

PONTIFICIA | PRO
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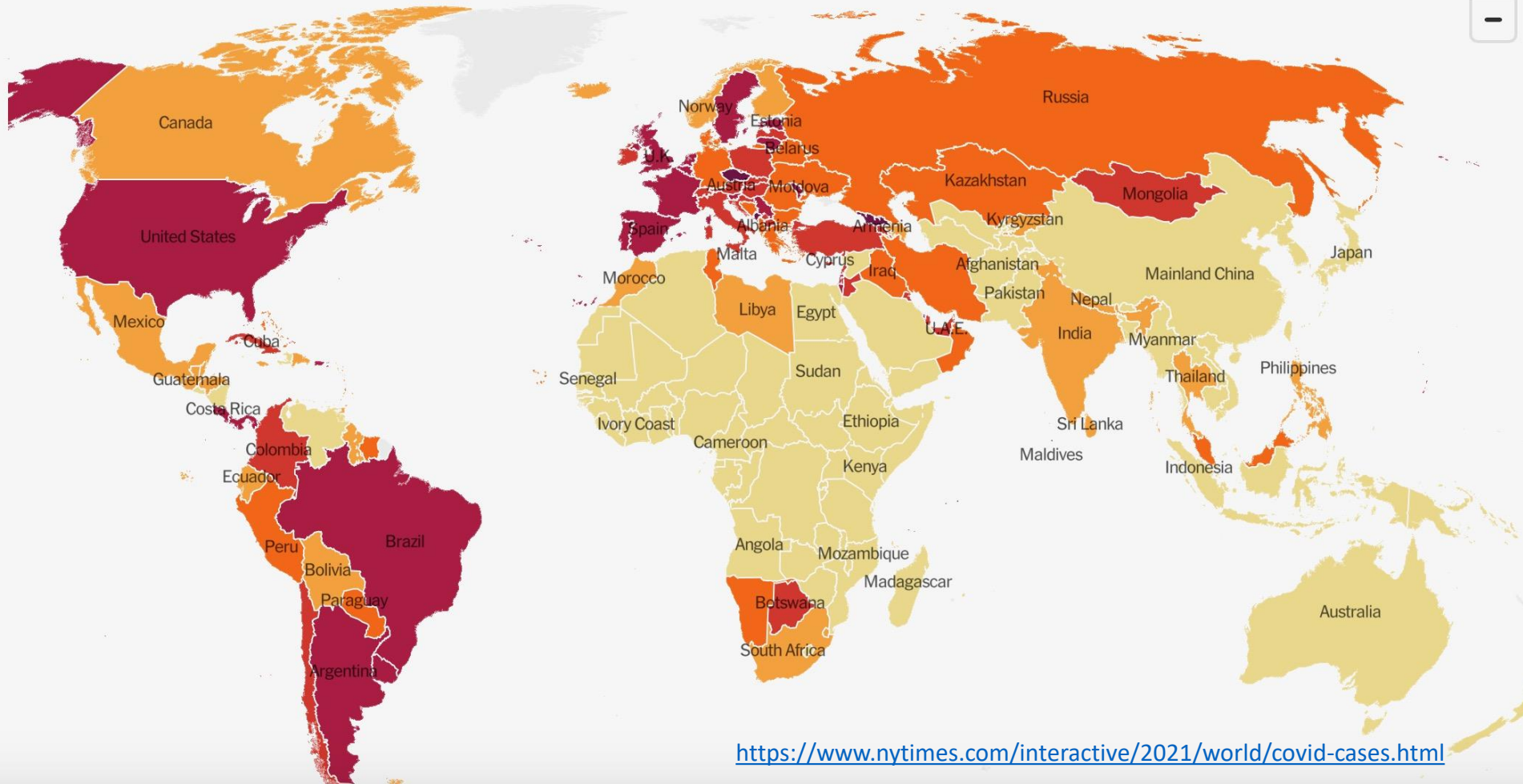
COVID-19 Vaccines

Katarina Le Blanc MD. PhD

Professor Karolinska Institutet, Stockholm, Sweden
Ordinary Member Pontifical Academy for Life

Cases per capita

SHARE OF POPULATION WITH A REPORTED CASE

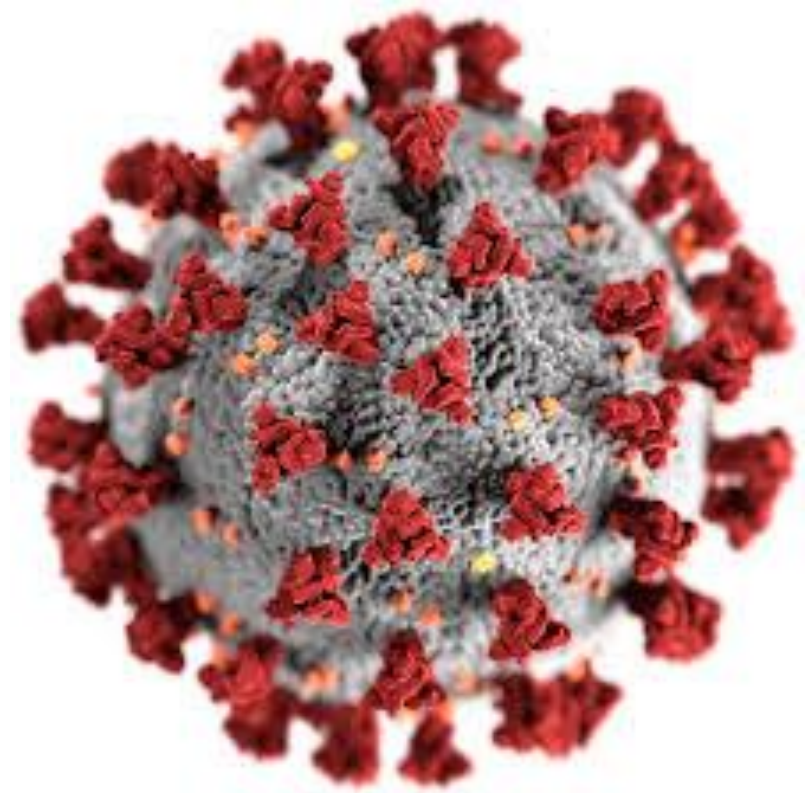


What does a vaccine do?

