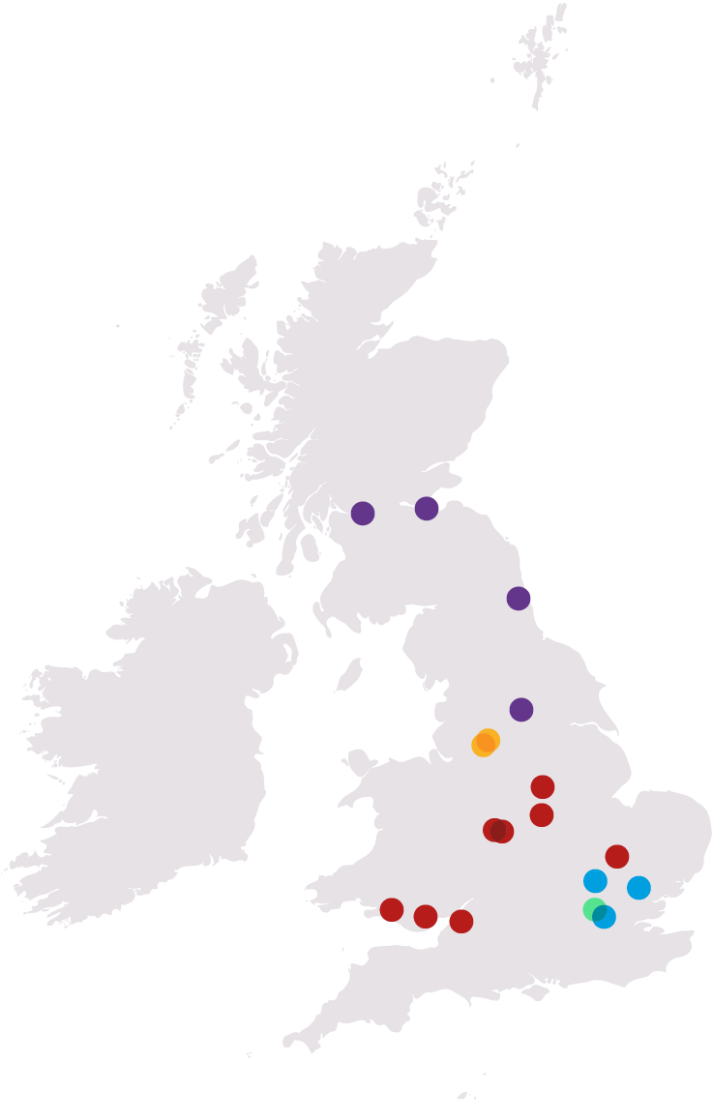
Advanced Therapy Treatment Centres

LONDON ADVANCED THERAPIES

The immunology of COVID-19: vaccines and treatments

Peter Openshaw,
Professor of Experimental Medicine, Imperial College, London

Chaired by Uta Griesenbach
Professor of Molecular Medicine, Imperial College London
President of the British Society for Gene and Cell Therapy



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Coordinated by

CATAPULT Cell and Gene Therapy

Who are LAT and the ATTCs?

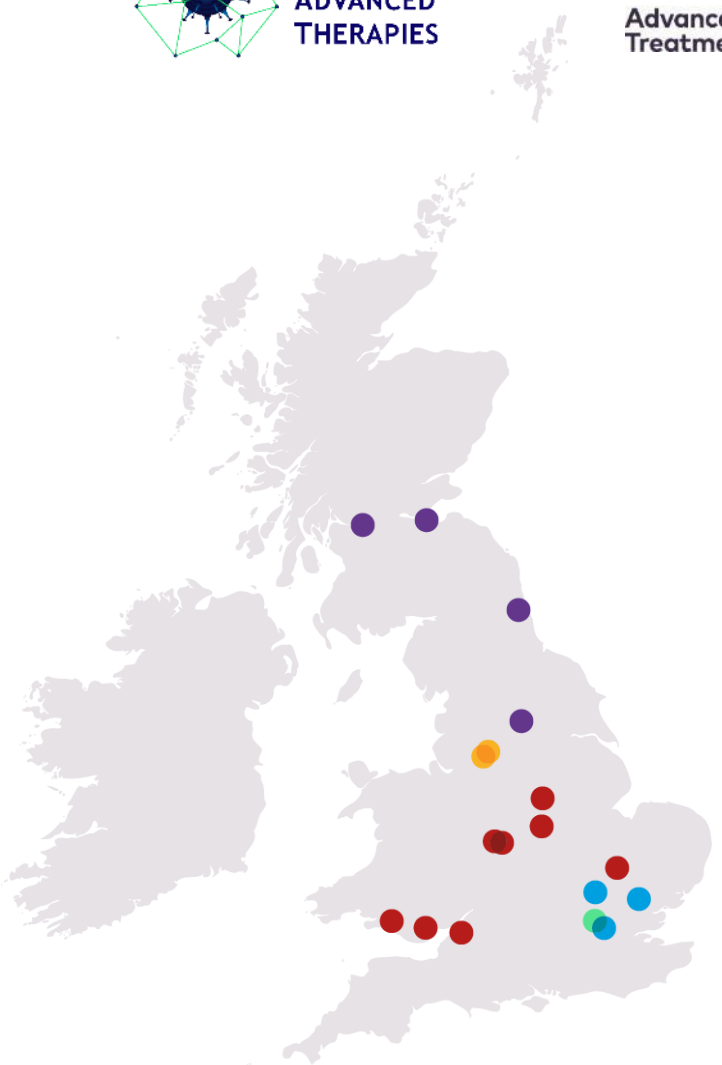
The ATTC (Advanced Therapy Treatment Centre) network is funded by Innovate UK and the Industrial Strategy Challenge Fund

London Advanced Therapies (LAT) is funded by Research England

The centres are working together, along with the Cell and Gene Therapy Catapult to specifically look at the training requirements for the current workforce and what needs to be put in place for them to be ready to deliver the treatments that are currently being developed.

This series of webinars is designed to help increase the awareness of advanced therapies and their impact in the clinic

Find out more at https://www.theattcnetwork.co.uk/



Coordinated by

Imperial College London

Seminar for NHS Staff
Tuesday 25the May

Webinar for Advanced Therapeutics series for NHS healthcare professionals

The immunology of COVID-19: vaccines and treatments

Peter Openshaw
p.openshaw@imperial.ac.uk
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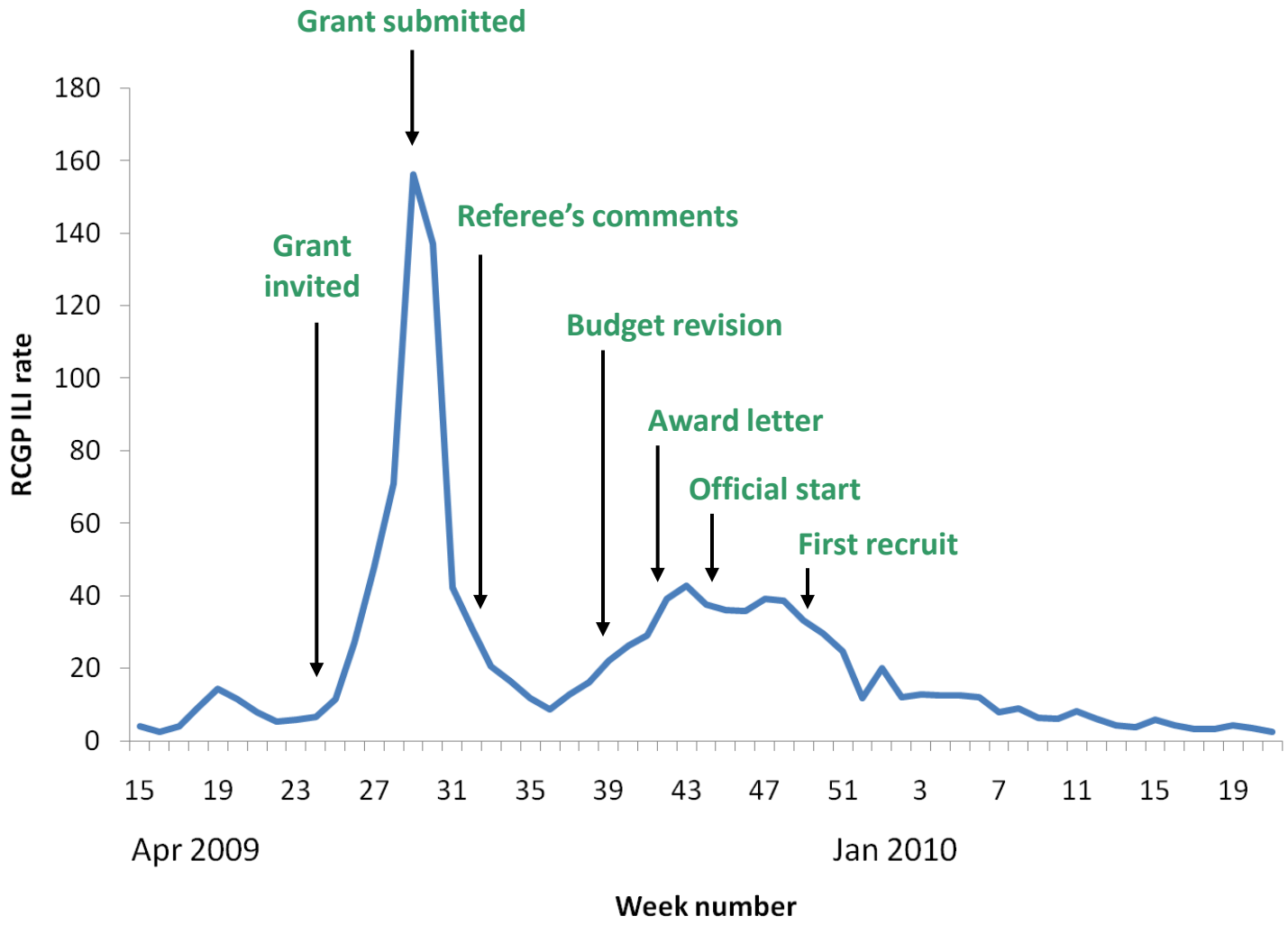
Imperial College London

MOSAIC Timelines



ILI, influenza-like illness; MOSAIC, Mechanisms of Severe Acute Influenza Consortium; RCGP, Royal College of General Practitioners.

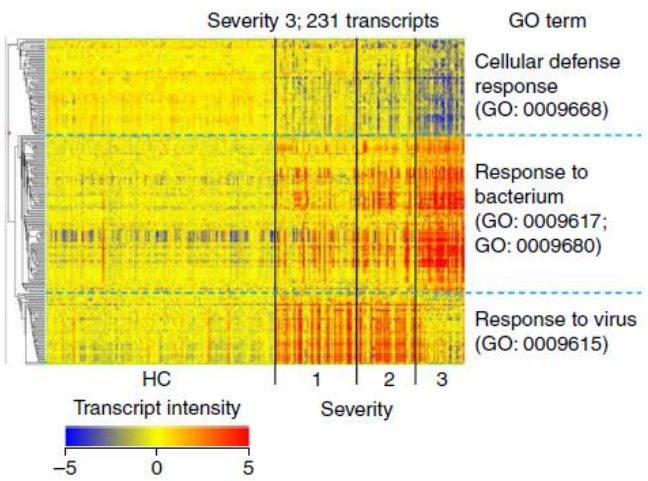
nature immunology

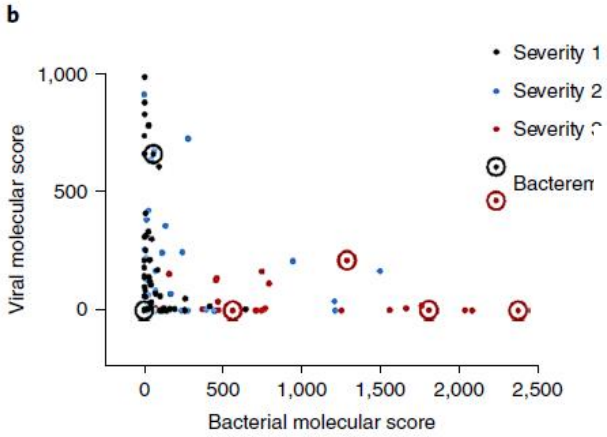
RESOURCE

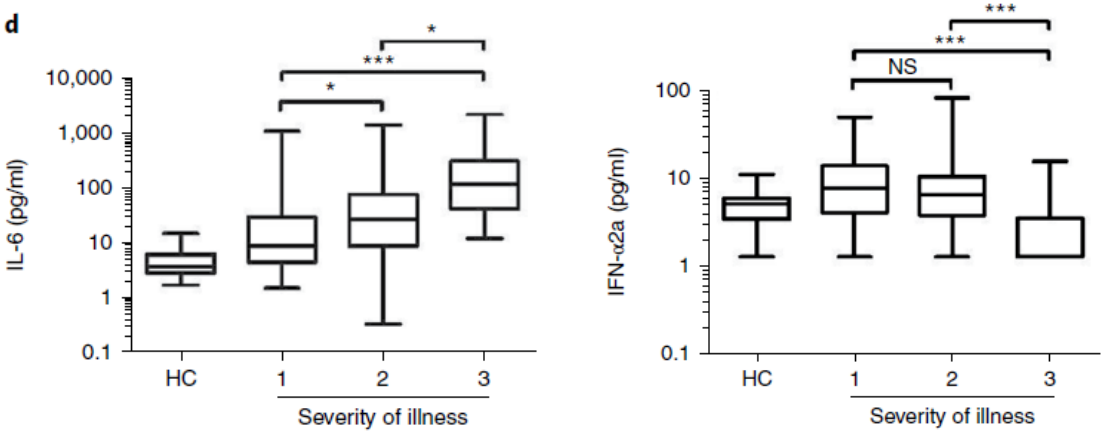
https://doi.org/10.1038/s41590-018-0111-5

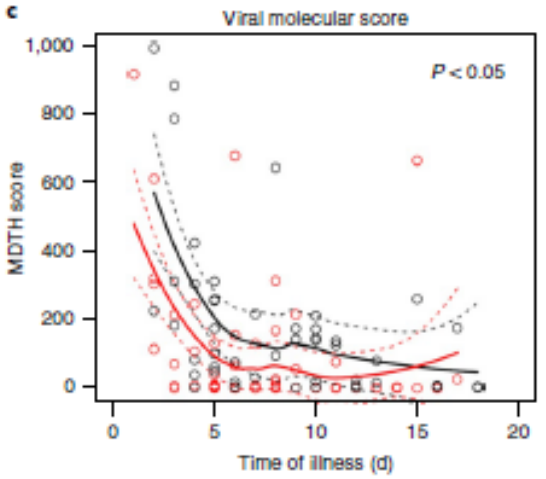
Progression of whole-blood transcriptional signatures from interferon-induced to neutrophil-associated patterns in severe influenza

