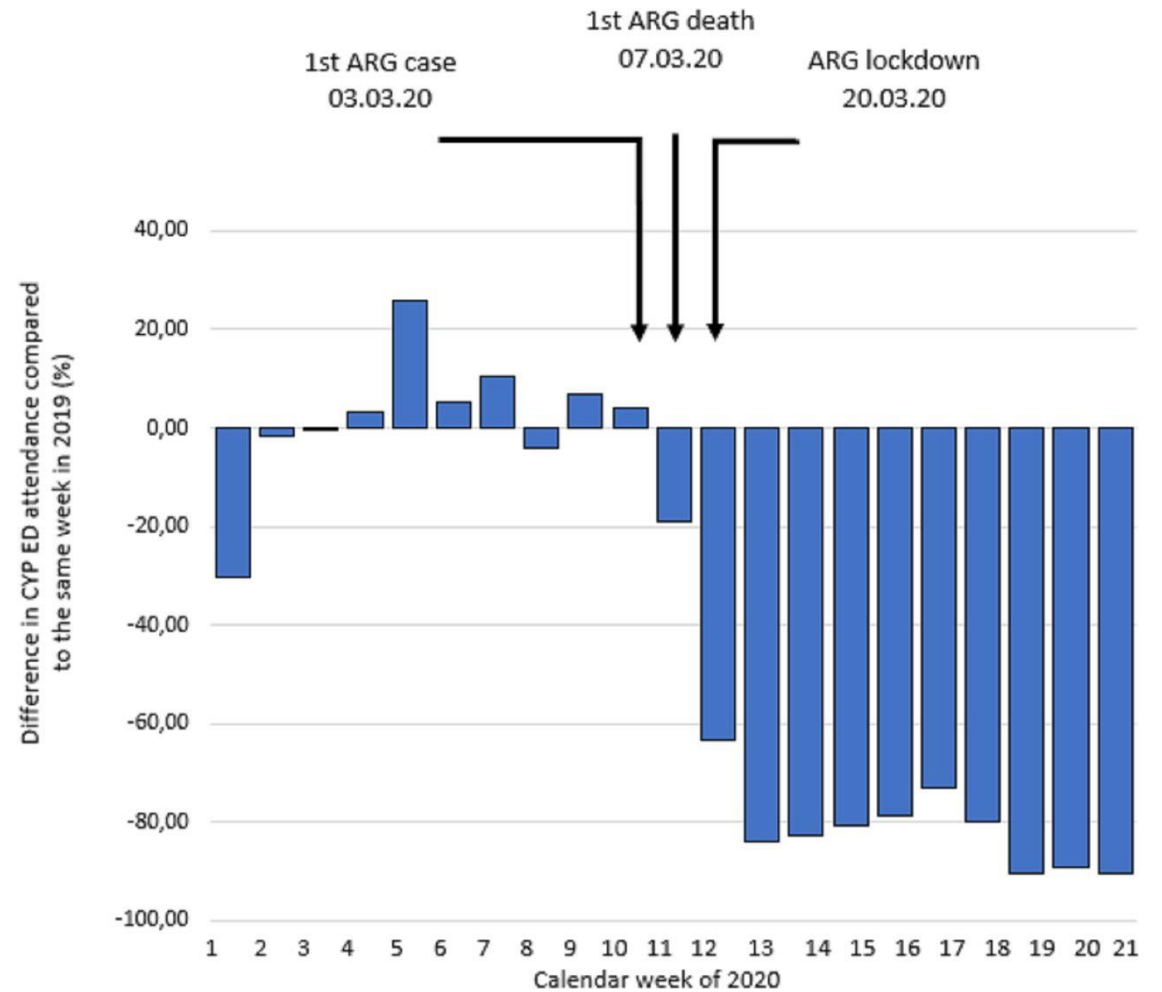
Epidemiology

- China 2143 children
 - Severe 112 (5%) hospitalised: fever, cough, diarrhoea, hypoxaemia
 - Critical 13 (0.6%), 9/13 (69%) under 5 years of age. ARDS, respiratory failure, shock, encephalopathy, myocardial failure, coagulopathy
- USA 2572 children (1.7%)
 - 5-20% hospitalized
 - 0.6-2% of children need ICU
- Spain, Italy, UK similar, *very low risk of severe disease* in children

Yuanyuan Dong, et al. Pediatrics 2020. Chinese Centre for Disease Control and Prevention, 2020
Guan W. New Eng J Med 2020. Clinical Characteristics of Coronavirus Disease 2019 in China
CDC COVID-19 Response Team. MMW Coronavirus Disease 2019 in Children - United States 2020



Decreases in paediatric emergency department attendances at the start of the COVID-19 pandemic of 2020. Arch Dis Child <http://dx.doi.org/10.1136/archdischild-2020-319385>



Impact of the COVID-19 pandemic in the paediatric emergency department attendances in Argentina Arch Dis Child <http://dx.doi.org/10.1136/archdischild-2020-319833>

The picture for paediatrics in many countries in 2020

- Paediatric patients in ED and paediatric wards ↓↓↓
- ↓↓ Respiratory virus infections
- Mental health presentations ↑↑↑
- Delayed presentations of common illnesses ↑↑
- Increased malnutrition

Why are children less susceptible to Covid-19?

1. Endothelial damage and thrombotic complications with age
2. Lower expression and affinity of angiotensin-converting enzyme 2 (ACE2) receptors in children: less readily infected by SARS-CoV
3. With age: cumulative exposure to circulating HCoVs → high levels of *non-neutralizing* antibodies which enhance virus entry into cells
4. Exposure to circulating HCoVs → high levels of *neutralizing antibodies* and T-cell immunity may produce cross-reactive protection against SARS CoV-2
5. Intensity of viral exposure (severity α viral load)
6. Higher melatonin levels in children (and bats) – may reduce ACE2 receptors, or inhibit SARS-CoV protease
7. Lower levels of vitamin D in elderly (anti-inflammatory, antioxidant)
8. Microbiota (differences in SARS CoV-2 and healthy controls)
9. Off-target effects of vaccines (BCG, MV, OPV)

Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections

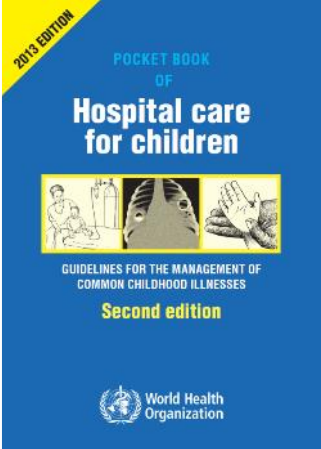
Treatment of Covid-19 in children

Mild disease

- If no signs of severe disease, manage at home, and instruct the family to isolate as best as they can for 14 days.
- Check immunization status and update if needed.