Protects from severe disease and death

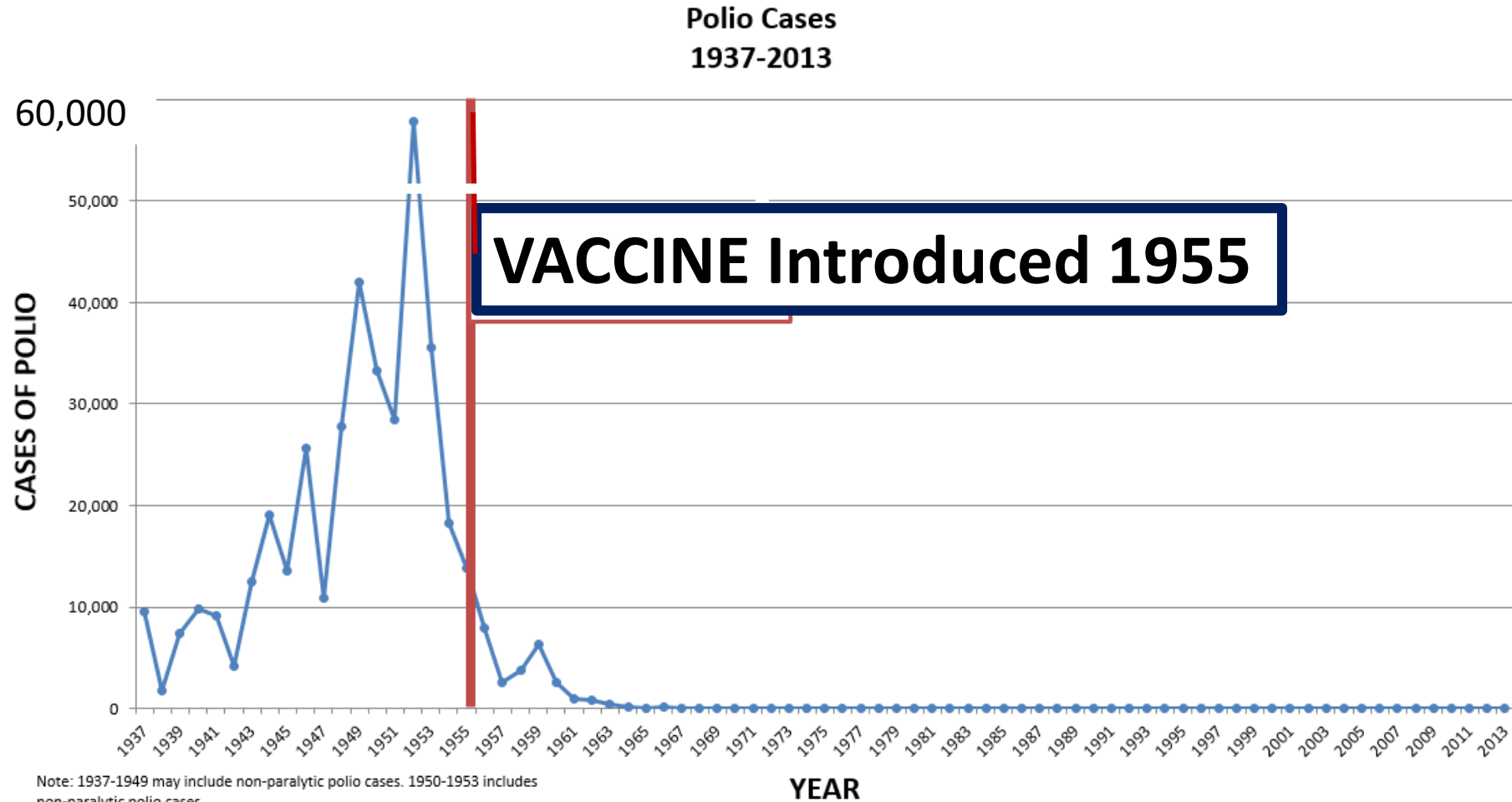
Limits spread of the disease

- Teaches the human body to recognize virus and bacteria and learn to destroy them
- Often resembles the microorganism causing the disease:
 - weakened or killed forms of the microbe
 - parts of the microbe surface proteins



Spike protein is the anchor that the virus uses to attach to a cell in order to infect it

Vaccines save lives: POLIO Incidence 1937-2013 in the US



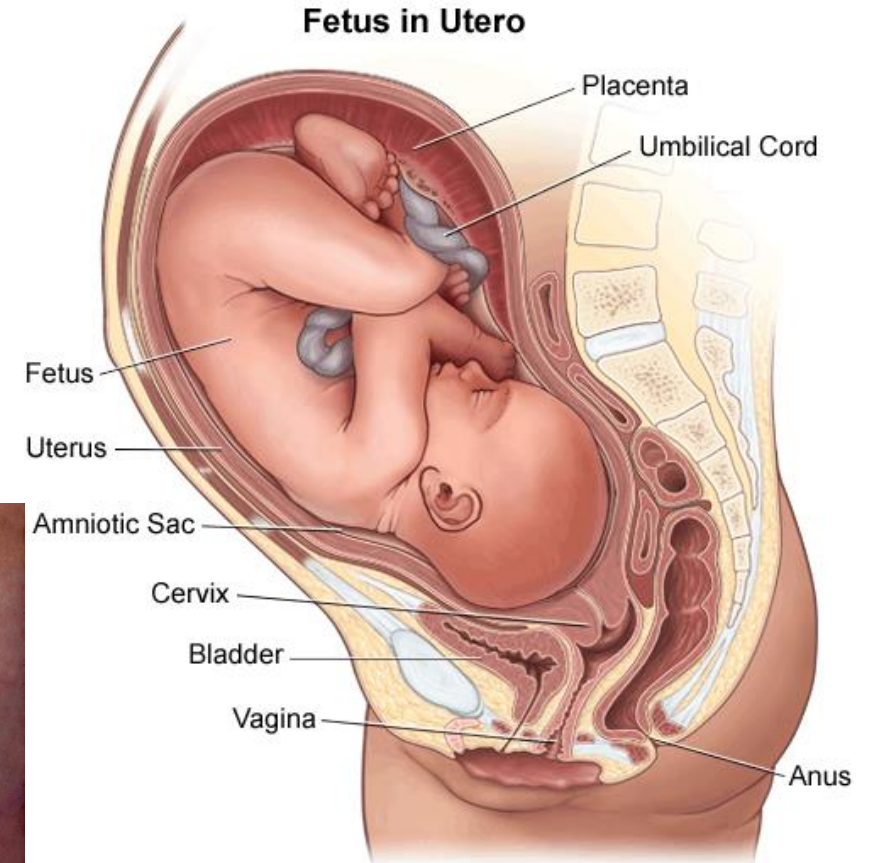
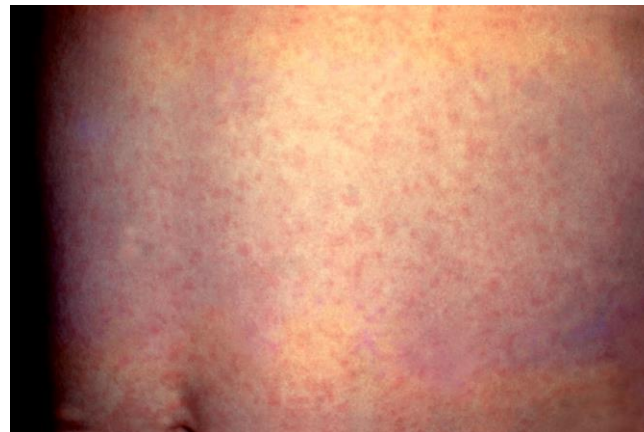
Rubella epidemic in the US 1964

The virus infects pregnant women
Spreads to the unborn child

Affected 20 000 unborn babies
2 100 neonatal deaths
11 600 cases of deafness
3 580 cases of blindness
1 800 cases of mental disability

The epidemic pushed for the
development and introduction of an
effective vaccine
against Rubella: █

Vaccination eliminated
Rubella in the US by 2004



Modern science and technology allows development of new vaccines in a short time

Within 1 year after COVID -19 occurred

- a pathogen was determined
- vaccine targets were identified
- vaccine constructs were created
- manufacturing to scale was developed
- phase 1 through phase 3 trials conducted
- data have been reported.

Pfizer/BioNTec vaccine phase III trial

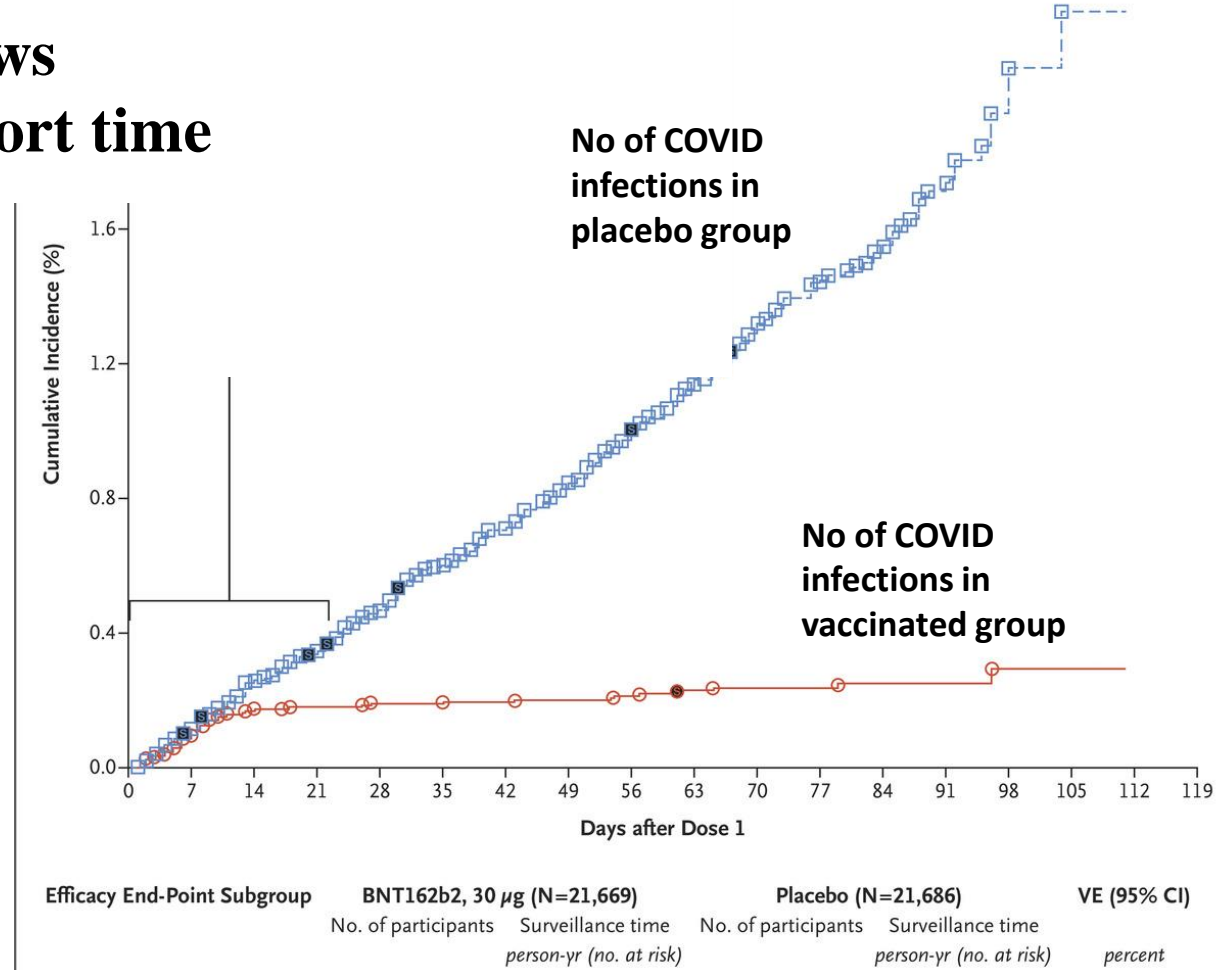
Study participants:

43,000 volunteers 2 doses

Moderna vaccine phase III trial

Study participants:

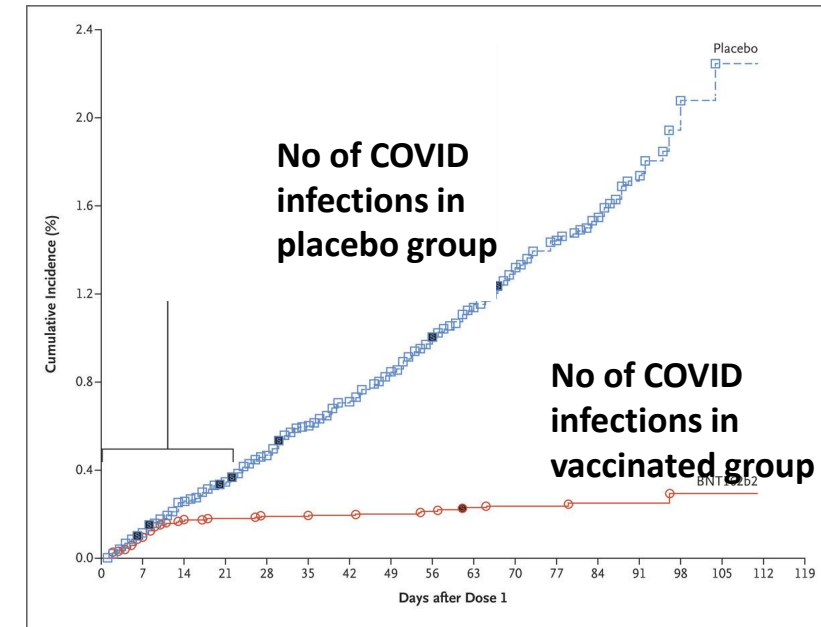
30,420 volunteers 2 doses



Polack F, Thomas S *et al.* N Engl J Med 2020;383:2603-15
Baden L *et al.* New England Journal of Medicine, Dec30, 2020
Voysey M *et al.* Lancet 2021; 397: 99–111

Efficacy and Safety of Pfizer and Moderna Vaccines

- mRNA vaccines
- Both vaccines reduced the risk of severe COVID
- Adverse Events: No serious long-term effects associated with these vaccines
- Most common: Injection site pain, fatigue, headache, muscle pain, joint pain
- Some: fever
- Side effects common after 2nd dose
- Neither vaccine has been tested in pregnant or lactating women; Animal studies to date have shown no concerning signs
- Anaphylaxis/anaphylactoid reactions are rare



Israeli experience of Pfizer's vaccine

ORIGINAL ARTICLE

Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting

Noam Barda, M.D., Noa Dagan, M.D., Yatir Ben-Shlomo, B.Sc., Eldad Kepten, Ph.D., Jacob Waxman, M.D., Reut Ohana, M.Sc., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Isaac Kohane, M.D., Doron Netzer, M.D., Ben Y. Reis, Ph.D., and Ran D. Balicer, M.D.

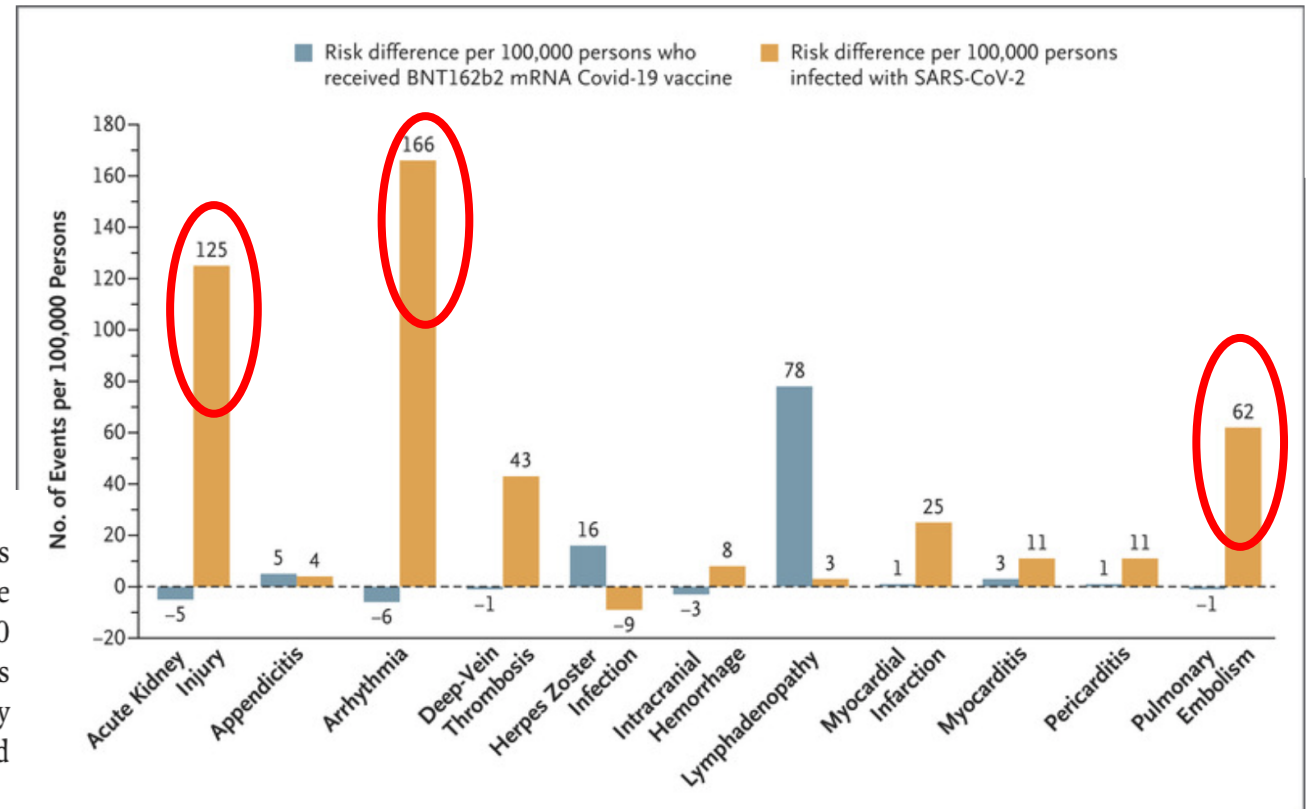
This article was published on August 25, 2021, at NEJM.org.

CONCLUSIONS

In this study in a nationwide mass vaccination setting, the BNT162b2 vaccine was not associated with an elevated risk of most of the adverse events examined. The vaccine was associated with an excess risk of myocarditis (1 to 5 events per 100,000 persons). The risk of this potentially serious adverse event and of many other serious adverse events was substantially increased after SARS-CoV-2 infection. (Funded by the Ivan and Francesca Berkowitz Family Living Laboratory Collaboration at Harvard Medical School and Clalit Research Institute.)