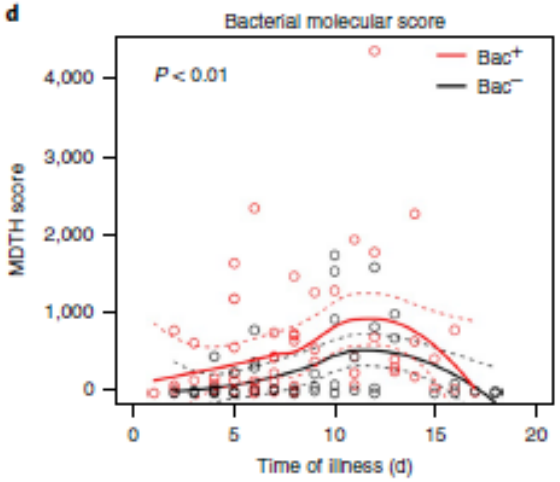
Jake Dunning[1,8], Simon Blankley[2], Long T. Hoang[1], Mike Cox[3], Christine M. Graham[2], Philip L. James[3], Chloe I. Bloom[2], Damien Chaussabel[4], Jacques Banchereau[5], Stephen J. Brett[6], MOSAIC Investigators[7], Miriam F. Moffatt[3], Anne O'Garra[2*] and Peter J. M. Openshaw[1*]











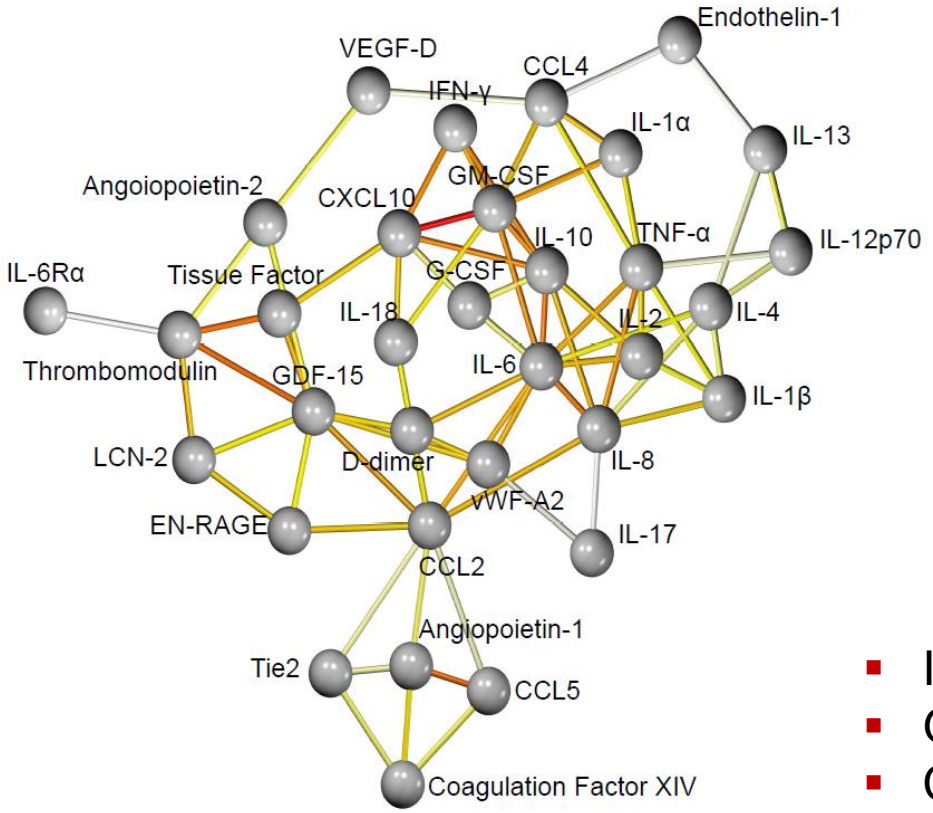
https://doi.org/10.1038/s41590-018-0111-5 (2018).

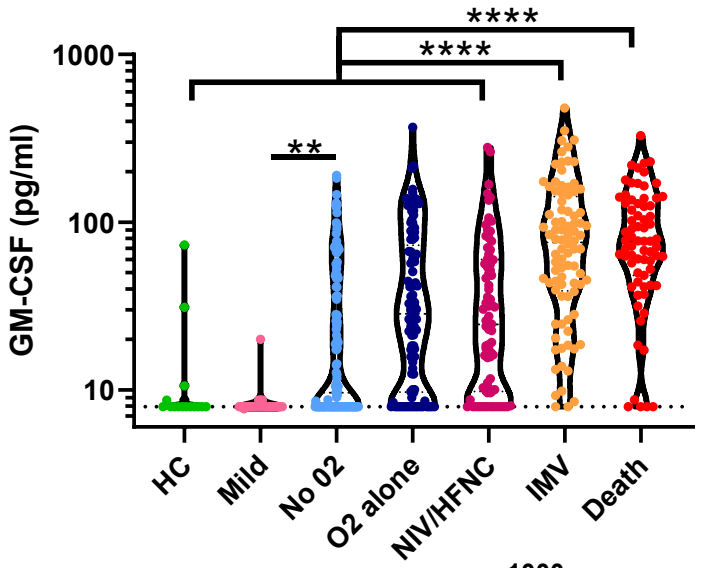
CORONAVIRUS

Science Immunology

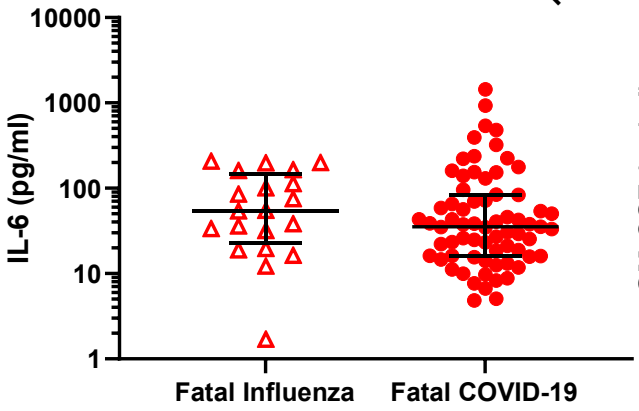
Inflammatory profiles across the spectrum of disease reveal a distinct role for GM-CSF in severe COVID-19

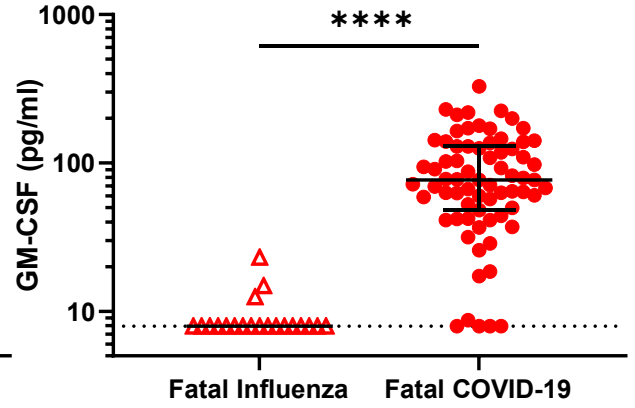
Ryan S Thwaites[1], Ashley Sanchez Sevilla Uruchurtu[1], Matthew K Siggins[1], Felicity Liew[1], Clark D Russell[2], Shona C Moore[3], Cameron Fairfield[4], Edwin Carter[5], Simon Abrams[3], Charlotte-Eve Short[6], Thilipan Thaventhiran[6], Emma Bergstrom[6], Zoe Gardener[6], Stephanie Ascough[6], Christopher Chiu[6], Annemarie B Docherty[4,7], David Hunt[8], Yanick J Crow[5], Tom Solomon[3], Graham P Taylor[6], Lance Turtle[3,9], Ewen M Harrison[4], Jake Dunning[10], Malcolm G Semple[11,12*], J Kenneth Baillie[7,13*], Peter JM Openshaw[1*] on behalf of the ISARIC4C investigators**





ISARIC 4C Coronavirus Clinical Characterisation Consortium



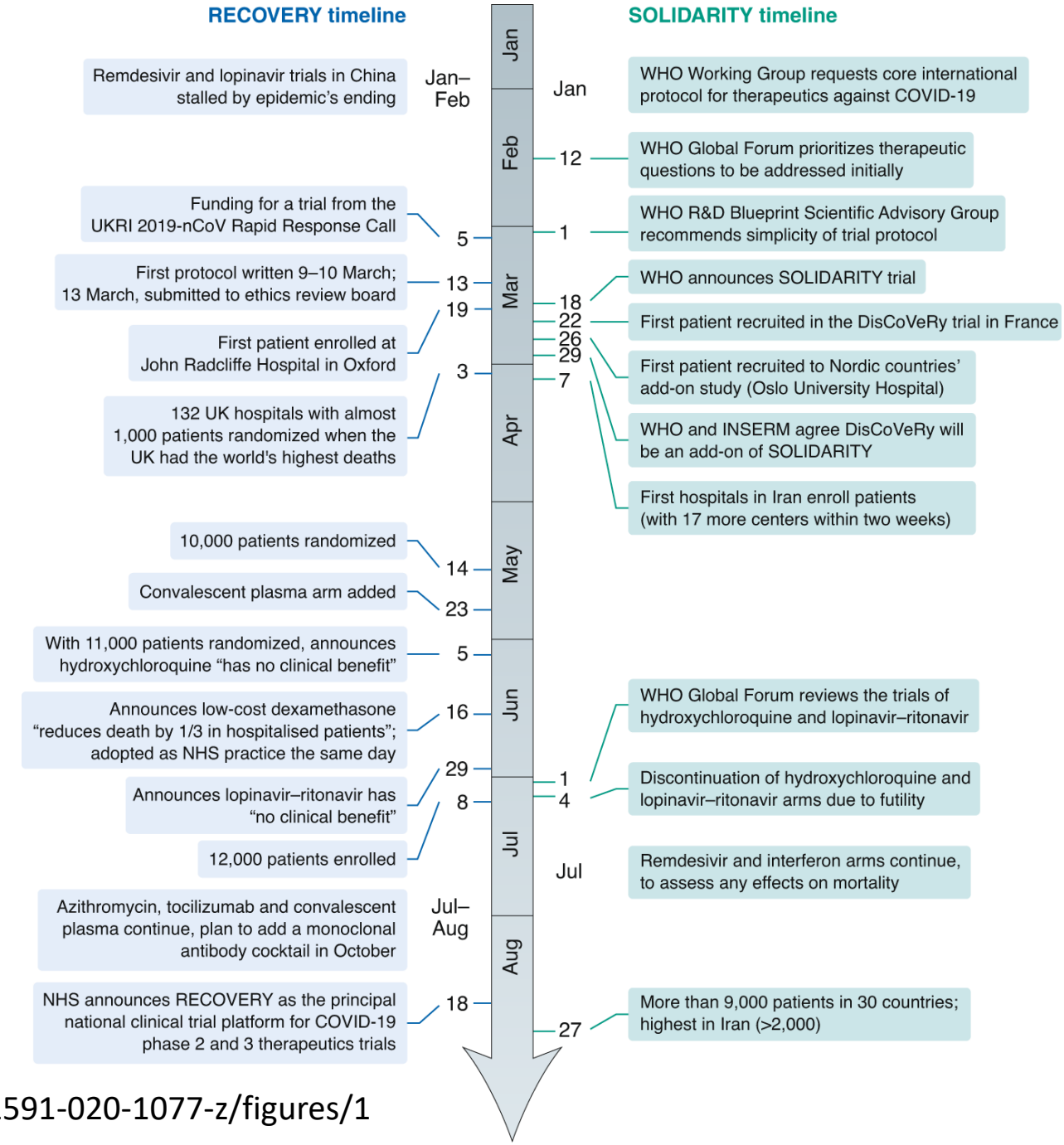


- IL-6 and GM-CSF are both hubs of the inflammatory network
- GM-CSF is raised in COVID-19, not in severe flu
- Close linkage to vascular and thrombotic elements

interactive 3D visualization: https://isaric4c.net/networks/

R. S. Thwaites *et al.*, *Sci. Immunol.* 10.1126/sciimmunol.abg9873 (2021)

"**RECOVERY and SOLIDARITY** have set new standards and have shown that a combination of old-fashioned randomization, established clinical-trials networks and imaginative use of modern information technology can provide many rapid and reliable therapeutic answers, following the recently published rationale for pursuing the magic of randomization rather than the myth of real-world evidence"



https://www.nature.com/articles/s41591-020-1077-z/figures/1

Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results

WHO Solidarity Trial Consortium
Hongchao Pan, Richard Peto, … Soumya Swaminathan

See also *Science*. doi:10.1126/science.abf4549

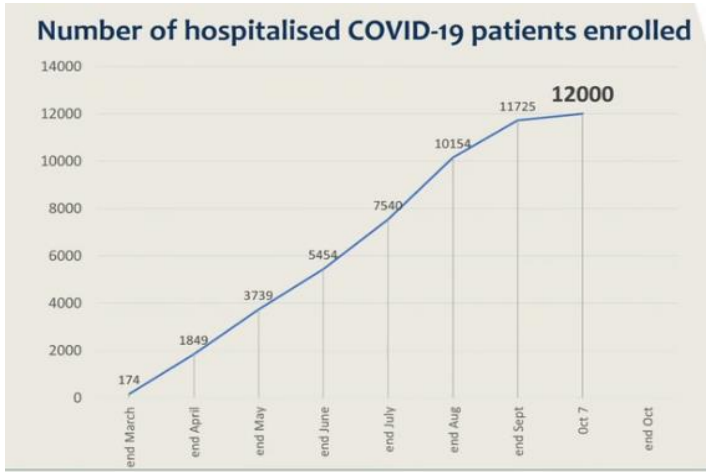
1. Albania
2. Argentina
3. Austria
4. Bangladesh
5. Belgium
6. Brazil
7. Canada
8. Colombia
9. Dominican Rep
10. Egypt
11. Ethiopia
12. Finland
13. France
14. Georgia
15. Honduras
16. India
17. Indonesia
18. Iran
19. Ireland
20. Italy
21. Kenya
22. Kuwait
23. Latvia
24. Lebanon
25. Lithuania
26. Luxembourg
27. Malaysia
28. Mali
29. Nigeria
30. North Macedonia
31. Norway
32. Oman
33. Pakistan
34. Panama
35. Paraguay
36. Peru
37. Philipppines
38. Portugal
39. Romania
40. Saudi Arabia
41. Sierra Leone
42. Slovakia
43. South Africa
44. Spain
45. Switzerland
46. United Arab Emirates