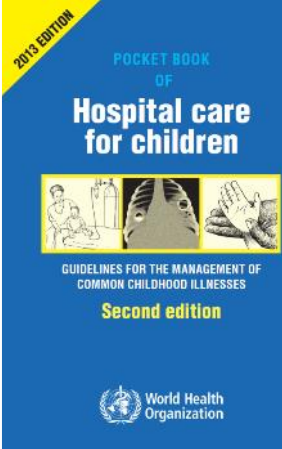
Treatment: If the child is unwell

- Check oxygen saturation, triage emergency signs and examine for signs of respiratory distress. Follow Hospital Care for Children.
- **Admit to hospitalise a suspected case if the child is hypoxic, or has any other signs of severe pneumonia or any danger signs (inability to feed, severe respiratory distress, obstructed breathing, cyanosis, shock)**
- Give oxygen therapy, other standard therapies for pneumonia (standard antibiotics for moderate or severe pneumonia).



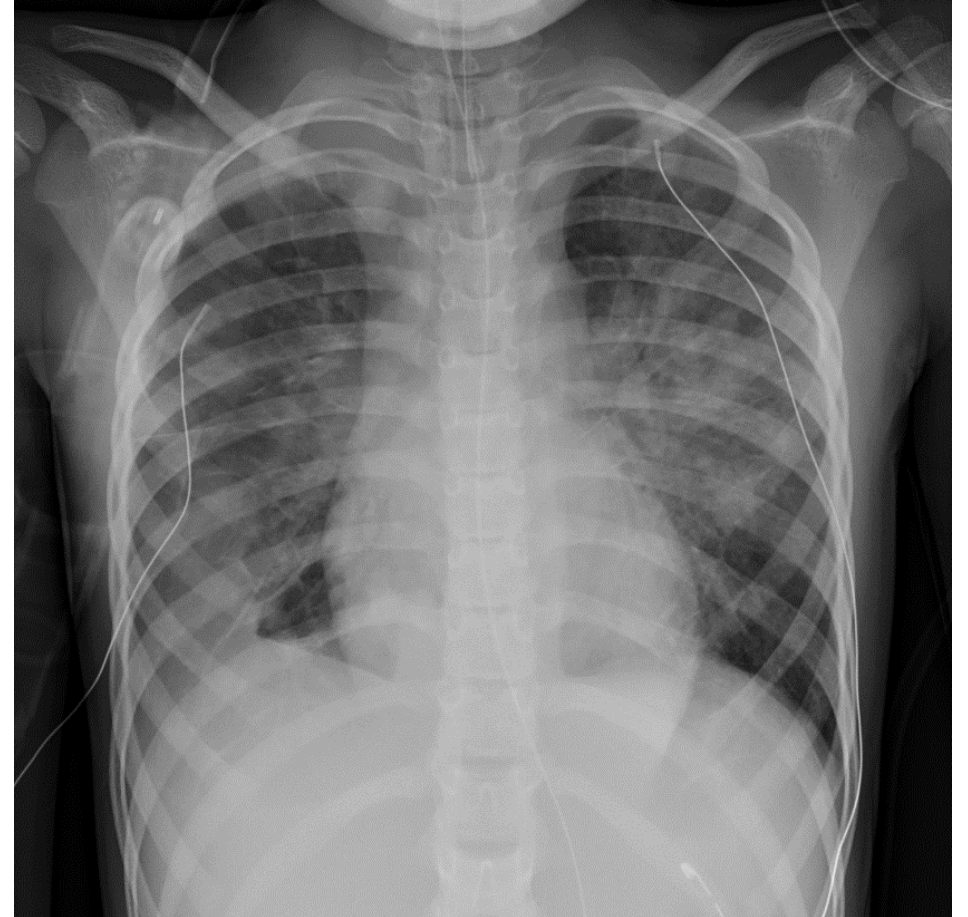
Treatment of severe sepsis that may be Covid

- **Triage:** Assess for emergency signs
- **Emergency treatment:** give oxygen, intravenous fluid to correct dehydration if present (10-20ml/kg)
 - If still signs of shock: adrenaline infusion. Put 6mg adrenaline in 1000 ml normal saline and run at 0.5ml/kg/hour (0.05 mcg/kg/min)
- **History / examination**
- **Diagnosis:** much more likely to be bacterial sepsis or another virus
- **Treatment**
 - **Antibiotic treatment** for sepsis
 - **Dexamethasone 0.15mg/kg Q12**
 - **Aspirin**
- **Monitor** vital signs, SpO₂, hydration state, and blood pressure
- **Supportive care:** avoid over-hydration, maintain blood glucose, nutrition



Intubation and mechanical ventilation

- Indications the same for all severe ALRI +/- sepsis syndrome – NOT early
- Anticipate deterioration post-intubation
 - Loss of auto-PEEP
 - De-recruitment, atelectasis
 - Hypoxaemia
- Loss of vasomotor tone
- Negative inotropy
- ↑↑ intrathoracic pressure
- ↓↓ venous return
- Hypotension







COVID-19 related paediatric multisystem inflammatory syndrome (MIS-C)

- Acute viral syndrome: high fever ($T > 39$ C), red skin rash, diarrhoea and vomiting
- *Rarely* associated with shock (hypotension), myocarditis (reduced LV function), encephalitis, coagulopathy.
- Lymphopenia, thrombocytopenia, hypoalbuminaemia, high ferritin and D-dimers, echo shows myocardial dysfunction
- Can look like toxic shock syndrome from Staph or Streptococcal infection, or Kawasaki disease or macrophage activation syndrome
- Most are not very unwell, just have fever, vomiting and diarrhoea

MIS-C - pathophysiology

- “2-4 weeks after peak of acute viral infection”
- IL-6 and IL-8 ↑↑↑
- Most patients positive for antibody, not RT PCR, therefore late inflammatory post-viral illness – **acquired immunity**
 - Antibody-antigen complex activation of macrophages, neutrophils, complement
 - T-cell immunity in 2-3 week after viral infection – injury to tissues that mimic virus
- May be genetically determined (African-American 35%, Hispanic 19%)
- But some related to *acute* Covid-19, with SIRS

Outcomes in COVID-19 infected children

- 129 studies, 31 countries (most from China and USA)
- 9335 children with Covid-19, 96 died (1%)
- Obesity, Racial differences (African-American, Hispanic / Latino)
- 27% comorbidity: chronic underlying conditions, such as cerebral palsy, chronic lung disease, heart disease, type 1 diabetes, immune problems, are more likely to be hospitalised (but this is similar to other viruses).