880 000 participants in each arm

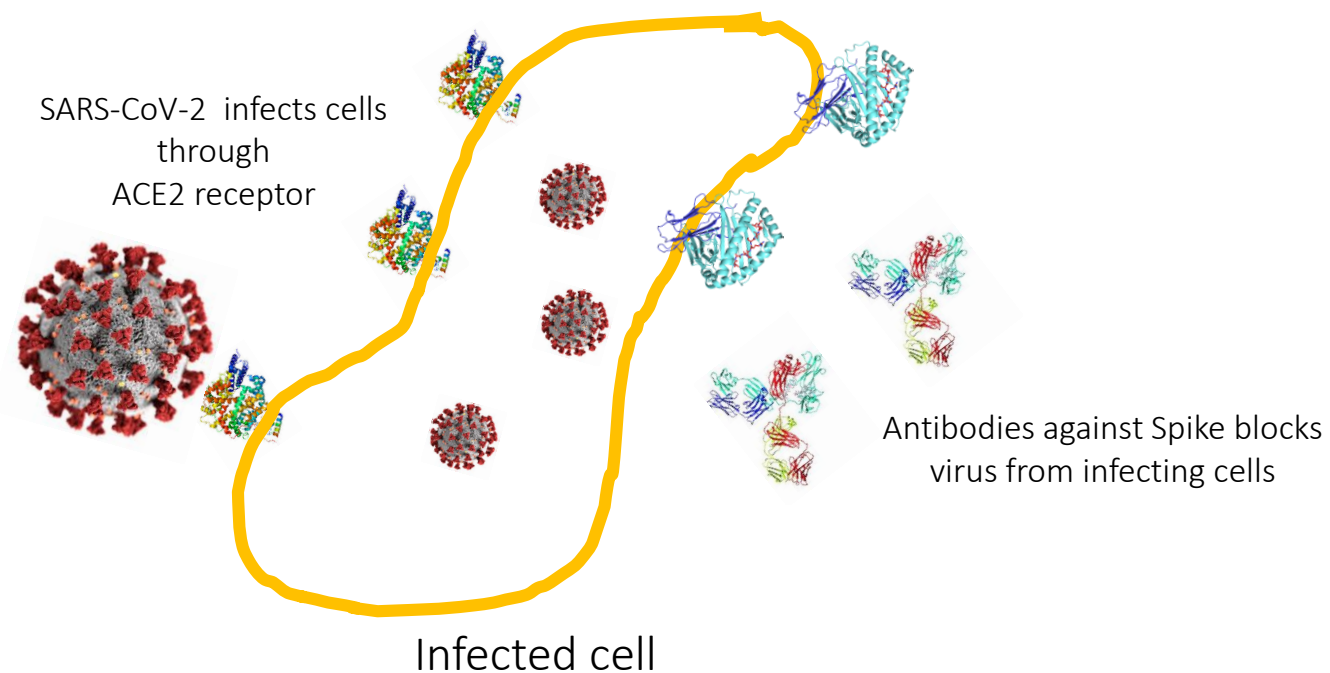
Figure 4. Absolute Excess Risk of Various Adverse Events after Vaccination or SARS-CoV-2 Infection.



Current vaccines against COVID-19

- All Covid-19 vaccines approved so far aim to stimulate formation of antibodies against the Spike protein

- mRNA based
 - *Comirnaty* Pfizer
 - *Spikevax* Moderna
- Adenovirus based
 - *Vaxzevria* Astra Zeneca
 - *Ad26.COVS.2.S* Janssen
 - *Sputnik V* Gamaleya, Russia
 - *Cansino* China.
 - *Covishield* Astra Zeneca (India)
- Inactivated virus vaccine
 - *Sinovac* (China)
 - *Sinopharm* (China)
 - *Covaxin* (India)



INSIDE AN MRNA COVID VACCINE

COVID-19 vaccines made from messenger RNA use lipid nanoparticles — bubbles of fats — to carry the molecules into cells. The mRNA contains the code for cells to produce the 'spike' protein that the coronavirus SARS-CoV-2 uses to enter cells. Here are key innovations in the design of these vaccines.

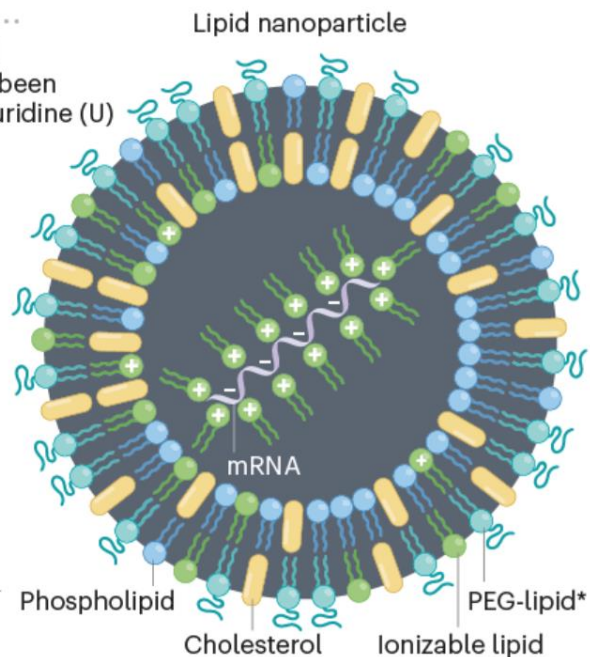


The vaccines made by Moderna and Pfizer-BioNTech use mRNA that has been chemically modified to replace the uridine (U) nucleotide with pseudouridine (Ψ). This change is thought to stop the immune system reacting to the introduced mRNA.

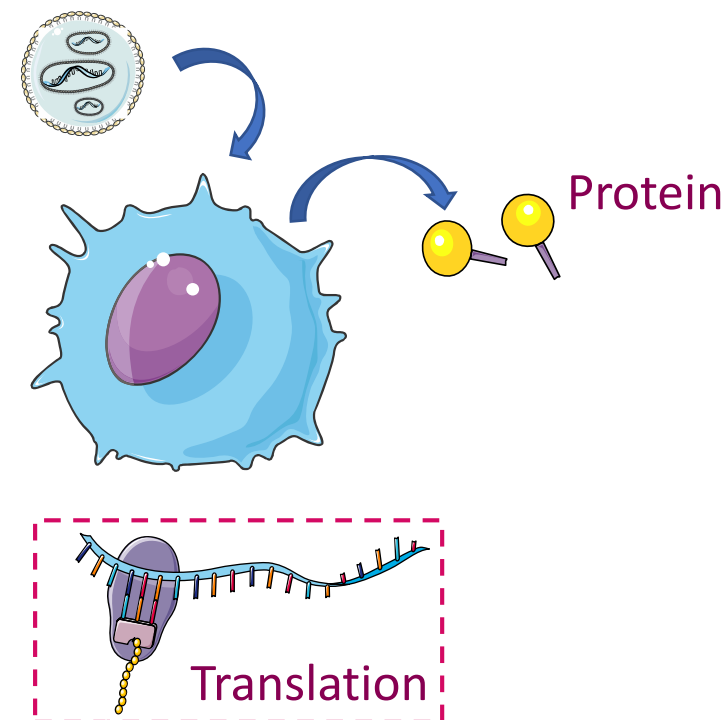
To help the body mount an effective immune response to later SARS-CoV-2 infections, the mRNA sequence is adapted to stabilize the spike protein in the shape it uses when fusing with human cells.



The fatty nanoparticle around the mRNA is made of four types of lipid molecule. One of these is 'ionizable': in the vaccine, many of these molecules have a positive charge and cling to negatively charged mRNA, but they lose that charge in the more alkaline conditions of the bloodstream, reducing toxicity in the body.



mRNA or vector vaccine



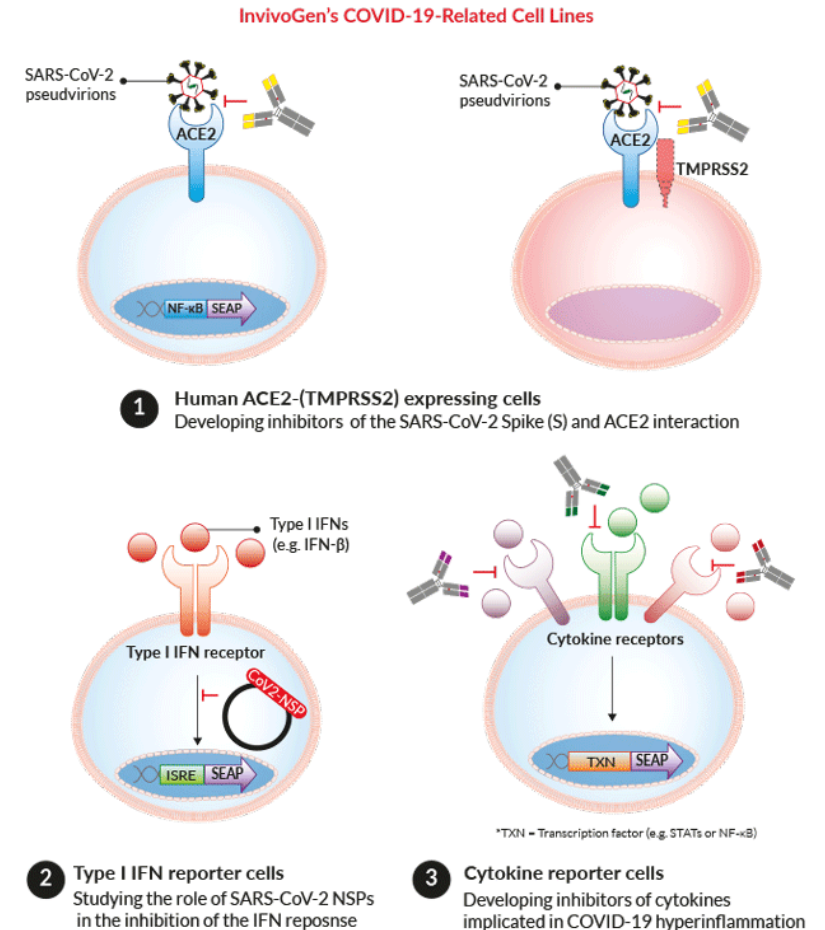
Fetal tissue has been used to generate genetically modified cell lines

The cell lines are an established laboratory tool used for over 40 years for culturing viruses and studying effectiveness of vaccines

Used for vaccines against Hepatitis A, Rubella vaccine, Varicella (chickenpox), Zoster (shingles) and Rabies

Reason:

- The cell lines are robust and well characterized
- They have been validated for their safety
- Approved by regulatory agencies like the U.S. Food and Drug Administration (FDA) and EMEA for human vaccine production.