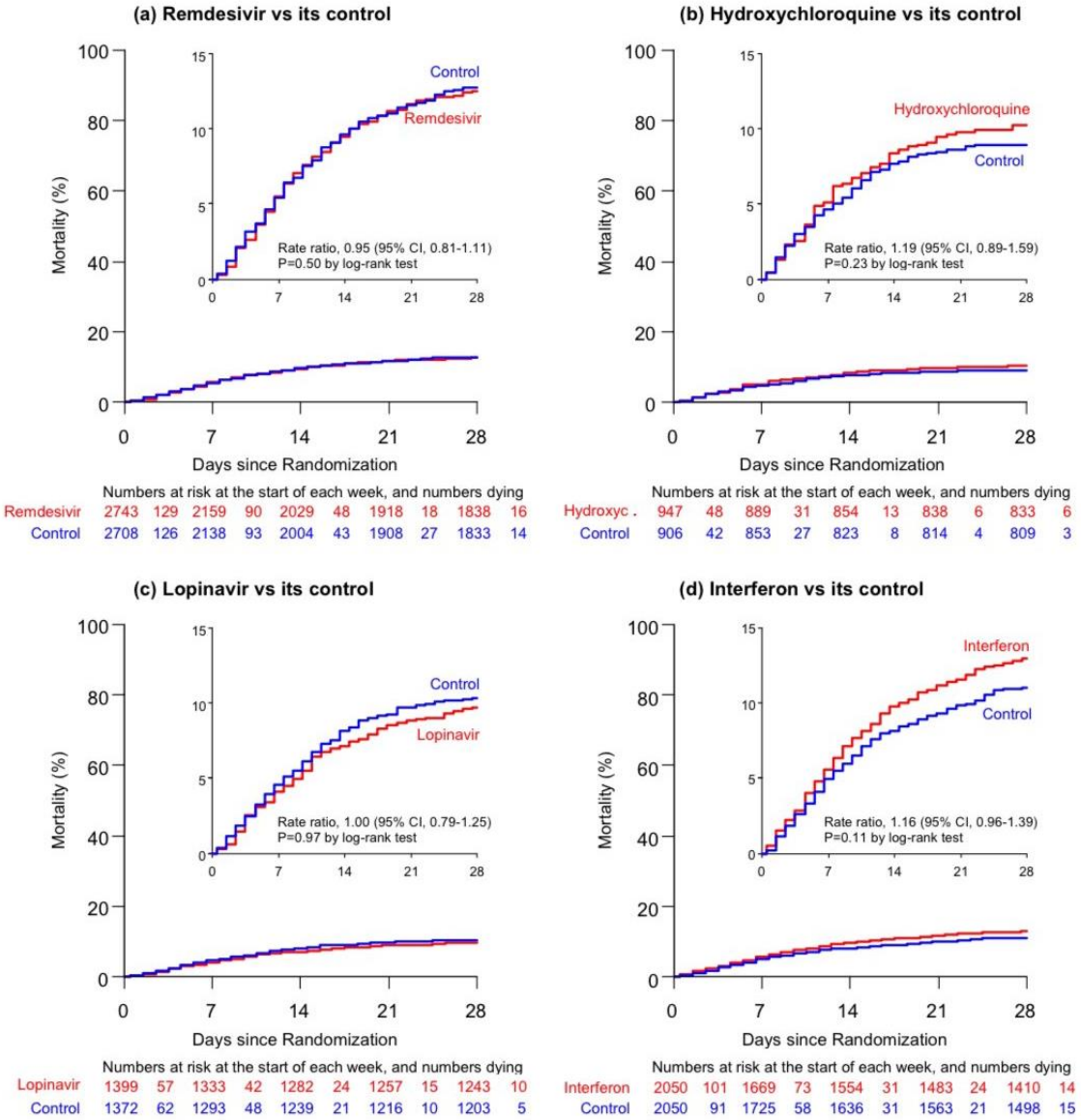
Nearly 500 hospitals

30 countries enrolling patients

16 other countries ready to start

All 6 Regions of WHO





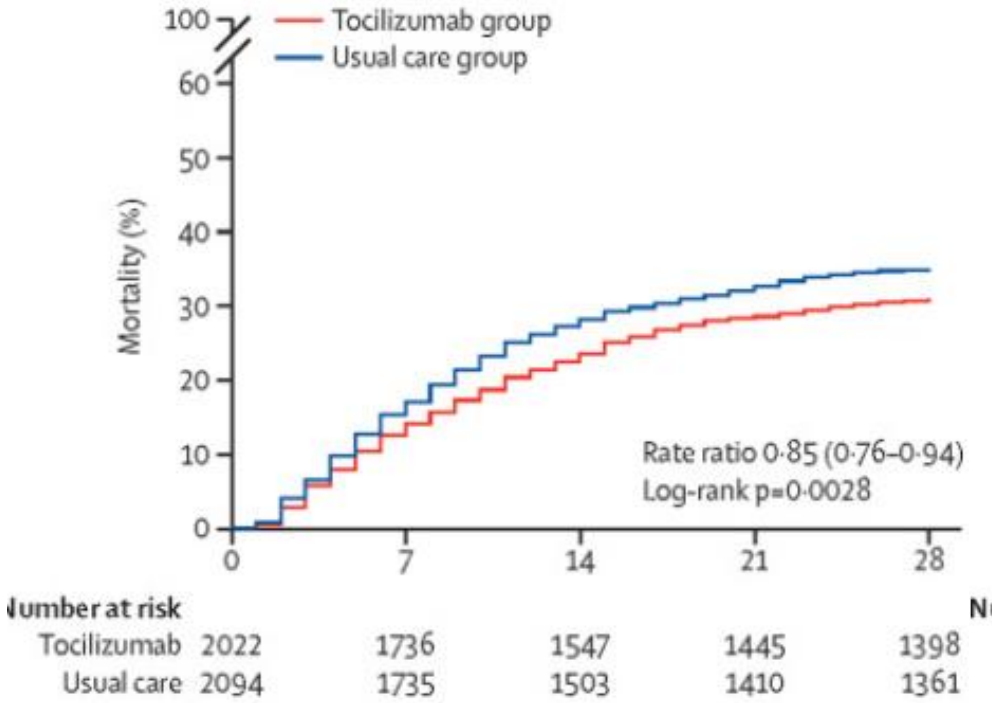
https://doi.org/10.1101/2020.10.15.20209817

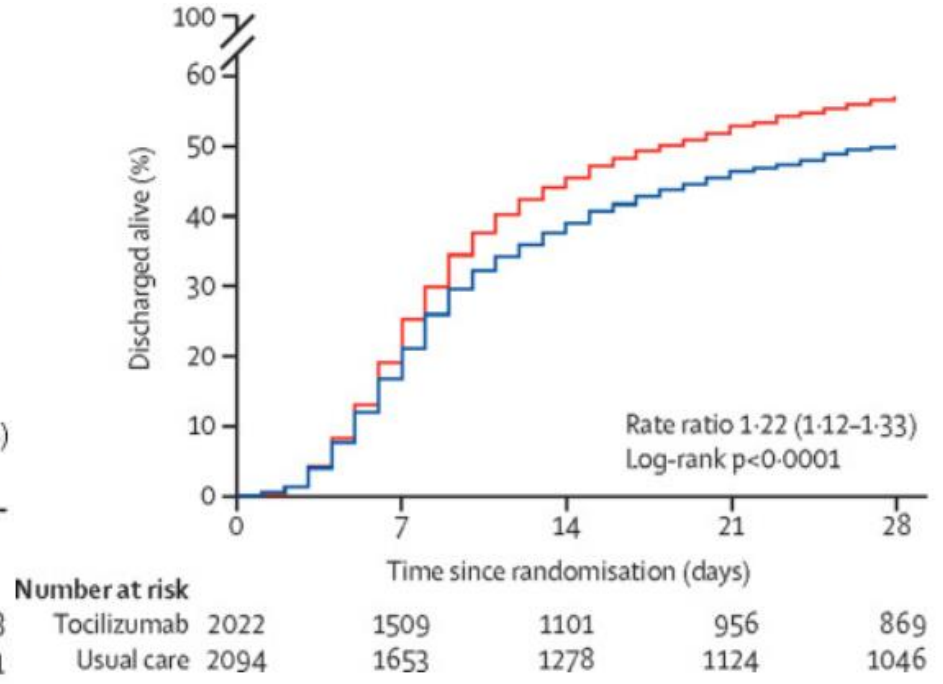
https://t.co/ohtTAFaSnc?amp=1

Lancet 2021; 397: 1637–45

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*





- Hypoxic, CRP>75mg/L
- Decreased mortality and progression to invasive ventilation
- 3x larger than all other studies combined
- 1-2x 400-800mg doses

Interpretation In hospitalised COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes. These benefits were seen regardless of the amount of respiratory support and were additional to the benefits of systemic corticosteroids

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00676-0/fulltext

Prof Peter Horby, Oxford UK

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- Adaptive randomised trial
- Over 11,500 COVID-19 patients, 175 NHS UK hospitals
- 8 June 2020: recruitment to dexamethasone halted. 2,104 patients given **dexamethasone 6 mg** (= 40mg of Prednisolone) **once per day** either by mouth or i.v. for **ten days;** cf. 4,321 patients on usual care
- Among the patients who received usual care, 28-day mortality:
  - 41% in those on ventilators
  - 25% in those on O2
  - 13% in those with normal O2 levels

Department of Health & Social Care

MHRA

NHS

COVID-19 Therapeutic Alert

Issue date: 16 June 2020
Alert ref: CEM/CMO/2020/026

Dexamethasone in the treatment of COVID-19
Implementation and management of supply for treatment in hospitals

Summary

For immediate action

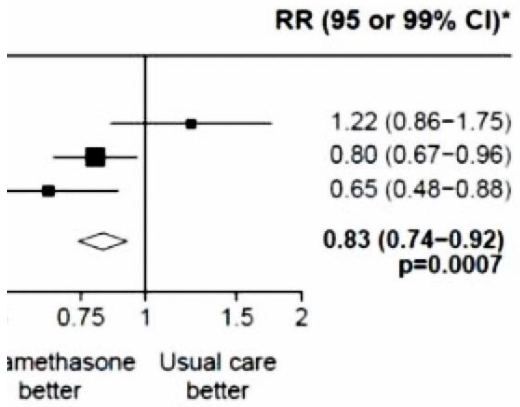
Dexamethasone has been demonstrated to have a clear place in the management of hospitalised patients with COVID-19.

There were no excess harms identified in using this dose of dexamethasone in this patient population. Dexamethasone was not used in pregnant women.

Clinicians should therefore consider dexamethasone for the management of hospitalised patients with COVID-19 who require oxygen or ventilation.

Out of hospital treatment is not appropriate.

There is no current or anticipated constraint on supply of the medicine in the UK.



Dexamethasone:

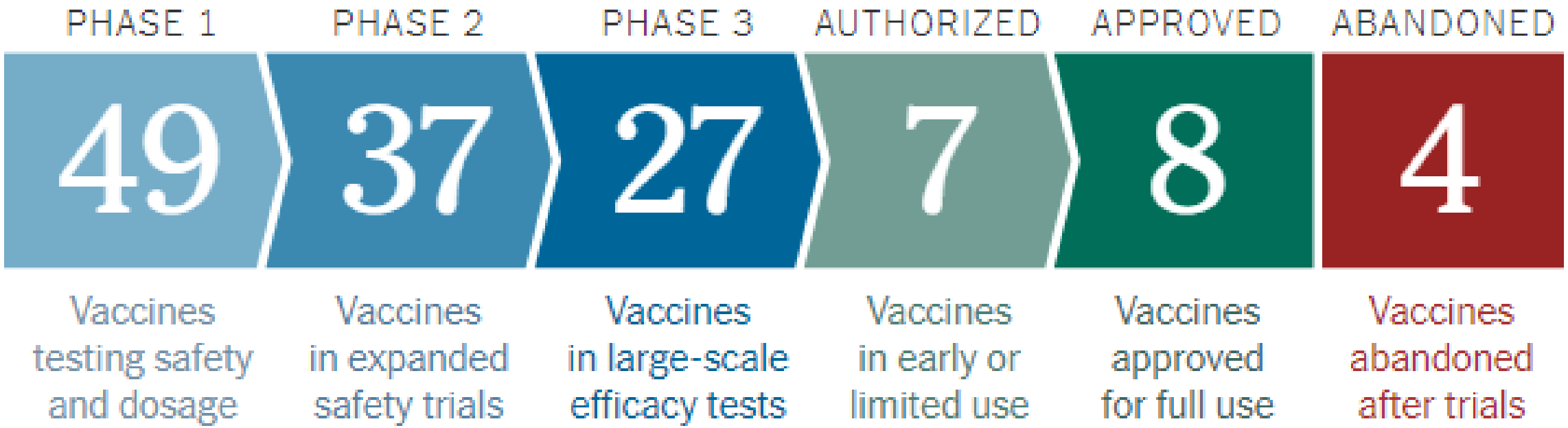
- **reduced deaths by one-third** in ventilated patients (0.65, CI 0.48 to 0.88; p=0.0003)
- **reduced deaths by on fifth** in other patients on oxygen (0.80 [0.67 to 0.96]; p=0.0021)

UK policy was immediately changed by the Chief Medical Officer

https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1 .

Coronavirus Vaccine Tracker

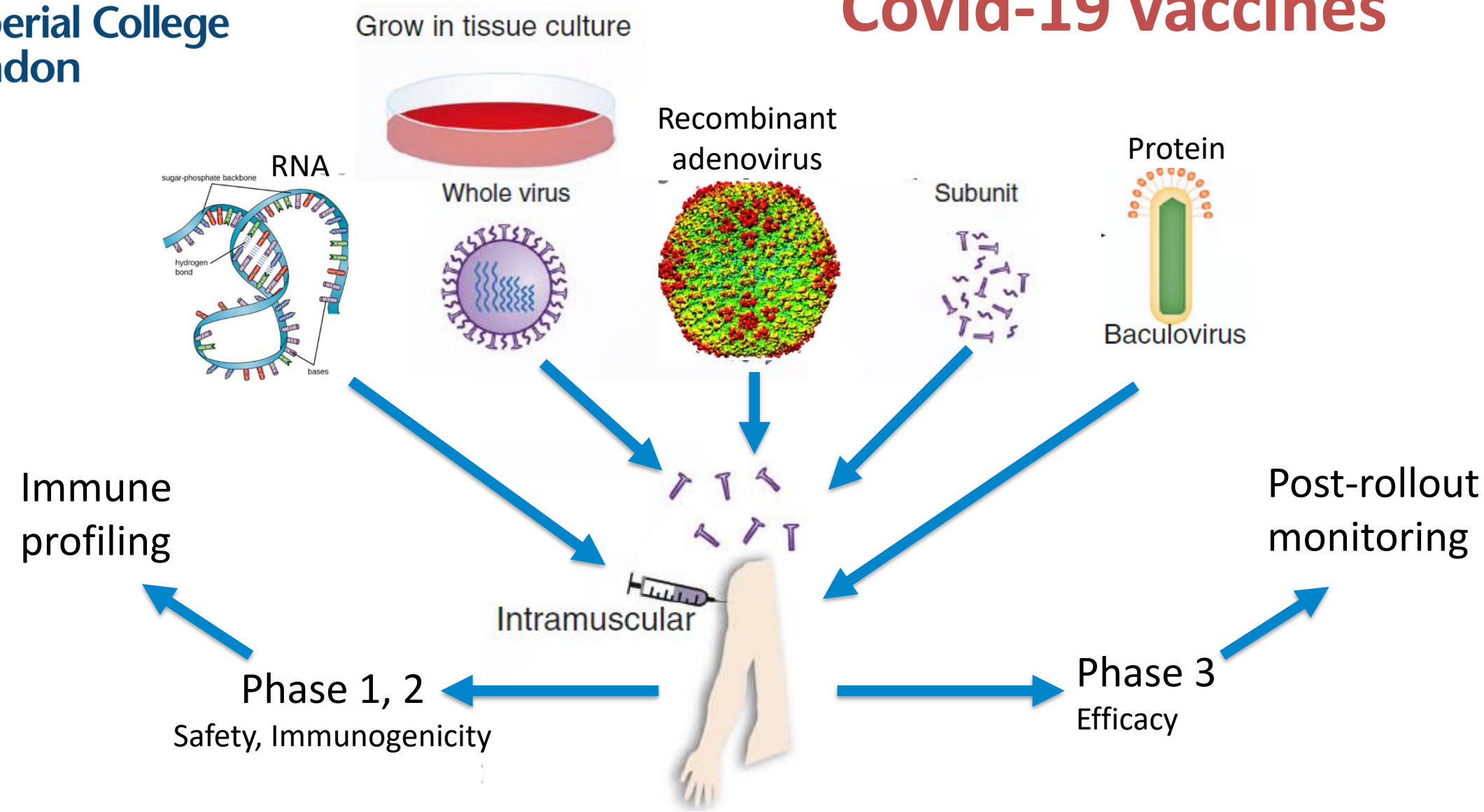
By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated May 18, 2021



https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Imperial College London