Research Paper

COVID-19 in 7780 pediatric patients: A systematic review

Ansel Hoang^a, Kevin Chorath^{a,†}, Axel Moreira^b, Mary Evans^a, Finn Burmeister-Morton^a, Fiona Burmeister^a, Rija Naqvi^a, Matthew Petershock^a, Alvaro Moreira^{a,*}

^a Department of Pediatrics, University of Texas Health Science Center San Antonio, San Antonio, Texas, USA

^b Department of Pediatrics, Texas Children's Hospital, Houston, Texas, USA

Clinical characteristics, treatment and outcomes of pediatric COVID-19: a systematic review and meta-analysis

Omar Irfan, et al. Archives of Dis Child, in press

MIS-C outcomes

- 39 studies (n = 662 patients)
- Age: mean 9.3 years
- Comorbidity 48%
- Overweight: 50%
- Admitted to ICU: 470 (71%)
- Mechanical ventilation 147 (22.2%)
- Aneurysms 47 (8.1%)
- Deaths: 11 deaths (1.7%)

Research Paper

Multisystem inflammatory syndrome in children: A systematic review

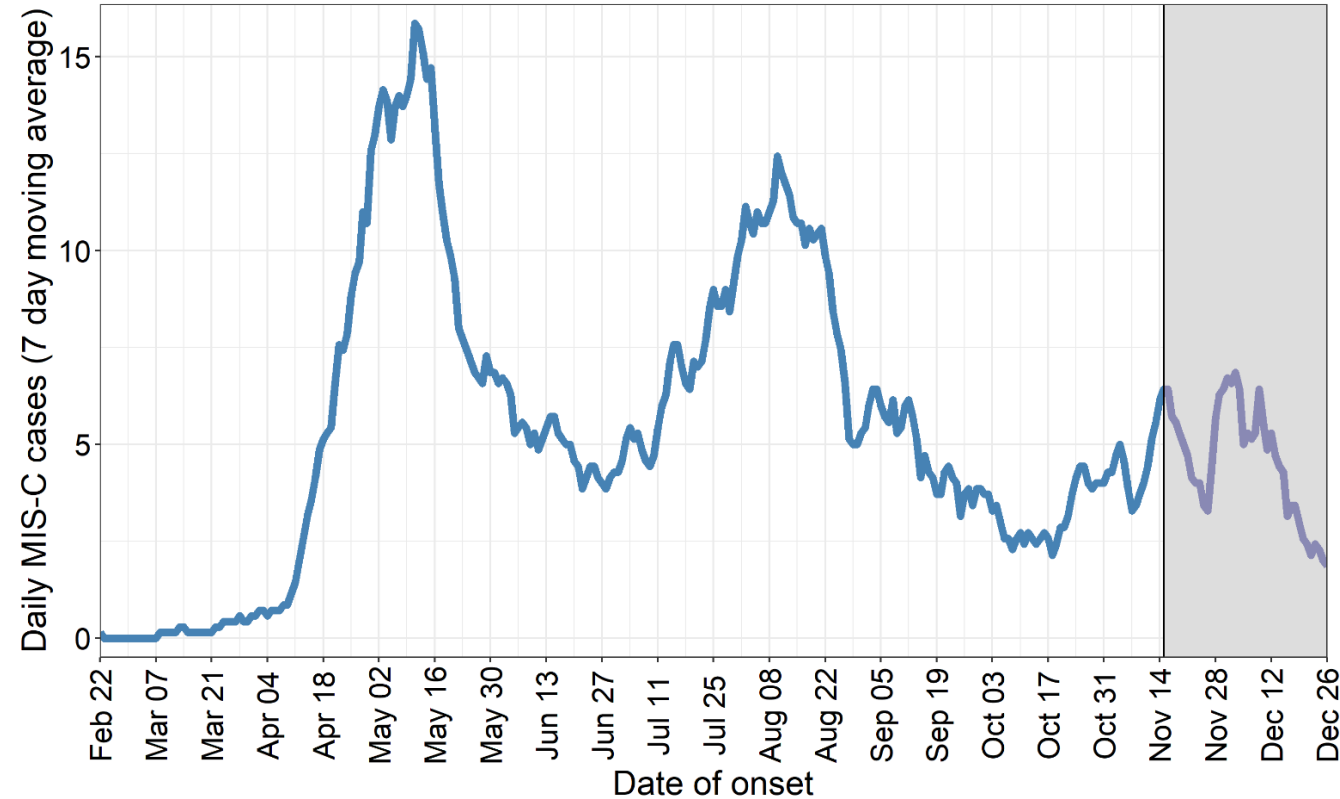
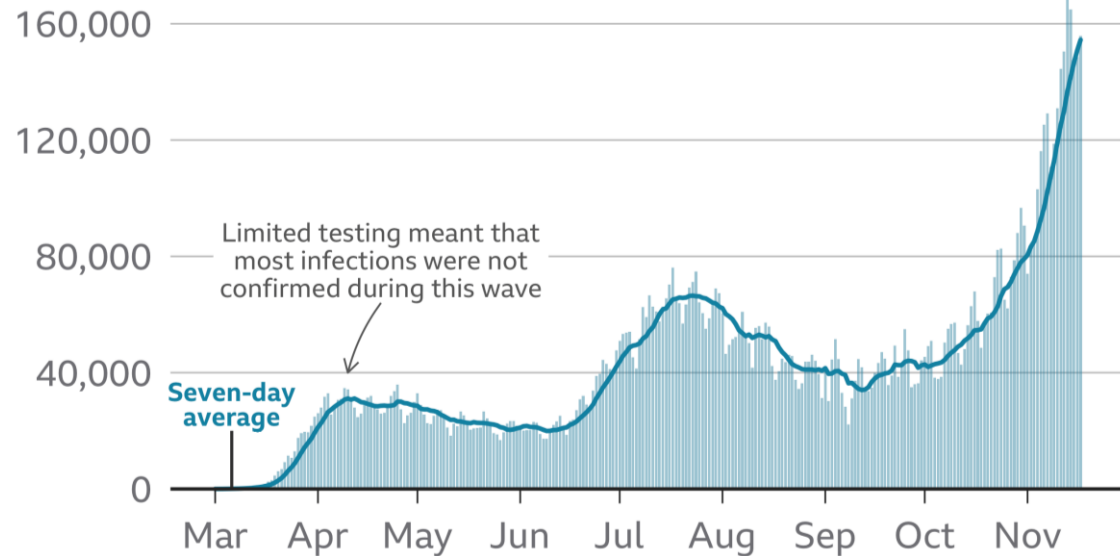
Mubbasheer Ahmed^a, Shailesh Advani^{b,c,1}, Axel Moreira^a, Sarah Zoretic^d, John Martinez^d, Kevin Chorath^e, Sebastian Acosta^a, Rija Naqvi^{a,b,c,d,e}, Finn Burmeister-Morton^d, Fiona Burmeister^d, Aina Tarriela^d, Matthew Petershack^d, Mary Evans^d, Ansel Hoang^d, Karthik Rajasekaran^e, Sunil Ahuja^d, Alvaro Moreira^{d,*}