Use of cell lines derived from fetal cells in vaccine production

WI-38 cells origin is fetal lung cells
abortion early 1960s;

MRC5 cells origin is fetal lung cells
abortion 1966

HEK293 cells origin fetal kidney cells
abortion 1973

>58 000 scientific papers used HEK 293

Cancer treatment CAR-T, Psychiatric research, Vaccine development

PER.C6 cells origin is fetal retinal cells
abortion 1985

The abortions were not performed for the purpose of vaccine development.

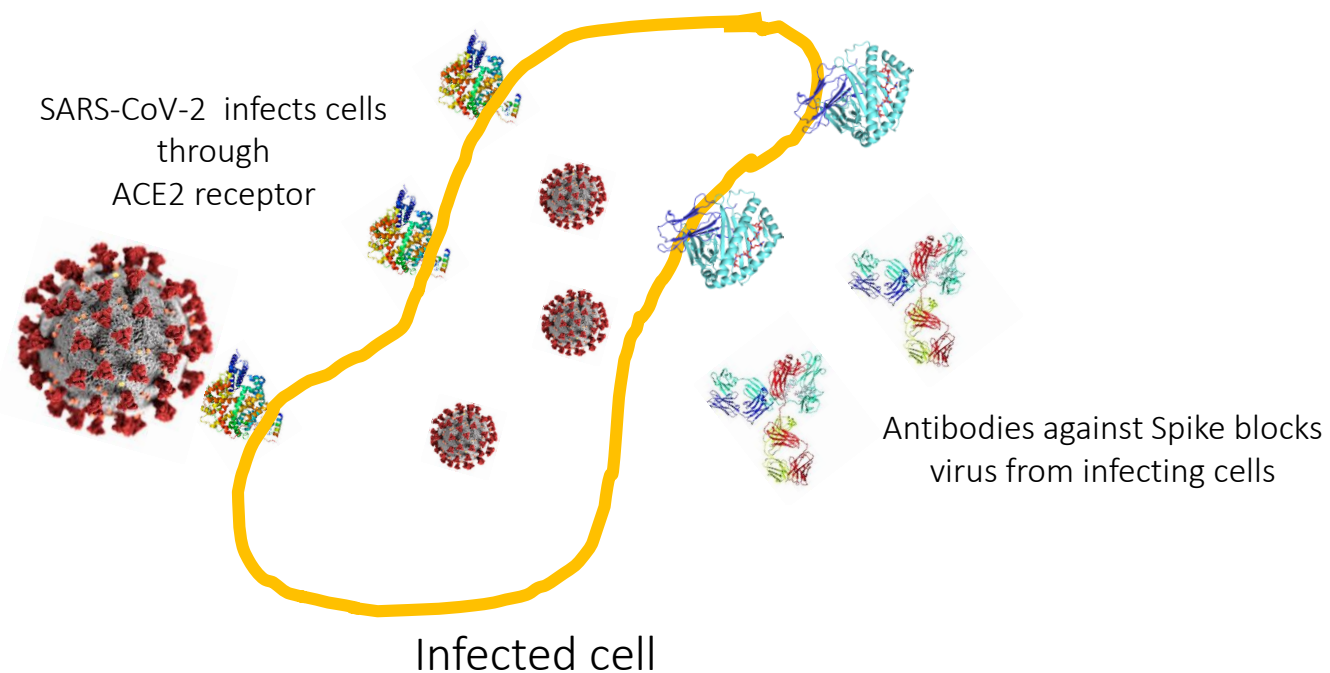
Fetal cells were genetically changed to grow indefinitely in a laboratory

There are no body parts or fetal tissue left

Accepting these vaccines will not mean consenting to future abortions

Current vaccines against COVID-19

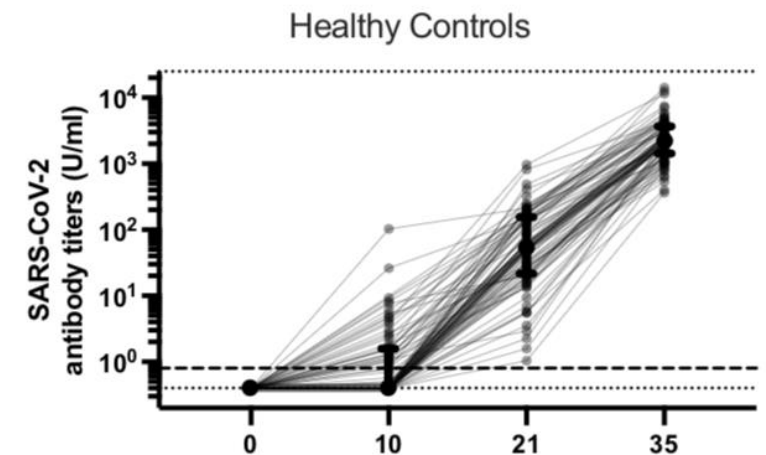
- All Covid-19 vaccines approved so far aim to stimulate an immune defence against the Spike protein
 - mRNA based
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 - **Spikevax Moderna**
 - Adenovirus based
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 - **Ad26.COVS.2.S Janssen**
 - **Sputnik V Gamaleya, Russia**
 - **Cansino China.**
 - *Covishield Astra Zeneca (India)*
 - Inactivated virus vaccine
 - **Sinovac (China)**
 - *Sinopharm (China)*
 - *Covaxin (India)*



<https://lozierinstitute.org/update-covid-19-vaccine-candidates-and-abortion-derived-cell-lines/>

Vaccine protection

- Protects against severe disease and death
- Does not halt all viral transmission
- Two vaccine doses needed for protection against disease
 - Dose 1 initiates antibody production
 - Dose 2 significantly increases antibody levels and those antibodies more effectively neutralize the virus



Bergman et al., MedRxiv, 2021

The Impact of Community Masking on COVID-19: A Cluster-Randomized Trial in Bangladesh

A randomized-trial of community-level mask promotion in rural Bangladesh during COVID-19 shows that the intervention tripled mask usage and reduced symptomatic SARS-CoV-2 infections, demonstrating that promoting community mask-wearing can improve public health.

Authors: Jason Abaluck (/people/jason-abaluck), Laura H. Kwong (/people/laura-h-kwong), Ashley Styczynski (/people/ashley-styczynski), Ashraf Haque (/people/ashraf-haque), Md Alamgir Kabir (/people/md-alamgir-kabir), Ellen Bates-Jefferys (/people/ellen-bates-jefferys), Emily Crawford (/people/emily-crawford), Jade Benjamin-Chung (/people/jade-benjamin-chung), Salim Benhachmi (/people/salim-benhachmi), Shabib Raihan (/people/shabib-raihan), Shadman Rahman (/people/shadman-rahman), Neeti Zaman (/people/neeti-zaman), Stephen Luby (/people/stephen-luby), Mushfiq Mobarak (/people/mushfiq-mobarak), Mohammad Ashraf Haque (/people/mohammad-ashraf-haque), Md Alamgir Kabir (/people/md-alamgir-kabir), Ellen Bates-Jefferys (/people/ellen-bates-jefferys), Shabib Raihan (/people/shabib-raihan), Shadman Rahman (/people/shadman-rahman), Neeti Zaman (/people/neeti-zaman)

Publication type: Working Paper

Date: September 01, 2021

Country: Bangladesh (/country/bangladesh)

Program area: Health (/program-area/health)