Covid-19 vaccines



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UK Vaccine Taskforce pre-orders

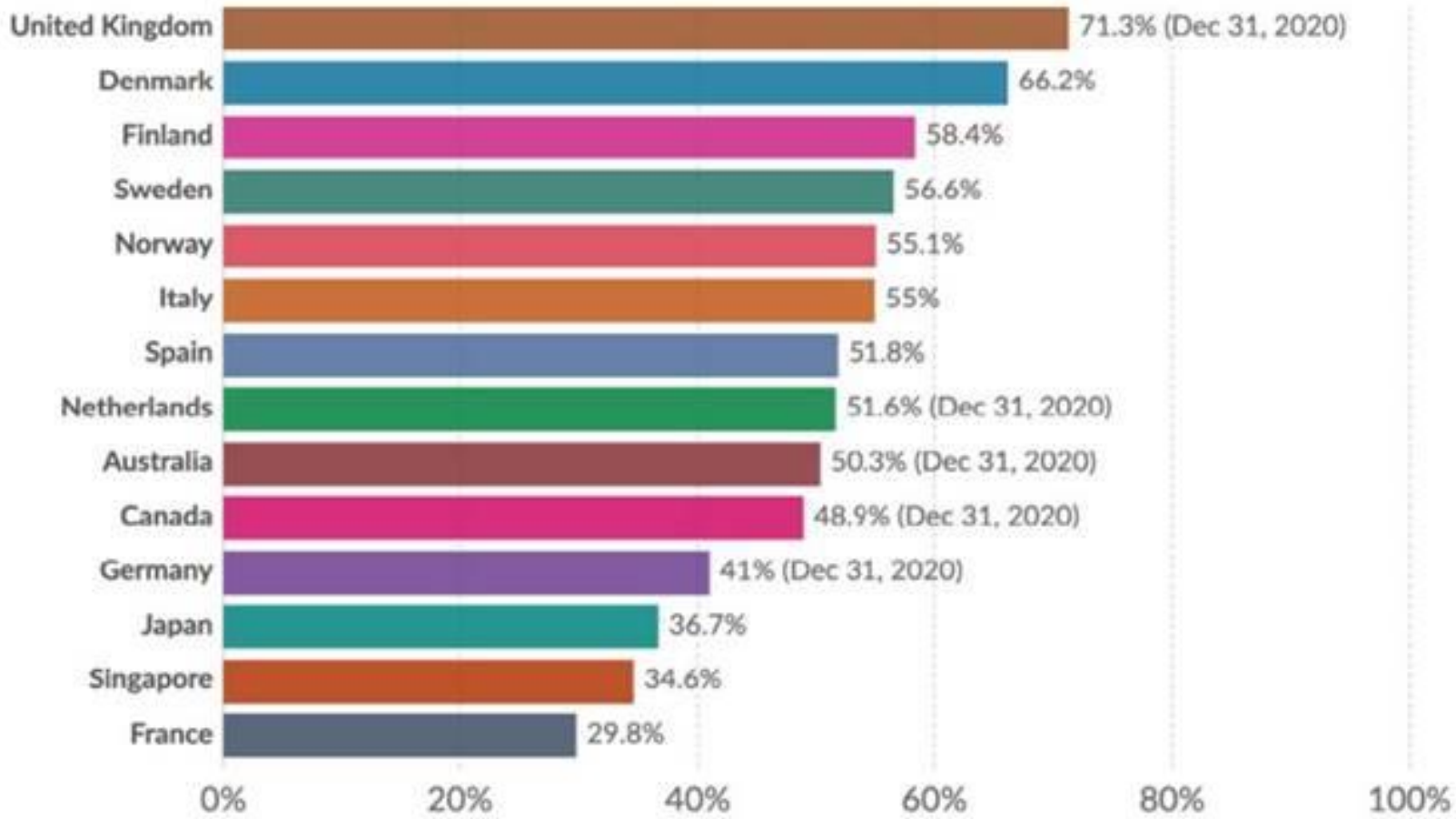
417 million doses commissioned by UK

• **Oxford/AstraZeneca:**	Approved Jan 21	100 million doses
• **BioNTech/Pfizer**.	Approved Dec 20	90 million doses
• **Moderna**	Approved Jan 21	17 million doses
• **Novavax**:	Phase 3	60 million doses
• **GSK/Sanofi**:	Delayed	60 million doses
• **Valneva** (Livingstone, Scot.):	Pre-clinical trials	60 million doses
• **Janssen/Johnson & Johnson**.		30 million doses

Share who would get a COVID-19 vaccine if it was available to them this week, Jan 14, 2021

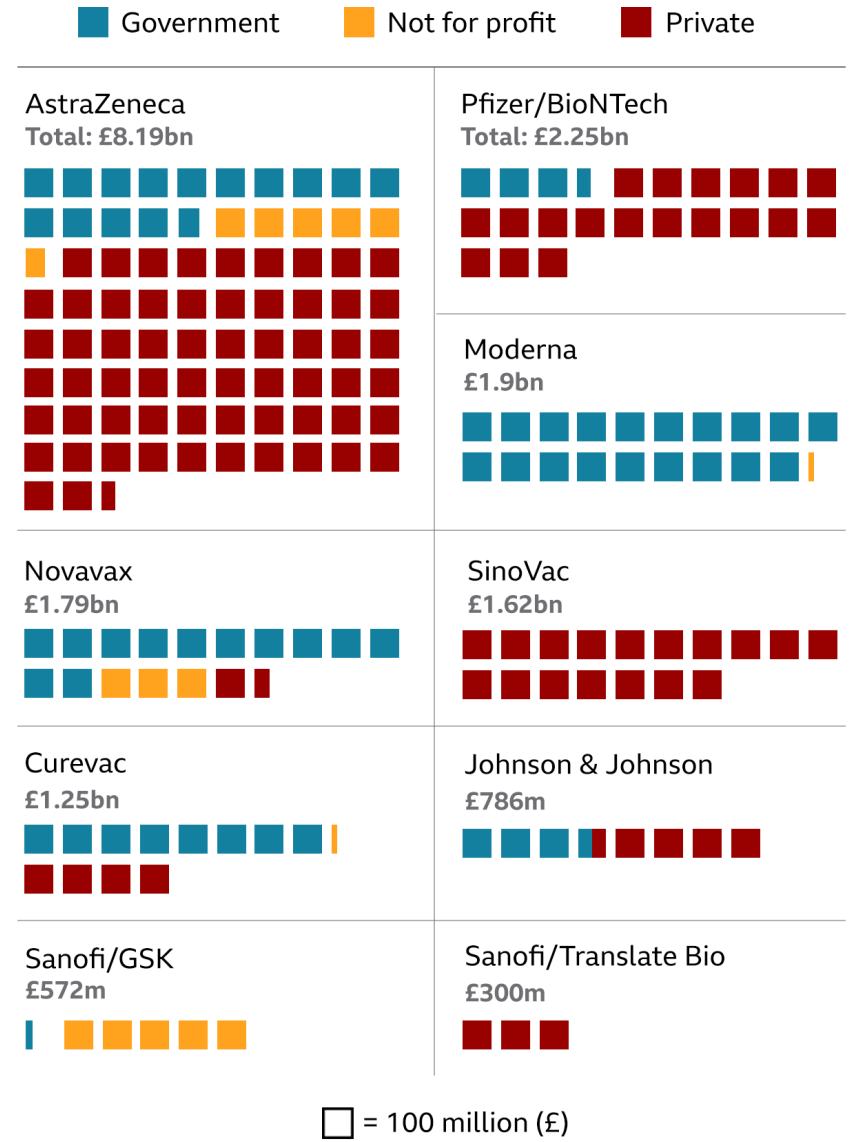
Our World in Data

Share of survey respondents who agree with the statement: "If a COVID-19 vaccine were made available to me this week, I would definitely get it."



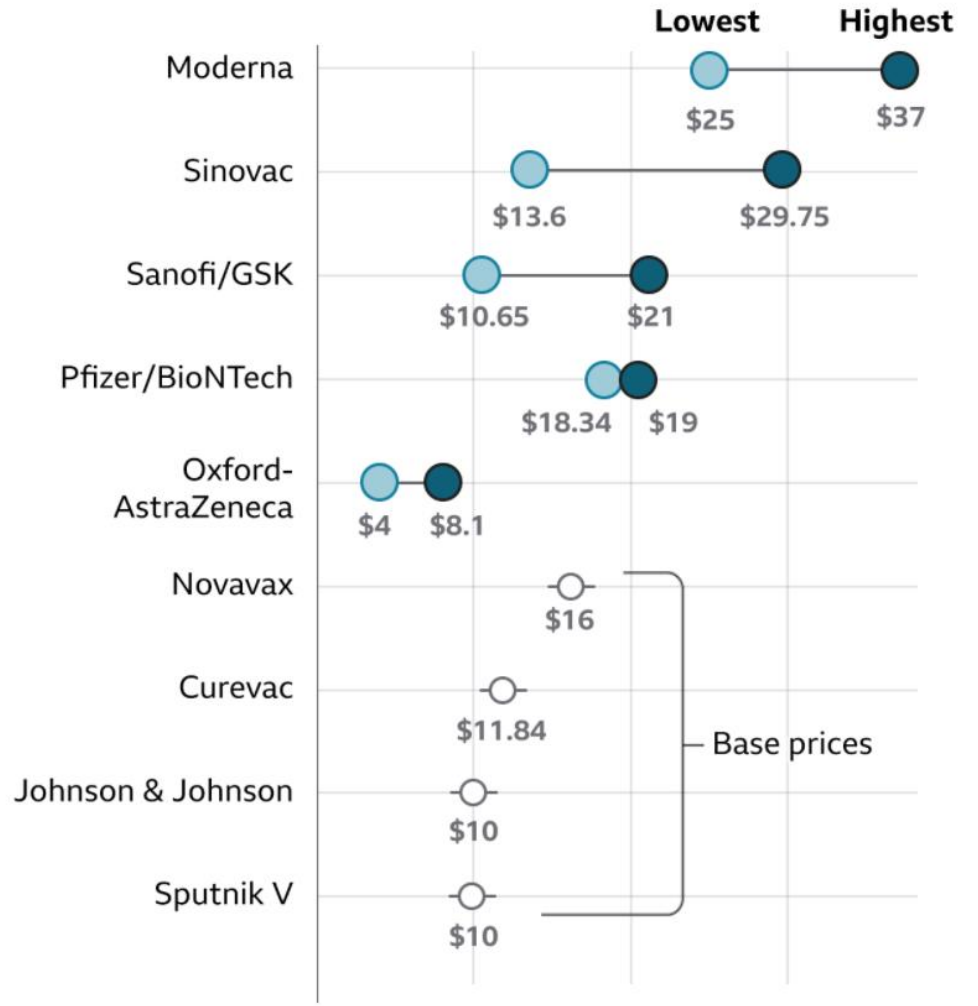
Source: Imperial College London YouGov Covid 19 Behaviour Tracker Data Hub – Last updated 18 January 2021, 09:52 (London time)
Note: Months containing fewer than 500 survey respondents are excluded. Respondents were presented with a 1 to 5 scale, ranging from "Strongly agree" (1) to "Strongly disagree" (5). We consider responses of 1 or 2 to be in agreement with the statement.
OurWorldInData.org/covid-vaccinations • CC BY

Who has funded the Covid vaccines?



Source: Airfinity BBC

Price per dose ($USD)



Note: all prices are subject to trade agreements

Source: Unicef, US Government contracts, WHO BBC

https://www.bbc.co.uk/news/business-55170756

What level of neutralising antibody protects from COVID-19?

David S Khoury… Miles P Davenport

Modelled relationship between in vitro neutralisation and observed protection (data from 7 current vaccines and cohorts.

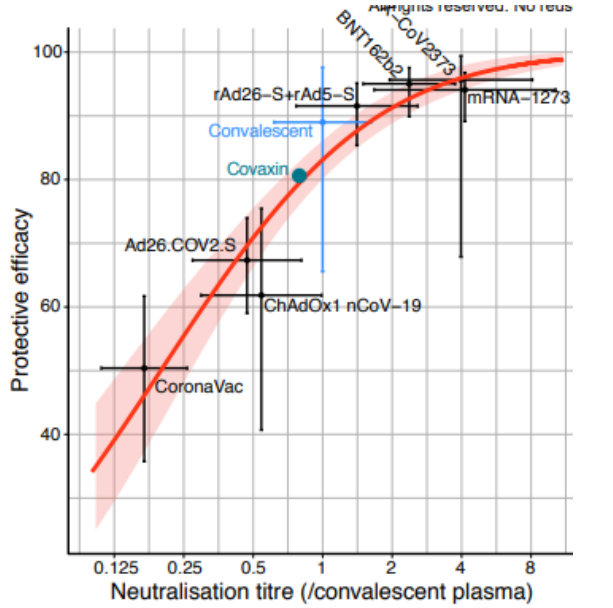
Neut titre is highly predictive of immune protection.