Ahmed M, et al. Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine*, Volume 26, September 2020, 100527

Is MIS-C disappearing?

Total cases of MIS-C in US: 1659, deaths: 26 (1.6%)

Number of daily confirmed coronavirus cases in the US

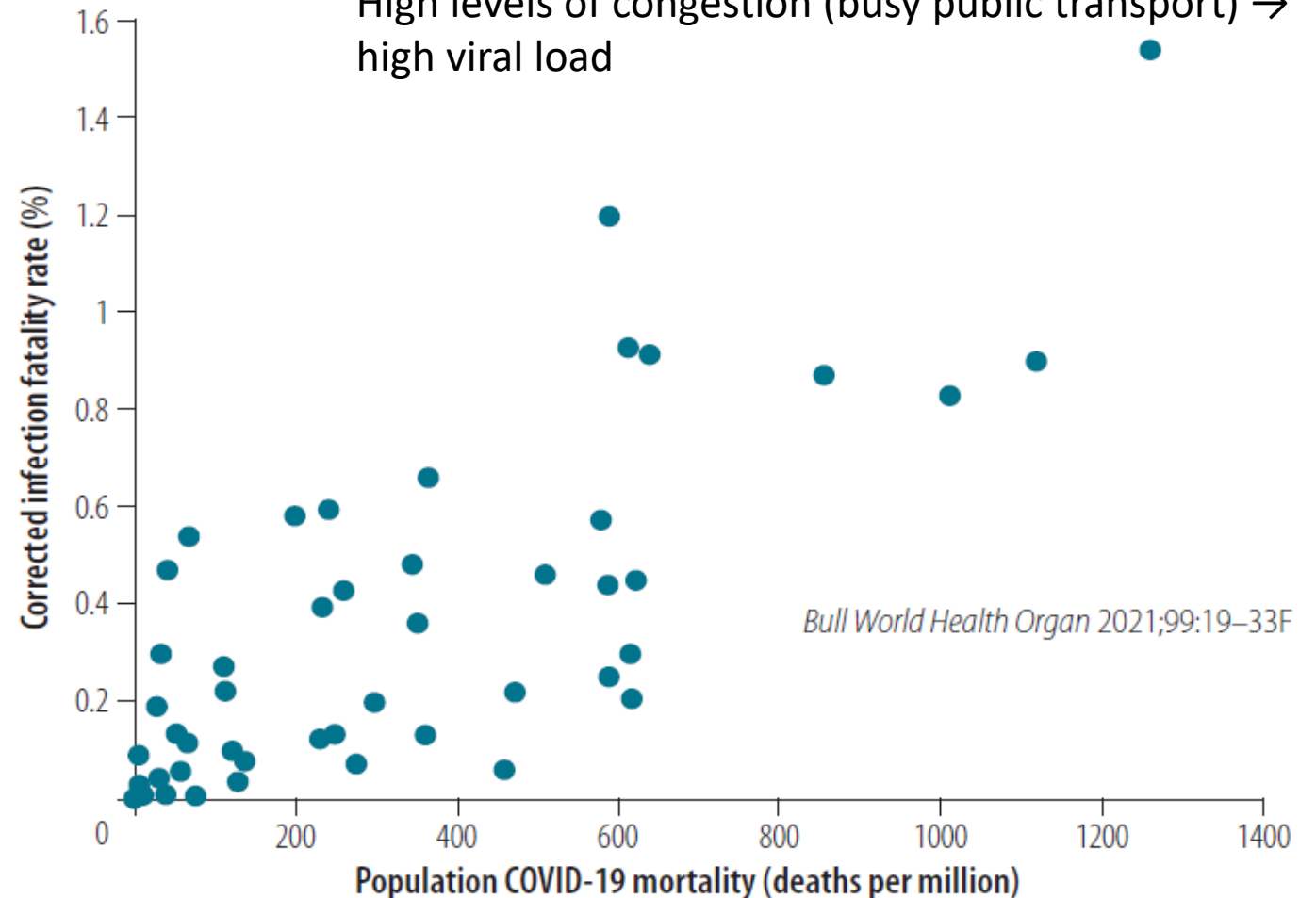


US CDC population-based data 2020-2021

Covid-19 case fatality rate

- 82 studies: **median fatality rate: 0.27%**
- Asia
 - younger population, less obesity, cough etiquette, previous coronavirus exposure, masks early
- Africa
 - 3 million cases (3.4% of worlds cases, 17% of global population)

Age structure of population
Nursing homes (UK)
Unnecessary mechanical ventilation
Unnecessary hydroxychloroquine
Overwhelmed hospitals (Italy, New York)
Nosocomial infections (China)
High levels of congestion (busy public transport) → high viral load