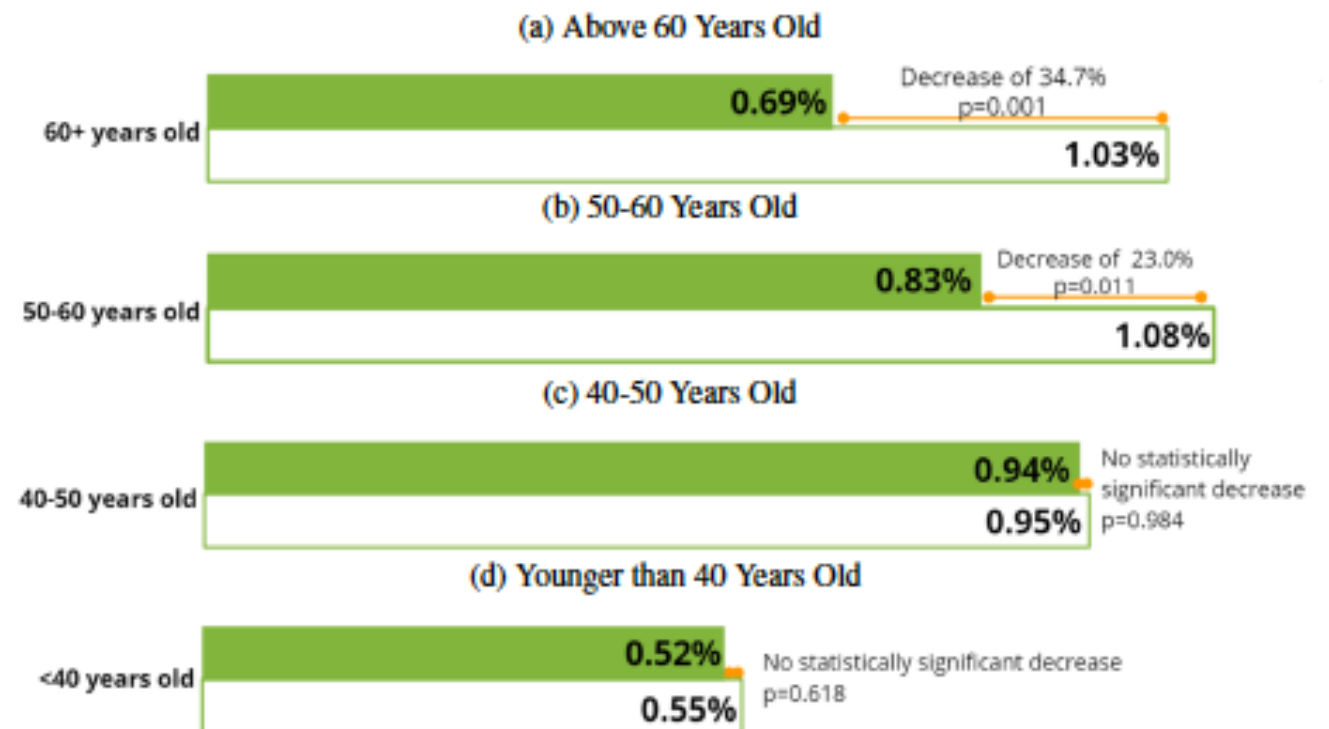
Topics: COVID-19 (/topics/covid-19)

350 000 participants

600 villages

Wearing surgical masks reduces spread of Corona

Figure 3: Effect on Symptomatic Seroprevalence by Age Groups, Surgical Masks Only



SARS-CoV-2 variants

Mutations in the Spike-protein can

- i) Increase the ability to infect cells
- ii) Render the virus more resistant to antibody neutralisation
(more difficult for the immune system to fend off)

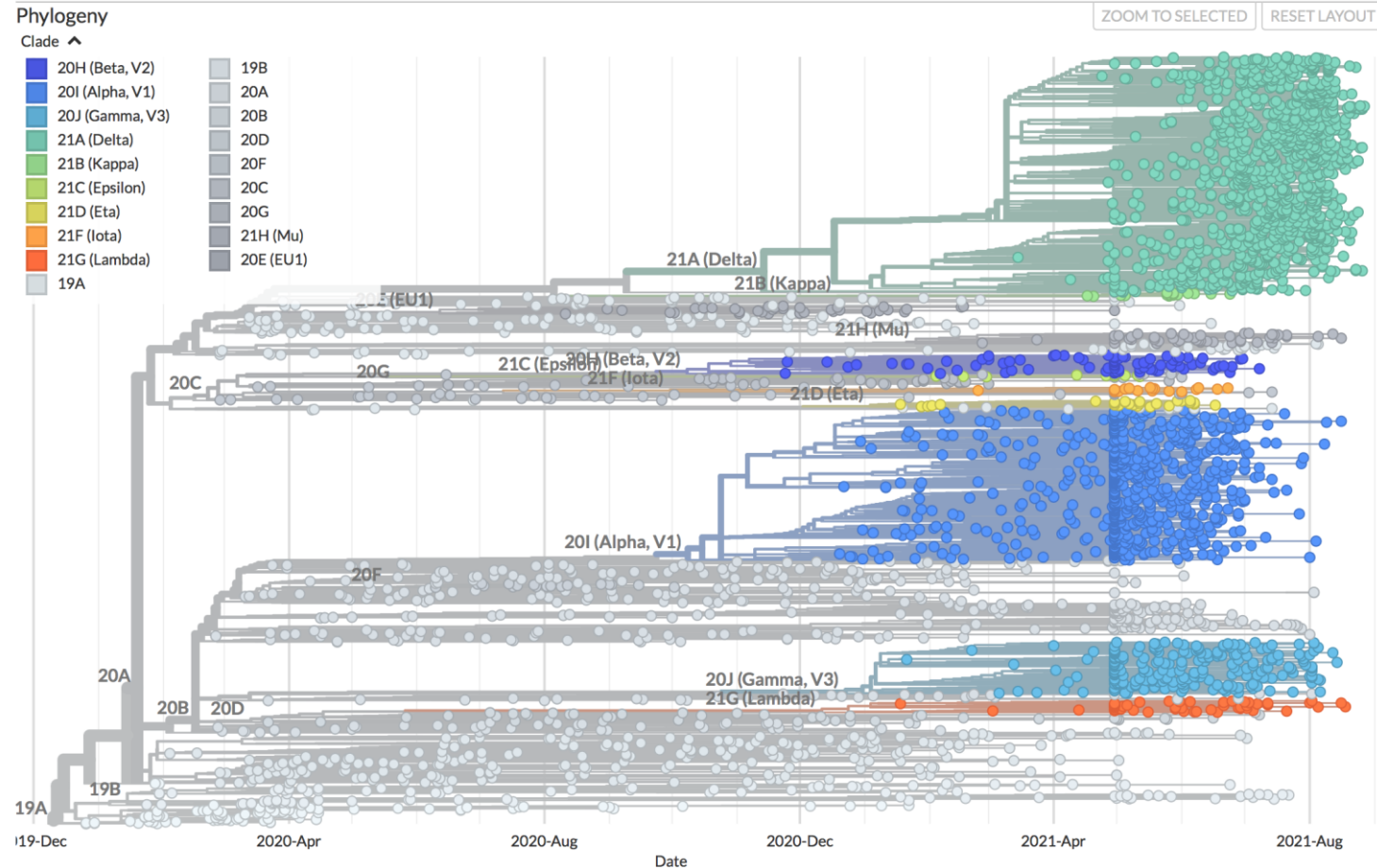
- Examples:

- Alfa B.1.1.7 (identified in UK)
- Beta B.1.351 (identified in South Africa)
- Gamma P.1 (identified in Brasil)
- Delta B.1.617.2 (identified in India)

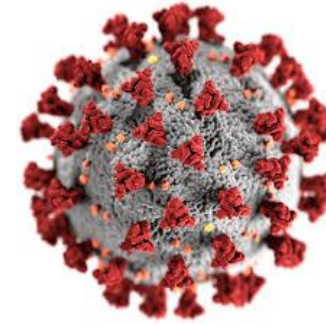
Genomic epidemiology of novel coronavirus - Global subsampling

Built with [nextstrain/ncov](#). Maintained by [the Nextstrain team](#). Enabled by data from [GISAID](#).

Showing 3493 of 3493 genomes sampled between Dec 2019 and Aug 2021.



The SARS-CoV-2 Delta variant



- SARS-CoV-2 Delta B.1.617.2 carries a mutation in the Spike protein, P681R, particularly important for the virus' ability to enter and infect cells
- People infected with the Delta variant carry more virus and secrete the virus longer than people infected with the Alpha and Beta variants

NEWS | 20 August 2021

The mutation that helps Delta spread like wildfire

A key amino-acid change might underlie the coronavirus variant's ferocious infectivity.