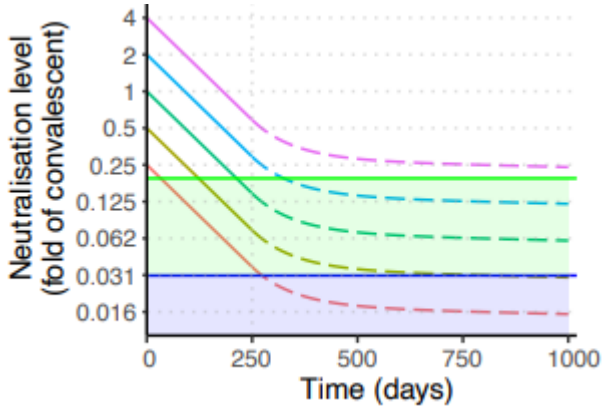
50% protective neut vs. SARS-CoV-2 infection was ~20% of the average convalescent level; 50% protection from severe infection was ~3% of the mean convalescent level

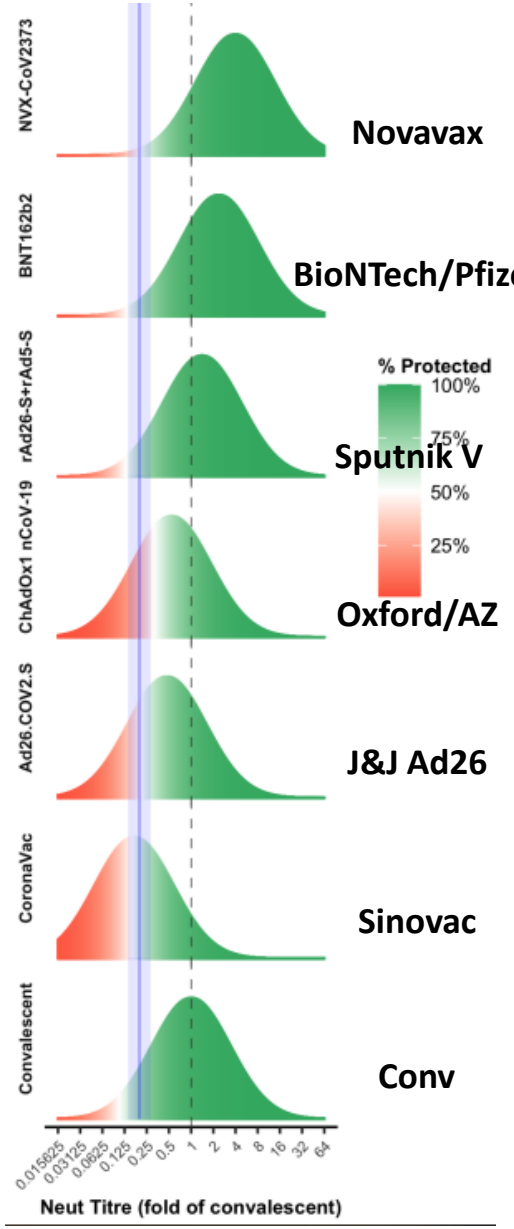
Modelling showed that neut Ab titre in vaccinated subjects was at least as rapid as the decay in convalescent subjects.

Decay over the first 250 days after immunisation predicts a significant loss of protection, although protection from severe disease should be largely retained.

Neut titres vs. some SARS-CoV-2 variants are reduced







Posted March 11, 2021: https://doi.org/10.1101/2021.03.09.21252641

Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial

https://doi.org/10.1016/S0140-6736(20)32466-1

Maheshi N Ramasamy, Angela M Minassian*, Katie J Ewer*, Amy L Flaxman*, Pedro M Folegatti*, Daniel R Owens*, Merryn Voysey*, Marion E E Watson, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Saul N Faust*, Andrew J Pollard*, and the Oxford COVID Vaccine Trial Group*

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-020-01179-4

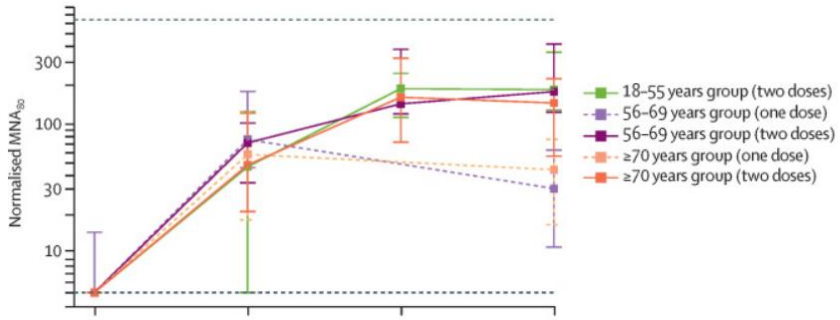
Check for updates

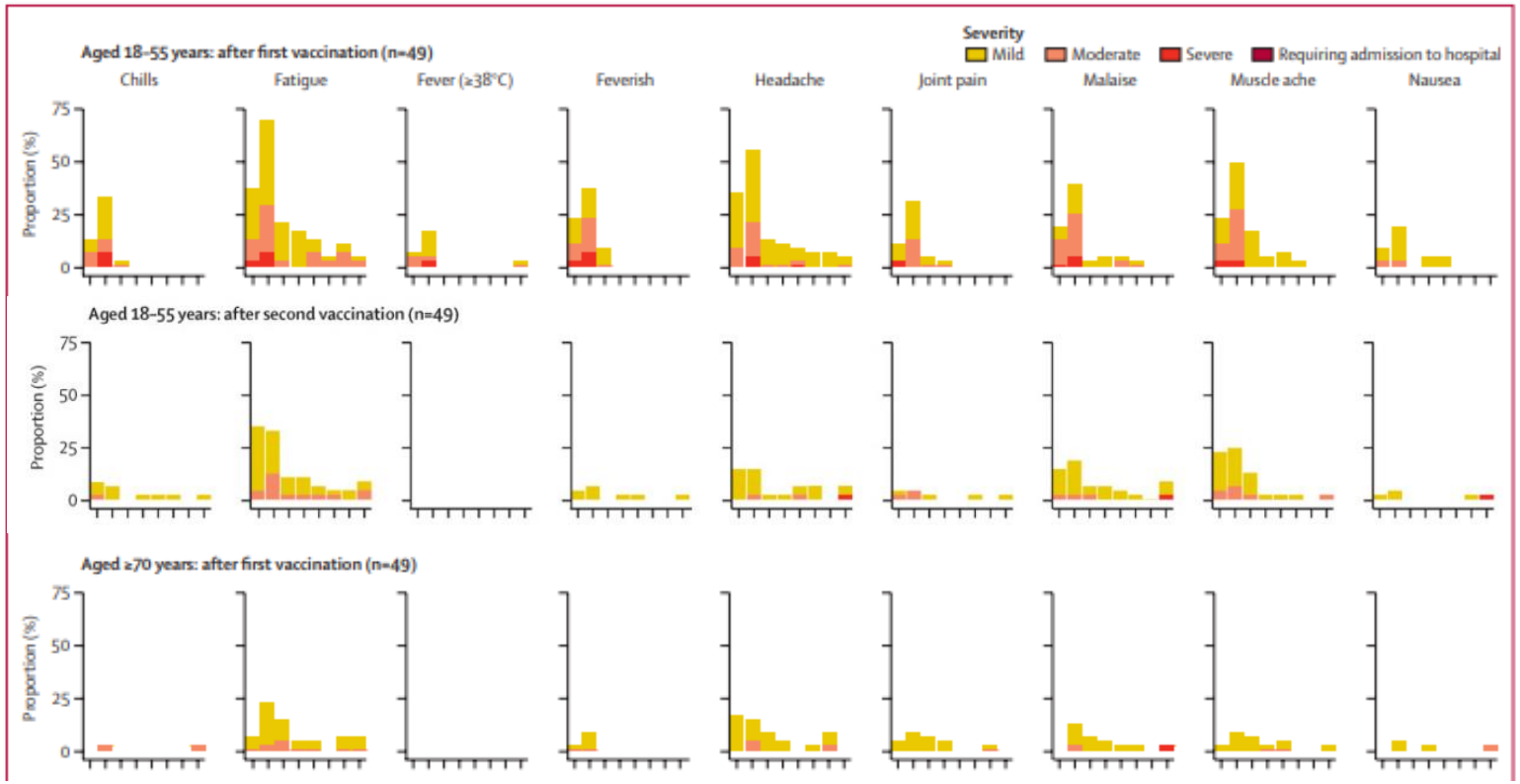
Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses

Jordan R. Barrett[1,22], Sandra Belij-Rammerstorfer[1,22], Christina Dold[2,22], Katie J. Ewer[1,22], Catherine M. Green[5,22], Adrian V. S. Hill[1,22], Teresa Lambe[1,22], Sarah Gilbert[1,22], Andrew J. Pollard[2,22] ✉ and the Oxford COVID Vaccine Trial Group*

ChAdOx1 nCoV-19:

- Systemic adverse effects transient
- Better tolerated in adults >70y than in younger adults
- Booster dose has <u>fewer</u> side effects
- Has similar immunogenicity across all age groups after boosting
- T-cell responses peaked at day 14 after a single standard dose





https://www.nature.com/articles/s41591-020-01179-4

Published **Online** December 8, 2020 https://doi.org/10.1016/S0140-6736(20)32661-1
See **Online/Comment** https://doi.org/10.1016/S0140-6736(20)32623-4

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

Merryn Voysey, Sue Ann Costa Clemens*, Shabir A Madhi*, Lily Y Weckx*, Pedro M Folegatti*, Parvinder K Aley, Brian Angus, Vicky L Baillie, Tonya L Villafana, Marion E E Watson, Christopher J Williams, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard* on behalf of the Oxford COVID Vaccine Trial Group†*

Design: Assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control (Men A, C, W, and Y conjugate vaccine/saline), given 2.5 or 5 × 10^{10} viral particles (UK subset given half dose 1st)
Outcome: Efficacy vs. symptomatic COVID-19 in seronegative participants (PCR+ve , >14 days after 2nd dose)

Findings: 23,848 participants enrolled; interim report of 11 636 participants (7548 in the UK, 4088 in Brazil)

Two standard doses:	efficacy 62.1% (95%; CI 41 to 76%]
Low dose/ standard dose:	efficacy 90% (95% CI 67 to 97%).
Pooled:	efficacy 70.4% (95% CI 54.8 to 80.6%)

From 21 days after the first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death.

Asymptomatic infections were detected in 69 participants. Vaccine efficacy in the 24 LD/SD recipients was 58·9% (95% CI 1·0 to 82·9), but 3·8% (−72·4 to 46·3) in the 45 participants receiving SD/SD (table 2).

175 severe adverse events in 168 participants
- 84 events in the ChAdOx1 nCoV-19 group
- 91 in the control group.

Three events possibly related to a vaccine: one in the ChAdOx1 nCoV-19 group, one in the control group and one in a participant who remains masked to group allocation.

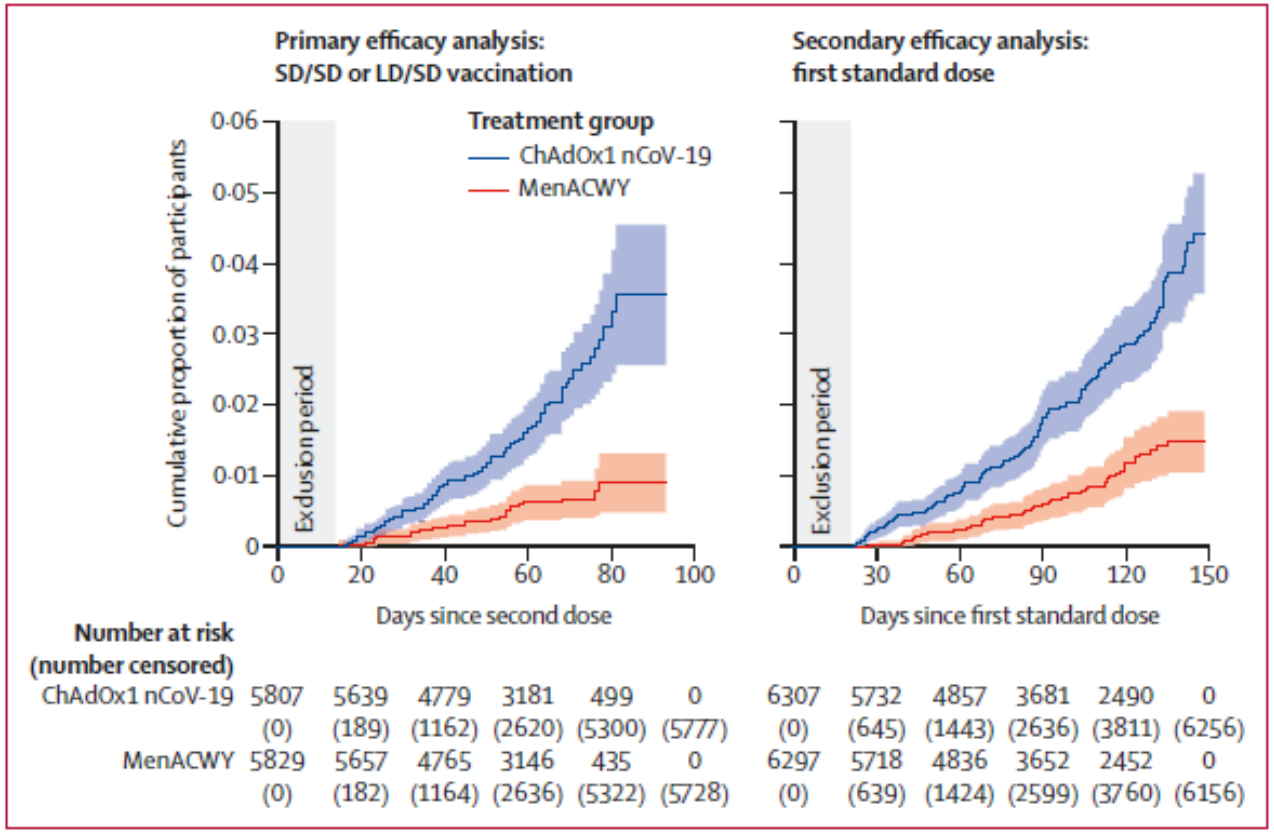


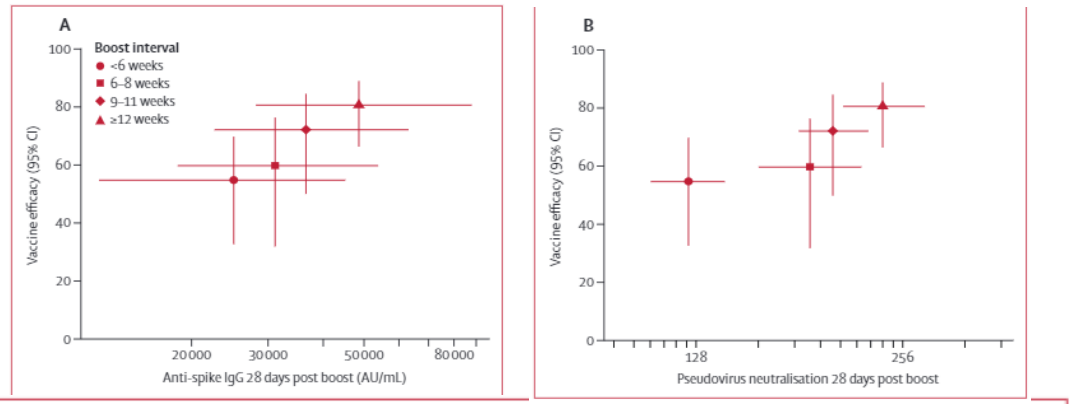
***Figure*: Kaplan-Meier cumulative incidence of primary symptomatic, NAAT-positive COVID-19**
Cumulative incidence of symptomatic COVID-19 after two doses (left) or after first standard dose in participants receiving only standard-dose vaccines (right). Grey shaded areas show the exclusion period after each dose in which cases were excluded from the analysis. Blue and red shaded areas show 95% CIs. NAAT=nucleic acid amplification test.