Risk to health care workers

- Greatest risk to health care workers:
 - Emergency intubation of an adult with COVID-19 (Italy)
 - Bed-space too close (SARS)
 - Lack of PPE, lack of hand-hygiene
 - Coming to work when unwell
 - Front line staff most at risk: including cleaners, porters, nurses (UK): adjusted HR 3.4 (95% CI 3.37–3.43) *
- Greater risk to HCW is from community transmission
 - Parents / families
 - Colleagues
 - Public transport, crowded markets
- No documented cases of an infected child passing COVID-19 on to a health care worker

* Nguyen. Lancet Public Health 2020; 5: e475–83

In perspective:

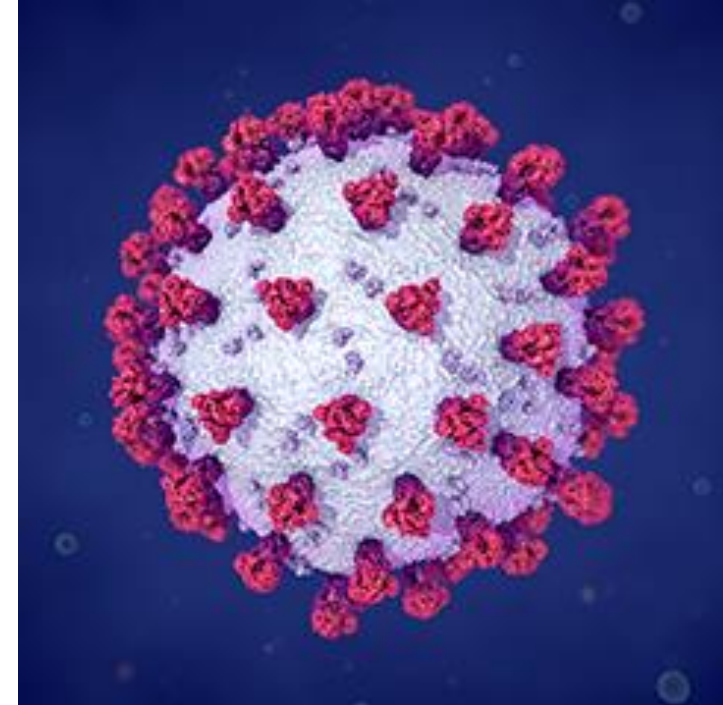
- Thousands of children will die of pneumonia and sepsis this year...from causes *other than* Covid-19
- Disruption to health services, social isolation and economic stress will kill more children than Covid-19

Maintain routine services

- Children with HIV, tuberculosis and other chronic conditions still need their medications and their conditions monitored, acute infections still need to be treated, high-risk newborns still need special care, and immunization programs still need to function so as to not lose ground in the control of many diseases

Covid-19 Vaccines

- mRNA
- Viral vector (adenovirus)
- Others (inactivated)
- The spike protein is the target for virus neutralizing antibodies



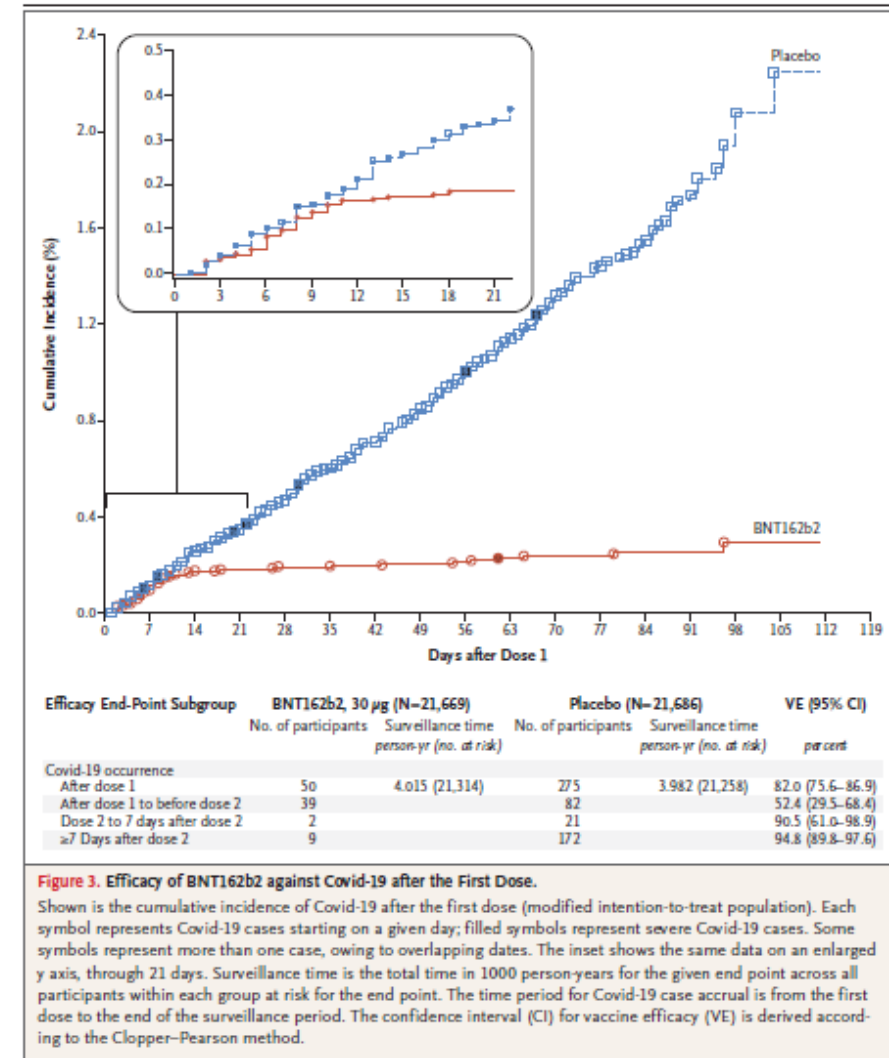
<https://www.nejm.org/covid-vaccine>

RNA (mRNA) vaccines

- Vaccine contains mRNA with the code to make the SARS-CoV-2 “spike” protein
- mRNA is taken up by the macrophages near the injection site and instructs those cells to make the spike protein
- The spike protein then appears on the surface of the macrophages, inducing an immune response to SARS-CoV-2
- Secret to development: mRNA inside a **lipid coating** to prevent it from degrading
- Technology first developed for immunotherapy for cancer