RELATED

How do vaccinated people spread Delta? What the science says

Shi's team and other groups have zeroed in on a mutation that alters a single amino acid in the SARS-CoV-2 spike protein – the viral molecule responsible for recognizing and invading cells. The change, which is called P681R and transforms a proline residue into an arginine, falls within an intensely studied region of the spike protein called the furin cleavage site.

The presence of this short string of amino acids set off alarm bells when SARS-CoV-2 was first identified in China, because

SARS-CoV-2 Delta variant and immunity

"In vitro, B.1.617.2 is:

- 6-fold less sensitive to serum neutralizing antibodies from recovered individuals
- 8-fold less sensitive to vaccine-elicited antibodies as compared to wild type (WT) Wuhan-1 ...
- serum neutralizing titers against B.1.617.2 were lower in ChAdOx-1 versus BNT162b2 vaccinees."
- Subvariants of the Delta virus already exist and will continue to appear if the viral load is high in society

nature

<https://doi.org/10.1038/s41586-021-03944-y>

Accelerated Article Preview

SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion

Received: 18 June 2021

Accepted: 23 August 2021

Accelerated Article Preview Published online 6 September 2021

Cite this article as: Mlcochova, P. et al. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. *Nature* <https://doi.org/10.1038/s41586-021-03944-y> (2021).

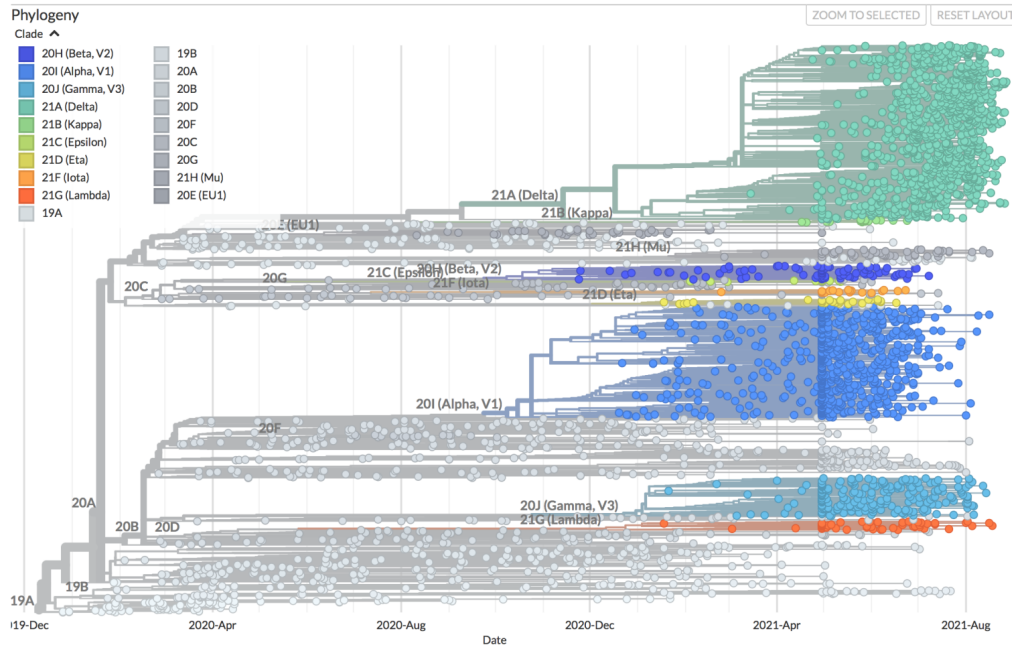
Petra Mlcochova, Steven Kemp, Mahesh Shanker Dhar, Guido Papa, Bo Meng, Isabella A. T. M. Ferreira, Rawlings Datir, Dami A. Collier, Anna Albecka, Sujeet Singh, Rajesh Pandey, Jonathan Brown, Jie Zhou, Niluka Goonawardane, Swapnil Mishra, Charles Whittaker, Thomas Mellan, Robin Marwal, Meena Datta, Shantanu Sengupta, Kalaiarasan Ponnusamy, Venkatraman Srinivasan Radhakrishnan, Adam Abdullahi, Oscar Charles, Partha Chattopadhyay, Priti Devi, Daniela Caputo, Tom Peacock, Dr Chand Wattal, Neeraj Goel, Ambrish Satwik, Raju Vaishya, Meenakshi Agarwal, The Indian SARS-CoV-2 Genomics Consortium (INSACOG), The Genotype to Phenotype Japan (G2P-Japan) Consortium, The CITIID-NIHR BioResource COVID-19 Collaboration, Antranik Mavousian, Joo Hyeon Lee, Jessica Bassi, Chiara Silacci-Fegni, Christian Saliba, Dora Pinto, Takashi Irie, Isao Yoshida, William L. Hamilton, Kei Sato, Samir Bhatt, Seth Flaxman, Leo C. James, Davide Corti, Luca Piccoli, Wendy S. Barclay, Partha Rakshit, Anurag Agrawal & Ravindra K. Gupta

SARS-CoV-2 Delta variant and immunity

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ORIGINAL ARTICLE

Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel

Yinon M. Bar-On, M.Sc., Yair Goldberg, Ph.D., Micha Mandel, Ph.D., Omri Bodenheimer, M.Sc., Laurence Freedman, Ph.D., Nir Kalkstein, B.Sc., Barak Mizrahi, M.Sc., Sharon Alroy-Preis, M.D., Nachman Ash, M.D., Ron Milo, Ph.D., and Amit Huppert, Ph.D.

ABSTRACT

CONCLUSIONS

In this study involving participants who were 60 years of age or older and had received two doses of the BNT162b2 vaccine at least 5 months earlier, we found that the rates of confirmed Covid-19 and severe illness were substantially lower among those who received a booster (third) dose of the BNT162b2 vaccine.

This article was published on September 15, 2021, at NEJM.org.

DOI: [10.1056/NEJMoa2114255](https://doi.org/10.1056/NEJMoa2114255)

1,137,804 persons
>60 years old

Patients with defective immune system are at particular risk for infection against SARS-CoV-2

- Hampered ability to respond to vaccine
- Studies performed for market registration focus on healthy individuals
- Therefore also less knowledge also on risks of vaccine side effects

Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial ¶

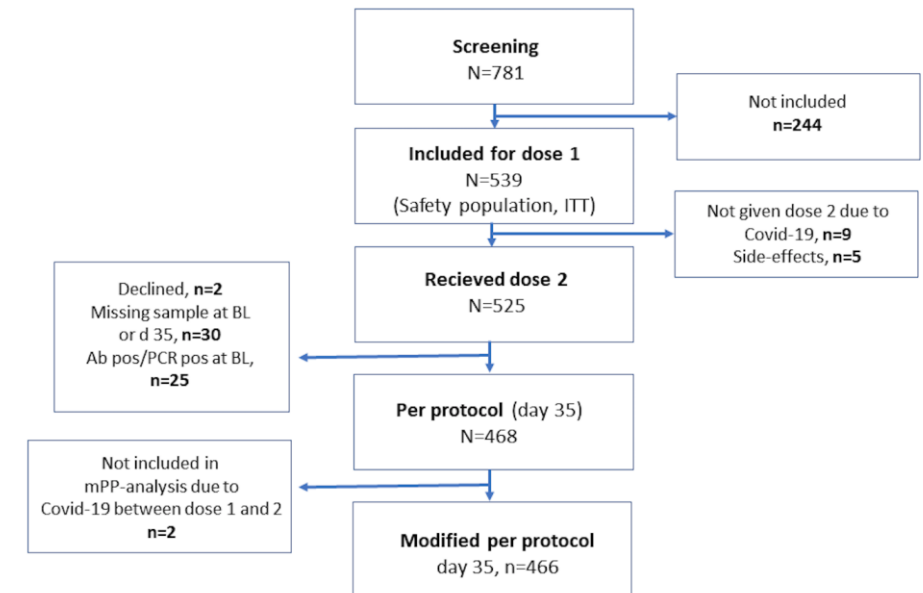


Peter Bergman, MD^{1,2*}, Ola Blennow, MD^{1,3,4*}, Lotta Hansson, MD^{5,6*}, Stephan Mielke, MD^{7,8*}, Piotr Nowak, MD^{1,9,10*}, Puran Chen, MD¹¹, Gunnar Söderdahl, MD^{3,4}, Anders Österborg, MD^{5,6}, C. I. Edvard Smith, MD^{1,8}, David Wullimann, MSc¹¹, Jan Vesterbacka, MD¹, Gustaf Lindgren, MD⁸, Lisa Blixt, MD^{5,6}, Gustav Friman, MD^{3,4}, Emilie Wahren-Borgström, MD¹, Anna Nordlander, MD⁸, Angelica Cuapio Gomez, MD¹¹, Mira Akber, MSc¹¹, Davide Valentini, PhD⁸, Anna-Carin Norlin, MD¹, Anders Thalme, MD¹, Gordana Bogdanovic, MD¹², Sandra Muschiol, PhD^{12,13}, Peter Nilsson, PhD¹⁴, Sophia Hober, PhD¹⁴, Karin Loré, PhD¹⁵, Margaret Sällberg Chen, PhD¹⁶, Marcus Buggert, PhD¹¹, Hans-Gustaf Ljunggren, MD¹¹, Per Ljungman, MD^{8,17}, Soo Aleman, MD^{1,9#}, and the COVAXID-collaborator group (shown separately). ¶