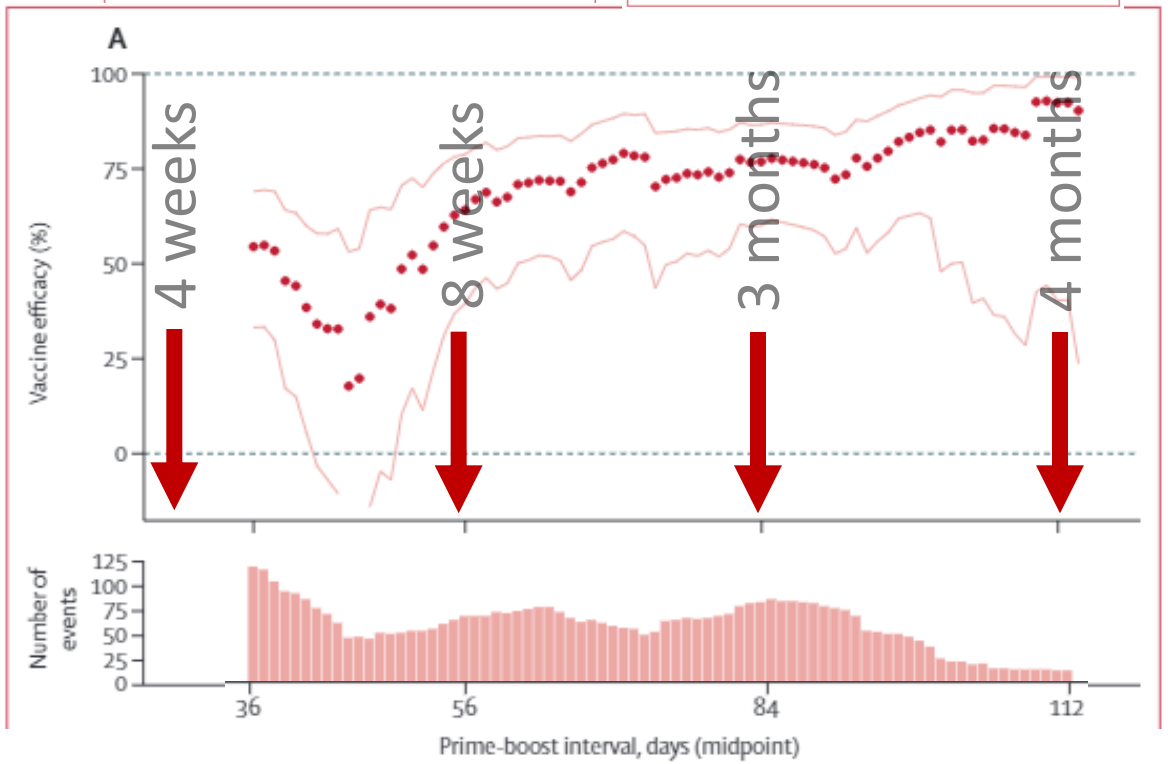
Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials

Merryn Voysey, Sue Ann Costa Clemens*, Shabir A Madhi*, Lily Y Weckx*, Pedro M Folegatti*, Parvinder K Aley, Brian Angus, Vicky L Baillie, Thomas White, Christopher J Williams, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard*, on behalf of the Oxford COVID Vaccine Trial Group†*

Oxford AstraZeneca vaccine shows sustained protection of 76% during the 3-month interval until the second dose

- Single standard dose efficacy from day 22 to day 90 post vaccination of 76%
- No decline in protection in 3-month period
- Efficacy from two standard doses is 82.4% with the 3-month interval, supporting use of 4-12 week prime-boost dosing interval
- Analyses of PCR positive swabs in UK population suggests vaccine may have substantial effect on transmission of the virus with 67% reduction in positive swabs among those vaccinated





Online February 19, 2021 https://doi.org/10.1016/S0140-6736(21)00432-3

ORIGINAL ARTICLE

Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant

S.A. Madhi, V. Baillie, C.L. Cutland, M. Voysey, A.L. Koen, L. Fairlie,

BACKGROUND

Safety and efficacy against emerging SARS-CoV-2 variant B.1.351 (501Y.V2)

METHODS

ChAdOx1 nCoV-19 vaccine (AZD1222) in South Africa age 18 to less than 65 years; Two doses, 21 to 35 days apart. Assessed >14 days after 2nd dose.

RESULTS

2026 HIV-negative adults (median 30 y). Pseudovirus and the live-virus neut showed resistance B.1.351 variant

Mild-to-moderate Covid in 23 of 717 placebo recipients (3.2%) vs. 19 of 750 vaccine recipients (2.5%)

(efficacy of 21.9% (95% CI −49.9 to 59.8).

39 cases (92.9%) were caused by the B.1.351 variant

Efficacy against this variant was 10.4% (95% CI, −76.8 to 54.8).

CONCLUSIONS

ChAdOx1 nCoV-19 vaccine did not protect against mild-to-moderate Covid due to the B.1.351 variant in younger people.

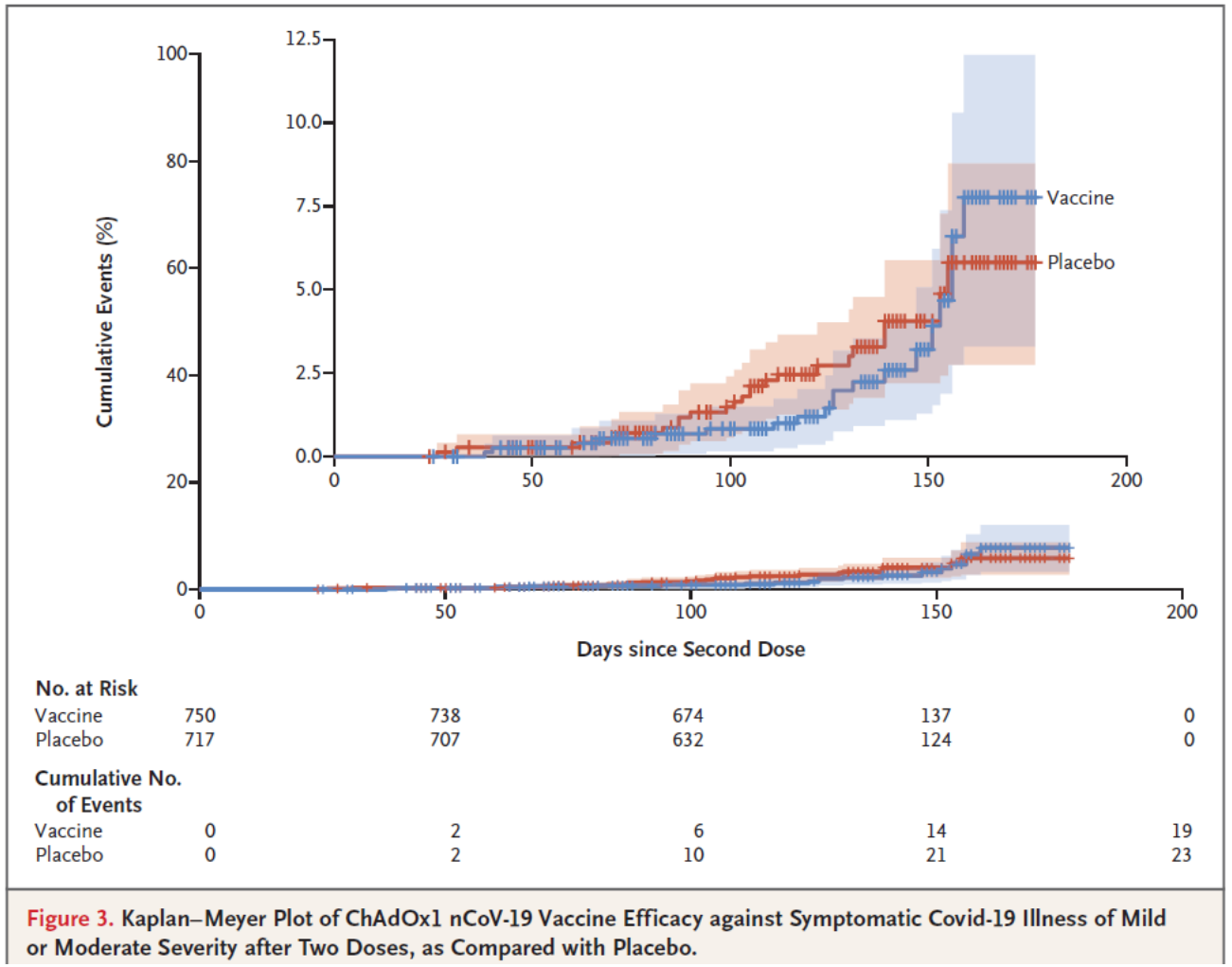


Figure 3. Kaplan–Meyer Plot of ChAdOx1 nCoV-19 Vaccine Efficacy against Symptomatic Covid-19 Illness of Mild or Moderate Severity after Two Doses, as Compared with Placebo.

This article was published on March 16, 2021, at NEJM.org.
DOI: 10.1056/NEJMoa2102214

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

170 cases of Covid-19 in trial of >43,000 persons
162 cases of COVID-19 in the placebo arm, 8 in the vaccine group.

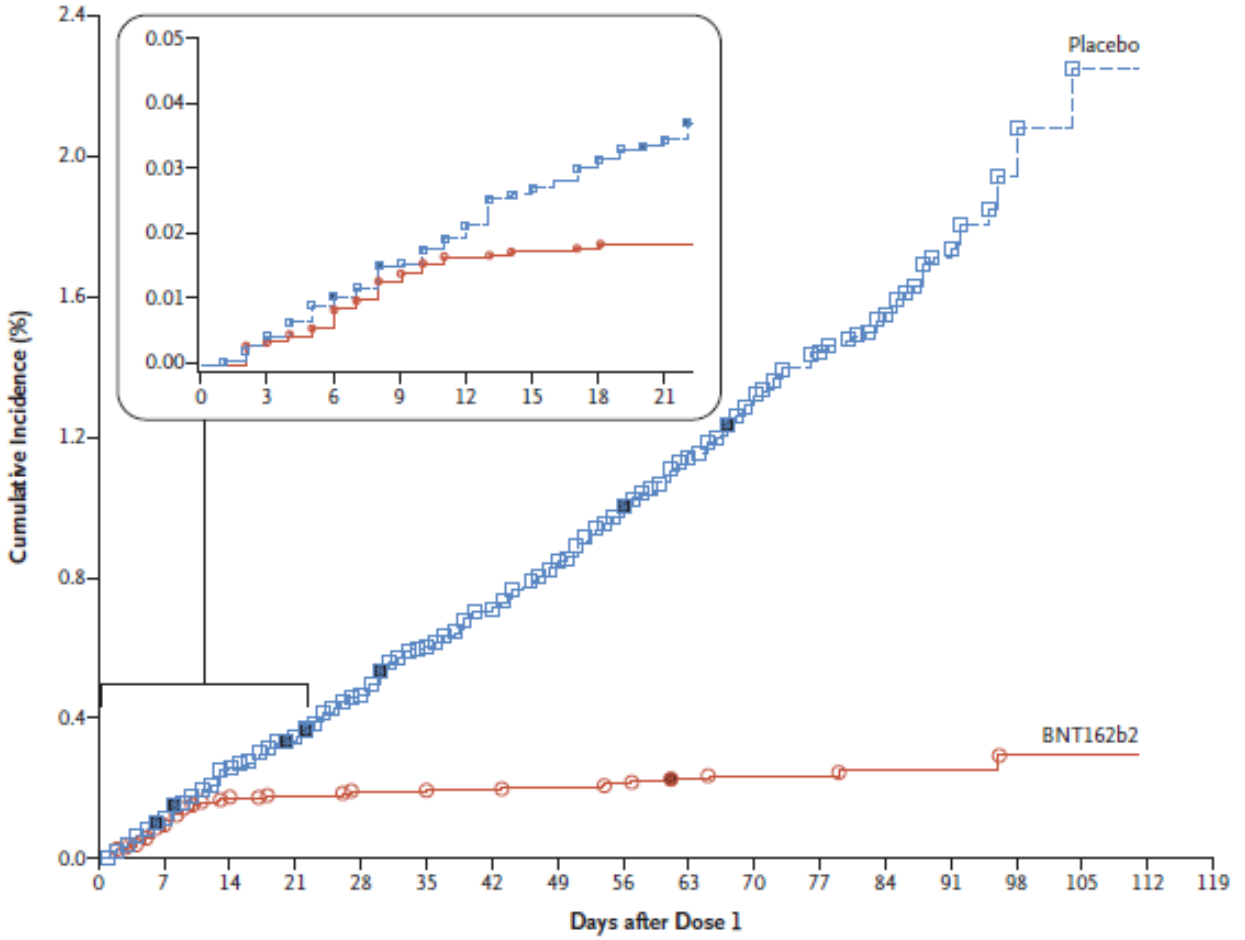
Efficacy in adults over 65 years >94%.

Ten people developed severe COVID-19, one in vaccine group.

'Severe' adverse events >2% of those vaccinated: fatigue (3.7%, 2nd dose). Some subsequent reports of 'severe' reactions.

Older adults tended to report fewer and milder solicited adverse events following vaccination.
About $20 per dose, $40 per person vaccinated

https://www.nejm.org/doi/10.1056/NEJMoa2034577
10th Dec 2020



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	BNT162b2, 30 μg (N=21,669) Surveillance time *person-yr (no. at risk)*	Placebo (N=21,686) No. of participants	Placebo (N=21,686) Surveillance time *person-yr (no. at risk)*	VE (95% CI) *percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Figure 3. Efficacy of BNT162b2 against Covid-19 after the First Dose.