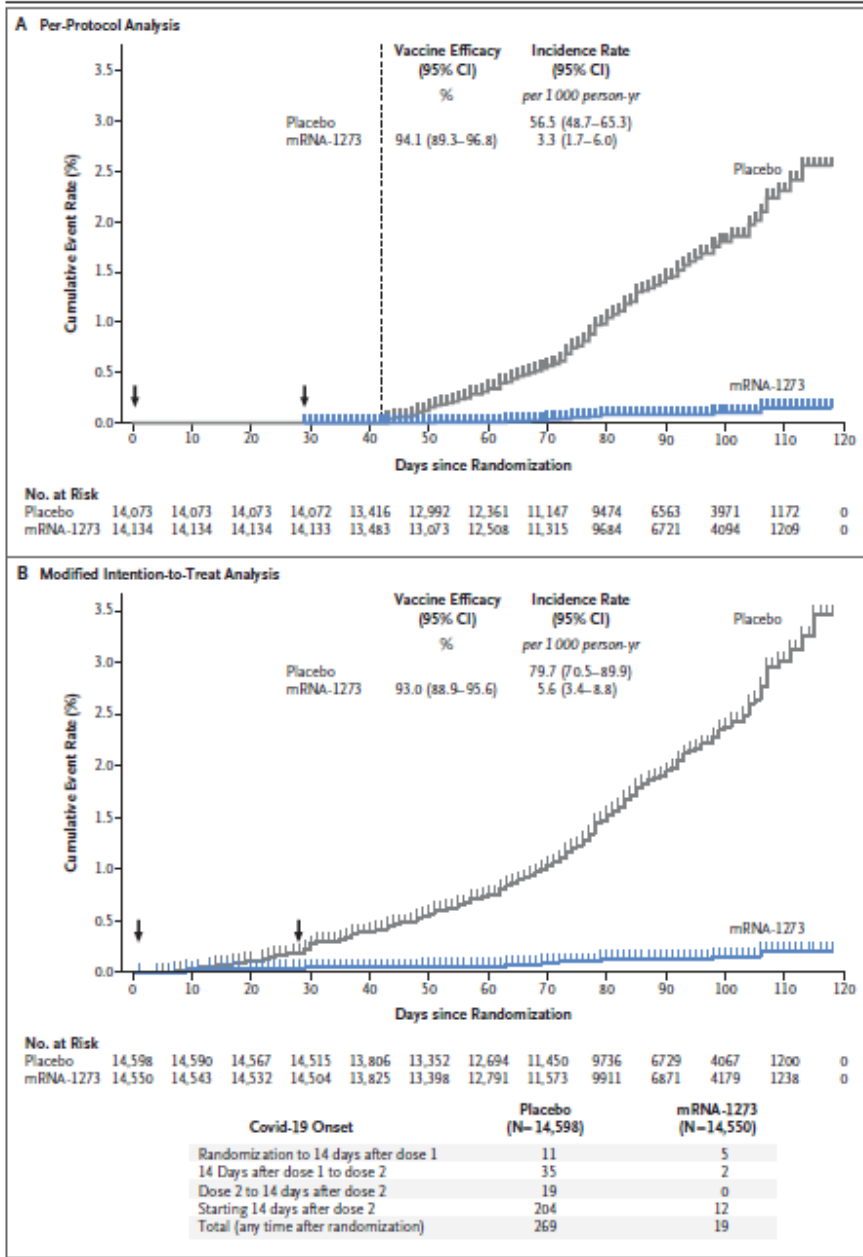
mRNA BTN162b2 (BioNTech / Pfizer)

- German company BioNTech
- 43548 participants (US, Argentina, Brazil, RSA, Germany, Turkey)
- 2 doses, 21 days apart
- 8 cases in vaccine arm
- 162 cases in placebo arm
- 95% effective (90.3% - 97.6%)
- Side effects: mild-moderate pain at injection site, fever, fatigue, headache