COVAXID Clinical Trial Karolinska Institutet

- "Open label", non-randomised prospective study in patients with weakened immune system
- Study subjects (539) divided into 6 groups
 - Healthy controls (n=90)
 - Primary immunodeficiencies (n=90)
 - Secondary immunodeficiencies
 - HIV infection (PLWH) (n=90)
 - Bone marrow transplant and CAR-T cancer treatment (n=9)
 - Solid organ transplantation (n=89)
 - Chronic lymphatic leukemia (n=90)
- Treatment: Two doses of mRNA BNT162b2 (Comirnaty, Pfizer/BioNTech) three weeks apart
- Primary end point: seroconversion
- Secondary endpoint: Safety

FLOWCHART for the COVAXID-study



COVAXID clinical trial, safety

- Local and systemic reactions
- Adverse events
 - Generally mild
 - More common in patients with immune defects
 - Most common in patients undergoing hematopoietic stem cell transplantation and immune cell treatment for cancer
- Severe Adverse Events
 - 27 severe adverse events, mainly in recipients of organ transplant (liver and kidney)
- Suspected Unexpected Serious Adverse Reaction
 - 2 patients with lung complications and respiratory failure

COVAXID trial conclusions

- mRNA BNT162b2 (Pfizer) vaccine is safe in patients with immunodeficiencies
- 72,2% of patients responded to vaccine compared to 100% of healthy controls
- Booster doses will be especially important for patients with impaired immune systems

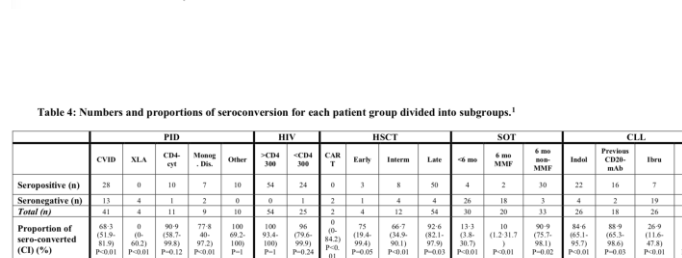
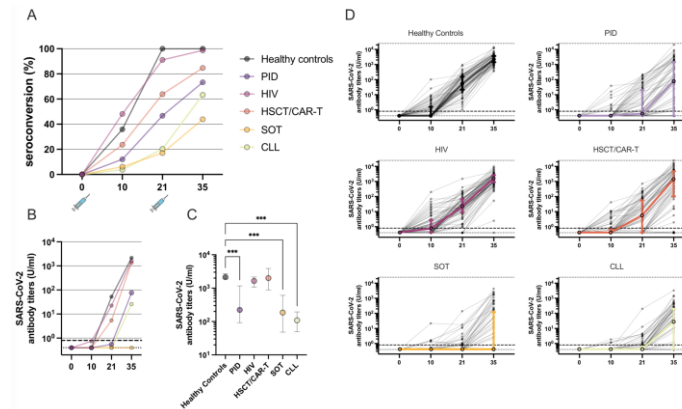
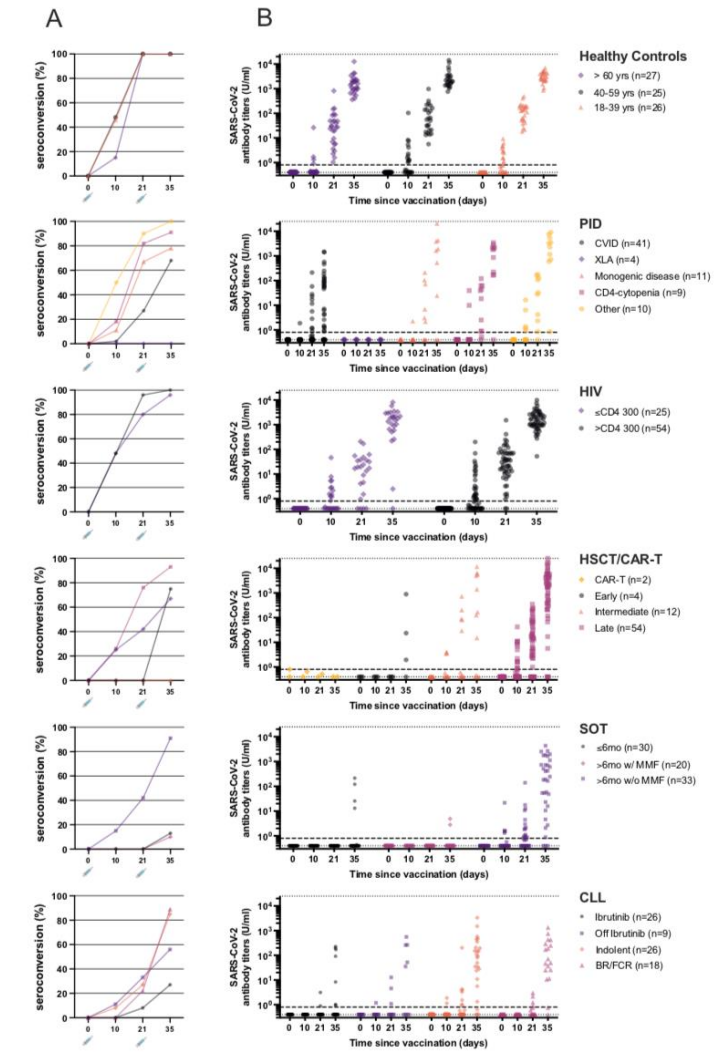


Table 4: Numbers and proportions of seroconversion for each patient group divided into subgroups.¹

	PID					HIV					HSCT					SOT					CLL				
	CVID	XLA	CD4-def	Monog Dis.	Other	<CD4 300	<CD4 300	CAR T	Early	Interm	Late	<6 mo	6 mo MMF	6 mo MMF	Indol	Previous CD20+ Mab	Ibru	Off Ibru	CVID	XLA	CD4-def	Monog Dis.	Other		
Seropositive (n)	28	0	10	7	10	54	24	0	3	8	50	4	2	30	22	16	7	5	5	0	0	0	0	0	
Seronegative (n)	13	4	1	2	0	0	1	2	1	4	4	26	18	3	4	2	19	4	0	0	0	0	0	0	
Total (n)	41	4	11	9	10	54	25	2	4	12	54	30	20	33	26	18	26	9	5	0	0	0	0	0	
Proportion of seroconverted (CI) (%)	68.3 (51.9-81.9)	0 (0-0)	90.9 (78.7-99.3)	77.8 (60.7-99.3)	100 (100-100)	100 (91.4-100)	96 (79.6-100)	0 (0-0)	75 (94.4-100)	66.7 (82.1-100)	92.6 (82.1-100)	13.3 (0.8-30.7)	10 (50)	90.9 (75.5-98.1)	84.6 (85.1-89.5)	88.9 (86.5-91.6)	26.9 (11.6-66.3)	55.6 (21.2-88.3)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)

Abbreviations: PID: primary immunodeficiency; CVID, common variable immunodeficiency; XLA, X-linked agammaglobulinemia; CD4-def: idiopathic CD4-cell lymphocytopenia; Monog Dis: monogenic disorder; HIV: human immunodeficiency virus; CD4: CD4+ T-cells; HSCT, hematopoietic stem cell transplantation; CAR T, chimeric antigen receptor T-cells; Early, <6 months after transplantation; Interm, 6-12 months after transplantation; Late, >12 months after transplantation; SOT: solid organ transplantation; MMF, mycophenolate mofetil; CLL: chronic lymphocytic leukemia; Indol, indolent and not treated; Previous CD20+ Mab, previous treatment with BR/FCR bendamustine and rituximab / Iudarabine, cyclophosphamide and rituximab; Ibru, ongoing ibrutinib treatment; Off Ibru, off ibrutinib treatment for >2 months; CI: 95% confidence interval.
Footnote: P-values of the differences vs. healthy controls were calculated.



**Vaccination is the only way to halt the Corona pandemic –
Social distancing is not enough**

The best vaccine is the vaccine you are offered

Global distribution is essential

Vaccine cannot be too expensive for poorer countries

Some vaccines require freezing during distribution

May be impossible to distribute in low income countries