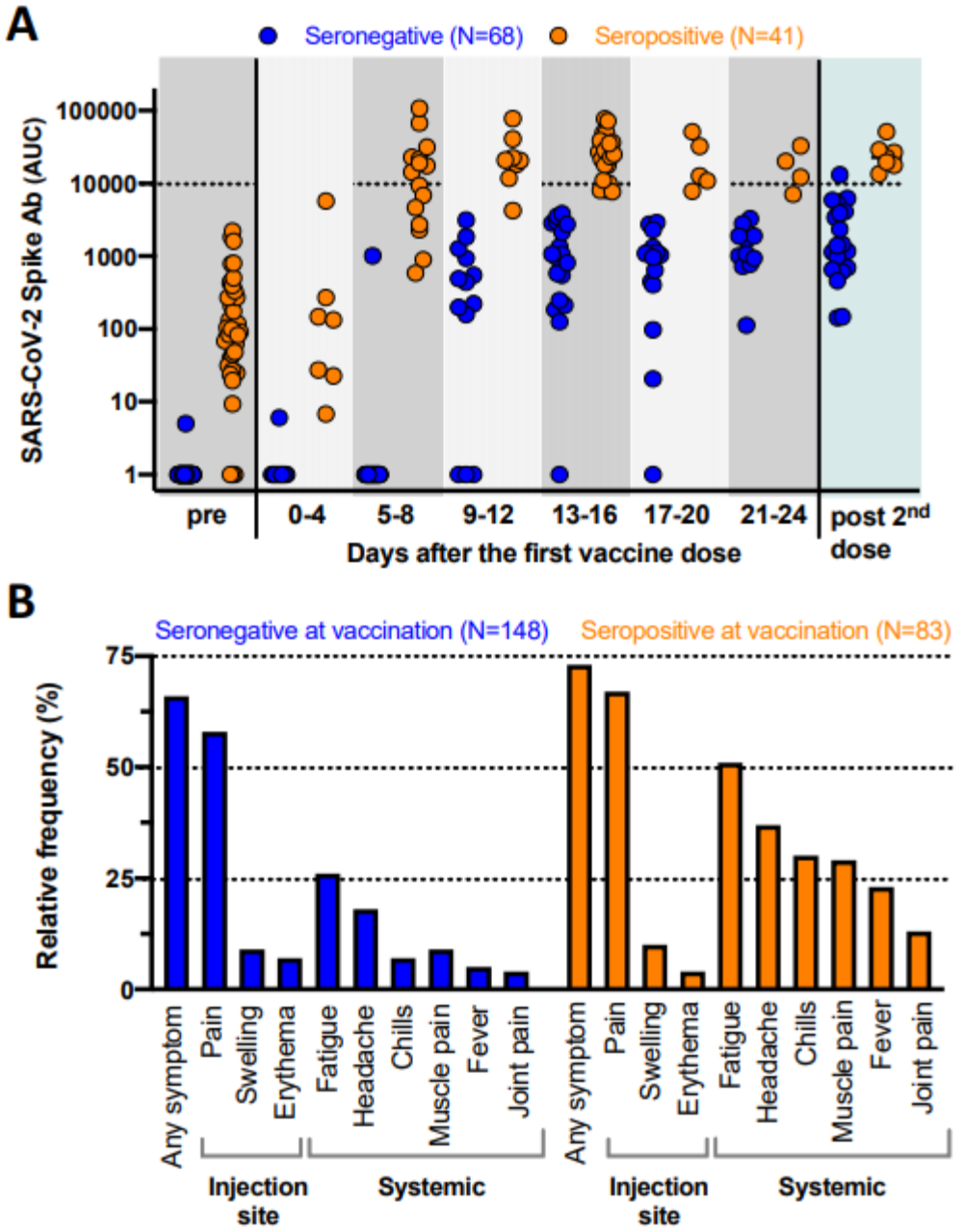
Robust spike antibody responses and increased reactogenicity in seropositive individuals after a 2 single dose of SARS-CoV-2 mRNA vaccine

Florian Krammer, Komal Srivastava, the PARIS team and Viviana Simon

A: Antibody response to the first vaccine dose in individuals with pre-existing immunity is equal to or exceeds those in seronegatives given 2 doses.

B: Adverse effects are increased in those who have been infected with SARS-CoV-2 in the past.

One dose of vaccine is enough for those who have been infected, would spare them from unnecessary adverse effects and free up vaccine doses for others.



https://www.medrxiv.org/content/10.1101/2021.01.29.21250653v1.full.pdf

See also **doi:** https://doi.org/10.1101/2021.01.30.21250843

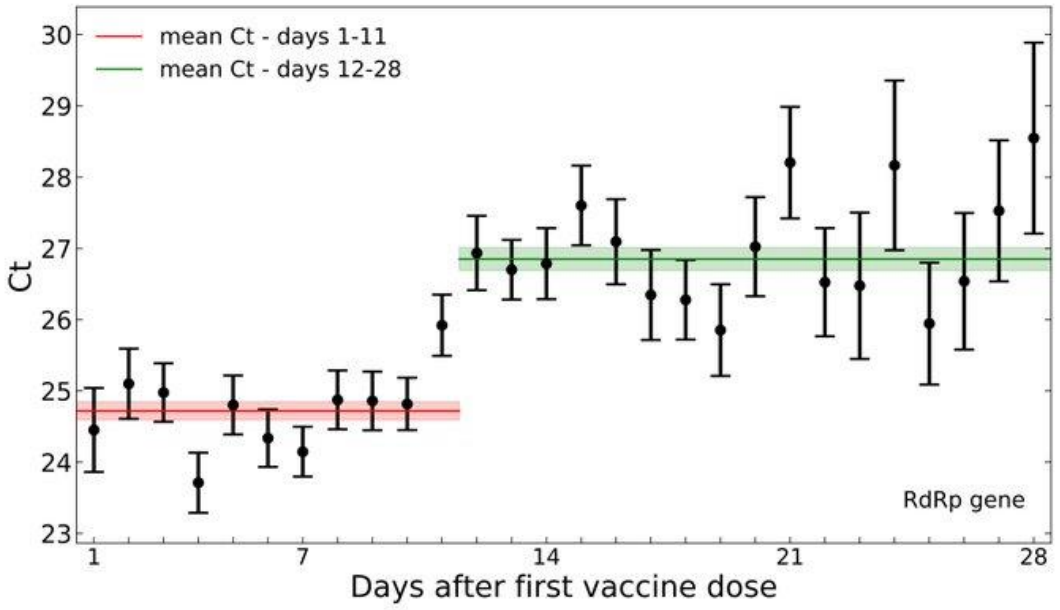
Reduced viral loads 12 days following Pfizer-BioNTech #COVID19 vaccine.

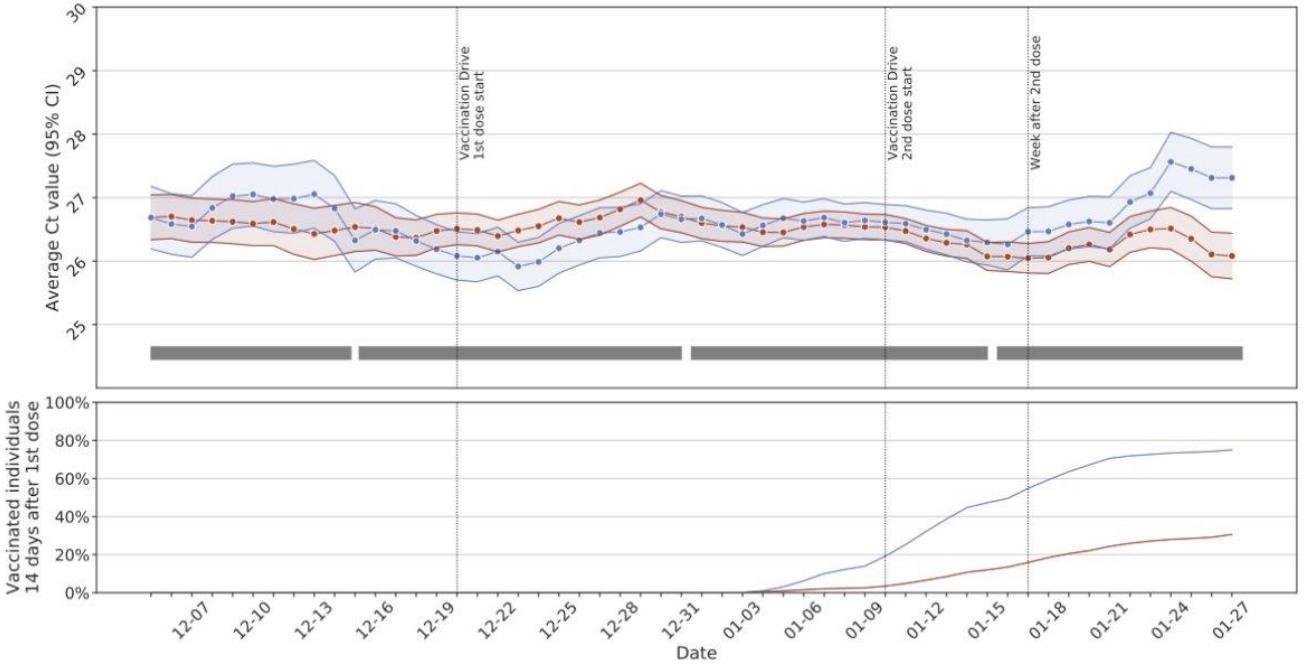
medRxiv (to appear soon). with @idanyelin @MatanLevine in collaboration with #MaccabiTech; @TechnionLive

https://twitter.com/RoyKishony/status/1358695273468469250

https://www.medrxiv.org/content/10.1101/2021.02.06.21251283v1.full.pdf

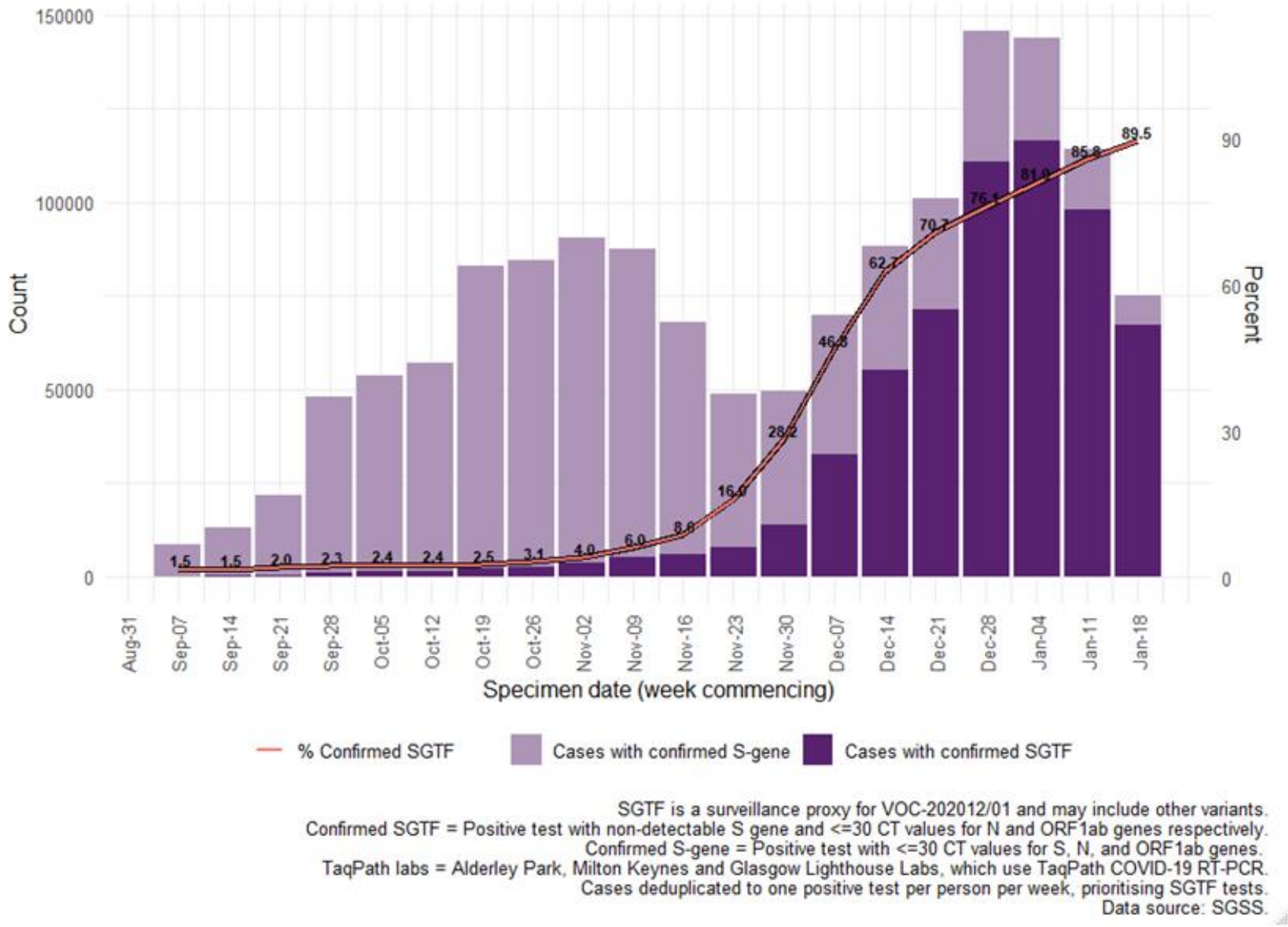
Since vaccination was started in Israel with 60+, we can compare the average Ct value positives in this age group as a function of time and compare to 40-60 as a control.
Here are the results: [Red: 60+;Blue:40-60]
https://twitter.com/erlichya/status/1358477762495930368





"We are in a national emergency," Netanyahu told reporters. "I want to give you a jarring fact: Over the last month - the last 30 days - 1,536 people have died (of COVID-19) in the State of Israel. More than 97% of them had not been vaccinated. Fewer than 3% had been vaccinated." https://www.reuters.com/article/us-health-coronavirus-israel-idUSKBN2A91KU

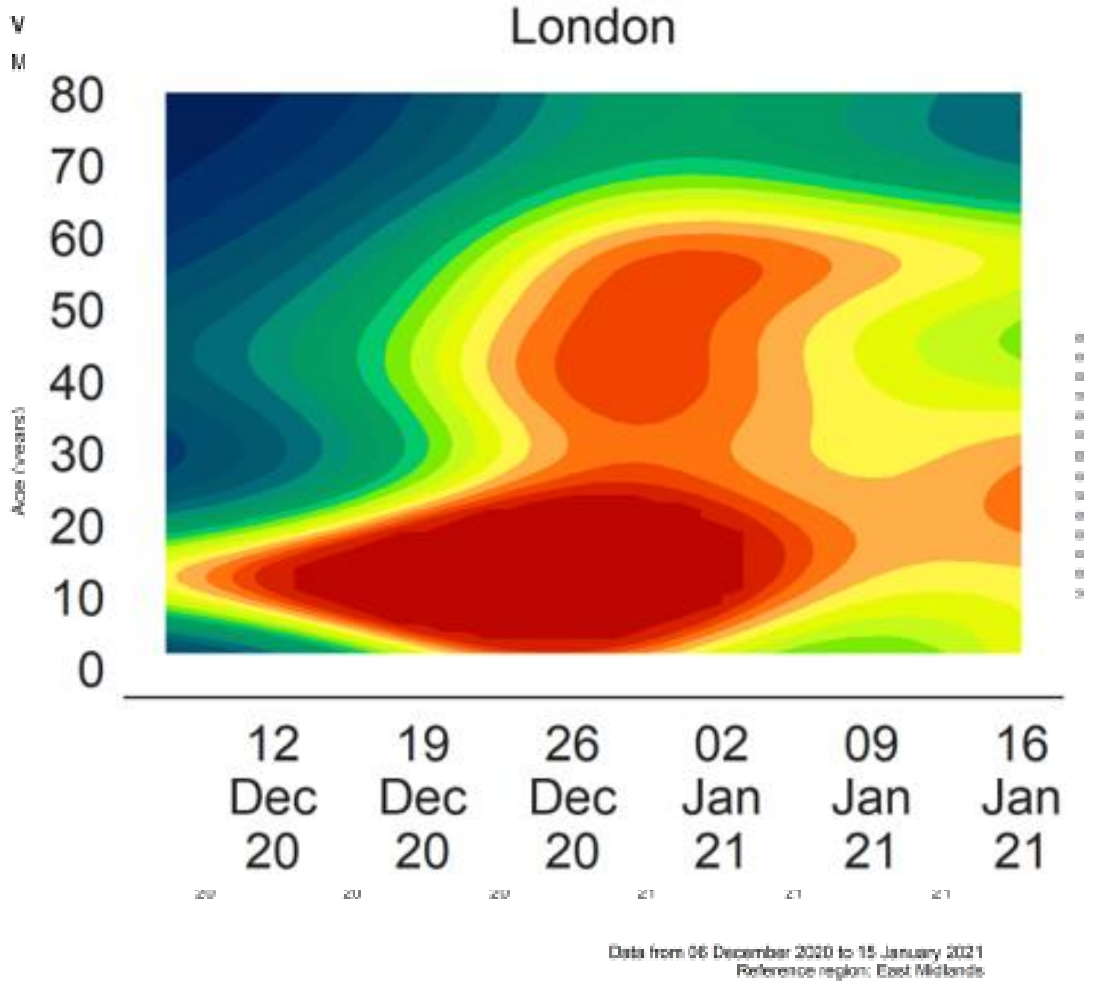
NERVTAG 29th Jan 21



SGTF is a surveillance proxy for VOC-202012/01 and may include other variants.
Confirmed SGTF = Positive test with non-detectable S gene and <=30 CT values for N and ORF1ab genes respectively.
Confirmed S-gene = Positive test with <=30 CT values for S, N, and ORF1ab genes.
TaqPath labs = Alderley Park, Milton Keynes and Glasgow Lighthouse Labs, which use TaqPath COVID-19 RT-PCR.
Cases deduplicated to one positive test per person per week, prioritising SGTF tests.
Data source: SGSS.