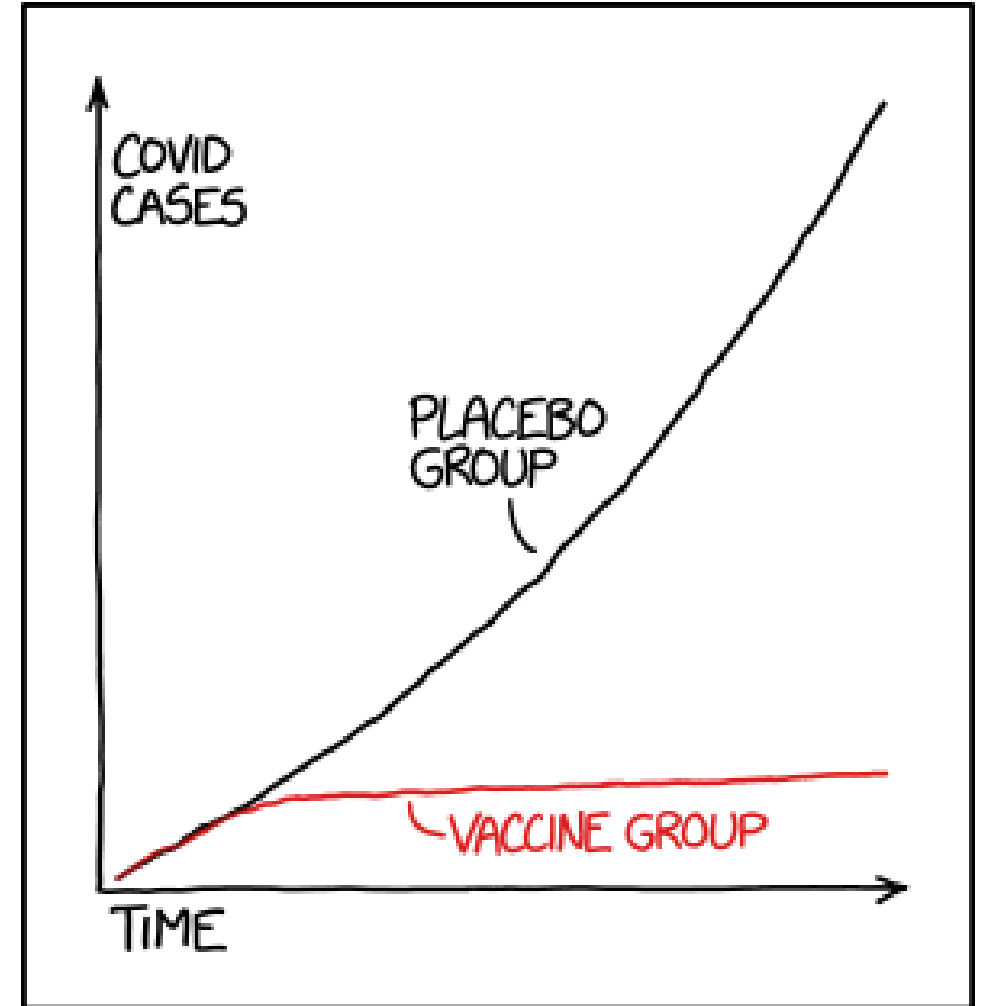


mRNA1273 (Moderna)

- 30,420 participants (US)
- 2 injections 28 days apart
- 11 cases in vaccine group, 185 cases in placebo group
- Side effects: fatigue, malaise, arthralgia, headache (50%)



Highly effective vaccines, more like measles (93-97%) and less like influenza (30-60%)



STATISTICS TIP: ALWAYS TRY TO GET DATA THAT'S GOOD ENOUGH THAT YOU DON'T NEED TO DO STATISTICS ON IT

ChAdOx1 (Oxford / Astra-Zeneca)

- Viral vector vaccine
- Chimpanzee adenoviral vector ChAdOx1, containing the gene for SARS-CoV-2 structural surface glycoprotein antigen
- Stimulates antibodies and T-cell response to spike proteins
- Vaccine cannot replicate as an adenovirus
- Phase II: neutralization response in 91% of the participants after one immunization and 100% after the second boost *
- Phase III: 4 trials in UK (n=2), Brazil, South Africa, not placebo controlled (meningococcal group A, C, W, and Y conjugate vaccine)

* Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen (COV002) phase 2/3 trial
Lancet 2020

ChAdOx1 (Astra-Zeneca)

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK



Lancet 2021; 397: 99-111

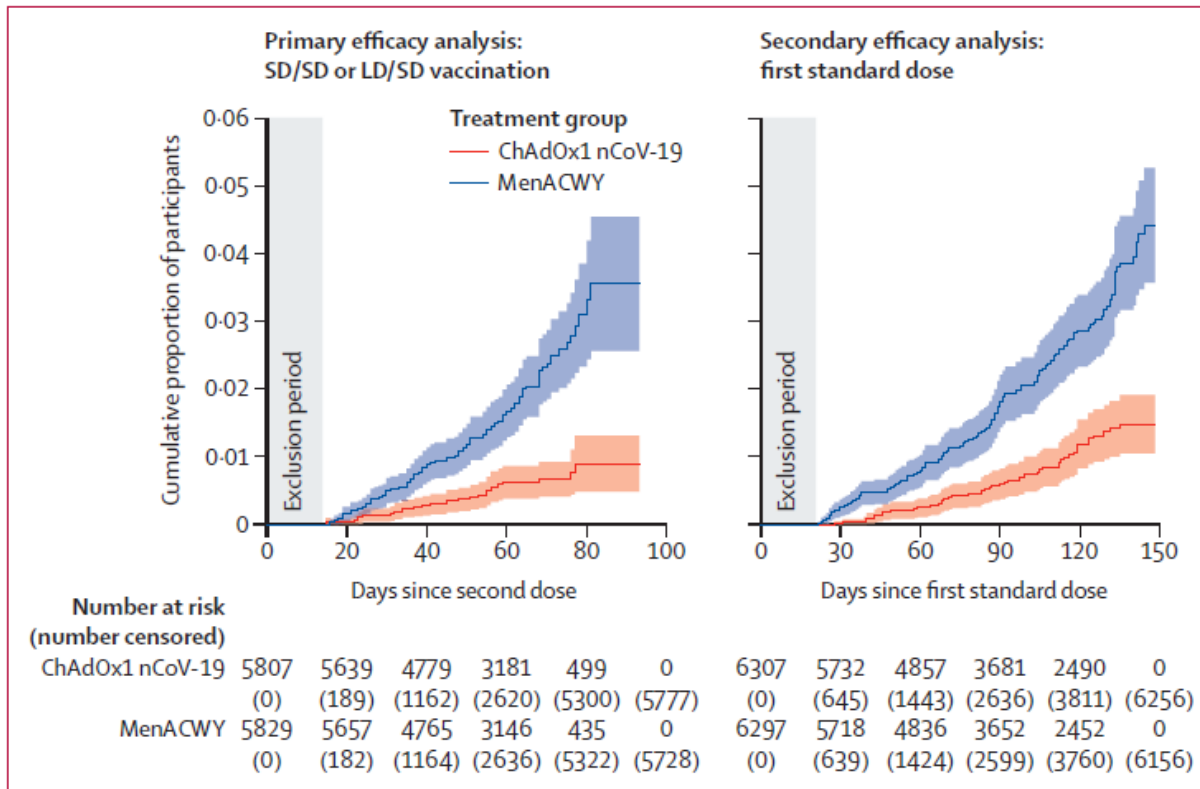


Figure: Kaplan-Meier cumulative incidence of primary symptomatic, NAAT-positive COVID-19. Cumulative incidence of symptomatic COVID-19 after two doses (left) or after first standard dose in participants receiving only standard-dose vaccines (right). Grey shaded areas show the exclusion period after each dose in which cases were excluded from the analysis. Blue and red shaded areas show 95% CIs. LD/SD=low-dose prime plus standard-dose boost. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. NAAT=nucleic acid amplification test. SD/SD=two standard-dose vaccines given.

23,848 participants enrolled
 11,636 participants (7548 in the UK, 4088 in Brazil) included in the **interim primary efficacy analysis**

Primary endpoint: symptomatic Covid-19 infection

Vaccine efficacy:
62% (95% CI 41-76%)

27 of 4440 in the vaccine group vs
 71 of 4455 in the control group

ChAdOx1 (Oxford / Astra-Zeneca)

- Reported efficacy of **90%** (67-97%) in those who received a low dose ($\frac{1}{2}$) as primary dose in the UK
 - 'Inadvertent' (related to the way the dose of vaccine was measured: spectrophotometry or qPCR)
- LD prime also reduced asymptomatic infection
- LD/SD may allow for wider distribution

ChAdOx1 (Oxford / Astra-Zenica)

- Side effects
 - Fever, headaches, body pain and malaise
 - 1 case of transverse myelitis occurring 14 days after a ChAdOx1 nCoV-19 booster vaccination (another 2 cases, one in a patient with MS, and another at 68 days)
- <4% of participants were older than 70 years of age
- US\$2–3 per dose agreement with the COVAX Facility

Side effects

- Pain, redness, swelling at the site
- Fever, fatigue, headache, muscle and joint pain
- *Rare* anaphylaxis
 - Not sure how rare given exclusions from trials
 - Likely mostly in people with existing food (e.g. shellfish, nuts, egg) or drug allergies
 - Incidence? CDC (US): 29 people so far anaphylaxis in response to Pfizer and Moderna mRNA vaccines. Rate 5.5 per million vaccine doses *

* BMJ 2021; 372 doi: <https://doi.org/10.1136/bmj.n74>

Duration of immunity?

- Moderna vaccine: neutralizing antibodies persisted for 4 months, titers declined slightly over time
- Given the absence of information on how long the vaccines will be protective, no specific recommendation for booster doses

Herd immunity?

- People without symptoms are less likely to transmit the virus to others
- Even after one dose, the mRNA vaccine has a protective effect in preventing asymptomatic infection
- Regardless of the vaccine, we need to continue social distancing, hand hygiene, wearing masks, avoiding crowds

Why do viral vector vaccines have lower efficacy than mRNA vaccines?

- Likely because of prior exposure to viral vector (adenovirus), which dampens the immune response (use of chimpanzee virus designed to reduce pre-existing immunity)
- Strong CD4+ and CD8+ response

Other vaccines

- Sputnik V (Russian)
 - Prime-and-boost approach, combines two different human adenovirus-based vectors: a recombinant adenovirus serotype 26 (Ad26) and serotype 5 (Ad5)
 - Each contains genetic fragments that encode the SARS-CoV-2 spike glycoprotein
 - Announced Dec 14th: “Vaccine efficacy 91.4% in phase 3 trials” (unpublished data)
 - Jan 2021: Astra-Zeneca joined Russia to boost vaccine production
 - Phase III trial is testing the efficacy of the vaccine on 40,000 participants with a 2 dose regimen, 21 days apart

Nature Biotechnology 2021: 39:11

Vaccines 2021, 9(1), 30; <https://doi.org/10.3390/vaccines9010030>

Other vaccines

- Janssen Vaccine (The Netherlands/US)
 - Adenovirus vector vaccine (Ad26.COV2.S) expresses the full length spike protein
 - A phase III trial (NCT04505722) is testing the efficacy of the vaccine in 60,000 participants after a single intramuscular dose
 - The EU has a contract with Johnson and Johnson for 400 million doses, the US for 100 million doses.
- CanSino and Sinovac Vaccines (China) Ad5 adenovirus vector
- Novavax (US)
 - Inactivated full length SARS CoV-2 spike protein subunit in glycosylated form
 - Plus adjuvant for immune boosting
 - Phase III trial in Mexico and US incomplete

Cold chain?

- mRNA vaccines:
 - *Ultra-low* temperature (-75°C Pfizer, -20°C Moderna) freezers needed to store; unaffordable and impractical in many countries
 - Moderna: “doses could be held in syringes for up to 8 hours at room temperature before administration.”
- Viral vector: normal refrigerated cold storage

Cost?

- \$2-3 for viral vector (Oxford / Astra-Zeneca)
- \$20 for the mRNA vaccines (Pfizer / Moderna)

Coverage of vaccine contracts

- ✓ Europe
- ✓ North America
- ✓ Australia
- ✓ Parts of Asia
- ? South America – Brazil (Sinovac)
- ? Africa
- ? Pacific – DFAT guarantee through COVAX?

Russia, China started vaccinating populations in 2nd half 2020

Other countries started in Dec 2020 (UK, US)

Australia: February

COVAX: <https://www.gavi.org/covax-facility>

- Goal is to deliver 2 billion doses of vaccines that have passed regulatory approval and/or WHO prequalification by the end of 2021.
 - Gavi (Global Alliance for Vaccines and Immunizations)
 - CEPI (Coalition for Epidemic Preparedness Innovations)
 - WHO, UNICEF
 - Member States (n=192, not US)
- \$2 billion already raised in Advanced Marketing Commitments (European Union member states have contributed – €850 million, Australia \$80M)
 - Astra-Zeneca: 170 million doses
 - Johnson & Johnson: 500 million doses of the Janssen candidate
 - Serum Institute of India: 200-900 million doses – of either the Oxford/Astra-Zeneca or Novavax

COVAX eligible countries

- Oceania: Papua New Guinea, Solomon Islands, Vanuatu, Fiji, Samoa, Tonga, Tuvalu, Kiribati, Marshall Islands and Federated States of Micronesia
- Southeast Asia: Indonesia, Timor-Leste, Cambodia, Laos, Myanmar, the Philippines and Vietnam

New SARS-CoV-2 genetic variants

- Mutations arise from viral replication normally
- Arise in heavily infected populations – in people with chronic Covid-19 infections, which allows time for virus to adapt and mutate
- Genetic variants only survive *if* they confer a competitive advantage
 - Replicate faster / easier
 - More transmissible
 - Escape immunity
- Many genetic variants don't survive because they are “inferior”
- Sometimes chance – if the first virus in a community, they will survive even if inferior (and may be less pathogenic) – “Founder effect”
- First spike protein genetic variant identified in March 2020 (but as early as Jan in China)

New SARS-CoV-2 genetic variants

- All variants affect the spike protein
- UK variant:
 - B 1.1.7 – more transmissible, require more strict public health measures (masks, social distancing, limitation on gatherings)
 - Mortality ratio 1.36 (1.18-1.56): means it is 36% more likely to cause death
- Brazil
- South Africa
- Questions
 - Will they affect vaccine efficacy?
 - Are they more pathogenic (more severe disease)?
 - When we vaccinate will there be selection pressure?
 - Can someone with a previous infection become re-infected with a variant?

BMJ Jan 2021: 372