1.13 England characteristics – further analysis on age over time

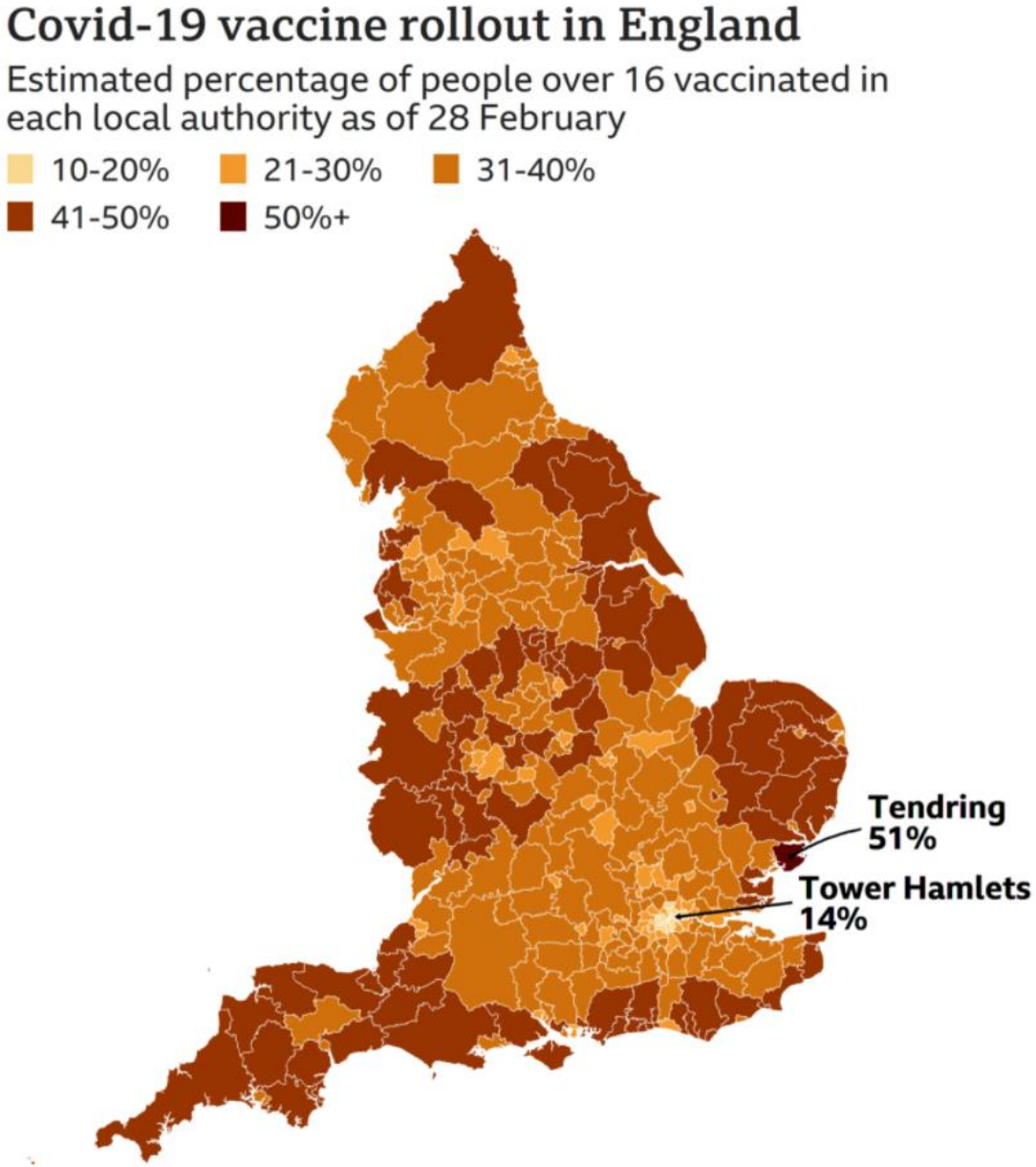
- This national analysis shown here reflects a varied position across regions as shown in the previous slide.
- In England overall, over the most recent week rates show a decrease in all age ranges apart from those aged around 20 to 30.
- The chart scale has been fixed and any positivity rates above 4% would appear in red. This is done so that all the charts for England are comparable.
- Dark blue areas of the chart indicate very low positivity rates, while red areas have the highest positivity rates.
- This analysis uses the same data as that presented on the previous slides, but age is analysed continuously, rather than being grouped into age categories.
- Given the interest on regional trends we will not be including England overall contour plots in the future.

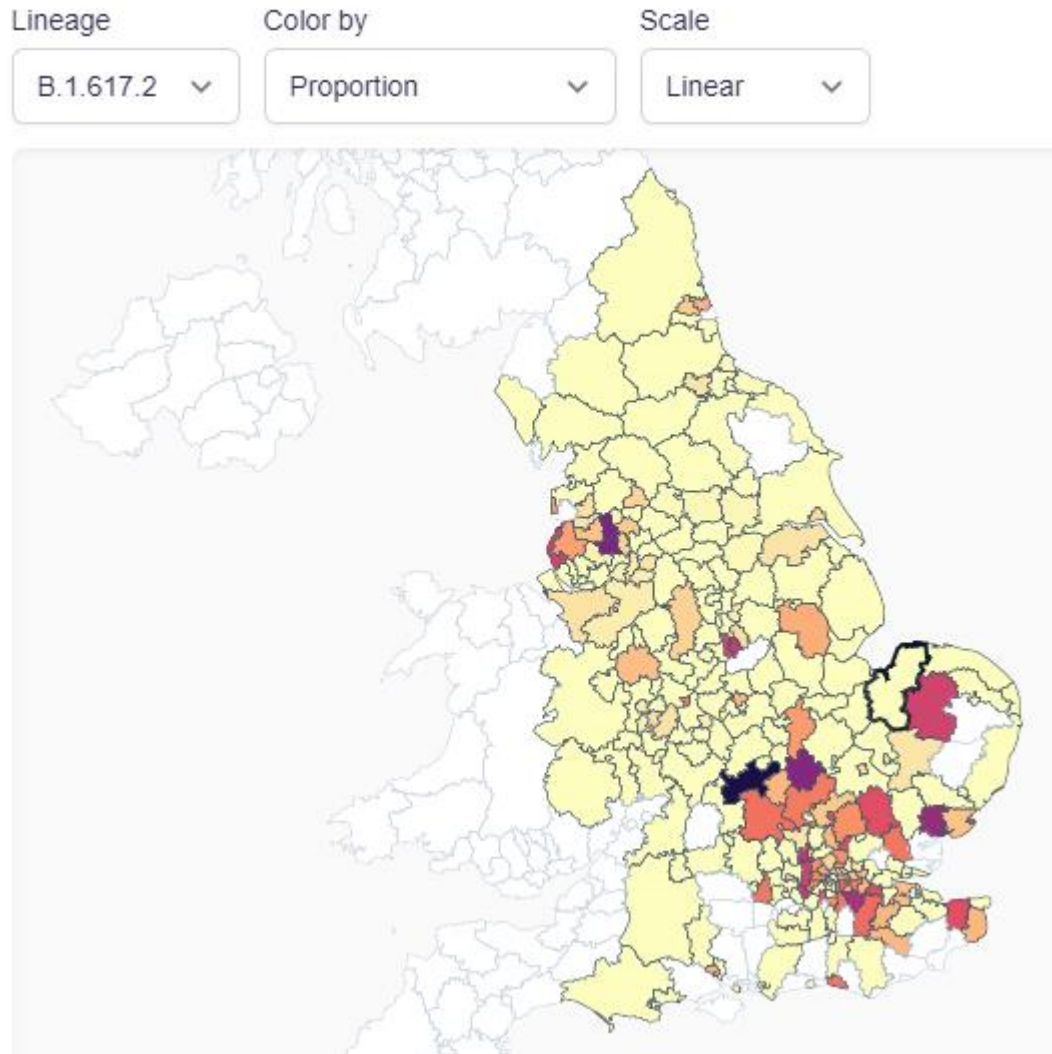


Office for National Statistics

22nd Jan 2021

The modelled estimates are presented at reference values for region. The reference value is the East Midlands. This does not affect the overall trend over time, but other reference values would vary in level between regions.





https://www.bbc.co.uk/news/uk-england-56293839

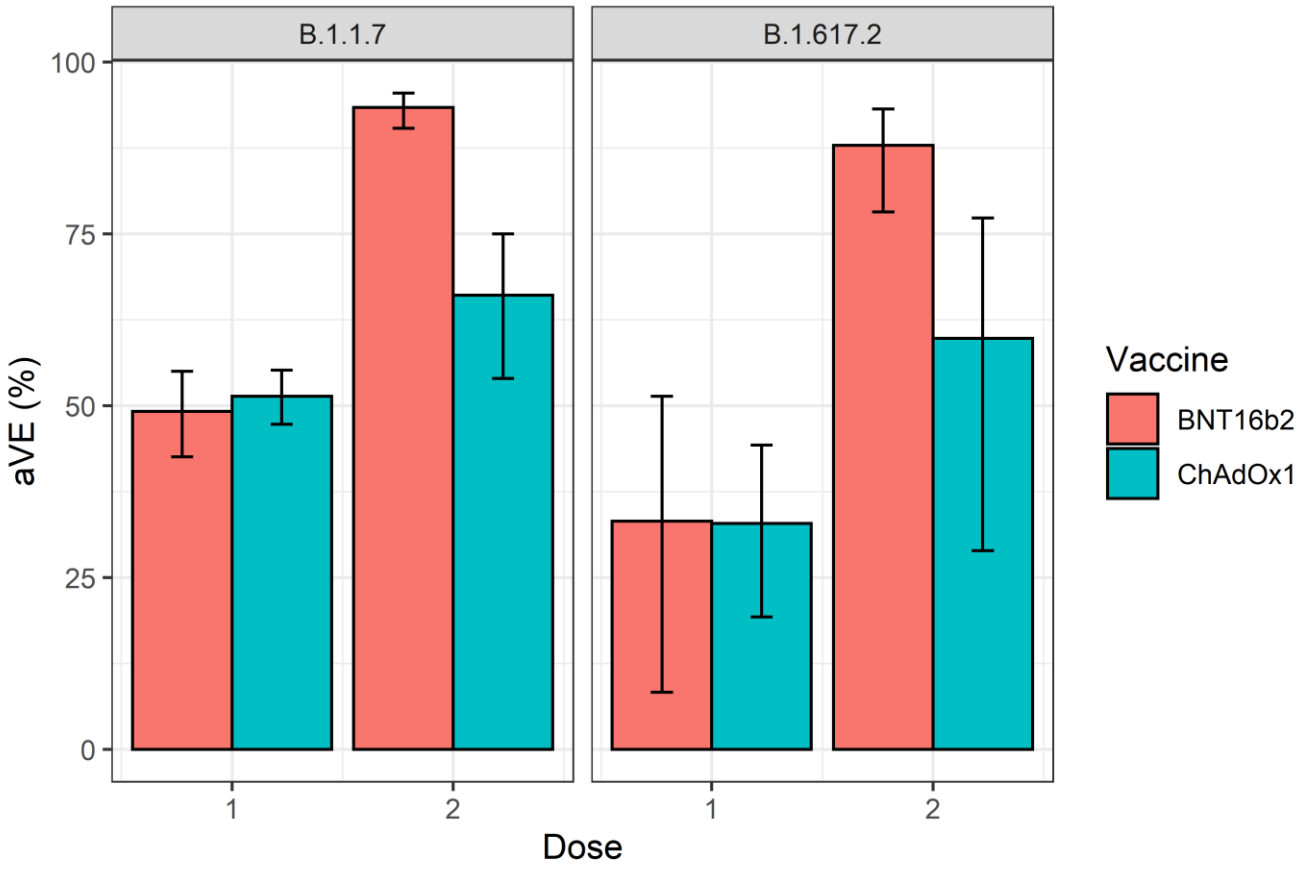
Effectiveness of COVID-19 vaccines against the B.1.617.2 variant

Jamie Lopez Bernal[1,2,3], Nick Andrews[1,2], Charlotte Gower[1], Eileen Gallagher[1], Dr Ruth Simmons[1], Simon Thelwall[1], Julia Stowe[1], Elise Tessier[1], Natalie Groves[1], Gavin Dabrera[1], Richard Myers[1], Vanessa Saliba[1,2], Shamez Ladhani[1,2], Colin Campbell[1,2], Gayatri Amirthalingam[1,2], Matt Edmunds[1], Maria Zambon[1,3], Kevin Brown[1,2], Susan Hopkins[1,4], Meera Chand[1,5], Mary Ramsay[1,2]

1. Public Health England, London, United Kingdom

- After one dose of either vaccine, there's lower protection against the 617.2 Indian variant cf. the 117 Kent variant
- After two doses of either vaccine, there's little difference in vaccine effectiveness against the B.1.617.2 variant.
- After 2 doses the Pfizer vaccine seems more protective than the AZ vaccine
- Supports giving 2nd doses to vulnerable groups.

Protection vs symptomatic disease



https://khub.net/documents/135939561/430986542/Effectiveness+of+COVID-19+vaccines+against+the+B.1.617.2+variant.pdf/204c11a4-e02e-11f2-db19-b3664107ac42

21st May 21

Imperial College London

What has immunology done?

- Helped understand the disease
- Identified mechanisms of acute and COVID
- Assisted in commercial/clinical tests
- Vaccine and therapeutics:
  - Prediction of outcomes
  - Discovered therapeutics
  - Enabled vaccines